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Hearts starts and ends with a heartbeat. This has been well-known since the times of Aristotle. Ironically, in many cases, we know how and why the heart stops beating, but we know very little about its very first beat, i.e., the origin of life itself! Of course, the first heartbeat is generated by ion movements across the sarcolemma of the sinus node cells. But how it happens, which is the first ion to move, and what causes the first action potential is still a mystery. What is extraordinary is that all of these ion movements across the heart membranes occur at the rate of at least 60 times per minute throughout our lifetime—night and day—and generate the heart rate. Although ancient civilizations, in one way or another, have always linked the heart and heart rate to life, the importance of heart rate has not been fully appreciated in recent years and actually, in some cases, was even neglected. This is perhaps because of its familiarity and ease of measurement, on the one hand, and the complex nature of its effect, on the other.

Interest in the impact of heart rate in cardiovascular disease was given new impetus with the discovery of new currents responsible for its regulation and with the introduction into clinical practice of the specific heart rate–lowering agent ibabradine in 2005. One of these newly discovered currents, the inward current $I_f$ (with “$I$” standing for “inward” and “$f$” for “funny”), seems to be the primary mechanism for initiating the slope of phase-4 depolarization. It was termed “funny” because Di Francesco and colleagues noted that it was unexpected that an inward current would be activated on hyperpolarization of the cell membrane. In general, this occurs on depolarization. Thus, this novel observation struck the investigators as “funny.”

This single finding generated several interesting discoveries. The first is almost philosophical, and is the recognition that heart rate could be considered as the language of the body as well as a metabolic marker. This is an old concept. The Ebers papyrus, circa 1500 BC, identified the heart as the center of the cardiovascular system and found a close correlation between the heart and the pulsations of blood vessels. The heart is in contact with virtually every cell in the body through the circulatory system and, more specifically, through the shear stress of the endothelium. Local shear stress is sensed by endothelial mechanoreceptors and induces endothelial gene expression. Shear stress, for example, promotes dilatation (flow-mediated dilatation) by upregulating and stimulating constitutive nitric oxide synthase (cNOS), which produces nitric oxide. This mechanism is highly sophisticated: night and day (throughout our lifetime), not only does the heart contract to drive the circulation essential for life, it also sends out signals to keep the arteries open and relaxed, contributing to the maintenance of vascular tone.

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An increase in heart rate favors bidirectional changes in flow, reduces the average shear stress, and thus the production of nitric oxide. This in turn produces vasodilatation, allowing more blood to reach the peripheral tissues, increasing metabolism, and producing a relative increase in energy consumption and heat loss. Heart rate is an indirect marker of the body’s metabolic rate, and hence controls how much energy the body consumes. This is of paramount importance because living creatures in this world compete for a fixed share of the vital energy available to them. If they consume or, more exactly, exhaust it too quickly, their lives will have to be shorter. One could then consider heart rate to be the time-piece or pacemaker, not only of the heart, but also, viewed more widely, of life itself. 

A partial confirmation of this theory can be found in the relationships in the animal kingdom described by Levine, and by the discovery that animals have approximately the same number of heartbeats during their lifetime. These intriguing observations have led to speculation on whether life could be extended in man by slowing down the heart rate. Indeed, Levine estimated that a decrease in heart rate from 70 to 60 bpm would increase life expectancy from 80 to 93.3 years in humans.

As a consequence, the scientific community has become interested in retrospectively evaluating whether heart rate is a prognostic indicator both in the general population and in cardiac patients. A considerable body of evidence indicates that elevated resting heart rate is an independent modifiable risk factor for cardiovascular events and mortality in the general population as well as in patients with coronary artery disease and heart failure.

More than 100,000 healthy males and females of various nationalities and ages (between 18 and 80 years of age) were monitored for 36 years. Overall, there was a correlation between basal heart rate and all-cause mortality, irrespective of demographic differences. Today, the scientific community no longer contests the concept that heart rate is a prognostic indicator in the general population, even though there are no trials investigating the effects of deliberate heart rate reduction on healthy individuals. As a consequence, the importance of heart rate as a risk factor has been recognized by the European Guidelines on Cardiovascular Prevention.

A large number of epidemiological studies have also shown that elevated heart rate is associated with mortality and cardiac events in patients with cardiovascular disease. Among them, three particularly large studies are at the forefront. The CASS study (Coronary Artery Surgery Study), the INVEST study (International VErapamil-trandolapril STudy) and, more recently, the ONTARGET/TRANSCEND trials (ONgoing Telmisartan Alone and in combination with Ramipril Global End-point Trial and Telmisartan Randomised AssesssmeNt Study in angiotension Converting Enzyme inhibitor (NTolerant subjects with cardiovascular Disease). All of these trials have shown a relationship between elevated heart rate and cardiovascular mortality with a threshold of 70-75 bpm. These data are, however, retrospective as prospective data on the effects of heart rate on cardiovascular mortality have been difficult to obtain. This is because several drugs, notably β-blockers and non-dihydropyridine calcium channel blockers, which reduce heart rate, have a wide range of other actions on the vascular system and elsewhere in the body. By contrast, ivabradine has essentially no direct effects on the vascular system other than reducing the heart rate.

Thus, ivabradine has allowed to prospectively test whether heart rate is a risk factor in cardiovascular disease. This was investigated in the BEAUTIFUL trial (morBidity-mortality EvAl-UaTion of the I inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction study). In the placebo arm of the study, the relationship between baseline heart rate and outcome was analyzed. Patients with baseline heart rates of ≥70 bpm had a markedly increased risk of cardiovascular death, admission to hospital for heart failure, myocardial infarction, and need for coronary revascularization.

The benefits of heart rate reduction with ivabradine were also evident in the subgroup of patients with heart rate ≥70 bpm, where there were risk reductions of 36% in myocardial infarction and 30% in coronary revascularization. Furthermore, in those patients with angina at entry, there was a significant decrease in the primary composite end point and the rate of myocardial infarction in the ivabradine group. These ivabradine-related benefits were clearly independent from baseline heart rate, although they were more evident in those patients with heart rate ≥70 bpm. These data therefore indicate that heart rate ≥70 bpm is a risk factor for coronary artery disease.

There are several reasons why reducing heart rate is beneficial in coronary artery disease:

- **Heart rate is a determinant of myocardial oxygen consumption.** In humans, the heart beats on average 100 800 times per day. This figure corresponds to 36.8×10^8 heartbeats in a year and 29×10^10 in a lifetime (80 years on average). The heart produces and immediately consumes approximately 30 kg ATP every day—such is its turnover—corresponding to nearly 11 000 kg per year and approximately 880 000 kg in a lifetime. It follows that each heartbeat has its own cost—approximately 300 mg ATP. This means that slowing down the heart rate by 10 bpm per day would result in a saving of about 5 kg ATP in a day. To produce ATP the myocardium needs oxygen, which is used by the mitochondria for oxidative phosphorylation. So, a reduction in heart rate would lead to a significant reduction in oxygen demand at the cellular level, and in coronary artery disease, lack of oxygen is the critical patho-genetic factor.
Coronary flow is primarily diastolic. A high heart rate shortens diastole and hence reduces coronary flow, even in the absence of coronary lesions. This is why severe tachycardia can induce ischemia, especially in hypertensive patients and the elderly. A decrease in heart rate results in an increase in coronary flow.\textsuperscript{7}

Elevated heart rate increases arterial stiffness. Mechanical damage due to aging or elevated heart rate causes changes in elastin fibers. Epidemiological evidence indicates that a chronically elevated heart rate is associated with an accelerated progression of arterial stiffness in normotensive and hypertensive subjects.\textsuperscript{16}

Elevated heart rate favors coronary atherosclerosis. An association between elevated heart rate and atherosclerotic plaque development was first reported in cynomolgus monkeys.\textsuperscript{17} Further evidence of a link between heart rate and atherosclerosis has come from the measurement of changes in endothelial function and markers of inflammation. In rats, increasing the heart rate by 10% by electrical pacing significantly increased cardiac oxidative stress and triggered mitogen-activated protein kinase pathways, without any increase in blood pressure. On the contrary, heart rate reduction with ivabradine reduced oxidative stress, improved endothelial function, and prevented atherosclerosis in apolipoprotein E-deficient mice. In men, microinflammatory markers were found to increase progressively across quintiles of heart rate.\textsuperscript{18}

Increased heart rate favors acute coronary syndromes. The mechanical stress exerted on the rim of the atherosclerotic plaque is related to heart rate. Hemodynamic wall stress damages intracellular junctions and increases endothelial cell permeability, thereby favoring the entry of atherogenic particles. These mechanisms explain why high heart rates are associated with plaque rupture and acute coronary syndromes.\textsuperscript{19}

Elevated heart rate is also detrimental in heart failure. One crucial feature of the failing heart is the reduction of the force-frequency relationship,\textsuperscript{20} which is one of the basic mechanisms for regulating inotropy, as first characterized in 1871.\textsuperscript{21} In heart failure patients with pacemakers, an increase in paced or exercise-induced heart rate is not accompanied by an increase in oxygen uptake or by an increase in exercise performance, indicating that in heart failure patients, elevated heart rate increases myocardial load and oxygen consumption,\textsuperscript{22} thus being potentially proischemic. Furthermore, all cardiovascular interventions that reduce heart rate, such as β-blocker treatment, have been shown to improve outcomes in patients suffering from heart failure, while treatment with β-adrenoceptor agonists adversely affect survival and morbidity.\textsuperscript{23} However, the beneficial effect of β-blockers in heart failure may also be due to reasons other than heart rate reduction such as blood pressure lowering, negative inotropism, arrhythmic action, and attenuation of catecholamine toxicity. Recently, however, the role of heart rate in heart failure has been elucidated thanks to the availability of ivabradine, which causes a selective reduction in heart rate without any other hemodynamic effects.

In a model of cardiac remodeling in rats, ivabradine was able to prevent the global phenotype (hemodynamic, cardiac metabolism, neuroendocrine, and structure alterations, etc) of ventricular remodeling.\textsuperscript{24} Similar findings were obtained in a substudy of the BEAUTIFUL trial assessing left ventricular remodeling by echocardiography in patients with coronary artery disease and left ventricular dysfunction.\textsuperscript{25} Ivabradine treatment reduced the development of left ventricular remodeling and improved ejection fraction. The recent SHIFT trial (Syntolic Heart failure treatment with \( \beta \)-inhibitor ivabradine Trial) in 6558 patients with systolic heart failure included observational elements in which the relationship between baseline heart rate and outcome was analyzed in the placebo group.\textsuperscript{26} The hazard ratio for all-cause mortality was 1.86 for patients in the highest quintile of heart rate (>87 bpm) and was linearly reduced until the lowest quintile (70 to 72 bpm). These data clearly suggest that in heart failure there is a direct link between baseline heart rate and a worse outcome. Regarding treatment, it should be mentioned that in SHIFT, a baseline heart rate of ≥70 bpm was an entry requirement, and ivabradine treatment resulted in an 18% reduction (\( P<0.0001 \)) in the primary end point (the composite of cardiovascular death and hospitalization for heart failure).\textsuperscript{27} The effects of ivabradine were linearly more evident as heart rate was reduced from 87 to <60 bpm. The observational and interventional elements of this trial therefore indicate that heart rate is a modifiable risk factor in heart failure—rather than merely a risk marker—and have confirmed the benefit of “pure” heart rate reduction in patients with heart failure and elevated heart rate.

Conclusions
Although never neglected, the concept of heart rate is undoubtedly having a revival with the discovery of the \( \beta \)-current in the sinus node of the right atria, and of ivabradine, a drug capable of reducing this current, and hence of reducing heart rate. There is now a mass of epidemiological, pathophysiological, and clinical trial evidence indicating the importance of heart rate control. However, recent surveys have revealed low rates of heart rate control among patients with coronary artery disease in clinical practice. In the European Heart Survey of patients with stable angina attending cardiology services throughout Europe,\textsuperscript{28} the mean resting heart rate was 73 bpm, and more than half of the patients (52.3%) had heart rates >70 bpm. Interestingly, approximately 40% of patients receiving \( \beta \)-blockers had heart rates >70 bpm. The European Heart Survey authors concluded that there was evidence that physicians and cardiologists gave inadequate attention to heart rate and that a therapeutic opportunity was being missed as a result. It’s time to act. This is what this issue of \textit{Medicographia} is about.
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La fréquence cardiaque dans la prise en charge des patients atteints d’affections cardio-vasculaires : il est temps d’agir

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La fréquence cardiaque est un marqueur indépendant de l’organisme qui contrôle la quantité d’énergie consommée. Elle est très importante, car les êtres vivants sont en compétition pour une part fixe d’énergie vitale. S’ils la consomment ou, plus exactement, l’éprouvent trop rapidement, leur vie sera raccourcie. La fréquence cardiaque est ainsi une horloge qui impose son rythme non seulement au cœur, mais également de façon plus large, à la vie elle-même.”

La vie commence et se termine par un battement de cœur. Cette vérité est connue depuis l’époque d’Aristote. Il est ironique de constater que, dans la plupart des cas, nous savons comment et pourquoi le cœur s’arrête de battre, mais que nous connaissons très peu de choses sur le tout premier battement, c’est-à-dire l’origine de la vie elle-même ! Bien sûr, le premier battement de cœur est généré par des mouvements ioniques à travers le sarcolemme des cellules du nœud sinusal de Keith et Flack. Mais la manière dont cela survient, quel est le premier ion à se déplacer et qu’est-ce qui provoque le premier potentiel d’action reste un mystère. Il est extraordinaire de constater que l’ensemble de ces mouvements ioniques à travers les membranes cardiaques se produisent à un rythme d’au moins 60 par minute pendant toute notre vie – nuit et jour – et génèrent la fréquence cardiaque.

Bien que les civilisations anciennes aient toujours lié d’une manière ou d’une autre le cœur et la fréquence cardiaque à la vie, l’importance de la fréquence cardiaque n’a pas été pleinement appréciée au cours de ces dernières années, et même, dans certains cas, elle a été négligée. Cela est probablement dû à sa familiarité et à sa facilité de mesure d’une part et à la nature complexe de ses effets d’autre part.

Un intérêt nouveau pour l’impact de la fréquence cardiaque sur les maladies cardio-vasculaires a été suscité par la découverte de nouveaux courants responsables de sa régulation, et avec l’introduction en 2005 dans notre pratique clinique de l’ivabradine, un médicament réduisant spécifiquement la fréquence cardiaque. L’un de ces deux courants récemment découverts, le courant entrant pacemaker I_{f} (la lettre « I » correspondant à « inward » et la lettre « f » à « funny » ce qui signifie bizarre), semble être le mécanisme principal de l’initiation de la pente de dépolarisation de phase 4. Il a été dénommé « funny », car Di Francesco et coll. ont observé qu’il était inattendu qu’un courant entrant soit activé par hyperpolarisation de la membrane cellulaire. En général, cela se produit au cours d’une dépolarisation. Par conséquent, cette nouvelle observation a été considérée par les investigateurs comme « bizarre ». Ce résultat a en lui-même conduit à plusieurs découvertes intéressantes. La première est avant tout philosophique : c’est la reconnaissance du fait que la fréquence cardiaque peut être considérée comme le langage du corps au même titre qu’un marqueur métabolique. Il s’agit là d’un concept ancien. Le papyrus Ebers, qui date d’environ 1500 avant Jésus-Christ, identifiait déjà le cœur comme le centre du système cardio-vasculaire et établissait une étroite corrélation entre le cœur et les pulsations des vaisseaux sanguins. Le cœur est en contact avec pratiquement toutes les cellules de l’organisme par l’intermédiaire du système circulatoire et, plus
spécifiquement, par le stress de cisaillement de l’endothélium. Le stress de cisaillement local est capté par des mécanorécepteurs endothéliaux et induit l’expression des gènes endothéliaux. Le stress de cisaillement, par exemple, favorise la dilatation (dilatation débit-dépendante) en stimulant la monoxyde d’azote synthase constitutive (constitutive nitric oxide synthase, cNOS), qui produit la monoxyde d’azote. Ce mécanisme est extrêmement élaboré : nuit et jour (pendant toute notre vie), non seulement le cœur se contracte pour assurer la circulation essentielle à la vie, mais il envoie également des signaux qui gardent les artères ouvertes et relaxées, ce qui contribue au maintien du tonus vasculaire.

Une augmentation de la fréquence cardiaque favorise des changements bidirectionnels de débit, réduit le stress de cisaillement moyen et par conséquent la production de monoxyde d’azote. Ce phénomène entraîne en retour une vasodilatation, permettant à une plus grande quantité de sang d’atteindre les tissus périphériques, augmentant ainsi le métabolisme et produisant une augmentation relative de la consommation d’énergie et de la perte calorique. La fréquence cardiaque est un marqueur indirect du taux métabolique de l’organisme qui contrôle la quantité d’énergie consommée. Elle est très importante, car les êtres vivants sont en compétition pour une part fixe d’énergie vitale. S’ils la consomment ou, plus exactement, l’épuisent trop rapidement, leur vie sera raccourcie. La fréquence cardiaque est ainsi une horloge qui impose son rythme non seulement au cœur, mais également de façon plus large, à la vie elle-même.

Une confirmation partielle de cette théorie se trouve dans les relations au sein du royaume animal décrites par Levine, et par la découverte que les animaux ont approximativement le même nombre de battements cardiaques au cours de leur vie. Ces observations étonnantes ont conduit à supposer que la vie humaine pourrait être étendue en ralentissant la fréquence cardiaque. En effet, Levine a estimé qu’une diminution de la fréquence cardiaque de 70 à 60 bpm augmenterait l’espérance de vie de 80 à 93,3 ans chez l’homme.

Par conséquent, la communauté scientifique a cherché à déterminer de manière rétrospective si la fréquence cardiaque pouvait être un indicateur pronostique à la fois dans la population générale et chez les patients cardiaques. Un nombre de preuves très important ont indiqué qu’une augmentation de la fréquence cardiaque au repos était un facteur de risque modifiable indépendant pour les événements cardiovasculaires et la mortalité dans la population générale, ainsi que chez les patients atteints de coronaropathies et d’insuffisance cardiaque.

Plus de 100 000 hommes et femmes sains de différentes nationalités et d’âges variables (entre 18 et 80 ans) ont été suivis pendant 36 ans. D’une manière générale, il a été établi une corrélation entre la fréquence cardiaque basale et la mortalité de toute cause, indépendamment des différences démographiques. Aujourd’hui, la communauté scientifique ne conteste plus le concept selon lequel la fréquence cardiaque est un indicateur pronostique dans la population générale, même en l’absence d’études portant sur les effets d’une réduction délibérée de la fréquence cardiaque chez des individus sains. Par conséquent, l’importance de la fréquence cardiaque comme facteur de risque a été reconnue par les Directives européennes sur la prévention cardio-vasculaire (European Guidelines on Cardiovascular Prevention).

Un grand nombre d’études épidémiologiques ont également montré qu’une augmentation de la fréquence cardiaque était associée à la mortalité et à des événements cardiaques chez des patients atteints de maladies cardio-vasculaires. Parmi elles, il faut souligner en particulier trois études importantes. L’étude CASS (Coronary Artery Surgery Study, Etude sur la chirurgie des artères coronaires), l’étude INVEST (International Vaparamil-trandolapril Study, Etude internationale sur le vérépamil et le trandolapril) et plus récemment les études ONTARGET/TRANSCEND (ONGOing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial [Etude sur le telmisartan seul et en association avec le ramipril] et Telmisartan Randomised AssessmeneNT In angiontension Converting Enzyme inhibitor NTolerant subjects with cardio-vascular Disease [Évaluation randomisée du telmisartan chez les sujets intolérants aux inhibiteurs de l’enzyme de conversion de l’angiotensine atteints de maladies cardio-vasculaires]). Toutes ces études ont montré une relation entre une augmentation de la fréquence cardiaque et la mortalité cardio-vasculaire avec un seuil de 70 à 75 bpm. Cependant, ces données sont rétrospectives, dans la mesure où des données prospectives relatives aux effets de la fréquence cardiaque sur la mortalité cardio-vasculaire ont été difficiles à obtenir. Cela est dû au fait que différents médicaments, notamment les bêta-bloquants et les inhibiteurs calciques non dihydropyridine, qui réduisent la fréquence cardiaque, ont un grand nombre d’autres actions sur le système vasculaire et les autres systèmes de l’organisme. En revanche, l’ivabradine n’a pratiquement aucun effet direct sur le système vasculaire, autre que la réduction de la fréquence cardiaque.

Par conséquent, l’ivabradine a permis d’étudier de manière prospective si la fréquence cardiaque constituait un facteur de risque pour les maladies cardio-vasculaires. Cette exploration a été effectuée dans l’étude BEAUTIFUL (morBidity-mortality EvAluation of the I, inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction study, Évaluation de la morbidité et de la mortalité de l’ivabradine, un inhibiteur du courant I, chez des patients atteints de coronaropathies et de dysfonctionnement ventriculaire gauche). Dans le bras placebo de l’étude, la relation entre la fréquence cardiaque initiale et les résultats a été analysée. Les patients présentant une fréquence cardiaque initiale ≥ 70 bpm ont montré une nette augmentation du risque de mortalité cardio-
La fréquence cardiaque est un déterminant de la consommation d’oxygène du myocarde. Chez l’homme, le cœur bat en moyenne 100 800 fois par jour. Ce chiffre correspond à 36,8 x 10⁶ battements cardiaques par an et 29 x 10⁶ au cours d’une vie (de 80 ans en moyenne), ce qui fait que le cœur produit et consomme immédiatement environ 30 kg d’ATP chaque jour, soit près de 11 000 kg par an et de 880 000 kg au cours de la vie. C’est-à-dire que chaque battement cardiaque a son prix – environ 300 mg d’ATP. Cela signifie que le ralentissement de la fréquence cardiaque de 10 bpm par jour entraînerait une économie d’environ 5 kg d’ATP par jour. Pour produire de l’ATP, le myocarde a besoin d’oxygène, qui est utilisé par les mitochondries pour la phosphorylation oxydative. Ainsi, une réduction de la fréquence cardiaque entraînerait une réduction significative de la demande d’oxygène au niveau cellulaire, et dans les coronaropathies, le manque d’oxygène est le facteur pathogène essentiel.

Le débit coronarien est principalement diastolique. Une fréquence cardiaque élevée raccourcit la diastole et par conséquent réduit le débit coronarien, même en l’absence de lésions coronariennes. C’est la raison pour laquelle une tachycardie sévère peut induire une ischémie, en particulier chez les patients hypertendus et les sujets âgés. Une diminution de la fréquence cardiaque conduit à une augmentation du débit coronarien.

L’augmentation de la fréquence cardiaque augmente la rigidité artérielle. Des lésions mécaniques dues au vieillissement ou une augmentation de la fréquence cardiaque provoquent des changements au niveau des fibres d’élastine. Des preuves épidémiologiques indiquent qu’une augmentation chronique de la fréquence cardiaque est associée à une accélération de la progression de la rigidité artérielle chez des sujets normotendus et hypertendus.

Une augmentation de la fréquence cardiaque favorise l’athérosclérose coronarienne. Une association entre une augmentation de la fréquence cardiaque et le développement de plaques d’athérosclérose a été observée pour la première fois chez des macaques cynomolgus. D’autres preuves d’un lien entre la fréquence cardiaque et l’athérosclérose ont été obtenues par la mesure des changements de la fonction endothéliale et des marqueurs de l’inflammation. Chez le rat, une élévation de la fréquence cardiaque et l’athérosclérose a réduit le stress oxydatif cardiaque et a activé les voies des MAP kinases, sans augmentation de la pression artérielle. En revanche, une réduction de la fréquence cardiaque par l’ivabradine a réduit le stress oxydatif, amélioré la fonction endothéliale et empêché l’athérosclérose chez des souris déficientes en apolipoprotéine E. Chez l’homme, une augmentation progressive des marqueurs micro-inflammatoires a été observée suivant les quintiles de fréquence cardiaque.

L’augmentation de la fréquence cardiaque favorise les syndromes coronariens aigus. Le stress mécanique exercé sur le bord de la plaque athéroscléreuse est lié à la fréquence cardiaque. Le stress hémodynamique sur le paroi entraîne des lésions au niveau des jonctions intracellulaires et augmente la perméabilité des cellules endothéliales, favorisant la pénétration des particules athérogènes. Ces mécanismes expliquent pourquoi les fréquences cardiaques élevées sont associées à une rupture des plaques et à des syndromes coronariens aigus.

L’augmentation de la fréquence cardiaque est également nocive dans l’insuffisance cardiaque. L’une des caractéristiques essentielles d’un cœur défaillant est la réduction de la relation capture d’oxygène ou des performances physiques, ce qui indique que, dans le cœur des patients insuffisants cardiaques, une élévation de la fréquence cardiaque imposée ou induite par l’exercice physique n’est pas accompagnée par une augmentation de la capture d’oxygène ou des performances physiques, ce qui indique que, dans le cœur des patients insuffisants cardiaques, une élévation de la fréquence cardiaque augmente la charge myocardique et la consommation d’oxygène, deux phénomènes potentiellement pro-ischémiques. En outre, il a été montré que toutes les interventions cardio-vasculaires qui réduisent la fréquence cardiaque, notamment un traitement par les bétabloquants, induisent une amélioration des critères d’évolution chez les patients souffrant d’insuffisance cardiaque, tandis qu’un traitement par des bétabimétiques entraîne des effets négatifs sur la survie et la morbilité. Cependant, l’effet bénéfique des bétabloquants sur la fréquence cardiaque n’est pas forcément dû à une réduction de la fréquence cardiaque, mais peut avoir d’autres causes comme par exemple un abaissement de la pression artérielle, un effet inotrope négatif, une action anti-arythmique et l’atténuation de la toxicité.
Les catécholamines. Cependant, le rôle de la fréquence cardiaque dans l’insuffisance cardiaque a récemment été élucidé grâce à l’ivabradine, qui entraîne une réduction sélective de la fréquence cardiaque sans autre effet hémodynamique.

Dans un modèle de remodelage cardiaque chez le rat, il a été montré que l’ivabradine peut prévenir le phénomène global (altérations hémodynamiques, du métabolisme cardiaque, neuroendocrines et structurelles, etc.) du remodelage ventriculaire. Des résultats similaires ont été obtenus dans une sous-étude de l’essai BEAUTIFUL évaluant le remodelage ventriculaire gauche par échocardiographie chez des patients atteints de coronaropathie et de dysfonction ventriculaire gauche. Un traitement par l’ivabradine a permis de réduire le développement du remodelage ventriculaire gauche et d’améliorer la fraction d’éjection. La récente étude SHIFT (Systolic Heart failure treatment with I, inhibitor ivabradine Trial, Traitement de l’insuffisance cardiaque systolique par l’ivabradine, un inhibiteur du courant 1) menée chez 6 558 patients atteints d’insuffisance cardiaque systolique, a inclus des éléments observationnels grâce auxquels la relation entre la fréquence cardiaque initiale et les paramètres d’évolution a pu être analysée dans le groupe placebo. Le risque relatif de mortalité de toute cause a été déterminé à 1,86 pour les patients du quintile supérieur de fréquence cardiaque (> 87 bpm) et a été réduit de manière linéaire jusqu’au quintile inférieur (70 à 72 bpm). Ces données suggèrent clairement que, dans l’insuffisance cardiaque, il existe un lien direct entre la fréquence cardiaque initiale et une issue défavorable. En ce qui concerne le traitement, il doit être mentionné que, dans l’étude SHIFT, une fréquence cardiaque initiale ≥ 70 bpm était l’un des critères d’inclusion, et que le traitement par l’ivabradine a entraîné une réduction de 18 % (p < 0,0001) du critère principal (composite regroupant la mortalité cardio-vasculaire et l’hospitalisation pour insuffisance cardiaque). Les effets de l’ivabradine se sont montrés linéairement plus manifestes lorsque la fréquence cardiaque a été réduite de 87 à moins de 60 bpm.

Conclusions
Bien qu’il n’ait jamais été négligé, le concept de fréquence cardiaque connaît indubitablement un renouveau avec la découverte du courant pacemaker I, dans le nœud sino-auriculaire de l’oreillette droite, et de l’ivabradine, un médicament capable de réduire ce courant, et par conséquent de réduire la fréquence cardiaque.

Nous disposons désormais d’un grand nombre de preuves épidémiologiques, physiopathologiques et issues d’études cliniques indiquant l’importance du contrôle de la fréquence cardiaque. Malgré cela, de récentes enquêtes ont révélé le faible taux de contrôle de la fréquence cardiaque chez les patients atteints de coronaropathie en pratique clinique. Dans l’Enquête européenne de cardiologie (European Heart Survey) menée chez des patients atteints d’angor stable suivis dans des services de cardiologie européens, la fréquence cardiaque moyenne au repos était de 73 bpm, et plus de la moitié des patients (52,3 %) présentaient une fréquence cardiaque > 70 bpm. Il est intéressant de souligner qu’environ 40 % des patients traités par les bêta-bloquants présentaient une fréquence cardiaque > 70 bpm. Les auteurs de l’European Heart Survey ont conclu à l’existence de preuves montrant que les médecins et les cardiologues n’accordaient pas l’attention nécessaire à la fréquence cardiaque, et qu’une opportunité thérapeutique était par conséquent manquée. Il est temps d’agir. C’est précisément l’objet de ce numéro de Medicographia.
There is increasing evidence that elevated resting heart rate is associated with increased cardiovascular morbidity and mortality, both in the general population and in patients with cardiovascular disease. Furthermore, data now suggest that heart rate is a treatable risk factor in patients with cardiovascular disease, and not simply a prognostic marker. Heart rate meets the key criteria for risk factor status. Until recently, despite considerable epidemiological evidence on the association between heart rate and cardiovascular outcomes, and the apparent benefit of reducing raised heart rate, there has been uncertainty whether the relationship between heart rate and cardiovascular disease is causal. This is because conventional drugs that reduce heart rate—such as β-blockers—have multiple effects on the cardiovascular system and so it has been difficult to separate their effect on heart rate from their other properties. Recent studies with ivabradine, a drug that lowers heart rate but has no other direct cardiovascular effects, have allowed the effect of heart rate lowering per se to be evaluated. The new data provide persuasive evidence that lowering raised heart rate is clinically beneficial in heart failure and coronary artery disease. In hypertension, heart rate is of prognostic importance, but has not yet been proven to be a modifiable risk factor.

The Bradford Hill criteria are intended as guidelines to help determine whether an observed association reflects cause and effect. The more criteria that are met, the more likely it is that the association is causal. There is increasing evidence for heart rate as a true risk factor rather than simply a marker of risk in cardiovascular disease: it meets the criteria of plausibility..., strength of association, dose response, consistency, and temporality.\textsuperscript{1}

Heart rate modulation and exercise capacity

Heart rate as a treatable risk factor in cardiovascular disease

by M. R. Cowie, United Kingdom

There is increasing epidemiological and clinical trial evidence that raised resting heart rate is independently associated with increased cardiovascular morbidity and mortality, both in the general population and in patients with cardiovascular disease.

In the literature, heart rate has to date tended to be described as a risk or prognostic marker, rather than as a risk factor, indicating that the observed association between heart rate and cardiovascular outcomes is not necessarily causal.

A risk factor needs to fulfill certain criteria of causation, as first put forward by epidemiologist and statistician Sir Austin Bradford Hill in 1965 (Figure 1, page 388).\textsuperscript{1} This article reviews current evidence on the importance of heart rate in cardiovascular disease (coronary artery disease, acute coronary syndromes, heart failure, and hypertension) and considers to what extent heart rate fulfills relevant Bradford-Hill criteria. With the increasing body of evidence, can heart rate now be described as a true modifiable risk factor and a target for treatment?
HEART RATE MODULATION AND EXERCISE CAPACITY

Plausibility
One of the risk factor criteria is plausibility, i.e., is there a pathophysiological rationale for the suggestion that raised heart rate is associated with increased cardiovascular disease?

In animal studies, accelerated heart rate is associated with cellular signaling events leading to vascular oxidative stress, endothelial dysfunction, and acceleration of atherogenesis. The precise mechanisms that link heart rate and cardiovascular outcomes have not been defined. However, elevated heart rate is thought to play a central role in the pathophysiology of coronary artery disease, leading to acute ischemia in patients with stable angina, and also directly affecting the progression of coronary atherosclerosis and plaque rupture.

Increased risk in patients with coronary artery disease may reflect autonomic imbalance, but experimental and clinical observations indicate that elevated heart rate per se may also have direct detrimental effects on cardiovascular function by increasing the ischemic burden or via local hemodynamic forces on the endothelium and arterial wall, which can promote progression of atherosclerosis and plaque rupture.

Elevated heart rate was shown to be a predictor of the progression of coronary atherosclerosis in young men after myocardial infarction, and this appeared to be independent of other well-established risk factors. Another study, which retrospectively analyzed angiographic data in 106 patients with coronary artery disease, showed a positive association between mean heart rate >80 beats per minute (bpm) and plaque disruption. In a recent population-based study of people without clinical cardiovascular disease at baseline, elevated resting heart rate was associated with increased incidence and progression of atherosclerosis, as demonstrated by increased coronary artery calcium. There is therefore considerable evidence for the biological plausibility of heart rate as a risk factor in coronary artery disease.

There is also a pathophysiological rationale for adverse outcomes from elevated heart rate in patients with heart failure, since increased heart rate is associated with increased oxygen demand, reduced ventricular efficiency, and reduced ventricular relaxation. Heart rate reduction decreases energy expenditure, increases blood supply by prolonging diastole, improves force-frequency associations, and reduces ventricular loading.

Strength and consistency of association and graded response
Other important considerations in determining causality are the strength and consistency of the association and whether there is a biological gradient (or “dose response”). Heart rate fares well on these criteria. Many studies have shown that elevated resting heart rate is associated with worse cardiovascular outcomes, both in the general population and in patients with cardiovascular disease.

**General population**
In the Framingham study, the 30-year follow-up showed increased heart rate to be associated with an increase in all-cause mortality and cardiovascular mortality at all ages in both men and women.

The Paris Prospective Study involved 5139 men aged 42 to 53 years, initially free of cardiovascular disease, in whom resting heart rate was measured every year for 5 years, with follow-up for a mean of 23 years. Heart rate at rest and heart rate change over 5 years were both predictors of mortality, independent from standard cardiovascular risk factors. After adjustment for confounding factors, and compared with sub-
jects with unchanged heart rates (from –4 to +3 bpm) during the 5 years, subjects with decreased heart rates (>4 bpm) had a 14% decreased mortality risk (P = 0.05), whereas subjects with increased heart rates (>3 bpm) had a 19% increased mortality risk (P < 0.012). The study also showed that the heart rate profile during exercise and recovery was a predictor of sudden death from myocardial infarction, and that sudden death increased in people with a resting heart rate >75 bpm (relative risk [RR], 3.92; confidence interval [CI], 1.91-8.00).

