Heart Rate and Heart Failure – Not a Simple Relationship –

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Resting heart rate (HR) is increased in patients with heart failure (HF). Sustained tachycardia can cause HF. The magnitude of HR reduction in treatment trials of patients with HF is associated with a reduction in mortality. Yet, the mechanistic and causal role of HR in HF is unclear, and recent trials with selective HR reduction have not consistently achieved benefit: the BEAUTIFUL trial in patients with coronary artery disease and left ventricular dysfunction did not achieve a significant benefit in the primary endpoint, and only the coronary outcome, not the HF outcome, was improved; in the SHIFT trial, however, patients with symptomatic heart failure had a significant benefit in the primary endpoint of cardiovascular mortality and hospitalization for worsening HF. The present review addresses the pathophysiology of tachycardia-induced HF, the force–frequency relationship, and the clinical potential of HR reduction in HF. (*Circ J* 2011; **75**: 229–236)

Key Words: Atrial fibrillation; Excitation–contraction coupling; Force–frequency relation; Heart failure; Tachycardia

The role of heart rate (HR) in myocardial ischemia is quite clear: increased HR causally contributes to plaque rupture and to the precipitation of myocardial ischemia distal to severe coronary stenoses; conversely, reduction of HR reduces plaque rupture and attenuates myocardial ischemia (for review see¹). The role of HR in heart failure (HF) is much less clear. In the present review, I will address 3 issues: (a) the causal role of tachycardia in inducing HF in experimental animals and in patients with tachyarrhythmias, (b) the force–frequency relationship in HF, and (c) recent studies on the reduction of HR in patients with HF.

Tachycardia-Induced HF

A sustained increase in HR by pacing in experimental animals and by tachyarrhythmias in patients without other underlying structural heart disease induces left ventricular (LV) dysfunction and HF.

Pacing-Induced HF

Apparently, Whipple et al were the first in 1962 to use rapid atrial pacing in dogs to induce congestive HF.² Subsequently, many investigators have used pacing (atrial and ventricular) in dogs,^{3–14} pigs,^{15–17} monkeys,¹⁸ rabbits^{19–25} and rats²⁶ to induce HF and characterize various aspects of it (for review see^{27–29}). The clinical symptoms in those animal models include dyspnea, cachexia, congestion and ascites, and exercise intolerance.

Functional and Morphological Features of Pacing-Induced HF Pacing-induced HF is to a large extent reversible^{12,30} and

Table. Features of Experimental Pacing-Induced Heart Failure

Clinical symptoms

Dyspnea
Cachexia
Ascites
Exercise intolerance

LV dysfunction

LVEDV ↑, EF ↓ (echocardiography)
Systolic wall thickening ↓ (sonomicrometry)
LVEDP ↑, LVP ↓, LV dP/dtmax ↓ (manometry)
Baseline heart rate ↑

Morphology

Apoptosis
Hypertrophy
Fibrosis

Systemic consequences

Catecholamines ↑
β-Adrenoceptor desensitization/downregulation
Renin ↑, angiotensin ↑, aldosterone ↑
Inflammation (TNFα ↑, iNOS ↑)
Coronary, skeletal muscle and splanchnic perfusion ↓

LV, left ventricular; LVEDV, left ventricular end-diastolic volume; EF, ejection fraction; LVEDP, left ventricular end-diastolic pressure; LVP, left ventricular pressure; TNF, tumor-necrosis factor; iNOS, inducible nitric oxide synthase.

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60.	30.	15.	10.	5.	4.	3.	2.	4.	5.	15.	60	Sec.
12.0	14.0	16.0	17.0	18.0	18.4	16.4	14.4	15.2	15.2	14.4	10.0	m.m.

Figure 1. Perfusion apparatus developed by Bowditch and the original table that he reported to characterize the relationship of heart rate (stimulus interval) and contractile force (magnitude of volume displacement in a fluid-filled column).⁸⁴

characterized by many features that resemble human congestive HF (Table). Of note, after a few weeks of rapid pacing, LV systolic dysfunction develops, as reflected by decreased cardiac output,^{3,5,6} ejection fraction,^{20,21,31} LV dp/dt_{max} ^{7,8} and elastance.^{9,11} The LV is dilated^{4,6,32} and its preload reserve is exhausted.¹⁰ Diastolic dysfunction also manifests as increased stiffness.^{31–33} Baseline HR is increased with pacing-induced HF in larger mammals, but not necessarily in rodents, possibly reflecting the different effect of vagal withdrawal and sympathetic activation in various species. Morphologically, there is a loss of cardiomyocytes and hypertrophy of the remaining cardiomyocytes.^{21,24,25,30,34} Apoptosis affects both cardiomyocytes^{24,25,35} and noncardiomyocytes in the failing heart.¹⁸ Fibrosis and increased collagen^{15,20–22,32} probably determine the observed increased stiffness.

Neurohumoral and Inflammatory Features of Pacing-Induced HF The pacing-induced HF model is associated with typical neurohumoral alterations: there is parasympathetic withdrawal³⁶ and sympathetic activation, with attenuation of baroreflexes.^{37–39} Plasma levels of catecholamines,^{3–5,23,24,40,41} renin,^{3–5,40} angiotensin II,³ aldosterone,^{3,5} atrial natriuretic peptide^{5,40,42} and endothelin⁴³ are increased. In response to the increased plasma catecholamine levels, myocardial β -adrenoceptor density and signal transduction are decreased.^{23,24,41,44–46} Probably as a consequence of sustained increases in plasma catecholamine levels, a meta-

bolic syndrome with elevated plasma levels of fatty acids and glucose, and with myocardial insulin resistance develops.⁴⁷ A generalized proinflammatory status is reflected by increased plasma levels of tumor-necrosis factor- α ,⁴⁸ which originates, however, not only from the myocardium but also from the congested liver and splanchnic circulation.²⁰ Inducible nitric oxide synthase is increased locally in the myocardium.²⁵

Coronary blood flow^{49,50} and coronary dilator reserve^{17,49} are reduced. Endothelium-dependent dilation is impaired in the coronary circulation,⁵¹ as well as in the skeletal muscles.⁵² Accordingly, skeletal muscle perfusion is reduced^{50,53} and there is skeletal muscle atrophy.⁵⁴

