

REVIEW

Heart rate in the pathophysiology of coronary blood flow and myocardial ischaemia: benefit from selective bradycardic agents

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Starting out from a brief description of the determinants of coronary blood flow (perfusion, pressure, extravascular compression, autoregulation, metabolic regulation, endothelium-mediated regulation and neurohumoral regulation) the present review highlights the overwhelming importance of metabolic regulation such that coronary blood flow is increased at increased heart rate under physiological circumstances and the overwhelming importance of extravascular compression such that coronary blood flow is decreased at increased heart rate through reduction of diastolic duration in the presence of severe coronary stenoses. The review goes on to characterize the role of heart rate in the redistribution of regional myocardial blood flow between a normal coronary vascular tree with preserved autoregulation and a poststenotic vasculature with exhausted coronary reserve. When flow is normalized by heart rate, there is a consistent close relationship of regional myocardial blood flow and contractile function for each single cardiac cycle no matter whether or not there is a coronary stenosis and what the actual blood flow is. β -Blockade improves both flow and function along this relationship. When the heart rate reduction associated with β -blockade is prevented by pacing, α -adrenergic coronary vasoconstriction is unmasked and both flow and function are deteriorated. Selective heart rate reduction, however, improves both flow and function without any residual negative effect such as unmasked α -adrenergic coronary vasoconstriction or negative inotropic action.

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Introduction

It is thoroughly well established that heart rate is a prognostic marker for longevity—the lower the better—and for the outcome of various cardiovascular diseases, notably ischaemic heart disease and heart failure (Guth *et al.*, 1987a; Hjalmarson *et al.*, 1990; Indolfi and Ross, 1993; Benetos *et al.*, 1999).

In this article, we want to focus on (1) the mechanism(s) by which increases in heart rate are detrimental in the setting of ischaemic heart disease, (2) why and how selective heart rate reduction is beneficial and more beneficial than β -blockade, and (3) what the acute and long-term consequences of selective heart rate reduction for the ischaemic and reperfused myocardium are.

Determinants of coronary blood flow and its regulation

Coronary blood flow is very sensitive to its mechanical determinants and exquisitely well regulated (Bassenge and Heusch, 1990; Baumgart and Heusch, 1995). As any other flow of fluid through a pipe, blood flow through the coronary vasculature can be described using the law of Hagen-Poiseuille:

$$F = \Delta P \Pi r^4 / 8\eta l$$

The length l of the coronary vasculature does not change in a given individual and changes in viscosity η can also be neglected when there are no major changes in haematocrit. Therefore, the formula can be reduced to

$$F = c \Delta P r^4, \text{ and } c \text{ is a constant}$$

ΔP is the driving pressure gradient between the origin of the coronary vasculature in the aortic root and its orifice, that is, of the coronary sinus into the right atrium. Now the coronary vasculature has one particular and unique

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property: it is being compressed by the contracting myocardium throughout systole, such that the pipe is—at least functionally—obstructed and no flow occurs during systole; the squeezing action of the contracting myocardium can even reverse coronary blood flow in an epicardial coronary artery and even more so in the subendocardial microcirculation (Chilian and Marcus, 1982; Toyota *et al.*, 2005). Thus, coronary blood flow occurs mostly during diastole, and the driving pressure gradient is the difference between mean diastolic pressure in the aortic root and mean right atrial pressure, which—during diastole, when the atrioventricular valves are open—is more or less equal to right and left ventricular pressure. Apart from this driving pressure gradient, the duration of diastole during which coronary blood flow occurs is of major importance. Both the driving pressure gradient and the duration of diastole are integrated into the diastolic pressure–time integral, which is the essential mechanical determinant of coronary blood flow (Figure 1; Buckberg *et al.*, 1972). Now, anything that decreases the diastolic pressure–time integral will decrease coronary blood flow, that is, any decrease in diastolic aortic pressure, any increase in right/left ventricular diastolic pressure, any reduction in diastolic duration and any delay in isovolumic ventricular relaxation will decrease coronary blood flow.

Having discussed the mechanical determinants to which coronary blood flow is very sensitive, its regulation will now be addressed. Regulation is achieved by changes in the diameter of the coronary microcirculation, that is, predominantly in small arteries and arterioles with a diameter of less than 100 μm (Marcus *et al.*, 1990; DeFily and Chilian, 1995;

Chilian and NHLBI Workshop Participants, 1997). From the above formula, where the radius of the pipe in its fourth power determines flow, it follows that very subtle changes in vascular diameter have a profound impact on blood flow, and therefore this is the effective site of regulation. There are several distinct regulatory mechanisms that govern coronary blood flow.

Autoregulation

Autoregulation is the response of the coronary vasculature to changes in perfusion pressure (Mosher *et al.*, 1964). Reductions or increases, respectively, in perfusion pressure are counteracted by increases or decreases, respectively, in microvascular diameter such that coronary blood flow is maintained independent of perfusion pressure over a relatively wide range of pressures, that is, there is a plateau of coronary blood flow between 50 and 130 mm Hg. Autoregulation is a myogenic response of the vascular smooth muscle cells to transmural pressure (Bassenge and Heusch, 1990).

Metabolic vasomotion

Metabolic vasomotion is the response of the coronary vasculature to changes in myocardial metabolism, which in turn are almost entirely a consequence of changes in myocardial performance. The mechanism(s) and signal mediators of metabolic coronary vasomotion have been a matter of debate over decades and are still not clearly understood (Bassenge and Heusch, 1990). Adenosine has

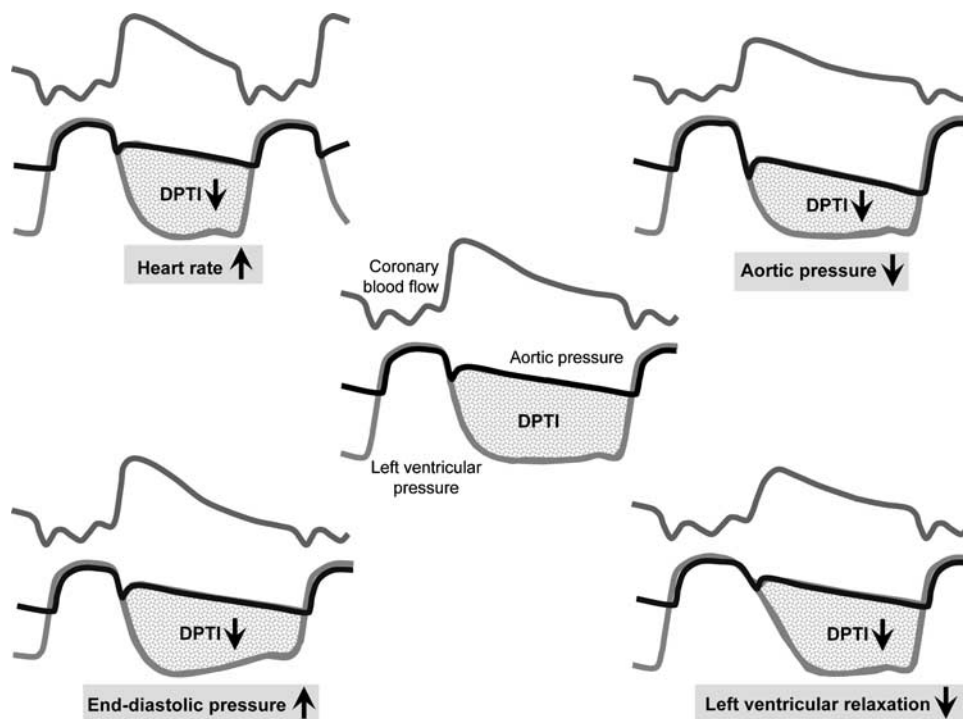


Figure 1 The diastolic pressure–time integral reflects the driving force for coronary blood flow. Any decrease in diastolic aortic pressure (upper right), increase in diastolic ventricular pressure (lower left), delay in isovolumic ventricular relaxation (lower right) and decrease in diastolic duration (upper left) impedes coronary blood flow.

