Development of heart failure in bradycardic sick sinus syndrome

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Mounting evidence shows that elevated resting sinus rate is an independent predictor of cardiovascular morbidity and mortality in the general population, in elderly subjects, and in patients with myocardial infarction or hypertension. Therefore, a rather slow sinus rate appears to be a protecting factor acting through several mechanisms. The present contribution focuses on the relationship between sinus rate and heart failure. Its major objectives are to discuss whether in patients with heart failure a rather slow heart rate is advisable and whether a sinus bradycardia secondary to sinus node dysfunction can facilitate the development of heart failure.

It has been reported that among patients with left ventricular dysfunction, increased sinus rate was a predictor of cardiovascular death at univariate analysis; however, a multivariate analysis to verify whether sinus rate was an independent predictor of mortality was not performed. Randomized trials carried out by utilizing beta-blockers or amiodarone in patients with heart failure showed that heart rate reduction by these drugs was a marker of their ability to reduce mortality. However, beta-blockers and amiodarone have additional pharmacological effects which interfere with the disease substrate. So, at present, though the results of these trials show that a rather slow sinus rate is advisable, we do not know whether in patients with heart failure sinus rate represents an independent predictor of mortality as in patients with myocardial infarction or hypertension and whether the reduction of sinus rate *per se* is beneficial.

The results of the recent randomized THEOPACE trial showed, for the first time, that in a patient population with symptomatic sinus bradycardia (sinus rate < 50 b/min), an increase in heart rate, induced by DDD pacing or oral theophylline, reduced the incidence of overt heart failure. Therefore, sinus bradycardia seems to play a role in the genesis of heart failure. In a *post-hoc* analysis of the results of this trial it emerged that in the control (not treated) group, the subjects with sinus bradycardia more prone to develop heart failure were those of old age, about 80 years, with organic heart disease and severe chronotropic incompetence. However, this conclusion needs further validation.

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Mounting evidence shows that elevated resting heart rate is a predictor of cardiovascular morbidity and mortality. In fact at multivariate analysis a high sinus rate emerged as an independent predictor of mortality in the general population[1,2], in elderly subjects[3,4], and in selected groups of patients with hypertension[5] or myocardial infarction[6,7]. In the Framingham study[8] the predictive power of heart rate for all-cause mortality was equal to that of smoking and of high systolic blood pressure. Therefore, a rather slow sinus rate appears to be a protecting factor acting through several mechanisms: a decrease in myocardial oxygen demand; an increase in coronary blood flow by prolonging diastolic filling time; an increase in ventricular fibrillation threshold; an antiatherogenic effect.

The present contribution focuses on the relationship between sinus rate and heart failure. Its major objectives are to discuss whether in patients with heart failure a rather slow sinus rate is advisable and whether a sinus bradycardia secondary to sinus node dysfunction can facilitate the development of heart failure.

Is elevated heart rate at rest an independent risk factor among patients with heart failure?

Elevated heart rate is frequently seen in patients with congestive heart failure. It seems to be predominantly the result of increased sympathetic activity and decreased parasympathetic activity. Increased sympathetic tone is one aspect of abnormal neu-

rohumoral activation which has been suggested to play a central role in the progression of heart failure[9,10]. It has been shown that increased plasma noradrenaline levels correlate with elevated sinus rates in patients with heart failure[11]. The level of circulating noradrenaline is directly proportional to the degree of left ventricular dysfunction and is a predictor of mortality[12].

In a recent substudy from the SAVE trial, St. John Sutton et al.[13] reported that, among patients with left ventricular dysfunction (ejection fraction < 40%), increased sinus rate was a predictor of cardiovascular death at univariate analysis; however, in this study a multivariate analysis was not performed. At present, we do not know whether in patients with heart failure, sinus rate represents an independent predictor of mortality, as in patients with myocardial infarction or hypertension. Recently, Maggioni et al.[14] have reported preliminary data from the Cardiac Heart Failure Italian Network project, concerning 2086 patients followed up for 1 year. Multivariate analysis, adjusted for main clinical-epidemiological variables, showed that the following variables were significantly associated with a higher 1-year mortality: age, NYHA functional class, hospital readmission, atrial flutter/fibrillation, creatinine levels and no treatment with ACE-inhibitors. Indeed, heart rate did not emerge as an independent predictor of mortality; however, the study is still ongoing.

Can heart rate be considered a therapeutic target and which are the clinical results of heart rate lowering interventions?

Since elevated heart rate implies metabolic and hemodynamic disadvantages, for clinicians, the most important question is whether lowering sinus rate leads to an improvement in survival in patients with heart failure. Beta-blockers have important effects on sinus rate. In three large trials carried out in patients with heart failure, carvedilol[15], bisoprolol[16] and metoprolol[17] reduced mean sinus rate by 12-14 b/min and decreased all-cause mortality by 34-65% during a follow-up period of 6-12 months. However, the effects of beta-blockers are not only rate-related but are more complex. A decrease in myocardial oxygen consumption and in cardiac noradrenaline levels, antiarrhythmic effects, antiapoptotic effects, an increase in β_1-receptor density, a reversal of ventricular hypertrophy and remodeling may all play a role[18].