Cellular, Subcellular and Molecular Features of Pacing-Induced HF At the cellular level, abnormalities in excitation–contraction are obvious. Action potential is prolonged, largely because of reduced repolarizing potassium currents.⁵⁵ The failing myocardium is particularly sensitive to stretch-induced ventricular extrasystoles.⁵⁶

Central to the excitation–contraction abnormalities appears to be a dysfunction of the sarcoplasmic reticulum, which is characterized by reduced ryanodine receptor binding,^{57,58} and reduced levels of sarcoplasmic ATPase mRNA^{59,60} and protein,⁶¹ as well as phospholamban protein.⁶¹ There is a compensatory increase in sodium–calcium exchange protein and activity,^{61,62} which is, in turn, dependent on the driving

sodium gradient and consequently the sodium-proton exchanger.^{22,23} The intracellular calcium transient is decreased in amplitude^{58,60,63} and increased in duration.^{61,64} Single cell shortening^{16,65,66} and shortening velocity⁵⁹ are reduced, as well as the peak tension of isolated trabeculae.⁶⁴ Apart from these changes in intracellular calcium homeostasis, there is oxidative protein modification⁶⁷ also affecting the contractile machinery,^{24,68} and the calcium responsiveness of myocardium with pacing-induced failure is impaired.⁶⁹

The cellular alterations of excitation–contraction coupling in pacing-induced HF resemble those seen in cardiomyocytes from patients with clinical HF.^{70–73} However, because HF in humans is in most cases not a consequence of tachycardia, alterations in excitation–contraction coupling may be a consequence rather than a cause of contractile dysfunction.

Potential Mechanisms of Pacing-Induced HF Whereas the features of the pacing-induced HF model are quite consistent and clear, the underlying mechanisms are still largely elusive. Both cardiomyocyte loss and fibrosis are at least temporal consequences of pacing and not severe enough to explain the profound functional deterioration. There is no evidence of overt ischemia in the model, but because of the reduced subendocardial blood flow per beat, regional ischemia at the pacing site with persistent stunning after discontinuation of pacing has been proposed as a potential mechanism.⁷⁴ Increased oxidative stress is thought to causally

contribute to activation of apoptosis⁶⁷ and to the oxidative modification of the contractile machinery.²⁴

HF in Patients With Tachyarrhythmia

Patients with sustained supraventricular tachyarrhythmia, but without other underlying heart disease, also display typical LV dysfunction and HF,^{75–77} both of which are typically reversible after pharmacological or ablation control of the tachycardia.⁷⁸ Biopsy specimens from such patients reveal nonspecific morphological alterations.^{75,76,79} Again, the mechanism(s) underlying the development of HF during sustained tachyarrhythmias is/are unclear. Apart from potential specific pathomechanism(s) (see earlier), prolonged exercise with the associated increase in HR also typically results in LV dysfunction in healthy people, even in athletes.^{80–83} Apart from LV dysfunction, increased troponin and B-type natriuretic peptide levels⁸² and decreased β -adrenergic signal transduction⁸³ have been reported after prolonged exercise, and terms such as (pseudo-) stunning⁸¹ have been used to characterize such LV fatigue. It is therefore entirely unclear to what extent LV dysfunction during tachyarrhythmia is a physiological response of LV contractile function to a rhythm pathology or a pathological response per se.

Force–Frequency Relationship

Apparently, Bowditch was the first in 1871⁸⁴ to report the effects of frequency of stimulation on contractile force.⁸⁵ He used rabbit serum-perfused isolated frog hearts, which ejected into a manometer (Figure 1). The phenomenon that contraction amplitude increased during stimulation at a constant frequency from rest over several cardiac cycles into a steady state was termed “Treppe”. He then varied the stimulation frequency between 1/min and 30/min and recorded contraction amplitude at steady state over several beats: contraction amplitude increased from stimulation at 1/min to 12–15/min and then declined again. Almost 100 years later, an increase in contraction amplitude/force with increasing stimulation frequency was also reported in isolated mammalian, including human, heart muscle preparations with an optimum at frequencies between 30–60/min during normothermia.^{86–89} In the in-situ dog heart on cardiopulmonary bypass (in order to control the loading conditions), increased HR from 120 beats/min by an average of 40 beats/min augmented isovolumic contraction and contraction velocity.⁹⁰ In conscious dogs, positive effects of atrial pacing on LV dP/dt_{max} are only modest (Figure 2), possibly secondary to decreased preload,^{13,66,91,92} and the relationship between HR and LV dP/dt_{max} is also flat in pigs.⁹³ Autonomic blockade abolishes any effect of stimulation frequency on LV dP/dt_{max}.^{66,91} A positive effect of increased HR on LV dP/dt_{max} (ie, positive force–frequency relationship) becomes more manifest during β -adrenergic activation in pigs,⁹³ and during exercise in dogs.^{94,95} In human non-failing hearts in situ, atrial pacing from 80 beats/min to 120 or 140 beats/min modestly increases regional myocardial function⁹⁶ and LV dP/dt_{max}.^{97–99}

There is a negative force–frequency relationship in isolated ventricular preparations from failing hearts.⁸⁸ However, the relationship between LV dP/dt_{max} and HR is displaced down-

wards from that in controls and entirely flat in both conscious dogs⁶⁶ and pigs⁹³ with pacing-induced HF. The same is true for patients with dilated cardiomyopathy (Figure 3).^{97,98,100} The shortening response of isolated cardiomyocytes from the failing human heart to increasing stimulation rate is also flat.⁷¹ The cardiac index even decreases with increased HR, possibly because of decreased filling and lack of any compensatory increase in inotropy.⁹⁷ The choice of LV function parameter to assess the force–frequency relationship is important: cardiac output should not be used, because it is the product of stroke volume and HR, and HR would therefore be plotted on both the x- and y-axes. LV dP/dt_{max} is both HR- and load-dependent and expected to increase with HR per se (though this may just reflect a modest force–frequency effect) and to decrease with reduced filling at higher HR.⁹² End-systolic elastance is largely load- and HR-independent, but technically more difficult to determine.^{9,11,99} In patients with HF and preserved ejection fraction or so-called “diastolic HF”,¹⁰¹ there is still a slightly positive relationship of LV dP/dt_{max} to HR, but a blunted frequency–acceleration of LV dP/dt_{min}.⁹⁹

