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**If in Cardiovascular Disease: A New Target to Address Challenging Conditions**

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If in Cardiovascular Disease: A New Target to Address Challenging Conditions
Heart rate is among the most fundamentally important of all physiological characteristics. It is one of the two primary determinants of cardiac output. Bodily function is directly dependent on the adequacy of the cardiac output; indeed, adequate cardiac output is a requisite for maintenance of life. Heart rate (or, more properly, peripheral pulse rate) variations have been associated with disease states for millennia, but the impact of heart rate variations on the pathophysiology of cardiac disorders has only been understood, to a greater or lesser extent, for a little over a century. Epidemiologically, the relation of heart rate to survival has been well demonstrated. Indeed, the highly significant direct association of heart rate with mortality, evidenced from epidemiological studies and actuarial data gathered by insurers, from long-term follow-up of patients with coronary artery disease, and from the effects of drugs in survivors of acute myocardial infarction and those with heart failure, strongly suggests the recognition of heart rate as a cardiovascular risk factor.

The potential benefits of modulating heart rate and, specifically, of heart rate slowing, have been demonstrated experimentally in animal models for decades, supported by epidemiological data in patients, and inferred from pharmacological interventions. However, until recently, heart rate–lowering interventions also have invariably affected other cardiac and systemic characteristics. Therefore, evaluation of the benefits of pure heart rate slowing could not previously be undertaken, because no available therapeutic modality was capable of producing such an isolated effect.

Nevertheless, the basis for pure pharmacological heart rate slowing had been well-understood for more than a quarter century, since the discovery of the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, or f-channels. These ion channels modulate the rate of rise of the spontaneous diastolic depolarization current of the specialized sinoatrial nodal cardiomyocytes, are responsive to hyperpolarization, and require the availability of cyclic adenosine monophosphate for their activation. The If current generated by the f-channels is of very low amplitude, but the effect of its modulation is striking. However, clinically useful pure heart rate slowing via f-channel blockade requires a drug that is specific for the channel, has no other cardiovascular effects, and has no untoward noncardiac actions that would limit its use in any important way. Attempts to develop such an agent began with the discovery of the channel, but the path to a practical therapy was arduous. The first drug with the relevant pharmacological and clinical characteristics was approved by regulatory bodies for marketing in 2005, 26 years after its target had been identified. This drug, ivabradine (Procoralan), has now entered clinical practice in Europe and elsewhere.

The most obvious benefit of heart rate slowing is in preventing manifestations of coronary artery disease. The most common symptom of coronary artery disease, angina pectoris, affects almost 4% of the population of Europe, and has a similar prevalence in the United States. Angina is triggered by transient imbalances in myocardial oxygen supply and myocardial oxygen demand. Drugs that can cause heart rate slowing, such as β-adrenergic receptor blocking drugs and certain calcium channel blockers, have been highly efficient in preventing angina. However, these
agents have additional cardiovascular effects, including vasodilation, reduction in inotropy and, in certain instances, reduction in lusitropy and dromotropy, that can mitigate clinical benefits. Also, like all drugs, they have other noncardiovascular effects that can reduce tolerability. Depending upon the specific type of drug, these can include constipation, abnormal fatigability, depression, sexual dysfunction, etc.9

Heart rate slowing is particularly well suited for improving the balance between myocardial oxygen supply and demand. As a primary determinant of cardiac work, heart rate defines the heart’s metabolic requirements and is the single most important determinant of myocardial oxygen demand.10-12 However, it is less well appreciated that heart rate also modulates myocardial oxygen supply. Coronary blood flow is greatest during diastole; heart rate variations predominantly affect duration of diastole and, thus, impact on flow.13 Diastole increases disproportionately as heart rate slows, enabling progressively greater increments in coronary flow with constant decrements in heart rate.14 In addition, among patients with atherosclerotic narrowing of the coronary arteries, heart rate increase causes coronary constriction with parallel reduction in coronary flow,15 an effect potentially preventable with therapeutic heart rate slowing. Moreover, because its lack of negative inotropic effect precludes lengthening of systolic ejection time, ivabradine is more efficient than β-blockade in enhancing diastolic coronary flow. Finally, recent experimental data suggest that heart rate reduction may stimulate angiogenesis, improving microvascular coronary flow, a further potential mechanism for mitigating inadequate myocardial oxygen supply.36

The effectiveness of ivabradine in preventing angina has been demonstrated in the largest clinical development program ever carried out for an antianginal anti-ischemic drug, involving almost 5000 patients in clinical trials. In these studies, ivabradine has been superior to placebo and equivalent to commonly used doses of atenolol18 and amlodipine.19 Indeed, in the formal comparison with atenolol 100 mg daily, ivabradine 7.5 mg twice daily was more efficient than atenolol, manifesting greater increment in treadmill exercise tolerance per decrement in heart rate than the more established drug, while demonstrating a parallel increase in time to electrocardiographic ST-segment depression, the measure of myocardial ischemia regularly employed in clinical studies.

Because of the profound effect of angina on capacity for work and recreation, angina prevention may be the most important therapeutic benefit of a drug that can mitigate ischemia. When tested formally, patients with angina report marked diminution in quality of life (QoL) compared with that of asymptomatic individuals. QoL scores correlate with the number of angina attacks experienced per week,20,21 and are impaired even by mild angina. Angina affects not only physical functioning, but also emotional well-being, quality of sleep and sexual function.22 Treatment-related reduction of angina is associated with improved QoL.23

Manifestations of coronary artery disease other than angina also may be mitigated by heart rate slowing, though additional data, from ongoing and future studies, must demonstrate that the theoretical and experimental data are confirmed in clinical practice. Thus, plaque rupture, which can trigger potentially lethal acute coronary events, is directly related to heart rate.24 The utility of pure heart rate slowing with ivabradine to prevent death and nonfatal infarction is now being assessed in the BEAUTIFUL study (morBidity-mortality EvAlUaTion of the I_NHibitor Ivabradine in patients with coronary disease and left ventricuLar dysfunction),25 which has already randomized its full complement of 10 500 patients; follow-up will be complete in 2008, and will provide the first assessment of secondary event prevention ever performed with an antianginal anti-ischemic drug among patients with chronic stable coronary artery disease. A complementary study, VIVIFY (eValuation of the IntraVenous I_NHibitor Ivabradine after ST segment Elevation MYocardial Infarction), is now planned to assess the value of ivabradine-based pure heart rate slowing in patients with acute coronary syndrome as an adjunct to current catheter-based mechanical therapy.

Coronary disease also is the primary problem underlying chronic heart failure, a markedly debilitating condition that consumes 1% to 2% of all health care expenditures in industrialized countries.26 Reduction in ischemia may also mitigate development of this very serious condition, a hypothesis that will be tested in the BEAUTIFUL study. However, evaluation of heart rate slowing as treatment for heart failure, to improve QoL and to reduce hospitalization and mortality rates, requires a trial design and inclusion criteria somewhat different from BEAUTIFUL. Indeed, heart failure may result from conditions other than coronary disease. Experimentally, heart rate slowing may directly alter intracellular energetics and calcium handling, thereby enhancing myocardial mechanics and reducing heart failure of any cause, even in the absence of ischemia. Ivabradine has enhanced left ventricular function and normalized left ventricular structure in
a rat heart failure model. Early clinical studies suggest that these theoretical benefits may have practical clinical correlates. Thus, in patients with systolic dysfunction, a single intravenous dose of ivabradine preserved left ventricular performance despite heart rate reduction. In more recent unpublished studies, oral ivabradine administered for 3 months to a small group of patients with heart failure and systolic dysfunction tended to increase left ventricular ejection fraction, while reducing left ventricular end-systolic and end-diastolic volumes; these findings were most marked among patients with the lowest ejection fractions prior to therapy. The implications of these suggestive findings now are being explored more rigorously in the SH/T trial (Systolic Heart Failure treatment with the I$_f$ inhibitor ivabradine Trial), which is assessing the effects of heart rate slowing on heart failure hospitalizations, mortality, symptomatic deility, and left ventricular function. At the time of this writing, almost 1000 of the projected 5500 study patients with heart failure and systolic left ventricular dysfunction have been randomized, including patients with and without underlying coronary artery disease.

Taken together, rapidly emerging data support the concept that heart rate is a legitimate and important cardiovascular risk factor. In addition, they suggest that pure heart rate slowing can relieve symptoms and, perhaps, improve the natural history of patients with coronary artery disease and, possibly, with heart failure of any etiology. As will be discussed in this issue of Medico-Graphia, I$_f$ inhibition is the only available therapeutic modality that can modulate the isolated risk factor to prevent angina and to determine if the other theoretical benefits can be translated into clinical practice.

Keywords: ischemic heart disease; coronary artery disease; acute coronary syndrome; heart failure; heart rate; risk factor

REFERENCES

L’inhibition \( I_f \) face aux défis posés par certaines situations cardiologicals critiques : bilan et perspectives

par J. S. Borer, États-Unis

La fréquence cardiaque est l’une des caractéristiques physiologiques les plus fondamentales. Elle représente l’un des deux déterminants principaux du débit cardiaque. Or, le fonctionnement de l’organisme dépend directement de l’adéquation du débit cardiaque à ses besoins, au point que cette adéquation conditionne véritablement le maintien de la vie. Les variations de la fréquence cardiaque (ou plus exactement, de la fréquence du pouls périphérique) ont été rapportées à divers états pathologiques depuis des millénaires, mais leur impact sur la physiopathologie des troubles cardiaques n’est plus ou moins bien compris que depuis un peu plus d’un siècle. D’un point de vue épidémiologique, la relation entre la fréquence cardiaque et la survie a été bien démontrée. L’association directe hautement significative entre la fréquence cardiaque et la mortalité a été mise en évidence par des études épidémiologiques et des données actuarielles recueillies par les assureurs, mais aussi à partir du suivi à long terme des patients atteints d’une maladie coronaire ou encore des effets des médicaments sur les malades qui ont survécu à un infarctus du myocarde, a fortiori associé à une insuffisance cardiaque. Cette association plaide fortement en faveur de la reconnaissance de la fréquence cardiaque en tant que facteur de risque cardio-vasculaire.

Les bénéfices potentiels offerts par la modulation de la fréquence cardiaque et, plus spécifiquement, par son ralentissement, ont été démontrés expérimentalement il y a des décennies sur des modèles animaux. Ces résultats sont en outre étayés par les données épidémiologiques recueillies chez les malades et extrapolés à partir de certaines interventions pharmacologiques. Cependant, jusqu’alors, les interventions thérapeutiques permettant de ralentir la fréquence cardiaque affectaient invariablement d’autres paramètres cardiaques et systémiques. Ainsi, l’évaluation du bénéfice lié au ralentissement exclusif de la fréquence cardiaque ne pouvait être entreprise, du fait de l’absence de modalités thérapeutiques capables d’engendrer isolément cet effet.

Il n’empêche que les bases du ralentissement pharmacologique exclusif de la fréquence cardiaque étaient bien comprises depuis plus d’un quart de siècle, avec la découverte des canaux ioniques HCN (hyperpolarization-activated cyclic nucleotide-gated ion channels = canaux ioniques activés par l’hyperpolarisation, modulés par les nucléotides cycliques), ou canaux \( I_f \). Il a été montré que ces derniers modulaient l’amplitude de la dépolarisation diastolique spontanée au sein des cardiomyocytes spécialisés qui composent le nœud sino-auriculaire, qu’ils étaient stimulés par l’hyperpolarisation, et que leur activation exigeait la présence d’AMP cyclique. Le courant \( I_f \) engendré par les canaux \( f \) est de très faible amplitude, mais sa modulation provoque des effets considérables. Toutefois, pour que le ralentissement exclusif de la fréquence cardiaque par inhibition des canaux \( f \) soit utile sur le plan clinique, il faudrait disposer d’un médicament spécifique de ces derniers, dépourvu d’autres effets cardio-vasculaires, et qui n’entraîne aucun effet non cardiaque susceptible de limiter notablement son utilisation. Les tentatives pour développer un tel médicament ont débuté dès la découverte des canaux \( f \), mais la voie vers un traitement utilisable en pratique a été ardue. En effet, ce n’est que 26 ans après l’identification de la cible thérapeutique qu’est intervenue la mise sur le marché du premier médicament.
possédant les caractéristiques pharmacologiques et cliniques voulues. Ce médicament, l’ivabradine (Procoralan®), approuvé par les agences de régulation en 2005, est maintenant utilisé en pratique clinique courante en Europe et ailleurs.

Le bénéfice le plus évident du ralentissement de la fréquence cardiaque réside dans la prévention de certaines manifestations de la maladie coronarienne. Le symptôme le plus courant de cette dernière est l’angor, qui affecte environ 4% de la population en Europe. Sa prévalence est similaire aux États-Unis. L’angor est déclenché par un déséquilibre transitoire entre les apports et les besoins myocardiques en oxygène. Les médicaments qui sont capables de ralentir la fréquence cardiaque, dont les bétabloquants et certains inhibiteurs calciques, ont fait la preuve de leur grande efficacité dans la prévention de l’angor. Cependant, ces agents thérapeutiques ont d’autres effets cardio-vasculaires, parmi lesquels figurent la vasodilatation, l’effet inotrope négatif et, dans certains cas, un effet lusitrope et dromotrope négatif, pouvant compromettre leurs bénéfices cliniques. En outre, comme tous les médicaments, ils ont aussi des effets non cardio-vasculaires qui diminuent leur tolérance. Selon leur type, il peut s’agir d’une constipation, d’une fatigueabilité anormale, d’une dépression, d’un dysfonctionnement sexuel, etc.

Le ralentissement de la fréquence cardiaque est particulièrement bien adapté quand il s’agit d’améliorer l’équilibre entre les apports et les besoins myocardiques en oxygène. En tant que déterminant principal du travail cardiaque, la fréquence cardiaque définit les exigences métaboliques du cœur, constituant à elle seule le déterminant le plus important des besoins myocardiques en oxygène. Cependant, il est moins connu que la fréquence cardiaque module aussi les apports myocardiques en oxygène. Le débit sanguin coronarien est maximal durant la diastole. C’est la durée de cette dernière qui est la plus affectée par les variations de la fréquence cardiaque et, de ce fait, le débit sanguin coronarien. La durée de la diastole augmente de manière disproportionnée quand la fréquence cardiaque diminue, de sorte que l’élévation du débit sanguin coronarien continue à croître progressivement, tandis que la fréquence cardiaque diminue de façon constante. De plus, chez les patients atteints de sténoses athéromateuses des artères coronaires, l’augmentation de la fréquence cardiaque induit une vasoconstriction coronaire qui entraîne un baisse correspondante du débit sanguin coronarien, cet effet pouvant être prévenu par le ralentissement de la fréquence cardiaque. En outre, l’ivabradine est plus efficace que les bétabloquants en ce qui concerne l’augmentation du débit sanguin coronarien diastolique, car elle n’exerce pas d’effet inotrope négatif susceptible d’allonger le temps d’éjection systolique. Enfin, les données expérimentales les plus récentes suggèrent que la réduction de la fréquence cardiaque peut stimuler l’angiogenèse et améliorer ainsi le débit coronarien microvasculaire, ce qui représente un autre mécanisme potentiellement utile pour s’opposer aux anomalies des apports myocardiques en oxygène.

L’efficacité de l’ivabradine dans la prévention de l’angor a été démontrée dans le cadre du plus grand programme de développement clinique jamais réalisé à ce jour avec un anti-angineux/anti-ischémique, au cours duquel plus de 5 000 patients ont été inclus dans divers essais cliniques. Ceux-ci ont montré que l’effet de l’ivabradine était plus efficace que celui du placebo et identique à celui de l’aténolol et de l’amlodipine aux doses communément utilisées. De fait, dans une comparaison formelle avec l’aténolol (100 mg/jour), l’ivabradine (en 2 prises quotidiennes de 7,5 mg chacune) s’est avérée plus efficace que le bétabloquant, avec notamment une augmentation supérieure de la tolérance à l’effort sur tapis roulant pour chaque palier de baisse de la fréquence cardiaque. Parallèlement, a été obtenue une augmentation du délai d’apparition du sous-décalage du segment ST, qui est le paramètre couramment utilisé dans les essais cliniques pour évaluer objectivement l’ischémie myocardique.

L’angor a un retentissement majeur sur la capacité à participer à des activités de travail ou de loisir et sa prévention est sans doute l’un des bénéfices thérapeutiques les plus importants attendus d’un médicament anti-ischémique. Dans les études évaluant spécifiquement la qualité de vie (QdV), celle-ci était nettement allégée chez les malades atteints d’angor, comparativement aux sujets asymptomatiques. Les scores de QdV sont ainsi corrélés au nombre hebdomadaire des crises d’angor et apparaissent détériorés, même quand il s’agit d’un angor léger. L’angor n’affecte pas que les performances physiques, mais aussi le bien-être émotionnel, la qualité du sommeil et la sexualité. La diminution de l’angor sous l’effet d’un traitement est donc associée à une amélioration de la QdV.

Les manifestations de la maladie coronarienne autres que l’angor peuvent être également améliorées par le ralentissement de la fréquence cardiaque, encore que des données supplémentaires, émanant d’études en cours ou à venir soient nécessaires pour démontrer que les hypothèses théoriques et les résultats expérimentaux ont bel et bien une traduction dans la réalité clinique.
Ainsi, la rupture de la plaque, qui déclenche habituellement des événements coronaires responsables de décès, est directement en relation avec la fréquence cardiaque. L’utilité d’un ralentissement exclusif de cette dernière au moyen de l’ivabradine dans la prévention des décès et des infarctus du myocarde non létaux est actuellement en cours d’évaluation dans le cadre de l’étude BEAUT\(\text{UL}\) (morBidity-mortality EvAlUaTion of the I\(_f\) inhibitor ivabradine in patients with coronary artery disease and left ventricular dysfunction). Dans celle-ci a d’ores et déjà été randomisée l’intégralité des 10 500 patients prévus. Le suivi sera terminé en 2008. Il s’agit là de la première étude de prévention secondaire jamais réalisée pour évaluer un médicament anti-ischémique/anti-angineux chez des patients atteints d’une maladie coronaire stable. Un essai complémentaire, l’essai VIVI\(\text{Y}\) (eValuation of the IntraVenous I\(_f\) inhibitor ivabradine after ST segment elevation myoccardial infarction) est actuellement planifié pour évaluer l’intérêt du ralentissement exclusif de la fréquence cardiaque induit par l’ivabradine dans les syndromes coronaires aigus, en complément des techniques actuelles de revascularisation myocardique reposant sur le cathétérisme coronaire.

La maladie coronaire est également le facteur principal sous-jacent à l’insuffisance cardiaque chronique, pathologie profondément invalidante à l’origine de 1 à 2 % de l’ensemble des dépenses de santé des pays industrialisés. La réduction de l’ischémie pourrait s’opposer au développement de cette pathologie grave : cette hypothèse sera testée dans l’étude BEAUT\(\text{UL}\). Cependant, l’évaluation du rôle du ralentissement de la fréquence cardiaque dans le traitement de l’insuffisance cardiaque, dans le but d’améliorer la QdV et de réduire la fréquence des hospitalisations et la taux de mortalité, requiert un autre protocole et des critères d’inclusion différents de ceux de l’étude BEAUT\(\text{UL}\). Il est vrai que l’insuffisance cardiaque peut résulter d’autres troubles que la maladie coronaire. Expérimentalement, le ralentissement de la fréquence cardiaque peut agir directement sur le métabolisme énergétique intracellulaire et les échanges calciques, améliorant ainsi les propriétés mécaniques du myocarde et réduisant l’insuffisance cardiaque quelle qu’en soit la cause, même en l’absence d’ischémie. L’ivabradine a ainsi amélioré la fonction du ventricule gauche, tout en normalisant sa structure, dans un modèle expérimental d’insuffisance cardiaque développé chez le rat. Les premières études cliniques suggèrent que ces bénéfices théoriques pourraient avoir une traduction clinique pratique. Ainsi, chez les malades atteints d’un dysfonctionnement systolique, l’administration d’une dose unique d’ivabradine par voie intraveineuse permet de préserver le fonctionnement ventriculaire gauche en dépit de la réduction de la fréquence cardiaque. Des études plus récentes non publiées montrent que l’administration d’ivabradine par voie orale pendant 3 mois à un petit groupe de patients ayant une insuffisance cardiaque et un dysfonctionnement systolique tend à augmenter la fraction d’ejection ventriculaire gauche, tout en diminuant les volumes télédiastrique et télésystolique. Ces résultats sont les plus nets chez les patients dont la fraction d’éjection ventriculaire gauche est la plus basse avant le traitement. Ces données encourageantes font actuellement l’objet d’une évaluation plus rigoureuse dans le cadre de l’étude SH\(\text{IT}\) (Systolic Heart failure treatment with the I\(_f\) inhibitor ivabradine Trial). Cette étude évaluera les effets du ralentissement de la fréquence cardiaque sur les hospitalisations pour insuffisance cardiaque, la mortalité, les symptômes débilitants et la fonction ventriculaire gauche. Au moment où sont écrites ces lignes, sur un effectif total initialement prévu de 5 500 patients atteints d’une insuffisance cardiaque et d’un dysfonctionnement ventriculaire gauche systolique, presque 1000 ont déjà été randomisés, qu’ils soient atteints ou non d’une maladie coronaire sous-jacente.

Considérées dans leur ensemble, toutes ces données qui émergent rapidement plaident en faveur du concept présentant la fréquence cardiaque comme un facteur de risque cardio-vasculaire à la fois légitime et important. En outre, elles suggèrent que le ralentissement exclusif de la fréquence cardiaque peut soulager certains symptômes et peut-être même améliorer l’histoire naturelle de la maladie coronaire, voire celle de l’insuffisance cardiaque, quelle qu’en soit l’étiologie. Comme cela sera discuté dans les articles constituant ce numéro de Medicographia, l’inhibition du courant I\(_f\) est la seule modalité thérapeutique actuellement disponible qui permette de moduler de façon spécifique et exclusive la fréquence cardiaque dans le dessein de prévenir l’angor, et de vérifier si les autres bénéfices théoriques attendus ont ou non une traduction dans la pratique clinique courante.
Heart rate in clinical practice: therapeutic implications in patients with coronary artery disease

by J. C. Tardif, Canada

The association between resting heart rate and mortality has been observed in patients with hypertension, the metabolic syndrome, and in the elderly. We recently assessed the relationship between resting heart rate and cardiovascular mortality and morbidity in patients with stable coronary artery disease (n=24,913) who were followed for a median of 15 years, with adjustment made for risk factors during analysis. All-cause mortality and cardiovascular mortality and rehospitalization were associated with an increased heart rate (P<0.0001). Compared with the control group, patients with a baseline resting heart rate of ≥83 beats per minute (bpm) had a significantly higher risk of total mortality (hazard ratio [HR], 1.32; confidence interval [CI], 1.19-1.47; P<0.0001) and cardiovascular mortality (HR, 1.31; CI, 1.15-1.48; P<0.0001) after adjustment for multiple clinical variables. When patients with heart rates of 77 to 82 bpm and ≥83 bpm were compared with patients whose heart rate was ≤62 bpm, the HRs for time to first cardiovascular rehospitalization were 1.11 and 1.14, respectively (P<0.001 for both). A high heart rate induces or exacerbates myocardial ischemia and angina, because it both increases oxygen demand and decreases myocardial perfusion, the latter via shortening of the diastole duration. Ibrudine is a selective and specific I inhibitor that acts on one of the most important ionic currents for regulation of the pacemaker activity of sinoatrial node cells. Ibrudine is a heart rate–reducing agent that has demonstrated dose-dependent anti-ischemic and antianginal effects in an extensive clinical trial program involving more than 5000 patients. The noninferiority of irudine was shown versus the β-blocker atenol and the calcium channel blocker amldipine. A wide range of patients with angina may benefit from exclusive heart rate reduction with irudine, including those with contraindications or intolerance to the use of β-blockers, and patients who are insufficiently controlled by β-blockers or calcium channel blockers.


Selected abbreviations and acronyms

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Effect of heart rate in stable angina and coronary artery disease

Chronic stable angina is a common and disabling condition, affecting between 30,000 and 40,000 per 1 million people in Europe and the US. Angina is the result of insufficient myocardial perfusion to meet metabolic demand. Individuals with typical chronic stable angina usually have significant narrowing of at least one major epicardial vessel, and experience pain that is related to an increase in physical activity or psychological stress. Heart rate is one of the most important determinants of myocardial oxygen demand. A high heart rate induces or exacerbates myocardial ischemia and subsequent angina, as it both increases myocardial oxygen demand and decreases myocardial perfusion, the latter via shortening of the duration of diastole.

Many investigators have concluded that heart rate triggers most episodes of ischemia in patients with stable CAD. Andrews et al found that 81% of ischemic episodes were preceded by an increase in heart rate of 5 bpm or more in their evaluation of heart rate during ambulatory monitoring of 50 patients with stable CAD participating in a comparison of propranolol, diltiazem, nifedipine, and placebo. The likelihood of development of ischemia was found to be related to baseline heart rate, with occurrences ranging from 8.7% in patients with a baseline heart rate of less than 60 bpm, to 18.5% when baseline heart rate was 90 bpm or more. When investigating the relationship between heart rate and ischemia, most studies have examined events 1 minute before the onset of ST-segment depression. However, in a study of 212 episodes of ischemia in 21 patients undergoing continuous ambulatory monitoring, significant increases in heart rate 5 to 30 minutes before each event were strongly associated with myocardial ischemia during daily life. The authors of this study postulated that because the development of ischemia is determined by both intensity of exercise and time, a modest rise in heart rate over a prolonged period may explain the reduced heart rate threshold for ischemia commonly described during daily life, and may play a part in the development of ischemia at lower heart rates during daily life than during standard exercise testing.

Relieving the symptoms of angina and improving quality of life and functional status are an integral part of the management of patients with chronic stable angina. Heart rate reduction is a well-recognized strategy for the prevention of ischemia in patients with stable CAD. It allows a decrease in myocardial oxygen consumption and an increase in the diastolic filling time (thereby increasing oxygen supply), and thus prevents the onset of angina attacks. In studies examining the effects of various antianginal agents, the greatest anti-ischemic efficacy has been reported with agents producing the most sustained reductions in heart rate. β-Blockers are effective at reducing angina largely because they decrease heart rate, and they have commonly been preferred as initial therapy for the condition in the absence of contraindications. Despite the demonstrated safety and effectiveness of β-blockers, physician use and patient compliance can be somewhat limited by the side effects of this class of agents, which include fatigue, sexual dysfunction, depression, cold extremities, light-headedness, gastrointestinal disturbances, bronchospasm, and atrioventricular (AV) block. β-Blockade can also increase coronary resistance and limit exercise-induced increases in coronary arterial flow. In addition, β-blockers can reduce LV contractility and have negative lusitropic effects. Finally, this class of agents can have detrimental effects on carbohydrate and lipid metabolism.

A novel concept of heart rate reduction: selective and specific $I_f$ inhibition with ivabradine

Heart rate has been shown to be modulated by the cardiac pacemaker $I_f$ current, a mixed Na- K inward current activated by hyperpolarization and modulated by the autonomic nervous system. Ivabradine is a novel specific heart rate–reducing agent that acts in sinoatrial node cells by selectively and specifically inhibiting the pacemaker $I_f$ current in a dose-dependent manner. It slows the diastolic depolarization slope of the action potential in sinoatrial node cells and reduces heart rate at both rest and during exercise in animals and human volunteers.

Ivabradine is devoid of intrinsic inotropic effects, and does not affect either LV systolic function or coronary vasomotion in experimental models both at rest and during exercise. Ivabradine has no detectable effect on AV node cells, as evidenced by the absence of any change in the PR interval and other intraventricular conduction parameters on its administration. In addition, an intravenous dose of ivabradine does not prolong the corrected QT interval or modify the conductivity and refractoriness of the atria, AV node, His-Purkinje system, and ventricles. Manz et al used echocardiography to study the impact of a single intravenous dose of ivabradine on LV function in patients with systolic dysfunction. The LV ejection fraction did not significantly decrease with ivabradine (0.2%) compared with placebo (1.7%). Other echocardiographic parameters, such as fractional shortening and stroke volume, were also unchanged after intravenous administration of ivabradine. LV relaxation is as crucial for optimal LV function as is contractility, and the negative lusitropic effect of β-blockers could therefore be potentially deleterious. Colin et al investigated the effects of ivabradine and atenolol on LV isovolumetric relaxation at rest and during treadmill exercise in chronically instrumented dogs. By contrast with atenolol, ivabradine did not exert any negative lusitropic effect for a similar reduction in heart rate at rest and during exercise. In addition, in contrast to β-blockers, ivabradine does not cause detrimental effects on coronary vasomotion.

The antianginal and anti-ischemic efficacy of ivabradine has been demonstrated in a large clinical program including more than 5000 patients. The results of placebo-controlled clinical trials involv-
ing ivabradine, as well as comparative studies not involving placebo, confirm the importance of heart rate in determining the frequency of angina and the severity of underlying ischemia. These studies importantly support the value of pure heart rate modulation for the prevention of angina and the minimization of underlying ischemia.

**Ivabradine versus β-blockers in stable angina**

The INternational Tral of the AnTianginal effects of IVabradinE compared to atenolol (INITIATIVE) was a randomized, double-blind, multicenter study evaluating the antianginal and anti-ischemic effects of ivabradine versus the β-blocker atenolol in 939 patients with chronic stable angina. The trial protocol and medication dosages are shown in Figure 1. After placebo wash-out of all antianginal medications, patients were randomized to one of three treatment groups: ivabradine 5 mg twice daily (bid) for 4 weeks increasing to 7.5 mg bid for 12 weeks; ivabradine 5 mg bid for 4 weeks increasing to 10 mg bid for 12 weeks; or atenolol 50 mg once daily (od) for 4 weeks increasing to 100 mg od for the following 12 weeks (Figure 1). The primary efficacy end point was the change from baseline to the end of treatment (16 weeks) in the total exercise duration during the treadmill exercise tolerance test performed according to a modified Bruce protocol at the trough of drug activity. Secondary end points included changes in time to limiting angina, time to onset of angina, and time to 1-mm ST-segment depression, both at the trough and peak of drug activity. Angina attack frequency and short-acting nitrate consumption were also evaluated from patient’s diaries.

The total exercise duration at the trough of drug activity increased from inclusion to end of treatment (16 weeks) by 14.0 bpm in favor of ivabradine, as well as comparative studies not involving placebo, confirm the importance of heart rate in determining the frequency of angina and the severity of underlying ischemia. These studies importantly support the value of pure heart rate modulation for the prevention of angina and the minimization of underlying ischemia.
A NEW TARGET TO ADDRESS CHALLENGING CONDITIONS

Heart rate in clinical practice: therapeutic implications in CAD – Tardif

Figure 3. Differences between ivabradine and atenolol in the change in time to limiting angina at trough of drug activity in the INITIATIVE. Based on data from reference 33.

Abbreviations: Ate, atenolol; bid, twice daily; Iva, ivabradine; od, once daily.

Treatment period to approximately 1 attack per week. Thus, INITIATIVE has shown the noninferiority of ivabradine 7.5 mg and 10 mg bid compared with atenolol 100 mg od in terms of their antianginal and anti-ischemic effects on all exercise parameters.33

**Combination antianginal therapy**

Considerable evidence indicates that combination therapy may be more effective than monotherapy for the treatment of angina pectoris.8,11 The efficacy and safety of combination therapy with ivabradine was established over a period of 1 year in 386 patients with stable angina who were already receiving treatment with nitrates or dihydropyridine calcium channel blockers.35 Two different dosages of ivabradine were used: 5 mg and 7.5 mg bid. Ivabradine was shown to reduce the heart rate of patients by 10 bpm at 5 mg bid and 12 bpm at 7.5 mg bid. Ivabradine maintained this heart rate reduction over the year of follow-up. The number of angina attacks reported by patients was significantly reduced by the addition of ivabradine.

**Conclusion**

Slowing of the heart rate is an integral part of an optimal pharmacological antianginal strategy. β-Blockers have traditionally been considered as a first-line therapy for stable angina, but their use may be limited by side effects, including fatigue, depression, and sexual dysfunction. Bronchospasm and AV block represent other limitations of β-blockers. Ivabradine is a selective and specific I\(_f\) inhibitor whose antianginal and anti-ischemic effects have been shown to be noninferior to those of the β-blocker atenolol and the calcium channel blocker amiodipine. Study data are consistent with the importance of heart rate in determining the frequency of angina and the severity of underlying ischemia, and demonstrate the value of pure heart rate modulation in the prevention of angina and the minimization of underlying ischemia. Unlike β-blockers, ivabradine is devoid of intrinsic negative inotropic effects and does not affect coronary vasomotion. A whole range of patients with angina may benefit from exclusive heart rate reduction with ivabradine, including those with contraindications or intolerance to the use of β-blockers and patients who are insufficiently controlled by β-blockers or calcium channel blockers.

Furthermore, the efficacy of ivabradine in reducing major cardiovascular events in patients with CAD is currently being tested in the large-scale morbidity-mortality Evaluation of the I\(_f\) inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTY/U/L), a randomized, controlled study in patients with CAD and moderate-to-severe LV dysfunction. This study is the first opportunity to investigate whether pure heart rate reduction reduces cardiovascular events.36

1195 patients with chronic stable angina and documented CAD.30 In this study, ivabradine 7.5 mg bid was found to have an efficacy that was indistinguishable from that of amiodipine 10 mg od for all measured bicycle exercise test parameters (Figure 4). The time to angina onset was increased by 64.7±104.8 seconds with ivabradine 7.5 mg bid and 66.6±99.1 seconds with amiodipine 10 mg od (95% CI, –15.2 to +14 seconds; P<0.001 for noninferiority). Time to 1-mm ST-segment depression was increased by 45 seconds in the ivabradine 7.5 mg bid group and by 40 seconds in the amiodipine 10 mg od group (P<0.001 for noninferiority). Statistical testing also revealed that ivabradine was noninferior to amiodipine (P<0.0001) in the prevention of angina attacks. As previously observed in large clinical trials, ivabradine significantly decreased the number of angina attacks by two thirds and reduced the consumption of short-acting nitrates.

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**Table 1:** Changes in the exercise tolerance test parameters in the ivabradine 7.5 mg twice daily group versus the amiodipine 10 mg once daily group, during a large randomized noninferiority clinical trial. Based on data from reference 34.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Atenolol</th>
<th>Ivabradine</th>
<th>E [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>6.5 [7.6; 20.6]</td>
<td>–1.8 [–14.6; 11.6]</td>
<td>P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>TLA</td>
<td>–0.6 [–15.2; 14.0]</td>
<td>–1.2 [–14.4; 11.7]</td>
<td>P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>TAO</td>
<td>–0.6 [–15.2; 14.0]</td>
<td>–1.2 [–14.4; 11.7]</td>
<td>P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>TED</td>
<td>6.5 [7.6; 20.6]</td>
<td>–1.8 [–14.6; 11.6]</td>
<td>P&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

---

**Table 2:** Changes in the equivalence interval for the exercise parameters in the ivabradine 7.5 mg bid group versus the amlodipine 10 mg once daily group, during a large randomized noninferiority clinical trial. Based on data from reference 34.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Atenolol</th>
<th>Ivabradine</th>
<th>E [95% CI]</th>
<th>P for noninferiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>5.4 [–9.3; 19.3]</td>
<td>9.3 [–9.6; 28.3]</td>
<td>15.1 [–3.9; 34.0]</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>

---

**Figure 4.** Changes in the exercise tolerance test parameters in the ivabradine 7.5 mg twice daily group versus the amiodipine 10 mg once daily group, during a large randomized noninferiority clinical trial. Based on data from reference 34.