attracted a lot of interest and is a mediator that intuitively has a logical charm, because the formation of adenosine in cardiomyocytes is stoichiometrically coupled to ATP breakdown, and its release and vasodilator action on coronary vascular smooth muscle cells can increase coronary blood flow and the delivery of oxygen and substrates and thus restore the myocardial energetic state (Berne, 1963; Gerlach *et al.*, 1963). Likewise, the activation of ATP-dependent potassium channels on the surface membranes of coronary vascular smooth muscle cells would imply a certain coupling to energetic state of smooth muscle cells rather than cardiomyocytes (Embrey *et al.*, 1997; Merkus *et al.*, 2005). Other proposed mediators of metabolic coronary vasomotion are interstitial P_{O_2} and P_{CO_2} *per se*, nitric oxide released from the endothelium, prostaglandins, potassium ions and so on. More recent studies indicate that metabolic coronary vasomotion is a complex concerted action, with indeed adenosine, adenosine-triphosphate-dependent potassium channels and nitric oxide as major players. It must be stressed that under physiological circumstances metabolic coronary vasomotion also operates in the reverse direction, that is, reduced myocardial performance and metabolism result in decreased coronary blood flow.

Endothelium

The endothelium plays a major role in coronary blood flow regulation. Tangential shear stress that goes along with increased blood flow and blood flow velocity in the longitudinal direction of the vessel as well as pulsatile stretching of the vascular wall in the transmural direction enhance the formation and release of nitric oxide from the endothelium, which acts to relax/dilate the smooth muscle cells of the vascular wall. Endothelial, nitric oxide-mediated dilation has its particular role in larger coronary conduit vessels to adapt larger coronary arterial diameter to flow and flow velocity changes, which are primarily initiated at the microvascular level. The endothelium is also the source of the vasoconstrictor endothelin (Bassenge and Heusch, 1990).

Neurohumoral regulation

Neurohumoral regulation of the coronary circulation is primarily by the release of norepinephrine from cardiac sympathetic nerves and by circulating epinephrine from the adrenal medulla. (Nor)epinephrine, apart from its β_1 -adrenoceptor-mediated effects on cardiomyocytes with the resulting increases in myocardial performance and metabolism and finally metabolic coronary vasodilation, exerts direct dilator actions on the coronary circulation through activation of β_1 - and β_2 -adrenoceptors (Trivella *et al.*, 1990; Miyashiro and Feigl, 1993), and constrictor actions through activation of α -adrenoceptors. α -Adrenoceptor-mediated coronary vasoconstriction largely prevails over direct β_2 -adrenoceptor-mediated dilation. The constriction of large epicardial conduit coronary arteries is mediated by α_1 -adrenoceptors, and that of the coronary microcirculation largely by α_2 -adrenoceptors (Heusch, 1990; Heusch *et al.*, 2000). Other neurotransmitters and hormones, for example, vasopressin and B-type natriuretic peptide, are also operative

in the coronary circulation, but of minor functional importance.

Heart rate and the physiology of coronary blood flow

Any increase in heart rate increases the number of cardiac cycles per time frame and thus—even at unchanged work per single cardiac cycle—cardiac performance, that is, work per time, and in the consequence myocardial metabolism. In fact, an increase in heart rate does not alter myocardial oxygen consumption for any given cardiac cycle, but linearly increases myocardial oxygen consumption per minute (Figure 2) (Tanaka *et al.*, 1990). This increase in myocardial oxygen consumption per minute results in a proportionate increase in coronary blood flow, through metabolic coronary dilation (Figure 3) (Colin *et al.*, 2004); increased myocardial oxygen extraction contributes only to a minor extent and a

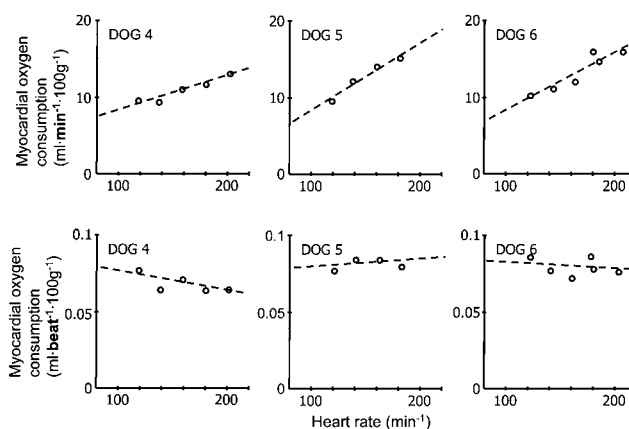


Figure 2 Myocardial oxygen consumption increases linearly with increasing heart rate. Myocardial oxygen consumption per single cardiac cycle is independent of heart rate. From Tanaka *et al.* (1990).

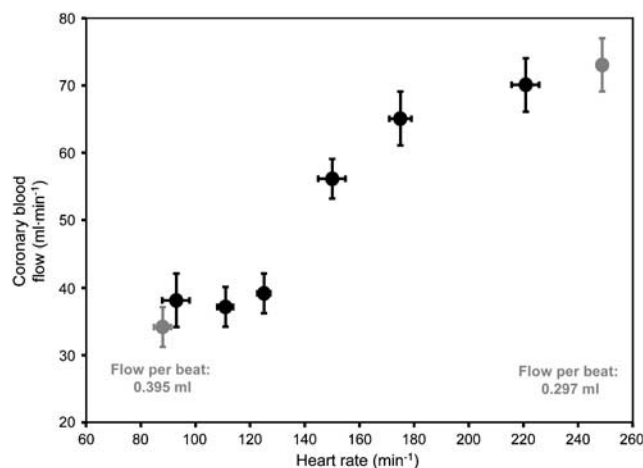


Figure 3 Coronary blood flow displays a typical dose–response curve to increasing heart rate. Blood flow per single cardiac cycle is reduced at increased heart rate, reflecting the decrease in diastolic duration. From Colin *et al.* (2004).

very high heart rate to matching of oxygen delivery to myocardial oxygen consumption, as myocardial oxygen extraction is already near maximal under baseline resting conditions. It should be noted that the blood flow per single cardiac cycle is decreased at higher heart rate (Figure 3).