Neither the mechanism of a modestly positive force–frequency relationship in the normal heart nor its lack in the failing heart is clear in detail; the force–frequency relationship rather reflects the entire excitation–contraction coupling process, including the calcium transient,¹⁰² the activity of the sarcoplasmic reticulum¹⁰³ and the calcium responsiveness of the contractile machinery,¹⁰⁴ all of which have distinct defects in the failing heart. Oxidative stress may again be of major importance.^{68,89} Cardiac mechanical restitution curves and postextrasystolic potentiation may be more sensitive than the steady-state force–frequency relationship to detect and characterize the impaired excitation–contraction coupling in the failing heart.^{66,105} On the other hand, although the force–frequency relationship is a steady-state response, it does not persist over longer periods of time. Otherwise pacing over several weeks would not induce HF (see earlier), but rather, slightly increased contractile function. Also, because the force–frequency relationship in HF is flat, no improvement in LV function is expected from moving to a lower HR along such a relationship.

HR Reduction in Patients With HF

An increased resting HR is associated with increased total and cardiovascular mortality, and HF is characterized by increased resting HR.^{106–108} Patients with HF and HR >70 beats/min have a significantly greater cardiovascular mortality and risk for hospital admission than those with HR <70 beats/min, and the discrimination by HR is better for HF than for coronary vascular outcomes.¹⁰⁹ Clearly, a number of recent trials on angiotensin-converting enzyme inhibition and β -blockade in patients with HF^{110–113} also suggest an association of the reduction in mortality with the magnitude of HR reduction (for review see^{106,114}). However, β -blockade has other potential effects to attenuate HF (ie, reduce apoptosis^{115,116} and/or improve adrenergic signal transduction^{117,118}), such that reduced HR may be an epiphenomenon or just the consequence of an improved situation. A causal role for reduced HR in the beneficial action of β -blockade is suggested by 2 small studies: the increased mechanical efficiency after acute intravenous propranolol was offset by atrial pacing in patients with HF,¹¹⁹ and in patients with HF under β -blockade therapy and a pacemaker implantation, ventricular function was worse after 14 months at a HR of 80 beats/min than at 60 beats/min.¹²⁰

Against this background, reduction of HR by a selective bradycardia agent that acts on the I_f channel in the sinus node^{1,121,122} (ivabradine is the only one available for clinical use) has been investigated for its effect on LV function and clinical outcome in patients with HF:¹²³ intravenous infusion of ivabradine in 10 patients with advanced HF decreased resting HR by a maximum of 20 beats/min and increased stroke volume.¹²⁴ In the BEAUTIFUL trial, patients with stable coronary artery disease and LV dysfunction, notably those with baseline HR >70 beats/min and with symptomatic angina, benefited from ivabradine in coronary vascular, but not in HF, outcomes.^{125–127} In contrast, in the very recent SHIFT trial, patients with symptomatic HF had a higher baseline HR and a greater HR reduction by ivabradine than in the BEAUTIFUL trial, and ivabradine significantly reduced the combined primary endpoint of cardiovascular death and hospital admission for worsening HF, largely through the latter.¹²⁸ In SHIFT, the benefit from ivabradine was related to the magnitude of HR reduction.¹⁰⁸ However, the benefit from ivabradine against myocardial infarction in pigs is largely independent of HR reduction¹²⁹ and possibly related to attenuated free radical formation during early reperfusion.¹³⁰ Ivabradine also attenuates adverse remodeling and improves angiogenesis post myocardial infarction in rats, but the causal role of HR reduction for such improvement is unclear because pacing was not performed to assess potential HR-independent benefits of ivabradine.¹³¹

Atrial fibrillation in patients with HF is of particular concern, and both sustained tachycardia and irregular cardiac contraction will likely contribute to poor LV function and clinical outcome. Studies that demonstrate a similar clinical benefit from rate control as from rhythm control in patients with atrial fibrillation, many of them also with HF,^{132–134} support a causal role for HR reduction in achieving this benefit. However, a recent study of patients with atrial fibrillation, and a major proportion of them also had HF, found no difference between more lenient HR control (with baseline HR <110 beats/min) than with stricter HR control (with baseline HR <80 beats/min) and thus questioned a causal role of HR reduction for the observed benefit, at least in quantitative terms.¹³⁵

In conclusion, sustained tachycardia causes HF, baseline HR is increased in HF, and the magnitude of HR reduction in treatment trials of patients with HF is associated with a reduction in mortality. Therefore, HR reduction in HF, particularly when it is associated with atrial fibrillation, is obviously beneficial. Nevertheless, the causal and mechanistic/quantitative role of HR in HF is still largely unclear.¹³⁶ Acute reversal of LV dysfunction along a negative force–frequency relationship probably plays no role. To what extent a more chronic reduction in HR would reverse the alterations in excitation–contraction coupling is as unclear as the causal role of HR in such alterations in excitation–contraction coupling and their causal role for HF. Also, a potential improvement in the energy metabolism of the failing myocardium¹³⁷ in response to reduced HR requires further detailed analysis.