---

**Abbreviations:** Ate, atenolol; bid, twice daily; Iva, ivabradine; od, once daily.
REFERENCES


L'association entre fréquence cardiaque de repos et mortalité a été observée chez les patients hypertendus, dans le syndrome métabolique et chez les sujets âgés. Nous avons récemment évalué la relation entre la fréquence cardiaque de repos et la morbi-mortalité cardio-vasculaire chez les patients dont la maladie coronaire était stable (n = 24 913) et qui étaient suivis en moyenne depuis 15 ans, les facteurs de risque ayant été ajustés pendant l'analyse. La mortalité toutes causes, la mortalité cardio-vasculaire et la réhospitalisation étaient associées à une augmentation de la fréquence cardiaque (p < 0,0001). Comparés au groupe témoin, les patients dont la fréquence cardiaque de repos initiale était supérieure ou égale à 83 battements/min (bpm) avaient un risque significativement plus élevé de mortalité totale (rapport de risques [RR] 1,32 ; intervalle de confiance [IC] 1,19-1,47 ; p < 0,0001) et de mortalité cardio-vasculaire (RR 1,31 ; IC 1,15-1,48 ; p < 0,0001) après ajustement pour variables cliniques multiples. Si l'on compare les patients dont les fréquences cardiaques sont comprises entre 77 et 82 bpm avec ceux dont la fréquence est inférieure ou égale à 62 bpm, les RR du délai pour la première réhospitalisation cardio-vasculaire étaient respectivement de 1,11 et 1,14 (p < 0,001 pour les deux). Une fréquence cardiaque élevée induit ou majore l’ischémie myocardique et l’angor, toutes deux augmentant la demande en oxygène et diminuant la perfusion myocardique, la dernière en raccourcissant la durée de la diastole. L’ivabradine est un inhibiteur spécifique et sélectif du courant I_f qui agit sur l’un des plus importants courants ioniques régulant l’activité pacemaker des cellules du nœud sino-auriculaire. L’ivabradine réduit la fréquence cardiaque et a montré ses effets anti-ischémiques et antiangoreux dans une grande étude clinique de plus de 5 000 patients. La non-infériorité de l’ivabradine a été démontrée versus l’aténolol (β-bloquant) et l’amlodipine (antagoniste calcique). La réduction de la fréquence cardiaque par l’ivabradine peut profiter à un large éventail de patients angoreux y compris ceux qui présentent une intolérance ou des contre-indications aux β-bloquants et ceux insuffisamment contrôlés par les β-bloquants et les inhibiteurs calciques.
Myocardial ischemia: clinical consequences of heart rate reduction
by A. Berdeaux, France

Regardless of its mechanism, any reduction in heart rate not only reduces myocardial oxygen demand and simultaneously improves oxygen supply, but also favors the perfusion of the subendocardium, which is highly vulnerable during coronary artery stenosis. These effects explain a large part of the antianginal properties of agents such as β-blockers, certain calcium channel antagonists, and more recently ivabradine, a selective inhibitor of the sinoatrial node pacemaker I_{1} current. However, besides this common pharmacological property of the ability to reduce heart rate, there are important differences between these drugs that can lead to different therapeutic implications. For example, β-blockers reduce myocardial oxygen consumption by an additive reduction in heart rate and contractility, but they simultaneously increase the duration of the ejection time and thus reduce the diastolic perfusion time of the ischemic myocardium. By contrast, because ivabradine is devoid of any effects on myocardial contractility and relaxation, it significantly improves the diastolic perfusion time at the ischemic threshold in patients with coronary stenosis. Hence, if the anti-ischemic effects afforded by ivabradine and β-blockers are roughly comparable, their mechanisms of action are quite different, and ivabradine is clearly of more benefit than β-blockers for the treatment of myocardial dysfunction such as stunning accompanying myocardial ischemia and reperfusion.

Mediographia. 2007;29:307-311. (see French abstract on page 311)

Keywords: heart rate; myocardial oxygen consumption, coronary and transmural blood flow, ischemia, diastolic perfusion time, ischemic threshold

Heart rate and myocardial oxygen demand

For a long time, administration of β-blockers was the only pharmacological tool available to decrease heart rate. However, the simultaneous blockade of both β1- and β2-adrenoceptors at the cardiac and coronary artery levels did not afford the possibility of differentiating between the respective contributions of heart rate reduction and myocardial contractility reduction on myocardial oxygen demand. More recently, it has been possible to investigate the respective contribution of these two major determinants of myocardial oxygen demand using ivabradine, a selective inhibitor of the sinoatrial node pacemaker I_{1} current, because ivabradine can reduce heart rate without significantly changing myocardial contractility. In this context, we compared the effects of atenolol, ivabradine, and saline on myocardial oxygen consumption, using a model involving conscious dogs linked to instrumentation that simultaneously recorded coronary blood flow (Doppler technique) and collected samples of blood from the aorta and coronary sinus to calculate the arterio-venous difference in oxygen content, both at rest and during a heavy treadmill exercise. At doses that induced a similar reduction in both heart rate (approximately –30%) and left ventricular mean ejection wall stress (ie, left ventricular afterload) during exercise, we observed equal and additive contributions of the reduction in heart rate and myocardial inotropy to the limitation of the exercise-induced increase in myocardial oxygen consumption. These results indicated that reductions in heart rate...
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**Heart rate and distribution of regional myocardial blood flow**

In addition to the fact that the myocardial oxygen demand must remain permanently in perfect equilibrium with its oxygen supply, the coronary circulation—by contrast with all other regional vascular beds in the body—is totally dependent on the cardiac cycle. On the one hand, because of the compression of coronary arteries during systole, the myocardial oxygen consumption per unit weight, its the reduction in subendocardial perfusion during systole, the majority of coronary blood flow is indeed limited to the duration of the coronary perfusion during diastole, and regardless of the mechanism, all reductions in heart rate will favor coronary blood flow (with the converse being true for tachycardia). On the other hand, because of extravascular compressive forces that are considerably greater in the subendocardial than subepicardial zones, subendocardial arterioles may be particularly susceptible to these compression forces as they arborize from long transmural vessels. Nevertheless, in conscious dogs under resting physiological conditions, the ratio of endocardial to epicardial blood flow averaged throughout the cardiac cycle is approximately 1.25:1 (Table I) because of the preferential dilatation of subendocardial vessels, which causes a large increase in diastolic flow in this zone. The greater subendocardial blood flow appears to be secondary to metabolic autoregulation, because wall stress, and therefore myocardial oxygen consumption per unit weight, is higher in this deep ventricular zone than in the subepicardium. As a consequence, the “reserve of coronary vasodilation” within the subendocardium is also more limited than in the subepicardium, and during maximal coronary dilation (eg, during perfusion of adenosine) or epicardial coronary artery stenosis (to approximately a 40% reduction in total coronary blood flow), the gradient of perfusion between these two zones decreases from its basal value (ie, 1.25:1), and the subendocardium becomes more vulnerable to ischemic damage.

As shown in Table I, under normal physiological conditions, the transmural distribution of myocardial flow measured with radioactive microspheres remains unchanged when heart rate is altered (eg, during atrial pacing from 100 to 250 beats per minute). However, this pattern of redistribution of transmural myocardial blood flow away from the endocardium becomes rapidly altered during pacing-induced ischemia, a process in which potent arteriolar vasodilators such as adenosine are simultaneously infused in order to abolish the metabolic autoregulation of coronary blood flow. The reduction in diastolic perfusion time caused by the pacing is directly related to the reduction in the endocardial/epicardial ratio under these conditions: the classic “coronary steal phenomenon,” previously described after administration of potent and long lasting coronary vasodilator drugs such as dipyridamole or lidoflazine, has been explained by this mechanism.

By contrast, reduction of heart rate with the use of β-blocker drugs or verapamil limits the reduction in subendocardial perfusion during myocardial ischemia. Moreover, during ischemia induced by coronary artery occlusion in dogs, the ratio of endocardial/epicardial blood flow is even increased after administration of these antiangiogenic drugs (Table II). This so-called “redistribution of coronary blood flow” phenomenon with β-blockers was explained by (i) an increase in diastolic perfusion time linked to bradycardia, as atrial pacing abolished this transmural redistribution of myocardial blood flow and (ii) an unmasking of α-adrenergic vasoconstriction of the epicardial coronary arteries, which redistributes the coronary flow toward the endocardium.

**Table I.** Heart rate and regional myocardial blood flow. Endo/Epi, ratio of subendocardial to subepicardial blood flow.

<table>
<thead>
<tr>
<th>PACING (beats/min)</th>
<th>100</th>
<th>150</th>
<th>200</th>
<th>250</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endo/Epi in normal conditions</td>
<td>1.10</td>
<td>1.14</td>
<td>1.13</td>
<td>1.04</td>
</tr>
<tr>
<td>Endo/Epi during maximal vasodilation</td>
<td>1.00</td>
<td>0.81</td>
<td>0.56</td>
<td>0.40*</td>
</tr>
</tbody>
</table>

* P<0.05 vs corresponding value for 100 beats/min

---

**Table II.** Heart rate, β-blockade, and transmural coronary blood flow. Abbreviations: Endo/Epi, ratio of subendocardial to subepicardial blood flow; Ex, exercise; propra, propranolol.

<table>
<thead>
<tr>
<th>Ischemic zone</th>
<th>Nonischemic zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>1.26±0.19</td>
</tr>
<tr>
<td>Control ex</td>
<td>0.39±0.14</td>
</tr>
<tr>
<td>Ex + propra + pacing</td>
<td>0.57±0.21*</td>
</tr>
<tr>
<td>Ex + propra + pacing</td>
<td>0.35±0.18†</td>
</tr>
<tr>
<td>Ex + propra + pacing</td>
<td>1.24±0.33</td>
</tr>
</tbody>
</table>

* P<0.05 vs Control ex
† P<0.05 vs Ex + propra

---

**Figure 1.** Determinants of the balance between myocardial oxygen demand and supply. LV, left ventricular.

and myocardial inotropy contribute almost equally to the decrease in myocardial oxygen demand during exercise in conscious dogs.
selective agent for reducing heart rate, a similar re-
distribution of regional myocardial blood flow to-
ward the subendocardium has also been reported,11
indicating that the reduction of heart rate is an in-
dependent and crucial factor in this mechanism,
which is also independent of any interaction of the
drug with the autonomic nervous system at the
level of the coronary arteries (Figure 2).

Heart rate and myocardial ischemic threshold

Surprisingly, clinical studies conducted using quan-
titative angiography in patients with isolated and
proximal stenosis of the left anterior descending
coronary artery revealed no significant correlation
between R-R intervals (ie, heart rate) at the ischemic
threshold (0.1 mV ST-segment depression) and the
degree of coronary stenosis during stress tests (up-
threshold (0.1 mV ST-segment depression) and the
degree of coronary stenosis during stress tests (up-
right and supine bicycle exercise or atrial pacing).12
By contrast, the correlation between diastolic per-
fusion time (DPT) expressed in seconds per minute
(DPT = RR interval − [S1−S2]×heart rate) and the
degree of coronary obstruction, was highly signif-
cient during these stress tests. A close correlation
between heart rate and DPT was found only at rest,
indicating that heart rate was the determinant of
diastolic duration only at rest. Because heart rate
and systole duration are the two factors that deter-
mine the value of DPT, alterations to left ventricu-
lar loading conditions, the myocardial inotropy/
lusitropy balance, and sympathetic nervous system
activity that operates on systole duration during ex-
dercise tests explain why the relation between DPT
and heart rate is quite different under resting con-
ditions compared with various stress tests, espe-
cially at the ischemic threshold. Indeed, in patients
with a marked reduction in the coronary lumen di-
ameter, a small reduction in DPT induces myocar-
dial ischemia—regardless of the type of stress test
employed—because the compensating mechanism
of subendocardial perfusion is rapidly exhausted. By
contrast, a large decrease in DPT is necessary to in-
duce myocardial ischemia in patients with minor
narrowing of the coronary vessels, because they
have a larger reserve of compensatory subendocar-
dial vasodilation.

Experimental studies conducted in conscious dogs
demonstrated that an approximate 1% increase in
DPT caused by a reduction in heart rate correspond-
ed with a 6% increase in subendocardial blood flow,6
a value which could be critical at the ischemic
threshold. Conversely, a 2% to 5% reduction in DPT
at the ischemic threshold might induce a dramatic
drop in the coronary vasodilator reserve and induce
myocardial ischemia, especially within the suben-
docardium.12

Differential effect of ivabradine
and atenolol on coronary diastolic
perfusion time

Because a selective pacemaker is, current inhibitor
such as ivabradine can reduce heart rate without
inducing significant changes in myocardial ino-

drop in the coronary vasodilator reserve and induce
myocardial ischemia, especially within the suben-
docardium.12

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Differential effect of ivabradine
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Because a selective pacemaker is, current inhibitor
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Table III. Differential effects of ivabradine and atenolol on diastolic perfusion time and left ventricular ejection time in conscious dogs during treadmill exercise with and without atrial pacing. Ms, milliseconds.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Exercise</th>
<th>Exercise +pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diastolic perfusion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>time (ms) saline</td>
<td>340±11</td>
<td>123±4</td>
<td>103±3</td>
</tr>
<tr>
<td>ivabradine</td>
<td>353±18</td>
<td>233±11*</td>
<td>111±3</td>
</tr>
<tr>
<td>atenolol</td>
<td>355±14</td>
<td>195±6*†</td>
<td>91±3*†</td>
</tr>
<tr>
<td><strong>Systolic ejection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>time (ms) saline</td>
<td>164±3</td>
<td>125±4</td>
<td>112±2</td>
</tr>
<tr>
<td>ivabradine</td>
<td>166±5</td>
<td>140±4*</td>
<td>107±3</td>
</tr>
<tr>
<td>atenolol</td>
<td>167±3</td>
<td>162±4*†</td>
<td>121±4*†</td>
</tr>
</tbody>
</table>

* P<0.05 vs saline;
† P<0.05 vs ivabradine

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</tr>
<tr>
<td><strong>Systolic ejection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>time (ms) saline</td>
<td>164±3</td>
<td>125±4</td>
<td>112±2</td>
</tr>
<tr>
<td>ivabradine</td>
<td>166±5</td>
<td>140±4*</td>
<td>107±3</td>
</tr>
<tr>
<td>atenolol</td>
<td>167±3</td>
<td>162±4*†</td>
<td>121±4*†</td>
</tr>
</tbody>
</table>

* P<0.05 vs saline;
† P<0.05 vs ivabradine

Table III. Differential effects of ivabradine and atenolol on diastolic perfusion time and left ventricular ejection time in conscious dogs during treadmill exercise with and without atrial pacing. Ms, milliseconds.


10%). Conversely, left ventricular ejection time, a
major determinant of DPT, was significantly in-
creased by atenolol, probably as a consequence of its
negative inotropic and lusitropic effects (Table III).
This argument is also reinforced by the fact that the
increase in DPT induced by ivabradine was totally
blunted by atrial pacing, whereas a significant re-
duction in DPT persisted when the reduction in
heart rate induced by atenolol was abolished by atri-
al pacing (Table III). It is, however, important to re-
force the fact that these differences between the

Myocardial ischemia: clinical consequences of heart rate reduction – Berdeaux

Figure 2. Ivabradine and transmural myocardial blood flow. Endo/Epi, ratio of subendocardial to subepicardial blood flow.

Prevented by atrial pacing. Under similar experimental conditions, Monnet et al15 observed that the beneficial effects of ivabradine on regional myocardial contractility within the ischemic zone (by combination of a heavy treadmill exercise and coronary stenosis) were abolished, but not reversed, when heart rate reduction was corrected by atrial pacing. Once again, these data confirm the consequences of the negative inotropic and lusitropic effects of β-blockers on coronary DPT at the ischemic threshold; two pharmacological properties that are not shared by β current inhibitors. Indeed, both drugs have quite different profiles in terms of their effects on the balance between myocardial oxygen supply and demand: a β-blocker will decrease MVO₂ more than a selective heart rate–reducing agent, because of the additivity of its negative chronotropic and inotropic effects on this parameter, but conversely, it will not increase DPT at the ischemic threshold because of the combination of these negative inotropic and lusitropic effects.

Differential effects of heart rate reduction with ivabradine and atenolol on myocardial contractile function

Although β inhibitors and β-blockers reduce MVO₂ and improve myocardial oxygen supply through quite different mechanisms, they both contribute to the reduction in the severity of ischemic injury (reduction of ST-segment elevation and/or reduction of regional contractile dysfunction), regardless of the experimental11,13,16–18 or clinical trial design used.19 There is, however, a major difference between the two drugs concerning myocardial stunning, a reversible but long-lasting regional contractile dysfunction that occurs despite complete reperfusion of previously ischemic myocardium and in the absence of tissue necrosis. Indeed, in an experimental model of myocardial ischemia induced in conscious dogs by the combination of coronary stenosis and 10 minutes of exercise on a treadmill (slope 13%), Monnet et al15 reported that atenolol and ivabradine administered at doses that reduced heart rate to the same extent (1 mg/kg), both redistributed myocardial blood flow toward the subendocardium (microspheres) and reduced myocardial dysfunction (as measured by sonomicrometry) during the ischemic period. Atenolol, however, worsened myocardial stunning during the recovery period in these experiments, whereas ivabradine decreased the severity and duration of stunning under the same conditions. This important difference between the two drugs is related mainly to the β1-adrenergic–mediated negative inotropic and lusitropic effects of atenolol, an effect that is considerably aggravated when the bradycardic effect of atenolol is neutralized by atrial pacing. By contrast, ivabradine reduces myocardial stunning through its ability to selectively reduce heart rate (this effect is abolished by atrial pacing) combined with its lack of effect on myocardial inotropy and lusitropy. Moreover, these differential effects of atenolol and ivabradine on myocardial stunning are independent of their ability to reduce myocardial ischemia, because this difference persists—and is even magnified—when the drugs are administered at the end of the exercise and when the coronary stenosis is released (Figure 3).15

Conclusion

As a result of their different pharmacological profiles, β-blockers and Iβ current inhibitors like ivabradine both exhibit anti-ischemic and antianginal properties but with different mechanisms of action. This leads to different therapeutic implications when additional pathologic syndromes like myocardial stunning are considered. Indeed, β-blockers reduce myocardial oxygen consumption by way of an additive reduction in heart rate and contractility, but simultaneously increase the duration of the ejec- tion time and thus reduce the DPT as well as the oxygen supply to the ischemic myocardium. By contrast, ivabradine significantly improves the DPT, which is of major importance at the ischemic threshold in patients with coronary artery stenosis. In addition, the absence of any intrinsic negative inotropic and lusitropic effects with ivabradine constitutes a real indication for this drug during myocardial stunning, a situation in which β-blockers are deleterious. A question to now be addressed is to what extent these drugs might exhibit complementary pharmacological activities, and to what extent they could be associated in patients who exhibit myocardial ischemic injury. □
ISCHÉMIE MYOCARDIQUE : CONSÉQUENCES CLINIQUES DE LA RÉDUCTION DE LA FRÉQUENCE CARDIAQUE

Quel que soit son mécanisme, toute réduction de la fréquence cardiaque diminue les besoins en oxygène du myocarde et améliore les apports en oxygène, en favorisant par ailleurs la perfusion du sous-endocarde, très vulnérable lors de la sténose coronaire. Ces effets expliquent en grande partie les propriétés anti-angoureuses des bétabloquants, de certains inhibiteurs calciques et plus récemment de l’ivabradine, un inhibiteur sélectif du courant I_{f}, stimulateur du nœud sinusal. Cependant, parallèlement à cette propriété pharmacocinétique commune de réduire la fréquence cardiaque, des différences importantes entre ces médicaments peuvent en faire diverger les implications thérapeutiques. Ainsi, les bétabloquants, qui diminuent la consommation myocardique en oxygène par une réduction synergique de la fréquence et de la contractilité cardiaques, augmentent également la durée du temps d’éjection et donc diminuent le temps de perfusion diastolique du myocarde ischémique. Au contraire, l’ivabradine, qui est sans effet sur la contractilité et la relaxation myocardiques, améliore significativement le temps de perfusion diastolique au seuil ischémique chez les patients ayant une sténose coronaire. Par conséquent, si les effets anti-ischémiques de l’ivabradine et des bétabloquants sont à peu près comparables, leurs mécanismes d’action sont très différents et l’ivabradine est nettement plus bénéfique que les bétabloquants dans le traitement de la dysfonction myocardique, en particulier lors de la sidération qui accompagne l’ischémie myocardique et la reperfusion.
Heart rate is a major determinant of cardiac performance, since both myocardial oxygen demand and myocardial needs are modified by variations in heart rate. Indeed, an increase in heart rate will enhance cardiac work, and thus myocardial oxygen consumption, but this increase in oxygen consumption is normally perfectly matched by an increase in myocardial perfusion and, to a lesser extent, by an augmented myocardial oxygen extraction.1 In the normal heart, ie, that with an intact coronary circulation, metabolic coronary vasodilation opposes the reduction in perfusion time induced by the increase in heart rate, resulting in an increase and/or preservation of myocardial perfusion.2 However, in patients with impaired coronary vasodilation, an increase in heart rate might compromise myocardial perfusion if metabolic coronary vasodilation is insufficient to compensate for the reduction in myocardial perfusion time induced by the increase in heart rate, resulting in an increase and/or preservation of myocardial perfusion.2 However, in patients with impaired coronary vasodilation, an increase in heart rate might compromise myocardial perfusion if metabolic coronary vasodilation is insufficient to compensate for the reduction in myocardial perfusion time. Moreover, an heterogeneous spatial impairment of coronary vasodilation, as is the case in many patients with coronary artery disease, might induce localized transient “under-perfusion” and/or ischemia of poststenotic myocardial tissue due to the redistribution of blood flow (so-called “steal phenomenon”) toward the myocardial tissue with intact coronary arteries, especially when myocardial oxygen demand is increased by, for example, intense physical effort. Thus, enhanced heart rate is dele-
terious for the ischemic myocardium, not only because of the imbalance between supply and demand that it provokes, but also because of the reduction in myocardial perfusion in the case of coronary dysfunction. These effects of enhanced heart rate on myocardial oxygen balance, as well as the impairment of left ventricular (LV) filling, are probably important factors in the progression of LV dysfunction toward chronic heart failure.3,4

These observations, together with the fact that heart rate is an independent predictor of mortality,5 suggest that heart rate reduction should be beneficial in heart failure. Indeed, in large-scale clinical trials conducted with β-blockers in chronic heart failure, the effects of β-blockers on cardiac function and survival are correlated with the magnitude of the heart rate slowing.5,7 Furthermore, in a dog model of chronic heart failure induced by mitral regurgitation, the increase in LV contractile function induced by long-term β-blocker treatment is abolished by pacing.6 Although these data support the hypothesis of an essential role of heart rate reduction in the beneficial effects observed after long-term β-blockade in heart failure, other mechanisms, such as prevention of β-receptor downregulation and/or direct myocardial damage caused by catecholamines,7 are potentially involved and cannot be excluded. This article reviews preclinical as well as clinical data illustrating the perspective of “pure” heart rate reduction induced by I(f) current inhibitors such as ivabradine in chronic heart failure, and the possible mechanisms involved.

The possible beneficial effect of “pure” heart rate reduction in congestive heart failure is revealed by selective inhibitors of the cardiac pacemaker I(f) current, such as zatabradine10 and ivabradine,11,12 the latter being the only one currently in clinical use. In contrast with other heart rate–slowing drugs, such as Ca2+ channel antagonists and β-blockers, I(f) current inhibitors induce a selective and dose-dependent heart rate reduction in humans and animals13-16 without modifying the atrioventricular and intraventricular conduction contractility and/or relaxation.15,17 Furthermore, the magnitude of the heart rate slowing induced by the I(f) current inhibitor ivabradine is proportional to the resting heart rate,16 and the relationship between plasma concentration and heart rate slowing tends to plateau at high doses,18 thus avoiding extreme sinus bradycardia. It should be stressed that the heart rate–slowing effect is independent of the pathophysiological status, i.e., reduced myocardial relaxation and/or contraction, since the magnitude of the heart rate reduction induced by I(f) current inhibitors observed in humans and animals with angina pectoris and/or congestive heart failure19,20 is similar to that observed in healthy volunteers21 and normal rats.22 This heart rate reduction does not seem to be caused by tachyphylaxis, since in rats with congestive heart failure, the magnitude of the heart rate slowing observed throughout the treatment period is stable (Figure 1).22 Indeed, the dose-dependent heart rate–slowing effect of ivabradine observed as early as 4 days after initiation of treatment is similar to that observed after 30 and/or 90 days of treatment. Finally, it should be stressed that despite the marked heart rate reduction, I(f) current inhibitors do not modify blood pressure (Figure 1). This, together with the fact that cardiac output is not modified, suggests that peripheral vascular resistance does not change, which illustrates the absence of any direct vascular tropism of I(f) current inhibitors in terms of vascular relaxation or contraction.15

Cardiac function and left ventricular remodeling

Preclinical data obtained in rats with chronic heart failure caused by permanent left coronary artery ligation clearly show that the reduction in heart rate induced by ivabradine is beneficial in congestive heart failure per se in terms of LV relaxation and contraction. Indeed, after short and long-term treatment with ivabradine dose-dependently reduces heart rate, reaching a plateau as early as 4 days after initiation of treatment. Moreover, the magnitude of the heart rate–slowing effect remains stable during the 90-day treatment period, illustrating the absence of tachyphylaxis. *P<0.05 versus untreated chronic heart failure.

Figure 1. Heart rate measured in rats with chronic heart failure, either untreated (○) or treated per os by the I(f) current inhibitor ivabradine at the dose of 0.3 (▲), 1 (▲▲), 3 (▲▲▲) or 10 (▲▲▲▲) mg/kg/day. Treatment with ivabradine dose-dependently reduces heart rate, reaching a plateau as early as 4 days after initiation of treatment. Moreover, the magnitude of the heart rate–slowing effect remains stable during the 90-day treatment period, illustrating the absence of tachyphylaxis. *P<0.05 versus untreated chronic heart failure.


ment, ivabradine increases the LV end-systolic pressure/volume relationship and decreases the LV end-diastolic pressure/volume relationship (Figure 2, page 314). These immediate and sustained improvements are probably related to the beneficial effects of heart rate slowing in terms of myocardial oxygen demand and/or supply. Indeed, heart rate slowing will not only reduce oxygen demand, which is most likely beneficial in a setting of congestive heart failure, but it will also improve myocardial oxygen supply, since a decrease in heart rate induced by I(f) current inhibitors results in an increase in the diastolic part of the cardiac cycle due to the nonlinear heart rate–diastolic time relation,23 which leads to an increased coronary perfusion time and hence myocardial perfusion, especially within the deeper layer.24,25

The beneficial effect on cardiac function is also illustrated by the fact that despite the dose-dependent heart rate slowing, ivabradine preserves cardiac...
output via the dose-dependent increased stroke volume that has been observed after short and long-term treatment (Figures 3 and 4). Several mechanisms seems to be involved in the increase in stroke volume induced by ivabradine: while the Frank-Starling mechanism seems to be the driving force involved in the increase in stroke volume after short-term treatment, both the Frank-Starling mechanism and LV remodeling contribute to the increase in stroke volume after long-term treatment. Indeed, after 4 days, the increase in stroke volume induced by heart rate reduction results from an increase in LV diastolic diameter without modification of LV systolic diameter. By contrast, after 90 days, the increase in stroke volume results from a decrease in LV systolic diameter without modification of LV diastolic diameter (Figures 3 and 4). The latter results illustrate that long-term ivabradine treatment prevents LV remodeling, ie, LV dilatation.

Moreover, modifications to the LV interstitial structure and/or myocyte properties might also contribute to the long-term effects of ivabradine on cardiac function. Indeed, intervention for 4 days after 90 days’ ivabradine treatment results in a normalization of heart rate close to values observed in untreated chronic heart failure animals, but does not abrogate the beneficial effect on stroke volume and LV systolic diameter, and thus results in an increase in cardiac output (Figure 5, page 316). Moreover, long-term heart rate slowing by ivabradine reduces interstitial collagen density as well as myocardiad capillary density (Figure 6, page 316). Finally, the improvement in LV function does not appear to be related to modifications in LV workload or to circulating neurohumoral factors, since heart rate reduction does not modify LV hemodynamics, and the improvement in LV function is also observed in isolated heart preparations at fixed preload and afterload.

While preclinical data clearly show the beneficial effects of “pure” heart rate reduction in terms of LV hemodynamics and remodeling when treatment is started after infarct healing in chronic heart failure, very little data are available concerning the effect of “pure” heart rate reduction in acute heart failure/myocardial infarction. Indeed, when treatment is initiated 30 minutes after coronary artery ligation, zatebradine preserves cardiac output and decreases infarct size in animals with small and large infarcts, but aggravates LV dilatation only in animals with small infarcts. However, it must be stressed that the magnitude of the heart rate reduction and the degree of LV dysfunction at the ini-
tiation of treatment might be important. Indeed, β-blocker treatment initiated during the healing phase, attenuates LV expansion only in rats with coronary stenosis, ie, minor LV dysfunction, but it is without effect in rats with coronary artery ligation.\textsuperscript{20,31}

**Myocardial structural effects: mechanisms**

We can only speculate about the mechanisms involved in the observed structural effects of \( I_f \) current inhibitors in chronic heart failure, but the increase in myocardial coronary perfusion induced by the heart rate reduction, as well as its effect on coronary vascular function, might play a pivotal role. Indeed, progressive deterioration of LV dysfunction as well as progressive reduction in myocardial perfusion occur simultaneously, and this might be caused—at least in part—by the development of coronary endothelial dysfunction observed in chronic heart failure.\textsuperscript{32-35} Furthermore, since long-term reduction in perfusion through vessels has been shown to be at the origin of vascular endothelial dysfunction,\textsuperscript{36} the decrease in myocardial tissue perfusion probably participates in the development of coronary dysfunction and thus to a further reduction in perfusion and, ultimately, to the installation of a vicious circle. Conversely, the increase in coronary perfusion caused by heart rate slowing would prevent the development/aggravation of vascular dysfunction\textsuperscript{36} and thus the progression of congestive heart failure. Moreover, by preventing local hypoxia, the increase in myocardial perfusion together with the reduction in myocardial oxygen demand could diminish the local production of...
Physiological perspectives of heart rate reduction in heart failure – Mulder and Thuillez

Figure 5. Heart rate, cardiac output, stroke volume and left ventricular diastolic as well as systolic diameters determined in anesthetized rats with chronic heart failure, either untreated (gray bars), treated for 90 days with ivabradine at the dose of 10 mg/kg/day (red bars), or treated for 3 days after interruption of the 90-day ivabradine administration (light red bars). Interruption of long-term ivabradine treatment, ie, normalization of heart rate to values observed in untreated chronic heart failure animals, does not abrogate the beneficial effect on stroke volume and left ventricular systolic diameter. *P<0.05 versus untreated chronic heart failure; †P<0.05 versus ivabradine-treated chronic heart failure.


Myocardial microcirculation

Finally, one of the most important structural effects of heart rate slowing is probably the effect on coronary rarefaction and thus reduction in myocardial perfusion observed in congestive heart failure. Indeed, long-term heart rate slowing induces myocardial angiogenesis not only in normal animals, but also, as illustrated in Figure 6, prevents the coronary rarefaction of the “viable” part of the myocardium in rats with congestive heart failure.23,25,42

We can only speculate on the mechanism(s) involved in prevention of coronary rarefaction, but augmented levels of hypoxia inducible factor–α and associated growth factor(s), in particular, vascular endothelial growth factor, mitogen-activated protein kinase, and fibroblast growth factor — all of which are involved in angiogenesis. However, it must be stressed that diminished hypoxia per se, caused by

Figure 6. Left ventricular weight, myocardial interstitial collagen, and capillary density determined in untreated sham rats (white bars) and chronic heart failure rats, either untreated (gray bars), treated with ivabradine at the dose of 10 mg/kg/day during the last 4 days of the 90 day observation period (light red bars), or treated with ivabradine at the dose of 10 mg/kg/day for 90 days (red bars). While ivabradine does not modify left ventricular weight, only the 90-day ivabradine treatment reduces chronic heart failure-related collagen accumulation as well as chronic heart failure-related myocardial capillary rarefaction. *P<0.05 versus untreated chronic heart failure; †P<0.05 versus time-matched untreated chronic heart failure; ‡P<0.05 versus pretreatment value.

the improved oxygen demand/needs balance induced by heart rate reduction, which, for example, reduces hypoxia-inducible factor–1x, might be involved in the preservation of coronary rarefaction. Whatever the mechanism(s), all these direct and indirect myocardial effects, together with a reduced oxygen requirement induced by the heart rate reduction⁶,¹⁰ as well as an improved oxygen supply/22,47 ratio, should be beneficial in terms of “coronary reserve”²⁸,⁴² and thus prevent the progressive degradation of cardiac function in heart failure.

Effect of ivabradine in humans with chronic heart failure

As already stated, several clinical studies confirm that the reduction in heart rate, and thus myocardial oxygen demand, occurs in the absence of any depressor effect on LV function, either in healthy volunteers²⁸ or in patients with stable angina pectoris.²⁹ However, whether selective inhibitors of the cardiac pacemaker If current will be beneficial in patients with LV dysfunction is to date unknown; the fact that in patients with regional (coronary artery disease) or global (cardiomyopathy) myocardial dysfunction, an intravenous administration of ivabradine induces a marked reduction in heart rate that is associated with a preservation of fractional shortening and stroke volume in both groups,²⁸ in a manner similar to that observed in the experimental model that revealed the beneficial effects of angiotensin-converting enzyme inhibitors, strongly suggests the potential interest of selective inhibitors of the cardiac pacemaker If current, such as ivabradine, in chronic heart failure. Although preclinical data are thus encouraging, the final response as to whether If current inhibitors will be beneficial for the improvement of prognosis in chronic heart failure, will come from the placebo-controlled Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHY/T). Indeed, this major clinical trial whose final results are expected in 2010, evaluates the effects of ivabradine on morbidity and mortality in patients with heart failure.³¹

Conclusion

In experimental heart failure, long-term heart rate slowing induced by selective If inhibitors improves LV function and increases stroke volume, resulting—despite the heart rate slowing—in a preserved cardiac output. This improvement of cardiac function is probably related to the heart rate slowing per se, but also to modifications of LV interstitial structure, myocyte properties, and/or improved myocardial perfusion secondary to long-term heart rate slowing. These direct and indirect effects of specific and selective heart rate slowing induced by If inhibitors should in theory be beneficial to humans with chronic heart failure.

