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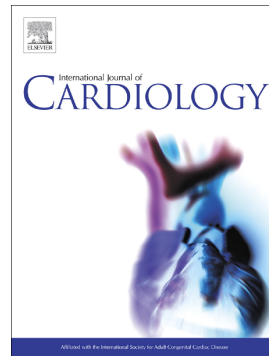
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## Accepted Manuscript

Is CRT response rate all about patient selection?

Steven A. Niederer, Christopher A. Rinaldi



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**Is CRT response rate all about patient selection?**Steven A. Niederer DPhil<sup>1</sup>, Christopher A. Rinaldi MD<sup>1,2</sup>

1) School of Biomedical Engineering and Imaging Sciences, King's College London, SE1 7EH, United Kingdom

2) Cardiology Department, Guys and St Thomas' NHS Foundation Trust, London, SE1 7EH, United Kingdom

Corresponding Author:

Steven Niederer

Steven.niederer@kcl.ac.uk

Under ideal conditions cardiac resynchronisation therapy (CRT) response is a function of the patient's baseline electrical substrate and the improvement derived from manipulating the electrical activation of the heart. Patient response to therapy is thus dependent on the degree to which baseline electrical asynchrony explains their degraded cardiac function and how well CRT manipulates their electrical activation to recover cardiac function. These factors have led to four broad directions for improving CRT response rate: patient selection, pacing technology, device settings and lead position. It is likely that a combination of all four will be required to maximise response in a specific patient.

The study by Strik et al., in the current edition of the journal [1] addresses two of these directions, by investigating the ability of the activation delay vector (ADV), an index that characterises the dispersion and direction of cardiac activation, to identify clinical responders to CRT and determine the optimal lead position. ADV is calculated using an inverse ECG system from approximately 2000 points across the left and right ventricular epicardium that provides a succinct summary of the epicardial activation pattern. ADV is able to differentiate between known electrical substrates (right bundle branch block, non-specific conduction delay, narrow QRS ( $\leq 120$ ms) and left bundle branch block). Consistent with previous studies, that found baseline scar [2], QRS duration and morphology [3] and anatomy [4] correlate with CRT response, Strik et al., found that the ADV classified electrical substrate was important for determining response to CRT. Importantly, ADV stands out from other indexes for its high specificity and sensitivity in predicting both the acute and chronic response.

The authors should be congratulated on their development of this metric however while the patient's underlying pathology is critical for CRT response, it is not the sole determinant. CRT is seldom performed under ideal conditions. Specifically, chronic response to CRT is dependent on many factors outside of the underlying pathology. Lead failures, failure to implant, venous anatomy, lead revision and lead dislodgment make up 8-10% [5, 6] of failed initial CRT implants. In addition 25-30% of CRT patient deaths are due to non-cardiovascular comorbidities [7] which places a limit on the ability to predict response rates based on baseline electrical substrate alone. These factors outside the patient pathophysiology will contribute to false positive CRT responder predictions and place an approximate upper limit on the predictive capacity of 85-90% specificity using patient pathology alone, with the additional assumption that lead placement, device timing and pacing technology are optimal.

In contrast to prior clinical CRT lead optimisation studies showing a benefit of LV lead guidance [8-10], Strik et al., [1] concluded that there was limited benefit in LV lead site optimisation, when

compared to the basolateral position. Notably however, in 18 of the 26 patients, where multiple sites were evaluated the optimal alternate pacing site outperformed the basolateral position and in 6 of these cases the incremental difference advanced the patient over the 10% acute haemodynamic responder threshold which has been shown to predict remodelling [10]. The small change in ADV observed at different pacing sites seems likely to indicate ADV may be a poor determinant to guide the optimal pacing lead location.

While ADV represents a potentially useful index for characterising underlying electrical substrates in CRT patients it does however require acquisition of large inverse ECG data sets. These promising results warrant further investigation, however, it is likely a combination of patient selection, pacing technology, device settings and lead positioning are required to maximise patient response rather than a single index.

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