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References

- Heusch G. Heart rate in the pathophysiology of coronary blood flow and myocardial ischaemia: Benefit from selective bradycardic agents. *Br J Pharmacol* 2008; **153**: 1589–1601.
- Whipple GH, Sheffield LT, Woodman EG, Theofilis C, Friedman S. Reversible congestive heart failure due to chronic rapid stimulation of the normal heart. *Proc N Engl Cardiovasc Soc* 1962; **20**: 39–40.
- Riegger AJ, Liebau G. The renin-angiotensin-aldosterone system, antidiuretic hormone and sympathetic nerve activity in an experimental model of congestive heart failure in the dog. *Clin Sci* 1982; **62**: 465–469.
- Armstrong PW, Stopps TP, Ford SE, De Bold AJ. Rapid ventricular pacing in the dog: Pathophysiological studies of heart failure. *Circulation* 1986; **74**: 1075–1084.
- Holmer SR, Riegger AJG, Notheis WF, Kromer EP, Kochsiek K. Hemodynamic changes and renal plasma flow in early heart failure: Implications for renin, aldosterone, norepinephrine, atrial natriuretic peptide and prostacyclin. *Basic Res Cardiol* 1987; **82**: 101–108.
- Wilson JR, Douglas P, Hickey WF, Lanoce V, Ferraro N, Muhammad A, et al. Experimental congestive heart failure produced by rapid ventricular pacing in the dog: Cardiac effects. *Circulation* 1987; **75**: 857–867.
- Shannon RP, Komamura K, Stambler BS, Bigaud M, Manders WT, Vatner SF. Alterations in myocardial contractility in conscious dogs with dilated cardiomyopathy. *Am J Physiol* 1991; **260**: H1903–H1911.
- Moe GW, Angus C, Howard RJ, Parker TG, Armstrong PW. Evaluation of indices of left ventricular contractility and relaxation in evolving canine experimental heart failure. *Cardiovasc Res* 1992; **26**: 362–366.
- Wolff MR, de Tombe PP, Harasawa Y, Burkhardt D, Bier S, Hunter WC, et al. Alterations in left ventricular mechanics, energetics, and contractile reserve in experimental heart failure. *Circ Res* 1992; **70**: 516–529.
- Komamura K, Shannon RP, Ihara T, Shen YT, Mirsky I, Bishop SP, et al. Exhaustion of Frank-Starling mechanism in conscious dogs with heart failure. *Am J Physiol* 1993; **265**: H1119–H1131.
- Rahko PS. Comparative efficacy of three indexes of left ventricular performance derived from pressure–volume loops in heart failure induced by tachypacing. *J Am Coll Cardiol* 1994; **23**: 209–218.
- Yamamoto K, Burnett JC Jr, Meyer LM, Sinclair L, Stevens TL, Redfield MM. Ventricular remodeling during development and recovery from modified tachycardia-induced cardiomyopathy model. *Am J Physiol* 1996; **271**: R1529–R1534.
- Asanai H, Ishizaka S, Joho S, Kameyama T, Inoue H, Sasayama S. Altered inotropic and lusitropic responses to heart rate in conscious dogs with tachycardia-induced heart failure. *J Am Coll Cardiol* 1996; **27**: 728–735.
- Patel HJ, Pilla JJ, Polidori DJ, Pusca SV, Plappert TA, Sutton MSJ, et al. Ten weeks of rapid ventricular pacing creates a long-term model of left ventricular dysfunction. *J Thorac Cardiovasc Surg* 2000; **119**: 834–841.
- Spinale FG, Tomita M, Zellner JL, Cook JC, Crawford FA, Zile MR. Collagen remodeling and changes in LV function during development and recovery from supraventricular tachycardia. *Am J Physiol* 1991; **261**: H308–H318.
- Spinale FG, Fulbright BM, Mukherjee R, Tanaka R, Hu J, Crawford FA, et al. Relation between ventricular and myocyte function with tachycardia-induced cardiomyopathy. *Circ Res* 1992; **71**: 174–187.
- Spinale FG, Tanaka R, Crawford FA, Zile MR. Changes in myocardial blood flow during development of and recovery from tachycardia-induced cardiomyopathy. *Circulation* 1992; **85**: 717–729.
- Park M, Shen YT, Gaussin V, Heyndrickx GR, Bartunek J, Resuello RR, et al. Apoptosis predominates in nonmyocytes in heart failure. *Am J Physiol Heart Circ Physiol* 2009; **297**: H785–H791.
- Masaki H, Imaizumi T, Ando S, Hirooka Y, Harada S, Momohara M, et al. Production of chronic congestive heart failure by rapid ventricular pacing in the rabbit. *Cardiovasc Res* 1993; **27**: 828–831.
- Aker S, Belosjorow S, Konietzka I, Duschin A, Martin C, Heusch G, et al. Serum but not myocardial TNF- α concentration is increased in pacing-induced heart failure in rabbits. *Am J Physiol Regul Integ Comp Physiol* 2003; **285**: R463–R469.
- Schulz R, Aker S, Belosjorow S, Konietzka I, Rauen U, Heusch G. Stress kinase phosphorylation is increased in pacing-induced heart failure in rabbits. *Am J Physiol Heart Circ Physiol* 2003; **285**: H2084–H2090.
- Aker S, Snabaitis AK, Konietzka I, van de Sand A, Böngler K, Avkiran M, et al. Inhibition of the Na^+/H^+ exchanger attenuates the deterioration of ventricular function during pacing-induced heart failure in rabbits. *Cardiovasc Res* 2004; **63**: 273–282.

