Non-pharmacological heart failure therapies : evaluation by ventricular pressure-volume loops

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CHAPTER 7

Pressure-volume measurements by conductance catheter during cardiac resynchronization therapy

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INTRODUCTION

The conductance catheter developed by Baan et al. enables continuous on-line measurements of left ventricular (LV) volume and pressure.[1,2] This method has been used extensively to assess global systolic and diastolic ventricular function and more recently the ability of this instrument to pick-up multiple segmental volume signals has been used to quantify mechanical ventricular dyssynchrony.[3-13,14,15] These characteristics offer interesting possibilities to apply this technique in patients considered for or treated with cardiac resynchronization therapy (CRT). The aim of the present review is therefore to give an overview of the (potential) applications of pressure-volume measurements by conductance catheter in relation to CRT, and discuss the possibilities and limitations of this approach.

METHODS

The conductance catheter method

The method has been described extensively in previous publications.[2,16,17] Briefly, the conductance methodology is based on the measurement of the electrical conductance of the blood contained in the LV cavity. To this end the catheter contains multiple electrodes to generate an intra-cavitary electric field and pick-up the resulting voltage gradients. In its present form the catheter has 12 electrodes and should be positioned along the long axis of the LV as depicted in figure 1. The two most distal and two most proximal electrodes are employed to generate an electrical field. This dual pair of current electrodes enables the use of a dual excitation mode, which has been shown to improve the accuracy of the method especially in dilated hearts.[16] The remaining 8 electrodes are used pair wise to measure up to 7 segmental conductance signals (G_i) which represent the instantaneous volumes of corresponding slices (note that the figure shows only 5 segments).

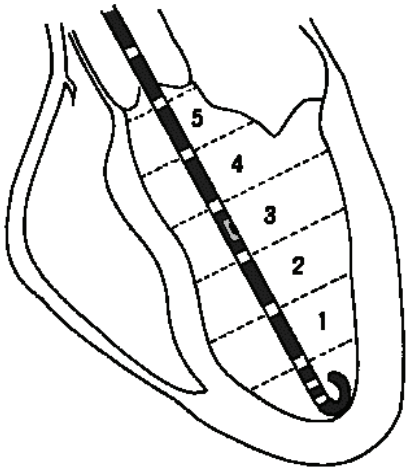

Figure 1. The combined pressure-conductance catheter positioned in the left ventricle. The electrodes are used to setup an intracavitary electric field and measure segmental conductances. Note the pressure sensor positioned in segment 3

To convert the measured conductance (i.e. applied current divided by the measured voltage gradient) to an absolute volume signal the specific conductivity of blood (σ) and the electrode spacing (L) have to be taken into account. In addition, the measured conductance contains an offset factor, which is due to the conductance of the structures surrounding the cavity. This so-called parallel conductance (G^P) may be determined by the hypertonic saline dilution method and subsequently subtracted.[2,17] Finally, the conductance-derived stroke volume generally underestimates actual stroke volume due to electrical field inhomogeneity and because the segments do not fully cover the LV long axis. This underestimation is corrected by introducing a slope factor (α), which may determined by comparing conductance-derived stroke volume with an independent estimate of stroke volume (e.g. determined by thermodilution). Consequently, absolute LV volume (V_{LV}) is derived from measured conductance $G(t)$ as:

$$V_{LV}(t) = (1/\alpha) \cdot (L^2/\sigma) \cdot [G(t) - G^P]$$

Note that $G(t)$ is the instantaneous sum of the segmental conductances:

$$G(t) = \Sigma\, G_i(t)$$

The equation also holds at a segmental level:

$$V_{seg,i}(t) = (1/\alpha) \cdot (L^2/\sigma) \cdot [G_i(t) - G_i^P]$$

As shown in figure 1 the conductance catheter also contains a solid-state, high-fidelity pressure sensor to measure instantaneous LV pressure.