The FINRISK study (FINland cardiovascular RISK study) confirmed a strong, graded, independent relationship between resting heart rate and incident cardiovascular disease in both men and women. This study involved over 20 000 people with no preexisting cardiovascular disease, with a median follow-up of 12 years. Hazard ratios for cardiovascular disease mortality for each 15-bpm increase in resting heart rate were 1.24 in men and 1.32 in women, after adjustment for standard risk factors. A resting heart rate of >80 bpm compared with one of <60 bpm was associated with an almost 2-fold greater risk of cardiovascular mortality in men and a 3-fold increased risk in women (Figure 3).

Coronary artery disease

The prognostic value of resting heart rate was shown in an analysis of the CASS registry (Coronary Artery Surgery Study). A total of 24 913 subjects with suspected or proven stable coronary artery disease were followed for a median of 14.7 years. High resting heart rate was a predictor for total and cardiovascular mortality, independent of other risk factors. The association was found in all subgroups analyzed. Patients with resting heart rates ≥83 bpm at baseline had a significantly higher risk of cardiovascular mortality (hazard ratio [HR], 1.31; CI, 1.15-1.48; P < 0.0001) compared with those with baseline resting heart rates ≤62 bpm.

More recently, investigators from the TNT trial (Treating to New Targets) reported increased resting heart rate to be a strong independent risk factor in a cohort of well-treated patients with stable coronary artery disease, followed for a median of 4.9 years. There was a linear relationship between resting heart rate and cardiovascular outcomes: the rate of major cardiovascular events was 11.9% in those with a baseline heart rate of ≥70 bpm versus 8.8% in those with a baseline heart rate of <70 bpm (Figure 4, page 390).

Figure 2. Suggested mechanisms whereby an elevated heart rate leads to adverse outcomes in patients with coronary artery disease.

Abbreviations: CV, cardiovascular; HRV, heart rate variability.


Figure 3. Cardiovascular disease mortality according to resting heart rate in healthy men and women in the FINRISK study (FINland cardiovascular RISK study).

Heart rate as a treatable risk factor in cardiovascular disease – Cowie

Analysis of data from the placebo group of the BEAUTIFUL randomized controlled trial (morBidity-mortality EvAlUaTion of the i, inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) demonstrated a gradient between heart rate and cardiovascular outcome and confirmed the prognostic importance of heart rate in patients with stable coronary artery disease and left ventricular dysfunction receiving appropriate background therapy. A subgroup analysis compared outcomes in patients with a baseline heart rate of \( \geq 70 \) bpm with those with a heart rate of \(<70\) bpm. Patients with the higher heart rates had increased risk of cardiovascular death (34%; \(P=0.0041\)), admission to hospital for heart failure (53%; \(P<0.0001\)), admission to hospital for myocardial infarction (46%; \(P=0.0066\)), and coronary revascularization (38%; \(P=0.037\), after adjustment for other predictors of outcomes. For every increase of 5 bpm, there were increases in cardiovascular death (8%; \(P=0.0005\)), admission to hospital for heart failure (16%; \(P<0.0001\)), admission to hospital for myocardial infarction (7%; \(P=0.052\)), and coronary revascularization (8%; \(P=0.034\)).

The prognostic effect of heart rate has also been shown in acute coronary syndromes. A US study of 1807 patients with acute myocardial infarction found that both in-hospital and 1-year mortality increased with increasing admission heart rate. Mortality from hospital discharge to 1 year was also related to heart rate at discharge. In this study, heart rate was a more powerful predictor of later mortality than assessment of left ventricular function after arrival in hospital, suggesting that elevated heart rate does not only reflect depressed cardiac function. Similarly, the GISSI studies of acute myocardial infarction (Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto miocardico) showed a progressive increase in in-hospital mortality with increasing heart rate, and multivariate analysis showed that heart rate was an independent prognostic factor. Increasing heart rate at discharge was also associated with increased 6-month mortality.

In the HARVEST study of individuals with stage 1 (untreated) hypertension (Hypertension and Ambulatory Recording VEnetia Study), a persistently high heart rate was an independent predictor of future sustained hypertension. Heart rate measurement at baseline and during the first few months of follow-up gave prognostic information over and above that provided by baseline office and ambulatory blood pressure. In the placebo arm of the Syst-Eur trial (Systolic Hypertension in Europe), which involved patients aged 60 years or older, a clinic heart rate >79 bpm was a significant predictor of all-cause, cardiovascular, and noncardiovascular mortality.

The association between resting heart rate and adverse outcomes in elderly hypertensive patients with coronary artery disease was assessed in the INVEST population (INternational VErapamil-SR/trandolapril Study), which showed that both higher baseline and, particularly, follow-up resting heart rates were associated with adverse outcome, with increased risk starting at a resting heart rate of 75 bpm.

In 2010, the Glasgow Blood Pressure Clinic study investigated the relationship between resting heart rate and outcomes in a cohort of 4065 patients with mild-to-severe hypertension. Heart rate was measured at baseline and at final follow-up (mean follow-up, 897 days; range, 7 to 7087 days). Heart rate

![Figure 4. Kaplan-Meier estimates of the cumulative incidence of a first major cardiovascular event during follow-up by baseline heart rate (\(\geq 70\) vs \(<70\) bpm) in patients with stable coronary artery disease in the TNT trial (Treating to New Targets). HR=hazard ratio; \(P\) value determined using log-rank test. After reference 15: Ho et al. Am J Cardiol. 2010;105:905-911. © 2010, Elsevier Inc.](image-url)
was an independent predictor of all-cause, cardiovascular, and ischemic heart disease mortality. In this study, change in heart rate during follow-up was a better predictor of risk than baseline or final heart rate, the highest risk being in patients whose heart rate increased by ≥5 bpm. After correction for rate-limiting therapy (β-blockers and calcium channel blockers), heart rate remained a significant independent risk factor, suggesting that the relationship between heart rate and mortality cannot just be explained by the use of heart rate–lowering interventions.

A further study measured resting heart rate annually during treatment in 9190 patients with hypertension and left ventricular hypertrophy. After a mean follow-up of 4.8 years, higher in-treatment heart rates were shown to be strongly associated with increased risk of cardiovascular and all-cause mortality, independent of blood pressure lowering or other risk factors.

**Heart failure**

Raised heart rate has also been shown to be associated with increased risk of mortality and morbidity in patients with heart failure. Analysis of data from the CHARMS trials (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) in patients with chronic heart failure showed an 8% increase in the risk of cardiovascular death or heart failure hospitalization for every 10-bpm increase in heart rate. The placebo groups of two major trials assessing the effect of β-blockers in heart failure have also provided data on the prognostic importance of heart rate, with evidence of increased mortality with increasing baseline heart rate.

More recent data come from the placebo arm of the SHIFT study (Systolic Heart failure treatment with the If inhibitor ivabradine Trial) in patients with chronic heart failure, which showed a continuous direct association between baseline heart rate and outcomes. Patients with the highest heart rates (≥87 bpm) had a more than 2-fold higher risk for the primary composite end point (cardiovascular death or first hospital admission for worsening heart failure) than patients with the lowest heart rates (70 to <72 bpm; HR, 2.34; 95% CI, 1.84-2.98; \( P < 0.0001 \)). The risk of these end-point events increased by 3% with every bpm increase from baseline heart rate and by 16% for every 5-bpm increase (Figure 5).

**Temporal relationship**

A temporal relationship is another risk factor criterion. This issue was specifically addressed in the FINRISK study of men and women without preexisting cardiovascular disease. To investigate whether raised heart rate was an independent risk factor or merely a marker of subclinical disease, data were reanalyzed excluding all fatal events that occurred in the first 2 years of follow-up. There was no change in hazard ratios, demonstrating a temporal sequence consistent with causality.

**Experimental evidence**

Experimental evidence is a key criterion for risk factor status, providing the strongest support for causation: do disease rates fall when the proposed causal agent has been eliminated? Experimental data in animals show that lowering heart rate reduces atherosclerosis. There is also considerable evidence of the impact of heart rate reduction in patients with cardiovascular disease: the beneficial effects of β-blockers in acute myocardial infarction and heart failure have been shown to be related, at least in part, to heart rate reduction. However, the specific effect of heart rate lowering has been uncertain as the drugs that lower heart rate (primarily β-blockers) have multiple pharmacological effects and it has not been possible to separate their effect on heart rate from other potential protective mechanisms—such as antiarrhythmic effects—and hence to determine whether the benefit is related to the drug class or to heart rate reduction per se.

The development of the pure heart rate–lowering drug ivabradine provided an opportunity to further evaluate the effect of heart rate lowering in randomized controlled trials. Ivabradine acts only on sinoatrial node If channels. It lowers heart rate and has no other known cardiovascular effects.
**Coronary artery disease**
Ivabradine was evaluated in the BEAUTIFUL trial in patients with stable coronary artery disease and left ventricular dysfunction. Ivabradine treatment did not significantly affect the primary composite end point (cardiovascular death, admission to hospital for acute myocardial infarction, and admission to hospital for new-onset or worsening heart failure) in the overall trial population. However, in a subgroup of patients with baseline heart rates above 70 bpm, ivabradine treatment reduced the risk of fatal and nonfatal myocardial infarction (a secondary end point) by 36% (P=0.001). This benefit was observed despite the fact that 87% of patients were receiving background β-blocker treatment. The study therefore strongly suggests clinical benefit from lowering raised heart rate.

There are as yet no data proving that heart rate reduction in acute coronary syndromes improves survival, but analysis of postmyocardial infarction β-blocker trials indicates that a reduction in resting heart rate is an important determinant of clinical benefit. A meta-regression of these trials investigated the relationship between reduction in resting heart rate and magnitude of clinical benefits. The results suggest that the beneficial effect of β-blockers and calcium channel blockers on mortality and nonfatal reinfarction in postmyocardial infarction patients is proportional to the extent of reduction in resting heart rate, with the benefit related to heart rate lowering rather than specific drug class. Each 10-bpm reduction in resting heart rate was estimated to reduce the relative risk of cardiac death by about 30%.

**Heart failure**
Analysis of the major heart failure trials showed that treatments that reduced heart rate were associated with reduced mortality while those that increased heart rate tended to increase mortality (Figure 6).

As with the postmyocardial infarction trials, data suggest that heart rate reduction contributes, certainly in part, to the clinical benefits of β-blockers in heart failure. For example, multivariate analysis of the CIBIS II trial of bisoprolol in chronic heart failure (Cardiac Insufficiency Bisoprolol Study II) showed that the best outcome (in terms of survival and reduction in hospital admissions) was in patients with the lowest baseline heart rate and the greatest heart rate change. The study also showed that the beneficial effect of bisoprolol on survival was similar at any level of baseline heart rate and heart rate change, indicating that heart rate reduction is not the only mechanism for β-blocker benefit in heart failure. In the COMET trial (Carvedilol Or Metoprolol European Trial), heart rate achieved with β-blocker therapy had prognostic value for mortality in heart failure patients.

A recent meta-regression analysis of β-blocker trials in heart failure showed a statistically significant association between the magnitude of heart rate reduction and survival benefit. For every heart rate reduction of 5 bpm the relative risk of death decreased by 18% (CI, 6%-29%). Another analysis of these trials found a close relationship between all-cause annualized mortality rate and heart rate and a strong correlation between change in heart rate and change in ejection fraction.

More definitive evidence of the benefit of heart rate lowering came from the SHIFT randomized placebo-controlled trial, which assessed the pure heart rate–lowering drug ivabradine in 6558 patients with symptomatic heart failure and an ejection fraction of ≤35%, sinus rhythm, and resting heart rates of ≥70 bpm. Patients were on stable background therapy, including a β-blocker if tolerated. Over a median follow-up of 22.9 months, there was an 18% relative risk reduction for the primary composite end point of cardiovascular death or hospital admission for worsening heart failure (P<0.0001). The effect was mainly driven by hospital admissions for worsening heart failure, which were reduced by 26% (P<0.0001).

![Figure 6. Relationship between change in heart rate and mortality in chronic heart failure trials.](https://example.com/figure6.png)

**Hypertension**
Resting heart rate has been shown to be a prognostic marker in patients with hypertension, but there is as yet no specific evidence that reducing heart rate is linked to improved outcome in patients with hypertension.
Conclusion: strength of evidence for heart rate as a cardiovascular risk factor

The Bradford Hill criteria1 are intended as guidelines to help determine whether an observed association reflects cause and effect. The more criteria that are met, the more likely it is that the association is causal. There is increasing evidence for heart rate as a true risk factor rather than simply a marker of risk in cardiovascular disease: it meets the criteria of plausibility (although the exact mechanisms remain to be determined), strength of association, dose response, consistency, and temporality. There is also now increasing evidence of improved outcomes following the reduction of raised heart rate, thus meeting the important “experimental evidence” criteria.

The recent studies with ivabradine provide persuasive evidence that heart rate is a true modifiable risk factor in heart failure and in coronary artery disease.

References


Keywords: causality; heart rate; ivabradine; risk factor
L’association d’une fréquence cardiaque élevée à une augmentation de morbidité et de mortalité cardiovasculaire, à la fois dans la population générale et chez des patients atteints de maladie cardiovasculaire, est de mieux en mieux démontrée. De plus, les données actuelles suggèrent que, chez les patients atteints de maladie cardiovasculaire, la fréquence cardiaque n’est pas simplement un marqueur pronostique mais plutôt un facteur de risque susceptible d’être traité. La fréquence cardiaque remplit les principales conditions de définition d’un facteur de risque. Jusqu’à récemment, la relation de causalité entre la fréquence cardiaque et la maladie cardiovasculaire n’était pas certaine malgré des preuves épidémiologiques importantes de liens entre la fréquence cardiaque, l’évolution cardiovasculaire et les avantages apparents du ralentissement de cette fréquence. Ceci en raison de la difficulté à séparer les effets sur la fréquence cardiaque de médicaments comme les bétabloquants, de leurs autres effets sur le système cardiovasculaire. Des études récentes sur l’ivabradine, un médicament qui ralentit la fréquence cardiaque sans autre effet cardiovasculaire direct, ont permis d’évaluer uniquement l’effet de la réduction de la fréquence cardiaque. Ces nouvelles données montrent de façon convaincante que ralentir la fréquence cardiaque est cliniquement bénéfique dans l’insuffisance cardiaque et la maladie coronaire. Dans l’hypertension, la fréquence cardiaque a une importance pronostique mais il n’est pas encore démontré qu’il s’agisse d’un facteur de risque modifiable.
Elevated heart rate is associated with cardiovascular outcome in the general population and in patients with hypertension, ischemic heart disease, and heart failure. During exercise the autonomic nervous system increases heart rate in response to increasing peripheral demand. In nondiseased hearts, increased rate is associated with enhanced myocardial contractility (Bowditch effect). In coronary artery disease, on the other hand, increased rate shortens diastole, thereby decreasing myocardial perfusion, with the risk of severe ischemia and angina. In heart failure, in addition to these mechanisms, the Bowditch effect is impaired. The combination of a negative force-frequency relationship and myocardial ischemia during exercise increases ventricular filling pressures and respiratory work, causing hypoxia, dyspnea, and impaired exercise tolerance. Thus, in heart failure, the hemodynamically optimal upper heart rate may be below the maximum achieved heart rate. Since heart rate determines oxygen consumption and delivery, its modulation, as by the \( I_f \) channel inhibitor ivabradine, strongly influences exercise tolerance, in particular in coronary artery disease and heart failure.

Heart rate response to exercise: impact on myocardial ischemia and left ventricular function

by M. Böhm and C. Ukena, Germany

Heart rate is a major determinant at rest and during exercise of the response to increased oxygen demand by working skeletal muscles and other vital organs. Adaptation to increased physical activity is accomplished by an increase in cardiac output, which requires an increase in heart rate in addition to adaptation of stroke volume in response to exercise. In special conditions, heart rate can afford to be low at rest when stroke volume is high (as in athletes), or is obliged to be high when cardiac function is compromised (as in heart failure). Stimulation of the sympathetic nervous system and withdrawal of parasympathetic activity during exercise increases heart rate (positive chronotropy), shortens atrioventricular conduction (positive dromotropy), increases intraventricular conductivity (positive bathmotropy), and enhances the force of contraction (positive inotropy).

The direct effects of heart rate on contractility were described in 1871 by the American physiologist Henry Pickering Bowditch (1840-1911), writing in German in the course of a 3-year stay in Europe. In nondiseased hearts, contractility increases with increases in rate. This positive Bowditch (or Treppe) effect is an important addition to sympathetic activation in adapting contractility and cardiac output to increased peripheral demand. When the heart rate response to exercise is subnormal, as in chronotropic incompetence, the increase in cardiac output remains inade-
Heart rate modulation and exercise capacity

Myocardial ischemia
In coronary artery disease, increased heart rate is accompanied by overproportional shortening of diastole. Since myocardial perfusion takes place predominantly in diastole, a high heart rate is the primary denominator of myocardial ischemia in the presence of significant coronary artery stenosis. Furthermore, relaxation and contraction at high heart rates consume extensive energy, predisposing to ATP deficiency during exercise. In critical coronary artery disease, this can result in severe ischemia with angina as its typical clinical manifestation.

During ischemia, in particular in the presence of high heart rate, ventricular muscle develops diastolic dysfunction. The resulting rise in filling pressure impairs exercise tolerance and increases pulmonary wedge pressure, causing shortness of breath. Compounding factors are an increase in pulmonary stiffness, responsible for an increase in ventilatory work, and an increase in diffusion distance, when interstitial pulmonary edema develops into alveolar fluid accumulation in advanced pulmonary edema. The result is intrapulmonary shunting, resulting in decreased oxygen saturation, aggragation of clinical congestion, and decreasing exercise tolerance. Heart rate reduction with β-blockers or the If channel inhibitor ivabradine, has been shown to reduce symptoms in myocardial ischemia by lengthening diastole, prolonging coronary perfusion, and reducing oxygen consumption. The example of ivabradine demonstrates that the effect of heart rate reduction is crucially and uniquely mechanistic: ivabradine is a pure If channel inhibitor with no other known cardiovascular effects.

Left ventricular dysfunction
In the failing heart, the Böwditch effect is impaired, resulting in a negative force-frequency relationship in vitro and in vivo. Initial evidence to this effect came from isolated cardiac preparations from patients undergoing heart transplantation. Failing heart preparations also develop a relaxation deficit at higher heart rates. Although a high heart rate is a key clinical finding in severe heart failure, one must assume that adaptation of contractility in response to the elevated heart rate is also blunted. The situation is aggravated by the fact that the mechanisms described for coronary artery disease and ischemia are replicated in the failing heart, since this is an energy-depleted organ. Systolic dysfunction with left ventricular dilatation results in an increase in wall tension. This in turn increases extracoronary/coronary resistance, resulting in reduced oxygen delivery to the myocardium. These findings were obtained in patients with systolic dysfunction. The situation in patients with a preserved ejection fraction is largely unknown.

The optimal heart rate in elderly individuals or in exercising heart failure patients is still debated. Experimental data suggest that heart rate limits should differ from those in individuals with normal myocardial function because the inverse force-frequency relationship limits the ability of cardiac output to increase exercise tolerance. In addition, the deleterious effects of oxygen deficiency at high heart rates persist in coronary artery disease or impaired left ventricular function, prompting speculation that high heart rates compound deterioration in myocardial function. In particular, cardiac pacemakers could be set to different parameters in patients with heart failure and those with normal left ventricular function.

A study in patients requiring pacemaker therapy compared those with impaired and normal left ventricular function. In those with normal left ventricular function, pacing at rates from 70 to 160 bpm showed a close association with increases in coronary artery disease or impaired left ventricular function, prompting speculation that high heart rates compound deterioration in myocardial function. In particular, cardiac pacemakers could be set to different parameters in patients with heart failure and those with normal left ventricular function.

Figure 1 summarizes the mechanisms of impaired exercise tolerance at high heart rates.

When patients develop dyspnea, the adverse effects of elevated heart rate, such as shorter diastole and ischemia, may be partly responsible for reduced exercise tolerance. A similar situation has been described in patients with critical low output due to acute decompensated heart failure. The positive inotropic effect of the β-adrenoceptor agonist dobutamine is often used to increase cardiac output and lower left ventricular filling pressure in acute heart failure. However, as a β-adrenergic agonist, it also increases heart rate to a variable extent, which can have adverse effects on outcome in
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acute heart failure. Delayed return of heartrate after exercise, while leaving the absolute increase in heartrate intact. Denervation reduces excessive sympathetic drive without inducing chronotropic incompetence and appears to restore sympathetic-parasympathetic balance during rest. More studies are required to determine whether improved heart rate recovery after exercise is associated with better outcome in conditions such as severe hypertension, ischemic heart disease and, in particular, heart failure, where such data are completely lacking. We need to know whether outcome in such common and serious conditions can be enhanced by modulating the exercise heart rate, whether pharmacologically with β-blockers and ivabradine, chronic endurance training, or sympathetic denervation.

Conclusion

Heart rate patterns at rest and during exercise predict cardiovascular outcomes. Since heartrate determines oxygen consumption and delivery, its modulation by ivabradine strongly influences exercise tolerance, in particular during ischemia. This property makes the drug a valuable component in the armamentarium of coronary therapy. Chronic heartrate reduction reduces cardiovascular hospitalizations in heart failure patients in sinus rhythm at heart rates ≥70 bpm, and cardiovascular death and all cardiovascular hospitalizations at heart rates ≥75 bpm. Heart rate elevation is a determinant of cardiovascular outcome in the general population, and in patients with hypertension, ischemic heart disease, and heart failure. Delayed return of heartrate to resting levels after exercise is a risk factor for cardiovascular death, and in particular, sudden death. In heart failure the force-frequency relationship reverses from positive to negative. As a result, increases in heartrate reduce contractility, increases myocardial stiffness, impair exercise tolerance, and precipitate dyspnea and cardiac congestion.

Clinical studies have provided pathophysiological proof of the benefits of heart rate reduction in conditions such as impaired left ventricular function and heart failure. We need further studies using novel techniques such as sympathetic denervation if we want to fully elucidate the role of heartrate not only at rest, but during and after exercise.

Figure 1. Mechanisms of dyspnea in heart failure.

Activation of the sympathetic nervous system during exercise increases phase 4 depolarization and increases heart rate. During exercise in heart failure, the increased heart rate shortens diastole, leading to an increase in right ventricular filling pressures, which in turn increases respiratory work, hypoxia, and hypercapnia. These changes signal to the brain stem that diuresis is taking place thereby triggering dyspnea. In chronic heart failure altered chemoreceptor sensing leads to dyspnea at lower hypoxia thresholds. Thus, there are vicious cycles in the interaction between sympathetic activation, heartrate, heart, lung, and central nervous system.

Heart rate regulates cardiovascular function and, in particular, cardiac output during exercise and other output conditions. Regulation by the autonomic nervous system, along with activation of sympathetic output and reduction of parasympathetic activity, increases heartrate and cardiac output, but also determines training condition and cardiovascular comorbidities. Heart rate elevation is a determinant of cardiovascular outcome in the general population, and in patients with hypertension, ischemic heart disease, and heart failure. Delayed return of heartrate to resting levels after exercise is a risk factor for cardiovascular death, and in particular, sudden death. In heart failure the force-frequency relationship reverses from positive to negative. As a result, increases in heartrate reduce contractility, increases myocardial stiffness, impair exercise tolerance, and precipitate dyspnea and cardiac congestion.

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Keywords: exercise; heart rate; heart rate reduction; ivabradine; left ventricular dysfunction; myocardial ischemia

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Réponse de la fréquence cardiaque à l’effort :
Effet sur l’ischémie myocardique et la fonction ventriculaire gauche

The important role of heart rate (HR) in cardiovascular disease is well established, but attention to HR has often been limited to discussion of resting HR or HR at peak exercise. This paper highlights the importance of evaluating HR profiles during and after exercise. The ability of the heart to increase HR to tightly match cardiac output to metabolic demand during exercise is critical to physical performance. The increase in HR during exercise is the largest contributor to the ability to perform physical work and therefore is an important determinant of quality of life. The high prevalence of impaired exercise HR response and its easy assessment in clinical practice provides the rationale for screening for inadequate HR responses during exercise testing and recovery after exercise. This condition is potentially treatable, and its management can lead to significant improvements in exercise tolerance and quality of life.

**Chronotropic incompetence and functional capacity in cardiovascular disease**

by D. W. Kitzman, USA

The ability to perform physical work is an important determinant of quality of life and is enabled by an increase in oxygen uptake (VO₂). During maximal aerobic exercise in healthy persons, VO₂ increases approximately 4-fold. This is achieved by a 2.2-fold increase in heart rate (HR), a 0.3-fold increase in stroke volume, and a 1.5-fold increase in arteriovenous oxygen difference. The increase in HR is thus the largest contributor to the ability to perform sustained aerobic exercise. Therefore, an abnormal HR response to exercise can be the primary cause of, or a significant contributor to, severe, symptomatic exercise intolerance.

**Heart rate control and recovery**

Instantaneous HR reflects the dynamic balance between the sympathetic and parasympathetic divisions of the autonomic nervous system. An intact HR response is critical to tightly match a subject’s cardiac output to metabolic demands during exertion. Failure to achieve maximal HR, inadequate submaximal HR, or HR instability during exertion are all examples of impaired chronotropic response. These conditions are relatively common in patients with sick sinus syndrome, atrioventricular block, coronary artery disease, and heart failure (HF). Immediately after the termination of exertion, sympathetic withdrawal and increased parasympathetic tone to the sinoatrial node combine to cause a rapid decline in HR. A delayed recovery of HR after exertion is independently associated with increased all-cause mortality in a variety of asymptomatic and diseased populations. In contrast, highly trained athletes often display a rapid and profound drop in HR of ≥30 to 50 beats during the first minute of recovery from strenuous exertion.”
in healthy men and women, there is a marked age-related decline in peak aerobic exercise capacity. There are also significant alterations in the sympathetic influence on HR response to exercise with aging, with increased circulating catecholamines and reduced responsiveness. Doses of isoproterenol that increase HR by 25 bpm in young healthy men produce an increase of only 10 bpm in older persons. The normal, age-related decline in maximal HR during exercise is not significantly modified by vigorous exercise training, suggesting that it is not due to the age-related decline in physical activity level. It also does not appear to be due to inadequate sympathetic stimulation, since both serum noradrenaline and epinephrine are increased rather than decreased at rest in healthy elderly individuals. Furthermore, with exertion or stress, catecholamines increase even more than in young persons under the same stress conditions.

The traditional equation to predict normal maximal HR (220 – age), was developed based on studies primarily conducted in middle-aged men, some of whom had known coronary artery disease and were taking β-blockers. This equation has large intersubject variability with a standard deviation of 11 bpm that increases to 40 bpm in patients with coronary heart disease receiving β-blockers. An alternative formula from Tanaka et al (208 – 0.7 × age) is becoming more accepted for determining age-predicted maximal HR (APMHR) even though it may still underpredict APMHR in older adults (Figure 1).

Several earlier studies suggested that gender affects the HR trajectory during exercise and recovery, and that the traditional equation (220 – age) overestimates maximal HR in younger women, but underestimates it in older women. A meta-

**Effect of age and gender on the maximal HR response to exercise**

There is no change in resting HR with adult aging. However, in healthy men and women, there is a marked age-related decrease in maximum HR in response to exercise that is inexorable and predictable and occurs in other mammalian species as well as humans. The age-related decline in maximal HR is the most substantial biological age-related change in cardiac function, both in magnitude and consequence. It is primarily responsible for the age-related decline in peak aerobic exercise capacity. Starting from early adulthood, maximal HR declines with age at a rate of approximately 0.7 beats per minute (bpm) per year in healthy sedentary, recreationally active, and endurance exercise–trained adults. Though the mechanism(s) of this decline are not fully understood, dual-blockade studies show that intrinsic HR declines by 5 to 6 bpm for each decade of age such that the resting HR of an 80-year-old is not much slower than the intrinsic HR. This indicates that there is reduced and minimal parasympathetic tone at rest. This is supported by the fact that the increase in HR after atropine in an older person is less than half that in the young.

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A large prospective study in over 5000 asymptomatic women showed that the traditional equation significantly overestimates maximal HR and thus proposed a new equation where maximal HR = 206 – (0.88 × age). Brawnner et al demonstrated that the 220 – age equation is not valid in patients with coronary heart disease taking β-adrenergic blockade therapy and subsequently developed the equation [164 – (0.7 × age)] for this population.

**Definition, criteria, and measurement of chronotropic incompetence**

Chronicotropic incompetence (CI) is most commonly diagnosed when HR fails to reach an arbitrary percentage (either 85%, 80%, or less commonly, 70%) of the APMHR (usually based on the 220 – age equation described earlier) obtained during an incremental dynamic exercise test. CI can also be determined by the HR reserve, which is the change in HR from rest to peak exercise during an exercise test. Since the proportion of HR achieved during exercise depends in part on the resting HR, the chronotropic response to exercise can also be assessed as the fraction of the HR achieved at maximal effort. Thus, adjusted HR reserve, determined from the change in HR from rest to peak exercise divided by the difference between resting HR and APMHR has been commonly used. The majority of studies have used failure to obtain ≥80% of the HR reserve obtained during a graded exercise test as the primary criterion for CI.

However, before concluding that a patient has CI, it is important to consider their level of effort and reasons for terminating the exercise test. Patients should be encouraged to continue exercising until true symptom-limited (exhaustive) maximal levels are achieved. Symptoms and subjective ratings of perceived exertion (RPE) can provide an estimate of exertion levels. However, the respiratory exchange ratio (RER, ie, volume of carbon dioxide produced/volume of oxygen consumed) obtained from expired respiratory gas analysis at peak exercise during the exercise test, is the most definitive, objective, reliable, clinically available measure of the physiological level of effort during exercise. RER is a continuous variable, ranging from <0.85 at quiet rest to >1.20 during intense, exhaustive exercise. Higher RER values increase confidence that
maximal effort was achieved while RER <1.05 at peak exercise suggests submaximal effort and should lead to caution in diagnosing CI.

Wilkoff et al utilized the expired gas analysis technique to more objectively evaluate CI using the relationship between HR and VO₂ during exercise. With this approach, the metabolic-chronotropic relationship (MCR) is calculated from the ratio of the HR reserve to the metabolic reserve during submaximal exercise. The advantage of using the MCR is that it adjusts for age, physical fitness, and functional capacity and it appears to be unaffected by the exercise testing mode or protocol. In normal adults, the percentage of HR reserve achieved during exercise equals the percentage of metabolic reserve achieved. This physiological concept allows determination of whether a single HR achieved at any point during an exercise study is consistent with normal chronotropic function. A specific CI exercise testing protocol that evaluates the MCR relationship from 2 stages of a treadmill protocol has been employed in some laboratories.

**Effect of medications and other confounding influences on chronotropic incompetence**

Many commonly used cardiovascular medications including β-blockers, digitalis, calcium channel blockers, amiodarone, and others can confound the determination of CI. β-Blockers may result in pharmacologically induced CI and obscure identification of an underlying intrinsic abnormality in neural balance. In one study, a suitable threshold for CI in HF patients using β-blockers was found to be ≤62% of APHRR. Using this lower HR threshold, CI could be reliably identified and was found to be an independent predictor of death. Care should be taken before applying these criteria to ensure that the patient is on a nontrivial dose and is compliant with the medication. The use of separate CI criteria for patients taking β-blocker medications has been challenged by other studies that failed to demonstrate any effect of β-blockers, including at high dose, on the occurrence of CI. Figure 2 shows the similar relationship between HR reserve and VO₂ at peak exercise (peak VO₂) in HF patients who were either taking or not taking β-blockers. Similarly, Jorde and colleagues examined the relationship between exercise time and HR during treadmill exercise testing in HF patients. As seen in Figure 3, the HR slope is abnormal in HF patients with CI, yet β-blockers have no impact on this relationship in these patients. Chronic treatment of HF patients with β-blockers may paradoxically improve chronotropic response by decreasing sympathetic tone and/or by increasing β-receptor activity. Furthermore, there appears to be potentially important differences between β-blockers in the relationship between HR reduction and exercise capacity.

Criteria for the diagnosis of CI in the presence of atrial fibrillation have not been established. Exercise testing can be used to assess the adequacy of response following pacemaker insertion for CI by reprogramming or suspending the device with a magnet, taking care to ensure the patient is not completely pacemaker-dependent beforehand.

**Contribution of impaired HR response to exercise intolerance in HF**

A hallmark of chronic HF is a markedly reduced capacity for physical exertion, with a subsequent 15% to 40% reduction in peak VO₂ compared with healthy matched controls. We have shown that patients with HF and preserved ejection fraction (HFrEF) have similar reductions in peak VO₂, exercise time, ventilatory anaerobic threshold, and 6-minute walk distance as patients with HF and severely reduced ejection fraction (HFrEF). Reduced peak VO₂ in HFrEF as well as HfPEF patients is due to a combination of reduced peak cardiac output and arterio-venous oxygen content difference. The latter is related to abnormalities of skeletal muscle and vascular function that limit the exercise intolerance associated with HF. The reduced cardiac output response in HF patients can be due to reduced stroke volume and reduced HR during peak exercise. In HfPEF patients, reduced peak HR appears to be a stronger contributor to reduced peak VO₂ than stroke volume. Where-as maximal HR during exercise may be only mildly reduced, HR reserve is often blunted more substantially in HF patients owing to the sympathetically driven increase in resting HR.

We recently demonstrated that HR reserve was significantly correlated (r=0.40) with peak VO₂ in elderly HF patients with either HFrEF or HfPEF (Figure 4). Furthermore, the increase
in HR during exercise accounted for an appreciable portion (ie, 15%) of the observed differences in peak VO₂. This was unchanged even after accounting for medications, including β-blockers. These findings were confirmed and expanded by Borlaug et al, who reported that HFrEF patients also had a slower HR rise and impaired HR recovery, indicating abnormal autonomic function (Figure 5).

**Prevalence of chronotropic incompetence in heart failure**

The reported prevalence of CI within the HF population has varied considerably, with a range of 25% to 70%. This substantial variability is likely to be influenced by the criteria employed to determine CI as well as differing patient characteristics. In older HFrEF patients, Witte et al found that 103 of 237 (43%) HF patients met the criterion of <80% of APHR, whereas 170 of 237 (72%) met the criterion of <80% of APHR. Patients taking β-blockers were more likely to have CI than those not taking β-blockers when <80% of APHR was used (49% vs 32%, respectively) or <80% APHR was used (75% vs 64%, respectively). When the criterion of ≤62% APHR was used for HF patients on β-blocker therapy, a significantly smaller percentage (22%) of patients were diagnosed with CI.