23. Leineweber K, Aker S, Beilfuss A, Rekasi H, Konietzka I, Martin C, et al. Inhibition of Na⁺/H⁺-exchanger with sabiporide attenuates the downregulation and uncoupling of the myocardial beta-adrenoceptor system in failing rabbit hearts. *Br J Pharmacol* 2006; **148**: 137–146.
24. Heusch P, Canton M, Aker S, van de Sand A, Konietzka I, Rassaf T, et al. The contribution of reactive oxygen species and p38 mitogen activated protein kinase to myofilament oxidation and progression of heart failure in rabbits. *Br J Pharmacol* 2010; **160**: 1408–1416.
25. Heusch P, Aker S, Boengler K, Deindl E, van de Sand A, Klein K, et al. Increased inducible nitric oxide synthase and arginase II expression in heart failure: No net nitrite/nitrate production and protein S-nitrosylation. *Am J Physiol Heart Circ Physiol* 2010; **299**: H446–H453.
26. Finckh M, Hellmann W, Ganten D, Furtwängler A, Allgeier J, Boltz M, et al. Enhanced cardiac angiotensinogen gene expression and angiotensin converting enzyme activity in tachypacing-induced heart failure in rats. *Basic Res Cardiol* 1991; **86**: 303–316.
27. Shinbane JS, Wood MA, Jensen DN, Ellenbogen KA, Fitzpatrick AP, Scheinman MM. Tachycardia-induced cardiomyopathy: A review of animal models and clinical studies. *J Am Coll Cardiol* 1997; **29**: 709–715.
28. Moe GW, Armstrong P. Pacing-induced heart failure: A model to study the mechanism of disease progression and novel therapy in heart failure. *Cardiovasc Res* 1999; **42**: 591–599.
29. Yarbrough WM, Spinale FG. Large animal models of congestive heart failure: A critical step in translating basic observations into clinical applications. *J Nucl Cardiol* 2003; **10**: 77–86.
30. Spinale FG, Holzgrefe HH, Mukherjee R, Arthur SR, Child MJ, Powell JR, et al. LV and myocyte structure and function after early recovery from tachycardia-induced cardiomyopathy. *Am J Physiol* 1995; **268**: H836–H847.
31. Komamura K, Shannon RP, Pasipoularides A, Ihara T, Lader AS, Patrick TA, et al. Alterations in left ventricular diastolic function in conscious dogs with pacing-induced heart failure. *J Clin Invest* 1992; **89**: 1825–1838.
32. Neumann T, Vollmer A, Schaffner T, Hess OM, Heusch G. Diastolic dysfunction and collagen structure in canine pacing-induced heart failure. *J Mol Cell Cardiol* 1999; **31**: 179–192.
33. Solomon SB, Nikolic SD, Glantz SA, Yellin EL. Left ventricular diastolic function of remodeled myocardium in dogs with pacing-induced heart failure. *Am J Physiol* 1998; **43**: H945–H954.
34. Kajstura J, Zhang X, Liu Y, Szoke E, Cheng W, Olivetti G, et al. The cellular basis of pacing-induced dilated cardiomyopathy: Myocyte cell loss and myocyte cellular reactive hypertrophy. *Circulation* 1995; **92**: 2306–2317.
35. Leri A, Liu Y, Malhorta A, Li Q, Stiegler P, Claudio PP, et al. Pacing-induced heart failure in dogs enhances the expression of p53 and p53-dependent genes in ventricular myocytes. *Circulation* 1998; **97**: 194–203.
36. Binkley PF, Nunziata E, Haas GJ, Nelson SD, Cody RJ. Parasympathetic withdrawal is an integral component of autonomic imbalance in congestive heart failure: Demonstration in human subjects and verification in a paced canine model of ventricular failure. *J Am Coll Cardiol* 1991; **18**: 464–472.
37. Chen JS, Wang W, Bartholet T, Zucker IH. Analysis of baroreflex control of heart rate in conscious dogs with pacing-induced heart failure. *Circulation* 1991; **83**: 260–267.
38. Chen JS, Wang W, Cornish KG, Zucker IH. Baro- and ventricular reflexes in conscious dogs subjected to chronic tachycardia. *Am J Physiol* 1992; **263**: H1084–H1089.
39. Grima EA, Moe GW, Howard RJ, Armstrong PW. Recovery of attenuated baroreflex sensitivity in conscious dogs after reversal of pacing induced heart failure. *Cardiovasc Res* 1994; **28**: 384–390.
40. Holtz J, Münzel T, Sommer O, Bassenge E. Sympathoadrenal inhibition by atrial natriuretic peptide is not attenuated during development of congestive heart failure in dogs. *Circulation* 1989; **80**: 1862–1869.
41. Delehanty JM, Himura Y, Elam H, Hood WB Jr, Liang CS. Beta-adrenoceptor downregulation in pacing-induced heart failure is associated with increased interstitial NE content. *Am J Physiol* 1994; **266**: H930–H935.
42. Lee ME, Miller WL, Edwards BS, Burnett JC Jr. Role of endogenous atrial natriuretic factor in acute congestive heart failure. *J Clin Invest* 1989; **84**: 1962–1966.
43. Margulies KB, Hildebrand FL Jr, Lerman A, Perrella MA, Burnett JC Jr. Increased endothelin in experimental heart failure. *Circulation* 1990; **82**: 2226–2230.