This is because any increase in heart rate also shortens the duration of diastole and thus creates an impediment to coronary blood flow. Increases in heart rate are associated with overproportionate decreases in diastolic duration, therefore, the relationship between heart rate and diastolic duration is hyperbolic (Colin *et al.*, 2004).

Nevertheless, metabolic coronary vasodilation is so powerful that it largely overcompensates for decreased diastolic duration and prevails. Increased oxygen extraction also contributes at very high heart rate. Under physiological circumstances, coronary blood flow and oxygen delivery are always matched to myocardial performance and oxygen consumption.

Heart rate and the pathophysiology of coronary blood flow

Atherosclerosis

Heart rate can contribute to the development and progression of atherosclerosis. In fact, baboons when exposed to a cholesterol-rich diet develop atherosclerosis, which is blunted when their sinus node is crushed and accordingly heart rate is decreased (Beere *et al.*, 1984). Of course, heart rate is a less dominant factor in coronary atherosclerosis development and progression than low-density lipoprotein cholesterol, blood pressure or smoking. Also, it is unclear how heart rate contributes to the progression of atherosclerosis, but aggravated shear and turbulence might be a mechanism.

Coronary stenosis: flow distribution and steal phenomena

Whereas we have discussed the mechanism(s) determining and regulating coronary blood flow under physiological circumstances above, the scenario with a significant coronary stenosis is more complex. Part of the heart is still perfused through a more or less normal coronary vasculature, whereas other parts of the heart are perfused through more or less severely stenotic coronary arteries. Distal to the stenosis, coronary perfusion pressure is reduced and the poststenotic coronary microcirculation responds to this reduction in coronary perfusion pressure with an autoregulatory (see above) vasodilation; this autoregulatory microcirculatory vasodilation can compensate for stenoses of up to about 70% diameter reduction such that coronary blood flow at rest is well maintained. Another and more long-term form of compensation for the coronary stenosis occurs through the formation of collateral vessels or increase in the diameter of pre-existing collaterals that connect the poststenotic microvascular bed with the normal surrounding coronary vasculature. Collateral blood flow then occurs along a pressure gradient between the origin of collateral vessels in the normal myocardium and the orifice of collaterals into the poststenotic myocardium. In the

presence of collaterals, the poststenotic myocardium still receives its blood supply to some extent through the stenotic segment, but also to a varying extent through collaterals. Autoregulation of the poststenotic coronary microcirculation plus collateral blood flow are responsible for the fact that perfusion even of myocardium distal to severe stenoses is well maintained at rest and that myocardial ischaemia is only precipitated during stress or exercise, that is, in situations of increased heart rate.

Why is ischaemia precipitated then at increased heart rate and why does the compensation for the stenosis fail? During stress or exercise, the increase in heart rate is still met by metabolic coronary dilation, which still overcomes the effects of shortened diastole in the normal myocardium (Figure 4 left side). In the poststenotic myocardium, coronary dilator capacity is largely reduced or finally exhausted due to the autoregulatory adjustment already at rest/baseline. Further metabolic coronary vasodilation during increased heart rate is no longer possible; in contrast, the reduction in diastolic duration now even further compromises coronary blood flow. In addition, collateral blood flow is reduced because metabolic coronary vasodilation in the normal myocardium reduces pressure at the origin of collaterals (Figure 4 left side) and concomitantly the decreased coronary blood flow or increased microcirculatory resistance (secondary to reduced diastolic duration) increases pressure at the orifice of collaterals into the poststenotic myocardium (Figure 4 right side). Thus, the driving pressure gradient for collateral blood flow is largely reduced (Figure 4); it should be noted that relatively subtle change in pressure, however, in opposing directions in the donor and the recipient vascular territory, adds up to a marked reduction in the driving pressure gradient for collateral blood flow (Heusch and Yoshimoto, 1983).

Accordingly, studies using a high spatial resolution technique for the measurement of regional myocardial blood flow demonstrated that, whereas blood flow distal to a severe coronary stenosis is well maintained and almost equal to that in remote normal myocardium at rest, stress induces metabolic coronary vasodilation and a flow increase in the normal remote myocardium, but precipitates a marked flow reduction in the poststenotic myocardium (Figure 5) (Baumgart *et al.*, 1993). The above mechanism of regional myocardial blood flow redistribution through collaterals, where poststenotic blood flow is well maintained at rest but reduced during stress, is termed 'collateral steal' phenomenon, somewhat inappropriately because there is no real 'steal' of blood flow away from the poststenotic myocardium, but rather a reduced donation. In any case, a similar redistribution of myocardial blood flow occurs between the subendocardial and the subepicardial layers of the myocardial wall through transmurally penetrating coronary vessels. This happens because autoregulation is exhausted in subendocardial layers prior to that in subepicardial layers and the subendocardium is exposed to intraventricular diastolic pressure whereas the subepicardium is exposed to pericardial pressure, which is close to zero. Such 'transmural steal' phenomenon is the basis for the greater vulnerability of the inner myocardial layers to ischaemia.

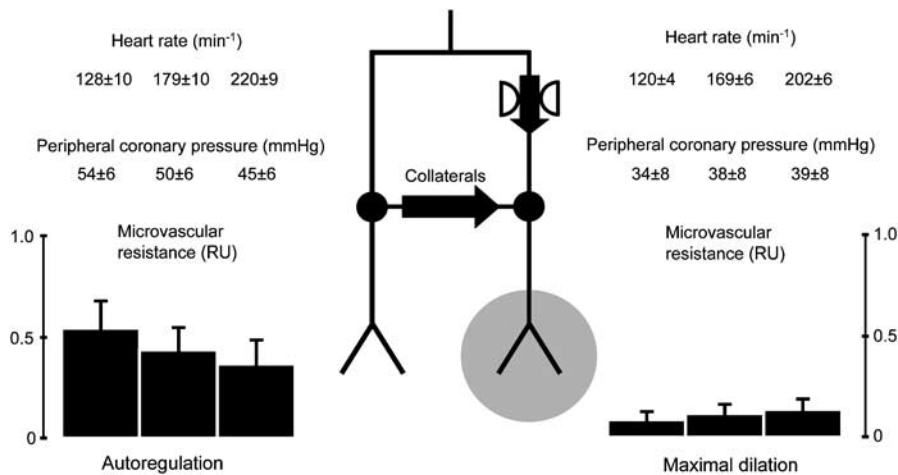


Figure 4 Schematic representation of changes in driving pressure gradient for collateral blood flow and in microvascular resistance in normal myocardium (left) and in poststenotic myocardium (right). At baseline heart rate, there is an autoregulatory decrease in microvascular resistance of the poststenotic myocardium. With increasing heart rate, there is metabolic dilation and accordingly a decrease in microvascular resistance in normal myocardium, resulting in decreased pressure at the origin of collaterals. In contrast, in poststenotic myocardium, no further dilation is possible and the reduction in diastolic duration prevails, such that microvascular resistance and pressure at the orifice of collaterals into the poststenotic coronary vasculature are increased. Note that subtle changes in perfusion pressure, yet in opposing direction in the normal and poststenotic myocardium, add up to a marked reduction in the driving pressure gradient for collateral blood flow (Heusch and Yoshimoto, 1983).