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**Perspectives physiologiques de la réduction de la fréquence cardiaque dans l’insuffisance cardiaque**

L’insuffisance cardiaque est devenue un problème majeur de santé pu-
blique car c’est l’une des rares maladies cardio-vasculaires dont la pré-
valence ait augmenté ces dix dernières années en raison du vieillissement de la population et de la survie améliorée après un infarctus du myocarde. La réduction de la fréquence cardiaque participe au bénéfice sur la mortalité ob-
servée avec certains médicaments cardio-vasculaires, en particulier les bêtablo-
Quants. L’utilisation de ces derniers est néanmoins limitée par leurs contre-indica-
tions et leurs effets secondaires qui diminuent l’observance des patients. L’inhibition du courant pacemaker \(I_f\), en réduisant sélectivement la fréquence cardiaque, représente une approche alternative chez ces patients. Cependant, les effets aigus et chroniques d’une réduction « sélective » de la fréquence car-
diaque dans l’insuffisance cardiaque sont inconnus. Les données précliniques montrent que l’ivabradine, un inhibiteur du courant \(I_f\), réduit de façon dose-
dépendante la fréquence cardiaque sans modification de la pression artérielle. La diminution de la fréquence cardiaque est associée à une amélioration des fonctions systolique et diastolique qui préserve le débit cardiaque malgré la ré-
duction de fréquence. Au cours d’un traitement à long terme, l’amélioration de la fonction cardiaque persiste après l’arrêt de l’ivabradine, ce qui montre une amélioration de la structure myocardique intrinsèque. Les effets bénéfiques de l’ivabradine peuvent s’expliquer par l’effet immédiat de la réduction de la fré-
quence cardiaque, comme une amélioration du rapport apoptose/besoins en oxy-
gène, mais aussi par les effets tissulaires myocardiques à long terme de cette ré-
duction, comme une diminution de l’accumulation du collagène extracel-
lulaire et une augmentation de la microcirculation myocardique. La grande étude en cours \(SHyT\) (Systolic Heart failure treatment with the \(I_f\) inhibitor iva-
bradine Trial), vise à confirmer la valeur pronostique de la réduction de la fré-
quence cardiaque avec l’ivabradine chez les insuffisants cardiaques.
The pacemaker funny channel: a tool to control heart rate

by D. DiFrancesco, Italy

Activation of the pacemaker (“funny”) \( I_f \) current is a crucial process in the initiation of diastolic (phase 4) depolarization of the action potential and the generation of spontaneous activity in pacemaker cardiomyocytes. As well as generatingautomaticity, the funny current controls heart rate by controlling the slope of diastolic depolarization, and mediates autonomic rate modulation. Because of its role in pacemaking, the funny channel has been the target of major investigation efforts aimed at establishing whether clinically relevant applications of the concept of \( I_f \)-based pacemaking can be developed and exploited. Two of the major advances in these investigations are discussed here. First, substances able to specifically bind to and inhibit funny channels can be used as pharmacological tools for heart rate reduction: given the highly selective function of funny channels in heart rate control, specificity of \( I_f \) inhibition translates into specificity of action on heart rate and a lack of side effects on other cardiovascular parameters. Icabradine is presently the only heart rate–reducing substance that can be prescribed for chronic angina, and investigation of its potential use in reducing mortality in patients with coronary artery disease is in progress. Second, defective funny channels can cause rhythm disturbances, as shown by the finding of a funny channel mutation associated with inherited sinus bradycardia. This short review addresses the main features of the funny current of pacemaker cells, its involvement in the generation and regulation of heart rate, and the recent clinically relevant developments with regard to funny channel–based pacemaking.

Medicographia. 2007;29:319-325. (see French abstract on page 325)

Keywords: pacemaker; “funny” current; \( I_f \); heart rate–reducing agents; icabradine; \( HCN \) channels; sinus bradycardia; \( HCN \) channelopathies

Selected abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AVN</td>
<td>Atrioventricular node</td>
</tr>
<tr>
<td>β-AR</td>
<td>β-adrenergic receptor</td>
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<tr>
<td>cAMP</td>
<td>Cyclic adenosine monophosphate</td>
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<tr>
<td>CNBD</td>
<td>Cyclic nucleotide–binding domain</td>
</tr>
<tr>
<td>CNG</td>
<td>Cyclic nucleotide–gated (channel)</td>
</tr>
<tr>
<td>HCN</td>
<td>Hyperpolarization-activated, cyclic nucleotide–gated (channel)</td>
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<tr>
<td>SAN</td>
<td>Sinoatrial node</td>
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Not surprisingly, given the physiological importance of pacemaking, the cellular mechanisms underlying spontaneous activity have constantly attracted the keen interest of investigators. What causes cardiac pacemaker cells to beat spontaneously? Although dense vagal and sympathetic innervation characterizes the SAN region, generation of spontaneous action potentials is an intrinsic property of SAN cells that is independent of innervation; indeed, SAN cells isolated enzymatically maintain spontaneous activity as long as the metabolic and environmental conditions allow it. The intrinsic ability to pace is associated with the presence of a special phase of the action potential in SAN cells, the so-called phase 4 diastolic (or pacemaker) depolarization, which is typical of spontaneously beating cells (see top right panel in Figure 1, page 320) and is lacking in working myocytes of the atria and ventricles. During this phase, following repolarization of an action potential, the membrane voltage slowly depolarizes until it reaches the threshold for activation of a new action potential. The diastolic depolarization phase is therefore responsible for generating repetitive activity, and since changing the slope of diastolic depolarization can modify the diastolic interval, ie, the time lag between termination of one action potential and the onset of a new one, it provides a tool for controlling heart rate. The attention of investigators has therefore been concentrated on the processes that give rise to, and control, the diastolic depolarization phase of the action potential.

The pacemaking mechanism of the heart was originally incorrectly explained in terms of the decay of an outward \( K^+ \) current during diastolic de-
polarization. A completely new interpretation of pacemaker initiation that totally upset the original view, was, however, only achieved in the late 1970s with the discovery in SAN cells of the funny current, i.e., an inward current activated on hyperpolarization in the diastolic range of voltages. According to this new vista, pacemaker depolarization was generated by activation of the inward funny current during diastole.

While the extent of the contribution of other mechanisms to pacemaking remains a debated issue, a wealth of data collected in the almost 30 years since its discovery clearly demonstrates that the cardiac funny channel has a major role in both the generation of pacemaker activity and the control of cardiac rate. Most importantly, the concept of the relevance of funny channel–mediated pacemaker activity. More specific discussion of the biophysical properties of HCN channels can be found elsewhere.

**Initiation of pacemaker activity and regulation of heart rate by funny channels**

The funny $I_f$ current, as originally described in the SAN, is an inward current activated on hyperpolarization at voltages below about –40/45 mV. Since its activation range appeared to coincide with the range of voltages at which diastolic depolarization occurs in SAN cells (approximately –40 to –65 mV), it was immediately clear from this early investigation that $I_f$ was a suitable candidate for generation of diastolic depolarization, therefore potentially acting as a true “pacemaker” current. In the same original paper, this view was strengthened by evidence that there was an increase of $I_f$ in the inward direction in the presence of adrenaline. As an increased inward current during diastole implies a faster diastolic depolarization and hence a faster spontaneous action potential rate, it was proposed that $I_f$ not only generated spontaneous activity, but also mediated the positive chronotropic action of sympathetic stimulation.

The basic physiological significance of this finding was obvious. $I_f$ appeared to solve, thanks to a self-contained, simple set of kinetic, ionic, and modulatory properties, one of the major problems of cardiac physiology — no less than the generation of pacemaker activity and sympathetic control of heart rate.

After its early description, $I_f$ underwent a thorough investigation aimed at characterizing its properties in fuller detail. These studies further extended the original observations and reinforced the concept of the relevance of $I_f$ to pacemaking.

The detailed mechanism of the $I_f$-dependent contribution to diastolic depolarization can therefore simply be inferred on the basis of the $I_f$ electrophysiological properties. Also, importantly, the $I_f$ contribution can be integrated into a computer model of electrical activity in which it generates a diastolic depolarization process. In short, the process leading to $I_f$-dependent generation of diastolic depolarization is as follows. The activation range of $I_f$ is about –40/45 mV to –100/110 mV; as mentioned, it overlaps with that of diastolic depolarization, and the current is inward within the same range. Indeed, the fully-activated I/V relation of $I_f$ has a reversal potential of about –10/20 mV, reflecting its mixed ionic Na$^+$/K$^+$ permeability. During the depolarized part of the action potential, at positive voltages $I_f$ is turned off, but during repolarization when the voltage hyperpolarizes below about –40 mV (the $I_f$ activation threshold), the current is switched on and gives rise to a depolarizing process; clearly, activation of an inward (depolarizing) current with a relatively slow time constant represents a mechanism suitable for the generation of the slowly developing pacemaker depolarization.

The mammalian SAN is densely innervated by the autonomic nervous system: sympathetic β-adren-
ergic stimulation accelerates, and parasympathetic muscarinic stimulation slows, cardiac rate. When isolated SAN myocytes are superfused with solutions containing low concentrations of adrenergic or cholinergic agonists, spontaneous rate changes are associated specifically with changes of the steepness of diastolic depolarization, without significant modifications of action potential duration and shape (Figure 1, top right panel). This clearly concurs with the view that the process responsible for diastolic depolarization (i.e., I_f activation) is a main target of autonomic neurotransmitters.

The original finding of the I_f response to adrenaliné represented in fact the first indication of the involvement of I_f in the autonomic modulation of heart rate, and a great deal of work was later devoted to this aspect of I_f function. Experimentation showed that β-adrenergic receptor (β-AR) stimulation increases I_f by displacing its current activation curve to more positive voltages, without modifying its conductance. The depolarizing shift of the I_f activation curve caused by β-AR stimulation is associated with an increased level of intracellular cyclic adenosine monophosphate (cAMP), the second messenger in the modulation of funny channels. cAMP molecules were found to activate funny channels by direct binding, and not by a phosphorylation-dependent process. This was the first sign—confirmed only later with the cloning of HCN channels—that funny channels and cyclic nucleotide–gated (CNG) channels share similar properties and in fact belong to the same super-family. The process by which the sympathetic nervous system accelerates rate therefore involves β-AR stimulation of adenylate-cy clase activity and cAMP synthesis, which shifts the I_f activation curve to more positive voltages and thus increases the inward current during diastolic depolarization, ultimately leading to a faster depolarization rate.

A fuller picture of the function of I_f in heart rate control was achieved in the late 1980s, when I_f was shown to also be strongly affected by parasympathetic stimulation via a mechanism opposite to that elicited by β-AR stimulation. It has long been known that vagal stimulation slows cardiac rate by causing the release of acetylcholine (ACh), and based on early experiments, the mechanism responsible for the slowing effect of ACh was thought to be the activation of an ACh-activated K^-current. This view was challenged, however, by the discovery of I_f, and by the finding that ACh strongly inhibits I_f by shifting its activation curve to more negative voltages, an action opposite to that induced by catecholamines and one that is caused by a muscarinic-induced inhibition of adenylate-cy clase and cAMP reduction.

This new evidence raised questions as to whether ACh-induced I_f inhibition was actually relevant to vagal-induced negative chronotropism, and why two distinct mechanisms—both potentially effective in slowing cardiac rate upon vagal stimulation—should operate simultaneously. These questions were answered by investigating the ranges of ACh concentration required to induce the two effects. The key finding was that these concentrations are quite different: whereas low doses of ACh (up to around 0.01-0.03 μM) are able to inhibit I_f and to slow the spontaneous frequency of SAN cells, some twentyfold higher concentrations are required to activate the K^-current conductance. This finding introduced a novel concept in the physiology of autonomic control of heart rate: namely, that the negative chronotropic effect of low-to-moderate vagal stimulation is mediated by I_f inhibition, not by activation of a K^-current! In Figure 1, a cartoon illustrating the basic features of funny channels and their role in autonomic rate regulation is shown.

Pharmacological inhibition of funny channels: a tool to control heart rate reduction

When funny channels were first discovered, it soon became clear that as well as representing important progress in the understanding of the basic physiology of pacemaker generation and modulation, they could also provide a tool for the development of a new class of drugs aimed at pharmacologically controlling heart rate.

As discussed above, the existence of a correlation between I_f and pacemaking is a direct consequence of the actual properties of the current, and an obvious question arising from this is whether the properties of the funny channel can be exploited to control heart rate in vivo. For instance, as is apparent from the effects of muscarinic stimulation (Figure 1), it is to be expected that inhibition of I_f, such as that achieved by partial funny channel block, will lead to slowing of cardiac rate.

Before the advent of I_f, or more precisely, before the concept of the role of I_f in the control of heart rate had gained widespread consensus, drugs with heart rate–reducing effects were already known about. These included firstly β-blockers and Ca++ antagonists, whose heart rate–reducing action was associated with the slowing of both the action potential depolarization and repolarization processes and a prolongation of action potential duration. These also included new, empirically developed substances, like alinidine (ST 567), falipamil (AQ-A 39), and later zatebradine (UL-FS 49), described originally as “specific bradycardic agents,” whose actions appeared to concentrate on diastolic depolarization and to differ substantially from standard Ca++ antagonists and β-blockers.

There was a keen pharmacological interest in these new substances, since as well as being able to slow heart rate more specifically than β-blockers and Ca++ antagonists, they also appeared to possess fewer side-effects on contractility. However, despite the background knowledge that was available for the identification of a role for I_f in the action of these drugs, the relevance of I_f was still not widely recognized, and the heart rate–reducing action of these substances was therefore attributed to interactions with other channels, including unlikely chloride and Ca++ currents. Only years after development of the drugs did more careful analysis reveal that they act by selective blockade of funny channels in both the Purkinje fibre and SAN node.
The pacemaker funny channel: a tool to control heart rate – DiFrancesco

A NEW TARGET TO ADDRESS CHALLENGING CONDITIONS

Ivabradine inhibition has been characterized in individual HCN isoforms contributing to native funny channels, such as HCN4 and HCN1. While ivabradine block of HCN4 is similar to that of funny channels, that of HCN1 is quantitatively and qualitatively different, and rather than behaving as an open-channel blocker, it has the uncharacteristic properties of a “closed-channel” block. A molecular explanation for these differences has yet to be elucidated, but they probably depend on the isoform-specific interactions between drug molecules.

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and individual residues lining the pore where binding occurs. The different binding modes can be exploited for the development of drug derivatives with a higher HCN subunit specificity, which would potentially be more useful in tissue-specific therapies that are based on HCN block.

**Genetic alterations of funny channels can lead to rhythm disorders**

The workings of ion channels, like those of all multi-subunit complexes, are determined primarily by their quaternary structure, and funny channels are no exception. Several mutations in different HCN isoforms, for example, are known to significantly alter the channel gating properties (see a discussion of this point in reference 7). Theoretical and experimental considerations therefore raise the intriguing possibility that inheritable funny channel mutations that are able to affect channel function, and hence normal heart rate regulation, exist in the general population.

Indeed, rhythm disturbances related to mutations in HCN4, the HCN isoform most densely expressed in the pacemaker tissue, have been reported.46-48 In particular, a study performed on a large (27-member) Italian family has shown that a missense mutation in exon 7 of the HCN4 gene coding for the protein mutation S672R, is associated with an inheritable form of asymptomatic sinus bradycardia.48

In the family investigated in this work, 15 bradycardic individuals had heart rates between 43 and 60 beats per minute (bpm; mean 52.2±1.4 bpm), while the remaining 12 individuals had normal rates in the range of 64 to 81 bpm (mean 73.2±1.6 bpm).

### Figure 4

A point mutation of human HCN4 associated with an inherited form of sinus bradycardia. Panel A shows sequences of the cyclic nucleotide–binding domain (CNBD) of the four human HCN isoforms; the site of the point mutation S672R found in the HCN4 sequence from a large family carrying sinus bradycardia, and showing tight correlation with the phenotype,48 is indicated by red background. Panel B shows a model reconstruction of the CNBD of human HCN4, obtained with the DeepView-Swiss-PdbViewer software on the basis of the HCN2 CNBD crystal structure.49 The reconstruction shows the proximity between the S672 residue and the bound cyclic adenosine monophosphate (cAMP) molecule (both drawn in stick mode). α-Helices (orange, A, B, C and P) and β-sheets (cyan, 1 to 8) are indicated in both panels.

Figure 3. Model representation of the interaction between ivabradine and the HCN4 channel pore. The top panel shows a model 3D HCN4 structure obtained by aligning the human HCN4 sequence with the K+ channel MthK with the ClustalX program, and modeling with the DeepView-Swiss-PdbViewer software based on the MthK crystal.42 The S5-S6 transmembrane domains of two of the four subunits are shown. White dots represent hypothetical positions of permeating (Na+/K+) ions. The bottom panel shows enlargement of the pore portion where ivabradine molecules could hypothetically bind. Arrows indicate the side chains of tyrosine 506 residues in the S6 segments. Ivabradine molecule and channel domains are drawn to scale, but their relative position is totally arbitrary.
reduced inward current during diastole and hence a slower rate. Interestingly, therefore, by shifting the activation range to more negative voltages, the mutation mimics the slowing action of a low dose of ACh, which explains the bradycardic phenotype. This is illustrated in Figure 5. In panel A, shifts of the \( I_f \) activation curve (black) and fractional slowing of spontaneous rate (green) recorded from SAN cells are plotted (an example of slowing induced by 100 nM ACh [19.1% in this cell] is shown for illustration in panel B). In panel C, the rate slowing caused by the mutation, measured by comparing mean rates of bradycardic versus wild-type individuals from the same family, is plotted (red bar) along with the slowing caused by 10 nM and 100 nM ACh (green bars) against the corresponding 

Conclusions

A wealth of experimental data collected since the funny current was first described has established its central role in the generation of the diastolic depolarization of cardiac pacemaker cells and the autonomic modulation of heart rate. Importantly, more recent results have highlighted the existence of practical developments of the basic concept of \( I_f \)-dependent pacemaking, and have shown that the relevance of funny channels to pacemaker activity applies not only to physiological, but also to pathological, clinically relevant conditions. Two specific examples of how this is achieved have been discussed in this review.

First, pharmacological control of cardiac rate can be managed with the use of “heart rate–reducing” drugs like ivabradine, which in a controlled way, reduces the amount of \( I_f \) current flowing during diastolic depolarization by selective funny channel inhibition, and hence slows heart rate.

Second, a general mechanism for rhythm disorders based on an altered function of funny channels may exist, as shown by the finding of a point mutation in the human \( HCN4 \) isoform responsible for an inherited form of sinus bradycardia. It is to be expected that a deeper understanding of the molecular details underlying the role of \( I_f \) in pacemaking will in the near future allow the development of more refined tools of clinical relevance for the control of heart rate.

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If in ventricular cells: role and pharmacological implications

by A. Mugelli and E. Cerbai, Italy

Pacemaker activity in the normal heart

In the normal heart, impulses are generated in the sinoatrial node (SAN), from where they propagate to activate the atria and then, traveling in the conducting system, the ventricles. As clearly described in the previous article, pacemaker cells of the SAN are endowed with the property of spontaneous activity: they spontaneously depolarize during diastole, thus generating repetitive action potentials. While multiple currents are involved in phase 4 depolarization, it is now generally recognized that If plays a major role in the generation of pacemaker activity and in the regulation of heart rate (see article by DiFrancesco also in this issue). In brief, for cells to have spontaneous activity, an inward current flowing during the diastolic phase (phase 4) is required. Normal cells of the working myocardium do not possess the property of spontaneous activity, phase 4 being completely flat, and it is generally thought that they do not possess an inward current such as If. This is, however, not the case.

If in ventricular myocytes

In 1993, Yu, Chang, and Cohen reported for the first time the presence of the so-called pacemaker current, If, in adult mammalian cardiac ventricles, in a preparation that was quiescent in the normal physiological voltage range. In this and a subsequent paper, they reported that in canine ventricular myocytes, If became activated at potentials much more negative than the equilibrium potential. Overexpression of f-channels in ventricular myocardium is a consequence of the electrophysiological remodeling process, which mainly consists of the re-expression of fetal proteins. Overexpression in ventricular cells may represent an arrhythmogenic mechanism in heart failure, a condition associated with a high risk of sudden cardiac death. The potential arrhythmogenic role of If and the availability of selective f-channel inhibitors make If a suitable therapeutic target in heart failure.

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Keywords: pacemaker channels; ventricular myocytes; heart failure; If, inhibitors; electrophysiological remodeling; arrhythmias

Selected abbreviations and acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>AngII</td>
<td>angiotensin II</td>
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<tr>
<td>ESC</td>
<td>embryonic stem cell</td>
</tr>
<tr>
<td>HCN</td>
<td>hyperpolarization-activated, cyclic nucleotide–gated channel</td>
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<tr>
<td>LV</td>
<td>left ventricular</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>RAAS</td>
<td>renin-angiotensin aldosterone system</td>
</tr>
<tr>
<td>SAN</td>
<td>sinoatrial node</td>
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<td>SHR</td>
<td>spontaneously hypertensive rat</td>
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tial for potassium ($E_K$) and more negative than in canine Purkinje cells. Steady-state activation occurred at potentials of –120 to –170 mV, potentials that are too negative and exclude any functional role for the current. In the 1993 study, they in fact discussed the potential importance of their observation in relation to the differentiation mechanism in nonpacaping regions of the heart: they hypothesized that shifting $I_f$ to very negative (and not physiological) potentials could be the mechanism for the avoidance of pacemaking in ventricular cells.

In our laboratory in Ferrara, we were at this time studying the electrophysiological basis for the enhanced arrhythmogenic effect of $\beta$-adrenoceptor ($\beta$-AR) stimulation in old spontaneously hypertensive rats (SHRs). Action potential duration was markedly prolonged in both normotensive (WKY) and hypertensive rats during aging, and it was significantly longer in 18-month old SHRs compared with the WKY rats. Furthermore, a “diastolic depolarization” was apparent in the oldest SHRs and its slope was increased by isoprenaline (1–10 nM). The observation was completely unexpected, but two facts excluded the possibility that it was caused by an experimental artifact: first, the diastolic phase was completely flat in the recordings from nonhypertrophied muscles studied in similar experimental conditions (Figure 1). Second, the diastolic depolarization phase was dose-dependently made steeper by $\beta$-AR stimulation with isoprenaline, and resulted in abnormal automaticity. The hypothesis of a possible contribution of the “pacemaker” current $I_f$ to this diastolic depolarization recorded in papillary muscles of hypertrophied rat hearts was immediately tested in left ventricular (LV) myocytes isolated from young (2-month old) and old (18 to 20-month old) SHRs who were studied in the whole-cell configuration. A barium-insensitive, cesium-sensitive, time-dependent inward current, i.e., a current having the properties of $I_f$, was recorded in a minority of myocytes from young SHRs but in almost all the myocytes from old SHRs (Figure 1, inset). The only difference that could be observed between these myocytes was regarding their size, the myocytes isolated from old SHRs being clearly hypertrophied. The current was also recorded in normal Tyrode solution from cells showing a diastolic depolarization phase. At variance with the results obtained in normal ventricular myocytes, the activation of $I_f$ in hypertrophied rat myocytes occurred at voltages near the physiological diastolic potential of these myocytes. As a consequence, we suggested that under certain circumstances, $I_f$ may play a major role, and we speculated that it could contribute to the increased propensity of the hypertrophied heart for arrhythmias, as observed both experimentally and clinically.

From that time on, $I_f$ in nonpacemaker cells has been the subject of extensive experimental investigation in our and other laboratories, in an attempt to gain insight into its possible role in the genesis of arrhythmias. In this article we will review the studies dealing with the presence of $I_f$ in ventricular myocytes and its possible role in the genesis of ventricular arrhythmias.

$I_f$ overexpression in the hypertrophied and failing heart

Cardiac hypertrophy and failure are associated with the development of cellular electrophysiological changes. Prolongation of action potential duration, caused by a selective reduction in the repolarizing transient outward current, $I_{to}$, is the most common change and is found in almost all models of cardiac hypertrophy and failure. However, the process of cellular electrophysiological remodeling that occurs in ventricular myocytes during hypertrophy and failure also involves other ionic currents, including $I_f$. As previously stated, a current that has the characteristics of the pacemaker current, $I_f$, was found to be expressed in LV myocytes isolated from the hypertrophied left ventricle of old SHRs. The next step was to evaluate the possible relationship between the degree of hypertrophy and the expression of the current. Obviously, the amplitude of an ionic current can only be larger if a cell is bigger; it is thus mandatory to evaluate the current density rather than amplitude — density being the amplitude normalized to cell capacitance, which is an index of cell size. In this way the contribution of cellular hypertrophy can be excluded.

In our studies, we found in fact that $I_f$ occurrence and density in SHRs was directly related to the severity of myocardial hypertrophy caused by pressure overload, independent of the cell dimensions. On the whole, $I_f$ was upregulated in LV myocytes from rats with mild or severe cardiac hypertrophy caused by aortic banding or long-lasting pressure overload, and also in rats with overt heart failure caused by high blood pressure or after myocardial infarction (MI) caused by coronary ligation (Figure 2, left panel, page 328). As current density was even greater in animals with symptoms of heart failure.
the obvious next step was to evaluate $I_f$ expression in ventricular myocytes isolated from human hearts that had been explanted for terminal heart failure.

Data documenting the expression of $I_f$ in failing human ventricles from transplanted patients were obtained almost synchronously in two different laboratories, adding further support to the proposed pathophysiological role of $I_f$ in ventricular myocytes.

Interestingly, functional expression of $I_f$ in human ventricular cardiomyocytes seems to be related to the etiology of the disease, with current density being higher in ischemic than dilated cardiomyopathy (Figure 2, right panel), as also confirmed by measurements of mRNA transcripts and protein expression in hyperpolarization-activated, cyclic-nucleotide gated (HCN) channel isoforms.

As with pacemaker cells, the $f$-channels in ventricular cells comprise the tetrameric association of four $\alpha$ subunits, namely the transcript of the HCN genes (see article by DiFrancesco in this issue). The subunits combine in diverse ways to form homomeric or heteromeric channels; the exact stoichiometry of native channels is unknown, but whereas the predominant isoforms in the SAN are HCN4, followed by HCN1 and HCN2, the predominant isoforms in the ventricle are HCN2 and HCN4.

In summary, the higher expression of functional $f$-channels associated with a reduced expression of inwardly rectifying potassium current, as occurs in human failing hearts, is likely to cause a predisposition to electrical instability, which, especially in the context of elevated $\beta$-adrenergic activation typical of these pathological conditions, might contribute toward triggering fatal arrhythmias.

### $I_f$ during ventricular development

Overexpression of cardiac HCN channels in the ventricle may represent an example of a general phenomenon termed cardiac remodeling, which consists of the reexpression of fetal proteins. Thus a better understanding of the changes that occur to the electrophysiological properties of $I_f$ throughout the embryonic and postnatal development of ventricular myocytes which, in the adult stage are physiologically quiescent and do not express $I_f$, appears to be important for gaining a better understanding of the mechanisms and factors leading to and controlling its reappearance during disease (ie, hypertrophy and heart failure).

For this reason, we have studied the changes in the occurrence and properties of the pacemaker current $I_f$ during postnatal development in freshly isolated rat ventricular cardiomyocytes. More recently, we characterized cardiomyocytes derived from human embryonic stem cells (ESCs) over a long 3-month maturation period using patch-clamp or intracellular recordings to assess their functional maturation, and reverse transcriptase polymerase chain reaction (PCR) to evaluate the expression of ion channel–encoding subunits.

$I_f$ in ventricular myocytes is abundantly expressed during fetal and neonatal life. $I_f$ occurrence and density are maximal at 1 to 5 days after birth, and decrease progressively during development. A minority of myocytes isolated from the hearts of rats at 1 month of age express $I_f$, which, when present, has a small amplitude. Thus $I_f$ is expressed in rat ventricular myocytes immediately after birth and probably during fetal life; it almost disappears with development, and is reexpressed during severe hypertrophy and failure. In other words, $I_f$ behaves in an opposite manner during natural cell growth and during pathophysiological hypertrophy. The disap-
pearence of $I_f$ in ventricular myocytes during early development occurs while the cell size is increasing during postnatal cellular growth. During pathophysiological hypertrophy, both cell size and $I_f$ density increase. Thus it is not the cellular growth per se that triggers this phenomenon, and other factors are involved (see below).

Moreover, in murine beating myocytes derived from ESCs, $I_f$ is detected early during differentiation.22 Naturally, at some stage of their electrophysiological maturation toward an adult ventricular phenotype in vitro, these cells lose their capacity to generate spontaneous activity. We carefully studied this process in human ESCs,22 and were able to demonstrate that $I_f$ undergoes developmental changes (Figure 3) during in vitro maturation of human ESC–derived cardiomyocytes, possibly toward a ventricular phenotype. In fact, the kinetics of $I_f$ activation were markedly slower in late-stage cardiomyocytes compared with early ones. Accordingly, molecular data showed that the HCN1 isoform, which is reported to have the fastest activation kinetics,23 was largely expressed in human ESCs and its expression was significantly reduced during cardiac differentiation and maturation.21 By contrast, the slower kinetic isoform HCN2 was expressed to a similar extent throughout the differentiation process, thus increasing its contribution to current properties in late cardiomyocytes. A similar pattern of expression of HCN mRNA characterized human adult heart tissue. Interestingly, as expected for cardiomyocytes that are likely acquiring a ventricular phenotype, the relative distribution of the HCN isoforms changed over the course of maturation: the quantitative amount of HCN1 and HCN4 (ie, the SAN isoforms in the adult heart) decreased significantly. Furthermore, the rate of diastolic depolarization, which is controlled by $I_f$ activation kinetics, was also significantly decreased in late-stage cardiomyocytes, and the spontaneous rhythm decreased correspondingly (Figure 3).

Factors implicated in electrophysiological remodeling

The renin-angiotensin aldosterone system (RAAS) plays a major role in ventricular remodeling (for a review, see reference 24). RAAS is chronically activated in many cardiovascular diseases, including hypertension, ischemic cardiomyopathy, and diabetes, resulting in an overproduction and increase of plasmatic and/or tissue levels of angiotensin II (AngII). It is widely documented that AngII promotes, mainly through the stimulation of type 1 AngII receptors (AT1), a variety of cellular responses in the myocardium, such as myocyte and fibroblast growth, collagen deposition, and myocytic apoptosis.25-28 RAAS is clearly involved in switching on and off $I_f$ expression in ventricular cardiac cells. In fact, 8 weeks of treatment with an AT1 antagonist (losartan or irbesartan) in old hypertensive rats is sufficient not only to reduce cardiac hypertrophy (and structural remodeling), but also to affect electrophysiological remodeling: $I_f$ overexpression is hampered and $I_m$ downregulation is reverted.27,28 These data do not obviously imply a unique and/or a direct role for AngII in the regulation of HCN transcription. In vitro studies aimed at investigating the direct effect of hypertrophic factors on cultured ventricular cardiomyocytes also indicate a relevant role for other Gq-protein agonists (such as endothelin–1 or noradrenaline).29

Potential therapeutic benefit of $I_f$ inhibition in heart failure

So far, the molecular basis of $I_f$ overexpression in human heart failure is largely unknown. A threefold increase in the mRNA coding for HCN4 has been reported in end-stage failing human hearts.30 Recent as yet unpublished work demonstrated an increased expression of HCN2 and HCN4 at both the mRNA and protein levels in samples obtained from hearts explanted for ischemic cardiomyopathy.31 A recent paper reporting detailed single-channel analysis of heterologously expressed HCN isoforms and native human $I_f$ demonstrated that recombinant HCN isoforms differ profoundly in their single-channel properties.31 Activation of single HCN/$I_f$ channels was observed at potentials more positive than previously reported for whole-cell experiments, strongly indicating a potential role for these channels in arrhythmogenesis. On the whole, these observations, in association with those previously described, support a potential role for HCN4 in the arrhythmogenesis of working myocardium in heart failure.

The concept that heart rate reduction per se might be beneficial in cases of heart failure has been addressed in other articles in this issue. The effect of long-term pure heart rate reduction on LV function and remodeling was recently studied experimental-ly in a rat model of congestive heart failure, known as the post–MI rat.32 Rats with congestive heart failure were treated with the selective $I_f$ current inhibitor ivabradine (administered with food for 90
days commencing 7 days after coronary artery ligation). Ivabradine decreased the heart rate over the 90-day treatment period (~18% compared with untreated; 10 mg/kg/day), without modifying blood pressure, LV end-diastolic pressure, or dP/dt max/min. Ivabradine significantly reduced the LV end-systolic but not end-diastolic diameter, which resulted in preserved cardiac output because of increased stroke volume. In the Langendorff preparation, ivabradine shifted the LV end-systolic but not end-diastolic pressure-volume relations to the left. Ivabradine decreased LV collagen density and increased LV capillary density without modifying LV weight. Three days after interruption of treatment, the effects of ivabradine on LV geometry, shortening, and stroke volume persisted despite normalization of the heart rate.

In this context of the possible role of $I_f$ overexpressed in ventricular myocytes, it appears particularly relevant to underline the recent observation that abnormal automaticity recorded in ventricular myocytes isolated from Spontaneous Hypertensive Heart Failure (SHHF) rats is abolished by zatebradine. The SHHF rat develops hypertension at an early age, in addition to consistently reproducible hypertensive heart failure in an age-dependent manner. In these myocytes, $I_f$ is increased and $K\text{ATP}$ decreased, and abnormal automaticity has been recorded. Zatebradine, an $I_f$ inhibitor able to inhibit $I_f$ in ventricular myocytes, abolished such abnormal automaticity. The possibility that $I_f$ in ventricular myocytes (as $I_f$ in the sinus node) may represent a suitable target for selective heart rate–reducing agents is an attractive hypothesis that merits determining experimental and clinical proof. From the experimental point of view, a study is currently in progress aimed at evaluating the effect of ivabradine on electrophysiological remodeling in the post-MI rat model. The protocol adopted for investigating this critical point is depicted in Figure 4. After acclimatization, rats are subjected to operation (Sham) or left coronary artery ligation, resulting in chronic infarct (MI) and congestive heart failure. At 1 week, rats are studied using echocardiography and randomly assigned to the placebo- (Sham-C, MI-C) or ivabradine-treated group (Sham-I, MI-I). After 3 months of treatment and in vivo ultrasonographic monitoring, rats are sacrificed and the hearts used for analyzing electrophysiological remodeling. To this aim, cells isolated from left and right ventricle and left atrium tissue samples are used for patch-clamp measurements of action potential and ionic currents; in parallel experiments, mRNA is extracted from tissue samples and used for quantitative PCR analysis of channel expression.