44. Juneau C, Calderone A, Rouleau JL. Myocardial beta-adrenergic and mechanical properties in pacing-induced heart failure in dogs. *Am J Physiol* 1992; **262**: H1458–H1467.
45. Kiuchi K, Shannon RP, Komamura K, Cohen DJ, Bianchi C, Homcy CJ, et al. Myocardial beta-adrenergic receptor function during the development of pacing-induced heart failure. *J Clin Invest* 1993; **91**: 907–914.
46. Tanaka R, Fulbright BM, Mukherjee R, Burchell SA, Crawford FA, Zile MR, et al. The cellular basis for the blunted response to beta-adrenergic stimulation in supraventricular tachycardia-induced cardiomyopathy. *J Mol Cell Cardiol* 1993; **25**: 1215–1233.
47. Nikolaidis LA, Sturzu A, Stolarski C, Elahi D, Shen YT, Shannon RP. The development of myocardial insulin resistance in conscious dogs with advanced dilated cardiomyopathy. *Cardiovasc Res* 2004; **61**: 297–306.
48. Kleinbongard P, Heusch G, Schulz R. TNF alpha in atherosclerosis, myocardial ischemia/reperfusion and heart failure. *Pharmacol Ther* 2010; **127**: 295–314.
49. Shannon RP, Komamura K, Shen YT, Bishop SP, Vatner SF. Impaired regional subendocardial coronary flow reserve in conscious dogs with pacing-induced heart failure. *Am J Physiol* 1993; **265**: H801–H809.
50. Neumann T, Heusch G. Myocardial, skeletal muscle, and renal blood flow during exercise in conscious dogs with heart failure. *Am J Physiol Heart Circ Physiol* 1997; **273**: H2452–H2457.
51. Wang J, Seyedi N, Xu XB, Wolin MS, Hintze TH. Defective endothelium-mediated control of coronary circulation in conscious dogs after heart failure. *Am J Physiol* 1994; **266**: H670–H680.
52. Kaiser L, Spickard RC, Olivier NB. Heart failure depresses endothelium-dependent responses in canine femoral artery. *Am J Physiol* 1989; **256**: H962–H967.
53. Wilson JR, Falcone R, Ferraro N, Egler J. Mechanism of skeletal muscle underperfusion in a dog model of low-output heart failure. *Am J Physiol* 1986; **251**: H227–H235.
54. Howell S, Maarek JM, Fournier M, Sullivan K, Zhan WZ, Sieck GC. Congestive heart failure: Differential adaptation of the diaphragm and latissimus dorsi. *J Appl Physiol* 1995; **79**: 389–397.
55. Kääb S, Nuss HB, Chiamvimonvat N, O'Rourke B, Pak PH, Kass DA, et al. Ionic mechanism of action potential prolongation in ventricular myocytes from dogs with pacing-induced heart failure. *Circ Res* 1996; **78**: 262–273.
56. Wang Z, Taylor K, Denney WD, Hansen DE. Initiation of ventricular extrasystoles by myocardial stretch in chronically dilated and failing canine left ventricle. *Circulation* 1994; **90**: 2022–2031.
57. Vatner DE, Sato N, Kiuchi K, Shannon RP, Vatner SF. Decrease in myocardial ryanodine receptors and altered excitation-contraction coupling early in the development of heart failure. *Circulation* 1994; **90**: 1423–1430.
58. Yamamoto T, Yano M, Kohno M, Hisaoka T, Ono K, Tanigawa T, et al. Abnormal Ca²⁺ release from cardiac sarcoplasmic reticulum in tachycardia-induced heart failure. *Cardiovasc Res* 1999; **44**: 146–155.
59. Igarashi-Saito K, Tsutsui H, Yamamoto S, Takahashi M, Kinugawa S, Tagawa H, et al. Role of SR Ca²⁺-ATPase in contractile dysfunction of myocytes in tachycardia-induced heart failure. *Am J Physiol* 1998; **275**: H31–H40.
60. Yao A, Su Z, Nonaka A, Zubair I, Spitzer KW, Bridge JHB, et al. Abnormal myocyte Ca²⁺ homeostasis in rabbits with pacing-induced heart failure. *Am J Physiol* 1998; **275**: H1441–H1448.
61. O'Rourke B, Kass DA, Tomaselli GF, Kääb S, Tunin R, Marbán E. Mechanisms of altered excitation-contraction coupling in canine tachycardia-induced heart failure, I: Experimental Studies. *Circ Res* 1999; **84**: 562–570.
62. Hobai IA, O'Rourke B. Enhanced Ca²⁺-activated Na⁺-Ca²⁺ exchange activity in canine pacing-induced heart failure. *Circ Res* 2000; **87**: 690–698.
63. Hobai IA, O'Rourke B. Decreased sarcoplasmic reticulum calcium content is responsible for defective excitation-contraction coupling in canine heart failure. *Circulation* 2001; **103**: 1577–1584.
64. Perreault CL, Shannon RP, Komamura K, Vatner SF, Morgan JP. Abnormalities in intracellular calcium regulation and contractile function in myocardium from dogs with pacing-induced heart failure. *J Clin Invest* 1992; **89**: 932–938.
65. Ravens U, Davia K, Davies CH, O'Gara P, Drake-Holland AJ, Hynd JW, et al. Tachycardia-induced failure alters contractile properties of canine ventricular myocytes. *Cardiovasc Res* 1996; **32**: 613–621.
66. Neumann T, Ravens U, Heusch G. Characterization of excitation-contraction coupling in conscious dogs with pacing-induced heart failure. *Cardiovasc Res* 1998; **37**: 456–466.