Amiodarone as well reduces heart rate and to this purpose a recent retrospective analysis of the GESICA study suggested that heart rate reduction by this drug was a marker of its ability to reduce mortality[19]. GESICA was a randomized trial of amiodarone in severe congestive heart failure. A significant 28% reduction in 2-year mortality was described in the initial study report[20]. Retrospective analysis of survival revealed that mortality was significantly reduced only in patients with a resting heart rate ≥ 90 b/min, while amiodarone did not alter survival in patients with a heart rate < 90 b/min. The investigators stated that elevated heart rate at rest in severe heart failure identifies a subgroup of patients at higher risk and who will particularly benefit from treatment. However, amiodarone, like beta-blockers, shows other pharmacological effects and in particular its antiarrhythmic effect may have contributed to the improved survival. Therefore, the results of these trials show that a rather slow heart rate is advisable, but so far it has not been conclusively demonstrated that slowing of heart rate *per se* has a beneficial effect in patients with heart failure. Since drugs that slow heart rate, such as beta-blockers and amiodarone, have additional pharmacological effects which interfere with the disease substrate, the question whether a reduction in heart rate *per se* is beneficial would require large clinical trials using drugs with purely or at least predominantly bradycardic action; such trials are yet not available.

Can sinus bradycardia facilitate the development of heart failure?

In the literature only few inconclusive data dealing with the relationship between sinus bradycardia and heart failure are available.

The hemodynamic pattern of sinus bradycardia has been scarcely investigated. To our knowledge, only the cardiac index was measured by Samet[21] in a group of 17 patients with sinus bradycardia and a low value was reported (average value, 1.9 l/min/m^2). However, the author did not report how many patients had organic heart disease and how many had heart failure and, therefore, this result appears to be of little use.

Among patients with sick sinus syndrome the prevalence of heart failure is rather high, ranging from 10 to 20%[22-26]. However, being elderly patients, several of these with organic heart disease, it is not possible to draw conclusions on this relationship.

Improvement in symptoms of heart failure, with or without the addition of digitalis, has been reported after pacemaker implantation in patients with sick sinus syndrome[27,28] and pacing is commonly considered an effective treatment for patients with sinus bradycardia and heart failure. However, this evaluation was done in retrospective and uncontrolled studies, which do not allow definitive conclusions to be drawn.

One recent prospective trial[29] suggested that during the long-term follow-up of patients with sick sinus syndrome, the incidence of heart failure was lower in AAI paced patients than in VVI paced ones. However, this only demonstrates that physiological pacing is hemodynamically better than ventricular pacing.

In patients with bradycardia and left ventricular dysfunction or heart failure cardiac pacing increased cardiac output; however, this rise was also observed in patients with normal left ventricular function[30].

Slowing of sinus rate by beta-blocker treatment improves survival in patients with heart failure, but we do not know the effects of this treatment in subjects with sinus node dysfunction. In fact, in the three large trials[15-17] dealing with the prognostic impact of beta-blockers, subjects with sinus rate < 50-60 b/min were excluded.

The recently published THEOPACE study offers, in our opinion, some knowledge on the relationship between sinus bradycardia and overt heart failure[26,31]. In this study 117 patients with symptomatic sick sinus syndrome (age 73 ± 11 years) were randomized to no treatment (control group), DDD rate-responsive pacemaker therapy and oral theophylline, a drug which improves sinus node function[32] and increases sinus rate during long-term follow-up[33-35]. Patients were evaluated for randomization if they met all of the following criteria: 1) age ≥ 45 years; 2) mean resting sinus rate < 50 b/min; 3) symptoms attributable to sinus node dysfunction such as syncope or dizziness and/or easy fatigue or effort dyspnea. The patients were followed up for 48 months (mean 19 ± 14 months). From a clinical point of view, no universally accepted definition of heart failure exists. Due to the design of the THEOPACE study, overt heart failure was defined as the appearance or worsening of dyspnea or peripheral edema requiring hospitalization, and during which the signs of pump failure were present. Minor clinical manifestations of heart failure are difficult to evaluate during a long-term clinical follow-up; therefore, they were not taken into account.

During the follow-up period, 17% of the patients in the no treatment arm, 3% in the theophylline arm and 3% in the pacemaker arm developed overt heart failure. The differences were statistically significant ($p = 0.05$). These results demonstrate, for the first time, that in a patient population with symptomatic sinus bradycardia an increase in heart rate induced by oral theophylline or DDD pacing reduces the incidence of overt heart failure. Therefore, sinus bradycardia seems to play a role in the genesis of heart failure. In a *post-hoc* analysis we investigated the development of overt heart failure in 35 control (not treated) patients[36]. Six developed overt heart failure during the follow-up period and 29 did not. The bradycardic subjects who developed overt heart failure were older (81 ± 4 vs 69 ± 10 years, $p < 0.01$), had a higher prevalence of underlying heart disease (100 vs 48%, $p < 0.02$), and showed a more marked chronotropic incompetence (maximum exercise heart rate 86 ± 12 vs 122 ± 23 b/min, $p < 0.0001$) than those who did not. Very likely, the latter plays a major role. Resting sinus rate, NYHA functional class and left ventricular ejection fraction appeared similar in patients who developed overt heart failure and in those who did not.

These results suggest that in a population of symptomatic sick sinus syndrome patients, sinus bradycardia can facilitate the appearance of overt heart failure and the subjects more prone to develop this complication are those of old age, about 80 years, with organic heart disease and severe chronotropic incompetence. In other patient populations, like subjects with acute myocardial infarction, age emerged as a powerful risk factor for the development of heart failure[37]. This is a pilot investigation which does not allow us to define therapeutic strategies. However, these results seem to suggest that elderly patients with sinus bradycardia, severe chronotropic incompetence and organic heart disease, even without left ventricular dysfunction, should be periodically checked for the possible appearance of overt heart failure.

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