Is the rapidly paced pig the optimal model for endocardial cardiac resynchronization therapy?

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Long-term outcome of transvenous pacemaker implantation in infants: a retrospective cohort study

In the *Europace* April 2017 issue, Vos *et al.*[1] reported long-term follow-up of infants and neonates receiving transvenous pacemaker systems. From their seven patients, they derived the conclusion that epicardial pacing should be favoured in this age group. The authors have to be congratulated on reporting these honest results. Their 15-year long-term follow-up is remarkable. From this long follow-up, we see terrible foreseeable and preventable problems occurring. Authors underlined that as most complications occurred only late in follow-up, most complications might not have been seen yet. One can easily imagine that lifespan follow-up will create even worse outcomes. To emphasize the message of this article, lessons learned from lead extraction and atrioventricular valve insufficiency must be put forward.

Transvenous pacing in the adult population is associated with acceptable long-term risks. Nevertheless, even in big adults with big vessels, long-term transvenous pacing expose to lead-related adverse events such as lead failure, venous occlusion, multiple leads, endocarditis, and atrioventricular valve insufficiency. These events often mandate complex extraction procedures and sometimes extensive venous reconstructive surgery with significant morbidity and costs.[2] Venous occlusion is even more common and extensive in the paediatric population with long-term consequences that are often not amenable to surgery and lead extraction risks are higher with long indwell lead time.

Regarding endocarditis, Vos *et al.* reported none in their cohort, but this is likely to change over a lifespan follow-up. Interestingly enough, epicardial pacing was recently proposed as a cost-effective approach in adults with lead-related endocarditis.[3] Epicardial pacing is a proven technology and paediatric patients should be considered for this approach.

Regarding atrioventricular valve insufficiency, it is recognized as a difficult problem to address both in kids[4] and adults, for which no perfect solution is offered.[5]

Epicardial pacing should not be perceived as a last resort procedure. Paediatric cardiovascular societies should recommend against the use of transvenous pacemaker in infants. Industry is asked to contribute to dealing with this difficult patient population by developing better tools for a less invasive approach to epicardial pacing. New smaller leadless technologies will be developed and may also be feasible in infants in the future. Magnetic resonance imaging compatible epicardial leads should also be developed.

Conflict of interest: none declared.

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Response to letter to the editor from F. Jacques *et al.*

We would like to thank colleagues Jacques *et al.*[1] for their valuable additional comments. We fully agree that the problems we currently encounter in transvenous pacing in infants are only the tip of the iceberg of long-term complications in this patient group. Our article focusses on a small group of neonates/infants who received a transvenous pacemaker system and have the greatest risk for long-term complications.[2] Unfortunately, in daily practice we encounter the complications mentioned by Jacques *et al.* in a significant proportion of our complete paediatric pacemaker population. Regarding pacemaker therapy in children in general we have to conclude that there is no satisfactory long-term solution available to date. This has to be kept in mind at all times when pacemaker implantation is considered. When the indication for pacemaker implantation is established, we agree that epicardial pacemaker placement is an excellent and often preferable alternative in the paediatric population. However, one major disadvantage in patients with congenital heart disease is that magnetic resonance imaging scanning is absolutely contraindicated due to heating of the leads, especially when disconnected.[3] Therefore, technical improvement of both transvenous as well as epicardial pacemaker leads is urgently needed to improve long-term outcome of the paediatric patients.

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Is the rapidly paced pig the optimal model for endocardial cardiac resynchronization therapy?