67. Cesseli D, Jakoniuk I, Barlucchi L, Beltrami AP, Hintze TH, Nadal-Ginard B, et al. Oxidative stress-mediated cardiac cell death is a major determinant of ventricular dysfunction and failure in dog dilated cardiomyopathy. *Circ Res* 2001; **89**: 279–286.
68. Heusch G, Schulz R. A radical view on the contractile machinery in human heart failure. *J Am Coll Cardiol* 2010 (in press).
69. Heusch G, Neumann T. Calcium responsiveness in canine pacing-induced heart failure. *J Mol Cell Cardiol* 1998; **30**: 1605–1613.
70. Beuckelmann DJ, Näbauer M, Erdmann E. Intracellular calcium handling in isolated ventricular myocytes from patients with terminal heart failure. *Circulation* 1992; **85**: 1046–1055.
71. Davies CH, Davia K, Bennett JG, Pepper JR, Poole-Wilson PA, Harding SE. Reduced contraction and altered frequency response of isolated ventricular myocytes from patients with heart failure. *Circulation* 1995; **92**: 2540–2549.
72. Toischer K, Lehnart SE, Tenderich G, Milting H, Korfer R, Schmitto JD, et al. K201 improves aspects of the contractile performance of human failing myocardium via reduction in Ca^{2+} leak from the sarcoplasmic reticulum. *Basic Res Cardiol* 2010; **105**: 279–287.
73. Kooij V, Boontje N, Zaremba R, Jaquet K, Dos RC, Stienen GJ, et al. Protein kinase C alpha and epsilon phosphorylation of troponin and myosin binding protein C reduce Ca^{2+} sensitivity in human myocardium. *Basic Res Cardiol* 2010; **105**: 289–300.
74. Helmer GA, McKimman MD, Shabetai R, Boss GR, Ross J Jr, Hammond K. Regional deficits of myocardial blood flow and function in left ventricular pacing-induced heart failure. *Circulation* 1996; **94**: 2260–2267.
75. McLaran CJ, Gersh BJ, Sugrue DD, Hammill SC, Seward JB, Holmes DR Jr. Tachycardia induced myocardial dysfunction: A reversible phenomenon? *Br Heart J* 1985; **53**: 323–327.
76. Packer DL, Bardy GH, Worley SJ, Smith MS, Cobb FR, Coleman RE, et al. Tachycardia-induced cardiomyopathy: A reversible form of left ventricular dysfunction. *Am J Cardiol* 1986; **57**: 563–570.
77. Nerheim P, Birger-Botkin S, Piracha L, Olhansky B. Heart failure and sudden death in patients with tachycardia-induced cardiomyopathy and recurrent tachycardia. *Circulation* 2004; **110**: 247–252.
78. Zwicker C, Becker M, Lepper W, Koch KC, Westenfeld R. Cardiogenic Shock due to tachycardiomyopathy after heart transplantation: Successful treatment with ivabradine. *Cardiology* 2010; **116**: 174–177.
79. Grogan M, Smith HC, Gersh BJ, Wood DL. Left ventricular dysfunction due to atrial fibrillation in patients initially believed to have idiopathic dilated cardiomyopathy. *Am J Cardiol* 1992; **69**: 1570–1573.
80. Neilan TG, Yoerger DM, Douglas PS, Marshall JE, Halpern EF, Lawlor D, et al. Persistent and reversible cardiac dysfunction among amateur marathon runners. *Eur Heart J* 2006; **27**: 1079–1084.
81. Scott JM, Warburton DE. Mechanisms underpinning exercise-induced changes in left ventricular function. *Med Sci Sports Exerc* 2008; **40**: 1400–1407.
82. Sahlén A, Rubulis A, Winter R, Jacobsen PH, Stahlberg M, Tornvall P, et al. Cardiac fatigue in long-distance runners is associated with ventricular repolarization abnormalities. *Heart Rhythm* 2009; **6**: 512–519.
83. Banks L, Sasson Z, Busato M, Goodman JM. Impaired left and right ventricular function following prolonged exercise in young athletes: Influence of exercise intensity and responses to dobutamine stress. *J Appl Physiol* 2010; **108**: 112–119.
84. Bowditch HP. Über die Eigenthümlichkeiten der Reizbarkeit, welche die Muskelfasern des Herzens zeigen. *Arb Physiol Inst Leipzig* 1871; **6**: 139–176 (in German).
85. Ross J Jr. On the first paper in Cardiovascular Research: Frequency, force, and beyond. *Cardiovasc Res* 2007; **75**: 445–447.
86. Buckley NM, Penefsky ZJ, Litwak RS. Comparative force–frequency relationships in human and other mammalian ventricular myocardium. *Pflügers Arch* 1972; **332**: 259–270.
87. Anderson PA, Manring A, Johnson EA. Force–frequency relationship: A basis for a new index of cardiac contractility? *Circ Res* 1973; **33**: 665–671.
88. Lamberts RR, Hamdani N, Soekhoe TW, Boontje NM, Zaremba R, Walker LA, et al. Frequency-dependent myofilament Ca^{2+} desensitization in failing rat myocardium. *J Physiol* 2007; **582**: 695–709.
89. Tan Z, Dai T, Zhong X, Tian Y, Leppo MK, Gao WD. Preservation of cardiac contractility after long-term therapy with oxypurinol in post-ischemic heart failure in mice. *Eur J Pharmacol* 2009; **621**: 71–77.
90. Covell JW, Ross J Jr, Taylor R, Sonnenblick EH, Braunwald E. Effects of increasing frequency of contraction on the force velocity relation of left ventricle. *Cardiovasc Res* 1967; **1**: 2–8.
91. Noble MIM, Wyler J, Milne E, Trenchard D, Guz A. Effect of changes in heart rate on left ventricular performance in conscious dogs. *Circ Res* 1969; **24**: 285–295.
92. Mahler F, Yoran C, Ross J Jr. Inotropic effects of tachycardia and poststimulation potentiation in the conscious dog. *Am J Physiol* 1974; **227**: 569–575.
93. Eising GP, Hammond HK, Helmer GA, Gilpin E, Ross J Jr. Force–frequency relations during heart failure in pigs. *Am J Physiol* 1994; **267**: H2516–H2522.
94. Miura T, Miyazaki S, Guth BD, Kambayashi M, Ross J Jr. Influence of the force–frequency relation on left ventricular function during exercise in conscious dogs. *Circulation* 1992; **86**: 563–571.
95. Ross J Jr. Adrenergic regulation of the force–frequency effect. *Basic Res Cardiol* 1998; **93**(Suppl 1): 95–101.
96. Erbel R, Schweizer P, Meyer J, Krebs W, Braun C, Effert S. Beurteilung der regionalen Myokardfunktion bei koronarer Herzerkrankung mit Hilfe der simultanen Druck-Dimensionsanalyse. *Angiocardiology* 1981; **3**: 132–144 (in German).
97. Hasenfuss G, Holubarsch C, Hermann HP, Astheimer K, Pieske B, Just H. Influence of the force–frequency relationship on haemodynamics and left ventricular function in patients with non-failing hearts and in patients with dilated cardiomyopathy. *Eur Heart J* 1994; **15**: 164–170.
98. Cotton JM, Kearney MT, McCarthy PA, Grocott-Mason RM, McClean DR, Heymes C, et al. Effects of nitric oxide synthase inhibition on basal function and the force–frequency relationship in the normal and failing human heart in vivo. *Circulation* 2001; **104**: 2318–2323.
99. Wachter R, Schmidt-Schweda S, Westermann D, Post H, Edelmann F, Kasner M, et al. Blunted frequency-dependent upregulation of cardiac output is related to impaired relaxation in diastolic heart failure. *Eur Heart J* 2009; **30**: 3027–3036.
100. Mullens W, Bartunek J, Wilson Tang WH, Delrue L, Herbots L, Willems R, et al. Early and late effects of cardiac resynchronization therapy on force–frequency relation and contractility regulating gene expression in heart failure patients. *Heart Rhythm* 2008; **5**: 52–59.
101. Heusch G. Diastolic heart failure: A misNomer. *Basic Res Cardiol* 2009; **104**: 465–467.
102. Allen DG, Blinks JR. Calcium transients in aequorin-injected frog cardiac muscle. *Nature* 1978; **273**: 509–513.
103. Kushnir A, Shan J, Betzenhauser MJ, Reiken S, Marks AR. Role of $\text{CaMKII}\{\delta\}$ phosphorylation of the cardiac ryanodine receptor in the force frequency relationship and heart failure. *Proc Natl Acad Sci USA* 2010; **107**: 10274–10279.
104. Ramirez-Correa GA, Cortassa S, Stanley B, Gao WD, Murphy AM. Calcium sensitivity, force frequency relationship and cardiac troponin I: Critical role of PKA and PKC phosphorylation sites. *J Mol Cell Cardiol* 2010; **48**: 943–953.
105. Prabhu SD, Freeman GL. Effect of tachycardia heart failure on the restitution of left ventricular function in closed-chest dogs. *Circulation* 1995; **91**: 176–185.
106. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, et al. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol* 2007; **50**: 823–830.
107. Ahmadi-Kashani M, Kessler DJ, Day J, Bunch TJ, Stolen KQ, Brown S, et al. Heart rate predicts outcomes in an implantable cardioverter-defibrillator population. *Circulation* 2009; **120**: 2040–2045.
108. Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): The association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet* 2010; **376**: 886–894.
109. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): A subgroup analysis of a randomised controlled trial. *Lancet* 2008; **372**: 817–821.
110. Lechat P, Escolano S, Golmard JL, Lardoux H, Witchitz S, Henneman JA, et al. Prognostic value of bisoprolol-induced hemodynamic effects in heart failure during the Cardiac Insufficiency Bisoprolol Study (CIBIS). *Circulation* 1997; **96**: 2197–2205.
111. Lechat P, Hulot JS, Escolano S, Mallet A, Leizorovicz A, Werhlen-Grandjean M, et al. Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in CIBIS II Trial. *Circulation* 2001; **103**: 1428–1433.