We evaluated the prevalence of CI in older (≥60 years) HFrEF and HFrpEF patients as well as in age-matched healthy subjects using ≤80% of APHR and the Wilkoff approach. While CI was uncommon in healthy older adults (just 2 out of 28 subjects, or 7%), the prevalence of CI was relatively similar between older HFrEF (12 of 46, or 26%) and HFrpEF (11 of 56, or 19%) patients. Phan et al reported that the prevalence of CI increased to 63% of HFrEF patients when the criterion of 80% of HR reserve was used as the definition of CI. Thus, a significant portion (one-third or more depending on the criteria employed) of both HFrEF and HFrpEF patients have significant CI, which contributes to their exercise intolerance.

**Mechanisms of chronotropic incompetence in heart failure**

CI in HF is associated with a 50% reduction in β-adrenergic receptor density in the left ventricular myocardium, down-regulation of β-receptors, and desensitization assessed by decreased responsiveness to norepinephrine infusion and exercise. HF patients also have significant sinus node remodeling. The relationship between change in HR and change in plasma norepinephrine is significantly correlated with anaerobic threshold, peak VO₂, and ventilatory efficiency (ventilatory equivalent to carbon dioxide output slope [VE/VCO₂]).

**Effect of exercise training on chronotropic incompetence in heart failure**

In addition to many other health benefits, endurance exercise training in healthy individuals results in favorable changes in chronotropic function such as decreased resting and submaximal exercise HR, as well as a more rapid decline in post-exercise HR. Most of these HR adaptations appear to be related to an alteration in the balance of the sympathetic and parasympathetic influence of the autonomic nervous system.

Endurance exercise training generally improves exercise tolerance in HF patients through a variety of potential central and peripheral mechanisms. A meta-analysis of 35 randomized studies of exercise training in HFrEF patients indicated that peak HR increased by an average of 4 bpm, or 2.5% of the pretraining level. Ketyian et al demonstrated that after 24 weeks of endurance exercise training, peak exercise HR increased by 7% (approximately 9 bpm) yet remained unchanged in a nonexercise control group. Furthermore, the training-induced increase in peak HR accounted for 50% of the increase in peak VO₂ in the exercise training group.

While alterations in β-adrenergic receptor sensitivity may explain these findings, the mechanisms responsible for the improved chronotropic response with exercise training in HFrEF are not known. We recently reported that exercise training in HFrpEF patients improved peak HR, but this was counterbalanced by a reduced stroke volume response, such that cardiac output did not change with training. Thus, in HFrEF, improved CI may not contribute to improved exercise capacity, which appears to be primarily due to improved peripheral mechanisms. More information is needed regarding the impact of exercise training on the chronotropic response of HFrEF and HFrpEF patients.
Effect of rate-adaptive pacing on chronotropic incompetence and exercise performance in heart failure

There is a linear relationship between HR and VO$_2$ during exercise in a variety of patient populations, including patients with HF.$^{42}$ Not surprisingly, rate-adaptive pacing has been shown to enhance functional capacity in a variety of patients with CI.$^{23,24}$ However, despite the prominent role of abnormal HR responses in HF, there has been relatively little attention to rate-adaptive pacing in this specific population.$^{34,45}$

Tse et al examined the potential benefit of rate-adaptive pacing, in conjunction with cardiac resynchronization therapy, on exercise performance in HFrEF patients. A total of 20 HFrEF patients with CI and an implanted cardiac resynchronization device underwent exercise testing with measurement of VO$_2$. In the overall group, rate-adaptive pacing during cardiac resynchronization therapy increased peak exercise HR and exercise time, but did not increase peak exercise VO$_2$. However, in the 11 (55%) HF patients with more severe CI (those achieving <70% APMHR), rate-adaptation significantly increased peak HR, exercise time, and peak VO$_2$. Further, in the majority (82%) of these patients, the improvement in chronotropic response was associated with an approximately 20% increase in peak VO$_2$. But in patients with less severe CI there was little or no benefit, and one-third of the patients experienced a reduction in exercise capacity with rate-adaptive pacing.$^{46}$ Thus, while it appears that rate-adaptive pacing may have potential benefits in carefully selected patients with HFrEF, advances in this area are hindered by the lack of standardized, accepted definitions and selection criteria. Furthermore, at this time it is unclear if CI is causal or simply a marker of advanced disease and if treating it with a pacemaker will improve functional status in HFrEF patients. Clearly, this issue will require further investigation in the future. Even less is known regarding pacing in patients with HfPEF, despite the significant prevalence of CI in this population and the contribution of impaired chronotropic response to their objectively measured exercise intolerance.$^{26,33,34}$ One trial was designed to help determine if rate-responsive pacing can potentially improve exercise function in HfPEF patients with overt CI.$^{47}$

A recent report noted that CI is common in clinical HF patients who already have implanted pacemakers and is associated with worse exercise capacity.$^{48}$ Further, the authors recommended periodic optimization of pacemaker settings and re-evaluation of β-blocker dosages.

Summary

CI is a common and important cause of exercise intolerance, and an independent predictor of major adverse cardiovascular events and mortality. The diagnosis of CI should take into account the confounding effects of aging, physical condition, and medications, but can be achieved objectively with widely available exercise testing methods and standardized definitions. If CI is found to be present, a search for potentially reversible causes is warranted.

In HF, β-adrenergic blockade may have a less detrimental effect on exercise capacity than previously thought, and may even paradoxically improve exercise performance. The potential of more novel β-blockers to reduce the prevalence of CI in HF patients is unclear. While exercise training and rate-adaptive pacing have been shown to improve chronotropic responses and exercise capacity in HF, more research is needed to fully evaluate the impact of these therapies on key clinical outcomes.

CI is a common, easily diagnosed, and potentially treatable cause of exercise intolerance and merits more attention by clinicians when they encounter patients with symptoms of effort intolerance.

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Keywords: aging; chronotropic incompetence; ejection fraction; exercise; heart failure; heart rate

**INCOMPÉTENCE CHRONOTROPE ET CAPACITÉ FonCTIONNELLE DANS LA MALADIE CARDIOVAŚCULAIRE**

L’importance du rôle de la fréquence cardiaque (FC) dans la maladie cardiovasculaire est bien établie mais l’atten- tion qui lui est portée se limite souvent à une analyse du repos ou à l’acmé de l’effort. Cet article souligne l’impor- tance de l’évaluation de la FC pendant et après l’effort. L’aptitude du cœur à augmenter la FC pour ajuster à la plus prête le débit cardiaque à la demande métabolique lors de l’effort est indispensable à la performance physique. C’est l’augmentation de la FC au cours de l’effort qui participe le plus à la réalisation du travail physique et c’est donc un déterminant important de la qualité de vie. La forte prévalence des anomalies de la réponse de la FC à l’effort et la facilité de leur évaluation en pratique clinique sont deux arguments en faveur d’un dépistage des réponses inadap- tées de la FC durant l’effort et lors de la récupération après l’effort. Cette pathologie peut se traiter et sa prise en charge peut améliorer significativement la capacité à l’effort ainsi que la qualité de vie.
Exercise testing is commonly undertaken in cardiology for both diagnostic and prognostic purposes. Aside from the diagnostic criteria, new parameters have been proposed for improving the prognostic value of exercise testing, including kinetic analysis of heart rate changes during and after exercise. Three main parameters are currently proposed: chronotropic incompetence, heart rate recovery after exercise, and heart rate increase at the beginning of exercise. All of these are regulated by the autonomic nervous system, and abnormal values are linked to a decrease in parasympathetic effect and an increase in sympathetic effect. Chronotropic incompetence and heart rate recovery are currently the two easiest parameters to determine and are the most predictive. Both a low maximal heart rate and a decreased heart rate recovery are predictors of all-cause and cardiovascular mortality, both in healthy adults with or without risk factors, and in patients with coronary artery disease or heart failure. Their prognostic value is independent of the classical cardiovascular risk factors. Although chronotropic incompetence seems a stronger predictor of cardiovascular mortality than heart rate recovery, the risk seems most powerfully stratified when the two parameters are used together.

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Heart rate adaptations to dynamic exercise in healthy people

The cardiovascular system plays a major role in the body’s adaptations to the acute hemodynamic and metabolic constraints imposed by physical exercise. These cardiovascular adaptations also play a major role in fitness capacity.

It is usual to describe two types of exercise; dynamic (or isotonic), and static (or isometric). Static exercise will not be discussed here, because the involvement of the cardiovascular system is quite minor. Dynamic exercise is characterized by alternating phases of contraction-relaxation of large skeletal muscle masses. It is performed with free ventilation, and its intensity gradually increases to a peak of effort, which corresponds to the individual maximum oxygen consumption (VO₂ max).

Here, we shall focus on cardiac—in particular HR—adaptations observed during exercise and in the recovery phases of maximal dynamic exercise. During exercise, cardiac output gradually increases in line with exercise intensity (from 5 L/min to 20-25 L/min in healthy, sedentary people). Its main role is to increase the supply of oxygen to the skeletal muscles involved so that they can provide the energy requested. Cardiac output depends on two factors, HR and stroke volume.

Stroke volume increases from the beginning of exercise, and it levels out at between 50% to 60% of VO₂ max, which corresponds to a HR of 110-130 beats per minute (bpm) in healthy, sedentary people. Normally, HR increases throughout the exercise duration, producing two broadly different slopes before and after the leveling of the stroke volume.

Individual resting HR depends on intrinsic HR (HR observed after a double autonomic pharmacological blockade) and the effects of the autonomic nervous system. Intrinsic HR is determined by the phase IV depolarization of the action potential of pacemaker cells in the sinus node. Intrinsic HR is 100 to 110 bpm in young healthy people, and it gradually decreases with age (5 to 6 bpm per decade). This intrinsic HR is continuously regulated by the two arms of the autonomic nervous system (parasympathetic and sympathetic), which play the main role in HR regulation both at rest and during exercise.

At rest, parasympathetic input slows the automatic discharge rate and acts as a brake, while sympathetic input, and blood catecholamines, act as an accelerator. Control of the autonomic nervous system is both centralized and reflexive. This double regulation allows rapid HR adaptation in cases of sudden stress, for example at the onset of physical exercise. It explains the fine regulation of the HR level to exercise intensity.

From the beginning of exercise, and sometimes before it (the anticipatory phase), the central autonomic control lifts the parasympathetic brake. This central effect is reinforced by the skeletal muscle reflexes, known as the exercise pressor reflex. These peripheral reflexes originate in contracting skeletal muscles. Mechano- and metabo-ergoreceptors activate these reflexes and thus continuously inform the cardiovascular control centers about the effort level. Thus, the initial HR increase is mainly due to the vagal “brake” release. Beyond 50% to 60% of VO₂ max, HR increases linearly due to the combined effects of the sympathetic nervous system and circulating catecholamines. During the recovery phase, the HR decrease is exponential. Its initial fall (in 1 minute or less) is marked. It is mainly due to the fast slowdown vagal effect and is independent of the level of exercise intensity. The second phase of HR decrease is slower. It is mainly caused by the cessation of sympathetic nervous system activity and the delayed effects of circulating catecholamines.

To summarize, during progressive and maximal dynamic exercise HR is regulated by the levels of parasympathetic and sympathetic activities and blood catecholamine levels. HR response to these factors also depends on the relative sensitivity of the sinoatrial node to catecholamines.

Heart rate regulation in chronic heart failure patients

It is interesting to note that this physiological relationship can be altered in cardiac patients. In patients with chronic heart failure, for example, several alterations of both the sinus node and its regulation by the autonomic nervous system have been reported. Indeed, chronic heart failure causes dysfunction of the sinoatrial and atrioventricular nodes. Intrinsic HR is thus decreased in heart failure. In experimental models, changes have been reported in the sensitivity of the sinoatrial node to acetylcholine and vagal nerve stimulation. These alterations are linked to extensive remodeling of ion channels, gap junction channels, ionic handling proteins, and receptors in the sinoatrial node. Impaired exercise-induced norepinephrine release associated with marked postsynaptic β-receptor desensitization influences HR regulation during exercise in these patients. The disturbances in autonomic balance can also create an electrically unstable substrate, which can play a role in the occurrence of arrhythmias.

Thus, HR is the easiest component of the cardiovascular system to study continuously, noninvasively, and repeatedly during exercise testing. Kinetic analysis of HR provides an opportunity to study cardiovascular regulation by the autonomic nervous system at various phases of rest, exercise, and recovery. It therefore seems interesting and appropriate to investigate the ability of the autonomic nervous system to appropriately regulate HR during exercise.
Chronotropic incompetence as a prognostic factor for mortality and cardiac events

In 1972, the first data were reported showing that a low peak HR response during exercise was associated with an increased risk of cardiac death. It is now well accepted that chronotropic incompetence is associated with a worse prognosis for all-cause mortality and for both cardiac mortality and cardiac events (for example, myocardial infarction). This relationship is independent of the traditional cardiovascular risk factors and individual exercise capacity. The association has been reported in large populations of men and women of different ages (but mainly over 40 years of age), in otherwise healthy individuals, in those with or without known risk factors, and in those with coronary artery disease, post–myocardial infarction, and/or heart failure (see Table). The predictive value is observed in coronary patients and cardiac heart failure patients even when they are taking β-blockers. Moreover, in coronary patients, this predictive value is independent of the severity of coronary artery disease, and in patients with coronary artery bypass grafting, impaired chronotropic response to exercise identifies subjects at risk for worse clinical outcomes such as myocardial infarction, stroke, or graft failure.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population (n)</th>
<th>Exercise test</th>
<th>Chronotropic incompetence</th>
<th>Heart rate recovery</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adabag 2008</td>
<td>12 555 males, 35-57 years old, asymptomatic, CV risk &gt;average Framingham; follow-up 7 years</td>
<td>Treadmill; Bruce protocol</td>
<td>Yes</td>
<td>HRR-3 min</td>
<td>All-cause mortality with both altered HRR and CI; CI predicts CAD and SD</td>
</tr>
<tr>
<td>Gulati 2010</td>
<td>5437 women, &gt;35 years old (52±11), asymptomatic; follow-up 15.9±2 years</td>
<td>Treadmill; Bruce protocol</td>
<td>&lt;1 standard deviation predicted HR (206-0.88 age); CI &lt;0.8</td>
<td>HRR-2 min</td>
<td>Relationship with all-cause mortality</td>
</tr>
<tr>
<td>Savonen 2011</td>
<td>1102 males, 42-61 years old, asymptomatic; follow-up 18 years</td>
<td>Ergocycle</td>
<td>Relationship with all-cause mortality</td>
<td>HRR-1 bpm</td>
<td>DTS and HRR independent predictors of mortality</td>
</tr>
<tr>
<td>Nishime 2000</td>
<td>9454 (78% male), &gt;30 years old (average 53), no HF, valve disease, pacemaker; follow-up 5.2 years</td>
<td>Treadmill; Bruce protocol (DTS)</td>
<td>% Max-PPHR &lt;85%; actual increase in HR from rest to peak exercise; CI at stage 2</td>
<td>HRR-1 bpm</td>
<td>Independent relationship with all-cause mortality and CAD incidence</td>
</tr>
<tr>
<td>Lauer 1996</td>
<td>1575 males, 43 years old, Framingham Offspring Study; follow-up 7.7 years</td>
<td>Treadmill; Bruce protocol; submaximal</td>
<td>% Max-PPHR &lt;80%; % HR reserve &lt;80%</td>
<td>HRR-2 min</td>
<td>No relationship with mortality; more frequent with BB; correlated with lower pVO2</td>
</tr>
<tr>
<td>Witte 2006</td>
<td>237 HF patients</td>
<td>Ergocycle</td>
<td>% Max-PPHR &lt;80%; % HR reserve &lt;80%</td>
<td>HRR-2 min</td>
<td>CI and HRR-2 min predict CV mortality; CI + HRR-2 min &gt;one parameter; CI &gt;HRR-2 min; low impact of BB treatment</td>
</tr>
<tr>
<td>Myers 2007</td>
<td>1910 male veterans; follow-up 5.1±2.1 years</td>
<td>Treadmill; individualized ramp protocol</td>
<td>% HR reserve &lt;80%; population specific</td>
<td>HRR-2 min</td>
<td>CI and HRR-2 min predict CV mortality; CI + HRR-2 min &gt;one parameter; CI &gt;HRR-2 min; low impact of BB treatment</td>
</tr>
<tr>
<td>Kahn 2005</td>
<td>3736 (68% male), 58±11 years old, with BB, without HF; follow-up 4.5 years</td>
<td>Treadmill</td>
<td>% HR reserve &lt;82%</td>
<td>HRR-2 min</td>
<td>Relationship with all-cause mortality</td>
</tr>
<tr>
<td>Kiviniemi 2011</td>
<td>494, recent myocardial infarction; follow-up 8 years</td>
<td>Low % HR reserve</td>
<td>Predictor of cardiac mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gayda 2012</td>
<td>4907, stable CAD; follow-up 14.7 years</td>
<td>Treadmill; passive recovery</td>
<td>HRR-3 min</td>
<td>Predictor of all-cause and CV mortality</td>
<td></td>
</tr>
</tbody>
</table>

Table. Results of some of the main studies to have investigated the prognostic value of chronotropic incompetence (CI) and heart rate recovery (HRR). The percentages for maximum age-predicted peak heart rate (% Max-PPHR) and heart rate reserve (% HR reserve) were calculated with a cut-off of <80%. Duke Treadmill Score (DTS) index is defined as: (exercise time) - (5 x maximum ST-segment deviation) - (4 x treadmill angina index).

Abbreviations: BB, β-blocker; CAD, coronary heart disease; CV, cardiovascular; HF, heart failure; pVO2, mixed venous oxygen tension; SD, sudden death.
occlusion.\textsuperscript{30,31} Maximal HR has also been proposed to calculate the ST segment/heart rate index (abnormal index >1.6 μV/bpm) to improve prediction of death from coronary artery disease in asymptomatic men.\textsuperscript{32} Chronotropic incompetence positively correlates with functional capacity in patients with mild and moderate cardiac heart failure and with diastolic dysfunction in healthy people.\textsuperscript{33,34} In subjects without apparent structural heart disease, chronotropic incompetence appears to be mainly induced by altered sympathetic activation that affects HR increase.\textsuperscript{25} Chronotropic incompetence produces a physiologically inappropriate HR response to metabolic demand. Several chronotropic incompetence indexes have been described, but the best method for clinical practice has not been established.\textsuperscript{8} Currently, there are three main widely used criteria.

The first, failure to achieve 80% to 85% of the maximum age-predicted HR, and the second, failure to achieve 80% of the HR reserve (maximal HR minus resting HR; or 100% age-predicted maximal HR minus resting HR) are usually closely associated. The reported prevalence of chronotropic incompetence in study populations is higher with the second criteria than the first.\textsuperscript{8} It must be noted that these two criteria are based on the assessment of maximal HR. The maximal HR of an individual must be determined during maximal effort with a symptom-limited exercise test. Several formulas have been proposed for the predicted value of maximal HR. Maximal HR depends mainly on age, but also on the ergometer used, and to a lesser extent on gender and fitness level. Briefly, maximal HR—which always decreases with age—is lower in women than in men, and is higher with treadmill exercise than with an ergocycle.\textsuperscript{26} Thus, an adapted equation for predicted maximal HR must be used for the two chronotropic incompetence indexes described above.

The third index is the chronotropic index, which takes into account age, physical fitness (exercise capacity), and resting HR. It quantifies the relationship between HR increment and oxygen consumption during exercise testing.\textsuperscript{8,25} The chronotropic index is the ratio of HR reserve to metabolic reserve. Age-predicted maximal HR is usually determined with the traditional formula of 220 – age (note that this formula was established with the ergocycle), although because of the aforementioned limits, a specifically adapted formula would seem more suitable. Ideally, individual metabolic reserve is calculated during a maximal cardiopulmonary exercise test with direct gas exchange analysis.\textsuperscript{5} Exercise capacity is estimated in metabolic equivalent tasks (METs; 1 MET = 3.5 ml/min/kg O\textsubscript{2}), and metabolic reserve is calculated as follows: (MET peak – 1)/(100% predicted MET peak – 1). The use of the chronotropic index enables evaluation of the chronotropic response at any stage of the exercise protocol. In healthy subjects, there is a direct and linear association between HR response and the metabolic work during exercise, and the chronotropic index is around 1.0. A lower chronotropic index is a sign of chronotropic incompetence. In healthy adults, a chronotropic index of <0.8 has been reported to be associated with a higher mortality risk.\textsuperscript{25}

It is thus now well acknowledged that determination of the presence of chronotropic incompetence has important diagnostic, therapeutic, and prognostic implications, although the exact mechanism underlying chronotropic incompetence is at present unclear. Autonomic dysfunction involving an attenuated sympathetic drive during exercise occurring in subclinical cardiovascular disease, with or without early manifestation of cardiac ischemia, has been proposed as a potential explanation. These disturbances could favor lethal arrhythmias with an increased mortality risk in predisposed individuals.\textsuperscript{8,14}

**Heart rate recovery as a prognostic factor for mortality and cardiac events**

There is increasing evidence that the recovery phase after exercise is a vulnerable period for cardiovascular events such as myocardial infarction, sudden cardiac death, and atrial fibrillation. Coactivation of both arms of the autonomic nervous system, which can occur during the recovery phase, may partly explain the clustering of various cardiovascular events in the recovery phase of exercise.\textsuperscript{13}

Measurement of autonomic function via the study of HR during the early phase of recovery can provide prognostic information on cardiovascular events in both the general population and various patient groups, independent of classical cardiovascular risk factors (see Table).\textsuperscript{27,36-39} In coronary patients, for example, mortality was predicted by abnormal HR recovery (hazard ratio, 2.5; 95% confidence interval, [CI] 2.0-3.1; P<0.0001) and by disease severity (hazard ratio, 2.0; 95% CI, 1.6-2.6; P<0.0001). Both variables gave additive and independent prognostic information.\textsuperscript{40} There is a significant correlation between abnormal postexercise HR recovery during the first minute (≤18 bpm) and both coronary artery calcium score (quantified with electron-beam computed tomography scanning) and the extent of major epicardial coronary involvement.\textsuperscript{41} Heart failure is also associated with blunted HR recovery after exercise, often in association with chronotropic incompetence, and it is more marked in severely affected patients with distinct echocardiographic, neurohormonal, and hemodynamic signs of the disease.\textsuperscript{42} Treatment with β-blockade has minimal impact on the prognostic power of HR recovery.\textsuperscript{43} In male veterans (n=5974), HR recovery at 2 minutes after treadmill exercise and low fitness were found to be associated with higher mortality risk both together and independently. However, mortality risk was overestimated when exercise capacity was not considered. When both low fitness (≤6 METs) and low HR recovery (≤14 bpm) were present, mortality risk was approximately sevenfold higher than in highly fit and high–HR recovery subjects.\textsuperscript{43} Last, it is known that regular physical activity decreases sympathetic tone, and to
a lesser extent increases parasympathetic tone, in healthy subjects and in patients. It was found that in patients undergoing exercise training in a phase II cardiac rehabilitation program, the increase in HR recovery after training was associated with an improvement in the prognosis for all-cause mortality. Conversely, persistence of abnormal HR recovery despite physical training is a marker of worse prognosis.44

Abnormal HR recovery is associated with several other altered functions. When used together, there seems to be an improvement in the power of risk prediction for all-cause and cardiovascular death in low-risk populations. Moreover, addition of both HR recovery and chronotropic incompetence to the Duke Treadmill Score improved (c-statistic from 0.61 to 0.68) the outcome prediction for all-cause mortality and nonfatal myocardial infarction in high-risk patients.46 Abnormal HR recovery and HR variability are both reduced in a parallel manner in coronary artery disease patients.41 Abnormal HR recovery is independently associated with diastolic dysfunction in subjects with normal systolic function at rest and during exercise. This relationship can be explained by the fact that diastolic dysfunction is partly due to an autonomic abnormality.44 The value of abnormal HR recovery as a predictor of mortality is improved when exercise capacity is also considered.43

Again, protocol methodology plays a major role in determining the prognostic value of HR recovery.46 First, the choice of the ergometer used for exercise testing is important, because individual values for maximal HR (maximal workload achievement) are higher when exercise is performed with a treadmill than with an ergocycle. Moreover, during the early phase of recovery, the drop in HR is slower after treadmill exercise.47 Indeed, in healthy subjects and heart failure patients, during active recovery after maximal exercise, recovery HR at 1 minute after exercise is lower after cycle exercise than treadmill exercise.48 By contrast, HR recovery 2 and 3 minutes after the end of exercise does not differ as a function of the ergometer used.46 During stress echocardiography, because of the supine position of the exercise, HR decrease during the recovery phase is blunted compared with exercise in the standing or sitting position. Thus, to avoid false individual prognostic predictions, the absolute values proposed for chronotropic incompetence and abnormal HR recovery must be adapted to the ergometer used.47,48 Second, variations in the exercise termination protocol may play a role in the magnitude of HR recovery. The mode of recovery, passive or active, must be specified. It may be easier to use a passive mode of recovery, because an active mode can have many specifics (workload, speed, rate of pedaling).22 Third, both HR recovery at 1 and 2 minutes after exercise seem higher in men than in women.49 Fourth, although HR recovery at 1, 2, 3, 4, or 5 minutes after exercise have all been found to be inversely associated with death,57 the recovery duration investigated does play a role. Indeed, as previously described, HR recovery during the first minute of recovery is mediated primarily by vagal reactivation. It is almost independent of both sympathetic activity and exercise intensity. HR recovery in the second minute is affected by sympathetic nerve activity and exercise workload.47 and it appears that HR recovery during the second minute does provide the best prognostic value.43,49 Last, there is no true agreement in the literature about the “gold” cutoff value; whether ≤12 bpm or ≤18 bpm for abnormal HR recovery during the first minute after exercise, or ≤22 bpm for abnormal passive HR recovery in the second minute after exercise.27,41,43,49

The precise mechanisms underlying the relationship between abnormalities in HR recovery and risk of mortality are not yet well understood. However, it is well known that impaired flow-mediated vasodilation in peripheral arteries is closely correlated with endothelial dysfunction in coronary artery disease. There is an involvement between the sympathetic nervous system and endothelial function.51 It has been shown that HR recovery is significantly correlated with large artery stiffness, and in coronary artery disease patients, those with attenuated HR recovery show lower endothelium-dependent flow-mediated vasodilation.41,52 Thus, HR recovery seems to be a predictor of endothelial dysfunction that is independent of classical cardiovascular risk factors.

**Initial heart rate response to exercise as a prognostic factor for mortality and cardiac events**

Recently, some investigators have focused on the early HR response to exercise.51,52 Initially, a fast HR increase at the onset of exercise was linked to an increased risk of adverse cardiovascular events including cardiac death, especially in patients with coronary disease.51

In animals with previous myocardial infarction, a large HR increase at the onset of exercise was associated with a risk of developing ventricular fibrillation. This relationship was thought to be due to enhanced cardiac sympathetic activation.5 The results of a more recent study, however, performed in a large population tested with symptom-limited exercise testing on a treadmill for routine clinical indications showed the opposite; ie, that a large early rise in HR during exercise is associated with increased survival.52 This last result is in accordance with data suggesting that the early HR profile during exercise is mainly dominated by parasympathetic nervous tone.53 The higher the parasympathetic tone, the greater the HR rise early during exercise. The discrepancy observed between current studies may be due to the exercise protocols used. It seems that an individualized ramp protocol is best for studying individual HR profiles during exercise.52 Thus, the exact relationship between early HR changes in response to exercise and prognosis still remains to be determined in humans.

Many studies have demonstrated the prognostic value of dynamic exercise HR response parameters. Although further studies are needed to truly determine the most useful param-
eter and to explain its pathophysiological relationship with mortality, use of HR response parameters must be recommended when exercise testing is performed. Chronotropic incompetence and HR recovery are currently the two easiest parameters to determine and are the most predictive.

Chronotropic incompetence appears to be a stronger predictor of cardiovascular mortality than HR recovery in patients referred for exercise testing for clinical reasons. However, when both parameters are used, the risk seems to be most powerfully stratified.

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412 MEDICOGRAFIA, Vol 34, No. 4, 2012 Prognostic value of heart rate response to exercise – Carré
LE PROGNOSTIC VAlue de la réponse de la fréquence cardiaque à l’effort

L’épreuve d’effort est couramment utilisée en cardiologie dans un but à la fois diagnostique et pronostique. Parallèlement aux critères diagnostiques, de nouveaux paramètres ont été proposés pour améliorer la valeur pronostique de l’épreuve d’effort, comme l’analyse cinétique des variations de la fréquence cardiaque pendant et après l’effort. Trois paramètres principaux sont actuellement proposés : l’incompétence chronotrope, la récupération de la fréquence cardiaque après l’effort et l’élévation de la fréquence cardiaque au début de l’effort. Tous ces paramètres sont régulés par le système nerveux autonome, des valeurs anormales étant liées à une diminution de l’effet parasympathique et à une augmentation de l’effet sympathique. L’incompétence chronotrope et la récupération de la fréquence cardiaque sont actuellement les paramètres les plus faciles à déterminer et les plus prédicifs. Une fréquence cardiaque maximale basse à l’effort et une récupération de la fréquence cardiaque plus basse que la normale après l’effort sont prédicteurs de mortalité toutes causes et cardiovasculaire, à la fois chez des adultes sains avec ou sans facteurs de risque, et chez des patients coronariens ou insuffisants cardiaques. Leur valeur pronostique est indépendante des facteurs de risque cardiaque et cardiovasculaire classiques. L’incompétence chronotrope semble être un prédicteur plus fort de la mortalité cardiovasculaire que la récupération de la fréquence cardiaque, mais le risque paraît mieux stratifié lorsque les deux paramètres sont utilisés ensemble.

Keywords: autonomic nervous system; cardiovascular prognostic factor; chronotropic incompetence; coronary artery disease; exercise; heart failure; heart rate response; mortality risk factor

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Heart rate in the assessment of cardiovascular prognosis

by L. Riva, G. V. Coutsoumbas, and A. P. Maggioni, Italy

Observational studies have shown that resting heart rate (HR) is an independent predictor of cardiovascular and all-cause mortality. In patients with heart failure, there are benefits to pharmacologically reducing HR. It seems desirable to maintain HR in the “normal” range, below the traditionally defined tachycardia threshold of 90 or 100 beats per minute (bpm). In coronary patients, including those treated with percutaneous coronary intervention, a HR greater than or equal to 70 bpm increases cardiovascular risk; and in patients affected by heart failure, a HR lower than 60 bpm is associated with fewer cardiovascular events than are higher HRs. Resting HR would be a particularly useful measure to include in risk models because it is extremely easy to apply and has no associated costs. For this reason, and its strong correlation with both in-hospital mortality and mortality in the subsequent follow-up period, HR is already included in a number of risk assessment models for acute coronary syndrome.

Medicographia. 2012;34:414-420 (see French abstract on page 420)

Heart rate (HR) is a major determinant of myocardial oxygen demand, coronary blood flow, and myocardial performance, and affects nearly all stages of cardiovascular disease.

It has been postulated that reducing HR might prolong life, but, until now, this effect has not been demonstrated. However, in the past two decades, there has been growing evidence that resting HR might be a marker of risk or even a risk factor for cardiovascular morbidity and mortality. The importance of resting HR as a prognostic factor or as potential therapeutic target is not yet generally accepted. Recent large epidemiological studies have confirmed earlier studies that showed resting HR to be an independent predictor of cardiovascular and all-cause mortality, with a global estimation of 30% to 50% mortality excess for every 20 beats per minute (bpm) increase at rest. Studies have found a continuous increase in risk with HR above 60 bpm. A considerable number of epidemiological studies have reported a strong association between HR and cardiovascular risk, and this association appears to be independent of other major risk factors for atherosclerosis. This relationship has been consistent and was observed in healthy populations among men and women, various races, hypertensive subjects, patients with coronary artery disease (CAD), and in those with heart failure. This increasing evidence suggests that HR does not merely predict outcome, but that elevated HR may be a true cardiovascular risk factor.
In clinical practice, risk models may be useful for patient risk stratification and treatment decisions. Resting HR would be a particularly useful measure to include in risk models because it is extremely easy to apply and has no associated costs.

HR, when adjusted for age, is higher in women than in men (approximately 2-7 bpm) and has been reported to decrease with age (around 1 beat/min over 8 years). It has a clear circadian rhythm and is substantially higher during waking hours, varying relatively little between 10 AM and 6 PM. HR is affected by posture, and is approximately 3 bpm higher in the sitting position than in the supine position. Resting HR varies widely, but there does seem to be a pattern of distribution within the population, albeit not a normal distribution: Palatini et al have shown a mixture of two subpopulations, the first with a “normal” mean resting HR and the second with a “high” mean resting HR. The segregation value between the subgroups varied between 75 and 85 bpm. The previous epidemiological data suggest that it is desirable to keep HR within the “normal” rather than the “high” range, and more specifically, to maintain resting HR substantially below the tachycardia threshold of 90 or 100 bpm.

Pathophysiological mechanisms linking elevated HR and cardiovascular disease

Increased HR, due to imbalances of the autonomic nervous system with increased sympathetic activity or reduced vagal tone, has an impact on perfusion-contraction matching, which is the dynamic that regulates myocardial blood supply and function. An increase in HR results not only in an increase in myocardial oxygen demands, but also in a potential impairment of oxygen supply resulting from a reduction in collateral perfusion pressure. The imbalance may promote ischemia, arrhythmias, and ventricular dysfunction, as well as acute coronary syndromes (ACS), heart failure, and sudden death. With increased HR, the diastolic perfusion time lessens while myocardial oxygen demand increases. Peak coronary flow increases markedly during diastole, subjecting the coronary arteries to enhanced endothelial shear stress and pulsatile wall stress. The stressed endothelium releases growth hormones and vasoconstrictor peptides, while rapid pulsatile changes are associated with increased mechanical damage on the already stressed endothelium. All these factors encourage the development of atherosclerotic lesions (Figure 1).