Catheters, equipment and software

Currently, most pressure-volume studies performed in humans use combined pressure-conductance catheters. Typically, these catheters are 7F, over-the-wire, pigtail catheters and are produced by several companies (e.g. CDLeycom, Zoetermeer, The Netherlands; Millar Instruments, Houston, Texas). To generate the electric field, measure the resulting voltages, acquire and handle the various signals the catheter must be connected to dedicated equipment. For this purpose all studies presented and discussed in this review used the Cardiac Function Lab CFL-512 or the Sigma 5 DF (CDLeycom, Zoetermeer, The Netherlands). Data analysis is generally performed with software installed on the CFL-512 or by using other commercially available physiological data-analysis software, or software that is custom-made by the various research groups.

Pressure-volume signals, loops and relations

When positioned in the LV, the combined pressure-conductance catheter yields continuous segmental volume signals and LV pressure. Total LV volume is calculated as the instantaneous sum of the segmental signals. An example of these signals obtained in a patient with coronary artery disease and relatively normal LV function and contraction pattern is shown in figure 2. The temporal resolution in this example is 4 ms. The volume signals show a normal ejection during systole and a biphasic filling pattern during diastole reflecting early rapid filling, diastasis and the atrial contribution to filling.

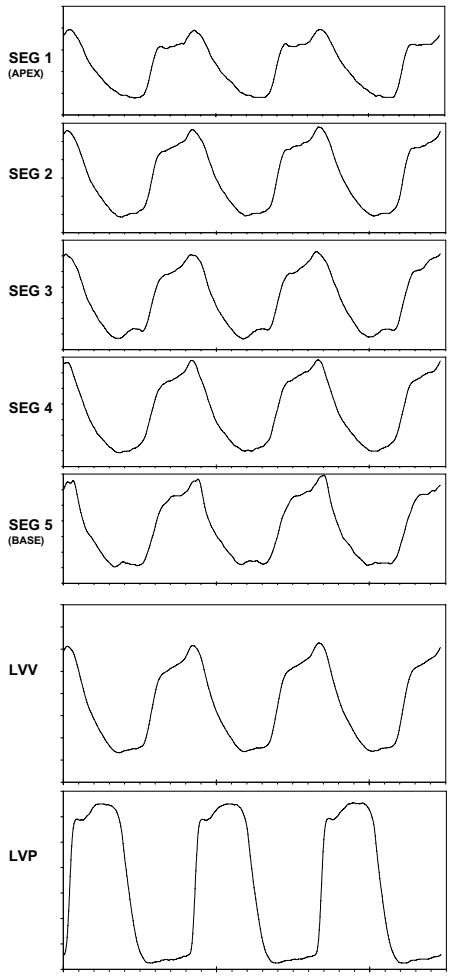

Figure 2. Typical left ventricular segmental (SEG 1 to SEG 5) and total LV volume (LVV) signals and left ventricular pressure (LVP). Corresponding pressure-volume loops are shown in Figure 3

To characterize pump-function of the LV, pressure and volume signals may be combined to construct pressure-volume loops as depicted in figure 3. Each loop represents one cardiac cycle. The distinct cardiac phases, filling, isovolumic contraction, ejection and isovolumic relaxation, are indicated in the figure. The phases are separated by opening and closure of mitral and aortic valves, which moments coincide with the 'corners' of the pressure-volume loop. Important parameters characterizing LV function can be directly determined from the pressure-volume loops, or from the pressure and volume-time curves and their derivatives. Such parameters include indices of pump function (stroke volume, cardiac output, and stroke work), systolic function (end-systolic pressure, end-systolic volume, ejection fraction, peak ejection rate (dV/dt_{MAX}), and dP/dt_{MAX}) and diastolic function (end-diastolic volume, end-diastolic pressure, peak filling rate (dV/dt_{MIN}), dP/dt_{MIN}, and relaxation time constant τ).

