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

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. Subsequently, many investigators have used pacing (atrial and ventricular) in dogs, pigs, monkeys, rabbits, and rats to induce HF and characterize various aspects of it (for review see). 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 and

Table. Features of Experimental Pacing-Induced Heart Failure

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>LV dysfunction</th>
<th>Morphology</th>
<th>Systemic consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dymsnea</td>
<td>LVEDV ↑, EF ↓ (echocardiography)</td>
<td>Apoptosis</td>
<td>Catecholamines ↑</td>
</tr>
<tr>
<td>Cachexia</td>
<td>Systolic wall thickening ↓ (sonomicrometry)</td>
<td>Hypertrophy</td>
<td>β-Adrenoceptor desensitization/downregulation</td>
</tr>
<tr>
<td>Ascites</td>
<td>LVEDP ↑, LVP ↓, LV dP/dtmax ↓ (manometry)</td>
<td>Fibrosis</td>
<td>Renin ↑, angiotensin ↑, aldosterone ↑</td>
</tr>
<tr>
<td>Exercise intolerance</td>
<td></td>
<td></td>
<td>Inflammation (TNFα ↑, iNOS ↑)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Coronary, skeletal muscle and splanchnic perfusion ↓</td>
</tr>
</tbody>
</table>

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.
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, ejection fraction, and elastance. The LV is dilated and its preload reserve is exhausted. Diastolic dysfunction also manifests as increased stiffness.

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 and noncardiomyocytes in the failing heart. Fibrosis and increased collagen 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 withdrawal and sympathetic activation, with attenuation of baroreflexes. Plasma levels of catecholamines, renin, angiotensin II, aldosterone, atrial natriuretic peptide, and endothelin are increased. In response to the increased plasma catecholamine levels, myocardial β-adrenoceptor density and signal transduction are decreased. Probable as a consequence of sustained increases in plasma catecholamine levels, a metabolic syndrome with elevated plasma levels of fatty acids and glucose, and with myocardial insulin resistance develops. A generalized proinflammatory status is reflected by increased plasma levels of tumor-necrosis factor-α, which originates, however, not only from the myocardium but also from the congested liver and splanchnic circulation. Inducible nitric oxide synthase is increased locally in the myocardium.

Coronary blood flow and coronary dilator reserve are reduced. Endothelium-dependent dilation is impaired in the coronary circulation, as well as in the skeletal muscles. Accordingly, skeletal muscle perfusion is reduced and there is skeletal muscle atrophy.

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. The failing myocardium is particularly sensitive to stretch-induced ventricular extrasystoles.

Central to the excitation–contraction abnormalities appears to be a dysfunction of the sarcoplasmic reticulum, which is characterized by reduced ryanodine receptor binding and reduced levels of sarcoplasmic ATPase mRNA and protein, as well as phospholamban protein. There is a compensatory increase in sodium–calcium exchange protein and activity, which is, in turn, dependent on the driving...
sodium gradient and consequently the sodium-proton exchanger. The intracellular calcium transient is decreased in amplitude and increased in duration. Single cell shortening and shortening velocity are reduced, as well as the peak tension of isolated trabeculae. Apart from these changes in intracellular calcium homeostasis, there is oxidative protein modification also affecting the contractile machinery, and the calcium responsiveness of myocardium with pacing-induced failure is impaired. The cellular alterations of excitation–contraction coupling in pacing-induced HF resemble those seen in cardiomyocytes from patients with clinical HF. 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. Increased oxidative stress is thought to causally contribute to activation of apoptosis and to the oxidative modification of the contractile machinery.

HF in Patients With Tachyarrhythmia Patients with sustained supraventricular tachyarrhythmia, but without other underlying heart disease, also display typical LV dysfunction and HF, both of which are typically reversible after pharmacological or ablational control of the tachycardia. Biopsy specimens from such patients reveal nonspecific morphological alterations. 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. Apart from LV dysfunction, increased troponin and B-type natriuretic peptide levels and decreased β-adrenergic signal transduction have been reported after prolonged exercise, and terms such as (pseudo-) stunning 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 1871 to report the effects of frequency of stimulation on contractile force. 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. 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. In conscious dogs, positive effects of atrial pacing on LV dP/dtmax isovolumic contraction and contraction velocity. 

In patients with HF and preserved ejection fraction or so-called “diastolic HF”, there is still a slightly positive relationship of LV dP/dtmax to HR, but a blunted frequency–acceleration of LV dP/dtmin.

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, the activity of the sarcoplasmic reticulum and the calcium responsiveness of the contractile machinery, all of which have distinct defects in the failing heart. Oxidative stress may again be of major importance. 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.

**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. 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. Clearly, a number of recent trials on angiotensin-converting enzyme inhibition and β-blockade in patients with HF also suggest an association of the reduction in mortality with the magnitude of HR reduction (for review see). However, β-blockade has other potential effects to attenuate HF (ie, reduce apoptosis and/or improve adrenergic signal transduction), 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 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.

![Figure 3. Relation between atrial pacing rate and left ventricular (LV) dP/dtmax in a control group of patients with normal LV function and in patients with dilated cardiomyopathy (DCM). There is a slightly positive force–frequency relationship in the controls; however in patients with heart failure it is entirely flat.](image-url)
Against this background, reduction of HR by a selective bradycardia agent that acts on the β channel in the sinus node1,121,122 (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.125,126,127 In contrast, in the very recent SHIFT trial, patients with symptomatic HF who 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.129 However, the benefit from ivabradine against myocardial infarction in pigs is largely independent of HR reduction130 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, also with ivabradine, support a causal role for HR reduction in achieving this benefit. However, a recent study of patients with atrial fibrillation, and a majority 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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