LETTERS TO THE EDITOR

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Atrioventricular dromotropathy: an important substrate for complete resynchronization therapy

We read with great interest the article by Salden *et al.*[1] that explored the effect of pacing therapy on atrioventricular (AV) dromotropathy. This work demonstrates haemodynamic improvement in cardiac output after restored AV coupling in a crystal clear fashion. The improved left ventricular stroke volume is related to an increased ventricular filling and reduced late diastolic mitral regurgitation.

These results and data from previous clinical trials[2,3] imply that biventricular (BiV) pacing might benefit patients with heart failure (HF) and prolonged PR interval. However, in our clinical experience, the long PR interval is not always associated with left-sided AV uncoupling. No data are provided on mechanical AV delay or uncoupling among the patient population in the present study. As only 19 out of 22 patients showed acute improvement of cardiac function after BiV pacing, it would be interesting to know whether the absence of mechanical AV delay was the reason for the lack of benefit in all patients. Could we speculate that identifying mechanical AV delay is of greater importance than the sole assessment of electrical AV delay derived from PR interval?

The prolonged PR interval is associated with an increased risk of developing atrial fibrillation and HF.[4] Mechanical AV delay causes temporal fusion of left atrial (LA) conduit and booster pump phases, prolongation of reservoir phase, and additional LA volume overload due to diastolic mitral regurgitation. In the present study, mean LA pressures did not significantly differ between prolonged and normal AV delay groups in a porcine model. However, do the authors have any data on the HF patient population's LA volumes and pressures? Namely, the LA unloading after restored AV coupling could be the mechanism behind the long-term beneficial effects of BiV pacing in this patient population.

Finally, the present study showed that marked ventricular dyssynchrony caused by right ventricular pacing hampers the haemodynamic benefits of restoring AV coupling. While BiV pacing increased cardiac pump function in this study, it still relies on two non-physiological wavefronts, thus inducing some degree of ventricular dyssynchrony. In fact, BiV pacing is harmful in patients with narrow QRS.[5] Since the mean baseline QRS duration in the present study was 128 ± 25 ms, it remains to be answered whether the beneficial effects of restoring AV coupling overcome the detrimental effects of inducing ventricular dyssynchrony in the long term. On this topic, what do the authors think of the interest of conduction system pacing?

Conflict of interest: none declared.

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Atrioventricular dromotropathy: an important substrate for complete resynchronization therapy—Authors' reply

Mežnar *et al.*[1] commented on our publication on the effect of biventricular pacing in patients with long PR interval and no Class I indication for cardiac resynchronization therapy.[2] They mention that in their clinical experience a long PR interval is not always related to left-sided atrioventricular (AV) uncoupling. Of course, this is possible if inter-atrial conduction is slow. However, in the present cohort, we found only three patients not responding haemodynamically to biventricular pacing (i.e. 85% of the cohort showed haemodynamic improvement). Interestingly, the three non-responders did not show fusion of the transmitral E- and A-waves at baseline and had a longer baseline E–A interval compared to responders (253 ± 81ms vs. 83 ± 119ms, respectively), indeed suggesting a role for actual mechanical AV delay. Therefore, the left ventricular (LV) filling pattern at baseline may be important for selection of patients with long PR for pacemaker therapy. Of course, a larger study is needed to support this hypothesis.

The point the authors raise about left atrial (LA) pressure is highly relevant. Indeed, elevated LA pressure has important clinical implications, such as higher risk for development of atrial fibrillation as well as lung oedema and congestion. We addressed LA pressure in several ways: in the animal studies we observed that at optimal AV delay of BiV pacing LV end diastolic volume (LVEDV) was larger while mean LA pressure was similar to baseline, due to the optimal timing of LA vs. LV contraction: larger forward flow and less mitral regurgitation. The latter two improvements were also observed in

the patients, but in patients we did not measure LA pressure due to unacceptable invasiveness of that procedure.