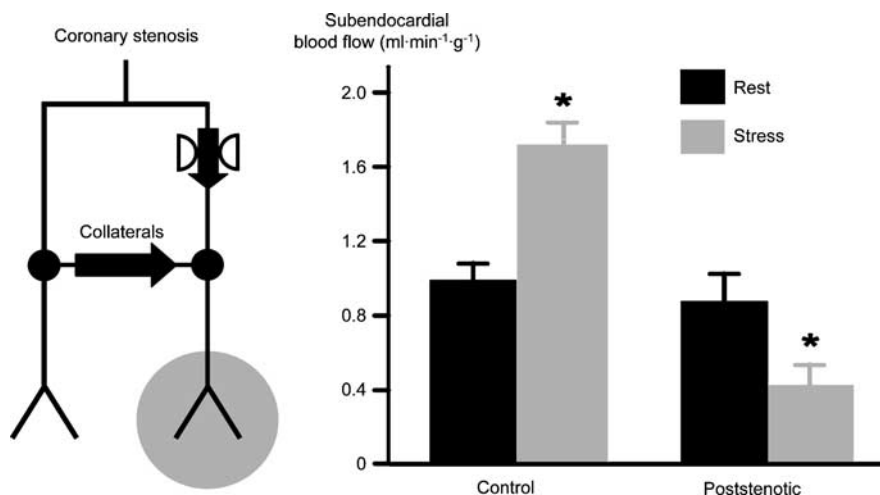


Figure 5 At rest, the compensatory decrease in microvascular resistance in the poststenotic myocardium maintains coronary blood flow. During stress, the normal myocardium responds with metabolic dilation and increased blood flow. In contrast, blood flow in poststenotic myocardium is reduced (Baumgart *et al.*, 1993).

Increased heart rate not only causes an unfavourable blood flow distribution between normal and poststenotic myocardium through collaterals and between subendocardial and subepicardial layers through transmural vessels, but also causes an increased turbulence and pressure loss along the stenotic segment, and this additional pressure loss along the stenotic segment also contributes to decreased poststenotic perfusion (Heusch *et al.*, 1982).

Coronary stenosis: relationship of flow and contractile function
In detailed experimental studies that measured simultaneously regional myocardial blood flow and contractile function distal to different degrees of coronary stenosis, there was a close linear correlation of flow and function

(Figure 6), that is, any reduction in regional blood flow was associated with a proportionate reduction in contractile function (Gallagher *et al.*, 1984). Such consistent relationship between flow and function in a series of studies led to the introduction of the concept of perfusion–contraction matching (Ross, 1991). In contrast to the classical view, where ischaemia is considered as a state of imbalance between supply and demand (of either blood flow, or oxygen or energy), the concept of perfusion–contraction matching relies on the fact that contractile function is proportionate to blood flow over the entire measured range (Figure 6), that is, an imbalance between blood flow (supply) and demand (contractile function) does not exist.

Such linear relation of blood flow and contractile function is also observed during exercise when heart rate is increased.

However, the relationship observed at rest is shifted rightwards and downwards during exercise, that is, there is less contractile function at any level of blood flow (Gallagher *et al.*, 1983). Now, when the increase in heart rate during exercise is taken into consideration by plotting blood flow per cardiac cycle rather than per minute on the x axis (in other words, by dividing blood flow per minute by heart rate), the relationships between contractile function and blood flow at rest and during exercise are superimposable (Gallagher *et al.*, 1983). The same is true with reduction of heart rate, in this case by a pharmacological intervention: with reduced heart rate, the relationship between flow per minute and function is shifted leftwards and upwards, that is, there is a better contractile function at any level of blood flow. In this particular study, a slight curvilinear plot was better suited than a linear plot to characterize the relationship between contraction and blood flow. Nevertheless, when normalizing blood flow to a single cardiac cycle and thus considering heart rate, the relationships at two different heart rates are superimposable (Figure 7) (Indolfi *et al.*, 1989).

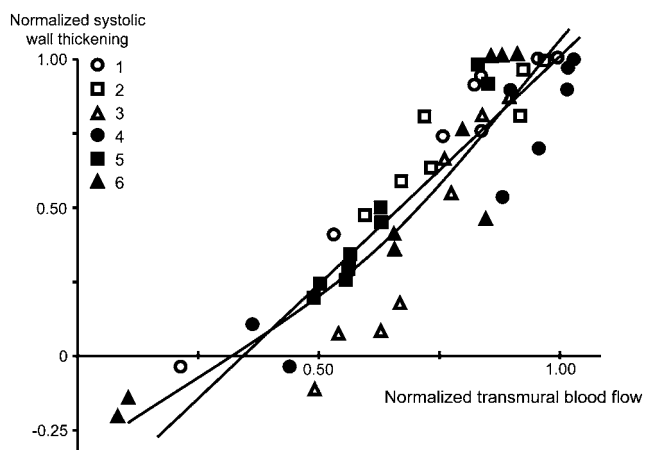


Figure 6 Systolic wall thickening and myocardial blood flow are closely and almost linearly correlated over a wide range of blood flow reduction by coronary stenoses of different severity. This is evidence for the concept of perfusion–contraction matching (Gallagher *et al.*, 1984).

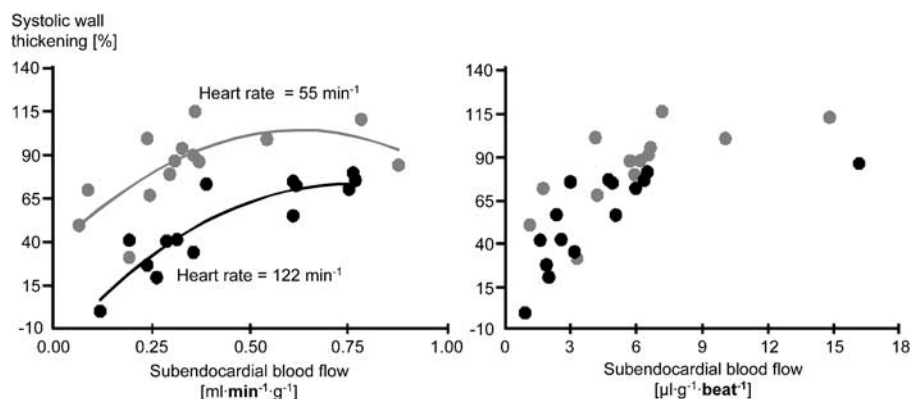


Figure 7 Left: when heart rate is reduced by a pharmacological agent, the relationship between systolic wall thickening and myocardial blood flow is displaced leftwards and upwards, indicating that contractile function for each level of blood flow is increased. Right: when myocardial blood flow is calculated for each single cardiac cycle, the relationships at two different heart rates are superimposable, again supporting the concept of perfusion–contraction matching (Indolfi *et al.*, 1989).

In a series of studies, all pharmacological agents that attenuate exercise-induced myocardial ischaemia (β -blockers, calcium antagonists, nitrates and their combinations) were demonstrated to operate along such consistent flow–function relationship, further strengthening the concept of perfusion–contraction matching (Matsuzaki *et al.*, 1984a, b, 1985; Guth *et al.*, 1986).

