The importance of heart rate control in the management of heart failure

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Heart rate is a major determinant of myocardial oxygen demand, coronary blood flow and myocardial performance and affects nearly all stages of cardiovascular disease. The recent literature indicates that an elevated resting heart rate represents a cardiovascular risk factor, independent of currently accepted risk factors and other potentially confounding demographic and physiological characteristics. Elevated heart rate is one of the key findings in acute and chronic heart failure and has been shown to be an important predictor of morbidity and mortality. Ivabradine, an inhibitor of the If channel in the sinoatrial node, reduces heart rate without any effect on cardiac contractility and without lowering blood pressure. The effects of additive heart rate reduction on outcomes in patients with heart failure were tested in the BEAUTIFUL and the SHIFT trial. Results of the BEAUTIFUL trial show that patients with ischemic heart disease and a heart rate above 70 bpm exhibit an adverse prognosis concerning coronary events, however the trial showed no effect with regard to the primary endpoint. However heart rate reduction with ivabradine added to the standard pharmacologic treatment improved the prognosis in the subgroup of CAD patients with reduced left ventricular function and a resting heart rate of more than 70 bpm. Results of the SHIFT trial support the importance of heart-rate reduction with ivabradine for improvement of clinical outcomes in heart failure and confirm the role of heart rate as a risk factor for patients with severe left ventricular dysfunction.

Keywords: Heart rate. Cardiovascular risk factor. Ivabradine. Heart failure.

PATHOPHYSIOLOGY

Under pathophysiological circumstances heart rate becomes relevant in coronary artery disease affecting both sides of myocardial oxygen balance. An increased heart rate contributes to an imbalance by both decreasing supply and increasing demand thereby mortality in cardiovascular disorders such as coronary artery disease, myocardial infarction, and chronic heart failure6-8. Experimental and clinical evidence suggest that sustained elevations in heart rate — irrespective of the underlying trigger — play a direct role in the pathogenesis of atherosclerosis and myocardial injuries, affect initiation and progression as well as the severity of the disease and contribute to precipitation of vascular and myocardial events9-13 (Table 1).

**Table 1**

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<tr>
<th>CONSENSUS RECOMMENDATIONS FOR MEASUREMENT OF RESTING HEART RATE^*</th>
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<tr>
<td>- patient should rest for at least 5 min.</td>
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<tr>
<td>- pulse palpation over a 30 sec. period.</td>
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<td>- palpation in sitting posture.</td>
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<td>- at least two measurements.</td>
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^: adapted from 27.
leading to myocardial ischemia and subsequent angina. With intact coronary circulation, metabolic vasodilation serves to increase coronary blood flow to match an increased oxygen demand. However, in the presence of a severe coronary stenosis, when the autoregulatory capacity of the coronary circulation fails to maintain a normal coronary blood flow any further increase in heart rate (or more precisely, any further reduction in diastolic perfusion time) will compromise coronary blood flow. In the case of regional myocardial ischemia, where a severely stenotic coronary artery is connected via collaterals with an intact coronary artery a typical redistribution (steal) of blood towards the intact coronary artery develops. In addition to such steal phenomenon, the hemodynamic severity of a coronary stenosis is increased at higher heart rate due to increased turbulence. This effect serves to further compromise coronary inflow.

Elevated heart rate at rest is one of the key findings in acute and chronic heart failure and represents a negative prognostic predictor. Neuroendocrine mechanisms, such as increases of sympathetic activity and activity of the renin-angiotensin-aldosterone system, are activated in heart failure and contribute to a progression of ventricular dysfunction. Increased sympathetic activity is associated with a rise of circulating catecholamines - especially norepinephrine - leading to a positive chronotropic stimulation and resulting in accelerated resting heart rate. Such an increase in heart rate may directly affect myocardial performance by alteration of oxygen consumption, reduction of diastolic filling and coronary perfusion by impairment of relaxation and finally proarrhythmic effects. Furthermore, high heart rates per se can cause heart failure. As known from patients with atrial fibrillation and an inadequate heart rate control, a decline in ventricular ejection fraction can occur within days. After control of ventricular rate, gradual improvement of left ventricular function can be achieved in the following weeks and months. Under physiologic conditions the heart exhibits a positive force-frequency relationship (Bowditch-effect) and develops a stepwise rise in contractility when heart rate is accelerated. This positive force-frequency relationship is abolished or even inverted in the failing myocardium. The heart rate-associated impairment of relaxation is especially important in hearts with diastolic heart failure. Diastolic heart failure is characterised by an impaired relaxation and/or decreased compliance of the ventricle while systolic function is largely preserved. Elevated heart rate shortens diastolic duration thereby additionally constrains ventricular filling and compromises the pre-existing relaxation disturbance of these hearts.