Selected Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
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<tr>
<td>bpm</td>
<td>beat per minute</td>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
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<td>GRACE</td>
<td>Global Registry of Acute Coronary Events</td>
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<td>GUSTO</td>
<td>Global Utilization of Streptokinase and t-PA for Occcluded coronary arteries</td>
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<tr>
<td>GWTG-HF</td>
<td>Get With the Guidelines–Heart Failure</td>
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<td>HR</td>
<td>heart rate</td>
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<tr>
<td>InTIME-II</td>
<td>Intravenous nPA for Treatment of Infarcting Myocardium Early</td>
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<tr>
<td>NRMI</td>
<td>National Registry of Myocardial Infarction</td>
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<td>OR</td>
<td>odds ratio</td>
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<td>PAMI</td>
<td>Primary Angioplasty in Myocardial Infarction</td>
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<td>PCI</td>
<td>percutaneous coronary intervention</td>
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<td>SHIFT</td>
<td>Systolic Heart failure treatment with the I beta inhibitor ivabradine Trial</td>
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<tr>
<td>STEMI</td>
<td>ST-segment–elevation myocardial infarction</td>
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<tr>
<td>TIMI</td>
<td>Thrombolysis In Myocardial Infarction</td>
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</table>
Epidemiological association between HR and cardiovascular morbidity/mortality

Observational studies have shown an elevated resting HR to be associated with future development of cardiovascular disease, but all data on the possible importance of HR are retrospective and a demonstration of the benefits of reducing HR pharmacologically is limited to patients with myocardial infarction or heart failure. HR is already included in many models of risk assessment in patients affected by CAD—including those treated with percutaneous coronary intervention (PCI)—or heart failure.

\textbf{Increased HR and CAD}

\textbullet{} **HR and angina pectoris**

HR reduction is helpful in preventing angina, and there is some evidence that it may improve coronary endothelial function and atherosclerosis. To assess whether a lower HR is also associated with a more favorable prognosis in patients with CAD, an analysis was performed in 24 913 patients with suspected or proven CAD from the Coronary Artery Surgery Study (CASS) registry followed for a median time period of 14.7 years.\(^\text{11}\) In this study, patients with resting HR between 77 and 82 bpm had a significantly higher risk of total mortality (hazard ratio 1.16), and this association was even stronger in patients with a resting HR \(\geq 83\) bpm (hazard ratio 1.32). The association between HR and total mortality held true in all analyzed subgroups. A high resting HR was also an independent predictor of time to first rehospitalization due to angina and congestive heart failure. Interestingly, the multivariable models were adjusted for the use of \(\beta\)-blockers and this confirmed resting HR as an independent predictor of overall and cardiovascular mortality.

\textbullet{} **HR and acute risk stratification in ACS**

Considerable variability in mortality risk exists among patients with acute coronary syndromes (ACS). Individual patients reflect a combination of clinical features that influence prognosis, and these factors must be appropriately weighted to produce an accurate assessment of risk.

In the thrombolytic era, a number of studies were performed to define prognosis in ST-segment–elevation myocardial infarction (STEMI), initially developing sophisticated multivariable models not readily applied in routine clinical practice, and later proposing more convenient bedside clinical risk scores. A multivariable analysis from GUSTO-I (Global Utilization of Streptokinase and t-PA for Occluded coronary arteries; a randomized trial of four thrombolytic strategies in 41 021 patients with STEMI) identified a large number of independent clinical predictors correlated with prognosis (30-day mortality), five of which contain most of the prognostic information: age, lower systolic blood pressure, higher Killip class, elevated HR, and anterior infarction.\(^\text{12}\) Similarly, a subsequent study derived from logistic regression analysis of the InTIME-II database (Intravenous nPA for Treatment of Infarcting Myocardium Early II trial, in which 15 078 patients with STEMI were randomized to

<table>
<thead>
<tr>
<th>Odds of death by 30 days</th>
<th>Z score</th>
<th>Multivariate OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (\geq 75)</td>
<td></td>
<td>11.0</td>
</tr>
<tr>
<td>Killip II-IV</td>
<td></td>
<td>9.3</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats/min</td>
<td></td>
<td>7.7</td>
</tr>
<tr>
<td>Anterior MI or LBBB</td>
<td></td>
<td>6.1</td>
</tr>
<tr>
<td>Systolic BP &lt;100 mm Hg</td>
<td></td>
<td>5.5</td>
</tr>
<tr>
<td>Time to thrombolysis &gt;4 hours</td>
<td>4.0</td>
<td>1.4 (1.2-1.6)</td>
</tr>
<tr>
<td>Weight &lt;67 kg</td>
<td></td>
<td>3.7</td>
</tr>
<tr>
<td>Prior angina</td>
<td></td>
<td>3.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>3.3</td>
</tr>
<tr>
<td>History of hypertension</td>
<td></td>
<td>3.2</td>
</tr>
<tr>
<td>Never smoked</td>
<td></td>
<td>2.9</td>
</tr>
<tr>
<td>Prior myocardal infarct</td>
<td></td>
<td>2.8</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td></td>
<td>2.6</td>
</tr>
<tr>
<td>Antiarrhythmic medication</td>
<td></td>
<td>2.4</td>
</tr>
<tr>
<td>Lipid-lowering medication</td>
<td></td>
<td>2.2</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>2.0</td>
</tr>
</tbody>
</table>

\textbf{Figure 2.} Independent predictors of 30-day mortality after STEMI in TIMI risk score.

\textbf{Abbreviations:} BP, blood pressure; CI, confidence interval; LBBB, left bundle branch block; MI, myocardial infarction; OR, odds ratio; STEMI, ST-segment–elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

two different thrombolytic strategies within 6 hours of symptom onset) identified 10 baseline variables that were independent predictors of 30-day all-cause mortality, accounting for 97% of the predictive capacity of the multivariate model (Figure 2). Based on these data, the Thrombolysis In Myocardial Infarction (TIMI) risk score was assessed, calculated from the simple arithmetic sum of point values assigned to each risk factor based on the multivariate-adjusted risk relationship (1 point for odds ratios [ORs] from 1.0 to <2.0; 2 points for ORs ≥2.0 to 2.5; 3 points for ORs ≥2.5). This score system was validated for the prediction of 30-day all-cause mortality in an external population of patients treated with fibrinolytics for STEMI, derived from the TIMI 9 A/B trial. In this model, HRs >100 bpm (OR 2.3 [1.9-2.8] at the multivariate analysis) received 2 points, as did Killip classes II-IV and ages 65-74 years.

In order to further simplify the prognostic risk stratification in the acute phase of STEMI, a simple risk index—the TIMI risk index—based only on age and vital signs, was derived from the InTIME-II trial. The TIMI risk index was calculated using the equation: (HR x [age/10]^2 / systolic blood pressure) and mortality in an external population of patients treated with fibrinolytics for STEMI, derived from the TIMI 9 A/B trial. In this model was validated for the prediction of 30-day all-cause mortality, accounting for the risk of 30-day and 1-year all-cause mortality. With the exception of age, all components of this score had the same statistical weight (2 points) (Table II).

<table>
<thead>
<tr>
<th>PAMI (0-15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;75 y</td>
</tr>
<tr>
<td>Age 65-75 y</td>
</tr>
<tr>
<td>Killip’s classification &gt;1</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats/min</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Anterior STEMI or left branch bundle block</td>
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</tbody>
</table>

With the increasing adoption of primary PCI as the preferable method for achieving reperfusion, risk scores based on primary PCI trials were developed and validated. The Primary Angioplasty in Myocardial Infarction (PAMI) score, developed from 3252 PCI-treated patients enrolled in the various PAMI trials, is based on only 5 clinical and electrocardiographic characteristics—similarly to the TIMI risk score (age, Killip >1, HR >100 bpm, diabetes mellitus, and anterior STEMI or new left branch bundle block)—which are strictly associated with 30-day and 1-year all-cause mortality. With the exception of age, all components of this score had the same statistical weight (2 points) (Table II).

### Table I. Odds ratios for mortality and discriminative capacity (C statistic) for individual components of the TIMI risk index.

<table>
<thead>
<tr>
<th>Component</th>
<th>OR</th>
<th>C statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (10 y)</td>
<td>2.3</td>
<td>0.75</td>
</tr>
<tr>
<td>BP (10 mm Hg)</td>
<td>0.89</td>
<td>0.56</td>
</tr>
<tr>
<td>HR (10 beats/min)</td>
<td>1.3</td>
<td>0.63</td>
</tr>
<tr>
<td>Index (10 U)</td>
<td>2.2</td>
<td>0.79</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>InTIME-II</th>
<th>NRMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (10 y)</td>
<td>2.3</td>
</tr>
<tr>
<td>BP (10 mm Hg)</td>
<td>0.89</td>
</tr>
<tr>
<td>HR (10 beats/min)</td>
<td>1.3</td>
</tr>
<tr>
<td>Index (10 U)</td>
<td>2.2</td>
</tr>
</tbody>
</table>

### Table II. Components of PAMI risk score.

<table>
<thead>
<tr>
<th>Component</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;75 y</td>
<td>7</td>
</tr>
<tr>
<td>Age 65-75 y</td>
<td>3</td>
</tr>
<tr>
<td>Killip’s classification &gt;1</td>
<td>2</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats/min</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
</tr>
<tr>
<td>Anterior STEMI or left branch bundle block</td>
<td>2</td>
</tr>
</tbody>
</table>

A new model to determine the risk of 90-day mortality in patients undergoing primary PCI was derived from the analysis of APEX AMI (Assessment of Pexelizumab in Acute Myocardial Infarction trial), which enrolled 5745 patients with STEMI undergoing primary PCI within 6 hours of symptom onset. Of the variables assessed at the time of presentation that were independently predictive of 90-day mortality, the 7 most significantly associated with prognosis were incorporated in the final model: older age (hazard ratio 2.03 per increments of 10 years), lower systolic blood pressure (hazard ratio 0.86 per increments of 10 mm Hg), higher Killip class (hazard ratio 4.28 per Killip 3-4), higher HR (hazard ratio 1.45; HR >70 to <110 bpm per increments of 10 bpm), baseline total ST deviations (hazard ratio 1.25 per increments of 10 mm), serum creatinine higher than 90 μmol/L (hazard ratio 1.23 per increments of 10 μmol/L), and anterior location of myocardial infarction (hazard ratio 1.47). It is remarkable that even though the reperfusion method is different and more effective, many of the most important predictors in STEMI remained the same, and, in particular, elevated HR was confirmed to have an independent inverse correlation with prognosis.

A general score applicable to all ACS (ST-elevated or not) was determined by the analysis of the large multinational, observational, Global Registry of Acute Coronary Events (GRACE) (43 810 patients presenting with ACS with or without ST-segment elevation) with two primary end points: all-cause death and the composite outcome measure of death or nonfatal myocardial infarction during admission to hospital or within 6 months from discharge. The GRACE risk score includes 8 variables (age, HR, systolic blood pressure, Killip class, initial serum creatinine concentration, elevated initial cardiac markers, cardiac arrest on admission, and ST-segment deviation).
containing most (>90%) of the predictive information. This model was externally validated using the GUSTO IIb dataset including 12,142 patients with ACS, confirming its excellent discrimination power. In GRACE, the hazard ratio for death in association with HR was 1.2 (1.16-1.31) per incremental increase of 30 bpm during the period from hospital admission to the 6-month follow-up assessment.

In conclusion, HR measured at presentation has confirmed prognostic value in the ACS setting and is predictive of inhospital mortality and mortality during follow-up.

**HR and subsequent risk stratification in ACS**

HR retains its prognostic value even when measured after the acute phase of ACS. An analysis of the GISSI-Prevenzione study (Gruppo Italiano per lo Studio della Streptochinasin nell’ Infarto miocardico – Prevenzione; including 11,324 patients recruited within 3 months of myocardial infarction and followed up for 4 years) identified major determinants of prognosis. Among other determinants, a HR >75 bpm was significantly associated with worse prognosis when compared with lower HRs (relative risk for HR >75 bpm in males, 1.32; in females, 1.52). Lower HR (64 bpm in males and 69 bpm in females) was associated with lower risk.

This study proved the existence of a strong correlation between HR and prognosis in ACS acute phase or in the short term, and showed that this correlation remains strong in the longer term—after years—as well.

**Increased HR and heart failure**

Elevated resting HR is one of the key findings in acute and chronic heart failure. The association of HR with mortality was retrospectively addressed in the subanalyses of CIBIS-II (Cardiac Insufficiency Bisoprolol Study II), MERIT-HF (METoprolol CR/XL Randomised Intervention Trial in-congestive Heart Failure), and the COMET trial (Carvedilol Or Metoprolol European Trial). The general trend of these three trials clearly demonstrated that high resting HR contributed to poor survival in patients with advanced systolic heart failure. However, it was unknown whether, or to what extent, the benefit from β-blockers in patients with heart failure is attributable to HR reduction per se or to other beneficial effects, such as protection of the myocardium from the effects of prolonged exposure to high levels of circulating catecholamines or improved β-receptor function.

In the SHIFT trial (Systolic Heart failure treatment with the \( I_f \)-inhibitor ivabradine Trial), the effect of pure HR reduction by ivabradine was evaluated in addition to guideline-based treatment on cardiovascular outcomes, symptoms, and quality of life in patients with systolic heart failure (left ventricular ejection fraction ≤35%). Similarly to the β-blocker trials, treatment with ivabradine was associated with an average reduction in HR of nearly 15 bpm from a baseline value of 80 bpm, which was associated with an 18% risk reduction for the primary composite end point: cardiovascular death or hospital admission for worsening heart failure. Therefore, SHIFT demonstrated for the first time the beneficial effects of HR reduction alone in patients with systolic heart failure. Previously, in the BEAUTIFUL study (morBidity-mortality EvAlUaTion of the \( I_f \) inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction), no overall benefit of ivabradine vs placebo was demonstrated in patients with coronary heart disease and left ventricular systolic dysfunction; however, in the prespecified subgroup with stable coronary heart disease and left ventricular systolic dysfunction, there was a significant reduction in the secondary end point of hospital admission for acute myocardial infarction or unstable angina and coronary revascularization.

Several existing predictive models for long-term mortality in heart failure include more than 20 variables, some of which are not frequently assessed in clinical practice for heart failure. The American Heart Association Get With The Guidelines–Heart Failure (GWTG-HF) risk score reliably predicts in-hospital mortality of patients with preserved or impaired left ventricular systolic function using 7 clinical factors routinely collected at the time of admission. Older age, low systolic blood pressure, elevated HR, low serum sodium, elevated blood urea nitrogen, presence of chronic obstructive pulmonary disease (COPD), and nonblack race predicted an increased risk of death. This model is widely applicable because it includes a relatively small number of variables routinely assessed at the time of patient hospital admission. The application of this risk score could influence the type and quality of care provided to patients hospitalized with heart failure by guiding clinical decision-making. Nevertheless, in the GWTG-HF risk score, age, systolic blood pressure, and blood urea nitrogen contributed most substantially to the overall point score, whereas HR, presence of COPD, serum sodium, and nonblack race contributed relatively few points to the overall score.

**Increased HR and hypertension**

Several studies have demonstrated that individuals with high HR have increased blood pressure readings and that this association is stronger in subjects with elevated sympathetic activity. This phenomenon may be due to hypertension and tachycardia having a common denominator: increased sympathetic tone. Thus, it is crucial to know whether HR also has independent predictive power for cardiovascular mortality in hypertensive individuals. Much less is known about the association of HR and mortality in hypertensive patients as only three studies have examined this relationship in such a population and only one study in elderly subjects with isolated systolic hypertension. In the Framingham Study, it was found that for an increment of 40 bpm there was a 118% and 114% increased age- and systolic BP–adjusted OR in men and women, respectively, for total mortality, and a 68% and 70% increased risk, respectively, for cardiovascular mortality. In the Syst-Eur study (Systolic Hypertension in Eu-
for stage 1 hypertension. Sustained hypertension in white, younger subjects evaluated risk of mortality than those with a HR ≤79 bpm.

On the other hand, data derived from HARVEST (Hypertension and Ambulatory Recording VEnetia SStudy) demonstrated that baseline resting HR and changes in HR in the first few months of follow-up were able to predict the development of sustained hypertension in white, younger subjects evaluated for stage 1 hypertension.

Even if all data on the possible relevance of HR lowering in hypertensive patients are retrospective, it is reasonable that patient outcome may be improved with drugs that reduce both blood pressure and HR. On the basis of the epidemiological data, for a 10%-12% reduction in HR, a 20%-40% decrease in cardiovascular morbidity–mortality should be expected.

**Increased HR and diabetes mellitus**

There are few data specifically exploring the relationship between resting HR and cardiovascular outcome in patients with diabetes mellitus. However, the association between HR, glucose, and insulin levels is strong. In addition, diabetes is commonly associated with abnormal function of the autonomic nervous system, the main regulator of resting HR. In the Swiss cohort of the World Health Organization Multinational Study of Vascular Disease in Diabetes, a relationship between resting HR and both all-cause and cardiovascular mortality was reported in patients affected by type 2 diabetes mellitus. Interestingly, a similar relationship was not observed in patients with type 1 diabetes mellitus.

Recently, the Euro Heart Survey investigators reported that, in diabetic patients, a higher resting HR was associated with an increased risk in all-cause mortality. In the ADVANCE study (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation), a higher resting HR was associated with a significant-ly increased risk in all-cause mortality, cardiovascular death, and major cardiovascular outcomes. The increased risk associated with a higher baseline resting HR was more obvious in patients with previous macrovascular complications. Moreover, the relationship between HR and metabolic derangement has been reinforced by data derived from the Chicago Heart Association Detection Project: in middle-aged patients, the adjusted risk of developing diabetes increased by 10% for each 12-bpm increment in baseline HR in patients older than 65 years. It remains unclear whether a higher HR directly mediates increased risk or whether it is a marker for other factors that determine a poor outcome. Conclusion

There is consistent evidence that resting HR is able to predict life expectancy and is an independent predictor of morbidity and mortality in healthy subjects. Furthermore, resting HR is a predictor of death in both stable CAD and ACS. Elevated resting HR is also able to independently predict clinical outcomes in patients with heart failure. In spite of the large body of evidence on the evaluation of cardiovascular risk, little attention has been paid to the role of HR in cardiovascular risk assessment in daily practice, even if this is a simple and easily measurable clinical parameter that can be utilized with no additional cost.

Recent evidence supports the concept that increased resting HR is an independent cardiovascular risk factor. A HR ≥70 bpm increases cardiovascular risk and this measurement should be used to guide therapy in coronary patients. HR is also an important target for the treatment of heart failure. Specifically, patients affected by heart failure with HRs lower than 60 bpm have fewer cardiovascular events than patients with higher HRs. For all these reasons and the strong correlation with both in-hospital and long-term mortality, HR has already been included in many models of ACS risk assessment.

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Keywords: cardiovascular disease; cardiovascular prognosis; heart rate; risk factor

**LA FRÉQUENCE CARDIAQUE DANS L’ÉVALUATION DU PRONOSTIC CARDIOVASCULAIRE**

Des études observationnelles ont montré que la fréquence cardiaque de repos (FC) est un facteur prédicteur indé-
pendant de mortalité toutes causes et cardiovasculaire. Il est bénéfique, chez les patients insuffisants cardiaques, de 
réduire la FC de façon pharmacologique. Il semble souhaitable de maintenir la FC dans des fourchettes normales, 
en dessous du seuil de tachycardie défini traditionnellement à 90 ou 100 battements par minute (bpm). Chez les pa-
tients coronariens, y compris ceux traités par angioplastie coronaire percutanée, une FC supérieure ou égale à 70 bpm 
augmente le risque cardiovasculaire ; et chez les insuffisants cardiaques, une FC inférieure à 60 bpm est associée à 
un nombre inférieur d’événements cardiovasculaires. La FC de repos est une mesure particulièrement utile à inclure 
dans des modèles de risque parce qu’elle est très facile à mesurer et n’induit pas de coûts supplémentaires. C’est 
pourtant la FC qui est déjà comprise dans un certain nombre de modèles d’évaluation du risque de syndrome coronaire 
aigu en raison de son association forte, à la fois avec à la mortalité hospitalière et avec la mortalité de la période de 
suivi ultérieure.
Why should we consider heart rate in patients with cardiovascular disease?

by B. D. Westenbrink and W. H. van Gilst, The Netherlands

Heart rate has a fundamental role in cardiovascular performance and is one of the most readily accessible and informative vital signs. An elevated heart rate is an independent risk factor for mortality and morbidity in people with and without cardiovascular disease. Accordingly, pharmacological agents that reduce heart rate can alleviate symptoms and improve clinical outcomes in several cardiac diseases. Unfortunately, perhaps because of our familiarity with heart rate, or the lack of clear data to support a specific heart rate range, heart rate is often overlooked. In this review we will discuss the value of elevated heart rate and its reduction in cardiovascular disease and attempt to provide practical, evidence-based recommendations for its management.

MEDICOGRAPHIA. 2012;34:421-425 (see French abstract on page 425)

How to measure heart rate

Heart rate is one of the most readily accessible vital signs. It can be determined in virtually any setting, by any health care provider, and by many patients themselves. In hospitalized patients, heart rate is documented at least daily, with every electrocardiogram, during most medical procedures, and/or continuously. Exercise equipment and commercial blood pressure monitors report heart rate values at home, familiarizing patients with their basic cardiovascular dynamics. Expanding indications for implantable medical devices allow us to remotely monitor heart rates, without even involving the patient. Cardiovascular clinicians are thus continuously informed about their patients’ heart rate. While electrocardiographic detection is the most accurate, palpation of the peripheral pulse may suffice in most instances and most patients. There are, of course, several other aspects of heart rate measurement that should be taken into account, including posture, physical activity, duration of measurement, temperature, and emotional factors, none of which we shall discuss in detail in this paper.

Why should we consider heart rate?

Heart rate has an intimate and complex involvement in several parameters of cardiovascular function and pathophysiology. Cardiac output, for instance, is determined by heart rate and stroke volume. Since it is vastly easier to modulate heart rate than stroke volume, variations in heart rate are our principal mechanism for adjusting cardiac output to metabolic demand. Heart rate is also, however, a major determinant of myocardial oxygen consumption. Sustained elevation in heart rate may lead to critical pathophysiological changes in the cardiovascular system. These in-
clude endothelial dysfunction and atherosclerotic plaque development, reduction in coronary blood flow, impaired systolic and diastolic left ventricular function, and a susceptibility to arrhythmia. Higher heart rates predict cardiovascular events and mortality in patients with or without prior cardiovascular disease.\(^1\)\(^2\)

While this association has been known for decades,\(^3\) it is still very timely. A subgroup analysis of the placebo arm of the BEAUTIFUL trial (morBidity-mortality EvaluAtion of the \(I_f\) inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction), for instance, demonstrated that a resting heart rate of 70 bpm or higher was a strong and independent predictor of long-term outcome in patients with coronary artery disease.\(^4\) In a similar analysis of the SHIFT trial (Systolic Heart failure treatment with the \(I_f\) inhibitor ivabradine Trial) in heart failure patients with a heart rate above 70 bpm despite optimal \(\beta\)-blocker therapy, risk of death in the highest heart rate quintile (>87 bpm) was more than that in the lowest quintile (70-72 bpm).\(^5\)

Prognostic value is not confined to resting rates. The chronotropic response to exercise and subsequent efficiency of heart rate recovery have also been associated with cardiovascular events and mortality in presence or absence of prior cardiovascular disease.\(^6\) The value of the exercise heart rate is extensively discussed in another review in this issue of Medicographia.

Heart rate is not only of prognostic importance, but is also an established therapeutic target. Pharmacological therapies that reduce heart rate are associated with improved coronary perfusion, reduced myocardial oxygen consumption, enhanced left ventricular function, and beneficial left ventricular remodeling.\(^2\)\(^7\)\(^9\) These functional changes translate into improvements in exercise capacity, cardiac function, angina, and quality of life.\(^2\)\(^7\)\(^9\) The beneficial effects of \(\beta\)-blockers on survival are also proportional to the degree of heart rate reduction achieved, suggesting that it is the most important therapeutic target.\(^10\) More direct and unequivocal evidence for heart rate reduction is currently emerging from studies with the specific heart rate-reducing agent ivabradine.\(^11\) In summary, there is thus ample pathophysiological, epidemiological, and clinical evidence that elevated heart rate has deleterious effects for cardiovascular patients. The evidence that supports heart rate reduction in clinical practice is discussed below.

**Which cardiovascular patients might benefit from heart rate reduction?**

**Hypertension**

The inverse relation between heart rate and prognosis can be extended to patients with hypertension.\(^12\) However, the value of heart rate reduction with \(\beta\)-blockers in patients with hypertension is disputed.\(^13\) The CAFE study (Conduit Artery Function Evaluation) compared the effects of atenolol and amiodipine on central and peripheral blood pressure.\(^14\) Atenolol was associated with a paradoxical increase in central blood pressure, while the converse was true for amiodipine.\(^14\) In addition, an atenolol-based antihypertensive regimen conferred less cardiovascular risk reduction than an amiodipine-based regimen.\(^15\) Heart rate reduction is therefore not a specific treatment target in patients with hypertension.\(^12\)

**Stable coronary artery disease**

Heart rate reduction is an important method of reducing myocardial oxygen consumption in patients with stable coronary artery disease. Heart rate reduction with \(\beta\)-blockers or calcium channel blockers reduces the manifestations of ischemia. Indeed, anti-ischemic drugs that reduce heart rate are often more effective than regimens with no effect on heart rate.\(^9\) There is, however, no evidence that heart rate reduction with these conventional agents improves prognosis or reduces the incidence of acute coronary syndromes.\(^7\) The benefits of ivabradine on angina are also fairly well established and seem at least proportional to those of \(\beta\)-blockers and calcium channel blockers.\(^16\)\(^17\) Ivalapradine did not reduce the incidence of the primary composite end point of mortality, myocardial infarction, or heart failure hospitalization.\(^18\) Clear survival benefit was, however, apparent in a prespecified subgroup analysis of patients with a resting heart rate above 70 bpm and in patients with limiting angina. These findings suggest that the lack of benefit in BEAUTIFUL could be explained by a relatively heterogeneous population with a large proportion of patients in whom heart rate was already well controlled. Thus, although three classes of heart rate-modifying drugs alleviate symptoms, unequivocal evidence of mortality benefit is lacking and recommendations for a specific heart rate range cannot be made. It would, however, be prudent to target heart rates to values between 50-70 bpm (see below), although treatment should always focus on symptom alleviation rather than on heart rate values themselves.

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**Selected abbreviations and acronyms**

- **BEAUTIFUL** morBidity-mortality EvaluAtion of the \(I_f\) inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction
- **CAFE** Conduit Artery Function Evaluation
- **COPERNICUS** CarvedilOl ProspEctive RaNdomized CLUmulative Survival
- **DIG** Digitalis Investigation Group
- **SHIFT** Systolic Heart failure treatment with the \(I_f\) inhibitor Ivabradine Trial

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**Why should we consider heart rate in patients with CVD – Westenbrink and van Gilst**
**Acute coronary syndromes**
The effect of heart rate on myocardial oxygen consumption is especially critical in acute coronary syndromes. Indeed, an elevated admission heart rate is one of the most important predictors of early mortality. Heart rate–lowering anti-ischemic drugs can reduce symptoms in patients with acute coronary syndromes. Furthermore, several trials and meta-analyses have demonstrated that β-blockers reduce mortality and prevent reinfarctions when initiated in the subacute phase after acute myocardial infarction. It is, however, unknown whether early heart rate reduction is beneficial in acute coronary syndromes. Indeed, early intravenous β-blockers followed by oral doses during acute ST-segment elevation myocardial infarction (STEMI) was not associated with net clinical benefit, due in part to an increased incidence of cardiogenic shock. These studies used very high doses of β-blockers and were conducted in the pre-reperfusion era, suggesting that results may have differed if performed with current drugs or titration schemes. The efficacy of early heart rate reduction with ivabradine is currently under investigation in patients with acute coronary syndromes. Oral β-blockers are recommended in all patients with acute coronary syndromes and calcium channel blockers in patients who remain symptomatic despite β-blockers and nitrates. There is no evidence to support specific heart rate targets during acute coronary syndromes. Considering the efficacy of β-blockers after myocardial infarction and the results of the SHIFT study (see below), targeting a heart rate range between 50 to 70 bpm appears sensible.

**Heart failure**
Myocardial workload and oxygen consumption are directly proportional to heart rate, while diastolic filling time and oxygen delivery are inversely related to heart rate. Elevated heart rates are especially detrimental to the failing heart, which relies heavily on diastolic filling and is relatively deprived of oxygen and nutrients. Accordingly, heart rate reduction in failing hearts is associated with decreased energy expenditure, improved perfusion, improved contractility, decreased afterload, and restoration of ventricular synchrony. The first evidence that heart rate reduction could enhance clinical outcome was presented in the DIG trial (Digitalis Investigation Group). Heart rate reduction with digoxin reduced hospital admission for worsening heart failure, although it did not reduce mortality. More robust evidence for heart rate reduction came from multiple randomized controlled trials that firmly established the efficacy of β-blockers in heart failure. Importantly, the mortality benefits of β-blockers are strongly related to the degree of heart rate reduction achieved. β-Blockers and digoxin have several cardiovascular and extracardiovascular (side) effects that may partially explain their efficacy, but also affect their tolerability. Indeed, only 56% of patients tolerated the target dose of carvedilol in the COPERNICUS trial (Carvedilol ProspectiveRandomized Cumulative Survival); and even fewer patients tolerate the target dose of β-blockers outside the clinical trial setting. While individual dose-response characteristics vary and careful titration may allow patients to tolerate higher doses, side effects significantly limit the degree of heart rate reduction that can be achieved. The SHIFT study specifically targeted those patients with heart rate control that remained suboptimal on conventional medication. In SHIFT, 65% of systolic heart failure patients in sinus rhythm with a resting heart rate ≥70 bpm despite a maximally tolerated β-blocker dose were randomized to ivabradine or placebo. Ivabradine was titrated to a target dose rather than a heart rate target, but the dose was reduced when heart rate dropped below 50 bpm. It achieved an average heart rate reduction of 11 bpm and reduced the occurrence of the primary composite end point of cardiovascular death or heart failure hospitalizations by 18%. This effect was mainly driven by a 26% reduction in hospitalizations for worsening heart failure or heart failure–related deaths. Prespecified post-hoc analysis also showed that heart rate reduction reversed left ventricular remodeling and improved both cardiac function and quality of life. This study not only shows ivabradine to be effective, but also unequivocally proves that heart rate is a nodal point for intervention in the cardiovascular system.

Which rate is best for the heart?
Extensive epidemiological studies and the evidence provided by the BEAUTIFUL and SHIFT trials indicate that heart rates above 70 bpm are unfavorable. More importantly, they show that reducing heart rate in these patients can improve clinical outcome. Although the SHIFT and the BEAUTIFUL studies did not target a specific heart rate range, the dose was adjusted when the heart rate fell below 50 bpm. We therefore propose that the optimal resting heart rate is between 50 and 70 bpm, at least in patients with heart failure, stable coronary artery disease, and left ventricular systolic dysfunction. However, the inclusion criteria for these studies were broadly defined and not mutually exclusive. The primary etiology for left ventricular dysfunction and heart failure, for instance, is a previous acute coronary syndrome. It is therefore likely that the findings of both trials can be extrapolated to other populations as well. The optimal heart rate range for patients with heart disease is probably between 50 to 70 bpm. Future studies with ivabradine will hopefully help us to further define the optimal heart rate targets. Moreover, new avenues for heart rate reduction will likely emerge.

Conclusions
Extensive data from pathophysiological and epidemiological studies and clinical trials have established heart rate reduction as an effective and feasible tool to alleviate symptoms and improve prognosis in patients with coronary artery disease and heart failure. Trials with the specific heart rate–reducing agent ivabradine have unequivocally proven this concept and provided us with a novel and specific tool to control heart rate.
HEART RATE MODULATION AND EXERCISE CAPACITY

References


Keywords: coronary artery disease; heart failure; heart rate; heart rate reduction; hypertension; ibradivine
POURQUOI FAUT-IL SURVEILLER LA FRÉQUENCE CARDIAQUE DES PATIENTS AYANT UNE MALADIE CARDIOVASCULAIRE ?

La fréquence cardiaque joue un rôle essentiel dans la fonction cardiovasculaire et c’est un des signes vitaux les plus facilement accessibles et instructifs. Une fréquence cardiaque élevée est un facteur de risque indépendant de mortalité et de morbidité chez les personnes ayant ou non une maladie cardiovasculaire. C’est pourquoi les traitements qui réduisent la fréquence cardiaque peuvent soulager les symptômes et améliorer les résultats cliniques dans de nombreuses maladies cardiovasculaires. Malheureusement, peut-être parce que la fréquence cardiaque nous est familière, ou parce que nous manquons de données claires pour la définir de façon spécifique, elle est souvent négligée.

Dans cet article, nous allons analyser l’importance d’une fréquence cardiaque élevée et de sa réduction dans la maladie cardiovasculaire et essayer de donner des recommandations pratiques, fondées sur des preuves, pour sa prise en charge.
The Question

Cardiac rehabilitation is an important component of the multidisciplinary approach to the management of cardiovascular patients. Cardiac rehabilitation has traditionally been provided to lower-risk patients, however, the demographics of patients who can be candidates for rehabilitation training has changed. Should we now consider cardiac rehabilitation as an essential component of the treatment of patients with multiple presentations of coronary heart disease and heart failure? If so, when should it be started?

When should cardiac rehabilitation be started after a cardiovascular event?

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When should cardiac rehabilitation be started after a cardiovascular event?

A recent systematic review showed that exercise training has a beneficial effect on LV remodeling in clinically stable post-MI patients. The greatest benefit occurs when training starts early after MI (from 1 week) and lasts longer than 3 months. For each week that exercise was delayed, an additional month of training was required to achieve the same level of benefit on LV remodeling.

Cardiac rehabilitation and secondary prevention are also recommended for all revascularized patients, and should be initiated during hospitalization. Counseling regarding physical activity can start as early as the next day after uncomplicated PCI or coronary surgery.

Over the past decades, mortality from acute cardiovascular diseases such as MI has dramatically declined, but the increasing number of patients subsequently affected by chronic conditions such as heart failure has driven up the costs and needs of health systems. Exercise training in compensated heart failure is safe and has several benefits, including enhanced peak oxygen uptake, improved muscle energetics, restoration of autonomic function, reduced neurohormonal activation, and reverse LV remodeling; it thus leads to better functional capacity, an important objective of heart failure management. These benefits are apparent as early as 3 weeks after commencement of training. Evidence from randomized controlled trials further indicates that physical rehabilitation may ultimately reduce heart failure–related hospitalization and improve health-related quality of life in patients with mild to moderate systolic heart failure.

The ESC recommends exercise training for all stable chronic heart failure patients. For hospitalized patients, inpatient counseling and education should begin as soon as possible after hospital admission.

