generally, evidence that a technology is merely effective can no longer be considered sufficient to justify adoption in a world increasingly conscious that health care resources are strictly finite.

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In the treatment of heart failure, faster may not always be better

See doi:10.1053/ehuj.2001.3078 for the article to which this Editorial refers

The paper ‘Defining the optimum upper heart rate limit during exercise — a study in pacemaker patients with heart failure’ by Kindermann et al. addresses a clinically relevant issue[1]. Basic physiology informs us that maximal exercise capacity is a function of stroke volume, heart rate and the arteriovenous oxygen difference[2]. In patients with heart failure the ability to increase stroke volume is markedly attenuated at an early stage and therefore cardiac output largely becomes a linear function of the increase in heart rate during light to moderate exercise[3]. An adequate chronotropic response is imperative in heart failure, but can it be too much of a good thing?

Decisions regarding the optimal programme in heart failure patients with chronotropic incompetence and rate-responsive pacemakers are largely empirical and there is little data on which to base decisions in the individual patient. The recently published ACC/AHA guidelines for exercise testing[4] emphasize the role of assessing the exercise response in patients with adaptive rate pacing using various physiological sensors. The guidelines cite several references addressing this issue[5,6] and recommend that patients undergo a 6-min walk test in order to assess the increase in heart rate during routine exercise and to permit fine-tuning of the rate adaptive programme[7]. Both the maximal attainable heart rate and the rate of increase of heart rate may be adjusted in rate-responsive pacemakers. The need for optimal programming has become even more topical as more patients with serious heart failure are treated by biventricular pacing. Additionally, beta-blockers, which are now routinely recommended in heart failure, have potent negative chronotropic effects and may increase pacemaker dependency.

Kindermann and his associates deserve praise for focusing our attention on the need for objective measurements that guide clinical decisions. The study attempts to define the optimum upper heart rate during exercise in 49 pacemaker patients with and without left ventricular systolic function. Two groups were recruited with ejection fractions >55% or <45%. Chronotropic incompetence was defined as a heart rate increase of less than 2 beats . min . ml . kg . min during cardiopulmonary exercise testing without the rate responsive function of the pacemaker activated.

Two methodologies were employed: maximal cardiopulmonary exercise testing and exercise Doppler...
echocardiography using a continuous ramp protocol of 15 Watt min⁻¹. The optimum heart rate was defined as the pacing rate, which still produced an increase in oxygen consumption or was linked to the lowest value for the Doppler-derived myocardial performance index (Tei index[8] and Z ratio[9]). The results indicate that in patients with preserved systolic function (EF>55%), the optimum rate was 86% of the age-predicted maximum heart rate whereas the corresponding rate was 75% in patients with evidence of left ventricular dysfunction (EF<45%). Importantly, the majority of the patients (71%) had optimum upper heart rate limits that were below the maximum pacing rates programmed for peak exercise. This means that there was a failure to increase oxygen consumption despite an increasing workload and increasing pacing rate.

However, a critical view of the authors’ conclusions is appropriate. Right ventricular pacing results in transmyocardial, asynchronous depolarization. This leads to complex mechanics and variable ventricular activation sequences, especially in patients with coronary artery disease and regional wall motion abnormalities. The reader will be more impressed with the gas exchange results in the study in that cardiopulmonary exercise testing reflects the physiology at the level of exercising skeletal muscle. Oxygen consumption is, after all, the most relevant measurement and directly relates to an individual’s ability to perform work. The reported echo/Doppler data provides interesting mechanistic information but does not directly indicate improved exercise capacity.

Systolic and diastolic echo/Doppler indices are derived measurements that are clearly influenced by the haemodynamics and structural state in individual patients. Ischaemia, hypertrophy, diastolic dysfunction, regional wall motion abnormality, valvular dysfunction and conduction abnormalities will all importantly affect systolic and diastolic time intervals and these changes may or may not be compensatory. Interpretation of these indices is complicated and fraught with potential pitfalls. Indeed in this study neither the Tei index or the Z ratio was able to differentiate between patients with or without left ventricular dysfunction. In contrast, there was a marked difference with regard to oxygen consumption both at peak exercise and at the anaerobic threshold between the two groups (see Table 3 in the paper).