Regional myocardial ischaemia also impacts on flow and function of adjacent and more remote normal myocardium. During acute coronary artery occlusion, the ischaemic region is surrounded by a narrow zone of normally perfused myocardium with depressed regional contractile function (Guth *et al.*, 1984; Gallagher *et al.*, 1986, 1987). This depressed contractile function in the immediate border zone surrounding the ischaemic zone is attributed to more or less well defined mechanical ‘tethering’ between nonischaemic and ischaemic myocardial fibers (Bogen *et al.*, 1980). The remote myocardium is often characterized by enhanced contractile function (Lew *et al.*, 1985; Buda *et al.*, 1990). Whether an increase in remote nonischaemic zone function can be considered as compensatory in that it acts to preserve global left ventricular function (Buda *et al.*, 1990) is not entirely clear, since a major proportion of nonischaemic zone hyperfunction occurs during isovolumic systole and does not contribute to ejection (Lew *et al.*, 1985). The increase in function in the remote nonischaemic zone is associated with a moderate, presumably metabolically mediated increase in coronary blood flow (Gascho and Beller, 1987). Both the increase in remote zone contractile function and the ensuing metabolic coronary dilation are attenuated by β -blockade with metoprolol (Vanyi *et al.*, 2006).

Plaque rupture

Increased heart rate is associated with an increased incidence of angiographically documented plaque rupture in patients with ischaemic heart disease (Heidland and Strauer, 2001). The mechanism(s) by which heart rate contributes to plaque rupture are not clear, but increased shear and turbulence at higher heart rate in stenotic segments are plausible

mechanisms. It is also possible that increased heart rate is just a marker of greater activity of the sympathetic nervous system and of a pro-inflammatory systemic condition, which then facilitates plaque rupture.

β -Blockade in myocardial ischaemia: the benefits

β -Blockade has negative chronotropic (reduction of heart rate), bathmotropic (reduction of excitation threshold of cardiomyocyte) and therefore anti-arrhythmic, inotropic (reduction of force of contraction) and lusitropic (more correctly lysitropic, reduction in the rate of isovolumic ventricular relaxation) properties.

With reference to the above schematic diagram of flow distribution through collaterals (Figures 4 and 5), β -blockade will reduce blood flow to the normal myocardium, that is, at reduced heart rate and contractile function, there is less metabolic vasodilation, such that the pressure at the origin of collaterals is better preserved. In the poststenotic myocardium, the reduced heart rate will prolong the duration of diastole, improve blood flow and reduce calculated microvascular resistance, such that the pressure at the orifice of collaterals into the poststenotic coronary vasculature is reduced. As a result of these opposing changes in pressures at the origin and at the orifice of collaterals, the driving pressure gradient for collateral blood flow is increased, and accordingly blood flow into the poststenotic myocardium is further improved. Apart from the increased diastolic duration that facilitates perfusion of the dilated poststenotic microvasculature with its exhausted autoregulatory reserve and from the favourable blood flow distribution through collaterals, there may be an additional, yet small improvement in blood flow through the stenotic segment because decreased heart rate also decreases turbulence and pressure loss along the stenotic segment. Whatever the mechanism is, clearly, as predicted by our haemodynamic considerations, blood flow to normal remote myocardium is reduced and, more importantly, blood flow to the poststenotic myocardium is increased (Figure 8), and thus the inhomogeneity of blood flow distribution is normalized (Buck *et al.*, 1981). Again, as predicted by our considerations of the flow–function relationship and the concept of perfusion–contraction matching, β -blockade operates along such relationship, that is, improves both blood flow and contractile function proportionately (Figure 9; Matsuzaki *et al.*, 1984b). Of note, in the poststenotic and ischaemic myocardium a negative inotropic action of β -blockade does not become apparent, because in ischaemia it is blood flow that governs contractile function, and therefore β -blockade, which increases post-stenotic blood flow, increases contractile function rather than displaying its negative inotropic action.

Apart from the improved blood flow, which also results in improved contractile function of ischaemic myocardium, β -blockade also reduces the size of myocardial infarction, which results from sustained severe ischaemia and subsequent reperfusion. Such infarct size reduction is beyond the improvement in collateral blood flow, that is, is even seen at any given blood flow when infarct size is plotted as a function of residual blood flow (Schulz *et al.*, 1995).

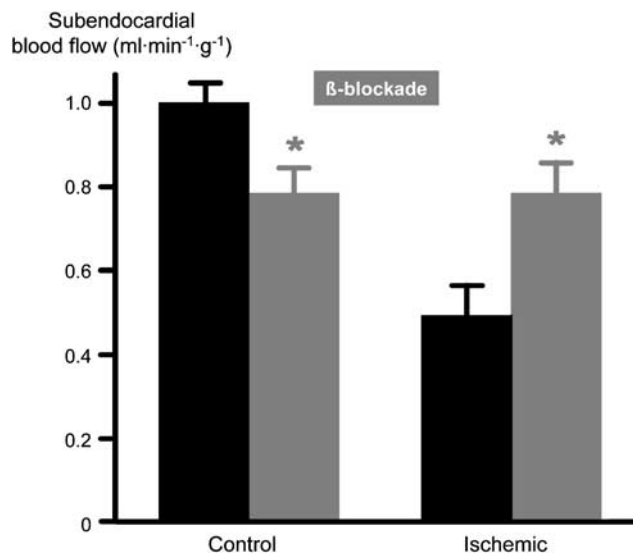


Figure 8 Reduced poststenotic blood flow in the ischaemic myocardium at rest. With β -blockade, blood flow in normal myocardium is reduced, whereas blood flow in ischaemic myocardium is improved (Buck *et al.*, 1981).

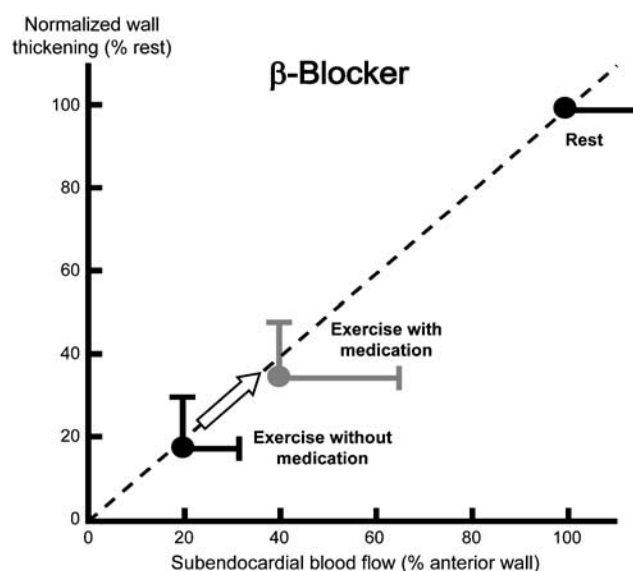


Figure 9 Relationship of systolic wall thickening and myocardial blood flow during exercise-induced ischaemia. β -Blockade moves the data point along the consistent relationship upwards and rightwards, reflecting improved blood flow and contractile function. Note that, in ischaemia, there is no negative inotropic action of β -blockade. The increase in blood flow even permits an increase in regional contractile function (Matsuzaki *et al.*, 1984b).