Hopefully this study will contribute toward clarification of the role and relevance of $I_f$ overexpressed in the working myocardium in heart failure, while the ongoing clinical studies with ivabradine will assess the role of pure heart rate reduction in the treatment of congestive heart failure.

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**Rôle et implications pharmacologiques du courant I_f dans les cellules ventriculaires**

Le rôle majeur du courant « pacemaker » I_f dans le rythme spontané du nœud sino-auriculaire est largement connu. L’expression et le rôle de I_f dans le fonctionnement des cellules myocardiques auriculaires et ventriculaires le sont beaucoup moins. I_f s’exprime dans les myocytes ventriculaires embryonnaires et post-nataux, où son expression est régulée négativement pendant la croissance. Les corps embryonnaires différenciés à partir des cellules souches embryonnaires récapitulent les propriétés du tissu cardiaque au cours des stades précoces de son développement et donnent naissance à des battements spontanés résultant, au moins en partie, de l’action du courant I_f. Par ailleurs, les données électrophysiologiques et moléculaires recueillies au cours des 10 dernières années ont démontré que les canaux I_f sont régulés positivement dans les cardiomyocytes ventriculaires des cœurs hypertrophiés et défaillants. La surexpression des canaux I_f dans le myocarde ventriculaire est due au processus de remodelage électrophysiologique, qui consiste principalement en la réexpression des protéines fœtales. La surexpression de I_f dans les cellules ventriculaires peut représenter un mécanisme arythmogène dans l’insuffisance cardiaque, état pathologique associé à un risque élevé de mort subite d’origine cardiaque. Le rôle potentiellement arythmogène de I_f et la disponibilité d’inhibiteurs sélectifs des canaux I_f font du courant I_f une cible thérapeutique appropriée dans l’insuffisance cardiaque.
Benefit of heart rate reduction in heart failure: past, present, and future

by M. Komajda, France

In heart failure, sympathetic hyperactivity increases resting heart rate. A relationship has been shown between basal heart rate and overall mortality, risk of rehospitalization, and — in one study — heart failure mortality and risk of cardiovascular rehospitalization, especially at markedly increased heart rates. Drug therapy studies in this area have been performed essentially with β-blockers, since heart rate-lowering cardiac glycosides have not been found to have any mortality benefit. There appears to be no relationship between basal heart rate and the benefit of β-blockade, and the METoprolol CR/XL Randomized Intervention Trial in chronic Heart Failure (MERIT-HF) failed to confirm the relationship between β-blocker benefit and the amplitude of heart rate reduction that was found in the Cardiac Insufficiency Bisoprolol Study II (CIBIS II). The development of new heart rate-lowering agents such as ivabradine, an I1 current inhibitor, will help to determine the potential of this new therapeutic class in heart failure. A major morbidity/mortality trial of ivabradine in patients with heart failure is ongoing: the Systolic Heart Failure treatment with the I1 inhibitor ivabradine Trial (SHyT).

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Keywords: heart failure; heart rate reduction; cardiovascular morbidity and mortality; clinical trials

Many studies, whether performed in the general population, in patients after myocardial infarction, in hypertensive individuals, or more recently in patients with stable coronary artery disease (CAD), have shown a relationship between a high heart rate and increased cardiovascular morbidity/mortality.1-7 Data on heart failure come mainly from major clinical trials using β-blockers (see Table I).5-7 In chronic heart failure, heart rate is increased by sympathetic hyperactivity, as shown by elevated plasma noradrenaline levels. There is also a decrease in heart rate variability, which is of prognostic significance, as it is associated in particular with a risk of sudden death.8,9

Increased heart rate has adverse consequences in heart failure, primarily involving an increase in oxygen consumption and a decrease in myocardial perfusion due to a shorter diastole. Sympathetic hyperactivity, for its part, promotes left ventricular (LV) hypertrophy, atherosclerosis, and severe ventricular arrhythmias. This hyperactivity is not confined to severe heart failure, being also observed in the early stages of the condition when symptoms are still moderate.10

One problem in correlating heart rate with prognosis is measurement reproducibility. The many confounders include body position, environmental factors (eg, stress), measurement methods, and the degree of psychological stimulation. This has prompted a recent consensus recommendation from a European expert group to standardize heart rate measurement with specific regard to the duration of premeasurement rest, environmental conditions, measurement method, number of measurements, duration of measurements, body position, and nature of the observer.11 They recommend that after 5 minutes’ rest in a quiet room at a comfortable temperature, at least duplicate measurements should be taken in the sitting position over a period of 30 seconds, so as to obtain a mean 30 to 40 cardiac cycles. Although this recommendation should help to validate studies of the correlation between heart rate and prognosis in various forms of heart disease, it has yet to be implemented in any study of heart failure.

Association between heart rate and mortality in heart failure

Two β-blocker trials have shown clear evidence of the association between heart rate and mortality in heart failure:

◆ The Cardiac Insufficiency Bisoprolol Study II (CIBIS II) showed a significant correlation between basal heart rate and morbidity/mortality, specifically rehospitalization risk and all-cause mortality.7

◆ More recently, the METoprolol CR/XL Randomized Intervention Trial in chronic Heart Failure (MERIT-HF) divided its population into five subgroups defined by quintiles of pretreatment resting heart rate ranging from 71 to 98 beats per minute (bpm).12 Patients with the lowest ejection fraction were in the group with the highest heart rate. The study showed that all-cause mortality risk was similar in the first four groups, but it was significant-
ly increased in the group with the highest heart rate (all-cause mortality was increased by 51% and heart failure mortality was increased by 90%), along with a nonsignificant 27% increase in the risk of sudden death. Analysis of hospitalizations yielded similar results: risk was higher in patients with the highest heart rate (all-cause hospitalizations were increased by 40%, cardiovascular hospitalizations by 55%, and heart failure hospitalizations by 78%).

Both studies convincingly confirmed that in heart failure, an increase in heart rate—especially if it is a marked increase—is associated with a substantial increase in morbidity/mortality, and in particular, cardiovascular morbidity/mortality. In addition, the Survival And Ventricular Enlargement (SAVE) study in patients with myocardial infarction and LV dysfunction, defined by an ejection fraction <40%, showed that an increased heart rate was an important predictor of LV dilatation at 2 years and of cardiovascular mortality.13

**Effect of heart rate-lowering agents on heart failure morbidity/mortality**

**Amiodarone**

The Grupo de Estudio de la Sobreviva de la Insuficiencia Cardiaca en Argentina (GESICA) study in dilated cardiomyopathy observed markedly reduced mortality in the subgroup of patients with a high basal heart rate (>90 bpm). Amiodarone significantly reduced mortality caused by sudden death.14 However, comparison of three treatment strategies (conventional treatment plus placebo, conventional treatment plus amiodarone, and conventional treatment plus an implantable cardioverter-defibrillator) in the more recent Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) failed to confirm these results in New York Heart Association (NYHA) class II and III patients with an ejection fraction <35%.15 The primary end point, all-cause mortality, did not differ between conventional treatment alone or conventional treatment plus amiodarone, irrespective of whether the heart failure etiology was ischemic or nonischemic. In addition, mortality in the most severe (class III) group was higher in those receiving amiodarone compared with placebo. A possible explanation for this is that many SCD-HeFT patients had received more modern heart failure treatment, specifically angiotensin-converting enzyme (ACE) inhibitors and β-blockers.

**Digoxin**

Conversely, digoxin, which increases the vagal bradycardic tone on the atroventricular node, showed no mortality benefit over placebo in patients with systolic heart failure in sinus rhythm.16 Its only benefit was to reduce hospitalizations for heart failure by 28%. Unfortunately, this study in patients with an ejection fraction <45% did not address changes in heart rate or undertake any subgroup analysis. It is therefore impossible to know whether there was any relationship between basal heart rate and the response to digoxin.

**β-Blockers**

Most studies to date on the morbidity/mortality effect of heart rate–lowering agents in heart failure have been undertaken with the use of β-blockers. In CIBIS II, patient analysis clearly showed that heart failure mortality and rehospitalization were influenced not only by basal heart rate, but also by β-blockade (bisoprolol) and the change in heart rate that was observed after 2 months. The benefit was maximal in patients with the slowest basal heart rate and in those whose heart rate decreased the most upon treatment. The authors observed no interaction between the three variables. On the one hand, this suggests that in this study, the improved morbidity/mortality associated with the decrease in heart rate was identical irrespective of initial heart rate, and on the other hand, it suggests that the improvement seen in patients receiving bisoprolol

### Table I. Bradycardic agents in heart failure.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mode of action</th>
<th>Outcome studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Class III anti-arrhythmic agent</td>
<td>+ GESICA (sudden death)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– SCD-HeFT (mortality)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>β-Adrenergic receptor blocker</td>
<td>+ Carvedilol US Program</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ CIBIS-II</td>
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<tr>
<td></td>
<td></td>
<td>+ MERIT-HF</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Na/K ATPase inhibitor</td>
<td>– DIG</td>
</tr>
<tr>
<td>Ibradivaine</td>
<td>I inhibitor</td>
<td>SH/T</td>
</tr>
</tbody>
</table>

+ positive outcome; – negative outcome.
Benefit of heart rate reduction in heart failure: past, present, and future – Komajda

Benefit of heart rate reduction in heart failure is past, present, and future. A new target to address challenging conditions.

In cardiovascular disease, pacemaker-dependent heart failure patients treated with metoprolol tartrate. Patients were in class II-IV with respect to the basal heart rate. It is possible to define a target heart rate. The investigators determined that it was impossible to define a target heart rate in heart failure patients treated with β-blockers. Furthermore, in terms of a decrease in either overall mortality or hospitalization for heart failure, this benefit did not depend on the observed decrease in heart rate. The investigators deduced that it was impossible to define a target heart rate in heart failure patients treated with β-blockers, and that it was best to prescribe the closest possible dose to that used in the clinical trials, irrespective of the basal heart rate.

The Carvedilol Or Metoprolol European Trial (COMET) differed from the two previous studies in that it compared two β-blockers: carvedilol and metoprolol tartrate. Patients were in class II-IV with heart failure with ejection fractions ≥35%. Unlike the previous studies, no prognostic significance was found for basal heart rate or any changes at 4 months. However, a heart rate >68 bpm (study median) at 4 months was associated with a subsequent 33% increase in total mortality. The other mortality predictors were systolic blood pressure at 4 months and failure to achieve the target dose of β-blocker.

Recently, a smaller-scale study addressed the effect of ventricular function of altering heart rate in pacemaker-dependent heart failure patients treated with β-blockers. It compared the impact of pacing at 80 bpm versus 60 bpm on LV functional end points. In the higher-rate patients, ventricular remodeling was observed, with an increase in LV volume and a decrease in ejection fraction. Although the sample sizes were small, this study suggests that the ventricular remodeling benefit of β-blocker treatment in heart failure is decreased when the heart rate is increased, and that a low pacing rate should be used in pacemaker-dependent patients to avoid impairing cardiac function.

Historical studies have suggested that β-blockers have mortality benefits for patients in the acute phase of myocardial infarction who have evidence of heart failure. More recently, the Carvedilol Post infarction survival with ConTrol in left ventricular dysfunction (CAPRICORN) study evaluated the effect of carvedilol in a large population with acute myocardial infarction and LV dysfunction defined by an ejection fraction ≤40%. The primary end point was a composite of all-cause mortality or hospital admission for cardiovascular problems. Although there was no significant difference between the carvedilol and placebo groups for the primary end point, all-cause mortality alone was significantly lower in the β-blocker group, in which risk was reduced by 23%. Cardiovascular mortality was 25% lower and there were also significantly fewer non-fatal myocardial infarctions. On the other hand, hospitalization for heart failure did not differ significantly, although deaths and hospital admissions for heart failure tended to be lower for patients on carvedilol. The CAPRICORN results confirm the benefits of β-blockade in severe heart failure (annual mortality in the placebo group was 18% versus the approximate 11% mortality observed in the three major heart failure trials: US Carvedilol Heart Failure Study Group [Carvedilol US], CIBIS II, and MERIT-HF).

Effects of the I_{f} channel inhibitor ivabradine in heart failure

The potential benefit of heart rate reduction prompted investigation into the effect of ivabradine, a specific and selective I_{f} channel inhibitor, in heart failure. A preliminary single-blind safety study tested the effects of an infusion of ivabradine 0.25 mg/kg compared with placebo in 31 patients with LV dysfunction (ejection fraction: 20% to 50%). Resting heart rate was found to fall by 17.6% after an ivabradine infusion of 1 hour. Absence of any change in LV ejection fraction, fractional shortening, or stroke volume compared with placebo forced the conclusion that a single ivabradine infusion does not depress LV function in patients with systolic dysfunction.

A double-blind study was carried out in which 65 patients with CAD and moderate LV dysfunction (ejection fraction, 30% to 45%) were randomized to ivabradine 5 mg twice daily or placebo for 3 months. All patients were in NYHA class II and were receiving an ACE inhibitor; none of the patients were receiving a β-blocker. At 3 months, heart rate in the test group had fallen significantly by 16 bpm, while LV function end points showed a trend toward reduced end-diastolic and end-systolic volumes in patients with low ejection fractions (<40%), suggesting that ivabradine enhances LV geometry in systolic dysfunction.

The effects of ivabradine 0.1 mg/kg infused over 90 minutes followed by a dose of 0.05 to 0.075 mg/kg over 90 minutes were recently tested in patients with severe heart failure (class III, mean ejection fraction 20%). Ivabradine infusion was found to safely lower heart rate by a significant 23% after 4 hours. Trends were also observed toward increases in cardiac index, which had been severely dysfunctional before treatment (2 L/min/m²), and systolic volume.

These three preliminary studies suggest that a pure heart rate–lowering agent has potential benefit in heart failure. The most likely explanation for this benefit lies in the associated greater cardiac efficiency: the lower heart rate allows a greater workload to be achieved for the same myocardial oxygen consumption. However, a recent animal study suggests a further mechanism of action. In dogs, it was found that ivabradine, unlike atenolol, did not increase the postsystolic wall thickening indicative...
of LV asynchrony. The \(I_f\) channel inhibitor preserved the part of thickening that contributes to ejection. It also did not impede LV isovolumic relaxation, again unlike atenolol. This mechanism could also help to conserve energy during the cardiac cycle. Taken together, these studies are clearly preliminary given the small numbers involved. However, the results are consistent in suggesting that, as a specific heart rate—lowering agent, ivabradine could be beneficial in heart failure. Confirmation is required from controlled morbidity and mortality studies, at least two of which are ongoing. The Systolic Heart failure treatment with the \(I_f\) inhibitor ivabradine Trial (SHAF/T),\(^\text{26}\) which has just commenced, is testing the benefit of ivabradine on cardiovascular mortality and hospitalization for heart failure in patients with mild to moderate heart failure and an ejection fraction of <35%. Interestingly, the great majority of patients in this trial are receiving \(\beta\)-blocker therapy, and it should therefore tell us whether slowing the heart rate provides benefit over and above that conferred by \(\beta\)-blockade.

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Bénéfices apportés par la réduction du rythme cardiaque dans l’insuffisance cardiaque: passé, présent et avenir

La fréquence cardiaque de repos est augmentée dans l’insuffisance cardiaque du fait de l’hyperactivité sympathique. Il existe une relation entre fréquence cardiaque basale et mortalité globale, risque de réhospitalisation et, dans une étude, mortalité par insuffisance cardiaque et risque de réhospitalisation cardiovaisseulement notamment lorsque la fréquence cardiaque est particulièrement augmentée. L’analyse de l’impact des interventions pharma-

cologiques a porté essentiellement sur les bêtabloquants puisque les digibetales n’apportent pas de bénéfice sur la mortalité, en dépit de leur action bradycar-
disante. Il ne semble pas y avoir de lien entre la fréquence cardiaque basale et le bénéfice apporté par les bêtabloquants. La relation entre effet bénéfice des bêtabloquants et amplitude de la réduction de la fréquence cardiaque n’appa-

rait pas univoque : cette relation a été démontrée dans une étude avec le bisoprolol (Cardiac Insufficiency BISoprolol Study–II (CIBIS II)) mais non avec le metoprolol dans un autre essai (METoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure [MERIT-HF]). Le développement de nouveaux agents capables de réduire la fréquence cardiaque, comme l’ibvabradine, inhibi-

biteur du courant \(I_f\), devrait permettre de mieux préciser l’intérêt potentiel de cette nouvelle classe thérapeutique dans l’insuffisance cardiaque. Une étude à large échelle de morbi-mortalité chez des patients ayant une insuffisance cardiaque traités par l’ibvabradine est en cours (Systolic Heart Failure treatment with the \(I_f\) inhibitor ivabradine trial [SHAF/T]).

Benefit of heart rate reduction in heart failure: past, present, and future – Komajda
Heart rate is one of the major determinants of myocardial oxygen consumption. As such, it is an important precipitating factor for myocardial ischemia and anginal symptoms. It is logical, therefore, that some of the most important treatments useful in preventing or treating myocardial ischemia and angina, such as \( \beta \)-blockers or some \( \) but not all \( \) calcium channel blockers, act by lowering heart rate. In fact, the American College of Cardiology/American Heart Association guidelines for the management of patients with angina recommend targeting a heart rate of less than 60 beats per minute (bpm) for patients with stable angina.1

There have been major advances in the treatment of acute coronary syndromes (ACS) over the past 20 years.2 The implementation of very effective antithrombotic therapies combining antiplatelet and antithrombin agents, the use of secondary prevention therapies such as statins and angiotensin-converting enzyme (ACE) inhibitors, the ever-increasing use of revascularization—particularly percutaneous coronary intervention (PCI)—and, in the case of ST-segment–elevation myocardial infarction (STEMI), the widespread implementation of rapid and effective reperfusion therapies, have all combined to substantially improve the short-term outcome of ACS.3 Yet, there have been few changes in the use of anti-ischemic therapy in this context. Ivabradine may represent a new opportunity to improve control of anginal symptoms and the treatment of ischemia, and, possibly, have an impact on the outcomes in ACS.4

There have been major advances in the treatment of acute coronary syndromes (ACS) over the past 20 years.5 The implementation of very effective anti-thrombotic therapies combining antiplatelet and antithrombin agents, the use of secondary prevention therapies such as statins and angiotensin-converting enzyme (ACE) inhibitors, the ever-increasing use of revascularization—particularly percutaneous coronary intervention (PCI)—and, in the case of ST-segment–elevation ACS, the widespread implementation of rapid and effective reperfusion therapies, have all combined to substantially improve the short-term outcome of ACS.6 Yet, there have been few changes in the use of anti-ischemic therapy in this context. Ivabradine may represent a new opportunity to improve control of anginal symptoms and the treatment of ischemia, and, possibly, have an impact on the outcomes in ACS.

Current evidence on the role of anti-ischemic agents in acute coronary syndromes

\( \beta \)-Blockers

\( \beta \)-Blockers remain the cornerstone of antianginal agents, because of their efficacy against ischemia and angina, but also because of their established...
prognostic benefits in the context of post–myocardial infarction. By decreasing heart rate and depressing left ventricular contraction, they reduce myocardial oxygen consumption. It is thought that the heart rate reduction is probably the most important effect, particularly during exercise. They may cause coronary vasoconstriction (particularly nonselective β-blockers), but this effect is offset by the longer diastolic filling time resulting from the heart rate–lowering properties, thereby resulting in improved diastolic myocardial perfusion. In addition to these anti-ischemic properties, β-blockers also have antiarrhythmic properties; in particular, they are associated with a reduction in ventricular tachyarrhythmias, even when the latter are not associated with myocardial ischemia.

**Early use of β-blockers in acute ST-segment–elevation myocardial infarction**

While the benefit of long-term β-blockers after acute myocardial infarction is well established, the role of their early, particularly intravenous, administration during acute ongoing myocardial infarction is less firmly established. Many trials of intravenous β-blockade have been undertaken in the acute phase of myocardial infarction, because of their potential to limit infarct size, reduce the incidence of fatal arrhythmias, and relieve pain. A pooling of data from 28 trials of intravenous β-blockade revealed an absolute reduction in mortality at 7 days from 4.3% to 3.7%, or 6 lives saved per 1000 patients treated. These studies were conducted prior to the use of fibrinolytic agents or the performance of primary PCI. Two randomized trials of intravenous β-blockade have been undertaken since the emergence of the widespread use of fibrinolysis. The number of events was too small, however, to allow conclusions to be drawn. A post-hoc analysis of the use of atenolol in the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries–1 (GUSTO-I) trial and a systematic review did not support the routine early intravenous use of β-blockers.

The ClOpidogrel and Metoprolol in Myocardial Infarction Trial (Chinese Cardiac Study 2) (COMMIT [CCS 2]) tested the use of intravenous, followed by oral, β-blockers in 45,852 patients with suspected acute myocardial infarction. Overall, no benefit was found in this strategy: despite a 22% reduction in early arrhythmic deaths, there was a 29% increase in fatal cardiogenic shock. The benefits of β-blocker therapy were mostly accrued after day 1, while the risks were greatest during the first day (Table I).

**Use of β-blockers after acute myocardial infarction**

Several trials and meta-analyses have demonstrated that β-blockers reduce mortality and reinfarction by up to 25% in patients who survived acute myocardial infarction. Positive trials have been conducted with propranolol, metoprolol, timolol, acebutolol, and carvedilol; results of studies with other β-blockers, although not significant, are com-

<table>
<thead>
<tr>
<th>Table I. The effects of metoprolol on a combined efficacy (death, reinfarction, ventricular fibrillation, or other arrest) and safety (cardiogenic shock) end point by shock index and day of event.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
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<tr>
<td>------------</td>
</tr>
<tr>
<td><strong>Day 0-1</strong></td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Medium</td>
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<tr>
<td>High</td>
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<tr>
<td><strong>Day 2-28</strong></td>
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<tr>
<td>Low</td>
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<td>Medium</td>
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<td>High</td>
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<td><strong>Day 0-28</strong></td>
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<tr>
<td>Low</td>
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<td>Medium</td>
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<td>High</td>
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</table>

Clinical perspectives of heart rate reduction in acute coronary syndromes - Steg

patible with a comparable effect. A meta-analysis of 82 randomized trials provided strong evidence for the long-term use of β-blockers to reduce morbidity and mortality after acute myocardial infarction, even if fibrinolytic agents have been given or ACE inhibitors are coadministered. The significant mortality reductions observed in general with β-blockers in heart failure further support the use of these agents after myocardial infarction. Evidence from all available studies suggests that β-blockers should be used indefinitely in all patients who have recovered from an acute myocardial infarction and are without contraindications. Use of β-blockers in non-ST-segment–elevation acute coronary syndromes

In patients with non-ST-segment–elevation ACS (NSTE-ACS), the evidence for the benefit of β-blockers (as opposed to any other class of anti-ischemic agent) is limited, and largely stems from pathophysiological reasoning and extrapolation of the evidence accumulated in stable angina and in the post–myocardial infarction setting. Two rather old randomized studies have evaluated β-blockers in unstable angina,13,14 and a pooled analysis has reported a 13% relative reduction in the risk of progression toward STEMI. The European Society of Cardiology (ESC) guidelines point out that despite the lack of adequate studies to support a mortality benefit, extrapolation from trials performed in “unselected” patients with myocardial infarction is possible, and indeed they recommend the use of β-blockers in NSTE-ACS in the absence of any contraindications. Oral use is deemed generally sufficient, with a target heart rate of 50 to 60 bpm.

Calcium antagonists

There are important pharmacological differences between the various calcium channel antagonists. Yet, they share some important properties that account for most of their antianginal effects: negative inotropic, chronotropic, and adrenotropic effects, and arterial vasodilation. In the case of dihydropyridines, the arterial vasodilation effect is predominant, and is associated with reflex adrenergic activation with tachycardia and stimulation of the renin-angiotensin system. Clinical evidence for calcium channel antagonists in acute myocardial infarction

A meta-analysis of trials involving the use of calcium antagonists early in the course of acute myocardial infarction showed a nonsignificant adverse trend. Therefore, according to ESC guidelines, “there is no case for using calcium antagonists for prophylactic purposes in the acute phase of myocardial infarction.”

In the post–myocardial infarction setting

In the post–myocardial infarction setting, the evidence for a possible benefit of calcium antagonists is much weaker than for β-blockers. Older trials with verapamil and diltiazem had suggested that they may prevent reinfarction and death. In a trial involving 874 patients with acute myocardial infarction but not congestive heart failure who were treated with fibrinolytic agents, the 6-month use of diltiazem (300 mg daily) reduced the rate of coronary interventions. The use of verapamil and diltiazem may be appropriate when β-blockers are contraindicated, especially in obstructive airways disease. Caution must be exercised in the presence of impaired ventricular function. With respect to dihydropyridine calcium channel antagonists, trials have failed to show a benefit in terms of improved prognosis after myocardial infarction; they should, therefore, only be prescribed for clear clinical indications.

In non-ST-segment–elevation acute coronary syndromes

The evidence to use of calcium channel antagonists in the acute setting of NSTE-ACS is limited. Their ability to relieve ischemia and anginal symptoms seems similar to that of β-blockers. In the Holland Interuniversity Nifedipine/metoprolol Trial (HINT), outcomes appeared similar for nifedipine and metoprolol, but with a trend toward improved outcomes with the latter. The role of calcium channel blockers after ACS is somewhat controversial. There is concern regarding the safety of short-acting dihydropyridines, but in A Coronary disease Trial Investigating Outcome with Nifedipine (ACTION), long-acting nifedipine appeared safe, and diltiazem was protective in the Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis post-Thrombolysis (diltiazem) (INTERCEPT).

Nitrates

Mechanism of action

The main mechanism of the anti-ischemic effect of nitrates and similar classes of antianginal agents such as nicorandil and synonymies, probably stems from the marked reduction in preload related to a venous vasodilation. The reduction in venous return and ventricular volume, along with a modest fall in arterial blood pressure (at standard doses), translates into reduced oxygen demand, but this is offset in part by a reflex increase in heart rate. The reduction achieved in myocardial oxygen consumption ranges from 20% to 40%. In addition, nitrates dilate large arteries and arterioles and contribute to blood flow redistribution to the subendocardium. Finally, they relieve exercise-induced coronary vasoconstriction, as well as spontaneous coronary artery spasm.

Clinical evidence for nitrates in acute coronary syndromes

A meta-analysis of 10 small trials of early intravenous nitrate therapy in patients with acute myocardial infarction showed a significant mortality reduction of about one-third. Three large trials (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico–3 [GISSI-3], International Study of Infarct Survival–4 [ISIS-4], and the European Study of PRevention of Infarct with Molsidomine [ESPRIM], which tested molsidomine, a nitric oxide donor) have failed to demonstrate a benefit for routine administration of nitrates in STEMI. Therefore, ESC guidelines do not recommend the routine use of nitrates in the initial phase of myocardial infarction. After acute myocardial infarction, nitrates may be used for the control of
anginal symptoms. In NSTE-ACS, the evidence to support the use of nitrates is scarce — although their use makes sense—and they are indeed recommended for symptom relief in the acute management of anginal episodes (grade I-C recommendation). 2

**Ivabradine**

Ivabradine is the first agent of a new class of heart rate–lowering agents that acts specifically on the sinus node by selective inhibition of the I_f current, which is responsible for the cardiac pacemaker. 34 It has no action on other cardiac ionic currents, 35 and does not compromise inotropism or affect blood pressure or the electrophysiological properties of the heart. In stable angina patients, ivabradine reduces resting heart rate. Importantly, the magnitude of the decrease in heart rate is directly proportional to the baseline heart rate: patients with the highest heart rate will experience the greatest decline, while heart rate will vary very little in patients with baseline bradycardia. 36

Since ivabradine selectively lowers heart rate, it is a potent antianginal agent: it leads to dose-dependent improvement in exercise tolerance and prevention of exercise-induced ischemia. 37 It produces similar effects to those of atenolol, as measured in a recent randomized double-blind comparison with atenolol. 38 It is a safe agent, with no impact on atrioventricular conduction or corrected QT interval and no negative inotropic properties, and it can be safely coadministered with other therapies usually prescribed in the relevant patients, including β-blockers. It has been tested in patients with left ventricular systolic dysfunction and coronary artery disease: in a double-blind, placebo-controlled trial, 65 patients with coronary artery disease, class II New York Heart Association (NYHA) heart failure, and a mean left ventricular ejection fraction of 40%, were randomly assigned to ivabradine 10 mg twice daily or placebo for 3 months. 39 As expected, ivabradine was associated with a more marked decrease in heart rate, but with an increased improvement in the distance walked during the 6-minute walking test. Possibly the most intriguing result of this pilot study was the finding of an improved ventricular geometry with ivabradine: after 3 months of therapy, end-diastolic and end-systolic volume were both reduced (albeit nonsignificantly), while they remained essentially unchanged with placebo.

Ivabradine has been approved for use in Europe for the treatment of patients with stable angina, and is currently recommended for management of patients with intolerance or contraindications to β-blockers. 40

An intravenous formulation of ivabradine has been developed. Its safety was first assessed in 60 healthy volunteers, using a single bolus with increasing dosages ranging from 1 to 24 mg: as expected, it led to dose-dependent decreases in heart rate within 1 hour after administration, with a relative reduction of up to 25% for the 24 mg dose. Subsequently, the effects of a 48-hour intravenous infusion were studied in 50 healthy volunteers using doses of 16 to 80 mg: again, a dose-dependent decrease in heart rate was shown, with a maximum reduction of 23% for the 48 mg dose. Finally, the effect of a single intravenous 60-minute infusion of ivabradine (0.25 mg/kg) on left ventricular systolic function was assessed in a placebo-controlled study in 43 patients with decreased left ventricular ejection fraction: heart rate decreased from 79±13 bpm at baseline to 65±10 bpm after the end of infusion, and remained essentially unchanged 2 hours later in the ivabradine group; by comparison, it remained stable in patients receiving placebo (79±15 bpm at baseline and 78±13 bpm 2 hours postinfusion). Left ventricular ejection fraction was not reduced with ivabradine (in fact there was a trend toward improvement), and stroke volume increased from 64.2±19.7 to 68.8±21 ml/m² while it decreased on placebo (from 67.1±18.7 to 60.4±15.1 ml/m²).

Given that tachycardia is frequently found in the acute phase of myocardial infarction and is deleterious, the use of intravenous heart rate–lowering agents in this emergency setting is appealing, as they increase oxygen demand and reduce the duration of diastole (thereby shortening the time available for coronary perfusion). A rapid reduction in heart rate may allow the myocardium to withstand longer durations of ischemia before irreversible myocardial necrosis occurs, and therefore “buy time” for reperfusion therapy (with intravenous thrombolysis or primary PCI) to achieve effective coronary recanalization and myocardial reperfusion.

Intravenous β-blockade may not, however, be the ideal method to achieve rapid reductions in heart rate in this setting: first, they are contraindicated or poorly tolerated in patients with obstructive pulmonary disease, hypotension, or pulmonary congestion. In addition, the main large trial testing intravenous β-blockade (followed by oral therapy) in the reperfusion era, COMMIT, 12 showed mixed results, particularly in moderate to high-risk patients. Overall, β-blockade with metoprolol appeared to be associated with an initial potential for harm during the first 2 days, followed by a benefit in the subsequent 4 weeks. Harm was greatest in moderate to high-risk patients, and appeared to be largely caused by the potential for an increased incidence of early cardiogenic shock with metoprolol. This suggests that ivabradine, which has the potential to reduce heart rate without affecting left ventricular inotropy and without the classic side effects of β-blockers, may be of interest in this setting.

The eValuation of the IntraVenous I_f inhibitor ivabradine after ST segment elevation myOcardial infarction (VIVIFY) is a phase 2 pilot, randomized, placebo-controlled blind trial established to evaluate the effects of intravenous ivabradine compared with placebo on heart rate and left ventricular dimensions and function in the setting of primary PCI for STEMI. This will be the first clinical experience of intravenous ivabradine in the setting of ACS. The study will enroll 75 patients treated with primary PCI for STEMI (50 randomized to ivabradine, 25 to placebo). Patients must be aged between 40 and 80 years and have been treated for STEMI less than 6 hours after symptom onset, they must
 weigh 50 to 100 kg and be in sinus rhythm at a baseline heart rate of 80 bpm or more (on two measurements 10 minutes apart), and have a systolic blood pressure of >90 mm Hg. The use of oral β-blockers before randomization is allowed, but patients who have received intravenous β-blockade will not be entered into the trial.

Treatment must be initiated less than 9 hours after symptom onset and is to be administered at the dose of 5 mg ivabradine or matching intravenous placebo over 30 seconds, followed by an 8-hour infusion of 5 mg ivabradine or matching placebo, regardless of weight and baseline heart rate. If heart rate falls to 60 bpm or below at any point, the infusion is stopped, but patient monitoring is continued.

The main end points for the study will be heart rate and left ventricular echocardiographic end-diastolic and end-systolic dimensions (as well as left ventricular ejection fraction determined using Simpson’s method). Safety assessments will involve monitoring of 12-lead electrocardiogram parameters (PR, QRS, and QT intervals) and blood pressure, and pharmacokinetic measurements will be performed on blood samples to measure ivabradine (S16257) and its main metabolite S18982. Laboratory measurements will also include creatine kinase, creatine kinase-MB, troponins, and b-type natriuretic peptide.

VIVY will be important in determining the feasibility, safety, and potential interest of using intravenous ivabradine in the setting of ACS, and will hopefully pave the way for studies powered to assess its effect on clinical outcomes. Given the critical role of heart rate in oxygen consumption and the pathogenesis of myocardial ischemia, ivabradine has therapeutic potential that ranges from the acute ischemic setting of ACS to the long-term treatment of patients with coronary artery disease, in which control of heart rate may provide benefits beyond control of anginal symptoms. This latter hypothesis is currently being explored in the pivotal phase 3 morBidity-mortality Evaluation of the I(3) inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTY UL) trial, which is testing ivabradine versus placebo in 10 000 patients with stable coronary artery disease and left ventricular dysfunction (left ventricular ejection fraction ≤ 39%).