References

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his question was resolved definitively in as early as 1968 in a document prepared by a working group of the World Health Organization Regional Office for Europe entitled, “A programme for the physical rehabilitation of patients with acute myocardial infarction” (Copenhagen, 1968). In the document, the recommendation after hospital admission of a patient with acute myocardial infarction was “…to start physical rehabilitation as soon as possible.” Today, with significantly reduced lengths of stay in the cardiology department, the first rehabilitation measures can be started as soon as relief of pain and serious cardiovascular complications have been successfully addressed.

The objectives of in-hospital rehabilitation are as follows: (i) to prevent the development of hypokinesia caused by the patient’s limited physical activity; and (ii) to provide early educational and psychological support to the patient to allow him/her to understand the need for further complex stepwise rehabilitation, including special exercise training that transforms into a lifetime secondary prevention measure.

The first objective is achieved by permitting the patient to be active early, and by allowing patients with a complicated disease course to perform therapeutic exercises. These exercises are started from the first or second day of the patient’s stay in hospital. At the earliest stage, rehabilitation of the patient with acute coronary syndrome begins through discussion of the concepts of myocardial infarction (or acute coronary syndrome), the importance of drug treatment, application of rehabilitation methods, and further long-term secondary prevention.

The patient must understand what, why, and in what time frame he or she should undertake activities, which are for lifesaving purposes, improvement of the disease course, fastest possible recovery of physical performance, and a return to work activities. Ensuring the patient’s awareness of the need for strict compliance with the medical and nonmedical recommendations of doctors during the stay in the coronary care unit is a good first step that will increase motivation for the upcoming treatment and rehabilitation and improve adherence to them.

Discussion with the patient and, if possible, with his or her relatives, has a favorable psychological effect. The doctor informs the patient about the purpose of rehabilitation, the methods, and the achievable results at different stages. The patients must understand that a combination of medical and nonmedical interventions (physical rehabilitation, adherence to an antiatherosclerotic diet, a training program, psychotherapy, and modification of risk factors) will allow them to quickly recover and return to an active life and their professional activities. Patient awareness of these interventions has been found to increase motivation and improve compliance with implementation of the treatment, rehabilitation, and secondary prevention measures.¹

There is also a physical aspect to rehabilitation. Depending on the severity of the patient’s state, the doctor will determine the tentative discharge date from hospital. In cases of uncomplicated myocardial infarction, patients can be discharged in about 1 week. They are not threatened by hypokinesia. However, if the prognosis is poor, the length of stay in hospital becomes longer. In such cases, the patient is prescribed a sparing regimen of physical activity and calisthenics in order to prevent hypodynamia and secure an early expansion of physical activity. So-called breathing exercises and exercises for small muscle groups are used, and are performed under the supervision of a physiotherapist or trained nurse.

Rehabilitation is carried out not only after myocardial infarction, but also after coronary artery bypass graft (CABG) and percutaneous coronary intervention. The 2011 recommendations of the American College of Cardiology Foundation/American Heart Association state: “Cardiac rehabilitation is recommended for all eligible patients after CABG. Class I, Level of Evidence: A.”²

References

Almost 7 decades ago, healing of a myocardial infarction was described as taking 3 to 4 weeks, and a theoretical 6 to 8 weeks of bed rest was considered necessary after an acute myocardial infarction (AMI). With technological advances and improvements in the management of cardiac disease, recovery has become faster and long periods of inactivity are generally no longer needed. On the other hand, as more people survive after a cardiovascular event, there are more patients in a poor health condition and with comorbidities, and these patients are considered for cardiac rehabilitation (CR).

Although there is some controversy regarding the effects of CR on heart failure mortality, CR leads to a 26% reduction in cardiovascular mortality in coronary heart disease. The core component of CR is exercise training, which has known benefits including positive effects on quality of life, anti-inflammatory effects, improvement in autonomic and endothelial function, an increase in fibrinolysis, and a decrease in coagulability. Although recommended by the American Heart Association, American College of Cardiology, and European Society of Cardiology in the treatment of patients with coronary artery disease and heart failure, CR is still underused.

Before starting exercise training after a cardiovascular event, exercise testing is recommended to guide prescription. Safety concerns regarding when to perform testing—and thus when to initiate the exercise program—stem from the risk of triggering a fatal arrhythmia, prolonged ischemia during exercise sessions leading to myocardial necrosis, or worsening of ventricular function with an unfavorable outcome in the long term. In addition, acute exercise may lead to a transitory prothrombotic state and elevated wall stress, which can raise concerns in patients with a coronary stent, especially in areas that are not covered by endothelium. This issue was investigated in a study in which patients with no recent myocardial infarction (within 1 week) were randomized to symptom-limited treadmill exercise testing or not the day after uncomplicated percutaneous revascularization with stent placement. There was no difference in AMI or access site complications between the groups, indicating that this approach is safe. Given that this was a single-center study, and also allowing time for healing of the access site, it seems appropriate to perform exercise testing and initiate CR 5 to 7 days after an elective percutaneous coronary intervention.

After an acute coronary syndrome, including AMI or unstable angina, symptom-limited exercise testing can be performed 14 days after an uncomplicated event, when an exercise training program can also be initiated. After a large and/or complicated myocardial infarction including heart failure, arrhythmias, pericarditis, or mechanical complications, physical activity should start only after clinical stabilization. With regard to possible deleterious effects on ventricular function, aerobic exercise for 3 months initiated within 2 weeks after AMI does not appear to cause unfavorable left ventricular remodeling and still reduces myocardial ischemia after 6 months.

Although low-intensity exercise can be started in hospital after cardiac surgery, the aim of this management phase is to prevent respiratory complications and profound venous thrombosis, and no study has specifically investigated when symptom-limited exercise testing can safely be performed. Upper body training can be started when the wound is stable. For patients submitted for cardiac transplantation, exercise training can start 2 to 3 weeks after the procedure, but should be discontinued during corticosteroid bolus therapy for rejection.

Clinical trials have generally included heart failure patients receiving optimal treatment at stable doses in the previous 5 to 12 weeks. After an episode of decompensation, it would seem appropriate to initiate CR when the patient is clinically compensated with maximal tolerated doses, also allowing for the use of exercise testing for appropriate prognosis evaluation.

**References**

Cardiac rehabilitation (CR) has been shown to accelerate physical and psychological recovery and reduce mortality after acute cardiac events. The programs help modify risk factors and increase the likelihood of a return to work. It is a cost-effective intervention that improves prognosis and reduces recurrent hospitalization and health care expenditure. When originally introduced, CR was primarily aimed at patients after cardiac surgery and myocardial infarction without intervention. Traditionally, Phase II CR commenced 4 to 6 weeks after the event when wound healing had occurred.

Over the past decade, the profile of patients that would benefit from CR has changed greatly. The duration of hospitalization following percutaneous coronary intervention (PCI) and even primary angioplasty has greatly reduced. Patients undergoing these procedures are fully mobile on discharge and mostly keen to return to work and normal activity. Yet recent surveys have indicated that less than 35% of heart attack and other cardiac event patients attend CR programs. The cause is likely multifactorial, and includes a lack of services, patient anxiety and lack of motivation, lack of social support, travel time, and needing to take time off from work. A major factor is undoubtedly the length of time between discharge and commencement of outpatient CR, during which many patients will have attempted to return to normal work and activity, and while remaining concerned as to the appropriate lifestyle and exercise level, they find themselves unable to engage in a delayed program.

Concern has existed regarding possible adverse effects of early CR after discharge from hospital. However, there is now extensive evidence that early CR does not have any adverse effect on left ventricular size or myocardial function, and that rates of completion of CR are greater if started within 14 days post discharge. Equally, CR exercise programs can be safely started—even in the elderly—2 weeks after discharge following cardiac surgery, and they lead to better exercise tolerance.

Ensuring higher levels of participation in CR will require significant multidisciplinary organization. Intensive in-hospital Phase I CR, enthusiastic physician endorsement, more accessible early programs, and tailoring of programs to patients’ needs, sex, and age are necessary. Community—rather than hospital-based programs should be more acceptable to patients, and initiatives such as home-based telemonitored exercise programs could support traditional CR. Issues such as the relatively poor take-up of CR by women will need to be addressed.

In summary, the value of CR is beyond doubt. The current low level of participation by patients following cardiac events will only be addressed by an enthusiastic multidisciplinary Phase I approach, followed by early (2 weeks ideally) enrolment in Phase II programs with a strong community element. Barriers to CR participation need to be identified. Databases on cardiac intervention, acute coronary syndromes, and cardiac surgery need to be linked to CR programs with regular local and national audit.
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Prolonged bed rest and hospitalization was the standard care for patients after acute myocardial infarction (AMI) some decades ago; exercise helped to reduce the hospitalization period and physical deconditioning, and to delay the onset of angina after AMI before the era of myocardial revascularization. With the advent of modern effective therapeutic interventions in AMI, physical training is now also aimed at improving psychological wellbeing, controlling depression and anxiety, improving adherence to medication, and controlling risk factors.

Exercise training after AMI has beneficial hemodynamic effects, producing an average 20% improvement in aerobic capacity. Improved functional capacity allows patients to return to work and helps elderly patients maintain independent living. A reduction in recurrent myocardial infarction and mortality in coronary artery disease patients included in physical training programs has been documented in a meta-analysis, and the results do not differ from those of trials conducted in the era of cardiac revascularization. A recent large observational study in more than 600 000 patients aged >65 years discharged after hospitalization for coronary disease showed a 21% to 34% decrease in all-cause mortality at 5 years in those patients included in physical training programs compared with controls.

When should physical training start after an acute coronary syndrome? The European Society for Cardiology (ESC) guidelines for the management of ST-segment elevation myocardial infarction recommend risk stratification and exercise testing. A position paper from the ESC on cardiac rehabilitation in secondary prevention makes recommendations as to the timing and intensity of physical training after AMI and in heart failure patients. In uncomplicated AMI, ambulation should begin after 12 to 24 hours (Class I); predischarge physical training may start in hospital after an electrocardiogram stress test. Patients with preserved exercise capacity may resume physical activity for 30 to 60 minutes daily at 75% to 80% of peak heart rate (Class I). After large or complicated infarcts with heart failure, shock, or arrhythmias, patients should maintain bed rest for longer and physical activity should begin only after stabilization. Patients with left ventricular systolic dysfunction should be tested for peak exercise capacity with maximal symptom-limited cardiopulmonary exercise testing, and physical training should resume gradually at 50% of maximal exercise capacity in hospital to verify clinical tolerability and stability. Daily moderate-intensity exercise after hospitalization is recommended (Class I).

Each stage of increased physical work capacity is associated with an 8% to 14% reduction in all-cause mortality risk. Physical training is safe, and data reported in clinical trials show one event (AMI, cardiac arrest) in 50 000 to 100 000 supervised patient-hours of physical training.

In patients with heart failure, which frequently has an ischemic etiology, the benefits of physical training are less clear. HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) randomized 2331 patients with left ventricular ejection fraction ≤35% to exercise training or control. There was an 11% decrease in total mortality or hospitalization (P=0.03) and a 15% decrease in cardiovascular mortality and cardiovascular hospitalization (P=0.03) with exercise training, suggesting that this has some beneficial effects in patients with heart failure—findings consistent with the results of 33 previous clinical trials and a meta-analysis.

Questions about the role of exercise training remain unanswered: the optimal amount, intensity, and combination of exercise training modalities in patients with systolic heart failure, as well as its utility in patients with cardiac resynchronization therapy. Although recognized as a core component of multifactorial cardiac rehabilitation, physical training is still underused (less than 50% in observational studies). Lack of knowledge, skills, and motivation on the part of health care providers, as well as patients’ lack of adherence in changing their lifestyle and insufficient insurance funding, are all possible causes and must be addressed.

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In recent years, there has been impressive progress in pharmacological therapies and sophisticated technology-based diagnostic and therapeutic procedures in cardiovascular diseases. As a consequence, a greater number of men and women now survive acute events, but with a heavier subsequent burden of chronic conditions and clinical need. Cardiac rehabilitation includes patient assessment, counseling on physical activity, exercise training, diet/nutritional counseling, weight control management, lipid management, blood pressure monitoring, smoking cessation, and management of psychosocial well-being.

Inpatient and outpatient cardiac rehabilitation for eligible cardiovascular patients is an essential component of care that should be incorporated into treatment plans. Increasing the number of people who participate in cardiac rehabilitation can also reduce health care costs associated with recurrent events and reduce the burden for families and caregivers of patients with serious sequelae.

Exercise training should be recommended to all patients after acute coronary syndrome or primary percutaneous coronary intervention (PCI) (supervised or monitored in moderate- to high-risk patients). The training program should include at least 30 minutes of aerobic exercise, 5 days per week. After uncomplicated procedures, physical activity can start the next day. After substantial and/or complicated myocardial damage, physical activity should start after clinical stabilization and be increased slowly according to the patient’s symptoms. Inpatient rehabilitation is focused on early mobilization, and starts as soon as patients are hemodynamically stable and free of symptoms of ischemia, arrhythmia, or heart failure. As the patient progresses to ECG telemetry, progressive ambulation becomes appropriate, initially with assistance and hemodynamic assessment before, during, and after exercise. Patients should first try to sit up, stand, and walk in their room. Subsequently, they should start to walk in the hallway at least twice daily, for certain specific distances or as tolerated, and should not be unduly pushed or held back.

Early outpatient rehabilitation includes surveillance of symptoms, hemodynamics, glycemic response to exercise (in diabetics), weight, tobacco use, emotional status, and adherence with medications, diet, and home exercise. It also includes review of each individual’s pharmacological and device therapy to ensure adherence with consensus guidelines. This monitoring phase is an intensive, multidisciplinary intervention focused on educating the individual about the disease, its manifestations, and all aspects of its treatment. This provides participants with the tools needed to slow disease progression, maintain optimal functional status, and become an informed and active participant in managing their condition.

Most cardiac rehabilitation participants progress to independent exercise without a transitional “Phase III.” The main goal of maintenance lifetime rehabilitation is to promote habits that lead to a healthy satisfying lifestyle. In patients with stable coronary artery disease and post–elective PCI, symptom-limited exercise testing can safely be performed the day after the intervention, but it scarcely is. In patients with multiple risk factors and moderate-to-high risk (ie, recent heart failure episode), medically supervised exercise training programs are recommended at initiation, and ensure the patient’s motivation for long-term adherence.

Exercise training in heart failure can improve both cardiac and noncardiac indices. Experience has shown that exercise is safe and well tolerated if appropriately prescribed. During the initial stage (first 1 to 2 weeks), intensity should be kept at a low level in patients with NYHA functional Class III (50% of peak VO₂), and the duration should be increased from 20 to 30 minutes according to the perceived symptoms and clinical status. During the improvement stage, a gradual increase in intensity (60% of peak VO₂, then 70% to 80%, if tolerated) is the primary aim. Prolongation of exercise is a secondary goal.

References

Cardiac rehabilitation (CR) is aimed at improving physical and psychosocial functioning after a cardiovascular event, and targets the underlying disease processes to prevent further events. CR is today relevant to a more diverse patient population than previously. The epidemic of chronic disease has resulted in younger patients of all ethnicities being affected by coronary events. Advances in cardiology have also led to more patients surviving major cardiac events and living with disabilities.

Today, CR extends beyond post-infarct to revascularized patients post-coronary artery bypass graft or percutaneous coronary intervention. It also includes patients with chronic stable angina and those who have sustained repeated events resulting in myocardial dysfunction and heart failure (HF). The stepwise process of rehabilitation begins immediately after the cardiac event and continues throughout life, with different interventions introduced at appropriate stages.

Standard drug therapy for post-infarct and HF patients is usually instituted while the patient is still in hospital. Target blood pressure is 140/90 mm Hg (lower in diabetes and chronic kidney disease). HbA1C should be maintained at <7% in diabetics. Latest guidelines recommend lower lipid targets, with statins as baseline therapy.

Provided the patient is clinically stable, physical activity should begin in hospital. This prevents complications of prolonged immobilization and acts as a psychological booster. After being able to sit up, patients may walk in the corridors for 2 to 5 minutes, 4 times daily. Heart rate (HR) should not exceed 120 beats per minute, while patients with resting tachycardia should not exceed a 20-beat increase from resting HR.

A graded exercise program is implemented at Phase III, and begins with a risk assessment based on history, physical examination, and resting electrocardiogram (ECG). Exercise stress testing and ECG is required in high-risk patients for assessment of ventricular function and residual ischemia and those who wish to participate in high-intensity exercise. High-risk patients (with residual ischemia or significant left ventricular dysfunction) require constant monitoring and the presence of health care professionals trained in advanced life support. HR should not be allowed to exceed 10 beats below the rate at which ischemia was provoked on stress testing. Impaired chronotropic response (failure to reach 80% of maximum HR) is associated with increased mortality post-myocardial infarction, especially with HF, and may be improved by β-blockade and ivabradine.

The following factors preclude participation in an exercise program: (i) myocardial infarction complicated by persistent HF, cardiogenic shock, or complex ventricular arrhythmias; (ii) angina or breathlessness at low levels of exercise; (iii) ST-segment depression >1 mm on resting ECG; and (iv) marked ST-segment depression (>2 mm) or symptoms experienced at <5 metabolic equivalent tasks during exercise stress testing.

Patients should be encouraged to stop smoking at every opportunity and be educated on other risk factor targets. The basic principles of a cardioprotective diet should be adhered to. Target body mass index is 21 to 25 kg/m². Overweight patients should aim for 10% initial weight loss through exercise and diet.

Low mood, anxiety, irritability, and tearfulness are natural after a cardiac event; however, persisting symptoms may suggest clinical depression or anxiety. A truly comprehensive rehabilitation program strives to assist in reintegrating the patient into the home, family, and work environments. Patients may return to work as soon as they are physically capable. Patients may return to sexual activity 2 to 3 weeks after an uncomplicated myocardial infarction.

There is strong evidence that exercise-based rehabilitation yields a 20% reduction in total mortality and a 26% reduction in cardiac mortality, compared with usual medical care. It is an essential component of the management of all patients with cardiovascular disease and should start immediately after an event and be maintained long term.

Further reading
Being a cardiac patient with multiple issues is never easy. An acute cardiac event is always devastating and persistently debilitating, so that complete management can never be truly accomplished. Assuming that all algorithms for recognized standards of care have been implemented, improvement of the condition does not necessarily indicate better overall functionality and disposition. Thus, the evolution of cardiac rehabilitation as a discipline has come about. The benefits of cardiac rehabilitation are multifaceted; exercise rehabilitation has a positive impact on a number of factors, including improvement in a patient’s lipid profile, blood pressure reduction, and prevention or treatment of type 2 diabetes. Other potentially contributory factors to the benefits of cardiac rehabilitation and exercise training include a reduction in inflammation, as indicated by a decrease in serum C-reactive protein, possible ischemic preconditioning, improved endothelial function, and a more favorable fibrinolytic balance. Such neurochemical improvements would thus anticipate the positive clinical outcomes seen in several studies involving patients who underwent cardiac rehabilitation.

Studies involving cardiac patients, particularly those investigating changes in clinical functional parameters and quality of life measures, have indicated that cardiac rehabilitation, whether exercise-based or focused on a comprehensive risk factor prevention program (which remains a contentious issue), has significant benefits. Exercise rehabilitation, with or without risk factor education and counseling, produced greater reductions in total cholesterol, triglycerides, systolic blood pressure, and self-reported smoking than control conditions, without significant differences in low-density lipoprotein or high-density lipoprotein cholesterol levels. Quality of life improved to a similar degree with both cardiac rehabilitation and usual care, although some studies found a trend toward a superior improvement with cardiac rehabilitation.

In a study of over 500 consecutive coronary patients enrolled in a cardiac rehabilitation program, depressive symptoms were assessed by questionnaire and mortality was evaluated at a mean follow-up of 40 months. Depressed patients had a fourfold higher mortality than nondepressed patients, and depressed patients who completed rehabilitation had a 73% lower mortality rate than control patients not completing rehabilitation. Only a mild improvement in fitness level was needed to produce the benefit on depressive symptoms and the associated decrease in mortality.

As of March 2006, the US Centers for Medicare and Medicaid Services concluded that cardiac rehabilitation is reasonable and necessary after acute myocardial infarction (within the prior 12 months), coronary artery bypass graft surgery, stable angina pectoris, percutaneous coronary intervention with or without stenting, heart valve repair or replacement, and heart or heart-lung transplantation. Despite this, enrollment remains low and the discipline is underutilized. It has also been documented that earlier enrolment stands to produce a greater reduction in symptoms and better cardiovascular outcomes. As it is, with an underrated and underappreciated modality that has confirmed benefits, the dictums of “the earlier the better” and “the more the merrier” are a must.

References
The role of cardiac rehabilitation (CR) in the continuum of care in cardiovascular disease is undisputed. It is a Class I recommendation in most evidence-based guidelines, but remains underutilized. Historically, in the early 1930s, patients with acute myocardial infarction (AMI) were recommended bed rest for 6 weeks. Chair therapy was introduced in the 1940s, but by the 1950s, clinicians realized that early ambulation was not harmful and could help avoid many of the complications associated with prolonged rest, and daily walking exercises beginning 4 weeks post-AMI were advocated. Comprehensive CR programs have since come a long way, but questions remain regarding the optimum initiation time.

Previously, CR patients were post–coronary artery bypass graft (CABG) surgery, post–valvular repair/replacement surgery, or post–acute coronary syndrome (ACS), and they attended an outpatient CR program typically 4 to 6 weeks after discharge. Recently, eligibility for CR has evolved to include patients after percutaneous coronary intervention (PCI) and heart transplantation, those with pacemakers, implantable cardiac defibrillators, and ventricular assist devices, and those with peripheral arterial disease, pulmonary arterial hypertension, heart failure (HF) with preserved ejection fraction, stable angina, and compensated chronic HF with impaired ejection fraction. Patients are increasingly older with multiple comorbidities. These complexities make the decision regarding how soon to implement CR more challenging.

There is no evidence as to when exercise training (ET) should commence after ACS or PCI to derive maximal benefits. Nevertheless, many national associations have formulated their own guidelines on a consensus basis. Most CR programs delay ET until ≥4 to 6 weeks after AMI and 3 weeks post-PCI. There are suggestions that clinically stable patients after uncomplicated AMI may begin 1 week after discharge, continuing for up to 6 months to achieve maximal antiremodeling benefits. There is no evidence that this causes any harm. Trials have shown no increase in the risk of complications with earlier physical activity. No additional adverse events occurred during 6-month ET sessions initiated approximately 1 week post AMI in patients with mild to moderate left ventricular (LV) systolic dysfunction. Earlier commencement of ET markedly increases participation in secondary preventive programs. Observational studies report that CR initiation after 1 week leads to a 90% increase in participation compared with initiation at 4 weeks, with an earlier return to work.

Drug-eluting stents may require 9 to 12 months before complete vessel healing occurs, but should we delay ET in these patients? There is no evidence of an increased risk from moderate exercise, and in a recent retrospective analysis, participation in CR following PCI was associated with a decrease in all-cause mortality.

Following CABG and surgical valvular procedures, 6 weeks are usually needed for adequate healing. Light weights, breathing exercises, and walking are possible before this time. Consensus papers recommend that CR commence 2 to 4 weeks post-CABG and valvular procedures in patients with normal/ slightly reduced LV function, 4 to 6 weeks following cardiac transplantation, and 1 to 2 weeks following minimally invasive heart surgery.

Patients with stable compensated HF were shown to benefit from ET in HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of exercise training) but there was no indication as to how early or late the training started after discharge. The ongoing EJECTION-HF (Exercise Joins Education: Combined Therapy to Improve Outcomes in New-diagnosed Heart Failure) may shed light on this matter.

Many issues regarding optimal ET wait times in CR programs remain unanswered, and there is no internationally accepted policy. Many factors need to be considered, including the resources and facilities available in each country. These in turn must then be guided by emerging science and results of future studies.

References
Although the incidence and mortality rates of coronary heart disease (CHD) have been decreasing in most countries, CHD still accounts for one third of deaths globally, and in Europe, it is the most common cause of death.1

Nearly half of the decrease in CHD mortality has been attributed to treatment (including 11% attributed to secondary prevention, 13% to heart failure treatment, 8% to initial treatment of acute myocardial infarction, and 3% to hypertension treatment), and about 50% of the decline has been attributed to population-wide risk factor reduction.2

Cardiac rehabilitation (CR) aids recovery from a cardiac event and reduces the likelihood of further illness.3 CR has been defined as the “coordinated sum of interventions required to ensure the best physical, psychological and social conditions so that patients with chronic or post-acute cardiovascular disease may, by their own efforts, preserve or resume optimal functioning in society and, through improved health behaviours, slow or reverse progression of disease.”4

Core components of CR in patients post–acute coronary syndrome, used in individually tailored programs, include systematic risk factor management and clinical assessment, patient education, counseling on physical activity and exercise training, diet/nutritional counseling and weight control management, lipid management, blood pressure monitoring, smoking cessation, and management of psychosocial wellbeing.5

Despite the high number of patients suffering from a cardiovascular event and the proven beneficial effects of CR, no study has addressed the question of when exactly the optimal time to start CR is. A CR program usually has three phases: Phase I, during hospital admission; Phase II, hospital-based outpatient cardiac rehabilitation; and Phase III, the late maintenance and follow-up phase. Most studies have focused on the effect of CR in Phase II; nevertheless, Phase I is of equal importance in improving patient uptake and increasing patient adherence to CR after discharge. Starting CR during hospital admission helps to emphasize that ischemic heart disease is a chronic disease that is not only treated with acute invasive treatment. CR is considered—and recommended to be—part of the overall treatment.

In recent years, attention has increasingly focused on the fact that patients are especially vulnerable during the transitions between phases due to a lack of coordination between the different phases and the efforts of all those involved, with the risk of a loss of the health benefits achieved. This emphasizes the importance of systematic assessment of all patients to determine their CR needs. Not all patients need CR, but all patients should be offered risk stratification, optimal medication, and counseling regarding their needs and the resources available.

Almost all clinical trials of CR have exclusively enrolled low-risk, middle-aged men after myocardial infarction. The exclusion or underrepresentation of women, elderly people, and other cardiac groups (post–revascularization and angina pectoris) not only limits the applicability of the evidence to contemporary cardiovascular practice, but also fails to consider those who may benefit most from rehabilitation.

In conclusion, CR is cost effective, reduces mortality and morbidity, and should be offered to all patients following a cardiovascular event. Optimally, CR starts during hospital admission to ensure that all patients know how to manage their disease after discharge and the importance of reducing risk factors and receiving optimal medical treatment. Phase II CR focuses on risk factor intervention, exercise training, psychosocial management, and patient education. Unfortunately, very few studies have focused on Phase III, the maintenance of CR. While it is important that CR begins during Phase I, it is equally important that interventions carried out during Phase II are maintained during Phase III, in order to maintain the effects of the interventions in Phase II.

### References
Cardiovascular disorders are the leading cause of mortality and morbidity worldwide. The survivors represent an additional reservoir of cardiovascular disease morbidity. Cardiac rehabilitation (CR) programs, first developed in the 1960s, are associated with significant reduction in mortality rates in individuals with coronary artery disease. At the beginning, exercise was the primary component of these programs, and they were predominantly offered to survivors of uncomplicated myocardial infarction and initiated at a time remote from the acute event. In recent years, there has been growing evidence to support a benefit of CR for patients with chronic heart failure, peripheral artery disease, and those who have undergone cardiac surgical procedures such as valvular or coronary artery bypass surgery.

Today, CR is a multifaceted and multidisciplinary intervention that improves functional capacity, recovery, and psychological well-being. The rehabilitation team includes a physician, one or more nurses with coronary care experience, and at least one exercise physical therapist. Other complementary staff such as a dietician and psychologist may be included, whether accessed onsite or through associated private practices. Core components of CR or secondary prevention programs are baseline patient assessment, physical activity counseling and exercise training, nutritional counseling, risk factor management (lipids, hypertension, weight, diabetes, and smoking), psychosocial management, vocational counseling, and optimized medical therapy.

CR should be started soon after discharge from the acute care setting. In disabled and unstable patients, the more immediate objectives of CR services are to achieve clinical stability, limit the physiological and psychological effects of cardiac illness, improve the overall functional status, and help the patient maintain their independence with an emphasis on quality of life. In the longer term, the objectives are to reduce the risk of future cardiovascular events, delay progression of the underlying atherosclerotic process and clinical deterioration, and ultimately, reduce morbidity and mortality.

CR programs vary in length, content, and the place of delivery. Different patterns of rehabilitative care are currently delivered by specialized hospital-based teams: (i) residential CR for more complicated, disabled patients; and (ii) outpatient CR for more independent, low-risk and clinically stable patients requiring less supervision.

Residential CR programs should be followed up with a long-term outpatient risk reduction and secondary prevention program, with appropriate clinical and functional monitoring. Some patients may benefit from a home-based comprehensive CR program validated for patients after myocardial infarction that incorporates education, exercise, and stress management components, with follow-up sessions with a trained facilitator. This should be offered to patients as part of a menu-based approach, but should not be used to replace a multidisciplinary hospital-based program, particularly for patients with complex conditions that need specialist assessment. A home-based program produces similar gains to hospital programs, and has been shown to be preferred by many patients.

In conclusion, CR is a structured program of care that helps patients through lifestyle modification and appropriate use of medication. There is a large body of evidence addressing the efficacy of short- and long-term CR programs for the secondary prevention of cardiovascular events. Consequently, effort should be made to include CR in every patient’s hospital discharge prescription.

References

When should cardiac rehabilitation be started after a cardiovascular event?

Heart failure is the most common discharge diagnosis, particularly in elderly hospitalized patients. Although cardiac rehabilitation is recommended for all eligible patients with stable coronary artery disease and New York Heart Association Class I–III heart failure (no serious arrhythmias or limitations to exercise), the start of cardiac rehabilitation is often delayed while waiting for the initiation of an exercise program. Exercise is the cornerstone of cardiac rehabilitation, but cardiac rehabilitation is a multidisciplinary approach and exercise prescriptions should be combined with psychological and medical educational components. Starting exercise programs immediately after hospitalization is not possible for most patients, and rehabilitation programs should not be delayed for the exercise prescription. Although most programs are outpatient based, cardiac rehabilitation should be started as soon as possible in hospital, and exercise programs should be added within 1 to 3 months after discharge. The duration and frequency of the exercise prescription are important elements in the cardiac rehabilitation program. Exercise should be practiced for 30 minutes 3 days a week, taking into consideration the results of HF-ACTION (Heart Failure: A Controlled Trials Investigating Outcomes of Exercise training). The regular continuation of a cardiac rehabilitation program is as fundamentally important as starting the program immediately. Long-term rehabilitation programs reduce cardiovascular mortality by approximately 1.5-fold compared with short-term interventions. A clinical nurse specialist and/or physiotherapist is the most likely person to coordinate the rehabilitation program. Home-based strategies can overcome the problems related to hospital-based programs. Home-based exercise programs are as effective as hospital-based programs in improving functional capacity, left ventricular ejection fraction, quality of life, and significantly reducing depression symptoms.

Heart failure is the most likely person to coordinate the rehabilitation program. The exercise training component of cardiac rehabilitation programs produces enhanced peak VO2, oxygen utilization, and endothelial function, improvement in cardiac symptoms and mortality, and reduced sympathetic tonus and neurohumoral activity comparable to that of younger patients with heart failure. Despite the effectiveness of cardiac rehabilitation, only one in four patients is referred for cardiac rehabilitation. In Turkey, the proportion of eligible patients who attend any cardiac rehabilitation program is very low compared with other European countries; 7.3% of patients after an index event. Clinical status, as well as demographics, the presence of comorbidities, logistics, and socioeconomic status are all barriers to enrollment in cardiac rehabilitation and secondary prevention programs after hospitalization. Cardiovascular event rates and hospitalization are higher in elderly patients. However, it is notable that patients over 75 years of age, as well as female patients and patients with comorbidities, are less likely to attend to these programs. Dobson et al demonstrated that the mortality benefits for these patient populations are greater than those in a young male cohort.

References
Clinical advantage of heart rate lowering with Procoralan in the management of cardiovascular patients

By I. Elyubaeva, France

Procoralan (ivabradine) is the first selective and specific If inhibitor, and provides pure heart rate (HR) reduction without alteration to myocardial contractility, the cardiac conduction system, or coronary vascular resistance. Experimental data have demonstrated the specific nature of the HR-lowering action of Procoralan, and suggest that the mechanism by which slowing of HR is achieved may affect the extent of its benefit. Selective HR slowing with Procoralan offers additional benefits not found with other HR-slowing agents, and enables the full benefits of HR reduction to be realized for improved coronary perfusion and pump efficiency. Dual cardiac and vascular protection through prevention of endothelial dysfunction and development of atherosclerosis may contribute to the reduction in cardiac events seen in the clinical setting with Procoralan. The ability of Procoralan to positively affect angina symptoms and myocardial ischemia and to improve clinical outcomes makes it an important agent in the management of patients with CAD. Following the breakthrough results of SHIFT (Systolic Heart failure treatment with If inhibitor ivabradine Trial), Procoralan was approved for use in heart failure (HF) patients with left ventricular systolic dysfunction, representing a major step forward in the management of these patients. This approval brings the promise of a better prognosis and improved quality of life for millions of patients with chronic HF.

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Pure heart rate reduction with Procoralan: anti-ischemic effect and dual cardiac and vascular protection in CAD and HF

Procoralan (ivabradine) is a specific heart rate (HR)–lowering agent, and the first agent of its type to be approved for therapeutic use. In contrast with other HR-lowering agents such as β-blockers, Procoralan acts uniquely on the pacemaker activity of the sinoatrial node of the heart, which results in important differences between Procoralan and other HR-reducing agents. Procoralan inhibits If, an ionic current that modulates pacemaker activity, and thus lowers HR without directly affecting cardiac conduction or contractility. Myocardial perfusion, particularly in the subendocardium, takes place almost entirely during diastole. Normal physiological changes in HR mainly involve adjustments to the duration of diastole, and a lower HR leads to prolonged diastole, both in absolute terms and as a fraction of the cardiac cycle, facilitating myocardial perfusion. Procoralan, in common with physiological HR reduction, lowers HR essentially by prolonging diastole. By contrast, β-blockers, because of their negative effect on myocardial con-
tricity, tend to also prolong systole, which reduces their beneficial effect on diastolic time fraction. β-Blockers also affect vasomotion in the coronary circulation by unmasking α-adrenergic vasoconstriction, resulting in constriction of large and small coronary arteries during exercise. By contrast, Procoralan maintains the vasodilation that occurs during exercise. All of the experimental data suggest that pharmacological HR reduction with Procoralan more closely resembles physiological changes in HR than does HR reduction with β-blockade, so that physiological changes in diastolic time fraction, left ventricular (LV) relaxation and synchrony, and coronary vasomotion are not compromised. As a consequence, the full benefit of HR reduction in improving coronary perfusion and pump efficiency can be realized.