THERAPEUTIC APPROACH

Based on the evidence from a multitude of clinical studies and large heart failure trials it is common knowledge that all treatment strategies resulting in heart rate reduction improved prognosis, while those accompanied by an increase in heart rate exhibited adverse effects on survival. The significance of heart rate on mortality was retrospectively addressed in sub-analyses of CIBIS II (bisoprolol), MERIT-HF (metoprolol) and the COMET trial (carvedilol/metoprolol). These large studies enrolled together a total of almost 10,000 patients with advanced systolic heart failure (NYHA class II–IV). The general trend of these three trials clearly demonstrates that high heart rate at rest contributes to poor survival. These experiences are in line with previous studies of ß-blockers and other drugs approved in heart failure therapy, demonstrating greater benefits with higher baseline heart rates (>80 bpm) as well as markedly reduced heart rates (>10 bpm) after drug treatment. However, it remains currently unknown whether or to what extent the benefit from ß-blockers in patients with heart failure is due to heart rate reduction per se or other beneficial effects derived from interrupting maladaptive - ß-signaling pathways (apoptosis, fetal gene expression, Ca2+ handling, etc.). A recent metaanalysis aimed at determining whether the survival benefits of ß-blockade in heart failure is associated to the magnitude of heart rate reduction or ß-blocker dose showed a close relation of outcome with the former, but not the latter. As ß-blockers considerably reduce heart rate (negative chronotropy) they are most appropriate to be compared with ivabradine, an inhibitor of the If(f) channel acting directly on the sinoatrial node. Ivabradine induces a rapid, sustained and dose-dependent reduction of heart rate at rest and during exercise, without significant effects on atrioventricular conduction, left ventricular contraction-relaxation or vascular tissues. Individual experiences with ivabradine can be drawn from case reports dealing with special hemodynamic alterations in heart failure. Patient with acute left ventricular decompensation on adequate heart failure medication developed sinus tachycardia (120 bpm) with dyspnoe under dobutamine infusion in the cardiac care unit. Consequently, ivabradine was carefully titrated orally up to a dose of 15 mg/day to reduce heart rate under ongoing dobutamine therapy. Within 5 days heart rate decreased (-34%) with a striking increase in stroke volume (+40%) accompanied by a simultaneously decrease in systemic and pulmonary vascular resistance. After ivabradine withdrawal hemodynamic values worsened again, but re-administration of ivabradine led to weaning from dobutamine therapy in the next 3 days and subsequent recovery. Considering these effects it is obvious that a
reduction in heart rate could improve the prognosis of heart failure.

§ The BEAUTIFUL study

The first prospective mortality and morbidity study on pure heart rate reduction in patients with heart failure and coronary artery disease was published by the BEAUTIFUL (morBidity- mortality EvAluaTion of the I(f)-inhibitor ivabradine in patients with coronary artery disease and left ventricUlar dysfunction) investigators. This international, multicentric trial was designed as randomized, double-blind, placebo-controlled investigation with 10917 patients enrolled who were afflicted with coronary artery disease and left ventricular dysfunction (EF<40%). The aim of the study was to investigate whether lowering heart rate with ivabradine reduces cardiovascular death and morbidity in these patients. The intervention group was treated with 5 mg b.i.d. of ivabradine with a target dose of 7.5 mg b.i.d. The patients continued optimal background medication: ARB-agents (90% of patients), ß-blockers (87%), Statins (76%). The mean heart rate at entry was rather low (71.6 bpm), the mean ejection fraction of LV (32.4%) was significantly reduced. The primary endpoint comprised a composite of cardiovascular death, admission to hospital for acute myocardial infarction, admission to hospital for new onset or worsening of heart failure and revascularization. The patients were investigated by intention to treat strategy.

Treatment with ivabradine did not reduce the primary composite endpoint compared with standard medical therapy (Fig. 1A). In the subgroup of patients with baseline heart rate higher than 70 bpm (mean 79.2 bpm) ivabradine decreased the risk for fatal and non-fatal acute myocardial infarction (-36%), and the risk of coronary revascularization (-30%) compared with placebo. In contrast to these beneficial results of the subgroup analysis for the vascular endpoint, ivabradine did not improve the morbidity associated with heart failure. A subanalysis of the placebo group of the trial tested the hypothesis that elevated resting heart rate at baseline is a marker for subsequent cardiovascular death and morbidity and confirmed that a resting heart rate >70 bpm is associated with cardiovascular events (Fig. 1B). Patients with elevated heart rates (mean 79.2 bpm) bear higher risks for coronary revascularization (+38%), admission to hospital for myocardial infarction (+46%) or heart failure (+53%), and cardiovascular death (+34%) compared with those with lower heart rates (64.1 bpm). The relatively low baseline heart rate (mean 71.6 bpm) and the small reduction in heart rate (mean 6 bpm) in the BEAUTIFUL study by ivabradine may be an explanation why ivabradine in this study failed to demonstrate improvement in heart failure-related outcomes in patients with stable angina and left ventricular dysfunction. These results may indicate that baseline heart rate possibly due to preexisting ß-blockade was too low that I(f)-channel inhibition was unable to gain further therapeutic impact in these patients.