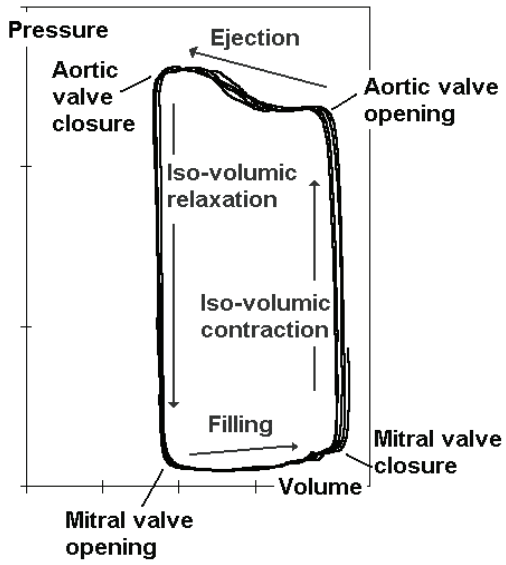

Figure 3. Pressure-volume loops. Cardiac phases and time-points of opening and closure of mitral and aortic valves are indicated

An important limitation of all of the above mentioned indices is that they are, more-or-less, load dependent. A possible approach to amend this is to construct pressure-volume relations from which indices can be derived which are less load-dependent and therefore better measures of *intrinsic* systolic or diastolic ventricular function. Construction of pressure-volume relations requires pressure-volume loops obtained at different loading conditions. Importantly, such alteration in loading should be induced by interventions that minimally affect intrinsic myocardial function. An elegant way to achieve this is to use a balloon occlusion of the inferior vena cava. This procedure enables a rapid, purely mechanical, reduction in preload, which prevents reflex mechanisms and is easily reversed by deflation of the balloon. This method has been described in detail in several publications.[5,6] A typical example of pressure-volume loops acquired during caval occlusion is shown in figure 4.

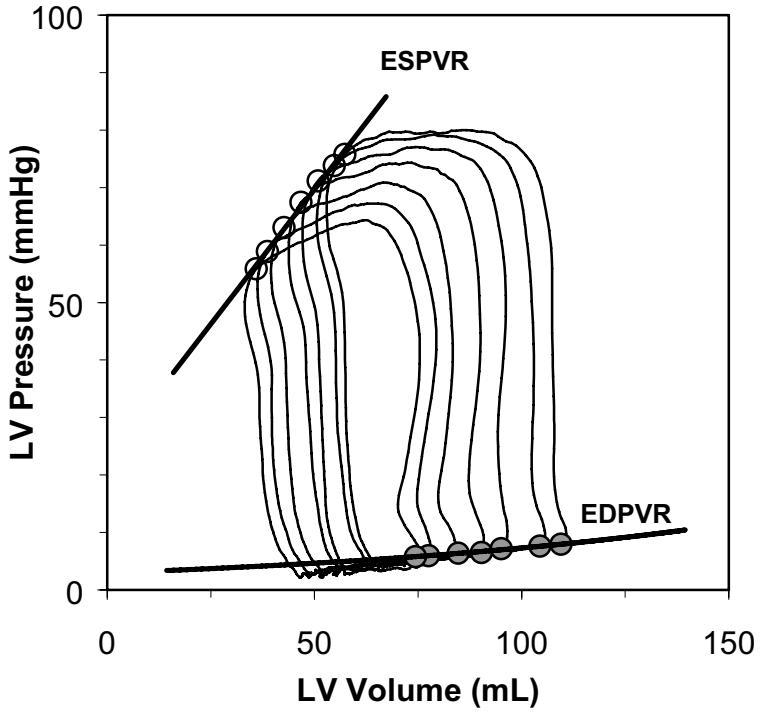

Figure 4. Pressure-volume loops during preload reduction by vena cava occlusion. Systolic and diastolic function indices are derived from the curves fitted to the end-systolic and end-diastolic pressure-volume points, respectively

The relation between the pressure-volume points at end-systole, the end-systolic pressure-volume relation (ESPVR) has been shown a sensitive and relatively load-independent description of LV systolic function.[18] Both the slope of the ESPVR, which determines end-systolic elastance (E_{ES}) and the position of the ESPVR (in recent generally papers characterized by the volume-intercept at a fixed pressure, e.g. end-systolic volume at 100 mmHg, ESV_{100}) are used as indices of systolic function.[19-21] The relation between the end-diastolic pressure-volume points, the end-diastolic pressure-volume relation (EDPVR), may be fitted with a linear curve. The slope of this curve (dEDP/dEDV) represents diastolic stiffness. More commonly, the term diastolic compliance is used, which is the inverse of this slope (dEDV/dEDP). If the EDPVR is constructed over a wider range it is generally clear that this relation is non-linear and better approximated by an exponential fit, such as $EDP = A \cdot \exp(k \cdot EDV)$ and diastolic function characterized by the diastolic stiffness constant (k).[7] In addition, several other relations, which may be derived from pressure-volume loops during a loading interventions have been used to quantify LV function, such as the relation between dP/dt_{MAX} and end-diastolic volume and the preload recruitable stroke work relation (i.e. SW vs EDV).[18,20,22-24]