It should also be noted that the patients with moderate systolic dysfunction and an ejection fraction <45% comprised a rather small sample (18 Patients) with various pacing modes (VVI, AAI, DDD). This does somewhat limit the applicability of the results to the heterogeneous population with symptomatic heart failure. The authors should have reported the peak respiratory exchange ratios (VCO₂/VO₂) as further evidence that peak exercise was achieved and effort was maximal. Lactate production during exercise, albeit slightly invasive, would also have provided the investigators with a sensitive method to detect the onset of anaerobiosis during submaximal exercise.

What are the practical implications of these results? If the maximal pacing rate is programmed too low, exercise capacity will be further impaired. Conversely, excess tachycardia will not be productive and is potentially harmful, especially in patients with symptomatic ischemic heart disease. It is not in the patient’s interest to have a programme that is too responsive or leads to an excessive chronotropic response that no longer provides a haemodynamically useful increment in heart rate or increase in exercise capacity. There is clearly a clinical need for a simple tool that would readily permit the physician to optimize the pacemaker programme in the individual patient with heart failure. The most realistic candidate in practice would be a 6-min walk test. Based on Kindermann’s study, it would appear that the optimal rate-adaptive programme in patients with evidence of left ventricular dysfunction should be modestly adjusted to a level approximately 10% lower than in patients with preserved ejection fraction. This study does not provide information about fine-tuning the programme in truly symptomatic patients with substantial LV dysfunction and this would be a fruitful avenue for future research.

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Eur Heart J, Vol. 23, issue 16, August 2002
D-dimer and platelet aggregation and peripheral arterial disease

See doi:10.1053/euhj.2001.3116 for the article to which this Editorial refers

‘Intermittent claudication has been considered to be a surgical disease . . .’. When cardiologists write about peripheral arterial disease there are always political and tactical as well as scientific issues. Intermittent claudication is the mildest symptom of peripheral arterial disease. In most parts of Europe patients with peripheral arterial disease are referred to a peripheral arterial surgeon because, over the years, improvements of intermittent claudication have been in part surgical. More recently endovascular management has become possible and intermittent claudication is frequently managed by vascular surgeons with an endovascular interest as well as by radiologists and cardiologists.

Intermittent claudication is now regarded somewhat differently. As a mild symptom of peripheral arterial disease, the presenting symptom heralds the opportunity to examine the whole patient and to consider more urgent arterial diseases of the coronary and carotid arteries. A ‘pecking order’ of arterial diseases has emerged and the risk of death from coronary artery disease is at the top. The second commonest cause of sudden death is stroke mainly from carotid artery disease, and aortic aneurysm rupture is third.

Intermittent claudication seldom progresses to amputation but as a marker of arterial disease elsewhere in the body intermittent claudication is seen as an trigger for investigating other aspects of the patient. Nevertheless the patient arrives complaining of pain in the calf on walking and that is what the patient wants to hear about during consultation.

Turning to correlation issues with mild peripheral arterial disease, these authors [70773] are to be congratulated on examining factors associated with thrombotic events in patients with peripheral arterial disease. They have demonstrated that D-dimer and low platelet aggregation are independently associated with the risk of thrombotic events. The authors are right to draw attention to the 26% incidence of mortality from thrombotic events and the high rate of vascular events during the observational period. They declare that ‘thrombosis accompanying atherosclerosis is the most important mechanism by which arteries become occluded’. The authors’ discussion of their findings indicates their thinking. They declare an uncertainty as to whether the hyper-coagulable state is a cause or a consequence of arterial disease. They recognize that much of the activation of blood coagulation is secondary to vascular disease predisposing the individual to further development of atherosclerosis and thrombosis. The authors explain that their results, which demonstrate that plasma concentration of D-dimer, a breakdown product of cross-linked fibrin, exceeded the expected upper limit of normal levels in patients with peripheral arterial occlusive disease. They emphasise that D-dimer level in circulating blood depends not only on fibrin formation but also on fibrinolytic activity and go on to say that a raised D-dimer level indicates the presence of active fibrinolysis. I think the authors ought more clearly to state that they have found a correlation but the significance of the finding is far from clear, or the order of events and cause and effect is not established therefore the significance of it is in question and requires further elucidation. Certainly D-dimer relates to thrombotic events in the future and has also been shown to be predictive of stroke and myocardial infarction in other studies, but the sequence of events of cause and effect are less obvious.