112. Metra M, Torp-Pedersen C, Swedberg K, Cleland JG, Di LA, Komajda M, et al. Influence of heart rate, blood pressure, and beta-blocker dose on outcome and the differences in outcome between carvedilol and metoprolol tartrate in patients with chronic heart failure: Results from the COMET trial. *Eur Heart J* 2005; **26**: 2259–2268.
113. Konishi M, Haraguchi G, Kimura S, Inagaki H, Kawabata M, Hachiya H, et al. Comparative effects of carvedilol vs bisoprolol for severe congestive heart failure. *Circ J* 2010; **74**: 1127–1134.
114. Flannery G, Gehrig-Mills R, Billah B, Krum H. Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure receiving beta-blockers. *Am J Cardiol* 2008; **101**: 865–869.
115. Sabbah HN, Sharov VG, Gupta RC, Todor A, Singh V, Goldstein S. Chronic therapy with metoprolol attenuates cardiomyocyte apoptosis in dogs with heart failure. *J Am Coll Cardiol* 2000; **36**: 1698–1705.
116. Chen G, Zhou X, Florea S, Qian J, Cai W, Zhang Z, et al. Expression of active protein phosphatase 1 inhibitor-1 attenuates chronic beta-agonist-induced cardiac apoptosis. *Basic Res Cardiol* 2010; **105**: 573–581.
117. Leineweber K, Rohe P, Beilfuss A, Wolf C, Sporkmann H, Bruck H, et al. G-protein-coupled receptor kinase activity in human heart failure: Effects of beta-adrenoceptor blockade. *Cardiovasc Res* 2005; **66**: 512–519.
118. Brodde OE. Beta-adrenoceptor blocker treatment and the cardiac beta-adrenoceptor-G-protein(s)-adenylyl cyclase system in chronic heart failure. *Naunyn Schmiedeberg's Arch Pharmacol* 2007; **374**: 361–372.
119. Yamakawa H, Takeuchi M, Takaoka H, Hata K, Mori M, Yokoyama M. Negative chronotropic effect of beta-blockade therapy reduces myocardial oxygen expenditure for nonmechanical work. *Circulation* 1996; **94**: 340–345.
120. Thackray SD, Ghosh JM, Wright GA, Witte KK, Nikitin NP, Kaye GC, et al. The effect of altering heart rate on ventricular function in patients with heart failure treated with beta-blockers. *Am Heart J* 2006; **152**: 713.
121. DiFrancesco D, Camm JA. Heart rate lowering by specific and selective I_f current inhibition with ivabradine: A new therapeutic perspective in cardiovascular disease. *Drugs* 2004; **64**: 1757–1765.
122. Chen PS, Joung B, Shinohara T, Das M, Chen Z, Lin SF. The initiation of the heart beat. *Circ J* 2010; **74**: 221–225.
123. Sata Y, Krum H. The future of pharmacological therapy for heart failure. *Circ J* 2010; **74**: 809–817.
124. De Ferrari GM, Mazzuero A, Agnesina L, Bertoletti A, Lettino M, Campana C, et al. Favourable effects of heart rate reduction with intravenous administration of ivabradine in patients with advanced heart failure. *Eur J Heart Fail* 2008; **10**: 550–555.
125. Fox K, Ford I, Steg PG, Tendera M, Ferrari R. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): A randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **372**: 807–816.
126. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: A subgroup analysis of the randomized, controlled BEAUTIFUL trial. *Eur Heart J* 2009; **30**: 2337–2345.
127. Heusch G. A BEAUTIFUL lesson: Ivabradine protects from ischaemia, but not from heart failure – through heart rate reduction or more? *Eur Heart J* 2009; **30**: 2300–2301.
128. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): A randomised placebo-controlled study. *Lancet* 2010; **376**: 875–885.
129. Heusch G, Skyschally A, Gres P, van Caster P, Schilawa D, Schulz R. Improvement of regional myocardial blood flow and function and reduction of infarct size with ivabradine: Protection beyond heart rate reduction. *Eur Heart J* 2008; **29**: 2265–2275.
130. Heusch G. Pleiotropic action(s) of the bradycardic agent ivabradine: Cardiovascular protection beyond heart rate reduction. *Br J Pharmacol* 2008; **155**: 970–971.
131. Mulder P, Barbier S, Chagraoui A, Richard V, Henry JP, Lallemand F, et al. Long-term heart rate reduction induced by the selective I_f current inhibitor ivabradine improves left ventricular function and intrinsic myocardial structure in congestive heart failure. *Circulation* 2004; **109**: 1674–1679.
132. Van Gelder I, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002; **347**: 1834–1840.
133. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002; **347**: 1825–1833.
134. Ogawa S, Yamashita T, Yamazaki T, Aizawa Y, Atarashi H, Inoue H, et al. Optimal treatment strategy for patients with paroxysmal atrial fibrillation: J-RHYTHM Study. *Circ J* 2009; **73**: 242–248.
135. Van Gelder I, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, et al. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med* 2010; **362**: 1363–1373.
136. Teerlink JR. Ivabradine in heart failure: No paradigm SHIFT yet. *Lancet* 2010; **376**: 847–849.
137. Neubauer S. The failing heart: An engine out of fuel. *N Engl J Med* 2007; **356**: 1140–1151.