such as beta-blockers and some calcium-antagonists with electrophysiological activity, also reduce heart rate. Therefore, could heart rate reduction be the simple explanation for the amazing results of ‘complicated’ large clinical trials on mortality?

Thus, let’s bring back heart rate — not only as a risk factor for cardiovascular patients (and the general population) — but also as a specific therapeutic target for ischaemic heart disease, heart failure and hypertension.

For this to be meaningful, the concept of heart rate is proposed to you in modern terms in all the topics of this *European Heart Journal Supplement*. We hope you enjoy reading this Supplement as much as we enjoyed preparing it. All the papers have been peer-reviewed and we would like to thank Roche for making this supplement possible.

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**Sympathetic overactivity and exercise intolerance in heart failure: a cause–effect relationship**

See page 880 for the article to which this Editorial refers

During the past 15 years a large amount of new data has been collected on the behaviour of the sympathetic nervous system in congestive heart failure. In most studies two main methodological approaches have been used to quantify adrenergic cardiovascular influences, i.e., (1) radiotracer-derived measurement of noradrenaline spillover, reuptake and clearance in the systemic circulation as well as in the main cardiovascular regional districts and (2) direct recording of efferent post-ganglionic sympathetic neural discharge to skeletal muscle vessels. These approaches have allowed the studies to establish that the state of sympathetic overactivity characterizing the heart-failure syndrome (1) is an early phenomenon in the clinical course of the disease, an increase in sympathetic nerve traffic being clearly detectable not only in patients belonging to the New York Heart Association functional class III or IV, but also in those belonging to the New York Heart Association class I or II[1,2], (2) involves cardiovascular districts such as the coronary, the renal, the cerebral and the muscular[1–4], the only exception to a rather generalized sympathetic activation being represented by an unchanged sympathetic neural outflow to the cutaneous circulation[5,6], (3) is inversely related to haemodynamic indexes of the myocardial inotropic state, such as cardiac stroke volume or stroke work, and (4) is usually coupled with, and probably caused by, a profound dysfunc-

Conclusive evidence has also been provided on the pathophysiological and clinical relevance of this phenomenon. Although initially representing a compensatory mechanism which allows tissue perfusion and cardiac output to be maintained, sympathetic overactivation with disease progression aggravates the heart failure condition by a number of adverse cardiovascular effects[7,8]. These include (1) an increase in the oxygen and metabolic demands of the myocardium, (2) a reduction in the myocardial oxygen supply, (3) augmented sodium and water reten-

The study by Notarius and co-workers[11], published in this issue, expands this evidence by showing that in heart failure sympathetic overactivation also contributes to the exercise intolerance that is a common hallmark of this condition. In the study’s population, oxygen consumption at peak exercise was inversely related to resting muscle sympathetic nerve
traffic, i.e., the greater the sympathetic activation the more limited was the exercise capacity.

Two additional results of the study by Notarius and co-workers need to be underscored. The first result refers to evidence that the significant correlation between resting sympathetic nerve traffic and peak oxygen consumption holds only in heart failure patients and that no relationship between the two parameters can be observed in individuals with normal cardiac function. The second is represented by the fact that the above-mentioned relationship was independent of left ventricular impairment. This emphasizes that the sympathetic overactivation that occurs in heart failure may carry a pathophysiological significance in that it is related to but also partly independent of the heart failure severity.

The intriguing results of the study by Notarius and co-workers raise a number of questions worthy of further investigation. First, is the relationship between sympathetic activity and reduced exercise tolerance specific to muscle sympathetic outflow (as the hypothesis prompted by the authors would imply) or does it hold true also when adrenergic tone is evaluated in other districts, such as the cardiac one? To answer this question (which would clarify whether more than a sympathetic-dependent abnormality of skeletal muscle circulation during exercise is involved) measurements of regional noradrenaline spillover are required. Second, because in heart failure patients there is a close relationship between sympathetic activation and baroreflex impairment, is this impairment responsible for exercise intolerance? Finally, can we assume that the improvement in exercise capacity induced by some cardiovascular drugs employed in heart failure treatment is related to the ability of these drugs to cause sympathoinhibition? In this context the authors properly emphasize that in heart failure the two effects are usually not strictly time-related, i.e., that at least when it is caused by drugs such as digitalis and angiotensin-converting enzyme inhibitors and beta-blockers, sympathetic deactivation precedes the occurrence of the increase in exercise capacity. This concept is also strengthened by the evidence that some drugs that improve exercise tolerance (e.g., hydralazine) do not reduce and may even increase sympathetic activity of congestive heart failure patients, at least when evaluation of the adrenergic function is based on plasma noradrenaline values.