Mechanical dyssynchrony

Several studies have confirmed the hypothesis that baseline dyssynchrony (i.e. pre-implantation) is an important determinant of the success of CRT in individual patients.[25-27] Currently the primary variable to identify patients that are most likely to benefit is QRS duration. However, electrical and mechanical dyssynchrony may diverge and recent studies indicate that direct analysis of mechanical dyssynchrony may have higher predictive value.[25,28] Mechanical dyssynchrony may be quantified by means of MRI, echocardiographic or tissue Doppler techniques.[26,29,30,31,32] Recently, we introduced indices of mechanical dyssynchrony derived from the segmental volume signals obtained with the conductance catheter.[33,34] The methods and indices are described and validated in detail elsewhere.[35] Briefly, a segmental volume signal is compared with the simultaneous global volume signal and a segment is marked as dyssynchronous at time-point *t* if the instantaneous change in the segmental volume signal is opposite to the change in the global volume signal at that same time-point. An index of regional dyssynchrony is obtained by calculation the percentage of time during the cardiac cycle that a specific segment is dyssynchronous. A global index of mechanical dyssynchrony is subsequently derived by calculating the mean value over all segments. Furthermore, nonuniform contraction and filling is associated with ineffective movements of blood volume within the LV. This 'internal flow' may be quantified by calculating segment-to-segment flow (i.e. segmental volume changes that do not result in effective changes in total LV volume). An internal flow fraction (IFF) is obtained by dividing the average internal flow by effective global LV flow. A comparative study in heart failure patients with LBBB showed good correlation between these conductance derived dyssynchrony indices and tissue-Doppler derived septal-to-lateral delay in peak systolic velocity.[31,36]

PRESSURE-VOLUME MEASUREMENTS DURING CRT

We may distinguish several fields of application where pressure-volume measurements by conductance catheter may play a role in the context of CRT. In principle, the methodology can be applied to study the basic physiological mechanisms involved, as a tool to select patients that might benefit from CRT, to optimize the therapy, and to evaluate the treatment effects of CRT. In the following we will briefly review several

applications of pressure-volume measurements, and discuss the possibilities and limitations in these four fields.

Mechanisms

We and several other groups have used pressure-volume analysis to investigate the physiological mechanisms of CRT. The two primary targets of CRT are normalization of the pattern of LV activation and optimization of the atrial-ventricular delay.[37] In patients with intraventricular conduction delay mechanical synchrony can be improved by pre-excitation of the otherwise late-activated region. As shown in figure 5 (unpublished data) this may result in dramatic acute systolic improvements evident from increased stroke volume and increased stroke work. In this case the improvements are obtained largely from a reduced end-systolic volume, whereas end-diastolic volume is unaltered. Similar results were presented by Nelson et al. who very elegantly demonstrated that the improvement in systolic function is achieved with a minimal change or even a reduction in myocardial oxygen consumption. [38]

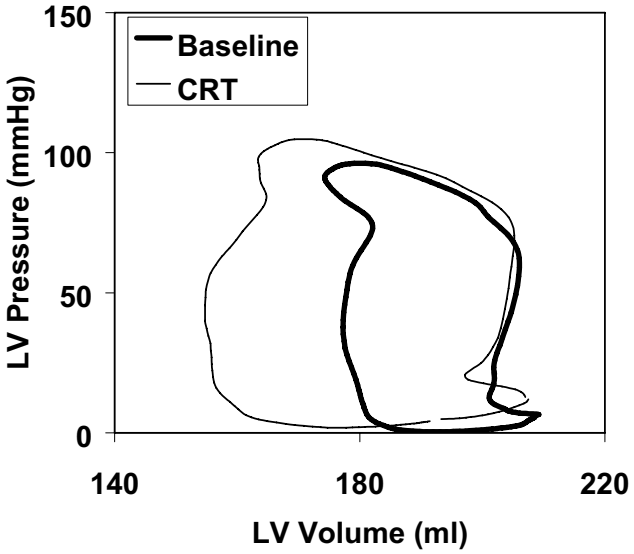

Figure 5. Acute effects of biventricular pacing on LV pressure-volume loops. Note the increased stroke volume (width of pressure-volume loops) and stroke work (area of pressure volume loop) during CRT