β -Blockade in myocardial ischaemia: the disadvantages

Within the framework of the present review, we focus, only on the myocardium and neglect the disadvantageous effects of β -blockade on the bronchial system, peripheral vasculature, metabolism and central nervous system, which are, of course, all of clinical relevance and depend to some extent on the β_1 vs β_2 selectivity, as well as on other properties of the individual β -blocker.

Although β -blockade is clearly beneficial in myocardial ischaemia, it still has disadvantages that limit its benefits. As discussed, the negative inotropic action of β -blockade is of no concern for the poststenotic ischaemic myocardium. In fact, a negative inotropic action and thus reduced need for coronary blood flow may even contribute to the more favourable blood flow distribution towards the ischaemic myocardium. Also, the potential negative inotropic effect on more remote myocardium appears not to be a problem. It is only when global left ventricular function is compromised that the negative inotropic action of β -blockade presents a problem, and again this may only be a problem with acute β -blockade as we have learned from the trials where β -blockade proved to be beneficial in the long-term treatment of heart failure. Thus, the problems of negative inotropic actions of β -blockade in the treatment of ischaemic heart disease have probably been overestimated in the past. True problems, however, exist with respect to coronary blood flow:

- The heart rate reduction achieved by β -blockade does not achieve the full potential that might be expected from the increase in the duration of diastole. This is because of the negative inotropic action of β -blockade. When we consider the diastolic pressure–time integral as the driving force for coronary blood flow, any slowing of isovolumic ventricular relaxation at any given diastolic duration will impede coronary blood flow, and this is in fact a true problem for β -blockade.
- Much more importantly, the competitive displacement of norepinephrine and epinephrine from β -adrenoceptors increases their effective concentration at α -adrenoceptors. In consequence, β -blockade increases or unmasks α -vasoconstriction. Unmasking of α -adrenergic coronary vasoconstriction in situations of increased sympathetic activity such as stress and exercise then actively reduces coronary blood flow and contributes to the precipitation of acute myocardial ischaemia (Seitelberger *et al.*, 1988). Unmasked α -adrenergic coronary vasoconstriction is particularly evident in atherosclerotic coronary vessels and seen at the level of epicardial conduit coronary arteries and mediated by α_1 -adrenoceptors, and it is even more prominent in the coronary microcirculation and mediated by α_2 -adrenoceptors (Baumgart *et al.*, 1999; Heusch *et al.*, 2000). Unmasked α -adrenergic coronary vasoconstriction is also manifested in the flow–function relationship, when the heart rate reduction achieved by β -blockade is artificially prevented by atrial pacing at the heart rate previously seen in the absence of β -blockade. Rather than moving upwards in the direction of improved blood flow and a proportionate improvement in contractile function as with β -blockade and heart reduction, β -blockade in the absence of heart rate reduction is characterized by decreased blood flow (consequence of α -adrenoceptor-mediated vasoconstriction and impaired isovolumic ventricular relaxation) and a proportionate decrease in contractile function (Figure 10) (Guth *et al.*, 1987b).

With respect to the distribution of regional myocardial blood flow and contractile function during acute myocardial ischaemia, no difference between β_1 -selective or less selective

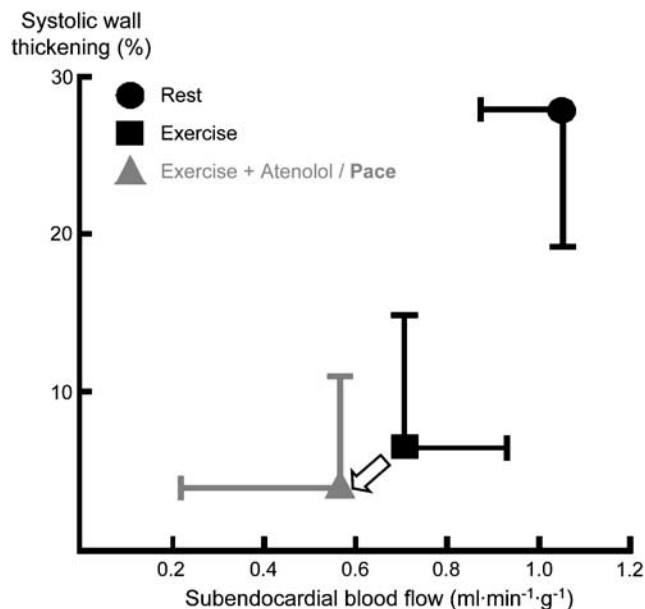


Figure 10 Relationship of systolic wall thickening and blood flow during exercise-induced ischaemia. When the reduction of heart rate by β -blockade is prevented by atrial pacing at a rate that was observed in the absence of β -blockade, the data point is moved along the consistent relationship leftwards and downwards, indicating reduced blood flow (a consequence of unmasked α -adrenergic coronary vasoconstriction and impaired isovolumic ventricular relaxation) and a proportionate reduction in regional contractile function (Guth *et al.*, 1987b).

β -blockers is apparent (Buck *et al.*, 1981; Matsuzaki *et al.*, 1984b).

Selective heart rate reduction by ivabradine and its benefits

Mechanism of action in the sinus node

The advantage of selective bradycardic agents can only be defined against the background of the disadvantage of β -blockade. Ivabradine acts on the I_f -channel. The 'f' in I_f stands for 'funny' because this ion channel has 'funny'/unusual properties. This channel is activated by hyperpolarization and is regulated not by phosphorylation through protein kinase A in response to increased intracellular cAMP, but by direct binding of cAMP. cAMP is the second messenger molecule that integrates intracellularly the balance between cardiac sympathetic nerves, which increase cAMP through the action of norepinephrine on surface β_1 - and β_2 -adrenoceptors and subsequent activation of the G-protein G_s , and cardiac vagal nerves, which decrease cAMP through the action of acetylcholine on surface muscarinic receptors and subsequent activation of the inhibitory G-protein G_i . The I_f -channel is genetically determined by the hyperpolarization-activated, cyclic nucleotide-gated channel gene family, which encodes four different isoforms. The hyperpolarization activated cyclic nucleotide-gated channel isoform 4 is the predominant one in the sinus node. The channel is composed of four subunits, which form a pore/channel (Zagotta *et al.*, 2003). The I_f -channel is

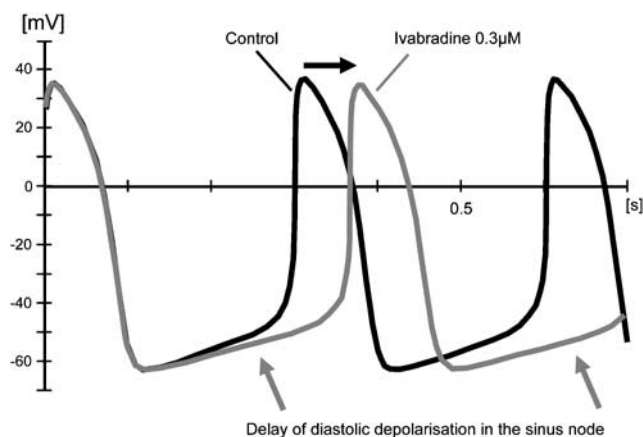


Figure 11 Typical original recording of the action potential in a sinus node cell. Ivabradine prolongs the diastolic slow depolarization phase. Note that ivabradine has no effect on action potential characteristics (DiFrancesco and Camm, 2004).

activated by the hyperpolarization in the terminal phase of action potential repolarization, and its activation increases the membrane permeability for both sodium and potassium ions. The resulting influx of sodium and potassium ions along the electrical (for sodium and potassium) and chemical (for sodium) gradient then depolarizes the cell, until the threshold for activation of the fast calcium channel is reached and an action potential is initiated. Thus, the I_f -channel is activated during the slow diastolic depolarization phase. The degree of activation of the I_f -channel determines the velocity of the diastolic depolarization and thus determines the time when the threshold for the initiation of an action potential is reached; this is the mechanism by which the I_f -channel controls heart rate.