By reducing HR, Procoralan decreases myocardial oxygen consumption and increases myocardial perfusion, both of which explain its ability to preserve cardiac energy metabolism, something that is profoundly impaired during heart failure (HF). Sustained HR reduction with Procoralan has been shown to improve cardiac function by significantly decreasing LV end-systolic diameter and stroke volume. Procoralan preserves cardiac output through its ability to increase stroke volume, reduces LV collagen density, and increases LV capillary density. Similar cardiac effects were observed in rats when Procoralan was given either immediately before or after myocardial infarction (MI), highlighting both the preventive and curative benefits of Procoralan in HF. These experimental data show that long-term HR reduction with Procoralan optimizes energy consumption, reverses remodeling, and prevents disease progression in HF.

Endothelial dysfunction is a common feature of many cardiac diseases, including coronary artery disease (CAD) and congestive HF. HR lowering with Procoralan may improve endothelial function and inhibit development of atherosclerotic plaque. In dyslipidemic mice expressing human apolipoprotein B 100, 3 months of treatment with Procoralan completely prevented deterioration of endothelium-dependent vasodilation in the aorta and cerebral arteries. Despite similar HR reduction, the protective effect of Procoralan was not fully reproduced by metoprolol, possibly due to inhibition of β-adrenoceptor–mediated activation of endothelial nitric oxide synthase. In another model involving severe hypercholesterolemia in apolipoprotein E–deficient mice, Procoralan treatment improved endothelial function and reduced the atherosclerotic plaque area in the aortic root (by over 40%) and ascending aorta (by over 70%).

These experimental data emphasize the specific nature of the HR–lowering action of Procoralan, and suggest not only that HR slowing is associated with cardiovascular benefits, but also that the mechanism by which HR slowing is achieved may affect the extent of the benefit. Selective HR slowing with Procoralan offers additional advantages that enable the full benefit of HR reduction to be realized for improved coronary perfusion and pump efficiency, and which may produce greater improvements in exercise capacity than β-blockade for a given reduction in HR. Dual cardiac and vascular protection through prevention of endothelial dysfunction and development of atherosclerosis may contribute to the reduction in cardiac events seen in the clinical setting.

**Clinical benefits of pure heart rate reduction with Procoralan**

The results of clinical trials have underlined the importance of HR in the pathophysiology of CAD and HF, and they support the value of pure HR reduction for the management of patients with stable CAD and HF.

- **Clinical benefits of heart rate reduction with Procoralan in stable coronary artery disease**
- **Heart rate**

Procoralan significantly reduces HR at rest and during exercise. In the large randomized, double-blind, controlled multicenter INITIATIVE trial (International Trial on the Treatment of angina with IvabradinE versus atenolol) involving 939 patients with stable angina, Procoralan significantly reduced HR after 1 and 4 months of treatment, both at rest and at peak exer-

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cise. At rest, HR was reduced by 14.3 beats per minute (bpm) in the Procoralan 7.5 mg twice-daily group and by 15.6 bpm in the atenolol 100 mg once-daily group.

A further characteristic of the HR–lowering action of Procoralan is that its effect is largest in those patients with the highest HR before treatment. This important property is related to the use-dependence of the HR-lowering mechanism of Procoralan: the magnitude of i inhibition is directly related to the frequency with which channels are open. Inverse linear correlations between pretreatment HR and changes in HR during treatment have been observed for all dosages of Procoralan (Figure 1). This property has important clinical implications, as it results in greater efficacy in patients with higher HR at baseline and protects against excessive bradycardia.

![Figure 1. Change in heart rate with Procoralan treatment according to heart rate at baseline. Data are from a pooled analysis of patients treated with Procoralan 7.5 mg twice daily (bid; n=940). Abbreviations: bid, twice daily; bpm, beat per minute.](image)

A randomized double-blind trial involving 386 patients with stable angina treated with Procoralan twice daily for 1 year (either 5 mg or 7.5 mg) showed that HR reduction with Procoralan in patients with stable angina is maintained during long-term treatment. Both doses of Procoralan were associated with a substantial reduction in resting HR: 10 bpm with Procoralan 5 mg twice daily (from 71 to 62 bpm) and 12 bpm with Procoralan 7.5 mg twice daily (71 to 59 bpm). This reduction is consistent in magnitude with that found in earlier studies, and confirms that patients can be optimally treated with Procoralan over the long term.

◆ Anti-ischemic efficacy

HR reduction with Procoralan is associated with a substantial decrease in angina symptoms and short-acting nitrate consumption, both with short-term and long-term treatment. In a randomized double-blind study, Procoralan substantially reduced the frequency of angina attacks compared with placebo from 4.14 attacks to 0.95 attacks per week (P<0.001). Procoralan also reduced the consumption of short-acting nitrates compared with placebo, which decreased from 2.28 units per week to 0.50 units per week (P<0.001). The antianginal efficacy of Procoralan was also confirmed in INITIATIVE: at 4 months, the number of angina attacks decreased by 1.6 with Procoralan 7.5 mg twice daily and by 1.2 with atenolol 100 mg once daily.

The aforementioned long-term study with Procoralan 5 mg and 7.5 mg twice daily in patients with stable angina demonstrated the maintenance of substantial antianginal efficacy over 1 year of treatment. The mean number of angina attacks per week decreased significantly by more than 50% with both dosages of Procoralan after 12 months of treatment (P<0.001). In a study comparing the efficacy of the combination of Procoralan 7.5 mg twice daily plus bisoprolol 5 mg once daily versus full-dose bisoprolol (10 mg once daily) in patients with stable angina and LV systolic dysfunction, 2 months of treatment with Procoralan substantially reduced the mean weekly number of angina attacks compared with bisoprolol alone (from 3.3 to 1.7 compared with 3.2 to 2.5; P<0.041). As a result, there were more patients with Canadian Cardiovascular Society (CCS) Class I stable angina in the Procoralan group than in the group receiving bisoprolol alone (82% versus 67%, respectively; P=0.037).

REDUCTION (Reduction of ischemic Events by reDUCtion of heartT rate In the treatment Of stable aNgina with ivabradine) confirmed the antianginal efficacy of Procoralan in routine clinical practice in 4954 patients with stable angina. After 4 months of treatment with Procoralan, angina attacks were reduced from 2.4 to 0.4 per week (P<0.0001). Consumption of short-acting nitrates was reduced from 3.3 to 0.6 units per week (P<0.0001). In the recent non-interventional, multicenter, prospective trial ADDITIONS (prActical Daily efficacY anD safety of Procoralan In combinaTION with beta-blockerS), which involved the treatment of 2330 patients with stable angina in routine clinical practice with Procoralan added to β-blockers, the addition of Procoralan resulted in a significant reduction in angina attacks and short-acting nitrate consumption (from 1.7 to 0.3 and from 2.3 to 0.4 units per week, respectively).

◆ Anti-ischemic efficacy and improvement of exercise capacity

HR is a major determinant of myocardial oxygen consumption and thus resting myocardial blood flow and coronary flow reserve (CFR). Autoregulation of coronary vessels maintains a marginal balance of oxygen supply and demand under physiological conditions. The coronary circulation is particularly sensitive to increased HR, particularly if endothelial dysfunction, atherosclerosis, or hypertensive wall thickening impair auto-
regulation. The effect of Procoralan on coronary blood flow velocity and CFR was assessed in a study involving 21 patients with stable CAD, in whom coronary blood flow was assessed invasively using intracoronary Doppler measurements. After 2 weeks of treatment with Procoralan, HR was found to be significantly lower (reduced by 13 bpm; \( P<0.001 \)). Treatment with Procoralan significantly improves hyperemic coronary flow velocity and CFR in patients with stable CAD (Figure 2). These data have important clinical implications, not only regarding the anti-ischemic effect of Procoralan, but also regarding the impact of Procoralan on ischemic events, as CFR predicts adverse cardiovascular long-term outcomes. Procoralan showed significant anti-ischemic efficacy compared with placebo in a randomized double-blind study. The time to 1-mm ST-segment depression improved by more than 1 minute compared with placebo \( (P<0.001) \). The anti-ischemic effect of Procoralan was also demonstrated using the treadmill stress test in INITIATIVE, where it produced an increase of approximately 1.5 minutes. The group receiving Procoralan 7.5 mg twice daily also showed an increase in total exercise duration of 86.8 seconds at trough of drug activity; this was compared with 78.8 seconds in the atenolol 100 mg once-daily group. Noninferiority with atenolol was demonstrated for all exercise tolerance test parameters \( (P<0.001) \).

The addition of Procoralan to bisoprolol in the treatment of patients with stable angina and LV systolic dysfunction resulted in an improvement in exercise capacity: workload increased from 5.9 ± 1.6 to 7.0 ± 1.4 metabolic equivalents \( (P=0.004) \) compared with bisoprolol alone \( (5.7 ± 1.4 \text{ to } 6.2 ± 1.4 \text{ metabolic equivalents, } P=0.141) \).

**Improvement of quality of life**

Poor quality of life (QOL) is a major issue for angina patients. Improvement of QOL is therefore an important goal and measure of therapeutic success in the management of angina. Few studies, however, have reported the effects of antianginal therapy on QOL, and those results that have been reported have been inconsistent. In ADDITIONS, the effect of Procoralan on QOL was assessed using the EQ-5D questionnaire. After 4 months of therapy with Procoralan, the proportion of patients at CCS Class I had more than doubled, and Procoralan significantly improved QOL (EQ-5D index as well as Visual Analogue Scale score). This improvement in QOL was consistent with the substantial reduction in the number of angina attacks and consumption of short-acting nitrates. Procoralan is thus an important treatment option for patients with stable angina for improvement of both symptoms and QOL.

**Prevention of coronary events in patients with stable CAD and LV systolic dysfunction with elevated heart rate**

Reduction of elevated HR in patients with stable CAD could be a potential approach to lowering the risk of cardiovascular events. Epidemiological studies and retrospective clinical analysis have shown that a high HR is an independent predictor of cardiovascular events in coronary patients. BEAUTIFUL (morBidity-mortality EvAlUaTion of the \( \beta \)-inhibitor Procoralan in patients with coronary disease and left ventricular dysfunction) was the first randomized controlled trial designed to assess the effect of pure HR reduction with Procoralan on cardiovascular events in patients with documented CAD and associated cardiovascular events. BEAUTIFUL was also the first clinical trial to prospectively determine that patients with elevated HR have a higher risk of cardiovascular events. In BEAUTIFUL, Procoralan significantly reduced all coronary end points in patients with an elevated resting HR \( \geq 70 \text{ bpm (n=5392): Procoralan significantly reduced admission to hospital for MI (relative risk reduction [RRR], 36%; } \text{ } P=0.001 \text{ (Figure 3, page 444), admission to hospital for MI or unstable angina (RRR, 22%; } P=0.023 \text{), and coronary revascularization (RRR, 30%; } P=0.016 \text{). These results were achieved in patients already receiving optimal treatment for CAD (87% of patients were taking } \beta \text{-blockers, 90% were taking renin-angiotensin-aldosterone system inhibitors, 94% were taking antithrombotics, and 74% were on statins). In patients whose limiting symptom at baseline was angina (n=1507), Procoralan reduced the composite end point of cardiovascular mortality or hospitalization for fatal and nonfatal MI or HF by 24% \( (P=0.05) \). Treatment with Procoralan resulted in a 42% reduction in the risk of hospitalization for fatal and nonfatal MI in all patients with limiting angina, and a 73% reduction in those with a resting HR of 70 bpm or higher.

Another major ongoing trial is evaluating the efficacy of Procoralan in patients with preserved LV function. SIGNIFY (Study assessInG the morbidity–mortality beNefits of the \( \beta \)-inhibitor ivabradine in patients with coronary artery disease) includes stable CAD patients with an ejection fraction of above 40%, a HR of 70 bpm or higher, and no clinical signs of HF. After a run-in period of 2 to 4 weeks, patients are randomized to placebo twice daily or Procoralan with a starting dose of 7.5...
mg twice daily, which is adjusted at every visit to a target HR of 55 to 60 bpm. Over 19,000 patients have been enrolled in the study, which is expected to end in 2014.

- **Clinical benefits of heart rate reduction with Procoralan in heart failure**
  - **Improvement of major outcomes**

Given the prognostic implications of HR in patients with HF, the ability of Procoralan to decrease HR without impairing key cardiovascular or hemodynamic parameters such as myocardial contractility and ventricular relaxation makes it a particularly pertinent treatment in HF.\(^{25}\) The ability of Procoralan to improve prognosis in HF was successfully tested in the SHIFT trial (Systolic Heart failure treatment with \(i_1\) inhibitor ivabradine Trial). This randomized placebo-controlled clinical trial evaluated the effects of Procoralan on morbidity and mortality in 6558 patients with moderate to severe chronic HF and LV systolic dysfunction (LV ejection fraction of ≤35%) and a resting HR of ≥70 bpm. Procoralan was taken on top of guideline-recommended therapies, and the median follow-up was 22.9 months.\(^{26}\) After 28 days, Procoralan reduced HR by 15.4 bpm (10.9 bpm, placebo-corrected). The primary composite end point (cardiovascular death or hospital admission for worsening HF) was significantly reduced by 18% \((P<0.0001)\). Procoralan significantly reduced HF death (RRR, 26%; \(P=0.014\)) and hospitalization for HF (RRR, 26%; \(P<0.0001\)) (Figure 4).

**Figure 3.** Kaplan-Meier time-to-event plots by treatment group (Procoralan or placebo) in the BEAUTIFUL trial in patients with stable coronary artery disease and left ventricular systolic dysfunction with an elevated resting heart rate (≥70 bpm).


**Figure 4.** Kaplan-Meier cumulative event curves for different end points in the Systolic Heart failure treatment with \(i_1\) inhibitor ivabradine Trial (SHIFT) in the Procoralan and placebo arms.

**Abbreviations:** CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio.

Results were consistent across all subgroups. On the strength of the absolute risk reduction on the primary end point, 26 patients would need to be treated for 1 year to prevent one cardiovascular death or HF-related hospital admission. Cardiovascular death and all-cause death diminished by 9% and 10%, respectively, and in patients with a HR of ≥75 bpm, there was a statistically significant 17% reduction in all-cause mortality (P=0.0109) and 17% reduction in cardiovascular mortality (P=0.0166) (Figure 5). Procoralan reduced the total burden of HF hospitalizations reducing the total number of hospitalizations by 25% (P=0.0002). During the almost 2 years of follow-up, Procoralan reduced the rates for both second and third hospitalizations for worsening heart failure by 34%; (P<0.001) and 29% (P=0.012), respectively.

These results are important for clinical practice as readmissions are not only distressing for patients and their families, but they are also associated with poor prognosis and are the major driver of the economic burden of heart failure (Figure 6). The results of SHIFT clearly demonstrate that Procoralan brings major prognostic benefits to patients with HF when taken on top of the best possible recommended therapy.

**Improvement of symptoms and quality of life**

In addition to improvement of outcomes, improvement of symptoms and well-being are also important targets for therapy in HF. In SHIFT, the New York Heart Association (NYHA) class was significantly improved in those patients receiving Procoralan (29.0% versus 24.2% in the placebo group, P=0.0156), as was the patient-reported global assessment score (65.9% versus 61.3% in the placebo group, P=0.0345) in the overall SHIFT population. Furthermore, a substudy of SHIFT in 1944 patients demonstrated that in parallel to the improved outcomes in SHIFT, Procoralan improved health-related QOL in patients with HF, as assessed by the specific Kansas City Cardiomyopathy Questionnaire (KCCQ). Treatment with Procoralan significantly improved both the overall summary score and the clinical summary score on the KCCQ. At 12 months, the overall summary score, which includes physical limitations, total symptoms, QOL, and social limitation scores, was improved by 6.7 points with Procoralan compared with 4.3 points with placebo (P<0.001) (Figure 7, page 446). After 12 months, the clinical summary score, which includes physical limitations and the total symptom domain scores, was improved by 5.0 points with Procoralan compared with 3.3 points with placebo (P=0.018). Qualitatively, similar benefits were found with Procoralan compared with placebo at 4 months, and these were maintained throughout the study follow-up period. These data demonstrate that the reduction in HF severity produced by Procoralan, as reflected by reduced hospital admissions and im-
Procoralan is able to reverse remodeling. An echocardiography substudy carried out in 611 patients from SHIFT showed a 7.9 mL/m² reduction in LV end-systolic volume index, as compared with 0.9 mL/m² in the placebo group (Figure 8). LV end-diastolic volume index was also reduced by 7.9 mL/m² as compared with 1.8 mL/m² in the placebo group; LV ejec-
tion fraction was improved by 2.4%, whereas there was no change in the placebo group at all. Moreover, these results occurred despite treatment with β-blockers and renin-angio-
tensin-aldosterone system antagonists, each of which was used in more than 90% of patients. Reversal of LV remodeling has important clinical implications in itself, since cardiac remodeling is a central feature of the progression of HF and is an established prognostic factor in patients with HF. The benef-
ficial impact of Procoralan on LV remodeling and function may contribute to the reduction in cardiac morbidity and mor-
tality found with Procoralan in patients with HF.

**Good tolerability profile and easy use in practice**

Throughout its entire clinical development program, Proco-
ralan has demonstrated a good safety profile consistent with its highly specific and selective mode of action on the I<sub>c</sub> current. Procoralan preserves the main electrophysiological pa-
rameters of the heart, including the refractory period of the atrium, the atrioventricular conduction time, and the dura-
tion of repolarization. The absence of any changes in the cor-
corrected QT interval throughout the clinical trial follow-up pe-
riods provides strong evidence of a lack of any significant direct
effect of Procoralan on the duration of ventricular repolariza-
tion, indicating an absence of proarrhythmic action. In some
patients, Procoralan can induce visual symptoms, mainly phos-
phores; this is related to inhibition of the I<sub>c</sub> current in retinal hyperpolarization-activated cyclic nucleotide-gated channels. These symptoms are generally mild and well tolerated, resolving spontaneously during or after treatment, and have led to withdrawal in less than 1% of patients, without safety concerns. Bradycardia was reported in 2.2% of angina patients treat-

The recent randomized open blinded end point trial, CAR-
VIVA HF (effect of CARVedilol, IVAbradine or their combination
on exercise capacity in patients with Heart Failure), assessed the effect of HR reduction with carvedilol (25 mg twice daily),
Procoralan (7.5 mg twice daily), and their combination (12.5/
7.5 mg twice daily) on exercise capacity and QOL in 121 HF
patients receiving the maximal dose of angiotensin-conver-
ting enzyme inhibitor. After 3 months of therapy, the NYHA class improved significantly more in patients receiving Proco-
ralan or combination therapy than in those allocated to car-
vedilol alone. Procoralan alone or in combination was also more effective in improving exercise capacity and QOL com-
pared with carvedilol alone.

**Reversal of ventricular remodeling**

Aside from the clinical standpoint, the results of SHIFT have important pathophysiological implications in that they demon-
strate that Procoralan is able to reverse remodeling. An echo-
cardiography substudy carried out in 611 patients from SHIFT found that 8 months of therapy with Procoralan produced a 7 mL/m² reduction in LV end-systolic volume index, as compared with 0.9 mL/m² in the placebo group (Figure 8). LV end-diastolic volume index was also reduced by 7.9 mL/m² as compared with 1.8 mL/m² in the placebo group; LV ejec-

![Figure 7. Change at 12 months in the Kansas City Cardiomyopathy Questionnaire overall summary score for the Procoralan and placebo groups of the SHIFT trial.](image-url)

**Figure 7.** Change at 12 months in the Kansas City Cardiomyopathy Questionnaire overall summary score for the Procoralan and placebo groups of the SHIFT trial. 

**Figure 8.** Change from baseline to 8 months in left ventricular end-diastolic volume index (LVEDVI) in the echocardiography substudy of SHIFT.

**Values in parentheses are standard deviations**
ed with Procoralan 7.5 mg twice daily, compared with 4.4% of angina patients treated with atenolol 100 mg once daily.

In HF patients receiving Procoralan in SHIFT, bradycardia led to permanent withdrawal from the study in only 1% of patients. This low percentage is explained by a clear plateau in the dose-response curve of heart rate reduction in patients with the highest pretreatment heart rate. Achievement of the target dose of Procoralan is simple, with uptitration from 5 mg (starting dose) through to 7.5 mg twice daily if HR remains above 60 bpm. This simplifies the management of angina or HF patients compared with other treatments. Importantly, the abrupt discontinuation of Procoralan does not result in a rebound phenomenon. The absence of rebound tachycardia with Procoralan not only simplifies the management of antianginal treatment, but also reduces the risk of adverse effects following missed doses or unscheduled gaps in medication administration. These characteristics of the HR-lowering action of Procoralan make it suitable and simple to use in most symptomatic patients with CAD or HF.

Conclusion
The pharmacological and clinical properties of Procoralan make it an important agent in the management of patients with stable CAD due to its ability to positively affect angina symptoms and myocardial ischemia and improve clinical outcomes. Following the breakthrough results of SHIFT, Procoralan was approved for use in HF patients, which represents a major step forward in the management of these patients. This approval brings promise of a better prognosis and improved QoL for millions of patients with chronic HF.

References
Procoralan (ivabradine) est le premier inhibiteur sélectif et spécifique du courant I_{f}, réduisant uniquement la fréquence cardiaque (FC) sans altérer la contractilité myocardique, la conduction cardiaque ou la résistance vasculaire coronaire. Des données expérimentales ont démontré la nature spécifique du mode d’action de Procoralan, qui abaisse la FC, et suggèrent que le mécanisme par lequel la FC est ralentie influe sur une grande partie de ses bénéfices. Le ralentissement sélectif de la FC avec Procoralan présente des avantages supplémentaires, inexistants avec d’autres médicaments abaissant la FC, ainsi que tous ceux permettant d’améliorer la perfusion coronaire et l’efficacité de la pompe cardiaque. La double protection cardiaque et vasculaire, grâce à la prévention de la dysfonction endothéliale et de l’athérosclérose, peut contribuer à la réduction des événements cardiaques observés en clinique avec Procoralan. Procoralan, en agissant positivement sur les symptômes angoreux et l’ischémie myocardique et en améliorant l’évolution clinique, occupe une place importante dans la prise en charge des patients coronariens. Après les résultats décisifs de l’étude SHIFT (Systolic Heart failure treatment with I_{f} inhibitor ivabradine Trial), Procoralan a obtenu l’indication chez les insuffisants cardiaques (IC) présentant une dysfonction systolique ventriculaire gauche, ce qui représente une étape majeure dans la prise en charge de ces patients. Cette autorisation apporte aux millions de patients IC chroniques la promesse d’un meilleur pronostic et d’une meilleure qualité de vie.

**Keywords:** coronary artery disease; heart failure, heart rate reduction; I_{f} current; ivabradine; Procoralan; sinus node; stable angina
Patients with stable coronary artery disease (CAD) have high event rates despite modern treatments. Large studies with long-term follow-up have shown that elevated heart rate (HR) is an independent predictor of all-cause and cardiovascular mortality in patients with cardiovascular disease, including CAD patients. A high resting HR is a potentially modifiable cardiovascular risk factor. Thus, lowering HR could reduce mortality and cardiovascular events in patients with cardiovascular disease. The data from the BEAUTIFUL trial (morBidity-mortality EvAluaTion of the I_inhibitor ivabradine in patients with coronary disease and left ventricU Lardysfunction) indicated that ivabradine prevents coronary outcomes in patients with stable CAD and left ventricular dysfunction who have a HR of ≥70 beats per minute (bpm). The aim of the ongoing SIGNIFY trial (Study assessInG the morbidity-mortality beNefits of the I_inhibitor ivabradine in patients with coronarY artery disease) is to test the hypothesis that HR reduction with ivabradine could improve cardiovascular outcomes in patients with CAD and preserved left ventricular systolic function. This trial is a randomized, double-blind, placebo-controlled, multicenter study designed to assess the superiority of ivabradine vs placebo on cardiovascular mortality or nonfatal myocardial infarction (composite primary end point) in patients with stable CAD without clinical heart failure who are receiving appropriate cardiovascular treatment for their disease. It includes patients aged 55 years or older with stable CAD without clinical heart failure who are receiving appropriate cardiovascular treatment for their disease. It includes patients aged 55 years or older with stable CAD without clinical heart failure who are receiving appropriate cardiovascular treatment for their disease. If the results of the SIGNIFY trial show that ivabradine treatment reduces cardiovascular morbidity in this population, it will constitute a breakthrough in the treatment of patients with stable CAD.

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Heart rate reduction in coronary artery disease management: what can we expect from the SIGNIFY trial?
Heart rate reduction in coronary artery disease management: what to expect from SIGNIFY – Fox

Introduction

Heart rate reduction is a well-recognized strategy for ischemia prevention in patients with CAD. HR reduction decreases myocardial work and myocardial oxygen consumption, and increases diastolic filling time and myocardial oxygen supply, thereby minimizing the pathophysiological substrate of angina. It is the primary mechanism of the anti-ischemic effects of agents that reduce HR nonselectively—like β-blockers—or selectively—like ivabradine.

Although HR slowing during exercise is important in the prevention of angina pectoris, even a reduction in resting HR may have an impact on long-term outcomes. Experimental and clinical findings suggest that an elevated resting HR predisposes to the development of atherosclerosis and plaque rupture, which can trigger the acute coronary events that are linked to mortality in patients with CAD. Furthermore, a meta-regression of randomized clinical trials with β-blockers and calcium channel blockers in post-MI patients strongly suggests that resting HR reduction could be a major determinant of the clinical benefit seen in these trials. In addition, the investigators of BEAUTIFUL (morBidity-mortality EvaAllUAtion of the I, inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) have also made a substantial contribution to the understanding of the importance of HR reduction for the prevention of coronary events. BEAUTIFUL was the first study to prospectively evaluate the impact of an elevated resting HR on outcomes in patients with stable CAD and left ventricular systolic dysfunction (LVSD). The prospective analysis of the data from the placebo arm demonstrated that elevated resting HR (≥70 beats per minute [bpm]) is a strong independent predictor of clinical outcomes. The BEAUTIFUL study also showed that in patients with HR ≥70 bpm, HR reduction with ivabradine significantly reduces coronary events. Given the important role of HR in the pathophysiology of CAD, it seems clear that HR reduction should be considered as a key therapeutic goal in patients with CAD.

What heart rate should be targeted in this population?

In keeping with the important role of elevated HR in the pathophysiology of myocardial ischemia, it is recommended to reduce resting HR to 55-60 bpm in stable coronary patients as well as in acute coronary settings. Thus, the current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of chronic stable angina stipulate that β-blocker dosages should be ad-

What is the importance of heart rate control in the treatment of coronary artery disease?

HR reduction is a well-recognized strategy for ischemia prevention in patients with CAD. HR reduction decreases myocardial work and myocardial oxygen consumption, and increases diastolic filling time and myocardial oxygen supply, thereby minimizing the pathophysiological substrate of angina. It is the primary mechanism of the anti-ischemic effects of agents that reduce HR nonselectively—like β-blockers—or selectively—like ivabradine.

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justed to reduce resting HR to 55-60 bpm, or to <50 bpm in patients with severe angina. In the management of unstable angina and non-ST-segment-elevation MI, the ACC/AHA and European Society of Cardiology (ESC) guidelines agree that when β-blockers are used as an initial intervention, a target resting HR of 50-60 bpm is appropriate. A new analysis of the TNT trial (Treating to New Targets) in 9632 patients with established CAD evaluated the optimal HR level in relation to the risk of cardiovascular events. In patients with CAD, the relationship between HR and outcomes follows a J-curve pattern. This analysis identified a nadir of 52.4 bpm, which was associated with the lowest event rate for the primary end point of death from CAD, nonfatal MI, resuscitated cardiac arrests, and fatal or nonfatal stroke. There was no target-organ heterogeneity and the nadir was similar for all outcomes, indicating that a target range of 50-59 bpm is optimal for best prognosis in patients with CAD.

The existing evidence suggests that a HR of 55-60 bpm may be considered as optimal for both ischemia prevention and—perhaps—the prevention of cardiovascular events.

**In daily practice, is heart rate controlled in coronary patients?**

Despite a large body of evidence indicating the importance of HR control, survey data have revealed that in a majority of patients, HR is not optimal. For example, in the European Heart Survey of patients with stable angina, the mean resting HR was 73 bpm, suggesting that a majority of patients had a HR above the recommended level of 55-60 bpm. The baseline data from the CLARIFY registry (prospective observational Longitudinal Registry of patients with stable coronary artery disease), which includes 33,177 contemporary outpatients with stable CAD, confirms the previous observations that HR is not well controlled among stable outpatients with CAD and that many coronary patients are still symptomatic. The mean pulse HR was 68.3 bpm, and 22% of coronary patients had angina symptoms. These findings suggest that there is room for improving HR control in CAD.

**What is the SIGNIFY trial?**

SIGNIFY (Study assessing the morbidity-mortality benefits of the I\(_i\) inhibitor ivabradine in patients with coronary artery disease) is an ongoing randomized, double-blind, placebo-controlled, multicenter study assessing the effect of ivabradine in patients with CAD without clinical heart failure (HF).

**What is the goal of the SIGNIFY trial?**

The SIGNIFY trial was designed to determine if lowering resting HR with ivabradine would reduce cardiovascular mortality or nonfatal MI (composite end point) in patients with stable CAD without clinical HF who are receiving appropriate cardiovascular treatment for their disease. The secondary objectives of the trial include assessment of the effect of ivabradine compared with placebo on all-cause mortality, cardiovascular mortality, nonfatal MI, coronary revascularization, and new-onset or worsening HF, as well as some composite coronary end points. In addition, the effect of ivabradine on quality of life and angina symptoms will be assessed in patients presenting with angina symptoms at baseline.

**Why was ivabradine chosen for the treatment of these patients?**

Ivabradine is a HR-lowering agent that selectively reduces HR by inhibiting the sinoatrial pacemaker I\(_i\) current and thereby decreases HR without having any effect on other cardiac functions. Existing evidence on the prevention of myocardial ischemia and coronary- and HF-related events make it an important agent in the management of patients with CAD as well as HF. Ivabradine has been proven to prevent myocardial ischemia effectively and to reduce symptoms in patients with chronic stable angina pectoris. In head-to-head comparisons, its effectiveness on exercise-induced ischemia is comparable with established drugs such as β-blockers or calcium channel blockers. The ASSOCIATE trial (evaluation of the Antianginal efficacy and Safety of the ASSociation Of the \(I_i\) Current Inhibitor ivAbradine with a beTa-blockEr) showed that, when added to chronic treatment with β-blockers, ivabradine further reduces HR and improves exercise capacity while being well tolerated. The BEAUTIFUL trial shed new light on the role of HR control in cardiovascular disease and showed that ivabradine prevents coronary outcomes in patients with stable CAD and LVSD with HR >70 bpm. Moreover, in 1500 BEAUTIFUL patients with angina as a limiting symptom at baseline, ivabradine not only provided significant benefit in the primary outcome as well as in secondary outcomes, but this benefit was also evident throughout the whole HR spectrum. The recent results from the SHIFT trial (Systolic Heart failure treatment with the \(I_i\) Inhibitor ivAbradine Trial), which showed significant, substantial reductions in CV death or HF hospitalization as well as in HF deaths in patients with chronic CHF, have significantly extended the range of the clinical benefits of ivabradine to patients with HF. Thus, by assessing the effect of ivabradine on cardiovascular outcomes in patients with stable CAD without clinical HF, SIGNIFY is a logical extension of the clinical program of ivabradine in CAD.

**What is the design of the study?**

SIGNIFY is a randomized, double-blind, placebo-controlled, multicenter trial in patients with stable CAD without clinical HF, with two parallel and balanced treatment arms. It is designed to demonstrate the superiority of ivabradine over placebo in the reduction of cardiovascular mortality or nonfatal MI (composite end point).
Following a run-in period of 14 to 30 days, patients will be randomly assigned to the active double-blind treatment period (ivabradine versus placebo). The study has enrolled over 19,000 patients, with a minimal follow-up of at least 18 months. In keeping with current recommendations, the target HR range is 55-60 bpm. Since the patients included in this trial are clinically stable patients with elevated HR (≥70 bpm), the starting dose of ivabradine is 7.5 mg twice daily, with a possible increase to 10 mg twice daily after 1 month (according to HR and the presence or absence of signs and symptoms indicative of bradycardia). Although a twice-daily dose of 7.5 mg is the current recommended dose for ivabradine after up-titration, the range of ivabradine doses selected for this study has been chosen based on the doses used in the patients with CAD and stable angina who were involved in the development program of ivabradine.

What patient population is included in the study?

The inclusion and exclusion criteria were designed to select a group of patients aged ≥55 years, with stable CAD and without clinical HF (ejection fraction ≥41%), in sinus rhythm, with resting HR ≥70 bpm, and receiving appropriate medication to treat their cardiovascular conditions. Patients should have additional risk factors, which may be either at least one risk factor such as angina symptoms (Canadian Cardiovascular Society class II or higher), objective evidence of myocardial ischemia induced by stress testing within the previous 12 months, and recent hospitalization for major coronary event (acute MI or unstable angina) within the previous 12 months; or at least two of the following risk factors: low HDL cholesterol and/or high LDL cholesterol, treated diabetes mellitus, presence of peripheral artery disease, current smoking, and age >70 years.

What is the importance of the expected results in clinical practice?

Patients with stable CAD have high event rates despite modern treatments. Large studies with long-term follow-up have shown that elevated HR is an independent predictor of all-cause and cardiovascular mortality in patients with cardiovascular disease including CAD patients. A high resting HR is a potentially modifiable cardiovascular risk factor and therefore HR lowering could reduce mortality and cardiovascular events in patients with cardiovascular disease. The aim of the SIGNIFY study is to increase the evidence on the prognostic benefits of HR reduction with ivabradine in a population of patients with CAD and preserved LV systolic function. The BEAUTIFUL trial demonstrated that ivabradine improves coronary events in patients with stable CAD and LVSD with HR ≥70 bpm.6 Other antianginal strategies have either never been tested or failed to demonstrate benefits on cardiovascular events in stable CAD patients. The well-known benefits of β-blockade in terms of reduction of mortality are limited to post-MI and HF. Moreover, the post-MI trials with β-blockers were performed without the extensive use of angiotensin-converting enzyme inhibitors and statins, which leaves uncertainty regarding their efficacy on top of modern management strategies. Calcium channel blockade failed to reduce cardiovascular mortality and morbidity in the CAMELOT (Comparison of AMLodipine vs Enalapril to Limit Occurrences of Thrombosis) and ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system) trials.14,15 In the IONA trial (Impact Of Nicorandil in Angina), treatment with nicorandil resulted in a lower event rate for the composite end point, which included refractory angina. This trial was not powered to show a benefit on major cardiovascular events, such as CAD mortality and nonfatal MI, or all-cause mortality. Therefore, it is not possible to draw conclusions regarding these end points.16

So, if the results of the SIGNIFY trial show that ivabradine treatment reduces cardiovascular morbidity and mortality in patients with stable CAD and preserved LV function, it will constitute a breakthrough in the treatment strategies for patients with stable CAD, allowing us to reach the two main goals of treatment in patients with stable CAD: to prevent cardiovascular events, and to reduce symptoms and improve quality of life.