The best control of mechanical AV delay was present in the computer simulations. In the simulations performed in the present study default right atrial (RA)–LA delay was 30 ms, so that actual LA–LV mechanical delay was effectively 30 ms shorter than the programmed A–LV 'stimulation' delay. The effect of larger RA–LA delay and, hence, smaller mechanical LA–LV delay has been studied in a recent, yet unpublished study from our group. It was shown that an increase in RA–LA conduction time indeed resulted in a shorter optimal AV delay. However, the shift towards shorter optimal AV delay was consistently smaller than the increase in inter-atrial conduction delay (i.e. a 28 ms decrease of optimal AV delay at a 40 ms increase of inter-atrial conduction delay). Therefore, we think that inter-atrial conduction delay has only a limited modulating effect on the optimal AV delay and haemodynamic effect. A yet unstudied factor that may be of importance is the role of myocardial stiffness on the response to AV delay optimization in those patients. Theoretically, larger stiffness leads to smaller volume effects at similar changes of diastolic pressures. As a result, haemodynamic response to AV optimization may be reduced in stiffer hearts, but further studies are required.

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Heart rate, exercise capacity, and the force–frequency relationship in chronic heart failure

We read with interest the article by Proff *et al.*[1] exploring the effects of closed-loop stimulation (CLS) in patients with mild left ventricular systolic dysfunction (LVSD), cardiac resynchronization devices, and severe chronotropic incompetence (defined as age-predicted maximum heart rate <75% and/or <50% heart rate reserve). The authors are to be congratulated for tackling a research question in an area where most feel the answers are already known.

Despite adjusting the response of the CLS algorithm which uses right ventricular contractility to increase heart rate to patient perception and device diagnostics there was no overall change in gas exchange variables, quality of life, activity status index, mental attention, or 6-min walk distance despite an increase in peak heart rate of 13 ± 9 beats per minute. *Prima facie* this neutral result is in line with most publications, except where more personalized approaches were used.[2–5] Most importantly, these data serve to remind us how little we understand about the most basic of exercise variables: heart rate, and how it relates to exercise capacity.

First, our approach to the diagnosis of chronotropic incompetence is simplistic, binary, and physiologically improbable. If we believe that heart failure with reduced ejection fraction (HFrEF) *causes* a limitation to heart rate rise during exercise, and that this contributes to exercise intolerance, it is illogical to employ an arbitrary cutoff. Even more dubious is to base treatment, specifically the target heart rate on any variable that does not take into account either resting left ventricular function or how this changes at different heart rates. The effect of heart rate rise on contractility, as determined by the force–frequency relationship (FFR) is highly variable between individuals. For instance, the FFR might be less abnormal in those with less severe LVSD, plausibly supporting the findings of the 'responder' analysis in which there was a reduction in the V_E/V_{CO_2} slope in a subgroup with mostly mild LVSD (mean ejection fraction 46 ± 3%) and Class II symptoms (88%).

Second, the relevance of the FFR extends to the endpoints that were chosen and how we interpret *changes* in these variables. Once one accepts that in the presence of an attenuated FFR in HFrEF, in which contractility is reduced and the heart rate at which peak contractility occurs is lower, increasing heart rate could lead to deteriorating heart function, whilst *reducing* cardiac output. Furthermore, 'time on the treadmill' or 'distance covered' might be more accurate assessments, considerably easier to measure and more relevant to patients.

Hence the data presented are important and take us closer to clarifying how we should (and should not) modulate heart rate during exercise in HFrEF and is a start to linking this to individual cardiac function. Current automated algorithms, however, cannot incorporate the variability required to provide optimal heart rate rise for individuals and a further degree of personalization is likely to be required. Whilst we work towards this, accepting the disadvantages of higher heart rates, we must consider the potential risks of indiscriminate utilization of rate-response algorithms which could adversely affect heart function and shorten battery longevity whilst not improving exercise capacity or outcomes.

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