In silico experiments explain the non-consistent benefit of conduction system pacing over cardiac resynchronization therapy. The need to personalize therapy.

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Editorial comment to: *"The Effect of Scar and His-Purkinje and Myocardium Conduction on Response to Conduction System Pacing"* by Marina Strocchi, Karli Gillette, Aurel Neicd, Mark K. Elliott, Nadeev Wijesuriya, Vishal Mehta, Edward J. Vigmond, Gernot Plank, Christopher A. Rinaldi and Steven A. Niederer.

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Short title: Need to personalize resynchronization therapy**.**

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Conduction system pacing (CSP) has emerged as an alternative treatment for patients with indication for cardiac resynchronization therapy (CRT). As opposed to biventricular CRT (BIV-CRT), which is based on left epicardial stimulation, CSP aims to restore the conduction through the His-Purkinje system pacing distally to level of block. Randomized evidence with His bundle pacing (HBP)(1–3) and left bundle branch pacing (LBBP)(4,5) is not extensive compared with the available BIV-CRT data. Non-inferiority of CSP as compared to BIV-CRT has been proven in a randomized trial (LEVEL-AT)(4); furthermore, the LBBP-RESYNC trial(5) has shown greater left ventricular (LV) ejection fraction improvement with LBBP versus BiV-CRT in non-ischemic patients with left bundle branch block (LBBB).

Randomized studies are currently underway to compare CSP with BIV-CRT and determine the superior technique. However, superiority in all clinical scenarios may be difficult to establish. Hypothetically, some patients may benefit more from one of these approaches according to their cardiac substrate.

In the study “Effect of Scar and His-Purkinje and Myocardium Conduction on Response to Conduction System Pacing” by Strocchi et al(6), the authors performed an elegant in silico study to provide theoretical insights into the differential response to CSP. They used a set of 24 heart geometries to simulate the presence of LBBB together with each of four conditions: (a) normal conduction through the His-Purkinje system beyond the blocked region; (b) reduced conduction velocity through the His-Purkinje system; (c) reduced conduction velocity in the myocardium; and (d) septal or lateral left ventricular scar. They applied five different CRT strategies including BIV-CRT, LBBP, HBP, HBP with left ventricular (LV) epicardial lead (HOT-CRT), and LBBP with LV epicardial lead (LOT-CRT). Consistent with prior observations from the same authors(7) and by Ponnusamy S et al(8), they hypothesized that virtual-patients with septal scar or severe His-Purkinje conduction disease –extending to the full His-Purkinje network and not only the blocked region– would not benefit from CSP. Benefit of the different therapies was quantified by various metrics of ventricular dyssynchrony.

Strocchi et al(6) used a very solid approach in their model building. They included electrocardiographic imaging data (ECGI) to validate their modeling pipeline and showed the model’s ability to replicate the LV activation sequence observed in a clinical setup.

They had to make assumptions on the effects of the pacing strategy delivery on myocardial scar areas and decided to model the His-Purkinje network in a scar region as non-conductive.

As highly suspected, they showed that when the impulse was delivered in a scarred area –where the His-Purkinje system was modeled as non-conductive–, CSP was not effective. In a totally dysfunctional region of the conduction system, BIV-CRT with stimulation of healthy myocardium proved more effective than CSP. The same observations applied when the full His-Purkinje network was altered or had a reduced conduction velocity everywhere and not only at the blocked area. In other words, CSP that makes use of a partially dysfunctional conduction system was less effective than pacing healthy myocardium with BIV-CRT. On the other hand, CSP overperformed CRT when the His-Purkinje system was functional and paced in a non-diseased area. Along this same line, Upadhyay et al(9) showed that patients with focal and proximal conduction block within the left-sided His fibers were most amenable to corrective HBP.

The study by Strocchi et al. stands out as a remarkable demonstration of how computational modeling can be helpful to understand clinical practice observations: a single CRT delivery approach could not fit all the patients with resynchronization indication. Identifying which therapy would be more beneficial in each specific case may be preferable to replacing BIV-CRT with CSP in all clinical scenarios.

The presence of LV scar and its location assessed with late gadolinium enhancement (LGE) magnetic resonance imaging (MRI) could be used to personalize the CRT strategy and avoid pacing scarred areas (10). As recently shown by Ponnusamy S et al (8) in humans (n=25), the presence of transmural-LGE in the LBBP-zone predicts implant failure with high sensitivity and specificity. Moreover, according to the results from Strocchi et al. the overall conduction velocity of the myocardium and the His-Purkinje system is highly relevant to the success of a CRT strategy. Preimplantation assessment of the myocardial conduction velocity would be very beneficial to personalize the CRT therapy; in the future, ECGI could be helpful in this context.