A nice demonstration of the influence of asynchronous activation on LV function was presented by Simantirakis et al.[39] They determined systolic and diastolic LV function by pressure-volume loops in patients with long-term right ventricular apical pacing. Restoration of normal activation was achieved by switching from DDD to AAI pacing mode. The results indicate an acute improvement in systolic function evident from an increased end-systolic elastance, preload recruitable stroke work and dP/dt_{MAX}-EDV

slope. Diastolic function was unaltered. Similar to the study by Nelson et al. it was found that myocardial oxygen consumption was unchanged and therefore the improvement in contractility must be attributed to a more economic functioning of the heart.[38] Although mechanical dysfunction arising from right ventricular apex pacing is not necessarily equivalent to that found in patients with intrinsic conduction delay (such as LBBB), this study clearly illustrates the acute improvements that can be obtained after restoration of normal activation.[40]

Pressure-volume loop analysis has been applied to study the influence of pacing site and AV-delay in an experimental animal model of left bundle branch block (LBBB) by Verbeek et al.[41] They show that experimental LBBB acutely induces inter- and intraventricular electrical asynchrony which is reflected in reductions in dP/dt_{MAX}, stroke volume and stroke work. LV pacing recovered LV function and maximal improvement was obtained with intra-ventricular resynchronization of activation, which depended on LV pacing site and required optimalization of the AV-delay.

An interesting alternative hypothesis regarding the working mechanism of CRT has been put forward by the group of Frenneaux.[42] They hypothesized that the mechanism of response may be an improvement in LV filling as well as ventricular systolic resynchronization. This hypothesis is based on the finding that patients with heart failure and high end-diastolic pressure (>15mmHg) often exhibit so-called diastolic ventricular interaction indicating that filling of the LV is constrained (external constraint) by the stretched pericardium and the pressure and volume overloaded the right ventricle.[43] In this condition LV pacing may advance LV filling relative to right ventricular filling and thereby delay the onset of diastolic ventricular interaction and improve LV filling. Recently, they have employed conductance catheter derived pressure-volume measurements during unloading by vena cava occlusion to assess external constraint (example is shown in figure 6) with and without LV pacing.[44] The results indicate a reduction in external constraint during LV pacing. The resulting increase in the effective filling pressure is followed by an increase in LV end-diastolic volume and a subsequent increase in stroke volume and stroke work via the Starling mechanism.

