Hemodynamic Evaluation of Cardiac Resynchronization Therapy Getting into the Pressure-Volume Loop

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160
140
120
100
80
60
40
20
0
Pressure (mmHg) →
0
90
100
110
120
130
Volume (m

Summary

The heart failure syndrome is a still growing health care problem with an expected increase in incidence and prevalence. Heart failure is usually characterized by decreased pump function of the left ventricle (LV). A substantial amount of heart failure patients have an impaired conduction system (left bundle branch block, LBBB) which leads to a dyssynchronous activation of the LV resulting in a delayed contraction of the lateral wall. A dyssynchronous contraction further impairs LV function and pump efficiency. Both systolic and diastolic hemodynamic parameters, in terms of LV pressure and volume, are decreased in dyssynchronous LV contraction. Theoretically, stimulation of the delayed wall segments by Cardiac Resynchronization Therapy (CRT) leads to restoration of synchronized and efficient LV contraction. Large randomized CRT-studies indeed showed significant reduction in morbidity and mortality, but treatment success is still hampered by high non-response rates. Efforts to optimize selection criteria for CRT such as measures of mechanical dyssynchrony failed to improve response rates.

The invasive hemodynamic study is considered the gold standard for evaluation of LV pump function. Small hemodynamic studies have shown the potential of pressure-volume derived measures in assessment of response to CRT. However, the literature on acute hemodynamic improvement in patients with end-stage heart failure, LV conduction delay and dyssynchronous LV contraction treated with CRT is still limited. In addition, the relationship between the different parameters for acute hemodynamic response and long-term response to CRT is ambiguous and topic of ongoing debate. Furthermore, the relationships between acute hemodynamic response and degree of conduction delay, location of therapy delivery and LV tissue characteristics is still unclear. Clarification of these relationships can be of clinical value since hemodynamic measurements might serve as a tool to guide LV lead placement and to optimize pacing settings. The present thesis describes the hemodynamic consequences of CRT in end-stage heart failure patients addressing the influence of conduction delay, LV mechanical properties as well as tissue characteristics both assessed by magnetic resonance imaging, and the relationship with long-term response to therapy.

In **chapter 2** the relationship is studied between two parameters frequently used to assess hemodynamic effects of CRT. Acute changes in dP/dt_{max} and Stroke Work (SW) by biventricular stimulation were acquired in thirty-four patients with end-stage heart failure. No significant correlation was found between both parameters. When defining response an increase of 10% relative to baseline for both parameters, almost half of patients demonstrated an ambiguous response. We concluded that

although both parameters display an average increase during pacing, the change relative to baseline values of SW and dP/dt_{max} was not related.

In **chapter 3** the acute hemodynamic effects of CRT are related to long term outcome. Pre-implant acute hemodynamic response was assessed, as well as the echocardiographic and clinical baseline patient characteristics. It was shown that in long-term responders (n=29, 71%) acute increase in SW was significantly higher compared with non-responders, whereas acute increase in dP/dt_{max} was not significantly different between responders and non-responders. Further analysis showed that SW was superior to dP/dt_{max}, QRS duration and LV dyssynchrony in prediction of response to CRT. A SW increase of >20% predicted reverse remodeling at 6 months with high accuracy. We concluded that invasive assessment of acute hemodynamics is a reliable tool to determine individual response to CRT.

In **chapter 4** the controversy on QRS duration cut-off values as well as on optimal lead location is addressed. Acute pump function improvement was evaluated on an individual basis in fifty-seven patients, using invasively obtained pressure-volume loops. Group analysis showed that pump function did not improve in the narrow QRS group (<120ms) but a significant increase was found in the intermediate (120-150ms) and wide (>150ms) QRS groups. CRT using antero-lateral LV stimulation evoked a consistently lower response compared to postero-lateral LV stimulation, resulting in a significant hemodynamic deterioration in the narrow QRS group. In this respect, acute hemodynamic effects of CRT generally agreed with long-term results from large randomized trials. However, we found individual variation to be substantial, both with respect to response and optimal location. Considering this substantial variation, a temporary pacing protocol may aid in individual patient selection and improvement of lead positioning.

Chapter 5 evaluated whether a poor LV pump function at baseline is associated with worse response to CRT. Thereto the relationship between invasive hemodynamic parameters at baseline and acute hemodynamic response to CRT was studied. Multivariate logistic regression analysis revealed that invasively and also non-invasively obtained baseline contractility (end-systolic elastance) was independently associated with acute pump function improvement. These results concurred with several previous studies showing that severely dilated hearts had a poor outcome of CRT. These data added to the concept that a part of non-response might be explained by application of CRT in patients with a LV which is “beyond repair”. This can be present in patients with severe LV dilatation or for example in extensive myocardial scarring.

In **chapter 6** the significance of myocardial scarring in relation to acute hemodynamic response in patients with ischemic cardiomyopathy is evaluated. Thirty-two CRT candidates with myocardial scarring assessed by cardiac magnetic resonance late contrast enhancement imaging were studied. The extent of LV scar tissue was found to be inversely related to acute pump function improvement during CRT. In general, pacing at the location of (transmural) scar tissue at any site of the LV deteriorated LV pump function. However, placing the LV lead over viable myocardium significantly improved pump function as compared with pacing at the location of scar tissue. It is therefore advisable to avoid scar tissue when targeting the LV lead during CRT implantation.

In **chapter 7**, different lead targeting strategies for optimal acute pump function improvement during CRT are compared. Recent studies advocated addition of an extra LV lead to avoid non-response, while others proposed to target the LV lead at the most delayed site. The main finding was that the optimal LV stimulation site achieved a significantly higher pump function improvement compared with bifocal LV stimulation in 33 patients. The best site coincided with the latest site of mechanical activation. Furthermore, bifocal LV stimulation yielded comparable pump function improvement compared with conventional PL stimulation. Therefore, effort should be directed towards individual patient characterization in terms of LV activation pattern and scar assessment to guide lead placement, rather than the arbitrary addition of an extra LV lead.

Chapter 8 presented a new approach for evaluation of the relation between cardiac mechanics and CRT response. It was demonstrated that the loss of opposite LV basal and apical rotation, quantified by the correlation between basal and apical rotation (i.e., BARC), was related to acute hemodynamic response to biventricular pacing. Therefore, BARC might be a good noninvasive alternative for measuring acute response to CRT. The findings underline the importance of the torsional wringing deformation of the heart by oppositely rotating base and apex for expelling blood.

In **chapter 9**, LV pump efficiency and acute response to CRT is studied. In twenty CRT candidates with LBBB regional myocardial work was calculated and related to CRT response. It was shown that the misbalance in regional myocardial work varied substantially between CRT candidates. Moreover, the results indicated that the amount of misbalance (expressed as the septal-to-lateral work ratio) was significantly related to SW improvement during CRT, with lower septal contribution to myocardial work (or higher the septal waste) at baseline leading to higher acute pump function improvement.