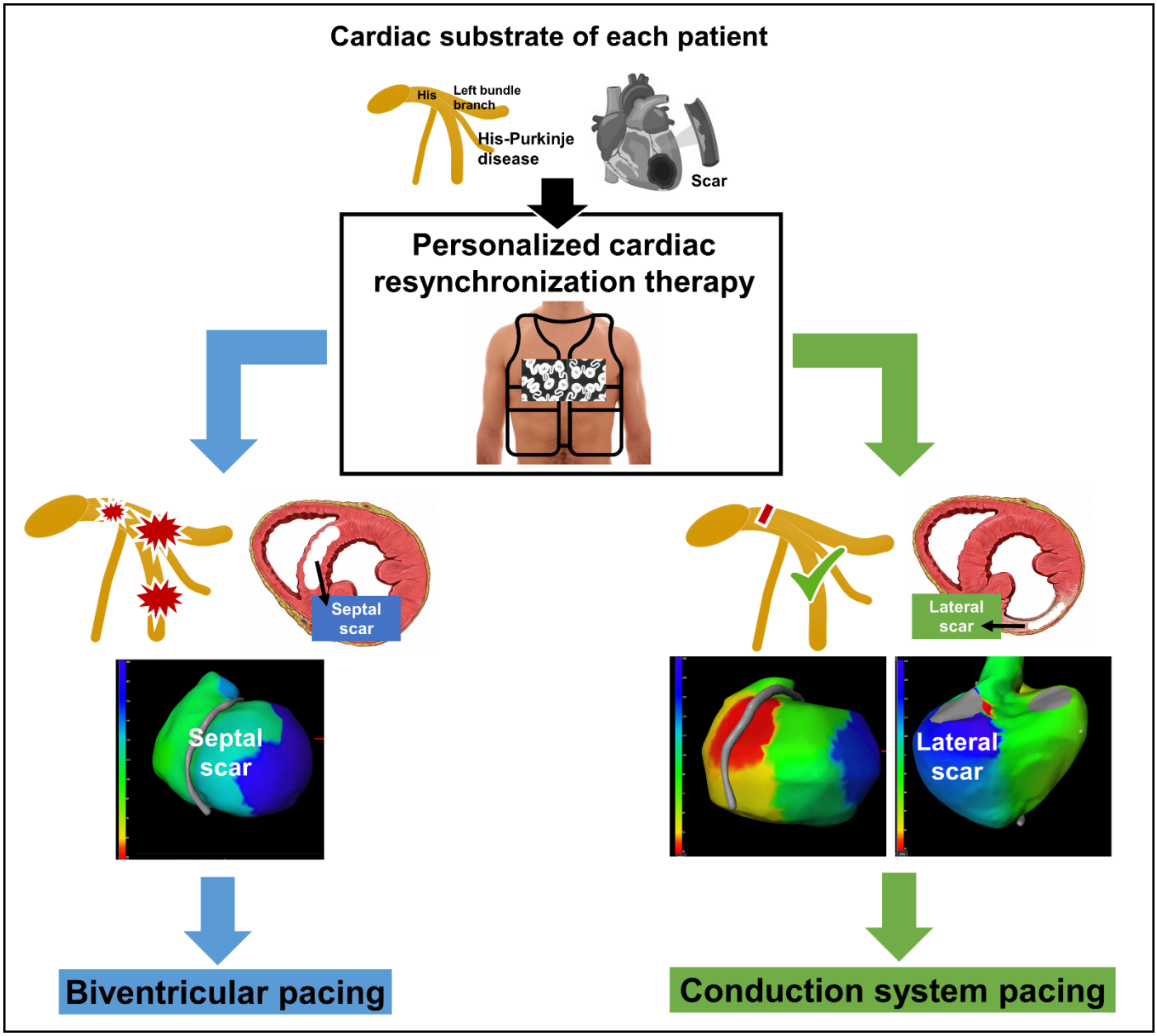
One of the limitations of the model presented by Strocchi et al. is that the stimulation within the intrinsic conduction system was always delivered perfectly and LBBP was always simulated with optimized auriculoventricular (AV) delay. In clinical

practice, it can be challenging to obtain the same results due to the difficulty of precisely locating the lead within the conduction system obtaining resynchronization and optimizing the device with the best synchronization programming; furthermore, AV optimization is not possible in patients with heart block or atrial fibrillation(11,12). In this scenario, a non-invasive method like ECGI (4,13–15) during device implantation and optimization could help to evaluate LV synchronization in real time and thereby improve outcomes.

The authors should be commended on their work, as this study adds evidence that choosing the CRT therapy according to the cardiac substrate of each patient could be beneficial. Perhaps the most appropriate approach in CRT would be to find the appropriate niche for each pacing method. It may be less about demonstrating the superiority of CSP and more about personalizing the therapy for each particular patient (**Figure**). That is, a patient with septal scarring or diffuse conduction system disease could benefit more from BIV-CRT. On the other hand, someone with lateral myocardial scar or localized pathology (focal or proximal disease) within the conduction system would benefit more from CSP. In this context, ECGI could eventually play a main role in selecting the best therapy for each patient.

In summary, a personalized resynchronization therapy aiming to provide the best pacing method according to the myocardial substrate and the pathology within the His-Purkinje system could be beneficial. More studies are needed to determine which characteristics are most favorable for each type of resynchronization therapy. In the future, personalizing CRT therapy rather than total replacement of one technique with another could be the key.

Figure



Personalization of cardiac resynchronization therapy. Severe His-Purkinje conduction disease attenuates the benefits of conduction system pacing (CSP) and septal but not lateral scar makes CSP ineffective according to Strocchi et al (6). In this context, personalized cardiac resynchronization therapy with a non-invasive technology like electrocardiographic imaging could be beneficial. Patients with diffuse conduction system disease or septal scar could benefit more from biventricular cardiac resynchronization therapy. Patients with focal or proximal His-Purkinje disease(9) could benefit more from CSP. Electrocardiographic imaging shows delayed activation of the left ventricle in blue. The anterior descending artery (gray) separates right ventricle from left ventricle.

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