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La réduction de la fréquence cardiaque est la pierre angulaire du traitement anti-ischémique. L’ivabradine obtient cet effet en exerçant une action spécifique sur le nœud sinusal. Elle est bien tolérée et présente une efficacité anti-ischémique et antiangoréuse identique à celle des β-bloquants ou des inhibiteurs calciques, sans leurs effets inotropes ou hypotenseurs négatifs. L’ivabradine est maintenant autorisée pour le traitement de l’angor stable. Les syndromes coronaires aigus s’accompagnent souvent d’une tachycardie préjudiciable. Les β-bloquants par voie intraveineuse n’ont démontré aucun avantage au cours de l’installation d’un infarctus du myocarde aigu avec élévation du segment ST (STEMI) (étude COMMIT : CIOPidogrel et Metoprolol in Myocardial Infarction Trial), les bénéfices liés à la réduction de la fréquence cardiaque étant probablement contrabalancés dans les 2 premiers jours par une augmentation du risque de choc cardiogénique. De plus, de nombreux patients présentent une intolérance ou des contre-indications aux β-bloquants, surtout à type d’hypotension, d’insuffisance cardiaque congestive ou de pathologie pulmonaire obstructive. L’ivabradine, en réduisant la fréquence cardiaque sans les effets hypotenseurs et inotropes négatifs des β-bloquants, peut présenter un intérêt dans le traitement du STEMI. L’étude VIVALIY (eValuation of the Intravenous I(f) inhibitor ivabradine after ST segment elevation Myocardial infarction), multicentrique, internationale, randomisée, en aveugle, évalue l’innocuité et l’efficacité de l’ivabradine intraveineuse (bolsus de 5 mg suivi d’une perfusion de 5 mg pendant 8 heures) versus placebo, sur la fréquence cardiaque et le volume ventriculaire gauche de patients STEMI traités antérieurement par une intervention coronaire percutanée. L’ivabradine, compte tenu du rôle essentiel de la fréquence cardiaque dans la consommation d’oxygène et la pathogénèse de l’ischémie myocardique, ouvre des perspectives thérapeutiques allant du syndrome coronaire aigu au traitement à long terme des patients coronariens, chez qui les bénéfices liés au contrôle de la fréquence cardiaque peuvent aller au-delà de ceux résultant du contrôle des symptômes angoréux.
Is the reliability of heart rate dependent on the methodology of measurement?

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Heart rate is one of the most informative and simple parameters to measure in cardiovascular disease. Research has shown that humans with a higher resting heart rate (RHR) have a greater risk of heart attack than those with a lower RHR. It has been known since 1980 that RHR is an easily assessable clinical parameter for discriminating prognosis and for predicting cardiovascular morbidity and mortality in coronary disease patients. Heart rate is also a traditional parameter used in any cardiovascular trial. Common questions that arise in relation to heart rate are: is the heart rate of this patient reliable? What conditions should be considered as the most influential confounders of heart rate? How can we accurately measure heart rate, which is as crucial as the measurement of blood pressure, to avoid these confounders? We know that running and physical work raise heart rate significantly. In such physical states, myocardial oxygen demand increases, as does the release of adrenaline and noradrenaline, compared with in the resting state. These factors can stimulate receptors in the heart that cause heart rate to increase. A rise in body temperature (which normally occurs during exercise or disease) can increase heart rate; a 1 degree Celsius temperature increase causes an increase in heart rate of 10 to 15 beats per minute, while a lower body temperature reduces heart rate. Under higher temperatures, water will be lost from our body and blood will become concentrated, with air resistance increased. To enhance heat dissipation, the cardiovascular system must divert more blood flow to the surface vascular network, and the higher blood temperature may have a direct impact on the circulatory center. At this point, heart rate will be increased. For the same reason, hotter or colder environments can also affect heart rate. Heart rate in hot environments is presumably higher than in colder ones. Do posture changes affect the heart rate? In the upright position, venous return is slightly decreased and the intrathoracic blood volume returning to the heart will be reduced through the Frank-Starling mechanism, causing a reduction in the stroke volume of 30% to 40%. As compensation, heart rate will increase in order to keep cardiac stroke volume constant. Heart rate can be expected to be 1 to 3 beats per minute faster in the sitting position compared with the supine position. Body position can thus affect heart rate. We can therefore draw the conclusion that physiological and environmental conditions may increase or decrease the human heart rate. The reliability of heart rate is dependent on the methodology of measurement. Many confounders, including resting period before measurement, environmental conditions, and posture of the patient should be considered when measuring heart rate. There is no international standard for measurement of heart rate. In order to achieve a reliable heart rate measurement, unified regulations should be developed. We recommend standardizing heart rate measurement, which is as crucial as the determination of blood pressure. The resting period before measurement should be about 5 to 10 minutes, body position should be, for example, the reclining position, and there should be a quiet environment with a moderate temperature. Heart rate should be counted for 1 minute rather than 15 seconds, as is commonly carried out, and only under conditions of total relaxation.

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Among mammals, there is an inverse semilogarithmic relation between heart rate and life expectancy, and this relation is particularly evident in patients with coronary heart disease, in whom it assumes a strong prognostic predictive value following myocardial infarction. Heart rate is the result of several factors influencing the activity of the sinus node, which is mainly influenced by the balance between sympathetic and vagal activity. It is clear that heart rate measurements can be influenced by several internal and external factors, such as physical stimuli, emotional stress, and body position. In addition, single or multiple recordings, ambulatory or resting evaluation, measurement before or after exercise, all have their significance and, in some instances, prognostic implications. However, if a slow resting heart rate is beneficial, it is also true that the heart must keep some chronotropic reserve to match metabolic demands. Chronotropic incompetence and inadequate recovery of heart rate after exercise have also been found to have a prognostic impact as predictors of sudden death. There are multiple methods to measure heart rate at rest: from a 30-second measurement in a sitting position to an arithmetic average of ambulatory recordings, all the possibilities have been described in published papers. The ambulatory measurement and the white-coat effect were both assessed in the Hypertension and Ambulatory Recording VEnetia STudy (HARVEST). In this study, the ambulatory heart rate and the white-coat effect did not add prognostic information to that provided by the clinic heart rate measured in triplicate by pulse palpation over 30 seconds with the subject in the lying position. A recently published paper by Vogel and coworkers analyzing 56 published papers in leading journals, concluded that methods of heart rate assessment were not reported in a scientifically appropriate manner. Who measures the heart rate? Medical doctor, nurse, or the technician? How long has the patient rested before the measurement? How many readings were used? What is the duration of the measurement? These are some of the questions arising from the literature without any clear and objective answers. How these aspects affect the prognostic implications of heart rate is the point of doubt. What is absolutely clear is that in spite of this hidden information in clinical trials and registries, a consistent prognostic significance of resting heart rate is reported in the literature. This consistency suggests that the methodology of heart rate measurement is not so important and the consistency persists beyond this lack of rigor. A recently published statement from the European Society of Hypertension regarding the management of hypertensive patients with elevated heart rate defined some precise points to be provided in clinical trials and studies reporting heart rate data: resting period before measurement; environmental conditions; method of measurement; duration of measurement; number of measurements; body position; and nature of the observer. According to this statement, the heart rate should be measured in a sitting position following a 5-minute period of rest and by pulse palpation over a 30-second period. Electrocardiographic recording is more precise than pulse palpation, but it has no clear advantage for prognostic purposes. As was proven in HARVEST, the prognostic information is contained completely within the office heart rate measurement by pulse palpation, evidence also shown in the Syst-Eur Study comparing office with ambulatory heart rate. Heart rate at rest is a simple and easily assessed cardiac marker and a strong predictor of cardiac events that is currently underestimated, and should be routinely measured. According to the evidence, slowing of the heart rate forms a part of the management of patients with heart disease. The number of beats per minute at rest should be included not only in algorithms for risk assessment, but also in clinical decisions as an important target for therapy.

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Resting heart rate as a prognostic factor

Resting heart rate has been validated as an important “prognostic factor” of cardiovascular prognosis. The quality of a prognostic factor strongly depends on the standardization of its measurement, which is usually rather easier in the case of “laboratory” factors than “biological” factors like resting heart rate, as the latter fall under many chronobiological influences and are affected by the autonomic nervous system.

Factors influencing heart rate measurement at rest

One can assume that the following factors are the most influential in the measurement of heart rate at rest: (i) resting period before measurement; (ii) posture of the patient; (iii) environmental conditions such as temperature or visual and acoustic stimuli; (iv) chronobiological influences; (v) underlying diseases influencing posture (eg, orthopnea due to severe heart failure) and modulating autonomic regulation of heart rate; (vi) medication that may interfere with basal heart rate and its autonomic regulation, ie, pharmacokinetic aspects; (vii) measurement by doctor (including medical environment), nurse, technician or the patient; (viii) method used to record heart rate; and (ix) data analysis, ie, derivation from raw data. A medical environment elicits an “artificial” rise in heart rate, and the reproducibility of heart rate is better for ambulatory than for office measurements. Nevertheless, no evidence is available to demonstrate an advantage for heart rate measured outside of the office.

How to measure heart rate?

Standardization and description of heart rate measurement carried out in clinical trials is poor, with only sparse information about accuracy, reproducibility, and validity. When investigating the degree of control exercised over influencing factors on heart rate measurement in clinical trials, Vogel et al had to state that only a mean 1.7 of the 5 criteria tested (resting period before measurement, posture of the patient, environmental conditions such as temperature or visual and acoustic stimuli, method used to record heart rate, and data analysis, ie, derivation from raw data) were met in 56 clinical studies. A first attempt at standardization has been carried out by the European Society of Hypertension, having recognized heart rate in hypertensive subjects as an independent risk factor for mortality. Their consensus recommendations for measurement of resting heart rate are as follows: the patient should be allowed to sit for at least 5 minutes in a quiet room at a comfortable temperature; heart rate should be measured over a 30-second period by pulse palpation; at least two measurements should be taken in the sitting position; in subjects in whom orthostatic blood pressure measurement is performed, heart rate should be measured after each blood pressure reading; the results may vary according to whether the heart rate is measured by a doctor, a nurse, or an automatic device; and patients performing self-blood pressure measurement should also collect heart rate data. A half of published studies report taking heart rate in the supine position, and the other half in the sitting position (one to two beats/min higher). The supine position may be preferable, as there are data available on the reproducibility of heart rate (or RR interval) measured serially by electrocardiogram. Palpation or electrocardiogram? Palpation is simple and has little impact in terms of biofeedback, but it lacks accuracy, especially if arrhythmias are present or a very short observation time (such as 15 seconds) is chosen. A period of 30 seconds appears to be sufficient. Electrocardiographic recording is more robust and precise, but it is more expensive, takes into account only a small number of heartbeats in a standard electrocardiogram strip, and provides no practical advantages. One, two or three measurements? In the follow-up Coronary Artery Surgery Study (CASS), baseline resting heart rate was obtained manually at enrolment with one single radial pulse measured during 60 seconds, with the patient in the sitting position. As shown in the Cardiovascular Study in the ELdery (CASTEL), a single heart rate measurement is as good a predictor of outcome as a mean of three measurements. Reviewing the literature one can give some general recommendations on how to measure resting heart rate: whatever condition you choose for measurement, define it exactly and use it in a reproducible manner! Take heart rate after at least 5° or 20 minutes of rest in a quiet, visually balanced (temperature 20-24°C) environment either in the sitting position, the supine position, or once in the supine position, once sitting, and once after standing up for 3 minutes; minimize chronobiological effects by taking heart rate in the morning phase; take heart rate by physical palpation and counting for 30 seconds or 1 minute, or determine it from electrocardiogram recording under hold expiration; and measure once, twice, or three times and calculate the average.

Is the reliability of heart rate dependent on the methodology of measurement?

The answer is yes, we might suggest it is, but we don’t know this in a scientifically sound manner. For clarification, precise declarations of methodology must be presented in studies reporting heart rate data—resting period before measurement, environmental conditions, method, number, and duration of measurement, body position, and nature of the observer—as is already well accepted for the measurement of blood pressure, heart rate variability, and blood catecholamine levels.
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Heart rate is a traditional and easily asssessable clinical parameter in everyday practice as well as in clinical trials. Heart rate is affected by a number of confounders, including psychological stimuli, body position, environmental factors, and methods of measurement. In contrast to blood pressure measurement, there is no general agreement on the position for heart rate measurement, the required resting period before measurement, and environmental conditions. These methodological problems may have led to an underestimation of the importance of resting heart rate. It might also lead to insufficient use of heart rate measurement in clinical practice, as doctors could consider it as a “soft” and poorly reproducible clinical variable. The human heart is expected to beat 100 000 times per day, making 2 billion beats in a lifetime. Nature has devised mammals in a special way so as to ensure the same relative heart mass, at about 0.6% of the total body mass. As body mass increases, relative cardiac output decreases by virtue of a reduction in heart rate rather than stroke volume (cardiac output = heart rate x stroke volume). Thus, larger animals have a lower heart rate and indeed a higher life expectancy. The same holds true for humans. Variation in heart rate is a well-known physiological phenomenon. Why do we need a standard, reliable, and reproducible heart rate measurement and what purpose does a dependable heart rate measurement serve? Increased heart rate is linked to higher blood pressure in men and women, and it predicts future hypertension, and it is also associated with higher cardiovascular and noncardiovascular mortality. Secular trends show an overall decline in the heart rate of young adults, which is in keeping with the decrease in cardiovascular mortality in this group. Normal daily activities such as exercise, sleep, eating, and stress, as well as pathological states (eg, atrial fibrillation, heart failure, and thyrotoxicosis) cause fluctuations in heart rate that may be indicative of normal physiology or disease states. The warning sign of a heart rate that is greater than systolic blood pressure—commonly used in hospitals and highlighted in resuscitation courses—is a well-known indicator of impending clinical deterioration. In summary, the heart rate can be a very useful clinical marker of health and it is imperative that there is a universally accepted methodology of measuring heart rate. As with any other autonomic function, one’s resting heart rate is a fine balance between the activities of the sympathetic and parasympathetic systems, with significant interplay from the higher cortical centers. The traditional measurement of heart rate relies on the 1-minute pulse counting method, heart rate monitors, and the use of automated blood pressure machines. Although these methods are.

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Is the reliability of heart rate dependent on the methodology of measurement? MEDICOGRAFIA, VOL 29, No. 4, 2007

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Resting heart rate (RHR) is a simple measurement with important prognostic implications. Previous epidemiological studies demonstrated that a high RHR is a strong predictor of total and cardiovascular mortality in the healthy population that should no longer be neglected in risk flow charts. Many researchers have analyzed heart rate variability (HRV) with the use of RHR, because such analysis can facilitate the early discovery of a variety of illnesses and health conditions. Heart rate monitoring is important in health management; for example, high blood pressure, diabetes mellitus, and obesity are accompanied by a decrease in HRV. Other factors like psychological stress and lack of exercise are also liable to affect HRV. Research has also been conducted on heart rate in relation to heart disease, particularly following myocardial infarction, regarding the effect of heart rate on prognosis. In such studies, researchers analyzed HRV in many cases with the use of RHR, because the resting HRV can serve as an index of sympathetic or parasympathetic dominance. On the basis of studies demonstrating that HRV frequency can predict the prognosis of lifestyle-related diseases, we should measure RHR with the non-restrictive method. The concept of heart rate tolerance was introduced to the medical community in 1999 by Schmidt et al (first published in the Lancet). Heart rate tolerance is the phenomenon of short-term fluctuation in sinus cycle length over a 10 to 15-beat period, which follows a ventricular premature contraction. After a ventricular premature contraction, heart rate increases for several beats before returning to baseline. The absence of heart rate tolerance is one of the best noninvasive predictors of cardiac mortality following myocardial infarction. The total number of heartbeats in a lifetime remains fairly constant across various species, and there exists an inverse relationship between heart rate and life expectancy. Epidemiological studies have addressed the issue of the seemingly important relation between RHR and mortality that has been observed in patients with hypertension, the metabolic syndrome, and in the elderly. There is strong evidence linking an increase in RHR to an increased risk of CV morbidity and mortality in the general population. The relationship between reduction in heart rate and decrease in mortality has been well established with β-blockers, especially after myocardial infarction and in patients with heart failure. A high heart rate leads to both greater myocardial oxygen consumption and decreased myocardial performance, the latter by shortening of diastole, which can exacerbate myocardial ischaemia.

Heart rate is significantly correlated with the severity and progression of atherosclerosis on coronary angiography among men who develop myocardial infarction at a young age. It is legitimate to assume that a reduction in the components of hemodynamic stress (heart rate and blood pressure) can be highly beneficial in coronary patients. In spite of powerful evidence, however, heart rate measurement has not yet become a daily routine in clinical practice. Doctors are still reluctant to rely on a parameter that they consider “soft” for two main reasons: first, because heart rate is considered a poorly reproducible clinical variable. Second, because it is considered more as a marker of sympathetic activity rather than as a cardiovascular risk factor per se. This is why in the whole strategy of cardiovascular risk detection, little attention has been paid to the measurement of heart rate. The notion that tachycardia is transient, however, has not been substantiated. In times of major health care budget burdens, heart rate can be utilized at no additional cost to further stratify patients into risk categories that may benefit to a great extent from preventive treatment. In some studies, it was found that a single measurement of heart rate was a good predictor of outcome, in addition to a mean of three heart rate measurements. This may explain why a single casual heart rate measurement remained a strong predictor of further events. In fact, the reliability of heart rate measurement depends to a great extent on the methodology. Heart rate should be ideally measured in the resting postabsorptive state, without caffeine intake during the previous 3 hours, and not following a ventricular premature contraction.

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Heart rate value is an independent mortality risk factor after an acute myocardial infarction, and it is also an independent risk factor for cardiovascular mortality in the healthy population. The measurement of heart rate variability (HRV) is an established noninvasive and quantitative method of assessing cardiac autonomic activity. Decreased indices of HRV are associated with diabetes and heart failure, and are also considered to be an independent risk factor for mortality and to predict the risk of arrhythmic events post-myocardial infarction or with advanced cardiac heart failure. Although these important cardiac parameters would need an accurate method for measurement, they are sometimes measured under very different conditions (ie, resting or with mild exercise, lying or upright, with or without controlled breathing). Moreover, the circadian heart rhythm produces variations in HRV, depending on the moment in time the measurement is taken. Because of all these factors, the reliability of heart rate value remains uncertain. Several studies have tried to assess the reliability of HRV in healthy and clinical subjects using different methods such as coefficients of variation (CV), intraclass correlation coefficient (ICC), or limits of agreement. The ICC can be interpreted as representing the correlation between different measures from the same individual. The CV for each individual can be calculated by dividing the square root of the variance associated with that individual by the mean of the HRV measurement.

Reliability depending on time of recording
Ambulatory 24-hour Holter recording is one of the most accepted methods to analyze HRV, but the use of this recording in research protocols involves considerable data collection and expensive analysis. In addition, this large ambulatory recording does not allow an accurate control of all external conditions. Short-term recordings appear to be an easier alternative that can be carried out under controlled conditions and can be supervised by a physician. Ponikowski carried out an analysis of the effect of the time length of measurement, and showed that HRV had an acceptable reproducibility from recording at least 20 minutes under stable, controlled conditions in patients with chronic heart failure. Sandercok used short-term (5-minute) recordings made under three different conditions—lying supine, standing, or lying supine with controlled breathing—to point out that biological variation and experimental error play a major role in determining the repeatability of HRV measurements: a wide range of values was found for CV and ICC depending on the HRV measurement assessed and the position in which the measurement had been made. Schroeder suggested taking recordings lasting at least 5 minutes, but the mean of several 10-second recordings should be considered as an useful method.

Reliability depending on interventional situations
In addition to resting stationary electrocardiogram recordings, several interventions are used to analyze HRV, such as mild exercise, head up tilt, active standing, the cold pressor test, or under pharmacological infusion of dobutamine or nitroglycerine. The reliability of HRV measurements during interventions appears to be generally poor in healthy subjects, although it is better than in clinical populations. The results may be different depending on the age of subjects. Reland showed a good reliability of HRV at rest and during orthostatic testing in healthy women around the age of 60 years. These results, however, would be questionable in other populations such as children: Winsley suggested that HRV measurements are unreliable at rest and during light exercise in children aged 11 to 12 years. On the other hand, Guijt observed a very good HRV and respiration reliability (ICC values between 0.74 and 0.85) in young healthy men and women measured under three different conditions: lying down in a laboratory, cycling in a laboratory, and sleeping in an ambulatory surrounding.

Conclusion
HRV in the clinical population appears to be more complex and less reliable than in healthy subjects. In large populations, short-term measurements can be a useful method ahead of Holter recording. Five to 20-minute recordings during rest seem to be reliable for the measurement of HRV; furthermore, the mean value of several very short-term measurements (10 seconds) would be another alternative. The specific conditions and time of recording should be standardized. In this way, suitable reliability coefficients can be well defined, avoiding the current confusion involved in HRV measurement.
Heart rate, one of the simplest and most informative of the cardiovascular parameters, is controlled by the autonomic nervous system and circulating adrenaline, and has been shown to predict cardiovascular morbidity and mortality. However, given that multiple factors are known to affect heart rate, the conditions under which heart rate should be measured are not well defined, and their clinical relevance is unclear. Even in many previous reports showing the relationship between heart rate and cardiovascular outcomes, the majority of papers did not specify how heart rate was measured consistently. The heart rate–related indices that have been reported to have a significant relationship with cardiovascular prognosis include resting heart rate, chronotropic competency, rate of postexercise heart rate recovery, and heart rate variability. The latter three are indices that can be observed or measured under conditions involving a certain amount of autonomic stimulation, such as exercise or respiration, and they may be considered relatively reproducible and reliable; however, they require an exercise machine, electrocardiogram or monitoring. On the other hand, resting heart rate (RHR) is one of the easiest indices to acquire during patient examination by simply palpating the peripheral pulse or by auscultation, yet it is relatively unreliable and is less reproducible compared with other indices—it is sensitive to any stimulation that affects cardiac workload or the autonomic nervous system, such as the basal metabolic rate, oxygen demand, psychological stimulation, and environmental factors. Even a deep breath or just adjusting one’s posture can change the heart rate, therefore the significance of the measured heart rate may differ according to the condition under which it was measured. Since there are no standardized recommendations on when and how to measure heart rate, unlike blood pressure where guidelines exist on the standard method of blood pressure acquisition, it is reasonable to say that the clinical and prognostic significance of the simple measurement of heart rate is sometimes underestimated. RHR is known to most accurately reflect baseline autonomic nervous system activity. It is controlled by the balance between the sympathetic and parasympathetic nervous systems, mostly by parasympathetic activity. The ideal measure of baseline RHR would be one that is obtained by oneself in the supine position just after waking up from a good night’s sleep; however, in reality, heart rate is usually measured by doctors or nurses at a clinic. In order to measure RHR as reliably as possible in the office, a few factors such as resting period before measurement, posture of the patient, environmental conditions like temperature or visual and acoustic stimuli, and method used to record heart rate should be considered and standardized. There are a few ways of recording the heart rate, such as pulse, auscultation, and electrocardiogram or heart rate monitor. Each method has its own advantages and is most useful under certain circumstances. The pulse is simplest and most straightforward, but it can be deceptive when some heartbeats do not have much cardiac output, as in the case of arrhythmias. Auscultation appears to be a little more precise. Electrocardiogram is one of the most precise methods of heart rate measurement, and heart rate monitors allow accurate measurements to be taken continuously and they can be used during exercise when manual measurement would be difficult or impossible. In conclusion, the reliability of measuring heart rate can vary according to the method used. Such variability calls for the development of a simple standardized method of measuring heart rate.
The pathophysiology of myocardial ischemia has traditionally been attributed to a mismatch between myocardial oxygen demand and coronary blood flow. An elevation of heart rate adversely affects both sides of the myocardial oxygen balance. Heart rate is considered to be the most important determinant of myocardial oxygen demand, overshadowing myocardial contractility and left ventricular wall tension. Because myocardial perfusion occurs primarily during diastole, and as heart rate increases, diastolic time is reduced to a greater extent than systolic time, an elevated heart rate also reduces myocardial perfusion.

Ambulatory monitoring has shown that increases in heart rate precede ischemic episodes in patients with coronary artery disease (CAD). The likelihood of developing ischemia is proportional to the baseline heart rate; patients with a mean heart rate of <60 beats per minute (bpm) have been found to have levels of ischemia that are more than two times lower than those of patients with a mean heart rate of >90 bpm. Furthermore, as the development of ischemia is a function of both intensity of exercise and time, a modest rise in heart rate over a relatively long period of time may lead to the occurrence of ischemia at lower heart rates during daily life than during standard exercise testing.

Thus, limiting the increases in heart rate that accompany exercise and mental stress so that they remain below the ischemic threshold, is the primary goal of antianginal therapy. From the physiological perspective, slowing of the heart rate directly minimizes myocardial oxygen demand and also enhances myocardial oxygen supply by improving subendocardial blood flow. The effect of an increase in perfusion time is most apparent in the subendocardial region, where increases in intravascular resistance caused by myocardial contraction will completely preclude blood flow during systole. Heart rate reduction has been shown to be the primary mechanism by which β-blockers are of benefit in CAD and heart failure. Experimental studies and clinical data have shown that the beneficial effects of β-blockade in myocardial ischemia and on left ventricular function are lost if the heart rate–lowering action is prevented by electrical pacing. In clinical studies examining the effects of various heart rate–reducing drugs for the treatment of stable angina, chronic obstructive pulmonary disease, peripheral vascular disease, conduction disturbances, fatigue, sexual dysfunction, glucose and lipid metabolic dysfunction, as well as the absence of the rebound phenomenon, make Procoralan the logical alternative to current treatments for stable angina and suitable for most patients, including those with contraindications or an intolerance to β-blockers. This role of Procoralan is outlined in the recent European Society of Cardiology algorithm for the medical management of stable angina. Ongoing large-scale clinical trials will help to determine whether the clinical benefits of Procoralan are much broader than solely in the prevention of angina, and extend to a reduction in cardiovascular mortality and morbidity.

Keywords: stable angina; t current; heart rate reduction; sinus node; long-term therapy
ment of stable angina and silent myocardial ischemia, those agents that produced more sustained heart rate reduction appeared to be more effective. When propranolol was compared with diltiazem, which has a lesser heart rate–reducing effect, propranolol was found to be more effective in relieving anginal symptoms and myocardial ischemic episodes.18

In theory, the full benefits of heart rate slowing can only be gained if the mechanism by which it is achieved does not result in other, possibly deleterious, cardiovascular actions. All traditional antianginal drugs have multiple pharmacological actions, which may be beneficial, but may also underlie adverse drug effects. Thus, a new drug for the prevention of ischemia would be of particular clinical value if its pharmacological effects were highly selective, and it achieved all of the benefits of heart rate slowing without engendering other counteractive cardiovascular effects.

Advantage of selective and specific \( I_f \) inhibition with Procoralan

Unlike other pharmacological agents, Procoralan (ivabradine) exerts a unique action on cardiac pacemaker activity by means of its selective and specific inhibition of the pacemaker \( I_f \) current. It has been demonstrated that \( I_f \) is the major current underlying spontaneous diastolic depolarization of the sinus node, the fundamental mechanism behind the generation of cardiac pacemaker activity.19-23 The importance of the \( I_f \) current is derived not only from its role in the generation of diastolic depolarization, but also from its involvement in the neurotransmitter-induced control of heart rate.20,24-26 Release of adrenaline as a result of \( \beta \)-adrenoceptor stimulation increases the activity of membrane adenylate cyclase and the production of intracellular cyclic adenosine monophosphate (cAMP), the second messenger in \( I_f \) modulation. Thus, \( \beta \)-adrenoceptor agonists will increase intracellular cAMP, which will lead to an increase in the conductance of \( f \)-channels and in heart rate. Additionally, through protein kinase A–mediated phosphorylation of the key proteins involved in the release or uptake of intracellular calcium and in the increase of myofilament sensitivity to calcium, cAMP increases the force of contraction. \( \beta \)-Adrenoceptor blockers will have the opposite effect to this, slowing the heart rate by diminishing cAMP and thus indirectly reducing the \( I_f \) current. However, they will also diminish all the other consequences of \( \beta \)-adrenoceptor activation, including inotropy.

By contrast with other heart rate–reducing agents, Procoralan is the only agent approved for clinical practice that slows heart rate by direct inhibition of the open channel, bypassing the cyclic AMP step, and thus, providing selective heart rate reduction. There are a number of other aspects of the action of Procoralan that make it unique in clinical use: its affinity for pacemaker \( f \)-channels results in pure heart rate reduction and use-dependent action, which by implication means a greater effect at faster heart rates—rates at which its clinical utility should also be greatest.27 This would also suggest that patients with the lowest heart rate will experience a small heart rate reduction, thereby minimizing the risk of excessive bradycardia.

The advantages of highly selective and specific activity, as with Procoralan, are not only theoretical and have been confirmed in experimental and clinical studies. Procoralan causes dose-dependent heart rate slowing and minimizes exercise-induced ischemia and stunning, while preserving myocardial contractility.28-30 The absence of a negative inotropic effect is of benefit in increasing diastolic time, which is important for myocardial perfusion. In an experimental study carried out in dogs, heart rate reduction with Procoralan markedly increased diastolic perfusion time, and to a significantly greater extent than a \( \beta \)-blocker.12,13 The negative inotropy produced by \( \beta \)-blockade increases left ventricular ejection time and thus limits the beneficial increase in diastolic perfusion time afforded by heart rate reduction.

Procoralan does not alter atrioventricular conduction, ventricular repolarization, or peripheral and coronary vascular resistance, and preserves mean arterial pressure.31 In exercising animals, Procoralan limits exercise–induced tachycardia but does not prevent the physiological adaptation of myocardial contractility and relaxation, and does not alter the increases in cardiac output and stroke volume during exercise. By contrast, the \( \beta \)-blockers atenolol and propranolol (at concentrations that produce a similar heart rate reduction) have been shown to significantly decrease these responses, limiting the hemodynamic adaptations to exercise via their negative inotropic and lusitropic effects and their tendency to produce coronary vasoconstriction.22,25

Selectivity of mode of action thus clearly distinguishes Procoralan from other heart rate–reducing agents and results in clear advantages over other effective therapies. Table I (page 352) compares the cardiac effects of Procoralan with those of \( \beta \)-blockers.

Clinical benefits of heart rate reduction with Procoralan

It is recommended that Procoralan be taken by patients with stable angina at a starting dose of 5 mg twice daily (bid) and a maintenance dose of 7.5 mg
Heart rate lowering with Procoralan

The key step in the prevention of ischemia is the control of factors related to ischemic episodes. As increased heart rate plays a critical role in the development of ischemia, limiting the increases in heart rate that accompany exercise and mental stress to below the ischemic threshold is essential for the prevention of ischemia during the daily lives of patients with stable angina. Procoralan significantly reduces heart rate, both at rest and at its maximal peak during exercise.

The initial large, randomized, double-blind, multicenter clinical trial of Procoralan was performed as a comparison with placebo in the absence of any other chronic (“background”) therapy, and involved 360 patients with stable angina. Substantial reductions in heart rate were observed with Procoralan at both the peak and trough of drug activity, and this was proportional to the dose: heart rate was reduced by 4.5 bpm (2.5 mg bid) and 15.3 bpm (10 mg bid) at rest, and by 5.5 bpm (2.5 mg bid) and 14.8 bpm (10 mg bid) at the peak of exercise (Figure 1). This effect appeared to be related solely to the specific mode of action of Procoralan, with no apparent influence of reflex or compensatory responses to other pharmacological changes: neither blood pressure reduction nor other functional changes were observed.[32]

The second large, randomized, double-blind, controlled, multicenter INternational Trial of the Anti-Inflammatory effects of ivabradine (INITIATIVE) was conducted to demonstrate the noninferiority of Procoralan, 7.5 and 10 mg bid, compared with atenolol, 100 mg once daily (od). This 4-month study, involving 939 patients with stable angina, confirmed at the end of treatment that Procoralan significantly reduced heart rate at rest and at the peak of exercise.[33] At rest, heart rate was reduced by 14.3 bpm in the Procoralan 7.5 mg bid group, and by 15.6 bpm in the atenolol 100 mg od group. These results demonstrate that Procoralan generates substantial and consistent heart rate reduction at rest on a scale that is very similar to that of β-blockade.

Heart rate reduction with Procoralan in patients with stable angina was found to be maintained during long-term treatment. A randomized, double-blind study was conducted in 386 patients treated with Procoralan, either 5 mg or 7.5 mg bid, for 1 year. Both doses of Procoralan were associated with a substantial reduction in resting heart rate: 10 bpm with Procoralan 5 mg bid (from 72 to 62 bpm), and 12 bpm with Procoralan 7.5 mg bid (from 71 to 59 bpm) at the end of treatment. This reduction is consistent in magnitude with that recorded in earlier studies, but was extended in this trial to the treatment interval of 1 year.[34]

Because of its use-dependent mode of action, heart rate reduction with Procoralan demonstrates a direct correlation between resting heart rate at baseline and changes in heart rate during therapy. The heart rate dependence of its heart rate–lowering efficacy was demonstrated by clinical trial analysis, which included data on 1328 patients with documented CAD and stable angina treated with Pro-
Procoralan 5 mg to 10 mg bid for 3-4 months. This dependence on the baseline resting heart rate for the magnitude of heart rate reduction provides a greater efficacy in patients with a higher heart rate at baseline, and protects against excessive bradycardia (Figure 2).35

**Antianginal efficacy**

The presence of angina symptoms in patients with CAD has a profound impact on their quality of life, impacting not only on their physical functioning and level of pain, but also on their emotional well-being.36-39 Improvement in the symptoms of angina results in a significant improvement in quality of life, and is one of the essential goals of medical treatment. Heart rate is a major determinant of myocardial oxygen demand, so heart rate reductions should make myocardial ischemia less likely, as confirmed by the substantial decrease in angina symptoms observed both in short- and long-term therapy with Procoralan. This decrease was significant and consistent in all clinical studies, with a reduction of approximately two thirds observed in the number of angina attacks, with no evidence of pharmacological tolerance.

In the study versus placebo, there were substantial reductions in the frequency of angina attacks and nitroglycerin use. In patients who continued into the open-label extension study, angina attacks decreased from 4.14±5.59 attacks per week at baseline to 0.95±2.24 attacks per week at the end of the open-label extension (P<0.001). Consumption of short-acting nitrates decreased from 2.28±3.74 U/wk to 0.50±1.14 U/wk during the same interval (P<0.001).37 These parameters worsened among those randomly withdrawn to placebo at the end of the open-label treatment phase, but were unchanged among those who continued treatment with Procoralan.

The antianginal efficacy of Procoralan was confirmed by INITIATIVE: the number of angina attacks decreased by two thirds at 4 months: -1.6±4.1 with Procoralan 7.5 mg bid, and -1.2±3.4 with atenolol 100 mg od.38

In another double-blind, parallel group, noninferiority trial conducted in 1195 patients with chronic stable angina and documented CAD, Procoralan 7.5 mg bid produced substantial antianginal efficacy similar to that of amiodipine 10 mg od, reducing the number of angina attacks by about two thirds and the consumption of short acting nitrates by about one half across the study.39

The substantial antianginal efficacy of Procoralan has been shown to be maintained in long-term therapy without the development of pharmacological tolerance. Procoralan significantly reduced the number of angina attacks per week: −1.9±4.8 with 5 mg bid and −1.2±4.1 with 7.5 mg bid during a 1 year study (Figure 3).34

**Anti-ischemic efficacy and improvement in exercise capacity**

Exercise tolerance during treadmill or bicycle ergometric testing is the established primary outcome variable employed to assess drug anti-ischemic efficacy. In accordance with the accepted principles for antianginal drug testing, the effect of Procoralan on exercise tolerance has been assessed at the end of the interdose interval (“trough”), as well as at the time of maximal drug effect (“peak”). In a randomized, double-blind study, Procoralan showed significant anti-ischemic efficacy compared with placebo.34 During the parallel arm 2-week phase, Procoralan significantly mitigated exercise-induced ischemia, as measured by the time to 1 mm ST-segment depression at the trough of drug activity. Again, a significant dose–response relationship was seen across all doses for this anti-ischemic effect. The open-label extension and randomized withdrawal periods demonstrated that this improvement was fully maintained for up to 3 months. Exercise tolerance was also evaluated at the peak of drug activity (approximately 4 hours after drug administration), and was generally higher than that at the trough. The changes in all the exercise tolerance test parameters that were evaluated were found to be significant relative to placebo for both 5 mg bid and 10 mg bid doses.