§ The SHIFT study

The aim of the "SHIFT" was to evaluate the effect of additive heart rate reduction by ivabradine in addition to guideline-based treatment on cardiovascular outcomes, symptoms and quality of life in patients with systolic heart failure. This international, multicentric trial was designed as randomized, double-blind, placebo-controlled investigation with 6558 patients enrolled who were afflicted with left ventricular dysfunction (EFd»35%, ischemic: 68%, non-ischemic: 32%), sinus rhythm (e>70 bpm) and symptomatic heart failure of more than 4 weeks duration (mainly NYHA Stage II-III). The intervention group was treated with an average dose of 6.4 mg b.i.d. of ivabradine on top of...
optimal standard therapy with ACE-I and ARB agents (about 91% of patients) as well as â-blockers (89%) at the highest tolerated dose. 56% of patients on â-blockers were treated with at least 50% of the guideline based target doses and 26% were at target doses despite explicit recommendation to increase doses by the study committee. Predominant reasons reported for patients not receiving target doses were hypotension and fatigue.

Treatment with ivabradine was associated with an average reduction of heart rate of 15 bpm from a baseline value of 80 bpm, which was mainly maintained throughout the course of the trial. Heart rate reduction by ivabradine reduced the risk for the primary composite endpoint of cardiovascular death or hospital admission for worsening of heart failure in the Shift study population by 18% (Fig. 2). This result was mainly driven by hospital admissions for worsening heart failure and occurred within the first 3 months after start of treatment. Moreover heart rate reduction with ivabradine reduced death from heart failure and hospital admissions for worsening heart failure and any other cardiovascular hospital admissions. Cardiovascular mortality was not affected by ivabradine. Corresponding to preceding clinical trials treatment with ivabradine was well tolerated. Fewer serious adverse events occurred in the ivabradine group than in the placebo group. 5% of ivabradine patients had symptomatic bradycardia compared with 1% of the placebo group. Visual side-effects (phosphenes) were reported by 3% of patients on ivabradine and 1% on placebo. A further analysis of the SHIFT data demonstrated that patients with heart rates higher than the mean value (80 bpm) had an increased risk for adverse effects and received greater benefit from ivabradine treatment than those patients with heart rates lower than the median. This finding corresponds to results from â-blocker trials. In patients with systolic heart failure, a continuous relationship between baseline heart rate and adverse outcomes existed. The risk was modified and significantly decreased by heart rate reduction via ivabradine25 (Fig. 3).

At least certain characteristics of the trial leave room for debate. The concomitant â-blocker doses in the study were low. As only 23% of the patients were at target dose and under a half (49%) were receiving 50% or more of the targeted â-blocker dose (despite explicit encouragement by the protocol), the study population rather reflects pattern seen in community practice. Further limitations were a rather low rate of patients...
with devices like implantable cardioverter defibrillators (3%) or cardiac resynchronisation therapy (1%), a low proportion of elderly patients and no patients with atrial fibrillation or flutter. A generalisation of the results to the overall population with chronic heart failure is hardly possible. Consequently the results should be interpreted as the effects of ivabradine in addition to normal clinical practice in the specific population of patients with heart failure and heart rates of 70 bpm or higher, who are unlikely to tolerate the highest dose of a blocker. However the results demonstrated for the first time beneficial effects of additive heart rate reduction on clinical outcomes in patients with chronic heart failure, reduced left ventricular function and a resting heart rate \( \geq 70 \) bpm. Moreover the study confirms that high heart rate is an independent risk factor in heart failure and an important treatment target.

**CONCLUSION**

Clinical and experimental studies support an association between elevated resting heart rate and a broad range of maladaptive cardiovascular effects. Elevated heart rate is one of the key findings in acute and chronic heart failure and has been shown to be an important predictor of morbidity and mortality. Heart rate reduction by \( \beta \)-blockade was shown to reduce mortality and morbidity in heart failure and therefore represents a cornerstone of medical therapy. Despite the high percentage of \( \beta \)-blocker treatment in patients with heart failure therapy, only about one-third of the treated patients are on prescribed \( \beta \)-blocker dose due to side effects and therefore on proper resting heart rate \(^{26}\). Results of the SHIFT trial showed that heart-rate reduction with the I(\( f \)) channel inhibitor ivabradine improves clinical outcomes in patients with chronic heart failure, reduced left ventricular function and a resting heart rate \( \geq 70 \) bpm. Patients with heart rates higher than the mean value (80 bpm) had an increased risk for adverse effects and received greater benefit from heart rate reduction than patients with heart rates lower than the median. SHIFT proved the concept of heart rate reduction as a therapeutic target in heart failure and provided an alternative for the population of patients with heart failure who are unlikely to tolerate the recommended target dose of \( \beta \)-blockers \(^{25}\). Several questions remain currently unresolved. It will be important to learn to what extent resting heart rate should be reduced to gain a benefit for patients with heart failure. Further investigations \(^{27}\) should elucidate whether heart rate reduction alone or together with its specific mode of action (\( \beta \)-blockade, I(\( f \))-channel inhibition, exercise training, etc.) may lead to improved outcome.

**BIBLIOGRAPHY**


Truth is beautiful; and so are some lies.  
EMERSON