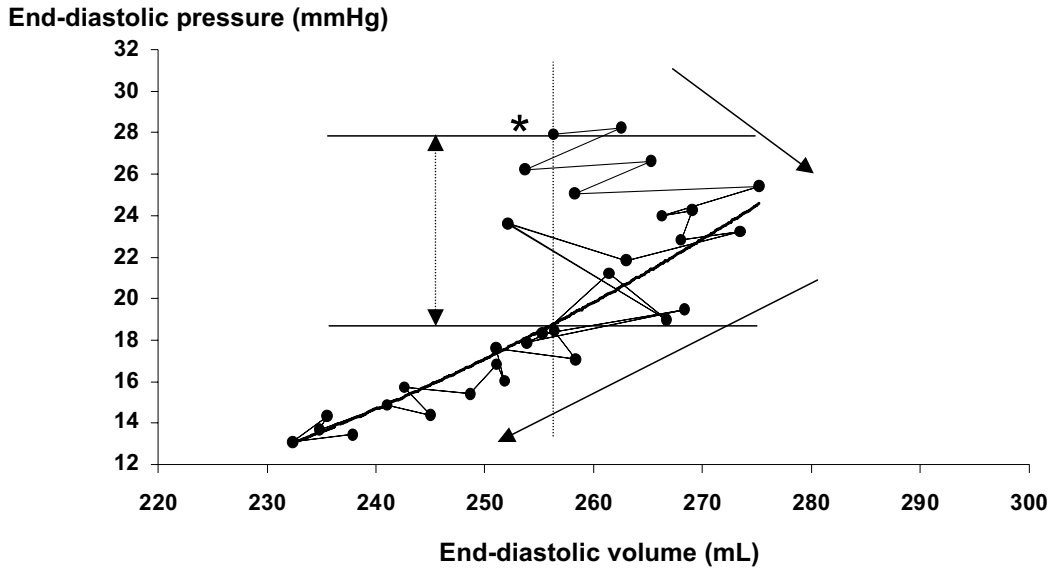

Figure 6. An example of the end-diastolic pressure-volume relation during inferior vena caval occlusion of a patient with significant external constraint. The baseline end-diastolic pressure-volume point is marked with an asterix. During vena cava occlusion LV end-diastolic pressure decreases but initially LV end-diastolic volume increases as represented by the initial right- and downward shift the pressure-volume points. Then LV end-diastolic volume also starts to decrease as indicated by the left- and downward movement of the pressure-volume points. A quadratic regression has been fitted to the subsequent points. External constraint was defined as the pressure difference between the baseline point and the regression line (distance between the two thin horizontal lines) indicated by the dotted vertical arrow

Patient selection

Currently, selection criteria for CRT are typically NYHA III-IV, poor LV function (LVEF < 30-35%) and a wide QRS (> 120-150 ms) with LBBB configuration. However a substantial percentage of patients that fulfill the traditional inclusion criteria do not benefit from CRT.[45] Several approaches to amend this problem have been used or suggested. E.g. the MIRACLE trial used two additional selection criteria: LV end-diastolic dimension of 55 mm or more and a six-minute walking distance of 450 m or less.[46] Recent studies indicate that acute hemodynamic improvement may be predicted by baseline mechanical dyssynchrony, therefore the number of nonresponders may be reduced by adding a pre-implantation assessment of mechanical dyssynchrony and exclude patients who do not show important dyssynchrony.[25-27] An alternative approach is followed by the group in Bad Oeynhausen by performing an invasive pre-implantation test procedure in all CRT candidates to identify responders, and optimize lead position and pacing mode: Temporary pacing electrodes are placed in the right atrium and the right ventricle, and the LV is paced through a temporary lead in a lateral cardiac vein.[47] Various pacing modes are tested and acute hemodynamic benefit is

quantified by measuring femoral artery pulse pressure as a surrogate for stroke volume. Subsequent permanent implantation of a CRT device is only considered in patients showing an increase in pulse pressure greater than 10%. In on-going studies measurements of pressure-volume signals have been added to this protocol. Figure 7 shows a typical example.