The efficacy of Procoralan was compared with that of representative examples of β-blockers and calcium antagonists, which are used widely in angina
therapy. In INITIATIVE, the Procoralan 7.5 mg bid group showed an increase of 86.8 seconds in the total exercise duration at the trough of drug activity, compared with 78.8 seconds in the atenolol 100 mg od group, and noninferiority was demonstrated for all exercise tolerance test parameters ($P<0.001$) (Figure 4). A comparison was also made between Procoralan 5 mg bid and atenolol 50 mg od at 1 month of treatment. The Procoralan 5 mg bid group showed an improvement of 64.2 seconds in the total exercise duration, compared with 60.0 seconds in the atenolol 50 mg od group; noninferiority was also demonstrated ($P<0.001$). Similar results were obtained at 1 month for the other main exercise tolerance test parameters. Procoralan thus significantly improved the anginal threshold, as demonstrated by the increase in the time to limiting angina (92 seconds) and the time to angina (145 seconds) with Procoralan 7.5 mg bid, compared with 85 seconds for limiting angina and 135 seconds for angina in the atenolol 100 mg od group. The results of INITIATIVE provide clear evidence of the major anti-ischemic and antianginal efficacy of Procoralan, which is comparable with the efficacy of atenolol.

![Figure 4. Effects on total exercise duration at trough of drug activity. Reproduced from reference 33.](image)

Furthermore, the magnitude of the improvement in exercise duration and the other main exercise tolerance test parameters was larger in the Procoralan groups than in the atenolol group, showing that Procoralan induces a greater improvement in exercise capacity than atenolol for a comparatively smaller reduction in heart rate: for every 1 beat reduction in heart rate, there was a 10.1 second increase in total exercise duration with Procoralan versus a 5.6 second increase with atenolol (Figure 5). This greater improvement in exercise capacity illustrates the clinical advantage of the novel concept of pure heart rate reduction, and demonstrates the advantage for patients with ischemia of heart rate-reducing treatment that is devoid of effects on other cardiovascular characteristics that may be involved in generating adverse effects that limit the heart rate–reducing benefit.

![Figure 5. Increase in exercise capacity related to heart rate reduction of one beat (after 4 months of treatment). Based on data from reference 33. TED, total exercise duration.](image)

In another large 3-month, double-blind, controlled trial, treatment with Procoralan 7.5 mg bid was shown to be at least as effective as amiodipine 10 mg od in 1195 patients with chronic stable angina and documented CAD. Total exercise duration at trough (primary end point), time to limiting angina, time to angina onset, and time to 1-mm ST-segment depression were consistently increased with Procoralan, confirming the noninferiority of Procoralan compared with amiodipine.

**Safety and tolerability**

The highly specific and selective mode of action of Procoralan provides effective and safe heart rate reduction, with good cardiac and general acceptability profiles. Bradycardia was reported in only 2.2% of patients treated with Procoralan 7.5 mg bid versus 4.4% of those receiving atenolol 100 mg daily. This low percentage is explained by a clear plateau in the dose-response curve of $I_h$ current inhibition and by the direct rate-related dynamics of the heart rate–lowering effect, which limit the risk of excessive bradycardia. Procoralan fully preserves the main electrophysiological parameters, including the refractory period of the atrium, atrioventricular conduction time, and repolarization duration. An absence of any change in the corrected QT interval throughout the follow-up period provides strong confirmation that Procoralan has no direct effect on the duration of ventricular repolarization.

In some patients, Procoralan can induce visual symptoms, mainly phosphenes. These have been mostly mild and transient, resolved during treatment (76%), and have never been reported as serious, leading to withdrawal from treatment in less than 1% of patients. Extensive preclinical and clinical investigations have not revealed any evidence of safety concerns. These symptoms are related to the reversible inhibition of the retinal $I_h$ current, without any alterations of retinal morphology, channel distribution, and pigment content.

Importantly, the abrupt discontinuation of Procoralan does not result in a rebound phenomenon.

**Future perspectives**

The ability of Procoralan to decrease heart rate without impairing key cardiovascular or hemodynamic parameters, such as myocardial contrac-
Merkus D, Kajiya F, Vink H, et al. Prolonged diastolic time fraction protects myocardial perfusion when... 

...the new treatment strategy for stable angina – Elyubova

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26. Manz M, Reuter M, Lauck G, et al. A single intravenous dose of ivabradine, a novel If inhibitor, lowers heart rate but does not depress left ventricular...
Procoralan: la nouvelle stratégie thérapeutique pour l’angor stable

L’âge est cédé dans la prévention de l’ischémie c’est le contrôle des facteurs liés aux épisodes ischémiques. L’augmentation de la fréquence cardiaque jouant un rôle crucial dans le développement de l’ischémie, la limitation des hausses de fréquence cardiaque qui accompagnent l’effort et le stress mental en-dessous du seuil ischémique est essentielle pour la prévention de l’ischémie dans la vie quotidienne des patients ayant un angor stable. Procoralan est le seul médicament approuvé en pratique clinique exerçant une action unique sur l’activité du “pace-maker” cardiaque grâce à une inhibition spécifique et sélective du courant If. Les résultats des études cliniques indiquent qu’une réduction de la seule fréquence cardiaque avec Procoralan est une stratégie efficace, sûre et bien tolérée pour la prévention de l’angor. L’innocuité et l’efficacité clinique de Procoralan ont été démontrées au cours du plus important programme de développement clinique sur l’angor stable jamais réalisé, qui a inclus plus de 5 000 patients et prouvé des améliorations avec Procoralan tant au niveau de la capacité totale à l’effort que du soulagement de la douleur angoureuse. Procoralan est au moins aussi efficace que les médicaments antangoriques de référence bien établis tels les bétabloquants et les antagonistes calciques, et son efficacité antangorique persiste à long terme sans échappement thérapeutique. L’absence de restrictions d’utilisation ou d’intolérance caractérisant les produits classiques réduisant la fréquence cardiaque, dans le cadre de l’asthme, des bronchopneumopathies chroniques obstructives, de la maladie vasculaire périphérique, des troubles de la conduction, de l’asthénie, des troubles sexuels, des troubles métaboliques des lipides et du glucose, ainsi que l’absence de phénomène de rebond, font de Procoralan une alternative logique aux traitements actuels de l’angor stable et un produit adapté à la plupart des patients, y compris ceux qui ont une contre-indication ou une intolérance aux bétabloquants. Ce rôle de Procoralan est schématisé dans l’algorithme de la Société Européenne de Cardiologie pour la prise en charge médicale de l’angor stable. Des études cliniques à grande échelle en cours aideront à déterminer si les bénéfices cliniques de Procoralan dépassent la prévention de l’angor et s’étendent à la réduction de la morbidité et de la mortalité cardio-vasculaires.
Mortality in patients with cardiovascular disease is strongly associated with increased heart rate. Consequently, lowering heart rate in patients with coronary artery disease (CAD) and left ventricular dysfunction (LVD), a group that still suffers from a poor prognosis despite existing treatment options, may have a significant and beneficial effect on morbidity and mortality. To test this hypothesis, treatment with ivabradine, a specific 1, current inhibitor that lowers heart rate without affecting the inotropic properties of the heart, is being compared with placebo in the morbidity-mortality Evaluation of the 1, inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL), a large, randomized trial of patients with CAD and LVD undergoing conventional treatment whose resting heart rate is $>60$ beats per minute. The primary end point is a composite of cardiovascular mortality and hospital admission for acute myocardial infarction or worsening of heart failure. Preliminary data on 9978 of the 11 000 patients enrolled have been analyzed. The mean patient age is 65 years, mean baseline heart rate is 72 beats per minute, and mean ejection fraction is 32.4%. Most patients have a history of myocardial infarction (89%) and are taking $\beta$-blockers (85%), antithrombotics, usually aspirin (91%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (89%), and lipid lowering drugs (76%). Thus, this is a landmark trial, because it will be the first to assess the effect of pure heart rate reduction on cardiovascular outcomes in optimally treated patients with CAD and LVD.

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Keywords: heart rate; coronary artery disease; left ventricular dysfunction; mortality; ivabradine; 1, inhibition

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those who had started β-blocker treat-
ment were still on therapy. In addition,
prescribed doses were generally ≤50% of those used in clinical trials.13
Experimental and clinical data have demonstrated that heart rate reduction is an important mediator of the effects of β-blockers on ischemia, left ventricular (LV) function, and reduction in post-MI mortality.4,6 However, despite the availability of β-blockers, resting heart rate may not be sufficiently controlled. In one study of data compiled in the Duke Databank for Cardiovascular Disease, patients with CAD had a mean heart rate of 70 bpm despite use of β-blockers by 61% of patients.14
On the basis of this understanding of the importance of heart rate, we reasoned that patients with CAD and LVD could derive particular benefit from heart rate lowering. We chose to investigate the ease and left ventricular dysfunction) was designed to assess the morbidity–mortality benefits of pure heart rate reduction above and beyond conventional treatment in CAD patients with LVD.

What is the goal of BEAUTyUL?

We designed BEAUTyUL to determine if lowering resting heart rate by adding ivabradine treatment to preexisting therapy would reduce cardiovascular morbidity and mortality in patients with CAD and LV systolic dysfunction. This is a landmark trial, because it will be the first to assess the effect of pure heart rate reduction on cardiovascular outcome. We are particularly interested to determine if ivabradine treatment on top of a background of β-blockers will further reduce morbidity and mortality.

What patient population is included in the trial?

We designed the inclusion and exclusion criteria to identify a group of patients who have documented stable CAD, normal sinus rhythm, and who are being treated for cardiovascular disease.4,6 We have now closed enrollment and have been able to evaluate the baseline data of 9978 out of 11 000 study patients.

Figure 1. Effects of heart rate on cardiovascular mortality. Panel A shows a survival curve in patients with suspected or proven coronary artery disease. Over time, the odds of cardiovascular mortality survival decrease with increasing resting heart rate. Data were adjusted for age, gender, body mass index, hypertension, diabetes mellitus, cigarette smoking, clinically significant coronary vessel disease, ejection fraction, recreational activity, treatment with antiplatelets, diuretics, β-blockers, and lipid lowering drugs. Panel B shows a cardiovascular mortality curve in patients who are post-myocardial infarction; the odds of cardiovascular mortality decrease with reductions in heart rate (P<0.001).

Abbreviations: bpm, beats per minute; RHR, resting heart rate.


Effect of ivabradine, an I1 inhibitor, in such a strategy, because of its specific effect on heart rate. Ivabradine reduces heart rate by a direct effect on the sino-
atrial node, without affecting other car-
diac ionic currents.5-17 In clinical trials, ivabradine has been shown to produce dose-dependent improvements in exercise tolerance and time to development of exercise-induced ischemia, and to be well tolerated, including in patients with LVD.18-20
Thus, the BEAUTyUL trial (morbidity–mortality Evaluation of the I1 inhibitor ivabradine in patients with coronary dis-

What is the design of the trial?

BEAUTyUL is a large, double-blind, randomized, placebo-controlled trial that is being carried out in approximately 660 centers throughout the world.21 After a 2-week run-in period, patients are randomized to take ivabradine 5 mg twice daily (bid) or placebo (Figure 2). If, after 2 weeks of treatment with 5 mg bid, a subject’s heart rate is ≥60 bpm, the patient will be switched to 7.5 mg bid. If, on the other hand, the patient’s heart rate drops below 50 bpm or the patient is showing signs of bradycardia, the patient will be dis-

continued from the trial. At each study visit, a similar assessment will be per-
fomed. The goal is for each patient to maintain a heart rate of between 50 and 59 bpm. The primary end point is a com-
posite of cardiovascular death and hos-
pitalization for acute MI or new onset or worsening heart failure.

 Patients were included if they were ≥55 years of age. Diabetic patients, type 1 or type 2, could be enrolled if they were ≥18 years of age. Patients needed to have documented stable CAD, a resting heart rate ≥60 bpm with a normal sinus rhythm, an LV ejection fraction <39%, and an LV dilatation at end of diastole of >56 mm. Patients had to be following a stable, conventional treatment for cardiovascular disease. This treatment had to be considered optimal by the investigator.

The main exclusion criteria were relat-
ed to the stability and severity of the CAD. Patients were not included if they had
had an MI or coronary revascularization within 6 months of randomization, if they had a history of stroke or cerebral transient ischemic attack within the previous 3 months, if they had severe liver or renal disease, or if they were planning on having a revascularization procedure. Patients were also excluded if they had severe symptoms of heart failure (New York Heart Association [NYHA] class IV), severe or uncontrollable hypertension (systolic blood pressure/diastolic blood pressure >180/110 mm Hg), sick sinus syndrome, sinoatrial block, congenital long QT, complete atrioventricular block, valvular disease that might require surgery within the next 3 years, or if they had a pacemaker implanted or an implantable cardioverter defibrillator.

Consistent with these criteria and based on our preliminary analysis, we know that the mean age of the population is 65 years, that 89% of patients have a history of MI, and that the mean ejection fraction is 32.4%. Diabetes mellitus is present in 36% of patients and 39% of patients have the metabolic syndrome. The population is 83% male. A large proportion of patients are taking β-blockers (85%). Other/additional medications include antithrombotics, usually aspirin (91%), angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (89%), and lipid lowering drugs (76%).

Thus, our current baseline data indicate that using our inclusion and exclusion criteria, we have been able to identify a group of patients who have been diagnosed with stable CAD and LVD and who, for the most part, are receiving substantial cardiovascular therapy. According to the most recent European Society of Cardiology guidelines, these patients, at baseline, can be considered as optimally and adequately treated.22

Why was ivabradine chosen for the treatment of these patients?

Ivabradine was chosen as a treatment because it met our criteria as a pure heart rate–lowering agent with good tolerability and combinability.

**Ivabradine selectively lowers heart rate**

Ivabradine is the first of a new class of heart rate–lowering agents that act specifically on the sinoatrial node. Ivabradine lowers heart rate by selective inhibition of the I(f) current of the cardiac pacemaker without affecting other cardiac ionic currents.15-17

Consistent with this mechanistic understanding, ivabradine lowers heart rate without compromising myocardial contractility, hemodynamic status, or the electrophysiological properties of the heart. In patients with stable angina, resting heart rate was significantly lower with ivabradine treatment at both peak and trough compared with placebo.23 Exercise tolerance and time to limiting angina during exercise were also improved with ivabradine compared with placebo. In another trial in patients with chronic stable angina in which ivabradine provided a similar or smaller heart rate reduction compared with atenolol, ivabradine was found to be at least as good as atenolol in improving exercise capacity; time to 1 mm ST segment depression and exercise capacity duration tended to be greater (not significant) with ivabradine treatment than with atenolol treatment (Figure 2).19 In a preliminary analysis of a 3-month trial in patients with LVD, myocardial performance improved with ivabradine treatment: LV volumes were smaller in patients treated with ivabradine than in patients treated with placebo.25

These effects are consistent with those observed in animal studies. Ivabradine has been shown to maintain the force of

![Figure 2. Study design of BEAUTIFUL.](image)

**Abbreviations:** B, bradycardia; bid, twice daily; bpm, beats per minute; discont, discontinuation; HR, heart rate; M, month; pl, placebo; rcv’d, received; W, week.


![Figure 3. Effects of treatment on total exercise duration at trough of drug activity.](image)

*Abbreviations:* ate, atenolol; bid, twice daily; CI, confidence interval; Iva, ivabradine; M, month; non-inf, non-inferiority; od, once daily.

contraction, to improve diastolic perfusion, and to not affect the coronary artery diameter increase in exercising dogs. In rats with congestive heart failure, long-term treatment with ivabradine modified the extracellular matrix and the function of myocytes, thereby leading to an improvement in LV function, increased stroke volume, and preserved cardiac output.

**Ivabradine is safe and well tolerated**

In clinical trials, which have included more than 5000 patients, ivabradine has been well tolerated. In rats with congestive heart failure, long-term treatment with ivabradine modified the extracellular matrix and the function of myocytes, thereby leading to an improvement in LV function, increased stroke volume, and preserved cardiac output.

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What kind of patients will benefit from the new approach?

This new approach should benefit CAD patients, especially those with LVD, whose resting heart rate remains high despite treatment. This represents a significant patient population, as the prevalence of LVD associated with CAD is high. In future years, as the general population continues to age, the number of patients in this clinical situation is expected to increase. For this reason, if ivabradine successfully lowers morbidity and mortality in these patients, this new approach will constitute an important public health advance.

What new insights is BEAUTIFUL expected to bring to clinical practice? – Fox
La mortalité des patients atteints de maladie cardio-vasculaire est associée de façon importante à une fréquence cardiaque augmentée. La réduction de la fréquence cardiaque chez les patients atteints de maladie coronaire (MC) et de dysfonction ventriculaire gauche (DVG), un groupe dont le pronostic est encore médiocre en dépit des traitements existants, pourrait donc avoir des effets bénéfiques significatifs sur la morbidité et la mortalité. Une étude randomisée à large échelle, BEAUTIFUL (morBidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction), compare pour évaluer cette hypothèse, un traitement par ivabradine, inhibiteur spécifique du courant If qui ralentit la fréquence cardiaque sans altérer les propriétés inotropes cardiaques, à un placebo chez des patients atteints de MC et DVG sous traitement classique et dont la fréquence cardiaque de repos est au moins de 60 battements par minute (bpm). Le critère primaire est un critère mixte de mortalité cardio-vasculaire et d’hospitalisation pour infarctus du myocarde (IDM) ou aggravation de l’insuffisance cardiaque. L’analyse a porté sur les données préliminaires de 9 978 patients sur les 11 000 inclus. La moyenne d’âge des patients est de 65 ans, la fréquence cardiaque initiale moyenne est de 72 bpm et la fraction d’éjection moyenne de 32,4 %. La plupart des patients ont des antécédents d’IDM (89 %) et prennent des bétabloquants (85 %), des antithrombotiques, habituellement de l’aspirine (91 %), des inhibiteurs de l’enzyme de conversion ou des antagonistes du récepteur de l’angiotensine (89 %) et des hypolipémiants (76 %). Cette étude va donc faire date car c’est la première à évaluer l’effet de la réduction de la seule fréquence cardiaque sur l’évolution cardio-vasculaire des patients atteints de MC et DVG traités de façon optimale.

**QU’EST-CE QUE L’ÉTUDE BEAUTIFUL PEUT APPORTER DE NOUVEAU DANS LA PRATIQUE CLINIQUE ?**
Heart rate: A cardiovascular risk factor that can no longer be ignored

by Å. Hjalmarsen, Sweden

Normal individuals and hypertensives

Several large population studies of healthy individuals have demonstrated that elevated heart rate is an independent risk factor for all-cause and cardiovascular mortality and morbidity. The summarized data from 14 studies of the general population and subjects with hypertension (approximately 160,000 individuals in total; follow-up period 8–36 years; Table I) showed that cardiovascular mortality increased with an elevated heart rate.1 This increase was more marked in men than in women. Although the increase in overall mortality with elevated resting heart rate was also more marked among men than women, it was also found to be significant in women and in both younger and older individuals (at first examination aged 36–64 years and 65–94 years, respectively).2 In the National Health and Nutrition Examination Survey–1 (NHANES I), in which an American population of noninstitutionalized subjects aged 1 to 74 years was followed for 6 to 13 years (n=5995), elevated resting pulse rate was found to be an independent risk factor for coronary heart disease or death among white and black men and women.3 The Spandau Health Test, carried out in citizens from Berlin, Germany, aged 16 years and older, found that heart rate was independently related to mortality in both men and women (Figure 1).4 In several studies of healthy men and women, it has been found that elevated resting heart rate is also an independent risk predictor of sudden cardiac death.5

Subjects with ischemic heart disease

In patients with established ischemic heart disease at baseline, elevated heart rate is an independent risk predictor of major ischemic heart disease trials of patients with acute myocardial infarction or congestive heart failure, β-blocking agents showed more marked effects on mortality in patients with higher pretreatment heart rates; such patients also showed a more marked reduction in heart rate than those with lower pretreatment heart rates. It seems reasonable to assume that heart rate reduction per se is of major importance in terms of these β-blocker effects. Calcium antagonists, also known to reduce heart rate, have also shown some benefit for prognosis after myocardial infarction. In patients with angina pectoris, the prognostic effect of heart rate reduction with β-blockers, calcium antagonists, or sinus node inhibitors has not been studied, but the symptomatic effects are well recognized.

Selected abbreviations and acronyms

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BCAPS</td>
<td>β-Blocker Cholesterol lowering Asymptomatic Plaque Study</td>
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<td>BEAUT/UL</td>
<td>morbidity-mortality EvalUaTion of the Ii inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction</td>
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<td>CIBIS II</td>
<td>Cardiac Insufficiency Bisoprolol Study–II</td>
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<td>MERIT-HF</td>
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<td>NHANES I</td>
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<td>SH/T</td>
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Keywords: heart rate; risk factor; cardiovascular disease; β-blocker; sinus node inhibitor

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heart rate was also a predictor of time to first re-hospitalization for congestive heart failure. In patients with acute myocardial infarction, the resting heart rate on arrival in the emergency room, the average heart rate during the hospital stay, and the heart rate at discharge have been found to be independent and highly significant predictors of later death (Figure 4, page 365). In this study carried out in five hospitals in San Diego (n=1807), heart rate was also found to be a more powerful predictor of later mortality than assessment of left ventricular function after arrival in hospital. Heart rate in these patients is, therefore, not only reflecting depressed cardiac function, which has for long been the general assumption. Neuroendocrine activation and heart rate may differ between patients with similar cardiac function, being normal or depressed to a greater or lesser degree. Very similar observations were made in a much larger trial on patients with events, cardiovascular mortality, and sudden cardiac death, in a manner very similar to that seen in healthy individuals. Recently, the relationship between resting heart rate and future cardiovascular events was assessed in a population of 24 913 patients with suspected or proven coronary artery disease. It can be seen in Figure 2 that over a median follow-up time of 14.7 years, resting heart rate was a predictor of overall and cardiovascular mortality; this was after adjustment for age, sex, diabetes, hypertension, cigarette smoking, left ventricular ejection fraction, number of clinically significant diseased coronary vessels, type of recreation and activity, and concomitant treatments (including β-blockers). The association between heart rate and overall mortality held true in all analyzed subgroups, regardless of sex, age, hypertension, cardiac function, body weight, presence of diabetes, or use of β-blockers (Figure 3, page 364). In this study, heart rate was also a predictor of time to first re-hospitalization for congestive heart failure.

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<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Population</th>
<th>Follow-up</th>
<th>CV mortality relative risk</th>
</tr>
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<tbody>
<tr>
<td>Chicago Gas Company’80</td>
<td>1233 M</td>
<td>15 y</td>
<td>&gt;94 vs ≤60 bpm: 2.3</td>
</tr>
<tr>
<td>Chicago Heart Ass Project ’80</td>
<td>33781 M&amp;W</td>
<td>22 y</td>
<td>≥90 vs &lt;70 bpm: M: 1.6 W: 1.1 (ns)</td>
</tr>
<tr>
<td>Framingham ’93</td>
<td>4530 M&amp;W HTN</td>
<td>36 y</td>
<td>&gt;100 vs &lt;60 bpm: M: 1.5 W: 1.4 (ns)</td>
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<tr>
<td>British Regional Heart ’93</td>
<td>7735 M</td>
<td>8 y</td>
<td>&gt;90 vs &lt;90 bpm: IHD death 3.3</td>
</tr>
<tr>
<td>Spandau ’97</td>
<td>4756 M&amp;W</td>
<td>12 y</td>
<td>Sudden death: 5.2 per 20 bpm</td>
</tr>
<tr>
<td>Benetos ’99</td>
<td>19386 M&amp;W</td>
<td>18.2 y</td>
<td>&gt;100 vs &lt;60 bpm: M: 2.2 W: 1.1 (ns)</td>
</tr>
<tr>
<td>Castel ’99</td>
<td>1938 M&amp;W</td>
<td>12 y</td>
<td>5th vs 3rd quintile: M: 1.6 W: 1.1</td>
</tr>
<tr>
<td>Cordis’00</td>
<td>3257 M</td>
<td>8 y</td>
<td>≥90 vs &lt;70 bpm: 2.0</td>
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<tr>
<td>Reunanen’00</td>
<td>10717 M&amp;W</td>
<td>23 y</td>
<td>&gt;84 vs &lt;60 bpm M: 1.4; &gt;94 vs &lt;66 bpm W: 1.5</td>
</tr>
<tr>
<td>Thomas’01</td>
<td>60343 M HTN</td>
<td>14 y</td>
<td>&gt;80 vs ≤80 bpm: &lt;55y: 1.5; &gt;55y: 1.3</td>
</tr>
<tr>
<td>Matis’01</td>
<td>2533 M</td>
<td>9 y</td>
<td>≥90 vs &lt;60 bpm: 2.7; 1.5 per 20 bpm</td>
</tr>
<tr>
<td>Ohasama’04</td>
<td>1780 M&amp;W</td>
<td>10 y</td>
<td>M: 1.2 W: 1.1 (ns) per 5 bpm</td>
</tr>
<tr>
<td>Okamura’04</td>
<td>8800 M&amp;W</td>
<td>16.5 y</td>
<td>M: 1.3 W: 1.2 per 11 bpm (1 SD)</td>
</tr>
<tr>
<td>Jouven’05</td>
<td>5713 M</td>
<td>23 y</td>
<td>Sudden death from AMI 3.92 (&gt;75 bpm)</td>
</tr>
</tbody>
</table>

Table I. Epidemiological studies on the relationship between heart rate and cardiovascular mortality in the general and hypertensive populations.

Abbreviations: AMI, acute myocardial infarction; bpm, beats per minute; CV, cardiovascular; HTN, hypertension; IHD, ischemic heart disease; M, men; ns, nonsignificant; W, women; y, years.


Figure 1. All-cause mortality after 12 years in men (n=1798) and women (n=2908) aged 40 to 80 years, as a function of resting heart rate levels. Bpm, beats per minute.

Figure 2. Prognostic value of heart rate in patients with suspected or proven coronary artery disease (n=24 913). Panel A shows adjusted survival curves for overall mortality and Panel B shows adjusted survival curves for cardiovascular mortality. Yellow lines indicate a heart rate of <62 beats per minute and green lines indicate a heart rate of >83 beats per minute.
β-blocker metoprolol CR/XL. Mean baseline heart rate was analyzed by quintiles of heart rate (the mean heart rate in the lowest quintile was 71 beats per minute [bpm] and in the highest quintile it was 98 bpm). With increasing baseline heart rate, patient age decreased, the number of females increased, ejection fraction was lower, more patients were in the New York Heart Association (NYHA) class III-IV, more patients had a nonischemic etiology, and there was a higher presence of diabetes.

**Effects of heart rate reduction**

In 1981, three large trials of patients with acute myocardial infarction demonstrated that the β-blockers timolol, metoprolol, and propranolol reduced mortality, cardiovascular and sudden cardiac death, and hospitalization.11-13 In these studies, it was also noted that patients with a heart rate above the median at baseline had a higher mortality rate during follow-up, and the effect of the β-blockers was most marked in patients with the highest heart rate at baseline. In the Göteborg Metoprolol Trial in Acute Myocardial Infarction, it was found that the effects of the β-blocker metoprolol were most marked in patients with a heart rate above the median at baseline (>70 bpm).12,14 This included the effects on all-cause mortality during a period of 3 to 24 months (Figure 5), sudden cardiac death, ventricular fibrillation, infarct development, and enzyme-estimated infarct size. After analyzing all placebo-controlled β-blocker studies in patients with acute myocardial infarction, it was proposed by Kjekshus and coworkers that there was a significant relationship between a reduction in resting heart rate and a decrease in all-cause mortality (Figure 6).15,16

After a review of studies of patients with chronic heart failure, the same authors proposed that in these patients there is a similar relationship between changes in heart rate and all-cause mortality—not only in conjunction with the use of β-blockers, but also, for example, with angiotensin-converting enzyme inhibitors.16 In the two large trials on patients with chronic heart failure, the Cardiac Insufficiency Bisoprolol Study–II (CIBIS II; n=2539; Figure 7) and the MERIT-HF Trial, patients with a higher heart rate at baseline had the highest rates of mortality, and among these patients, there was a more marked effect with the β-blockers bisoprolol and metoprolol CR/XL.17,18

**Pathophysiological mechanisms**

The data presented demonstrate a strong correlation between elevated heart rate and increased cardiovascular mortality and morbidity. The high heart rate reflects an imbalance of the autonomic ner-
vous system, with increased sympathetic activity and/or reduced vagal activity. Heart rate is a major determinant of myocardial oxygen consumption and energy utilization. Furthermore, an increase in heart rate reduces the diastolic coronary perfusion time. Through these two mechanisms, an increase in heart rate may trigger ischemic events. Experimental studies of myocardial ischemia have shown that an increase in sympathetic activity and/or lowering of vagal activity increases the risk of ventricular fibrillation. It is well known that psychosocial stress accompanied by an increase in heart rate can trigger sudden cardiac death. This was reported both after the earthquake in San Francisco in 1994,19 and from Israel during the attack by Iraqi squad missiles. During these events, there was a severalfold increase in sudden cardiac death reported at hospitals in the region. Elevated heart rate during mental stress may play a key role in the development of sudden cardiac death. Among men who develop myocardial infarction at a young age, it is well known that elevated heart rate correlates significantly with the severity and progression of atherosclerosis, as measured by coronary angiography.20 Experimental data have also demonstrated that a reduction in heart rate can delay the progression of coronary atherosclerosis in monkeys.21 It has additionally been shown that monkeys subjected to sinus node ablation or treated with $\beta$-blockers have significantly less coronary atherosclerosis than animals not receiving these treatments and with a higher heart rate.22,23

High heart rates have been associated with coronary artery endothelial dysfunction in experimental studies.24,25 These observations are supported by results from the $\beta$-Blocker Cholesterol lowering Asymptomatic Plaque Study (BCAPS), a randomized trial that showed that a $\beta$-blocker reduces the rate of progression of carotid artery intima thickness in asymptomatic subjects.26 Furthermore, in a multivariate analysis study, elevated heart rate during mental stress may play a key role in the development of sudden cardiac death. Among men who develop myocardial infarction at a young age,
anisms behind development and progression of myo-
cardial ischemia, acute ischemic events, and of 
sudden cardiac death and elevated heart rate are 
summarized in Table II.

**Conclusion**

In conclusion, heart rate is an independent risk 
predictor of the onset of acute coronary events, 
including all-cause mortality, cardiovascular mortal-
ity, sudden cardiac death, acute coronary syndrome, 
and the development of myocardial infarction. Mea-
surement of heart rate should be carried out in pa-
ients with or without established ischemic heart 
disease, and should be considered in the same light 
as other risk factors, such as blood pressure, smok-
ing, cardiac function, and diabetes. It is known that 
elevated blood pressure, depressed cardiac func-
tion, and diabetes are all associated with elevated 
heart rate, and that intervention against these risk 
features improves prognosis. In several large place-
bo-controlled trials of patients with acute myocar-
dial infarction or chronic heart failure, β-blocking 
agents have shown more marked effects on mor-
tality in patients with higher pretreatment heart 
rates. It is reasonable to believe that the heart rate 
reduction per se is of major importance for these 
effects of the β-blockers. With the introduction of 
ivabradine, the first selective and specific If inhibit-
or, heart rate reduction can be obtained without ef-
fects on sympathetic activity or contractility. Wheth-
er heart rate reduction per se with ivabradine will 
have the potential to reduce not only anginal atta-
cks and myocardial ischemia, but also improve 
prognosis in coronary artery disease patients with 
left ventricular dysfunction and in patients with 
chronic heart failure, is presently being tested in 
the ongoing large-scale studies, morBidity-mortal-
ity EvaLUaTion of the If inhibitor ivabradine in pa-
tients with coronary disease and loFt ventricULar 
dysfunction (BEAUTIFUL) and Systolic Heart 
failure treatment with the If inhibitor ivabradine 
Trial (SHI/T).21

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**Table II. The effects of a reduction in heart rate.**

<table>
<thead>
<tr>
<th>ifT</th>
<th>heart rate</th>
<th>lower oxygen consumption</th>
<th>improved diastolic coronary flow</th>
<th>anti-ischemic effects</th>
<th>increased ventricular fibrillation threshold</th>
<th>antithromboxaetherosclerotic effects</th>
<th>prevention of plaque rupture</th>
<th>prevention of cardiomyopathy</th>
<th>slowed development and progression of IHD</th>
<th>prevention of acute and chronic ischemic events (CV death, sudden death, angina, AMI, CHF)</th>
</tr>
</thead>
</table>

**Focus**

Heart rate: a cardiovascular risk factor – Hjalmarson
Plusieurs grandes études de population chez des individus sains ont démontré qu'une fréquence cardiaque élevée est un facteur de risque indépendant de morbidité et de mortalité toutes causes et cardio-vasculaire. D'autres études ont aussi constaté qu'une fréquence cardiaque élevée est un facteur de risque indépendant de morbidité et de mortalité toutes causes chez des patients ayant une pathologie coronaire, un infarctus aigu du myocarde ou qui sont en post-infarctus ou en insuffisance cardiaque congestive. Chez les patients qui ont eu un infarctus aigu du myocarde, les fréquences cardiaques à l'arrivée aux urgences, au cours de l'hospitalisation (moyenne des fréquences) et à la sortie, sont des facteurs prédictifs indépendants et hauteur significatifs de décès ultérieur. La fréquence cardiaque est d'ailleurs un facteur prédictif plus puissant que la fonction ventriculaire gauche. Ceci signifie que chez ces patients, la fréquence cardiaque ne reflète pas seulement l'altération du fonctionnement cardiaque, ce qui a été l'hypothèse générale pendant très longtemps. La mesure de la fréquence cardiaque en tant que facteur prédictif de risque devrait être désormais prise en compte, au même titre que d'autres facteurs de risque tels que la pression artérielle, le tabagisme, le fonctionnement cardiaque, ou le diabète. Il est reconnu que les interventions contre ces facteurs améliorent le pronostic. Les bétabloquants ont montré, au cours de plusieurs grandes études contrôlées contre placebo chez des patients ayant eu un infarctus aigu du myocarde ou une insuffisance cardiaque congestive, des effets plus marqués sur la mortalité des patients dont la fréquence cardiaque était plus élevée avant le traitement. La diminution de la fréquence cardiaque de ces patients a aussi été plus marquée que celle des patients qui avaient une fréquence cardiaque plus basse avant le traitement. Il semble raisonnable de penser que la réduction de la fréquence cardiaque en soi joue un rôle majeur dans l'effet des bétabloquants. Les antagonistes calciques, également connus pour réduire la fréquence cardiaque, ont aussi montré des effets bénéfiques dans le pronostic post-infarctus. Quant au patients présentant un angor, si l'effet pronostique de la réduction de la fréquence cardiaque avec les β-bloquants, les antagonistes calciques, ou les inhibiteurs du nœud sinusal n'a pas été étudié, les effets symptomatiques sont, quant à eux, tout à fait indubitables.
Heart rate reduction has long been considered an important therapeutic principle, because it decreases oxygen consumption and increases the diastolic interval, during which 80% to 90% of myocardial perfusion occurs. Not surprisingly, chronic heart rate reduction has been shown to reduce the incidence of angina in patients with coronary heart disease, and to stimulate myocardial angiogenesis in experimental animals undergoing hypertrophy due to pressure or volume overload, as well as in those with myocardial ischemia and infarction. Heart rate reduction with either alindidine, a potassium-adenosine triphosphate (KATP) channel antagonist, atenolol, a β-blocker, or ivabradine, an If current inhibitor acting on sinoatrial node cells, was shown to preserve coronary reserve and maximal myocardial perfusion in rats with myocardial infarction. Atenolol was found to enhance arteriolar growth, while ivabradine reduced perivascular collagen in arterioles. Thus, different mechanisms may underlie the improvements in coronary reserve and maximal perfusion obtained from the two pharmacological treatments. Moreover, ivabradine, but not atenolol, preserved ejection fraction. The importance of heart rate reduction was also demonstrated in a model of ischemia where two groups of dogs were subjected to gradual coronary artery occlusion, one with normal heart rate, the other with heart rate reduced by pacing after sinoatrial node ablation. The paced dogs had higher maximal perfusion, arteriolar length, and volume density, and capillary density in the collateral-dependent region compared with the dogs with normal heart rates. Moreover, collateral remodeling was more advanced in the dogs with reduced heart rates. Taken together, considerable evidence indicates that heart rate reduction is an effective therapy for the heart when subjected to pathological hypertrophy or ischemia and/or infarction.