Current endocardial cardiac resynchronization therapy (CRT) is performed predominantly in non-responders to CRT.[1] Previous clinical,[2] preclinical,[3] and simulation[4] comparisons found

endocardial CRT offered a more physiological and rapid activation pattern to epicardial CRT. In contrast the study by Amorós-Figueras *et al.*[5] found endocardial pacing induced similar haemodynamic changes to epicardial pacing in a porcine animal model of right ventricular (RV) pacing induced non-ischaemic cardiomyopathy. While these results are interesting, highlighting the need to identify the optimal pacing site for both epicardial and endocardial CRT, the choice of animal and disease model may limit clinical translation. Specifically, the study was performed in pigs without left branch bundle block, as found clinically or in canine studies where the Purkinje network is ablated. The resulting cardiomyopathy confounds both rapid pacing induced and dyssynchronous heart failure making it a distinct pathological model from the conventional clinical case. The degree of wave-front fusion may also confound results. Pigs have a short PR interval (50–120 ms),[6] close to the atrioventricular (AV) delay (80/110 ms) used in the study thus slow transseptal conduction may produce significant left ventricular activation through the intact Purkinje network. Porcine models have not been used to study CRT previously partly due to differences in Purkinje network compared with humans. The finding of no-difference between endocardial and epicardial CRT in the current pig heart model[4] is consistent with previous work in sheep. The contrast between undulates (pigs/sheep) and canine or human studies may reflect a deeper penetrating Purkinje network in sheep and pigs, potentially facilitating retrograde activation during epicardial pacing reducing the difference in activation pattern with endocardial pacing.[5] While the authors should be commended for beginning the development of a porcine model of dyssynchronous heart failure, ensuring the activation pattern and resulting cardiomyopathy closely match the clinical case will be crucial for using these results to inform clinical decisions.

Conflict of interest: none declared.

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Is the rapidly paced pig the optimal model for endocardial cardiac resynchronization therapy?—Authors' reply

We very much appreciate the insightful letter by Niederer *et al.*[1] about our recent publication in *Europace*.[2] Most of the scientific evidence supporting the hypothetical superiority of left ventricular endocardial pacing comes from animal studies using canine models or simulation studies also based on this model.[3] Unfortunately, these results have not been reproduced in clinical studies. The large multicentre prospective human trial ALternate Site Cardiac ReSYNChronization (ALSYNC), which included only patients who had failed or were unsuitable for conventional cardiac resynchronization therapy (CRT), showed that the rate of responders to endocardial pacing was similar to the rate of responders to classical CRT.[4] Furthermore, a recent meta-analysis and systematic review of the literature reports not superior, but comparable, response rate of endocardial CRT vs. conventional epicardial CRT.[5] We have developed a new swine model of heart failure and dyssynchrony. The results of our study using this model are in accordance with clinical studies. Our model has specific characteristics that mimic more accurately those of patients with advanced cardiomyopathy, thus explaining the results. First, studies in humans with heart failure and advanced myocardial disease have demonstrated damage of the distal Purkinje network and conduction remodelling.[6] These changes result in slower conduction velocities at the level of the human diseased endocardium not much different to the conduction velocities of the epicardium. The Purkinje distribution of swine determines similar endocardial and epicardial conduction velocities. Additionally, although no left bundle branch block was produced, the certain degree of intraventricular conduction defect present in the electrocardiogram of our model suggests conduction remodelling. These circumstances together resemble the scenario present in the diseased dilated human heart. Canine models based on proximal damage of the left bundle branch probably preserve a distal Purkinje network integrity and conduction pattern that is far from the conditions present in most patients. Second, we achieved maximal dyssynchrony in the model by pacing from the right ventricle at the top of a much dilated heart, improving the interpretation of the results of resynchronization from different sites. Finally, our animals showed, after induction of the model, a marked prolongation of the PR interval, from 80–114 ms baseline to 126–146 ms (min–max). Therefore, selecting an AV interval of 80 and 110 ms during CRT was appropriate, disregarding the possibility of slow transseptal conduction that could altered the results. Although any animal disease model has its own limitations, we think that our model is a valid model for CRT research and its results of entire clinical application. Obviously, current understanding of the mechanisms involved in endo-epicardial pacing in CRT is still incomplete and warrants further research.

Conflict of interest: none declared.

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