Ivabradine specifically and concentration-dependently binds to the I_f -channel in its open/activated form, and its binding inhibits the channel, thus reducing the velocity of diastolic depolarization. Of note, while specifically prolonging the phase of diastolic depolarization, all other characteristics of the action potential remain unaltered (Figure 11). In this way, ivabradine indeed reduces heart rate selectively (Thollon *et al.*, 1994; DiFrancesco and Camm, 2004).

Effects of ivabradine on coronary blood flow and contractile function

The reduction of heart rate by ivabradine prolongs the duration of diastole. Of note, in contrast to β -blockade, which not only prolongs diastolic duration but also impairs isovolumic ventricular relaxation and thus offsets part of the benefit in terms of the diastolic pressure–time integral (see Figure 1 above), selective heart rate reduction by ivabradine is not at the expense of impaired isovolumic ventricular relaxation, such that the full benefit of prolonged diastole is available for coronary blood flow (Colin *et al.*, 2002).

Ivabradine reduces myocardial oxygen consumption in normal myocardium and this effect prevails over the increase in diastolic duration in normal myocardium. In consequence, there is less metabolic vasodilation and reduced

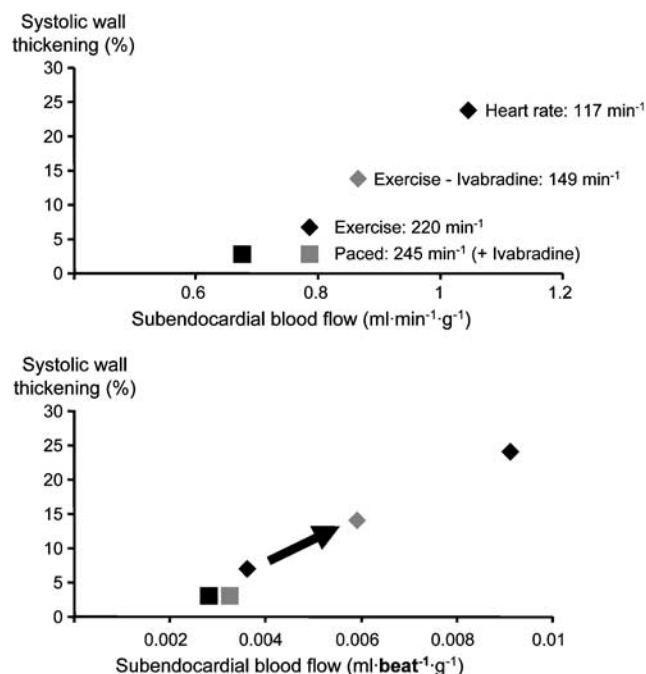


Figure 12 Calculated relationship between systolic wall thickening and myocardial blood flow from data (Monnet *et al.*, 2001). Heart rate reduction by ivabradine improves both blood flow and contractile function along the consistent relationship. When a heart rate reduction is prevented by atrial pacing, ivabradine has no residual effect on either blood flow or contractile function.

blood flow in normal myocardium. Considering our above scheme for collateral and transmural blood flow distribution (see Figure 4), a reduction in blood flow in normal myocardium together with the facilitation of blood flow through increased diastolic duration will increase blood flow to the poststenotic ischaemic myocardium and also improve its transmural distribution. In fact, ivabradine attenuates exercise-induced myocardial ischaemia in pigs (Vilaine *et al.*, 2003).

Considering the above flow–function relationship, selective heart rate reduction by ivabradine during exercise-induced myocardial ischaemia improves both regional blood flow and contractile function in a proportionate fashion (Figure 12). In contrast to β -blockade, there is no residual detrimental effect when the heart rate reduction by ivabradine is artificially prevented by pacing; this lack of residual detrimental effect confirms the selectivity of ivabradine in terms of achieving a heart rate reduction and it excludes unmasking of α -adrenergic coronary vasoconstriction, as seen with β -blockade (Monnet *et al.*, 2001).

Ivabradine does not only not unmask α -adrenergic coronary vasoconstriction but also preserves the endothelium-mediated vasodilation that is typically observed in large epicardial conduit vessels in response to enhanced shear stress and pulsatility when blood flow is increased following metabolic vasodilation in the coronary microcirculation (Figure 13) (Simon *et al.*, 1995).

Thus, ivabradine offers the same advantages as β -blockade in terms of heart rate reduction, but not at the expense of impaired isovolumic ventricular relaxation and unmasking of α -adrenergic coronary vasoconstriction. The lack of a

negative inotropic action of ivabradine contributes to better preservation of global left ventricular function. Also, ivabradine permits adequate increases in left ventricular function and cardiac output during exercise (Monnet *et al.*, 2001; Colin *et al.*, 2003; Du *et al.*, 2004).

Benefits of ivabradine for the ischaemic/reperfused myocardium

Apart from the improvement in blood flow and contractile function in ischaemic myocardium outlined above, ivabradine improves the recovery of contractile function during reperfusion following exercise-induced myocardial ischaemia,

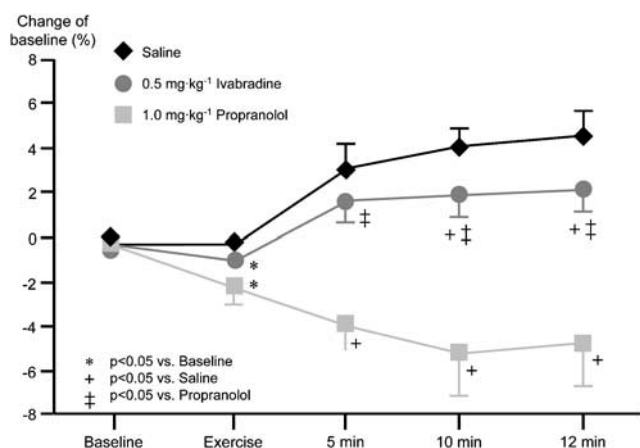


Figure 13 During exercise, epicardial coronary arterial diameter is increased with increasing duration of exercise. This dilation is mediated by the endothelium in response to increased blood flow through enhanced shear stress and pulsatility. With β -blockade by propranolol, α -adrenergic coronary vasoconstriction is unmasked and the dilation is reversed to vasoconstriction. Equal reduction of heart rate by ivabradine does not interfere with the endothelium-mediated dilation. The slightly less pronounced increase in vascular diameter than with placebo is a physiological response to lower blood flow and consequently less shear stress and pulsatility at lower heart rate (Simon *et al.*, 1995).