Keywords: angiogenesis; arteriogenesis; ventricular function; myocardial infarction; coronary vessels; myocardial perfusion; coronary reserve

Epidemiological studies have shown that a high heart rate enhances the risk for cardiovascular mortality (reviewed by Laperche et al.). Increases in heart rate have been shown to precede episodes of nocturnal angina pectoris. Moreover, increases in heart rate that exceed the ischemic threshold commonly precede episodes of myocardial ischemia in ambulatory patients. Not surprisingly, heart rate reduction has long been considered an important therapeutic principle, primarily because it is accompanied by reduced oxygen consumption. In 2003, using a novel selective If inhibitor, ivabradine, to decrease heart rate in patients with a history of stable angina, Borer and colleagues reported improvements in exercise tolerance and time to development of ischemia. A reduction in heart rate also facilitates a redistribution of blood flow toward the subendocardium. Another benefit of lowering the

A need for neovascularization occurs when the heart’s ventricles undergo hypertrophy in response to pressure or volume overload or after myocardial infarction (reviewed by Tomanek and Dedkov1 and Tomanek and Torry2). Thus for cardiac hypertrophy to be an effective compensator for an increased workload, sufficient vascular growth must occur in order to preserve maximal myocardial perfusion and coronary reserve. Stimulation of angiogenesis and arteriogenesis in the hypertrophic myocardium is therefore an important goal aimed at preserving ventricular function. Considerable evidence now exists to indicate that mechanical factors promote coronary vascular growth (reviewed by Hudlicka et al3 and Tomanek and Torry2). Both in vivo and in vitro data indicate a role for increased blood flow and related factors (e.g., shear stress), and stretch (such as that induced by increased diastolic filling). The latter appears to be the stimulus for coronary angiogenesis/arteriogenesis when heart rate is reduced.

Heart rate reduction: a potent angiogenic factor
Heart rate is that it delays the onset of atheromas, as documented in monkeys on an atherogenic diet. Furthermore, there is ample evidence to support the thesis that a chronic reduction in heart rate also stimulates myocardial capillary and arteriolar growth (reviewed by Brown et al.). Wright and Hudlicka (1981) carried out experiments in which they chronically paced rabbit hearts at 60% of their resting valves, which was found to result in a 40% increase in myocardial capillary density. The magnitude of the increases correlated with the duration of pacing (1-50 days). A 50% reduction in resting heart rate over a period of 4 weeks in rabbits not only increased the myocardial capillary/cardiomyocyte ratio and capillary density, but also enhanced mitochondrial volume by 16%. These anatomical changes were associated with higher maximal oxygen consumption in response to a gradual increase in preload. Subsequent studies by this group revealed increases in myocardial capillarity in pigs subjected to a 30% chronic heart rate reduction by electrical pacing.

Pharmacologically-induced heart rate reduction has also been shown to stimulate coronary vessel growth. Chronic treatment of rats with the potassium-adenosine triphosphate (KATP) channel antagonist, alinidine, which increases the effective refractory period in the atrioventricular node, enhanced capillary length density by 23%. Heart rate was reduced by 10%, 14%, and 18% during the 3 weeks of treatment. The fact that exercise endurance training causes resting bradycardia also provides another model of heart rate reduction: experiments from my laboratory documented an increase in capillary numerical density in rats trained on a treadmill for 12 weeks. However, it is not clear if the exercise stress was the major stimulator of the capillary growth per se, or whether it also involved the resting bradycardia.

The most likely explanation for myocardial vascular growth associated with lowering of heart rate is enhanced diastolic filling (Figure 1). When this occurs, blood vessels as well as myocytes are subjected to increased stretch. Our experiments on isolated cardiomyocytes and microvascular endothelial cells have documented that cyclic stretch enhances both angiogenic growth factor and receptor proteins. This work firstly shows that the addition of conditioned medium from cardiomyocytes to coronary microvascular endothelial cells enhances their proliferation, migration, and tube formation. Stretch of these cells increases the angiogenic growth factors vascular endothelial growth factor (VEGF) and angiopoietins 1 and 2. These data indicate a role for stretch-activated paracrine signaling from cardiomyocytes to endothelial cells. Second, cyclic stretch of endothelial cells upregulates the VEGF receptor, Flk-1, and the angiopoietin receptor, Tie-2, and enhances their proliferative, migratory, and tube forming abilities.

**Figure 1.** Mechanisms involved in angiogenesis induced by heart rate reduction. When heart rate is reduced, diastolic volume is increased, causing cardiomyocytes and endothelial cells to be stretched. Stretch upregulates vascular endothelial growth factor (VEGF) and angiopoietins in cardiomyocytes, in addition to their receptors (Flt-1 and Tie-2) in endothelial cells, thus facilitating angiogenesis.

**Heart rate reduction as a therapeutic tool for coronary circulation**

- **Cardiac hypertrophy caused by increased afterload or preload**
  Pathological cardiac hypertrophy is often associated with a reduction in myocardial vascularity and maximal myocardial perfusion (reviewed by Tomaneck and Dedkov). Chronic administration of alinidine has been found to increase the capillary/myocyte ratio in rats with hypertension without modifying the degree of cardiac hypertrophy, and to reduce the heart rate by 24%. Electrical cardiac pacing for a period of 4 weeks in rabbits with volume overload–induced hypertrophy was found to reduce heart rate by 45%, but to enhance the magnitude of hypertrophy. Despite this enhancement of hypertrophy, marked capillary growth was documented.

  Heart rate reduction occurs when commonly prescribed β-blockers are used after myocardial infarction to reduce myocardial oxygen consumption and to protect the myocardium against the deleterious effects of catecholamines. Nagatsu and colleagues (2000) found, however, that when heart rate reduction was blocked in dogs with mitral valve regurgitation who had been treated with β-blockers, the beneficial effects of the β-blockers (improved contractile function and myocardial stiffness) were not realized. Thus, heart rate reduction associated with β-antagonist therapy is the key factor involved in the improved function attributed to this class of drugs.

- **The heart postinfarction**
  A compensatory hypertrophy of the heart also occurs in response to a loss of cells in the infarcted heart. As maximal perfusion is compromised in such hearts, it has generally been believed that compensatory growth of the coronary vasculature does not occur. Although substantial arteriolar growth has been documented in the postinfarcted hearts of rats, it has not been found to be sufficient to preserve maximal myocardial perfusion. The fact that lowering of the heart rate with aspirin or methylprednisolone stimulates capillary growth in young rats after myocardial infarction is consistent with
data on young normal rats treated with alinidine. Work in my laboratory has focused on heart rate reduction as a means of preserving maximal myocardial perfusion and coronary reserve after infarction or during gradually developed coronary artery stenosis. In view of the improvements in ventricular function and stiffness attributed to chronic β-blockade, we tested the hypothesis that atenolol would stimulate a sufficient growth of the coronary vasculature to preserve maximal myocardial perfusion and coronary reserve. The left anterior descending coronary artery of midlife (12-month-old) rats was ligated, after which they were split into two groups, with one group receiving treatment with atenolol for 4 weeks. Although both groups had similar-sized myocardial infarctions, the treated group demonstrated a 25% to 28% reduction in heart rate. Maximal coronary perfusion in response to maximal vasodilation and coronary reserve was reduced in the untreated group with myocardial infarction and sham controls by 35% and 50%, respectively. By contrast, the values for these parameters were normal in the rats treated with atenolol. We documented arteriolar growth, as indicated by length density, in both treated and nontreated rats with myocardial infarction. However, treatment stimulated a greater magnitude of growth than that observed in the untreated rats, as evidenced by arteriolar length densities that exceeded those of the nontreated rats by 41% and 14% in the septum and left ventricular (LV) free wall, respectively. Thus, the better myocardial perfusion in the surviving myocardium of the treated rats is most likely attributable to the enhanced growth of coronary arterioles. However, ejection fraction and LV volume were not affected by chronic β-blockade treatment.

Having shown that alinidine enhances myocardial capillary growth in noninfarcted young rats via a VEGF-dependent mechanism, we applied chronic treatment with this KATP channel antagonist to 4-month-old rats, 2 days after coronary artery ligation. We found that both capillary and arteriolar length densities were greater after 4 weeks of treatment, and that coronary reserve was preserved. During the first week of treatment, VEGF, VEGF receptor 1 (Flt-1) and fibroblast growth factor (FGF)-2 proteins were elevated compared with levels in nontreated rats with infarcts, and VEGF protein remained elevated after 3 weeks. Ejection fraction was not as markedly reduced as it was in nontreated rats, and the increase in ventricular volume was also less. In summary, this study documented an important role for pharmacologically induced heart rate reduction in the infarcted heart. However, these studies were conducted in 10- to 12-week-old rats, in contrast with the 12-month-old rats used in the β-blockade study previously described.

Accordingly, we tested the effectiveness of a 4-week period of treatment with ivabradine—which selectively inhibits the If current in sinoatrial cells and is devoid of effects on inotropy, cardiac conduction or peripheral vascular tone—in 12-month-old rats with myocardial infarction. Ivabradine treatment normalized maximal myocardial perfusion and coronary reserve, and limited the increase in end-diastolic pressure and the decrease in ejection fraction. Surprisingly, we did not find enhanced arteriolar growth consistent with the higher myocardial perfusion and coronary reserve. Rather, we found a reduction in interstitial and perivascular collagen. We then assayed for plasma angiotensin II and found that the characteristic rise after infarction in rats did not occur with ivabradine treatment. Moreover, AT1 receptor and transforming growth factor (TGF)–β1 levels in the heart were lower in the treated group than in the untreated group with myocardial infarction.

These data suggest that chronic ivabradine treatment either directly or indirectly lowered factors that regulate perivascular and interstitial collagen in the heart. Previous work with young (11-week-old) rats also revealed that ivabradine treatment after myocardial infarction reduced LV collagen density. We believe that the likely explanation for the preservation of maximal coronary perfusion and coronary reserve is a consequence of more compliant resistance vessels due to the lower perivascular collagen with ivabradine treatment. The regulation of collagen turnover is unquestionably a complex process that involves a diverse array of proinflammatory/profibrogenic regulatory peptides and cytokines, including TGFβ1, as well as hormonal interactions and the involvement of reactive oxygen species.

**Comparison of the effects of ivabradine and β-blockade on the coronary circulation**

The two studies described above document a preservation of coronary maximal myocardial perfusion and coronary reserve in 12-month-old rats either with β-blockade (atenolol) or the If inhibitor, ivabradine. However, with the β-blocker, but not ivabradine, the normalization of the coronary perfusion and reserve was associated with a greater angio-genic response. The improved coronary characteristics with ivabradine involved a different mechanism, which we believe to be the reduction of perivascular collagen in arterioles, thereby enhancing their vasodilatory capacities. The finding that β-blockade with atenolol enhanced postinfarction ventricular hypertrophy, whereas ivabradine did not, may be caused by the attenuation of angiotensin II and its AT1 receptor noted in the ivabradine-treated rats. Recent evidence indicates a role for angiotensin II and its receptors in the development of cardiac hypertrophy. Thus, attenuation of angiotensin II and the AT1 receptor in the postinfarcted rats treated with ivabradine may have limited the enlargement of cardiomyocytes.

**The ischemic heart**

An important question concerns the value of heart rate reduction in the setting of myocardial ischemia in the absence of a myocardial infarction. To answer this question, we placed an ameroid occluder on the left anterior descending coronary artery of dogs with normal heart rates and on those with heart rates reduced by about 21% as a result of atrioventricular nodal ablation and an implanted pacemaker. The ameroid occluder gradually constricted the
coronary artery, with total occlusion occurring after about 2 weeks. At 4 weeks after occlusion, maximal myocardial perfusion of the collateral-dependent region (the area served by the occluded left anterior descending coronary artery) was higher in the dogs with a reduced heart rate. Moreover, arteriolar length and volume densities and capillary density were also higher in the collateral-dependent region of these dogs, despite evidence of cardiomyocyte hypertrophy. Thus, perfusion of this region was enhanced by pacing the heart at a reduced rate. Myocardial perfusion was also higher in the collateral-independent epicardial region of the dogs who underwent pacing. These data indicate that a reduction in heart rate during gradual occlusion of a coronary artery stimulates collateral as well as noncollateral artery growth. Evaluation of coronary collateral vessels by electron microscopy revealed a remodeling of these vessels in both the paced and nonpaced dogs. However, in the paced group, the wall/lumen ratios were higher, indicating that remodeling progressed further when heart rate was reduced.

Conclusions

The lowering of heart rate has important benefits over and above the reduced oxygen consumption that accompanies it; namely, the preservation of coronary reserve and maximal myocardial perfusion of the collateral-dependent region of the dogs after reduced heart rates. Moreover, arteriolar length and volume densities and capillary density were also higher in the collateral-dependent region of these dogs, despite evidence of cardiomyocyte hypertrophy. Thus, perfusion of this region was enhanced by pacing the heart at a reduced rate. Myocardial perfusion was also higher in the collateral-independent epicardial region of the dogs who underwent pacing. These data indicate that a reduction in heart rate during gradual occlusion of a coronary artery stimulates collateral as well as noncollateral artery growth. Evaluation of coronary collateral vessels by electron microscopy revealed a remodeling of these vessels in both the paced and nonpaced dogs. However, in the paced group, the wall/lumen ratios were higher, indicating that remodeling progressed further when heart rate was reduced.

Table 1. Studies investigating the effects of heart rate lowering on the coronary circulation after myocardial infarction (*) or gradual coronary artery occlusion (†). Comparisons are between groups with coronary artery occlusion and experimentally lowered heart rate and those with coronary artery occlusion and normal heart rates.

<table>
<thead>
<tr>
<th>Treatment; duration; species</th>
<th>Age</th>
<th>Maximal myocardial perfusion</th>
<th>Coronary reserve</th>
<th>Growth density</th>
<th>Ejection factors</th>
<th>Frac tion</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Alinidine; 3 weeks; rats</em></td>
<td>11 weeks</td>
<td>Higher</td>
<td>Higher</td>
<td>Higher</td>
<td>Higher VEGF, Flt-1, and FGF2 higher</td>
<td>Preserved</td>
<td>Capillary length density higher</td>
</tr>
<tr>
<td><em>Atenolol; 4 weeks; rats</em></td>
<td>12 months</td>
<td>Higher</td>
<td>Higher</td>
<td>Higher</td>
<td>Higher NA</td>
<td>Not preserved</td>
<td>NA</td>
</tr>
<tr>
<td><em>Ivabradine; 4 weeks; rats</em></td>
<td>12 months</td>
<td>Higher</td>
<td>Higher</td>
<td>Same</td>
<td>Tie-2 higher</td>
<td>Preserved</td>
<td>Decreases in plasma angiotensin, myocardial AT-R1 &amp; TGFβ, and perivascular collagen</td>
</tr>
<tr>
<td>AV node ablation &amp; pacing; dogs*</td>
<td>Adult</td>
<td>Higher</td>
<td>NA</td>
<td>Higher VEGF higher</td>
<td>NA</td>
<td>Capillary length density higher</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AV, atrioventricular; FGF2, fibroblast growth factor 2; NA, not applicable; VEGF, vascular endothelial growth factor.

REFERENCES


Effect of heart rate reduction on myocardial perfusion and vascular density – Tomane

Mediographia, Vol 29, No. 4, 2007 371
La réduction de la fréquence cardiaque a longtemps été considérée comme un principe thérapeutique important car elle diminue la consommation d’oxygène et augmente l’intervalle diastolique pendant lequel intervient 80 à 90 % de la perfusion myocardique. Comme on pouvait s’y attendre, la réduction prolongée de la fréquence cardiaque diminue l’incidence de l’angor chez des patients coronariens et stimule l’angiogénèse myocardique dans des modèles d’animaux de laboratoire ayant une hypertension cardiaque obstruée par une surcharge de pression ou de volume ainsi que chez ceux ayant une ischémie myocardique et un infarctus. Il a été montré que la réduction de la fréquence cardiaque, qu’elle soit obtenue par l’alimédrine (un antagoniste des canaux potassiques liés à l’ATP [K₁₉₇₉]) par l’âtenolol (un bétabloquant) ou par l’ivabradine (un inhibiteur du courant Iᵥ agissant sur les cellules du nœud sinusal) préservait la réserve coronaire et la perfusion myocardique maximale chez des rats ayant un infarctus du myocarde. Chez ces animaux, l’âtenolol augmente la croissance artériolaire alors que l’ivabradine diminue le collagène périvasculaire dans les artérioles. Ainsi, des mécanismes différents pourraient être à l’origine de l’amélioration de la réserve coronaire et de la perfusion maximale obtenue avec ces deux traitements. De plus, l’ivabradine, contrairement à l’âtenolol, préserve la fraction d’éjection. L’importance de la réduction de la fréquence cardiaque a également été montrée dans un modèle d’ischémie dans lequel deux groupes de chiens avaient été soumis à une occlusion coronaire progressive, l’un ayant une fréquence cardiaque normale, l’autre une fréquence cardiaque diminuée par stimulateur cardiaque après ablation du nœud sinusal. Comparés aux chiens à fréquence cardiaque normale, les chiens dont la fréquence cardiaque avait été réduite présentaient une augmentation de la perfusion maximale, de la densité artériolaire (en longueur et volume) ainsi que de la densité capillaire dans la circulation collatérale de la région dépendante. De plus, le remodélage collatéral était plus avancé chez les chiens dont les fréquences cardiaques étaient réduites. Il existe ainsi un faisceau important d’arguments montrant que la réduction de la fréquence cardiaque est un traitement efficace pour le cœur soumis à une hypertrophie pathologique, une ischémie et/ou un infarctus.
In the mid 17th century, the Spanish possessions in the Americas were the envy of the other great European nations who came late to the conquest of the New World. Spain exercised exclusive dominion and a commercial monopoly over her colonies, ratified in Pope Alexander VI’s bull *Inter Caetera* (1493) and the subsequent Treaty of Tordesillas (1494), which granted Spain and Portugal exclusive trading rights with the New World. Depending which way the political alliance barometer swung, England, Holland, and France sought to divert (and steal) some of the wealth transported aboard the Spanish galleons. This became the freebooter era: the French and English monarchs issued seamen with warrants known as “letters of marque and reprisal” authorizing them to pass beyond the borders of the nation (“marque” meant “frontier”), and there to search, seize, or destroy assets or personnel of the hostile foreign party (“reprisal”). Bearers of letters of marque were entitled to open fire “in complete legality” on Spanish ships and relieve them of their cargo.

As infrastructure for their maritime piracy policy, these European powers established bases to control maritime traffic to and from the Spanish Americas. Some freebooters had considerable fleets at their disposal, comprising several dozen vessels. This enabled them to attack the Spanish treasure transit ports in Peru and Chile. Plunder was also reported from Panama (Boca del Drago and Chagre) and Maracaibo (modern Venezuela).1-3

In the mid 17th century, a number of Protestants expelled from France and Catholics fleeing England became freebooters in the Caribbean and along the Atlantic and Pacific coasts. Their purpose, backed by their respective monarchs, was the organized plunder of treasure-laden Spanish galleons. They were soon joined by the Dutch with their considerable naval strength. The adventurers included a number of barber-surgeons whose faiths prevented them from practicing in their own countries. The freebooter surgeons, whose knowledge of anatomy and therapeutics was rudimentary (very few had seen the inside of a medical school), maintained basic ship hygiene, ruled on injury compensation scales, performed routine surgery, and took part in the division of booty. They were as powerless as qualified physicians against such scourges of seafaring life as typhus, scurvy, yellow fever, and dysentery. Their best-known representative was the Frenchman, Alexander Exquemeling, whose account of his adventures, published in Amsterdam in 1678, proved a huge success in several languages with a public avid for exotic tales. The golden age of freebooting came to an end in 1714 with the Treaty of Utrecht, confronting freebooter surgeons with a variety of options: taking up conventional terrestrial practice, going “legit” as ship’s surgeons in the Navy or colonial companies, embracing full-blown piracy, or practicing another profession. Some ex-freebooter surgeons were taken on by the Royal Navy surgery schools later established in Rochefort (1722), Toulon (1725), and Brest (1731).

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Less well defended, more vulnerable, and less prosperous than the mainland colonies, the islands of the Spanish West Indies became easy prey for the French, English, and Dutch navies. They also afforded any number of creeks, beaches, headlands, rocks, and reefs for ensnaring, surprising, and attacking a fat flota.

The French seized St Christopher (modern St Kitts) in 1627 and the British Jamaica in 1655, both originally claimed for Spain. Individual West Indian islands changed hands frequently between the 17th and 19th centuries, reflecting acute political and economic rivalries among the great powers. Settlers from a variety of backgrounds were either pushed or pulled toward the New World. They included adventurers, ex-convicts, French Protestants fleeing Cardinal Richelieu (1585-1642), and English Catholics persecuted by Oliver Cromwell (1599-1658). Among them were barber-surgeons and, more rarely, physicians, and apothecaries.

Surgeons and freebooters: necessity and the law

In France as elsewhere until the 18th century, the profession of surgeon did not require a medical education. Surgeons had in fact formed themselves into a corporation unrelated to the Faculties of Medicine. Their status was that of artisans without degrees or official recognition. They underwent an apprenticeship with a master and passed a symbolic examination (thus without submitting a thesis, as is required for an MD degree in France). In addition, a royal decree of 1666 forbade Protestants to practice surgery in France. At the same time, Catholic surgeons were being driven out of England. In addition, until the decree in 1689 by Louis XIV’s naval secretary, Jean-Baptiste Colbert (1651-1690), son of the Sun King’s minister of finance, there was no such thing as a naval health service. There was only a royal decree of 1642 requiring captains to choose “very good surgeons” for their naval campaigns. Failing that, Louis XIV’s previous naval secretary, Charles-Jean Colbert (1618-1684), cousin of the great Colbert,
had made it mandatory for ships to carry a first-aid kit prepared by cer-
tified apothecaries.6-9 Surgeons taking up the freebooting life knew that
their share in the booty snatched from the Spanish would exceed their
fees earned in royal or merchant navies. Theirs was a hand-to-mouth ex-
istence, with no hope of leaving anything lasting behind them. The rea-
sions attracting surgeons onto privateers are understandable. The only
evidence of competence required was to present the captain with a cer-
tificate provided by reputable surgeons from their corporation, attesting
their skill.

Before embarking, surgeons signed “articles of agreement.” This pi-
irate code, also known as the chasse-partie, charter party, or custom of
the coast, set out the objectives of the expedition, the ships to be attacked,
the percentage shares of the booty, and the expedition leader. As a rule,
captain, carpenter, and surgeon received equal shares. A typical clause
might read: “The surgeon shall receive 200 crowns for his medicine chest,
whether we capture a ship or not. In addition to that, if we do capture a
ship, he shall have a share like the others. If he cannot be given enough
silver, he shall be given two slaves.” All the French governors of Tortuga
between 1648 and 1675 owned privateers, which they fitted out to plunder
Spanish ships. So did certain rich planters. The articles of agreement were signed by boat owner, captain,
and crew. Rules could be very strict: men who became drunk before all enemy crew had been captured
risked losing their share or even being hanged. The same penalties applied to rape (of white women) or
cowardice in action.1,4,10,11

Surgeons treated the wounded (for no charge), sometimes with a couple of assistants. Based on the in-
ventory of a surgeon from Nantes, Joret, who was to die at sea, the equipment taken on board had to be
fairly basic: two lancet holders each with six lancets (for bleeding), four razors, five tooth extractors (four
forceps and one pelican), two combs, two bullet extractors, one rasp (bone surgery), a spatula, a hollow
sound, two scalpels, and an abscess lancet. Depending on their experience, intrepidity or skill, surgeons

A BRIEF FREEBOOTER GLOSSARY2,11

- **Buccaneers** were merchants who broke the Spanish colonies’ trading monopoly laws. They sold
goods to Indians at prices below those fixed by the authorities in Cadiz. Their name was derived from
the French boucan, itself an Arawak word for the wooden frames on which the Indians smoked their
meat and burned their prisoners. Buccaneers also hunted wild cattle and sold the smoked meat and
leather to ships arriving in port. Their governments allowed them to arm their ships and defend them-
selves against the Spanish.

- **Corsairs** were armed by a powerful figure in the kingdom (France or England), with government
approval. Their warships attacked vessels flying enemy flags. They received a fixed wage and a share of
the booty. Corsairs flourished during wartime, harassing the maritime trade of enemy countries.
They were required to safeguard the ships they captured and deliver them to their country’s navy.

- **Freebooters** were seamen sailing in the Americas on merchant ships bearing royal “letters of marque
and reprisal” authorizing them to arm themselves against Spanish ships and rob them of their cargo.
A share of the booty—approximately 10%—was earmarked for the royal treasury. The word “free-
booter” is derived from the Dutch *vrījbuiter*.

- **Pirates** were seamen who obeyed only the laws or rules that they themselves had set. They attacked
any ships from any country in any sea. They were ocean-going highwaymen who sailed for the pur-
pose of robbing and pillaging. All goods and monies seized were shared out more or less equally among
the crew. The only difference between piracy and freebooting was the latter’s “letters of marque.”
performed routine procedures: they treated saber wounds, disentangled fingers shredded by runaway ropes, debrided shot wounds, amputated crushed hands, splinted legs fractured by recoiling canon, and sutured foreheads and scalps cut open by swinging pulleys. They were also masters in the art of bleeding. During battle, surgeons set themselves up at the foot of the main mast to tend the wounded. Swigs of rum were their anesthetic. After the battle, when the ship had anchored in a sheltering cove, the surgeon and his assistant would line up the wounded on deck to treat them in turn. If, on the other hand, the battle went the other way, the captured surgeon was generally spared and commandeered to the victor’s employ. Surgeons on merchant ships captured by pirates were a special case: if caught, they were acquitted in trials for piracy since they had never signed articles of agreement.6,7,10,12

Freebooter surgeons were also in demand on medical questions, where their competence was poor, to say the least. Deplorable on-board living conditions—crowding, lack of ventilation, swarming rats and fleas, and a rank hold containing barrels of rotting food—conspired to encourage infection, parasitic disease, and vitamin deficiency. Slapping in the inaccessible bowels of the hold was a stagnant pool of thick and putrid bilge water in which dead rats and other debris floated; this seagoing bog was a perfect medium for the proliferation of mosquitoes and their larvae—Anopheles, the vector of malaria, and Aedes aegypti, the vector of yellow fever and dengue. The commonest condition was “ship fever,” thought to be an exanthematic form of typhus transmitted by fleas. Dysentery, malaria, dengue, venereal disease, and scurvy also decimated the crews. Successive epidemics of yellow fever, or “black vomit,” ravaged the region—Cuba in 1620, Guadeloupe in 1635, Barbados in 1647, and Martinique in 1690. Surgeons were totally powerless where these diseases were concerned, as were the physicians of the time (the impotence of the latter being underlined by the fact that no ship ever carried them). On board, the surgeon enforced basic hygiene: hosing down the blood-stained decks and batteries after boardings, lighting torches against the damp, opening port holes and hatches to the air, and disinfecting with vinegar vapor.

In the Caribbean, morbidity levels among the crew during campaigns longer than 2 months could reach 40% and mortality levels 30%.13 Death during combat did not exceed 10%, although this appears high for wars during this period: “What made these battles so bloody and murderous was the impossibility of flight,” wrote Claude, Count of Forbin (1656-1733) in his Memoirs. “It left a stark choice between victory or death.”6,7,10-12 Freebooter surgeons also played an important “expert” role in assigning disabled seamen to the correct indemnity scale: “for the loss of the right arm, they receive 600 piasters or six slaves; for the loss of the left arm (or right leg or body wound [with cannula]), they receive 500 piasters or five slaves;
Alexander Exquemeling: a bookshop success in 1678

Exquemelin for the Dutch, Oexmelin for the French, and Exquemeling (and sometimes Schimmelin) for the English and Spanish, was an adventurer whose biography has remained frustratingly bare of hard facts to this day. In 1678 in Amsterdam, he published an account of the lives of adventurers and buccaneers in the Americas that proved a runaway success among a public avid for exotic tales. Four translations were published within 8 years: in German in 1679, Spanish in 1681, English in 1684, and French in 1686. In France, the translator, Jean de Frontignières, added a number of anecdotes and moralizing observations, but few details on Exquemeling’s surgical practice. Many of his additions were invented or plagiarized from other accounts. A measure of his embroidery is the fact that the Dutch edition comprised around 84 000 words, and its French counterpart 144 000 words. The book gave a fairly clear account of the political and economic rivalries between European powers in the American theater. It also described how the first colonists lived. For example, from 1664 onwards, at the instigation of the great Colbert, Louis XIV’s minister of finance, the West Indies Company enjoyed a monopoly on trade with the French colonies in the Americas. It was unpopular among the colonists, who preferred to buy their goods more cheaply from the Dutch.

Son of a Protestant apothecary in Honfleur, Exquemeling em­­barked at Le Havre on May 2, 1666, aboard a French West Indiaman. He is thought to have started medical studies in Paris, but exactly when and for how long is not known. He later attended lectures by the master surgeon Guérinier. On disembarking on the island of Tortuga on July 7, he was sold into slavery: “My indignation knew no bounds… to be sold into slavery in our era (…) to the very same individuals who had made me sign a (3-year) surgeon’s contract in Holland, kinder to the Protestants, where he died in 1707. Photo courtesy of Association Le Pays d’Auge.

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Only extant portrait of a man of few faces, but many names: Alexandre Olivier Exquemelin, aka John Esquemeling, Alexander Exquemeling, Alexander Oliver Schimmel, Alexandre Exmelin, Hessequemelain, Oexmelin. Son of an apothecary, he was born in 1646 in Honfleur (Normandie, France), studied medicine, and in 1662 started working as a surgeon on board the Saint-Jean as he was forbidden as a Protest­­ant to do so in France. Arriving in Tortuga the same year he was sold as a slave, then “bought” in 1669 by buccaneers who made him serve as a surgeon for 30 years. At last he was able to return to Europe and settle in Holland, kinder to the Protestants, where he died in 1707. Photo courtesy of Association Le Pays d’Auge. All rights reserved.

Alexander Exquemeling described for the loss of the left leg, they receive 400 piasters or four slaves; for the loss of an eye (or one finger), they receive 100 piasters or one slave.” The wounded were entitled to treatment for 60 days after their injury. Surgeons also had a final grim duty, namely to tip the bodies of dead seamen overboard in a sail-cloth ballasted with cast iron in a ceremony marked by a three-cannon salute.

A T OUCH OF FRANCE
the capture of Vera Cruz, Maracaibo, and Panama. With little taste for battle or fighting in general, he was more interested in observing flora, dissecting manatees, and describing the circulatory system of the turtle. After a brief stay in Europe when he re-enrolled in medical school in Amsterdam (in 1677), Exquemeling returned to the Caribbean to practice as a surgeon for the Spanish, English, and Dutch. In 1679, he obtained permission to practice in Santo Domingo (modern Haiti) on the island of Hispaniola, the north of which was occupied by the French and the south by the Spanish. The French part of the island practiced *matelotage*, literally “seamanship.” This contractual association between two freebooters or buc-

**CLINICAL ANATOMY CASE REPORT: CROCODILE BITE**

by French freebooter surgeon Alexander Olivier Exquemeling

In 1670, during the capture of Chagre (Panama), Exquemeling attended a Portuguese freebooter wounded by a crocodile: “After examining him, I found that all that was left of one leg were some torn dangling muscles and tendons; the genitalia had been taken with the rest. I dressed him, and the fever, which shortly beforehand had abated, returned 2 days later. The leg became gangrenous and I had to amputate it. After this operation, his wounds progressed well and we were planning to fashion him a wooden leg when he developed erysipelas in the healthy leg overnight. (…) I gently purged him, and bled him, and attempted to relieve the inflammation with suitable remedies. However, the leg began to rot and despite all the treatments I gave, he died. I was curious to open the leg along its length (…) I found the periosteum eaten away by a black, serous, and foul-smelling substance. (…) Having seen several cases of crocodile bites that have healed without complications, I cannot attribute his death to crocodile venom. I can only think that death in this case was to his previous unhealthiness and a dark and melancholic disposition.”

Reignier

Pirates, corsairs, freebooters, buccaneers... and surgeons too – Régnier
careers extended from rota duties on board ship to the sharing of land and possessions, and mutual sup-
port in problems of everyday life. It subsequently inspired the name behind the loose coalition of free-
booters across the Americas, the “brethren of the coast” (Frères de la Côte).