What kind of patients will benefit from the new approach?

The results of the SIGNIFY trial will be important for the large spectrum of patients with stable CAD. In future years, as the general population continues to age, the number of patients with stable CAD is expected to increase. According to global and regional projections of mortality and disease burden, CAD will remain the leading cause of death for the next 20 years. Moreover, a recently published estimation indicates a significant growth in the projected crude prevalence of cardiovascular disease—including CAD—in the next 2 decades.17 In the USA, these increases will translate into an additional 8 million people with CAD in 2030, relative to 2010. Despite all the advances in modern treatments, patients with stable CAD have high event rates. HR reduction is a modifiable risk factor that provides an important therapeutic opportunity to improve prognosis in coronary patients.

However, despite the recommendation to reduce HR to 55-60 bpm, resting HR remains uncontrolled in a significant proportion of patients in clinical practice. Many surveys conducted in coronary patients have revealed low rates of HR control.

As mentioned previously, the results of the European Heart Survey of patients with stable angina suggest that a majority of patients have a HR >70 bpm. Therefore, the data from SIGNIFY will provide a great therapeutic opportunity for the large population of patients with stable CAD.
Le taux d’événements (cardiaques) des patients coronariens stables est élevé malgré les traitements modernes. De grandes études au suivi à long terme ont montré qu’une fréquence cardiaque (FC) élevée est un facteur prédic-tif indépendant de mortalité toutes causes et cardiovasculaire chez les patients atteints de maladie cardiovascu-laire, y compris les patients coronariens. Une FC de repos élevée est un facteur de risque cardiovasculaire potentiel-lement modifiable. Abaisser la FC pourrait ainsi diminuer la mortalité et les événements cardiovasculaires chez les patients ayant une maladie cardiovasculaire. Les données de l’étude BEAUTIFUL (morBidity-mortality EvAluAtion of the I\(_f\) inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) ont montré que l’iva-bradine prévient les événements coronaires chez les patients coronariens stables ayant une dysfonction ventriculaire gauche dont la FC est ≥ 70 battements par minute (bpm). Le but de l’étude SIGNIFY en cours (Study assessing the morbidity-mortality bNeFits of the I\(_f\) inhibitor ivabradine in patients with coronary artery disease) est d’analyser l’hypothèse que la réduction de la FC due à l’ivabradine peut améliorer les événements cardiovasculaires des patients coronariens dont la fonction systolique ventriculaire gauche est préservée. Cette étude est randomisée, en double aveugle, contrôlée contre placebo, multicentrique, conçue pour évaluer la supériorité de l’ivabradine vs placebo sur la mortalité cardiovasculaire ou sur l’infarctus du myocarde non fatal (critère primaire composite) chez des patients coronariens stables sans insuffisance cardiace clinique qui reçoivent un traitement cardiovasculaire adapté à leur maladie. Des patients âgés de 55 ans ou plus, coronariens stables, sans insuffisance cardiaque clinique (fraction d’éjection > 41 %), en rythme sinusal, et dont la FC au repos est ≥ 70 bpm, ont été inclus. Si les résultats de l’étude SIGNIFY montrent que le traitement par ivabradine diminue la morbidité cardiovasculaire dans cette population, cela constituera un pas décisif dans le traitement des patients coronariens stables.
Heart rate in registries: an important, yet still neglected opportunity

by P. G. Steg, France

Registries are the key to understanding the characteristics, management, and outcomes of patients with coronary artery disease (CAD), particularly since information gathered from randomized clinical trials often has limited external validity given the stringent selection criteria used to select trial participants. Resting heart rate is emerging as a key prognostic determinant of outcomes, particularly cardiovascular mortality in patients with stable and unstable forms of CAD and heart failure. Yet, while heart rate is the most commonly measured physiological parameter, surprisingly little information has been gathered regarding actual heart rate in patients with CAD and its relation to the use of heart rate–lowering medications (particularly β-blockers) and subsequent outcomes. In recent years, many registries from various countries in Europe and elsewhere have gathered information on the characteristics of patients with CAD. They have consistently found that although the majority of patients receive β-blockers, resting heart rate is very frequently above 70 bpm. In addition, they have showed that elevated resting heart rate is associated with a greater prevalence of anginal symptoms and, more importantly, with increased cardiovascular mortality. In patients with acute coronary syndromes, however, very low heart rates were also associated with increased mortality, suggesting that the relationship between heart rate and survival in CAD may follow a “J curve.” The large international CLARIFY registry (Prospective observational Longitudinal Registry of patients with stable coronary artery disease), which has enrolled more than 33 000 patients worldwide, will provide robust information about resting heart rate in relation to anginal symptoms, the use of heart rate–lowering agents—particularly β-blockers—and, most importantly, clinical outcomes up to 5 years.

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The importance of registries in understanding the epidemiology of cardiovascular disease

Cardiovascular medicine has made major strides in the past 30 years, with substantial progress in the diagnosis, evaluation, management, and prevention of cardiovascular disease. In fact, progress in the field of cardiovascular disease accounts for most of the increase in life expectancy witnessed in the Western world between 1970 and 2000. Advances have largely stemmed from evidence accumulated via large randomized clinical trials (RCTs) testing new interventions, devices, and drugs. While randomized clinical trials provide the highest level of evidence regarding the value of interventions, they have some important shortcomings.
First, they tend to recruit highly selected patient populations who are more compliant with medical care and therapies than the average patient encountered in routine clinical practice. Additionally, because of the often stringent inclusion and exclusion criteria, patients enrolled in RCTs tend to be healthier and suffer from fewer comorbidities than patients encountered in routine care. It is therefore important to complement the information gathered from randomized clinical trials with additional information, more representative of routine clinical practice and collected via observational registries. Registries have important additional advantages over RCTs: they are much cheaper and thus can be conducted on a very large scale. They do not require the same level of training or infrastructures as RCTs and can enroll patients from all types of hospitals (not necessarily academic or tertiary institutions), from both hospital and outpatient settings, and can gather data from broad geographic sources. They can collect comprehensive information regarding the clinical characteristics of patients, their management, and their outcomes, and they tend to have greater external validity than RCTs. External validity is critical to the interpretation and application of evidence-based medicine: there is ample evidence that patients enrolled in clinical trials tend to have better clinical outcomes than patients in routine practice. Yet, we tend to extend the results of RCTs to patients from routine clinical practice who have characteristics similar to those of the participants in RCTs. There have been demonstrations, for example in ST-segment elevation myocardial infarction (STEMI), that even “trial-eligible patients” from registries actually experience much worse outcomes than actual trial participants.

Information on patients with coronary artery disease is limited

Despite a steady decline in the Western world over the past 30 years, coronary artery disease (CAD) is still the first cause of death worldwide and is expected to remain so due to an epidemic of coronary heart disease in emerging countries. Yet, our knowledge of the clinical epidemiology of CAD remains limited. Much of the information available predates the emergence of percutaneous coronary intervention (PCI) as the dominant form of revascularization, and therefore, reflects patient profiles that differ markedly from current clinical practice. Most of the information stems from highly selective RCTs or from registries enrolling patients hospitalized for an acute coronary event or a procedure (PCI or coronary artery bypass grafting [CABG]). This wealth of data regarding patients who are admitted to hospital for an acute event does not necessarily reflect the situation of stable outpatients. There are some large registries, but they have focused mostly on patients with anginal symptoms, such as, for example, the Euro Heart Survey on stable angina, which enrolled patients with angina. Finally, most of the information comes from sources located in North America or Europe, overlooking the important differences in patient characteristics, management, and environment in other regions of the world. The fact is that our knowledge of the global characteristics of patients with CAD is scant. Little is known about their clinical characteristics, functional status, quality of life, clinical management (including the use of functional testing and imaging) and the use of evidence-based therapies and medications and their outcomes. Gathering such information is critical to identifying gaps in evidence as well as gaps between evidence and routine clinical practice, which can then inform quality assurance initiatives.

Heart rate is emerging as an important prognostic and physiological parameter in coronary artery disease and chronic heart failure

Heart rate is probably the most frequently measured physiological parameter. Despite its considerable variability, it is emerging as a parameter of utmost physiological and prognostic importance in cardiovascular disease. It is one of the major determinants of myocardial oxygen consumption, and therefore, increased heart rate is an important precipitating factor for myocardial ischemia and anginal symptoms. Indeed, some of the most effective treatments to prevent or treat myocardial ischemia and angina, such as β-blockers or some (but not all) calcium channel blockers, act by lowering the heart rate. In fact, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of patients with angina recommend targeting a heart rate of less than 60 beats per min (bpm) for patients with stable angina.

In addition, despite the short-term variability in heart rate, large epidemiological observational studies, such as the Chicago epidemiological studies’ or other large studies in apparently
healthy individuals, have consistently linked resting heart rate with long-term cardiovascular risk in subjects without established cardiovascular disease: the higher the heart rate, the greater the risk of cardiovascular and even all-cause mortality. An analysis of the CASS registry (Coronary Artery Surgery Study) also showed the long-term prognostic value of resting heart rate in patients with suspected or proven CAD: 24,913 patients from the CASS registry were followed for a median duration of 14.7 years. All-cause mortality and cardiovascular mortality increased with increasing heart rate. This persisted after adjustment for multiple baseline clinical variables (Figure 1). Likewise, Cope et al showed that resting heart rate and heart rate variability were important predictors of outcomes after myocardial infarction. More recently, pre-specified analyses of the placebo arm of the BEAUTIFUL randomized trial (morBidity-mortality EvAlUaTion of the I_i inhibitor ivabradine Trial) were conducted. In patients with CAD and left ventricular systolic dysfunction, elevated heart rate (70 bpm or greater) identifies those at increased risk of cardiovascular outcomes. Similar observations regarding the prognostic importance of heart rate in congestive heart failure were made in the SHIFT randomized trial (Systolic Heart failure treatment with the I_i inhibitor ivabradine Trial). SHIFT was a double-blind placebo-controlled trial comparing ivabradine—a specific I_i inhibitor (which is a pure heart rate-reducing agent)—with placebo, in addition to optimal medical therapy in patients with chronic heart failure. In the placebo group, patients with the highest heart rates (≥70 bpm) had a more than 2-fold higher risk of cardiovascular death or hospital admission for worsening heart failure than patients with the lowest heart rates (70 to <72 bpm; hazard ratio, 2.34; 95% CI, 1.84-2.98; P<0.0001). The risk increased by 3% with every bpm increase from baseline heart rate. Ivabradine improved outcomes with an 18% relative reduction in cardiovascular deaths or hospital admissions for heart failure (P<0.0001). Interestingly, the effect of ivabradine was accounted for by heart rate reduction, as shown by the neutralization of the treatment effect after adjustment for change in heart rate after 4 weeks of treatment (hazard ratio, 0.95; 95% CI, 0.85-1.06, P=0.352).

![Figure 1. Survival curves for overall mortality (A) and cardiovascular mortality (B) in the Coronary Artery Surgery Study (CASS) registry. A high resting heart rate is an independent predictor of mortality in coronary artery disease patients. Data from the CASS registry in 24,913 patients, with 14.7 years of follow-up.](https://example.com/figure1)

### Heart rate in coronary artery disease registries

As surprising as it may seem, there is relatively little large-scale data on the resting heart rate of patients with CAD. In addition, interpretation of heart rate data requires access to information regarding the use of β-blockers and other heart rate-lowering agents as well as information on the doses and types of β-blockers used as some β-blockers may exhibit sympathomimetic activity and therefore not result in heart rate lowering at rest.

### Stable angina registries

In the European Heart Survey of stable angina the mean baseline heart rate in patients with stable CAD was 73 bpm and approximately half of the patients had a baseline heart rate above 70 bpm, despite the fact that some guidelines recommend a target heart rate of 55 to 60 bpm for patients with stable angina on β-blockers. Interestingly, over half of the patients were not on any chronicotropic medication (ie, no β-blockers or any other heart rate-lowering medication). Among pa-

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Heart rate in registries: an important, yet still neglected opportunity – Steg
tients receiving β-blockers, the doses used were lower than those found to be effective in clinical trials. Finally, a higher heart rate at baseline was associated with higher rates of mortality and hospitalization for heart failure at follow-up.

In a British registry of 500 patients with chronic stable angina, a large proportion of patients did not achieve the target resting heart rate of <60 bpm; 27% had a resting heart rate >70 bpm and an additional 40% had a heart rate between 60 and 69 bpm, despite the fact that 78% of patients were receiving β-blockers. The resting heart rate was not related to the dose of β-blocker. Similar or higher proportions of patients with elevated heart rate and similar rates of β-blocker use were seen in other studies from Portugal, Italy, France, Austria, and Poland. Studies focusing on older patients tend to find lower rates of β-blocker use. The Lycoregistry enrolled 8922 hypertensive patients with stable CAD. In this study, the mean resting heart rate was 70 ± 6 bpm, with 54% of the patients having a heart rate ≥70 bpm and 62% of the population receiving β-blockers. In the above-mentioned studies, patients with higher resting heart rates experienced more frequent anginal symptoms. One study found that the link between a higher resting heart rate and adverse clinical outcomes in patients with stable CAD may be limited to patients with diabetes mellitus, possibly because it reflects autonomic disturbances. This study was, however, limited by a relatively short follow-up of only 1 year.

**Acute coronary syndromes registries**

Heart rate is an independent predictor of outcomes in patients with acute coronary events. For example, the GRACE risk score (Global Registry of Acute Coronary Events), the most widely recommended risk score for acute coronary syndromes, collects information regarding heart rate at presentation and correlates this with the in-hospital risk of death and myocardial infarction. Interestingly, heart rate does not solely predict in-hospital outcomes in ACS, but also postdischarge outcomes, indicating that it is a robust marker of long-term outcomes (Figure 2). Likewise, heart rate is also a predictor of outcomes in the PURSUIT risk score (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integri

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**Figure 2. Risk calculator for 6-month postdischarge mortality after hospitalization for acute coronary syndrome.**

Computation of the GRACE (Global Registry of Acute Coronary Events) risk score, a validated risk prediction model, to predict 6-month postdischarge outcomes after acute coronary syndrome.


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**Medical history**

<table>
<thead>
<tr>
<th>Points</th>
<th>Age in years</th>
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**Findings at initial hospital presentation**

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**Findings during hospitalization**

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<td>4</td>
<td>1.6-1.99</td>
</tr>
<tr>
<td>5</td>
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**Summary**

Heart rate in registries: an important, yet still neglected opportunity – Steg

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to which the detrimental prognostic impact of heart rate may have been confounded by heart failure and whether more modern studies of acute coronary syndromes in which PCI is widely used may fail to show a link between resting heart rate and survival. In a recent analysis of 1453 STEMI patients treated with primary PCI, Antoni et al found that heart rate at discharge after STEMI is a strong predictor of mortality following STEMI, with patients with a heart rate ≥70 bpm having twice the mortality of patients with a lower heart rate, at 1 and 4 years. Every increase of 5 bpm in heart rate at discharge was associated with a 29% and 24% increased risk of cardiovascular mortality at 1 and 4 years of follow-up, respectively.29

The CLARIFY registry

CLARIFY (Prospective observational Longitudinal Registry of patients with stable coronary artery disease) is an ongoing international, prospective, observational, longitudinal cohort study in stable CAD outpatients, with a 5-year follow-up. The study rationale and methods have been published previously.29 The enrolled population is representative of the broad spectrum of CAD patients and detailed information on heart rate was collected at baseline and will continue to be collected on a yearly basis for up to 5 years. CLARIFY will provide a robust database to assess the determinants of outcomes in CAD, prospectively explore the role of heart rate, and evaluate the degree of heart rate reduction achieved with the different types of heart rate–lowering medications used at various doses. In particular, it will help build a robust model of outcomes in CAD and test the importance of heart rate.

Patients were enrolled in 45 countries in Africa, Asia, Australia, Europe, the Middle East, and North, Central, and South America. These patients are being treated according to usual clinical practice at each participating institution, with no specific tests or therapies defined in the study protocol. Patients eligible for enrollment were outpatients with stable CAD proven by stress electrocardiogram, stress echocardiography, or myocardial imaging; and history of CABG or PCI (performed >3 months before enrollment).

Patients hospitalized for cardiovascular disease within the previous 3 months (including for revascularization), patients for whom revascularization was planned, and patients with conditions expected to hamper participation in the 5-year follow-up (eg, limited cooperation or legal capacity, serious noncardiovascular disease, conditions limiting life expectancy, or severe cardiovascular disease [advanced heart failure, severe valvular disease, history of valve repair/replacement, etc]) were excluded from the study.

In order to enroll a population of stable CAD outpatients that mimicked the epidemiological patterns of each country, recruitment was based on a predefined selection of physician specialties (cardiologists, internists, and primary care physicians) and aimed for consecutive enrollment of eligible patients. Physician selection was based on the best available sources—either local or regional—of epidemiological and medical care data, including available market data and epidemiological surveys. A general target of 25 patients per million inhabitants was used (range, 12.5–50) to ensure a balanced representation of the participating countries. Each physician recruited between 10 and 15 outpatients with stable CAD, as defined by the inclusion criteria, over a brief period of time, in order to avoid selection bias. Information collected at baseline included: demographics, medical history, risk factors and lifestyle, results of physical examination, heart rate (determined by both pulse palpation and the results of the most recent electrocardiogram performed within the previous 6 months), current symptoms, laboratory values (eg, fasting blood glucose, hemoglobin A1c, cholesterol, triglycerides, serum creatinine, hemoglobin, if available), and current chronic medical treatments.

Data are collected centrally using an electronic, standardized, international case report form (translated into local languages) and sent electronically to the data management center, where checks for completeness, internal consistency, and accuracy are run. Data quality control is performed onsite in 5% of sites chosen at random in each country with, at each site, monitoring of 100% of case report forms for source documentation and accuracy. All patients gave written informed consent to participate, in accordance with national and local guidelines. The CLARIFY registry is registered in the ISRCTN registry of clinical trials with the number ISRCTN43070564. All CLARIFY data are collected and analyzed at an independent academic statistics center at the Robertson Centre for Biostatistics, University of Glasgow, UK. The baseline data and 1-year outcome data from CLARIFY were presented at the 2011 and 2012 European Society of Cardiology (ESC) congresses, respectively.29,31

References

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Keywords: clinical outcome; coronary artery disease; heart failure; heart rate; mortality; registry

LA FRÉQUENCE CARDIAQUE DANS LES REGISTRES : UNE CHANCE À SAISIR ENCORE NÉGLIGÉE

Les registres sont la clé de la compréhension des caractéristiques, de la prise en charge et de l’évolution des patients coronariens. Ceci en particulier étant donné que la validité externe de l’information recueillie lors des études cliniques randomisées est souvent limitée par les critères rigoureux de sélection des participants. La fréquence cardiaque de repos apparaît comme un déterminant pronostique clé de l’évolution, en particulier de la mortalité cardiovasculaire chez les patients aux formes stables et instables de maladie coronaire et d’insuffisance cardiaque. Cependant, bien que la fréquence cardiaque soit le paramètre physiologique le plus couramment mesuré, il n’existe que très peu d’information sur la fréquence cardiaque véritable des patients coronariens et son lien avec l’utilisation des médicaments abaisant la fréquence cardiaque (en particulier les β-bloquants) et l’évolution ultérieure. Ces dernières années, de nombreuses registres émanant de différents pays d’Europe et d’ailleurs ont recueilli des informations sur les caractéristiques des patients coronariens. Bien que la majorité des patients reçoivent des β-bloquants, ces registres ont enregistré une fréquence cardiaque de repos très souvent supérieure à 70 bpm. De plus, ces registres ont montré qu’une fréquence cardiaque de repos élevée est associée à une prévalence plus importante des symptômes angoreux et à une mortalité cardiovasculaire accrue. Cependant, chez les patients ayant un syndrome coronarien aigu, des fréquences cardiaques très basses sont elles aussi associées à une augmentation de la mortalité, ce qui suggère que la relation entre la fréquence cardiaque et la survie au cours de la maladie coronarienne pourrait suivre une courbe en « J ». Le grand registre international CLARIFY (prospective observational Longitudinal Registry of patients with stable coronary artery disease), avec un effectif de plus de 33 000 patients dans le monde entier, va fournir des informations solides sur les relations entre la fréquence cardiaque de repos et les symptômes angoreux, l’utilisation des médicaments abaisant la fréquence cardiaque (en particulier les β-bloquants), et le plus important, l’évolution clinique à 5 ans.
Heart rate is one of the major determinants of myocardial oxygen consumption and myocardial blood flow... and heart rate reduction is an established and important therapeutic strategy in the prevention of ischemia. A strong association between elevated heart rate and increased risk of total and cardiovascular mortality has been shown in the general population, as well as in patients with hypertension, diabetes, and coronary artery disease.”

Heart rate reduction and coronary flow reserve: mechanisms and treatment

by P. E. Vardas, Greece

Heart rate is a major determinant of myocardial oxygen consumption and therefore myocardial blood flow and coronary flow reserve. Consequently, heart rate reduction is an established important therapeutic strategy in the prevention of ischemia. Ivabradine reduces heart rate by inhibition of the I_f-channels in the sinus node. Treatment with ivabradine not only reduces resting myocardial blood flow, but also significantly improves hyperemic coronary flow and coronary flow reserve in patients with stable coronary artery disease. These effects remain even after heart rate correction, indicating improved microvascular function. Although the pathophysiological explanation of our findings remains to be elucidated, if the effect of ivabradine on microvascular function is confirmed in similar studies then we have an additional therapeutic approach for patients with coronary artery disease, targeting microvascular function.

Medicographia. 2012;34:460-465 (see French abstract on page 465)

Coronary blood flow control

The heart, like all other organs, cannot function without blood flowing through its vessels. Coronary vessels carrying 5% to 10% of the cardiac output run over the surface of the heart, giving rise to branches which penetrate the heart muscle and which in turn branch into smaller vessels (microcirculation) that supply the heart’s capillary network (vessels only 5 µm in diameter) with blood.

This coronary blood flow is regulated by the heart, changing according to the heart’s metabolic needs, and maintained near the minimum level required for the supply of oxygen. Under normal conditions, the heart extracts roughly 70% of all the oxygen from the blood. Increases in myocardial oxygen consumption which occur during exercise must be accommodated by an increase in coronary blood flow through changes in microvascular resistance.1 The microcirculation (vessels <200 µm in diameter) consists of a channel of passive networks, but it is also an active site for blood flow control through a number of metabolic, myogenic, and other mechanisms. Capillary hydrostatic pressure is held constant within the myocardium at approximately 30 mm Hg, made possible by the strong and immediate myogenic response (autoregulation) of arteriolar smooth muscle.

At rest (baseline), the ability to regulate blood flow is high, since 60% of total myocardial vascular resistance is offered by arterioles.2,3 However, when hyperemia is induced, smooth muscle vasodilatation results in dilatation of the arterioles and venules
with no change in the capillaries. Total myocardial vascular resistance decreases and capillary resistance now accounts for 75% of the total myocardial vascular resistance. Thus, capillaries offer the most resistance to coronary blood flow during hyperemia and provide a ceiling to hyperemic blood flow.\textsuperscript{2,3}

It is clear that under normal circumstances, coronary blood flow is much lower than maximum, which allows the coronary control vessels to be able to adjust the flow to an increased level of metabolism. The extent to which coronary blood flow can increase above control is generally referred to as coronary flow reserve (CFR).

**Physiological and pathophysiological disturbances of coronary blood flow**

Coronary blood flow is subject to physiological disturbances created by the contraction of the heart. When pressure is generated in the left ventricle, the vessels in the heart muscle are compressed as well, impeding coronary blood flow (often referred to as extravascular resistance). Consequently, coronary blood flow occurs predominantly during diastole, paralleling the large changes in input impedance caused by ventricular contraction and relaxation of intramyocardial vessels.

Heart rate is one of the major determinants of myocardial oxygen consumption and myocardial blood flow. An increase in heart rate does more than increase metabolic demand for blood flow, it also increases extravascular resistance by decreasing myocardial perfusion time. Thus, by increasing heart rate, arteriolar dilatation must compensate for both increase in demand and increase in extravascular resistance. Balance between demand and supply may also be disturbed by (patho-)physiological factors such as perfusion pressure (defined as the difference between central aortic pressure and left ventricular pressure).\textsuperscript{1}

Atherosclerosis is a well-recognized pathophysiological mechanism negatively affecting the supply of blood. This disease process can lead to local or more diffuse narrowing of the larger coronary arteries, adding to the resistance of the coronary system. Such obstruction, interpreted by local flow control processes as a reduction in pressure, would lead to a vasodilatory response. The added resistance to flow reduces the range of oxygen demand that the coronary circulation is able to accommodate, thus the need to compensate for the arterial narrowing would overwhelm the vasodilatory capability of the coronary resistance vessels and bring the control system to the limit of its working range.\textsuperscript{1}

**Heart rate reduction as an important therapeutic strategy**

Heart rate, as previously mentioned, is a main determinant of myocardial oxygen consumption and heart rate reduction is an established and important therapeutic strategy in the prevention of ischemia. A strong association between elevated heart rate and increased risk of total and cardiovascular mortality has been shown in the general population, as well as in patients with hypertension, diabetes, and coronary artery disease (CAD).\textsuperscript{4}

BEAUTIFUL (morBidity-mortality EvAlUaTion of the \textit{i} inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) has provided significant data relating to the prognostic importance of heart rate,\textsuperscript{5} and to the importance of heart rate reduction with ivabradine\textsuperscript{6} for reduction of coronary events in CAD patients with left ventricular dysfunction. The results showed that elevated resting heart rate (>70 bpm) is a strong predictor of outcome in patients with stable CAD and left ventricular dysfunction. Patients in the subgroup with resting heart rate >70 bpm were 34% more likely to die from cardiovascular causes and 53% more likely to be hospitalized for new or worsening heart failure. Similarly, elevated heart rate was associated with a 46% increased risk of fatal and nonfatal myocardial infarction and a 38% increase in the need for coronary revascularization. Also, BEAUTIFUL investigated the effect of ivabradine on outcomes in stable CAD patients.\textsuperscript{7} Although ivabradine did not affect the primary composite end point, in patients with a heart rate of 70 bpm or greater, ivabradine had a significant impact on all end points linked to coronary events. There was a 36% reduction in the relative risk of hospitalization for fatal and nonfatal myocardial infarction in the patients treated with ivabradine and a 30% relative risk reduction for coronary revascularization. Nevertheless, the underlying mechanism remains unknown.

**Effects of ivabradine on coronary blood flow and coronary flow reserve**

Although CFR predicts long-term adverse cardiovascular outcome\textsuperscript{8} and decisions for coronary revascularization are based on a physiological assessment of coronary artery lesions,\textsuperscript{9,10} there were previously no data in humans concerning the effect of ivabradine on coronary hemodynamics. In a recently published study from my department,\textsuperscript{11} we examined the effects of ivabradine on coronary blood flow and flow reserve in patients with stable CAD. In this study, we assessed 21 pa-
patients with stable CAD of one or two vessels, amenable for percutaneous coronary intervention. Immediately following coronary angiography, the culprit vessel/s for coronary intervention were defined according to guidelines and a non-culprit vessel was selected for coronary flow measurements. The non-culprit vessel was selectively engaged with a guide catheter. Intracoronary nitroglycerin (200 µg) was given every 15 minutes of the procedure to prevent catheter-induced coronary artery spasm and to avoid changes in coronary artery diameter. A 0.014-in, 15-MHz Doppler guide wire (FloWire, Volcano Therapeutics Inc) was advanced through the catheter to the non-culprit vessel.

Once resting flow-velocity data had been collected, a 30-µg bolus injection of intracoronary adenosine was given to obtain data during hyperemia. To confirm that maximal hyperemia had been achieved, doses increasing in 30-µg increments were infused until a plateau in flow velocity was reached.

All measurements were made in the non-culprit vessel: i) during diagnostic coronary angiography (baseline); ii) during programmed coronary intervention in the culprit vessel/s (before the procedure), 1 week after treatment with ivabradine (5 mg twice daily) at the same location at the intrinsic heart rate (ivabradine); and iii) at a pacing heart rate similar to baseline (ivabradine-pace), accomplished by pacing the right atrial appendage via a temporary pacing lead. Time-averaged peak coronary flow velocity (APV cm/s) was measured and CFR was determined as the ratio of APV at maximal hyperemia (h-APV) to APV at rest (r-APV).
Since at the beginning of the diastolic period extravascular compressive forces are minimized and coronary perfusion pressure is highest, maximum coronary blood flow occurs in the early diastolic period. Consequently, changes in maximum diastolic peak coronary flow velocity (MPV cm/s) at maximal hyperemia were used as an index of early diastolic blood flow alterations. As expected, heart rate was significantly lower after treatment with ivabradine (78±14 bpm vs 65±9 bpm, P<0.001).

There was a significant effect of ivabradine treatment on both r-APV and h-APV hyperemia APV. With ivabradine treatment (nonpaced heart rate), r-APV was significantly lower than at baseline. However, there was no significant difference in r-APV with ivabradine treatment + pacing and baseline. In contrast, h-APV with ivabradine treatment (nonpaced heart rate) was significantly higher than at baseline. Similarly, h-APV with ivabradine + pacing was significantly higher than at baseline. Iivabradine treatment also had a significant effect on CFR. CFR after ivabradine was significantly higher than at baseline. Similarly, CFR with ivabradine + pacing was significantly higher than at baseline (Figures 1 and 2).

In summary, we found that ivabradine treatment significantly reduces resting coronary blood flow and increases hyperemic coronary flow, leading to CFR improvement in patients with stable CAD. Also, although resting coronary blood flow returns to the pretreatment values after heart rate correction, the enhancement of hyperemic coronary blood flow remains. Therefore, even after heart rate correction, CFR remains significantly higher than the pretreatment values, indicating improved microvascular function with ivabradine treatment. As heart rate is a major determinant of myocardial oxygen consumption, it thus influences myocardial blood flow and CFR. However, hyperemic coronary blood flow in the absence of hemodynamically significant epicardial coronary artery stenosis is not heart rate dependent and is associated with the integrity (either functional or structural) of the microcirculation.

How does ivabradine affect r-APV and h-APV?
Ivabradine is a selective inhibitor of the I_f-channel and reduces heart rate by inhibiting these channels in the sinus node. Consequently, changes in r-APV are easily explained by corresponding alterations in heart rate during ivabradine treatment both at the intrinsic heart rate and at the pacing rate similar to that before treatment. However, changes in h-APV are more complicated. Hyperemic coronary blood flow increases after ivabradine treatment because the diastolic period is prolonged (per cardiac beat and per minute) as expected. The most possible explanation behind h-APV enhancement after heart rate correction may be the improvement of ventricular relaxation caused by ivabradine treatment which in turn enhances coronary blood flow during hyperemia. As mentioned earlier, Ivabradine is an I_f-channel inhibitor. The gene for the I_f-channel was first discovered in the mouse brain, and four isoforms of this hyperpolarization-activated, cyclic nucleotide-gating channel protein (HCN 1, 2, 3, and 4) have been identified in animal hearts.

In the animal heart, HCN4 levels are higher than HCN1 in the sinus node, while HCN2 levels are lower in ventricular myocardium. Despite that, HCN2 is considered to be the dominant isoform because of the larger mass of ventricular myocytes compared with sinus tissue. Nevertheless, HCN channels expressed in other cardiac tissues seem to be nonfunctional at these locations under normal conditions. The most positive activation is in the sinoatrial node and is associated with the highest pacing rate, whereas the most negative activation (ventricular myocytes) normally exhibits no diastolic depolarization at all. Ivabradine, by blocking I_f-channels reduces entry of Na+ into the myocytes, leading to reduced cytosolic calcium. Moreover, ivabradine improves reuptake of calcium by the sarcoplasmic reticulum. The cumulative effect of those ivabradine actions is improvement of ventricular relaxation. Furthermore, Heusch et al. and Fox et al. have previously reported a beneficial effect of ivabradine that was at least
in part heart rate independent and supports the pleiotropic actions of ivabradine. In addition, it is possible that enhanced diastolic relaxation may increase early diastolic coronary blood flow by a "suction effect." In fact, the increase in heart rate after ivabradine treatment is related not only to the increase in the diastolic period, but also to the overall improvement of flow, since h-MPV—which represents early diastolic flow—is higher. Therefore, as can be seen in Figure 3 (page 463), despite the shortening of the diastolic period after heart rate correction by pacing, the improvement of flow remains because the average flow (C) which will replace the missing period per minute is not less than the average flow during the missing period (B).

Other studies showing improvement of coronary flow reserve with pharmacological intervention in stable CAD patients

To the best of our knowledge, there are only two invasive studies showing improvement of CFR with pharmacological intervention in patients with stable CAD. One involved metoprolol and the other nebivolol. These studies (from the same research group) used different methodologies. Both were carried out in the stented artery of patients with CAD; significant changes in rate pressure were detected after treatment, since heart rate was not stable, and vasodilating actions were allowed because intracoronary nitroglycerin was not used—at least in the second study. Consequently, the observed increase in CFR could be explained by differences in heart rate, endothelial function, and/or coronary artery diameter, and not as a result of an improvement in microvascular function. In support of this is the control group of the latter study, but also the control group from a study recently published from our department. In both of these, no changes in hyperemic coronary flow were observed with β-blocker treatment.

Conclusion

Ivabradine treatment significantly improves hyperemic coronary flow and CFR in patients with stable CAD. These effects remain even after heart rate correction, indicating improved microvascular function.

Although the pathophysiological explanation remains to be elucidated, if the effect of ivabradine on microvascular function is confirmed in similar studies, then we have an additional therapeutic approach for patients with CAD, targeting the microvascular function, with profound clinical implications.