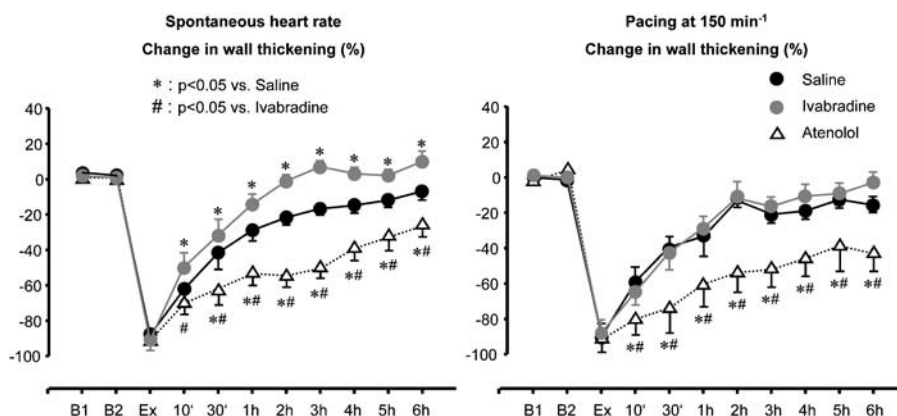


Figure 14 Left: following an episode of exercise-induced ischaemia, regional contractile function only slowly recovers back to normal over several hours, that is, there is myocardial stunning. Heart rate reduction by ivabradine largely accelerates the recovery, whereas an equal reduction in heart rate by the β -blocker atenolol even impairs the recovery of contractile function, reflecting the negative inotropic action of β -blockade. Right: when changes in heart rate are eliminated by atrial pacing, ivabradine does the same as saline, whereas the negative inotropic action of atenolol is even more pronounced (Monnet *et al.*, 2004).

that is, ivabradine attenuates stunning. Again, when the reduction of heart rate is prevented by atrial pacing, no residual detrimental effect on contractile function remains, that is, there is no negative inotropic action of ivabradine (Figure 14) (Monnet *et al.*, 2004).

Post-ejection wall thickening is a typical sign of asynchrony of ventricular contraction and relaxation, which is associated with reversible regional myocardial ischaemia and reperfusion (Heusch *et al.*, 1987; Ehring and Heusch, 1990; Rose *et al.*, 1993). Ivabradine, different from β -blockade (Lucats *et al.*, 2007a), has the unique property of not only improving ischaemic and postischemic regional myocardial function but also reversing post-ejection wall thickening to wall thickening during ejection and thus making this contraction available for cardiac output (Lucats *et al.*, 2007b). It is currently unclear how this property of ivabradine relates to its preservation of isovolumic ventricular relaxation and what the exact mechanism(s) of conversion of post-ejection to ejection wall thickening are, but in any event it is functionally beneficial.

Preliminary studies in rabbits also indicate a reduction of infarct size by ivabradine (Langenbach *et al.*, 2006); reduced infarct size is to be expected but the preliminary studies are on their way to be confirmed in a clinically more relevant large mammal model in pigs where ivabradine's effects on coronary blood flow are also taken into consideration.

Benefits of ivabradine for the long-term outcome after myocardial ischaemia

A study in a rat model of permanent coronary ligation with subsequent myocardial infarction, ventricular remodelling and finally heart failure revealed not only a dose-dependent improvement in left ventricular function by ivabradine, which was associated with dose-dependent reductions in heart rate (Figure 15), but also structural benefits, that is, reduced fibrosis and collagen deposition and increased vascularity in the surviving myocardium (Mulder *et al.*,

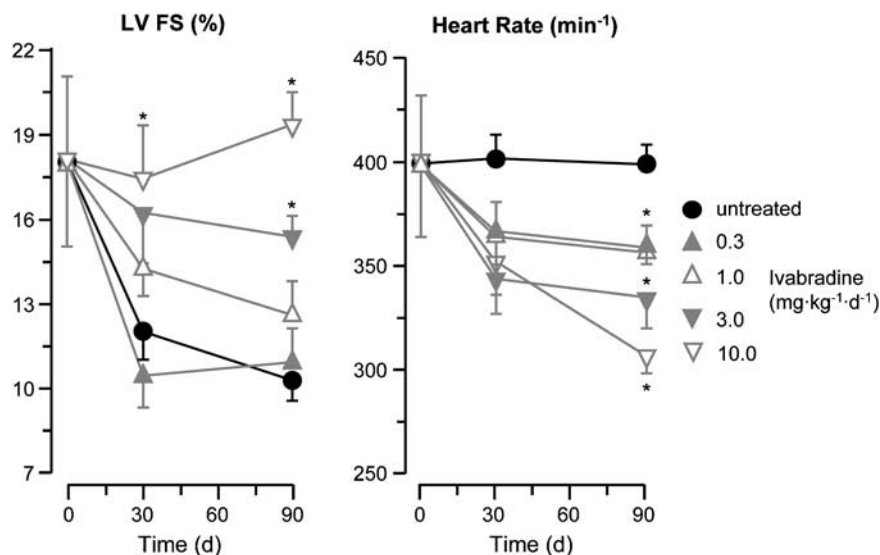


Figure 15 Heart failure develops following permanent coronary ligation in rats. Dose-dependent decreases in heart rate by ivabradine (right) are associated with proportionate improvements in fractional left ventricular shortening (left). At the highest dose of ivabradine, fractional shortening remains entirely normal (Mulder *et al.*, 2004).

2004). Again, these promising findings must be confirmed in larger mammals.

Conclusions and perspectives

There is solid pathophysiological evidence that selective heart rate reduction by ivabradine improves blood flow to, and its distribution within, ischaemic myocardium. This improvement in ischaemic myocardial blood flow is associated with proportionate improvements in ischaemic myocardial contractile function. Different from β -blockade, ivabradine does not impair isovolumic ventricular relaxation, does not unmask α -adrenergic coronary vasoconstriction and does not exert a negative inotropic action. In consequence, endothelium-mediated coronary vasodilation and left ventricular function, in particular during exercise, are better preserved than with β -blockade.

More mechanistic analyses on the benefits from ivabradine in settings of myocardial ischaemia/reperfusion must be carried out and are underway. Nevertheless, a proof of concept study has unequivocally confirmed the anti-ischaemic action of ivabradine in patients with chronic stable angina and also demonstrated its safety (Borer *et al.*, 2003). Other studies have also documented its non-inferiority to atenolol or amlodipine in the treatment of chronic stable angina (Ruzylo *et al.*, 2004; Tardif *et al.*, 2005). We are looking forward to the results of the Beautiful-Study (morbidity-mortality Evaluation of the I_f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction), which assesses the morbidity and mortality benefits of ivabradine in patients with coronary artery disease.

Conflict of interest

Professor Heusch has received unrestricted educational grant support from, held lectures and served as consultant for Servier. No honorarium was paid for the present article.

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