On returning to Paris in 1684, Exquemeling was forced publicly to renounce the Protestant religion in the church of Saint Germain des Prés. History loses all trace of him after 1707.7,10-12,15

Epilogue
French port notary records from the late 17th century show that Exque-
meling’s career was fairly typical of those of Protestant apprentice or master surgeons. In La Rochelle, for example, the names are record-
ed of François Sablon, Louis Lauron, Marquet, and Giraud—but their names only: their biographies are unknown and all trace of them has disappeared. Other freebooter surgeons are recorded as sailing from Dieppe and Honfleur.7,8

After the Duke of Anjou acceded to the Spanish throne in 1700, Louis XIV turned the family alliance to advantage by ensuring he was granted the privilege of trading with the Spanish territories (and of de-
fending Spanish possessions in America). Over in the Caribbean, many French freebooters preferred serving under the English. The treaty of Utrecht (1714), by which Spain recognized the right of the English to trade with its American colonies, finally put an end to freebooting. An-
other factor in its demise was the increasing intolerance of the great powers toward the ferocious independence of the freebooters, whose methods resembled those of pirates.1,3,4

Released from maritime service, many freebooter surgeons set up practice on dry land. Whether attached to plantations, supplying medicines, or treating the wounds of colonists and slaves, surgeons in Santo Domingo were plentiful: “there’s not a district without one or two of them,” wrote Father Jean-Baptiste du Tertre (1610-1687).18 “Their duties are to shave and trim the French each week, and those who are in demand soon become rich, because the remedies they prescribe cost them little.” The account by Father Jean-Baptiste Labat (1663-1738), who was a priest in Santo Domingo in the late 17th century, was consist-
tent in confirming that the competence of the ex-freebooter surgeons was as mediocre as their cupidity was great. “Of all those who grow rich through their work,” wrote Father Labat, “none do so more surely and more rapidly than the surgeons; for them it’s a real Peru. Although most are ignorant to the highest

Father Jean-Baptiste Labat (1663-1738) was a highly colorful French clergyman and a missionary to the West Indies who published in 1722 a fascinating 8-volume account of the decade he spent there (Voyage aux Isles, recently republished in French by Phébus, Paris 1993). He was appointed procurator general of all the Dominican convents in the Antilles, owned a sugar plant, with slaves, and is credited with being the inventor of rum (a rum distillery still bears his name today, and produces one of the strongest white rums available on the market). © Roger-Viollet.
A TOUCH OF FRANCE

FRENCH WEST INDIES DEMOGRAPHICS (1713-1720)\(^{3,4}\)

Total inhabitants (number [percentage] of Europeans):

- Santo Domingo: 25 000 (6668 [23%])
- Martinique: 36 000 (8890 [25%])
- Guadeloupe: 16 000 (4991 [30%])

In 1714, there were an estimated 2500 freebooters (including 25% runaway slaves).\(^5\)

REFERENCE


degree, they earn all they want.”\(^1\) In 1694, the physician Devaux de la Martinière, inspecting the islands on behalf of the king, considered it essential “to require the surgeons already set up in practice to take an examination (for) they have no knowledge of the composition or structure of the human body, any more than of diseases and their remedies.”\(^2\) However, some ex-freebooter surgeons were taken on by the Royal Navy surgery schools later established in Rochefort (1722), Toulon (1725), and Brest (1731). The first hospitals in Santo Domingo and Martinique were opened in 1698 and 1701, respectively. Doctors arriving from France began to exert their influence, but the benefits of the health regulations governing the activity of surgeons were not really felt until some 50 years later.\(^6\)

ALEXANDRE OEXMELIN ET LES CHIRURGIENS DES XVII\(^{e}\) ET XVIII\(^{e}\) SIÈCLES AU SERVICE DES PIRATES, DES CORSAIRES, DES FLIBUSTIERS ET DES BOUCANIERS

Au milieu du XVII\(^{e}\) siècle, des catholiques chassés d’Angleterre ou des protestants expulsés de France tentèrent l’aventure de la flibuste aux Antilles et sur les côtes de l’Atlantique. Avec l’aval des souverains anglais et français, il s’agissait de participer au pillage organisé des galions espagnols chargés de richesses. Les Hollandais dont la puissance maritime était considérable se joignirent bientôt à ces chasse-parties contre les Espagnols. Parmi ces aventuriers chassés d’Europe ou volontaires, on dénombrait des chirurgiens interdits d’exercice dans leurs pays d’origine en raison de leurs confessions religieuses. N’ayant souvent pas suivi d’études de médecine, dotés de connaissances anatomiques et thérapeutiques sommaires, ces chirurgiens devenus flibustiers participaient au partage du butin, exerçaient les opérations courantes, établissaient le barème d’indemnisation des blessés, veillaient au maintien de l’hygiène à bord. Comme les médecins, ils se montraient impuissants à lutter contre les fléaux maritimes comme le typhus, le scorbut, la fièvre jaune ou la dysenterie. L’un des plus célèbres de ces chirurgiens flibustiers français fut Alexandre Oexmelin qui témoigna de ses aventures, de sa vie, de ses “campagnes”, de sa pratique, dans un livre paru en 1678 à Amsterdam. Ce livre fut traduit en plusieurs langues et rencontra un tel succès auprès d’un public féru d’aventures extrêmes. La biographie d’Oexmelin est représentative de ces chirurgiens flibustiers (le plus souvent protestants) qui participèrent à l’histoire de la colonisation française dans les Caraïbes. L’âge d’or de la flibuste s’acheva en 1714 au traité d’Utrecht, les chirurgiens flibustiers furent alors placés devant des choix déchirants : s’installer à terre, s’embarquer sur les bâtiments de la marine royale ou ceux des compagnies coloniales, devenir pirate, exercer un autre métier. Quelques uns furent engagés dans les écoles royales de chirurgie navale nouvellement créées à Rochefort (1722), Toulon (1725) et Brest (1731).
town’s origins are often shrouded in legend, in this case the decision by a Welshman from the kingdom of Gwent, known as Maclou, Maclob, or more simply Malo, to leave the monastery he had entered when very young and embark on a voyage of exile. He is said to have eventually settled on Cézembre, an arid and rocky island off modern Saint-Malo. It was from there, in around 538, that he joined forces with the Breton hermit Aaron on the neighboring “rock (or islet) of Aaron,” which was to become the “rock of Saint-Malo” on Aaron’s death in 541.

Malo later moved to the nearby settlement of Aleth (present-day Saint Servan, a district within present-day Saint-Malo), which was devastated by Norman onslaughts in the 9th and 10th centuries. This may have been the reason why the last bishop of Aleth, Jean de Chatillon, transferred his see to Saint-Malo between 1146 and 1152. By the mid-12th century, Saint-Malo had become the capital of one of the nine Brittany dioceses.

The early history of Saint-Malo, until the beginning of the 14th century, is poorly documented. The port must have become active soon after the Normans departed, but the first written confirmation dates from 1296 and the end of the Middle Ages. By this time Saint-Malo, as the most northerly Breton port, occupied a key strategic position in this rapidly developing corner of northwest Europe. Its proximity to the Cotentin (Cherbourg) peninsula and southern England also made it an ideal staging post on the great northeast-southwest maritime axis, running from northern Germany and Flanders to Spain and Portugal, via Normandy, the British Isles, La Rochelle, Bordeaux, and Aquitaine. Looking inland, its location at the mouth of the Rance enabled it to serve Dinan and a number of villages along the river banks. Malouins were also expert in building and sailing the bewildering variety of boats that underpinned their maritime-cum-

he port city of Saint-Malo owes much of its renown to the hardy “Malouin” character, backed by a unique constellation of historical and often religious circumstance. It is remarkable that a rocky outcrop battered by waves and prevailing winds, and cut off from the mainland by every high-water large tide and major storm, should have developed into a port of international standing. There are paradoxes on several levels. The site may have suited 6th-century hermits, 12th-century pirates, and 20th-century tourists, but for a commercial port it had serious disadvantages, including a coastline bristling with islets and rocks, and made more hazardous still by the violent currents caused by the spring tides. During neap tides, the port was inaccessible. Yet the site also had advantages. During spring tides, the port could harbor ships of 600 or even 800 tons, between 200 and 300 at a time. Thus, Saint-Malo was always turned toward the ocean, while at heart, and often in fact, virtually all Malouins were seamen or merchants, or even both.
merchant vocation: from simple rowing boats or estaffes, and the long, narrow, flat-bottomed pinasses or sloops for river and coastal shipping, to fishing boats, whalers, and the light, maneuverable, and multi-purpose caravelles on which Malouin mercantile prowess depended from the 15th century onward, not to mention the high-tonnage, ocean-going, and often armed trading ships that the corsairs later used in hunting warfare.

King Charles VI granted Saint-Malo the status of free port, and port and city activities became even more wide-ranging. A dynamic merchant class developed a trading network operated by Breton bargemen who kept Saint-Malo regularly supplied with large volumes of goods: blocks of granite and limestone from Caen, lime and slate from the Cotentin peninsula, together with fish, meat, and dairy and agricultural products. Saint-Malo became a renowned regional trading hub by the end of the 15th century. Beginning in the 16th century, and over the course of a century and a half, the city underwent an exponential boom, thanks to the expansion of Atlantic trade with Newfoundland and Cadiz.

The fishermen

Fishing off Newfoundland is first documented after the voyages of the Genoese Giovanni Caboto, known as John Cabot since he sailed on behalf of the English king Henry VII in 1497, and the Portuguese Gaspar Corte Real in 1500. Bretons were the first to fish for cod there from 1504 onward, even before the discovery of Canada by Jacques Cartier.

By 1517, 50 ships were being reported in Newfoundland waters, from Spain, Holland, and France. By 1578, the number increased to over 150 from France, mostly Brittany, 100 from Spain, and 30 to 50 from England. Newfoundland was a highly coveted corner of the world. It prompted bitter territorial rivalry and a determination to destroy the maritime power of national adversaries. By 1542, Spaniards intent on seizing Jacques Cartier had captured no less than 27 of the three-masted “terre-neuvas” or “Newfoundlander.” In 1555, the Grande-Françoise lost 72 men, with 100 wounded, to the corsair Juan de Erasco. The scale of this slaughter prompted the city in the following year to build the Saint Ciel, the first warship dedicated to protecting French fishermen from English and Spanish corsairs off northern Newfoundland, in the area known to the French as the Petit Nord. In the 17th century, the fleet comprised multiple frigates and three-masted flûtes. For example, in 1628, 112 ships from Saint-Malo spent the season between mid-April and mid-August in Newfoundland. Cod fishing was the major contributor to the prosperity of the Saint-Malo shipowners. At the end of a season, the ships did not bring all their cargo back to Saint-Malo. They unloaded part of it in Marseille and Sète, before carrying return freight back to Saint-Malo in the shape of soap, oil, honey, and other products from Provence, further swelling the shipowners’ coffers.
The merchants

◆ Cadiz

Every spring, keeping jealous guard over its trade with Latin America, Spain dispatched a merchant fleet flanked by an imposing escort to Vera Cruz in Mexico. Although the armada left from Cadiz, not all the goods it carried were Spanish. The galleons also carried produce from England, France, and Holland. Settlers were barred from manufacturing in the New World and were required to import everything: hats, shoes, clothes, etc. Malouins were in the forefront of this Old to New World trade. Before the flota cast off, they dispatched their ships to Cadiz, replete with cloth from Brittany, the Mayenne, and the fortified towns of Northern France, lace from the Auvergne and Limousin, silk from Lyon, and a whole range of manufactured goods (the Spanish held “cannon ball-proof” sailcloth in particular esteem). When the flota returned 18 months later, after all the goods had been sold and paid for, the Malouins would journey to Cadiz to collect their dividends or bills of exchange. In 1628, the abrupt declaration of war by France against Spain created a wave of panic among the shipowners and merchants of Saint-Malo who traded with Cadiz. Yet despite such hazards, a special relationship persisted into the late 18th century, with families from Saint-Malo settling in Cadiz and Spanish families settling in Saint-Malo.

◆ Cape Horn

The first French sailors to round Cape Horn, reputed to be one of the most dangerous in the world and the graveyard of many ships, were two Malouins: from west to east by Jacques Gouin de Beauchêne (1652-1730), and from east to west by Alain Porée (1665-1730). France alternately banned and tolerated voyages into the Southern Seas, according to the barometer of its relationship with Spain, at least until 1712, on the eve of the negotiations for the Treaty of Utrecht, when everything changed. Responding to representations by Madrid, which denounced the violation of its laws, Louis XIV categorically banned all commercial activity in the Southern Seas. Shipowners had to undertake never to venture there, on pain of having their ships and cargo confiscated plus a fine. But the ordinance went unheeded. Shipowners continued to trade with Peru and Chile.

This undercover commerce, practiced mainly between 1698 to 1724, consisted of exchanging European manufactured goods for South American gold and silver. On departing France, captains would be deliberately misleading about their destinations. For example, between 1703 and 1705, Bécard des Aulnais on board the Baron de Breteuil, Alain Porée on board the Saint-Esprit, and Trulet de Mermont on the Saint-Joseph left for the Southern Seas. The investors included most of the best-known merchants of Saint-Malo, including Magon de la Lande and Locquet de Granville. After rounding Cape Horn, the flotilla headed for Callao, the port of Lima.
As reported by Fouqueron, the historian of Saint-Malo, Bécard des Aulnais placed his ship in the employ of the viceroy of Lima. He joined forces with the Saint-Joseph to try and destroy the English squadron, which held sway over the entire coast of Peru, the Spanish colonies being powerless to intervene. The Baron de Breteuil was duly rewarded with permission to trade in Callao. On their return, the ships’ cargoes were priced at 2,150,000 gold and silver piastres."

Responding to a complaint from the Compagnie de la Mer du Sud (Southern Seas Company), founded in 1698, the shipowners stated that the vessels had gone directly to Lima without landing at any Compagnie concession. Release of the goods was therefore granted. Profits reportedly ranged from three to twelve million livres, with 7,175,453 livres being declared to the authorities.

**The explorers**

*Jacques Cartier and the discovery of Canada*

The fame of Jacques Cartier (1491-1557), one of Saint-Malo’s most celebrated sons, rests on his discovery of Canada, and on the unusual achievement of having done so without bearing arms against the Indians. Thanks to his cousin by marriage, the seigneurial justice administrator (fiscal procurator) of the Mont Saint-Michel, and to its absentee abbot, the royal chaplain, Jean Le Veneur de Tillières (d 1543), Jacques Cartier was presented to François I during the latter’s visit to Saint-Malo. Cartier told the king of his plan to explore the Newfoundland region and discover a passage to Cathay (China).

A northwest passage to Cathay was an *idée fixe*, ever since the account given by Marco Polo (1254-1324). In his *Travels*, the Venetian described Asia as a fabulous paradise rich in silks, spices, and precious stones. Every navigator fell under its spell, with greed a powerful motive. The quest became more urgent after Byzantium fell to the Turks in 1453, and overland trade with the East appeared threatened. Once the Silk Road was wrested from Christian control, the potential of a westward sea route became that much greater.

On April 21, 1534, Jacques Cartier left Saint-Malo on two 60-ton vessels with 60 crew, arriving off Newfoundland 19 days later. He sought a passage between Cape Breton and Newfoundland. A month and a half later, he had discovered no new territory. He eventually entered a large gulf where he met Micmac Indians. Later, poor weather forced him to take refuge in Gaspé Bay, where he came upon a camp of some 200 Iroquois. They told him there was no passage westward from the Gulf of St Lawrence. A disappointed Cartier planted a cross at two sites and negotiated with the Indian chief for permission to take his two sons back to France. Worried about how François I would react to the failure to discover the fabled northwest passage, Cartier considered that a pair of Indians who would learn French and provide information on the unknown territories would serve as well-crafted compensation. He arrived back in Saint-Malo on 5 September, and by October 30, the king had duly consented to a new expedition.

On May 16, 1535, Cartier set sail again with three vessels, *Grande-Hermine, Petite-Hermine,* and *Émerillon.* They weathered a storm that separated the ships and did not reach Blanc-Sablon, on the coast of present-day Quebec, until 2 months later. They then sailed up the St Lawrence estuary, with the two sons of the Indian chief acting as their interpreters. The sons explained that they were entering the fabled kingdom of Saguenay, and approaching Hochelaga (present-day Montreal), and the country that the Indians called Canada. Cartier discovered several islands, and was met by the Indian chief, Donnacona, who was relieved to find his sons safe and sound. Cartier sailed up the St Charles river and encamped at Sainte Croix, opposite the village of Stadacona where Samuel de Champlain was later to found Quebec City. On October 2, he reached a large Indian village at Hochelaga.
The following day, with great ceremony, he climbed Mount Royal. But Cartier was becoming aware of tribal rivalries and his relationships with the Indians were beginning to deteriorate. In addition, the harsh winter was taking its toll, compounded by the scurvy that affected the Indians as well as the French. Cartier lost 25 men, the remainder being saved by a brew of white cedar bark (Thuya occidentalis), an Indian remedy. Cartier then seized Donnacona, both sons, and several other Indians, promising to bring them back within 12 moons. Leaving Petite-Hermine behind, he set sail for Saint-Malo, arriving with 10 Indians on July 16, 1536. Despite the important information that he had gathered, Cartier had to defer plans for a third expedition. The king was too beset by financial difficulties. In 1541, François I agreed to support a third expedition, but this time he appointed Jean-François de la Roque, Sieur de Roberval (1500-1560), as its commander.

Cartier was ready to leave by May, way ahead of de Roberval, who did not set sail until August. Cartier could not afford to wait: he had already drawn up his will, in the knowledge that Spain had ordered his ships to be seized and his men to be hurled overboard. This third crossing took 93 days. The Indians gave him a warm welcome. Cartier took up his exploration where he had left off, sailing up river from Cap Rouge, where he found better anchorage for his ships and left men to build a fort for the settlement of Charlesbourg Royal (now part of Quebec City). Cartier became convinced he had discovered diamonds and “gold leaf as thick as a fingernail.” He sailed up toward Hochelaga, reached the first St Mary Rapids (Sault Sainte-Marie), then the Lachine Rapids. Finding them impossible to cross, he turned back. On reaching the fort, he found that the behavior of Viscount de Beaupré had soured relations with the Indians. In June 1542, he decided to head home. He met with de Roberval, who proposed sailing back together. Cartier refused, as he could not wait to reach Saint-Malo and present the king with his precious discoveries. Sadly, his diamonds proved to be quartz, and his gold and gold leaf nothing other than iron pyrite and mica. Hence

**Jacques Cartier Museum**

This manor 4 miles from Saint-Malo where Jacques Cartier spent his final years is all the more remarkable in that it is one of the few houses belonging to a Renaissance explorer to have survived to the present day. It is also a major memorial to the special relationship that has existed between France and Canada since the 16th century, hence the idea in 1975 by the Montreal philanthropist, David M. Stewart, to buy and restore the building. A nonprofit Canadian company set up to gather the necessary finance completed the purchase in 1976 and opened the building to the public. Rooms were decorated and furnished in 16th century style. Maps in the more recent part of the building illustrate Cartier’s various voyages and his principal discoveries.

Musée Jacques Cartier Limoëlou, rue du Docteur David Macdonald Stewart, 35400 Saint-Malo. Tel. +33 (0)2 99 40 97 73. [www.musee-jacques-cartier.com](http://www.musee-jacques-cartier.com). 10 AM to 11.30 AM and 2.30 PM to 6 PM (June 1 to September 30). Guided tours at 10 AM and 3 PM from October 1 to May 31 (only by reservation).
the French proverb: “as false as a diamond from Canada” (which long antedated Canada’s emergence as a leading diamond producer). Although Cartier’s voyages proved a double failure (he discovered neither northwest passage nor “treasure”), they provided much valuable information about the region. In addition, he chose the sites of the future Quebec City and Montreal, mapped channels, recorded the country’s resources, and supplied a mine of ethnographic data on the Indians.

It would have taken only a little more to establish a permanent colony, except that France in the 16th century had no such ambitions for Canada. But it meant that a Malouin had played a leading role in the astonishing maritime discoveries that marked the era. Very soon, the ever-mercantile Malouins awoke to the potential unleashed by Cartier’s discoveries, and launched into the fur trade, mainly beaver, with the Canadian Indians.

**Other famous Malouin explorers**

The aforementioned Jacques Gouin de Beaufchene (1652-1730) sailed into the strait of Magellan in 1699 and named one of the islands there after Louis XIV, then explored the Galapagos islands and returned via Cape Horn, which he passed on 9 January 1701, and discovered an island that was named for him, Beaufchêne Island. He died in Saint-Malo, at the age of 78 years.

Bértrand-François Mahé de La Bourdonnais (1699-1753) entered the service of the French East India Company in 1718. In 1724, he captured Mahé, off the Malabar Coast, and added the name of the town to his own. He was named Governor of Île de France (now Mauritius) in 1735 and of Île de Bourbon (now La Réunion). He fought the British in the Indian waters in 1740 and saved Mahé. On 6 July 1746 he defeated Commodore Peyton and his fleet, before participating in the siege of Madras. In spite of these successes, his later years were marred by a quarrel with Dupleix, the French colonial administrator of India. He returned to France in 1748 to defend his case there, but was arrested on a charge of speculation and maladministration and imprisoned in the Bastille for 2 years, before being tried in 1751 and acquitted. He died in Paris in 1753.

Marc-Joseph Marion du Fresne (1724-1772) joined the French East India Company at the very young age of 11 as a sublieutenant aboard the **Duc de Bourgogne**. In 1745, he was named captain and eventually settled as harbormaster of Port Louis on Mauritius, until the East India Company dissolved in 1769. The civil administrator, Pierre Poivre, then sent him on a mission with two ships, the **Mascarin** and the **Marquis de Castries**, to bring back a Tahitian, Ahu-Toru, who had been taken to Paris and “exposed” there, back to Tahiti, and search for the “southern continent.” On his expedition, he discovered the Prince Edward Islands and the Crozet islands, and sailed on to Tasmania and New Zealand. His relations with the Maori there were initially friendly, but his crew broke some “tapu,” probably by fishing in a sacred place, and du Fresne and twelve crew members were killed and eaten by the Maori.

**HÔTEL D’ASFELD: A CORSAIR MANSION**

All Saint-Malo merchants had a townhouse, in most cases within the city walls, in which they did business and lived during the winter months, in addition to a stately country house known as a “malouinière,” where they spent the summer. One such malouinière was the Hôtel d’Asfeld, built in 1725. It belonged to François Auguste Magon de la Lande, shipowner, commissioned corsair, one-time director of the celebrated East India Company, and one of the richest merchants of Saint-Malo. A listed historical building, it has some 60 rooms, numerous secret staircases, and two floors of magnificent cellars for the storage of goods. Some of these houses interconnected via underground passages, enabling merchants to do business with one another away from prying taxmen’s eyes.

5, rue d’Asfeld, 35400 Saint-Malo.
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www.demeure-de-corsaire.com.
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The “Hotel D’Asfeld” built in 1725 for François Auguste Magon de la Lande, Corsair to the King, and one of the most powerful shipowners of Saint-Malo, and a director of the East India Company. © La Demeure de Corsaire, Saint-Malo.
The corsairs

“Hunting warfare” (guerre de course) refers to the practice by corsairs or privateers of disrupting or destroying another country’s trade and shipping in times of war using vessels armed by private individuals backed by their sovereign or state. How did a corsair differ from a pirate? It was not always easy to tell. Pirates sometimes acted as corsairs, while corsairs, despite their clear rules of engagement, sometimes acted like pirates. However, there were some basic differences. Pirates were “common-or-garden brigands” or “open-sea highwaymen.” Corsairs, on the other hand, were “commissioned seamen” or “maritime militiamen,” who were duly empowered to attack enemy vessels in times of war only, and otherwise closely supervised. Corsairs were warrior seamen who pillaged by force of arms in pirate fashion, but under the aegis of international law, codified to variable degrees.

Their freedom of action was limited and subject to a number of conditions. The first was that the countries of the attack vessel and its victim had to be at war. The second was that the corsair had to have been granted a commissioning document, or lettre de course (or lettre de marque), authorizing him to attack and seize enemy merchant ships. He was required to bring the vessel back to a home or allied port or, failing that, to sink or burn it. He also had the right of life and death over its crew; if they refused to surrender, he was free to kill them, at best take them prisoner, or put them up for ransom. In other words, the corsair was a kind of licensed pirate. Protected by their commissioning documents, corsairs remained closely bound to their country’s authorities. In addition to complying with the clauses in their contract, corsairs also had to give regular accounts of their actions and maintain a log in the same manner as naval officers.

On June 25, 1689, after a period of rapid unbroken growth, the “world port” of Saint-Malo received a broadside in the shape of the French declaration of war on England. Like the rest of Brittany, Saint-Malo was in the front line against England. The shipowners held a meeting and decided that their Newfoundland fishing plans for 1690, with England lying in wait, were simply too dangerous. They therefore diverted all their resources to hunting warfare, using the large number of crews who would otherwise have been inactive.

The citizens of Saint-Malo responded loyally; volunteers enlisted on registers opened in each district of the city. The plan was to operate no less than 40 corsair vessels. Volunteers included the young René Duguay-Trouin, René Moreau, Alain Porée, and the shipowner Noel Danycan, who fitted out no less than six corsair vessels of his own. Shipowners vied for the documents from the French admiralty, granted for a deposit of 15 000 livres, that would commission their novel corsair vessels.

*René Duguay-Trouin (1673-1736)*

Although the Trouin family were Breton shipowners, they did not destine the young René Trouin du Gué, or Duguay-Trouin, for a naval career. Intending him for a life in the church, they enrolled him in a Jesuit college. However, René’s high-profile lifestyle prompted the family to direct him toward a new career by enrolling him in the Saint-Malo naval school. After he witnessed the triumphant arrival of the famous corsairs, Jean Bart (1650-1702) and his lieutenant Claude de Forbin (1656-1733), who had just escaped from England, René dreamed of volunteering for corsair service. His family owned a corsair vessel and he duly left on *La Trinité* in 1689 and 1690. After distinguishing himself by his bravery, in particular after killing the English captain of the *Europe* with a saber thrust, he was made captain of his family’s vessel, the *Hercule* at the tender age of 18 years, going on to captain several other vessels that his family had loaned to the king.
In 1694, on board the *Diligente*, Trouin, outnumbered, was forced to surrender to the English commander of the *Monck*. He was taken to Plymouth. After buying a rowing boat from a friendly Swedish captain, he and his companions managed to escape, rowing across the Channel for 30 hours until they finally arrived in Saint-Malo. His mission the following summer was to lay waste the enemy whaling fleet in Spitzberg, but a slow start put paid to this plan. In 1696, he captured the *Nonsuch* from the English, and rebaptized it with the same name in French (the *Sans-Pareil*). Louis XIV rewarded him with a sword of honor and ordered him to join Admiral Nesmond’s fleet at La Rochelle. Captaining the *Sans-Pareil*, the ship he had captured earlier, he seized two fat Dutch merchantmen and successfully negotiated the English blockade of Belle-Île. In 1697, he was ordered to attack an Anglo-Dutch fleet in Bilbao, in a fierce battle with Baron Wassenaer-Starrenburgh, future vice-admiral of the United Provinces.

Duguay-Trouin's most daring scheme was the capture of Rio de Janeiro. He assembled an impressive expeditionary force: 17 ships of the line, many corsair vessels, and even ferry boats, totaling 6139 men and 734 cannon, but drawn from a total of 5 ports (Brest, La Rochelle, Rochefort, Saint-Malo, and Dunkirk), to avoid arousing suspicion. On September 12, 1711, the squadron forced its way into Rio harbor, past the protecting forts and after several days’ fighting, Duguay-Trouin entered the town. Negotiation with the Portuguese governor resulted on October 10 in the payment of a ransom of 600,000 crusados, to which the governor added 10,000 crusados from his privy purse, 100 crates of sugar, and livestock sufficient to maintain the fleet during its return journey, all payable within 2 weeks. The squadron left Rio on November 13, 1712, achieving a 92% profit for its investors, despite the loss of two vessels in a storm off the Azores. Duguay-Trouin was promoted to rear-admiral by Louis XIV. After the king's death in 1715, he began his memoirs and became naval advisor to the Regent. He was to die in Paris, in straitened circumstances, at the age of 63.

In 1697, the peace that followed the Treaty of Ryswick put a temporary hold on Duguay-Trouin’s career. He spent his winters in Brest and his summers in Saint-Malo. In 1702, he captained various vessels belonging either to the king or his own family. He then asked the king to build him two ships, the *Jason* and the *Auguste*. He sailed the *Auguste* for several years, and was elevated to the rank of captain in 1705. The following year he managed to scatter the 200-strong Brazilian fleet, despite the presence of 6 Portuguese men-of-war. In 1707, he joined forces with Forbin to intercept a fleet of around 100 merchantmen escorted by 6 English men-of-war. The English suffered heavy losses in the ensuing Battle at The Lizard: 5 ships of the line, 350 cannon, 15 merchantmen, 3000 men, 200 officers, and 600 horse, not counting ammunition and goods. The battle was celebrated for the destruction of the *Devonshire* and all but 2 of its 900 hands.

Robert Surcouf (1773-1827)
The “King of Corsairs” earned his nickname through a combination of outrageous daring and remarkable seamanship. His enemies also knew him as the “Gentleman,” such was his adherence to his code of honor. Unruly and no respecter of authority, he absconded from home and school until finally enlisting as an apprentice on board the brig Héron at the age of 13 years. Three years later, in 1789, he left Saint-Malo on board the Aurore, a 700-ton three-master, for the Indian Ocean. Later he embarked on a number of slave ships sailing to and from Mozambique. He also journeyed to Pondicherry (present-day Puducherry) in India and to Île de France (present-day Mauritius). Surcouf’s first command was the Créole, a slave ship (despite the French Revolution having abolished slavery at home in 1791 and in its colonies in 1794). Some time later, in the mouth of the Ganges, he seized several English ships, including the 1000-ton Triton. But these prizes were confiscated from him on his return because he had acted on his own initiative, without a commissioning document. He went to Paris to plead his case. The Council of Five Hundred, the Revolution’s lower legislative chamber, returned his prize to him by way of reward, incidentally confirming that failure to comply with maritime law was not always punished. Returning to Saint-Malo, he postponed his wedding and took command, in the summer of 1798, of the Clarisse, seizing four ships before reaching the Mascareigne archipelago off Madagascar. He then launched a campaign in the Indian Ocean, seizing the Anna-Maria and the Coturrebok as they were loading pepper in Aceh (modern Indonesia). He narrowly escaped massacre by the natives. On May 10, 1800, he was put in command of La Confiqance and sailed for the Sunda Strait between Java and Sumatra. On June 15, he seized the Alknomack, then headed for the Seychelles and the Coromandel Coast (the south-eastern coast of the Indian peninsula), where he outsailed the Sybille, a 56-gun English frigate, by offloading 8 cannon of his own. After streamlining his ship’s hull in southern India, he captured a further six ships (Praise, Harriet, Tiger, Union, Charlotte, and Rebecca). On October 7, in the Gulf of Bengal, he came in sight of the 1200-ton Kent. Totally undaunted, he decided to take her on, unaware that the crew was backed by a sister ship, the Queen. He nevertheless managed to board her after a 2-hour struggle. Returning to Mauritius, he headed for France and Saint-Malo, marrying in 1801 and buying the townhouse of Beauregard.

He was the first citizen of Saint-Malo to be awarded the Legion of Honor, by the first consul, Napoleon Bonaparte, on July 17, 1804. In March 1807, he left Saint-Malo for Mauritius, and then the Indian Ocean. As soon as news spread of his return to the Mascareigne Archipelago, the Bengali authorities ordered him to return to Saint-Malo and marry in 1801 and buy the townhouse of Beauregard.

The Museum is located in the Château’s main keep, a large tower in the shape of a horseshoe on which work began in 1424, under Jean V, Duke of Brittany. It houses many documents and objects relating to deep-sea fishing off Newfoundland and the customs and lifestyles of the Saint-Malo region. There are also paintings, photographs, and souvenirs involving two famous men: the writer Chateaubriand (1768-1848), author of Memoirs From Beyond the Grave, who remained so attached to his place of birth that he obtained permission to be buried on Grand Bé Island off Saint-Malo, and Jean-Baptiste Charcot (1867-1936), physician and polar explorer, who died when his ship, the Pourquoi Pas? (The Why Not?), was wrecked off Reykjavik.

Château de Saint-Malo. Tel. +33 (0)2 99 40 71 57. Open daily (closed Mondays from October through March) from 10 AM to 12.30 PM and from 2 PM to 6 PM (5.10 € adults, 2.55 € concessions)
rupees on his head. Within 3 months, he had captured eight English ships, including the *Fortune*, which he chased for 52 hours. On returning home, he concentrated on investments in shipping, sending 15 corsair vessels to the Indian Ocean between 1804 and 1813. Five were captured in the English Channel and Atlantic. One of his most famous ships was the *Renard*, which in 1813 destroyed the British schooner *Alphea*. The *Renard* was the last corsair to be refitted in Saint-Malo, in 1814. After the abdication of Napoleon in 1815, Surcouf expanded his merchant shipping investment, covering Africa, the Caribbean, Indian Ocean, America, and Newfoundland, operating a total of 18 ships; they included the *Victor*, which was designed for harvesting marine mammal fat off the Falkland Islands in late 1819. As colonel of the guard in Saint-Malo, he foiled a plot to hand over La Conchée, a fort built on a rock some 3 miles out at sea, to the English, but he refused to denounce its instigators. After the defeat of Waterloo, Surcouf resigned from his various posts. Finding himself under political surveillance, he withdrew to the manor of Raincourt where he died an agonizing death in 1827 from a gastric disease.

Thus the most glorious era in the history of Saint-Malo in the 17th and 18th centuries was marked, among other things, by the hunting warfare that several European nations waged against one another for reasons that were at once colonial, political, and commercial. It accelerated the development of navigation and naval warfare techniques. But the city’s history is greater than that of its corsairs. The Malouins were, above all, superb seamen, excellent merchants, and formidable shipowners. Thanks to them, the city continues to enjoy pride of place in international maritime history.

FURTHER READING

SAINT-MALO ET SES NAVIGATEURS LÉGENDAIRES : MARCHANDS, PÊCHEURS, EXPLORATEURS ET CORSAIRES

Le caractère bien trempé des Malouins ainsi qu’un ensemble de circonstances religieuses et historiques ont largement contribué à la renommée du port de Saint-Malo. Cependant, il est étonnant que ce rocher battu par les flots et tous les vents dominants, isolé de la terre ferme à chaque grande marée ou tempête d’une certaine ampleur, ait pu devenir un port de dimension internationale. Disons que cela relève à plus d’un titre du paradoxe. Si le site apparaissait comme idéal pour un ermite au VIe siècle, pour une poignée de pirates au XIIe siècle et pour une station balnéaire au XXe siècle, il présentait, en revanche, divers inconvénients pour devenir un port de marchandises. Si le littoral, hérissé d’îlots et de rochers avec des courants violents dus aux grandes marées, rendait le port inaccessible aux navires en période de morte-eau, le site présentait néanmoins des avantages. Lors des grandes marées, le port pouvait accueillir des navires de 600 voire 800 tonneaux et, par ses dimensions, recevoir deux à trois cents vaisseaux. Ainsi, Saint-Malo a toujours regardé vers la mer et les Malouins ont presque tous été des marins ou des marchands, parfois les deux.
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