References

La fréquence cardiaque est un facteur déterminant majeur de la consommation d’oxygène myocardique et donc du débit sanguin myocardique et de la réserve coronaire. La réduction de la fréquence cardiaque est par conséquent une stratégie thérapeutique importante, éprouvée dans la prévention de l’ischémie. L’ivabradine diminue la fréquence cardiaque en inhibant les canaux \( I_f \) dans le nœud sinusal. Le traitement par ivabradine non seulement réduit le débit sanguin myocardique de repos mais aussi améliore significativement le débit coronaire hyperémique et la réserve coronaire chez les patients coronariens stables. Ces effets persistent même après correction de la fréquence cardiaque, ce qui témoigne d’une fonction microvasculaire améliorée. Nos résultats ne sont pas clairs sur le plan physiopathologique mais si l’effet de l’ivabradine sur la fonction microvasculaire est confirmé dans des études équivalentes, cela signifiera alors que nous disposons d’un traitement supplémentaire pour les patients coronariens, ciblant la fonction microvasculaire.

**Keywords:** coronary artery disease; coronary blood flow; coronary flow reserve; heart rate; ivabradine
Rochefort, on the French Atlantic coast, is steeped in history, boasting a Royal dockyard, Royal Rope Factory (once the longest building in Europe), the world’s first School of Naval Medicine, and the extravagant “multicultural” house of novelist and navy officer Pierre Loti. Today, history is relived as a replica of La Fayette’s ship, the Hermione, is being rebuilt in the same dockyard it originally came from, and will soon be setting sail for Boston, in America.

“The School of Naval Medicine occupied the left wing of the Maritime Hospital in Rochefort. Detail of a lithograph by Charles Mercereau, 19th century. Private Collection. © Archives Charmet/Bridgeman Art Library.”

“A TOUCH OF FRANCE

“Call back yesterday, bid time return”

Rochefort, the town where the past comes alive

I. Spaak, France

Sickness and health on the high seas in the 18th century

The Former Rochefort School of Naval Medicine and the birth of the French Navy Health Service

C. Régnier, France

“The 374-meter long Royal Rope Factory (Corderie Royale) in Rochefort, completed in 1669. © Bruno Barbier/Photononstop.”

MEDICOGRAPHIA, Vol 34, No. 4, 2012 467
Rochefort, the town where the past comes alive

by I. Spaak, France

In 1997 a group of enthusiasts formed a nonprofit organization (Hermione–La Fayette) dedicated to reconstructing the dockyards of yore and building a replica of the Hermione, the legendary frigate aboard which the 23-year-old Marquis de La Fayette set sail in 1780 to join forces with George Washington in fighting the English crown and winning independence for America. This, and much more in Rochefort, the French sea port built by the Sun King Louis XIV...

Rochefort, built on a bend of the river Charente close to its estuary, owes its fame to Louis XIV who in 1666 made it into France’s greatest and largest military and maritime arsenal. The sea port of Rochefort has the richest heritage of naval architecture in France, epitomized by an extraordinary limestone rope factory almost 400 meters long. It was also the site of the prestigious Rochefort School of Surgery founded in 1722 (see companion article by Dr Christian Régnier). One of Rochefort’s most famous scions was undoubtedly Julien Viaud, (1850-1923), who enjoyed a long and distinguished career as an officer in the French navy. Better known by his pen name Pierre Loti, his literary career was crowned in 1891 by his election at the Académie Française. Most intriguing was Loti’s abiding passion for the house in which he was born and which bore the impress of his wanderings over the years, like shifting scenery on a theater stage. Loti refurbished his home as the muse took him, in harmony with his peregrinations around the globe, while leaving no outward sign of the transformations taking place within. Now a museum, the house tells the tale of his voyages, of his nostalgia, his wont to hark back to times long past. Loti was a likeness of his birthplace, the town of Rochefort: quiet, low-key, yet possessed of a steely determination, an eagerness to rise to a challenge. In recent times, following the abandonment of the dockyard in the early 20th century, of the Naval School of Medicine in 1964, and the closure of the hospital attached to it in 1983, Rochefort has resembled a sleeping beauty. Yet something is stirring. Craftsmen and journeymen are working on a technical and historical challenge—the recreation of an 18th-century shipyard and the building of a replica of the Hermione, the sixty-five-meter frigate aboard which the Marquis de La Fayette crossed the Atlantic to join George Washington in the American Revolutionary War.

With a stroke of his pen in 1665, King Louis XIV changed forever the desirity of a sleepy little town on the right bank of the Charente River, a few kilometers from the Atlantic Ocean. On the advice of his chief naval administrator Colbert du Terron, the king chose Rochefort in southwestern France as the site for a new shipyard able to vie with the ports of Holland and England.

Each newcomer was allotted 200 m² of land on which to build his house, and by the end of the 17th century the first wooden huts for the dockyard workers had been replaced by stone residential quarters for naval officers, and by military build-
A vast rope factory was erected, the longest building in Europe at the time, and naval construction proceeded apace, with 49 ships built between 1688 and 1692, and about 350 by 1710.

**A shipyard rises from the wetlands**

When the Sun King, Louis XIV, took possession of Rochefort in 1666, it was a rural parish of some four hundred communicants. In his recommendation to the king, Colbert du Terron called attention to the safety of the harbor protected by the natural barrier that is the Île d’Oléron, the ease with which the site could be defended, the depth of the Charente, the natural barrier to a land-based attack offered by surrounding marshland, and the richness of the hinterland and its forest, which would be a ready source of timber for shipbuilding.

As a bulwark of sorts against the Protestant town of La Rochelle a mere thirty kilometers away, the king seized the opportunity to impose a Catholic stronghold, and to build the naval dockyard that France so sorely lacked.

By the time Louis XIV died in 1715, the dockyard had built, armed, and repaired dozens of ships, the town had 12 to 15,000 inhabitants, and the countryside had been transformed. These profound changes were not achieved effortlessly. The naval dockyard arose at great cost from wetlands liable to flooding and better suited to grazing livestock, the town constantly suffered from a lack of drinking water and from the disease-breeding unwholesomeness and “bad air” of the neighboring swamplands. No one built a decent parish church, the countryside was stripped of its forest and blighted by the construction of a suburb, and the locals swapped tilling for work at the naval shipyard.

**Sixty thousand ropes a month**

The dockyard’s production was exceptional, thanks to refits in stone-lined dry docks on the banks of the Charente and Rochefort’s main monument, its remarkable 374-meter-long Royal Rope Factory (Corderie Royale), which produced cable lengths of two hundred meters. Begun in 1666 and completed in 1699, the rope factory is in itself a page of history.

![View of the Sea Port of Rochefort](Image)
How was such a structure raised on the vast meadowland prone to flooding alongside the river? The soil was too loose for the traditional building techniques of the area, in which foundations were not dug but placed directly on the grassland. The architect François Blondel (1618-1686) raised the edifice slightly on a sort of raft, a gigantic supporting grid fashioned from oak beams. Some lying flat, others vertical under the main walls, these wooden piles support the whole length of the two magnificent galleries built one above the other, the lower for producing strands of fibers and the upper for spinning. Resplendent before a huge lawn, the palace-like frontage is reminiscent of Versailles, with its finely-worked limestone from the quarries at Crazannes, its whiteness set against the orange tiles and gray slates of the two-tiered roof. The walls are pierced on the first floor and on the second, with its sloping roof and dormer windows surmounted by semicircular pediments, to air the building and thus better preserve the hemp used in rope making. Its elegant architecture, like a “long hull of beige stone” in the words of writer Erik Orsenna, has contributed to its fame. The rope factory also had four warehouses for the hemp used to make ropes, two others to keep the ropes, two more for barrels of tar, and a last one for cutting, along with a gigantic cast iron boiler. Considered the most efficient in the kingdom, the Rochefort rope factory produced up to sixty thousand pieces of rope a month.
Then came the 19th century with its larger vessels and steamships and steel cables signaling the decline of the shipyard and its rope factory, which was closed in 1927 and set alight by the Germans in 1944. A twenty-year hiatus followed before Admiral Maurice Dupont, Naval Commander at Rochefort, undertook to restore the partially destroyed buildings. By 1988 the work was done, and the opening of a museum complex of over 300 square meters devoted to the history of the naval dockyard marked Rochefort’s first step in reclaiming its maritime past.

Curious fellow this naval officer, baptized Loti after the name of a sweet-smelling red flower “at the age of twenty-two years and eleven days,” by a Tahitian girl he fell for during a stay in Polynesia. During and after a long and distinguished career as an officer in the French navy, Loti wrote highly personal books steeped in exoticism, accounts of his loves and adventures at the four corners of the world, in a literary career crowned in 1891 by his election as one of the forty so-called “immortals,” or members of the Académie Française, winning a head-to-head contest with Émile Zola (who in 19 attempts never achieved “immortality”).

Frail and solitary, Loti was torn between his passion for foreign lands and the comfort of the familiar, of childhood memories of home life, of halcyon days. His was a lifelong struggle between the pain of leaving and the ardent desire to venture forth. Imbued with exoticism, the writer–traveler drifted ever...
further afield, yet dreamed of but one thing: home, the haven of the house where he was born in Rochefort. “A very modest provincial house where Huguenot austerity was felt,” a peaceful atmosphere, a muffled interior, where there was “no unruliness, we chatted, sowed, wrote, prayed. Free of distractions from the outside world, we were self-sufficient. Affection was shared like bread…” wrote Loti in 1890 in Le Roman d’un Enfant, an autobiographical account of his childhood, which greatly influenced Marcel Proust.

Bordering on fetishism, this passion for things past, for a sort of stasis, paradoxically fueled his obsessive need to transform his home. Returning from his travels, Loti converted his abode, expanded in 1895 by the acquisition of the adjoining terrace house, into a sort of museum of faraway places. It became a mosaic of civilizations, dramatized decors, baroque fantasies, a literary phenomenon. Between oriental bazaar and flights of fancy, Loti transmogrified, converted, anchored his excesses, fixed his travels in amber. Memories of family and of departed loved ones—his grandmother Berthe, his mother Nadine, his elder brother Gustave (a naval surgeon who died at age 29 off the coast of Ceylon, as Sri Lanka was then known)—haunted his home, as it mutated into settings of the Far East on the first floor, orientalism on the second, eclectic historicism, while the house’s frontage remained untouched, such that should his grandfather one day return to the land of the living he would recognize his “ancient abode.”

An anatomy of restlessness

Among the trunks and chests, the closets filled with piously preserved relics, quirkiness reigned in the image of Loti: withdrawn, yet unbridled and flaunting. In an everlasting fight against the ravages of time, his obsession, Loti used greasepaint, rouged his cheeks and colored his lips, heightened his stature by a few centimeters with a device inside his socks, dressed as a pasha, a Chinese, a medieval lord, an acrobat, in unison with the metamorphoses of his house. “One must defend oneself against old age,” he wrote to justify his primping, “one has no right to become an object of disgust.”

Loti converted his grandmother’s former bedroom into a Turkish living room where Moorish influence dominated. Inspired by the Alhambra in Granada, two columns support a polychromed arch suggestive of the gallery of the Court of the Lions as reinterpreted by Loti through his instructions to local plasterers. The whole forms a skilful blend of predominantly blue ceramics, with marbles, textiles, and hangings. Once there was a Chinese pagoda, little of which remains, described by Loti’s private secretary as being of “unrivalled magnificence with its yellow gold, red gold, bright or soft golden tints… a dizzying array of colors flaming in air heavy with musk and sandalwood.” Three altars, tiered seating, golden thrones amidst a jumble of religious symbols presided over by “an ancient god with six arms and five eyes, gesticulating, sniggering, ferocious.” The Empire chamber and its ceiling studded with stucco bees, his childhood bedroom transformed into a peasant room with rustic fittings, a tomb-like chamber of Egyptian mummies at the end of a dark corridor—women, a child, cats, a small painted wood sarcophagus. And even a mosque. Not forgetting the Renaissance room for which Loti added a floor to the house, lending to the space the majesty of a mansion, a precious tapestry from the Gobelins Manufactory, a monumental chimney, stained glass windows, armor, and three stone lions atop columns. All of which contrasts starkly with the abnegation and frugality of Loti’s monastic bedchamber.

Old Cathay comes to Rochefort

Fanfares of olifants and horns rang out. Disguised as Louis XI (1423-1483), his wife Blanche as the queen consort Charlotte of Savoy, My Lord Pierre Loti advanced, hooded falcon on his right fist, left hand in his lady’s. Behind the couple, a retinue formed and proceeded to the Gothic dining room. Dressed in duns and browns, “as befits people who have spent four hundred years in their clothes” advised the invitation written in old French, the guests crossed the Japanese salon and ceremoniously took to the stairs.

Despite appearances, this scene did not unfold “in the year of grace MCCCC’L’XX under the reign of our good King Louis the Eleventh,” as intimated by the invitation card, but
on the 12th of April 1888 at the unforgettable medieval banquet hosted by Loti in his home in Rochefort. Pitchers on the tables, goblets, bowls, flaming torches, pageboys “who stood waiting motionless”, and valets in livery to serve the interminable thirteen-course dinner. A succession of soups, sea and freshwater fish, roast venison, squirrel, and hedgehog, desserts, tarts, wines, barley beer, mead, candied fruits, spices, and the showpiece, a roasted peacock, served in its feathers, borne on a golden platter by two equerries, accompanied by torchbearers and bagpipers, and ceremoniously presented to each lady in turn before being given up to an equerry’s carving knife. The whole meticulously staged by Loti with interludes between courses: jugglers, sorceresses, pilgrims returning from Jerusalem, yellow- and green-clad jesters leaping through a trap door to dance a saraband, a chained Saracen prisoner brought to the feet of the master of the house, a minstrel, table games, dice, chess, merrymaking till dawn when “the cruel meanness of the 19th century returned to crush the poetic and the beautiful, the noble 15th century roused for one night from its eternal slumber.”

As Loti wrote of the gargantuan feast of 1888 in his Journal Intime: “I had an unadulterated vision of the Middle Ages at two brief moments: on arrival, when I was the first to enter the room bathed in red light from the torches held by long-haired valets, and again on the arrival of the peacock, preceded by bagpipers and the mounted servant.”

Other memorable events followed—a water sprite party and a celebration of country life—until the last great staging in 1901, when Old Cathay came to Rochefort, and two hundred guests in Chinese garb and trappings strolled between the port or railway station and the house, past the mild-mannered townsfolk of Rochefort gaping in awe.

Hermione and the Marquis de la Fayette

On August 4th, 1808, Emperor Napoléon came to Rochefort, on his return from a visit to Bayonne on the Atlantic coast, accompanied by Joséphine and his staff. Ships of the line lay at anchor in the harbor of the nearby Island of Aix. The Emperor’s second and last visit, in July 1815, was a less joyful affair. Recently defeated at Waterloo, Napoleon spent his last days on French soil on the Island of Aix before his journey into exile on Saint Helena.

Rochefort experienced a joyful episode in 1966, when Jacques Demy fell in love with the townscape and had it repainted—walls white, shutters blue, pink, or yellow—as a backdrop for his film Les Demoiselles de Rochefort (The Young Girls of Rochefort), which played to full houses around the world. In 1997 a group of enthusiasts and French author and Academician Erik Orsenna, the founding president, formed a nonprofit organization (Hermione–La Fayette) dedicated to reconstructing the dockyards of yore and building a replica of
Hermione, the legendary frigate aboard which the 23-year-old Marquis de Lafayette set sail in 1780 to join forces with George Washington in fighting the English crown and winning independence for America.

Traditional methods are being used in a sort of immense in situ laboratory, which has already attracted 3.4 million visitors. A few figures will suffice to illustrate the scope of this project: a hundred or so people working on site daily, 400,000 pieces of wood and metal, 2000 oaks selected from French forests, 1000 pulleys, 1 tonne of tow for caulking, 24 km of ropes, 2200 square meters of sail, three masts, the tallest of which will rise 54 meters above the keel, 26 cannons for 12-pound cannonballs on the gun deck, and 8 cannons on the forecastle—nonfunctional of course and lightened for safety reasons.

What would Pierre Loti have thought of today’s Hermione? Of this three-masted, 65-meter, 1166-tonne frigate with a petrol blue hull embellished with gold? Faithfully recon-
structured step by step since July 4th, 1997 using the original plans, the Hermione will in all regards be true to the original when it takes to sea in 2015 to retrace La Fayette’s voyage to Boston, with, it is true, some concessions to modernity in the shape of a small motor system and a few computerized navigational aids, manned by a crew of 80, compared with the 316 seamen needed in the 18th century.

The Hermione at one end of the rope factory in one of the dry docks on the banks of the Charente River, together with the visitor center, attracts over 250 000 visitors a year, and guided visits fund a good part of the work, which visitors can watch from a system of catwalks.

More than a reminder of the glorious maritime history of France and of the bonds of friendship between France and America in the early days of the War of Independence, the Hermione is above all the fruit of an incredible technical challenge. Work on the vessel is overseen by the historical committee, which ensures the authenticity of the building methods, adapted to meet current seaworthiness regulations. From engineering to carpentry, from the weaving of the linen sails to the manufacture of the rigging, traditional know-how is being used to recreate the vessel and its three decks, 2200 square meters of sail, oak hull 70 cm thick in parts (plating, ribbing, lining), unimaginable today but vital for repelling 18th-century cannonballs. La Fayette’s original Hermione was built in less than a year, while today’s replica, it is true, only emerged from its dry dock in the summer of 2012, some fifteen years after the first hammer blow was struck. The first voyage—to the Island of Aix — is planned for 2013, and the final touches will be made at sea in 2014 before the transatlantic crossing.

What would Loti have said? Remembering his staging of events designed to create and sustain the illusion of time travel, to suspend time, we can wager that he would have been the first to rejoice in this epic return to the 18th century. To an age unhurried, to a past when the dance to the music of time was more sedate. In Rochefort as elsewhere.

Private collection © Archives Charmet.

**Rochefort, la ville à remonter le temps**

Rochefort, située dans un méandre de la Charente jouxtant son estuaire, doit son destin à Louis XIV qui y fit implanter, en 1666, le plus grand arsenal militaire et maritime de la France. Port maritime au patrimoine architectural le plus riche de l’hexagone, avec son extraordinaire Corderie Royale en pierre calcaire longue de près de quatre cent mètres, Rochefort fut également le site de la prestigieuse École de Médecine Navale fondée en 1722 (Cf. article suivant, par le Dr Christian Régnier). Un des fils les plus célèbres de Rochefort est incontestablement l’écrivain Pierre Loti (1850-1923), de son vrai nom Julien Viaud, qui porsuivit une brillante carrière d’officier de marine dans la Royale, doublée d’une carrière d’écrivain couronnée par son élection à l’Académie Française en 1891. Ce qui intrigua sans doute le plus dans le parcours hors normes de Loti fut la passion entretenue pour sa maison natale à Rochefort façonnée au gré de ses voyages comme un décor de théâtre. Son logis devenu musée est un résumé de ses équipées autour du globe et de son goût pour le passé. Loti est à l’image de sa ville d’origine : ville d’apparence tranquille mais qui ne cesse de se lancer des défis. En effet, Rochefort ressemblait à une belle endormie, son arsenal abandonné au début du vingtième siècle, son École de Médecine Navale fermée en 1964, puis l’Hôpital en 1983. Mais ce sommeil est trompeur. À Rochefort aujourd’hui, un groupe d’artsans et de compagnons est à pied d’œuvre pour un nouveau projet fou : la construction à l’identique de l’Hermione, frégate historique de soixante-cinq mètres de long sur laquelle embarqua le marquis de La Fayette pour rejoindre l’armée insurgée de Georges Washington en Amérique. Un challenge technique et historique, un chantier à remonter le temps, un « work in progress » sous les yeux des touristes passionnés.
In the mid-18th century, the mortality rate aboard squadrons making the two- to two-and-a-half-month crossing of the Atlantic to the West Indies was an estimated 0.5% to 17.2%, and the morbidity rate ranged from 5.4% to over 32%. These rates depended on age (cabin boys were more resistant) and position (officers were four times less likely to die at sea than ordinary seamen), as well as time of year, length of crossing, crowding (number of sailors per unit area of deck space), and the type of expedition.”

Not yet five years old at his father’s death in 1643, Louis XIV reigned over France for the next 72 years, during what Voltaire dubbed “an eternally memorable age.” Keen to assert the maritime power of his kingdom, to defend the coasts of France, and to develop trading links with colonies in the Americas (Quebec, Louisiana, the West Indies, Guiana), around 1660 Louis ordered the creation of a fine new naval dockyard on the Atlantic coast. The site chosen was Rochefort, a nondescript village in a disease-infested swamp. Centrally located on the Atlantic coast of France, Rochefort had strategic advantages: it afforded protection by the islands of Ré, Aix, and Oléron, as well as being linked by the Charente River to inland forests planted to supply wood for shipbuilding.

The task of building the naval dockyard was entrusted to Nicolas-François Blondel, the Royal Naval Engineer, and to Louis Nicolas de Clerville, Commissioner General of Fortifications, and work started in May 1666. Soon branded the “navy’s grave,”
General view of the Maritime Hospital in Rochefort. Lithograph by Charles Mercereau, 19th century. The School of Naval Medicine occupied the left wing of the building. Private Collection. © Archives Charmet/Bridgeman Art Library.
Rochefort was long prey to epidemics of malaria and dysentery that wiped out thousands of shipyard workers, townspeople, and convicts from the local penal colony doing forced labor. Yet, by 1690 the French royal navy boasted the largest war fleet in Europe, with 110 ships of the line and 690 other vessels crewed by 100,000 men. From 1666 to the French Revolution, nigh on 1300 ships were commissioned at Rochefort.1-4


Life before the mast
Outbreaks of disease were common in the crowded conditions on board ship, notably during the transport of troops or slaves: “malignant fevers,” typhus, dysentery, pneumonia, dermatoses, typhoid. Hygiene was woeful. Rationing of fresh water meant sailors could wash neither their bodies nor their clothes. They slept in steerage, cramped quarters choked with the stench from buckets of excrement. Bilge water stagnated in the hold, a sort of nautical cesspool and breeding ground for insects. Poor preservation of food and drinking water, lack of space for foodstuffs, often led to shortages at sea. Atlantic crossings were interminable, since a squadron of ships could sail no faster than its feeblest laggard. With no ports of call to take on supplies, want of fresh produce led to vitamin deficiencies, first and foremost scurvy. And to add insult to injury, unlike Spanish sailors, who were issued with warm woolen clothes, French mariners had slow-drying linen garments which soon wore out. Captains reported that by the end of a long voyage their men were in rags, chilled by the rain and cold. On arrival, the sailors, their immune defenses already much weakened, fell victim to endemic and parasitic diseases.

In the mid-18th century, the mortality rate aboard squadrons making the two- to two-and-a-half-month crossing of the Atlantic to the West Indies was an estimated 0.5% to 17.2%, and the morbidity rate ranged from 5.4% to over 32%. These rates depended on age (cabin boys were more resistant) and position (officers were four times less likely to die at sea than ordinary seamen), as well as time of year, length of crossing, crowding (number of sailors per unit area of deck space), and the type of expedition.5,6

Treatises on preserving the health of people at sea led to significant improvements in naval hygiene in the first half of the 18th century. The most famous were those by the botanist Henri Louis Duhamel du Monceau, the navy lieutenant Sébastien François Bigot de Morogues, and the doctors Antoine-Marie Poissonnier-Desperrières and Étienne Chardon de Courcelles, the founder of the naval medical school at Brest. Medical studies on questions of health at sea were formalized in new naval regulations and orders.

A navy health service is born

Around 1640, the first surgeons sailed on French ships; small hospital ships (fluyts) sailed with squadrons; and a naval hospital opened in Marseille. Soon after, a royal order required sea captains to take on board a good surgeon to tend to the ship's company. The Tonnay-Charente naval hospital (40 beds), the first of its kind in France, was founded in the Saint-Éloi Priory in 1666. Some 17 years later, having become too small for its purpose, it was transferred to the vicinity of the Rochefort naval dockyard and renamed the Charente Hospital (480 places, ie, 240 beds). Many thousands passed through this hospital over the next 105 years; some 30,000 died there—sailors, of course, but also convicts and locals who succumbed to the ills emanating from the disease-ridden environs.

From 1673, each of the three great ports of war—Brest, Rochefort, and Toulon—had a doctor and a navy surgeon who were “provided for,” to wit, paid a wage. This number soon increased to two doctors and six surgeons, who took turns to embark.

One of Louis XIV’s principal ministers, Jean-Baptiste Colbert, the Controller-General of Finances, issued an order stipulating that all ocean-going ships manned by over 36 men had to have aboard a surgeon (two for crews of more than 50 men), whose skills were tested before embarkation. Surgeons had to attend dissection classes and acquire from a senior doctor knowledge of internal diseases and remedies. In practice, this rule was little applied and the surgeons or “boy surgeons” who went aboard were uneven in their skills.

Colbert sent his son to the naval dockyard at Rochefort with clear instructions to learn what it took to be... the Secretary of State for the Navy. Some years later, having been appointed to this position upon the death of his father in 1683, Colbert the younger promulgated an order which organized the medical service of the naval hospitals and of the fleet. The Col-
berts, father and son, were of the view that the state should control and supervise rather than organize health care. Colbert the younger expressed his view thus: “I consider it not in the least necessary to increase the number of surgeons. In the past when needed they were found when none were waged, and I am convinced that the same will be true now, all the more so, since as there are already eight waged, fewer will be needed.”  

The problem arose of differences in status and training between doctors, on the one hand, and surgeons and apothecaries, on the other. The former were university-trained and bore the title of doctor; the latter, often of humbler origin and sometimes illiterate, belonged to the world of guilds and served a short apprenticeship to an older guild member. Surgeons varied greatly in skill and their hierarchy was somewhat ill-defined. The best boasted credentials in surgery, served the navy for years, and when their onboard careers came to an end were rewarded with a post in one of the three shipyards as assistant navy surgeon or better still as a “waged surgeon.”

At the end of the 17th century doctors alone were authorized to make diagnoses in internal medicine and to stipulate treatment; they rarely wielded a scalpel. Until the Revolution, surgeons and apothecaries prepared medical prescriptions, and answered to the quartermaster’s office. Owners of their own medicine chests, for which they received an allowance, surgeons were the only medical men on board ship. Placed under the authority of the captain, only the surgeon major was
allowed access to the officers' mess. Not all captains understood or accepted the presence of surgeons on their ship. It is true that the care provided at this time was of limited value in diseases and only surgery (usually amputations) could save lives. The Navy Board was flooded with complaints about the mediocrity of the onboard surgeons, who were accused of rote and artless use of what little they had learnt of anatomy and surgery. The creation of the Academy of Surgery in 1731 heralded a gradual shift of naval medical training towards joint studies with doctors.

It was against this background that the first doctor of the port of Rochefort, Jean Cochon-Dupuy, who studied at the Faculty of Medicine in Toulouse, proposed the foundation of a school for the instruction of ship's surgeons attached to the naval hospital. The Rochefort School of Surgery was inaugurated on 5 February 1722, the first of its kind in the world. Its success was immediate. The Minister of the Navy decided to create schools in Toulon (1725) and Brest (1731), modeled on Rochefort, the three schools developing their own specific features and particular practices.

The Rochefort School of Naval Medicine and the Cochon-Dupuy dynasty

Jean Cochon-Dupuy opened the Rochefort School of Naval Medicine to students under 15 years of age able to read and write, with good eyesight and healthy hands without deformities. Preference was given to children of the families of waged surgeons or of respectable families attached to the navy. The candidates had to be of the Catholic faith and to pass an entrance examination before the medical authorities of the naval dockyard. The school fees were paid by the navy, except for any auditors allowed to attend. Cochon-Dupuy organized the life of the school according to three successive sets of regulations, and wrote the lecture notes for several courses, notably on anatomy and surgery, which he taught.

The teaching program also included bedside training to learn the techniques of bandaging, bloodletting, and operations, the copying out of medical prescriptions, courses at the pharmacy, and botany classes. (Regularly supplied with seeds and plants brought from overseas, Rochefort’s botanic garden was famous and one of its special features.) The students studied on average for five years, and advancement to the next stage of training was by competitive exam. Those who wished to become waged surgeons had to pass the “double masterpiece” test, which consisted of two randomly selected questions, one on anatomy, the other on surgery.

The school had eight ordinary surgeons and twelve students in 1725. Two years later, the Count of Maurepas, Secretary of State for the Navy, attended in the school's amphitheater two anatomy classes on the cadavers of galley slaves. Impressed by the organization, he accorded his protection to the school. Apart from the botanic garden, the school had a rich library with some 14,000 volumes, a cabinet of curiosities of the natural sciences and a remarkable anatomy collection of sections and anatomic preparations injected with wax after the manner of the Dutchman Frederik Ruysch. In 1736, a dental surgeon was appointed at the school, notably for the treatment of people with scurvy, and this became a new specialty at Rochefort. From its creation in 1722, the Rochefort School of Surgery continued to the start of the French Revolution, through the reigns of Louis XV and Louis XVI, which were marked by three wars ruinous for the crown and punctuated by maritime disasters: the War of the Austrian Succession (1740-1748), the Seven Years’ War (1756-1763), and the American War of Independence (1775-1783).

Names

Referred to today as the “Former School of Naval Medicine in Rochefort” (Ancienne École de Médecine Navale de Rochefort), now a museum, and the Hospital (the left wing of the same building) changing names several times. “Rochefort” may or may not be added to the names of the school and hospital. Some names are “official,” others not… This article makes no attempt harmonize its reference to the School and Hospital to a single name for each.

◆ The School: Ecole de Chirurgie (et d’Anatomie) de Rochefort; Ecole de Médecine Navale de Rochefort; Ecole de Santé Navale de Rochefort; or simply nicknamed “La Navale.”
◆ The Hospital: Hôpital-Charante; Hôpital de la Butte; Hôpital de la Fraternité (so named during the French Revolution); Hôpital Maritime; Hôpital de la Marine de Rochefort.

Boxwood urns for drawing the names of the candidates and the questions for medical exams at the Rochefort School of Naval Medicine. 19th century, Rochefort School of Naval Medicine Museum. © Musée National de la Marine/P. Dantec.
The Rochefort hospital saw a huge influx of wounded and sick from the squadrons engaged in the War of the Austrian Succession. A typhus epidemic spread through the town on the return of one such squadron, and of the 2000 navy men who fell sick almost one third died, including 23 so-called “second-class doctors” (who had passed certain examinations, after a six-year apprenticeship with a doctor or five years working in a hospital or three years studying at medical school). The school’s activities and recruitment had to be suspended for a year, as the staff were assigned to care for the sick. The following year another squadron arrived at Rochefort, this time from Canada, and 8000 men died of typhus and scurvy.1,3,4,8,10-13

Gaspard Cochon-Dupuy, a graduate of the Paris Faculty of Medicine, took over the running of the school upon the death of his father in 1757. Two years later, as the Seven Years’ War was raging, the school had 400 beds, 30 surgeons, and a 100 or so junior surgeons. 1788 saw the inauguration of the “hospital on the hill,” located high up to guard against “pestilence” and which replaced the now too-cramped Charente Hospital. The school of surgical anatomy was located in one of the wards near the entrance. The same year, upon the death of his cousin Gaspard, the navy surgeon Pierre Jacques Thomas Cochon-Duvivier took over the running of the school. Thus it was that the same family headed the Rochefort School of Surgery from its founding to the start of the French Revolution (1789), by which time the school had trained more than 700 navy surgeons.8,11

The Rochefort legacy

Apart from the goal of training doctors practiced in treating the afflictions of sailors, the naval schools of surgery led to the inclusion of “waged personnel” in a single administration which prefigured a future navy health service. By awarding diplomas through competitive examination, the naval schools gradually established a hierarchy between navy surgeons receiving different emoluments: funded students, assistant surgeon (two classes), second surgeon, ordinary surgeon, aboard or not. From 1750, all commissioned navy surgeons studied at one of the three schools.
The post of inspector general of the navy hospitals created in 1763 was occupied by Dr Pierre Poissonnier, the inventor of a process of desalination of seawater, who implemented a single set of regulations for the three schools, a joint annual competitive exam for junior surgeons, and the wearing of a uniform (first step towards the inclusion in the military hierarchy that only became effective in 1835).

The second half of the 18th century saw the formation of a specific and stable body of navy surgeons. Rather closed, it was organized along civilian lines and defined a clear career path. The dominant role of the doctors running the schools was progressively challenged by the surgeons who were far better acquainted with the diseases of sailors and had wide-ranging practical experience. “In their [the doctors’] eyes, surgery was a purely mechanical art, they considered that the surgeon was but a skillful workman, armed with iron and fire, who employs one or other as suggested by his own or traditional experience,” lamented the surgeon Étienne Billard in 1790, in an address to the deputies of the Constitutional Convention.

At the end of the American War of Independence (1783), it was reckoned that 859 surgeons and apothecaries of all grades were needed to meet the fleet’s regulatory requirements, but the personnel paid by the King could provide only 155 surgeons. The shortfall was made up by civilian doctors, and volunteer or conscripted surgeons.

On the eve of the French Revolution, the navy’s body of physicians lacking the official title of doctor essentially comprised an estimated 200 well-trained surgeons accustomed to life on board ship. Deploring that they were not integrated into a military career, they exercised nepotism in recruiting for the naval medical schools. What’s more, the body of “waged surgeons” was aging and becoming costly, a good number were unfit for life aboard, and they kept their post (and their emoluments) until they died.

**Revolution and beyond**

During the French Revolution (1789-1799), the royal navy hospital at Rochefort was renamed “Fraternity Hospital,” and the competitive examinations and the surgeons’ certificates were replaced by a nationwide selection process. The medicine and surgery teaching unit was consolidated in the École de Médecine Navale (Naval Medical School) and the program was aligned with that of the medical faculties of Paris, Montpellier, and Strasbourg.

Medical students completed their studies with a doctoral thesis defense in one of the three faculties. Trainee apothecaries began studies in pharmacy, but the naval medical schools were not authorized to award doctorates after the four years of compulsory classes. At the Bourbon Restoration (1814-1830), a bachelor’s degree was required of all those seeking admission
to these medical schools. Soon after, classes in exotic diseases and naval medicine were included in the course of study, and as steamships began to supplant sailing vessels the title of “naval surgeon” was replaced by “naval doctor.” Bacteriology and therapeutics were still little known, but the frequency of epidemics of typhus and dysentery and the ravages of scurvy dropped considerably thanks to stricter hygiene aboard ship. The death rate at sea in the French navy decreased tenfold between 1810 (one man in 30) and 1913 (one in 308).

A law passed on 11 April 1890 stipulated the setting up of a military health service in Bordeaux, and thereafter students did just the first year of their studies in medicine and pharmacy at Brest, Rochefort, or Toulon, before continuing their studies in Bordeaux. The three schools continued to operate up until 1963, when they were closed. At Rochefort, this ended 241 years of prestigious history, and in 1986 the Ministry of Defense converted the school into a museum under the authority of the National Naval Museum.
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