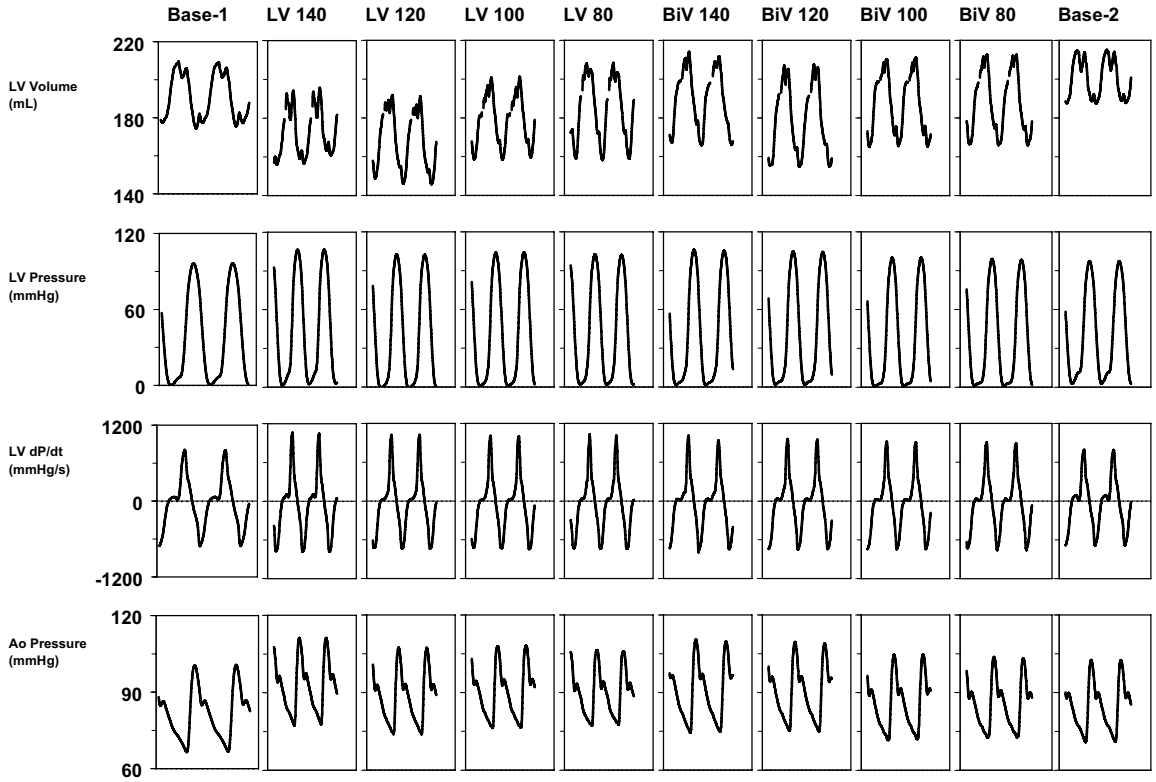

Figure 7. Pre-implantation hemodynamic testing. LV volume, LV pressure, LV dP/dt and femoral artery pressure at baseline and during CRT with LV pacing and biventricular pacing with AV delays set at 140, 120, 100 and 80 ms. Note that the optimal stroke volume (amplitude of LV volume signal) with a reduction in end-diastolic volume is obtained during LV pacing with an AV delay of 120 ms. Similar effects, but with a less pronounced reduction in end-diastolic volume are obtained in this example with biventricular pacing

Optimization

Current CRT involves atrial synchronized ventricular pacing to optimize AV timing, and biventricular pacing to improve intraventricular and interventricular synchrony. Acute hemodynamic studies indicate that optimal contractility and stroke volume requires a patient-specific AV interval[48,49], whereas an optimal RV-LV timing may contribute to a further improvement in synchrony and ejection fraction.[32] Comparison between LV and biventricular pacing has been the subject of several studies[50] but this issue remains unresolved.[37] With regard to lead position the best hemodynamic

response of LV pacing is generally obtained through pacing in the mid-lateral or posterior LV[51-53], which is achieved with leads placed in the posterior or lateral branches of the coronary sinus. Despite advances in percutaneous techniques, special guiding sheaths and improved lead design[47,54], suboptimal lead positioning may still be an important cause of non-response to CRT. Intraoperative epicardial lead placement is currently mainly used as rescue in patients with failed endocardial leads, but may provide an alternative approach with possibilities for optimal lead placement.[55,56] Finally some studies suggest that multiple LV sites may be required for optimal hemodynamic results.[57] Despite a large number of studies many questions regarding optimization of CRT remain disputed. Conceivably studies with the conductance catheter may resolve some of these issues by providing on-line pressure-volume loops which may guide optimization of CRT.

Evaluation

Studies have demonstrated acute hemodynamic improvement after CRT, followed by improvement in symptoms, quality of life and exercise capacity.[46,48,58] More recent studies have provided objective evidence for improved systolic performance and reversed remodeling during long-term CRT which may provide the basis for the clinical improvements.[27,59] The evaluation of long-term hemodynamic effects is complex because it involves alterations in both systolic and diastolic function, and in loading conditions. Although initially the improved systolic function most likely largely reflects improved contraction synchrony, long-term alternation in intrinsic myocardial function may be present e.g. due to alterations in wall stress or sympathetic activity.[60] Interpretation of traditional diastolic indices is complicated because alterations in filling time and mitral insufficiency are present and may interact with changes in intrinsic myocardial function. Analysis in terms of pressure-volume loops and pressure-volume relations is attractive because it provides relatively load-independent indices of systolic and diastolic function. In on-going studies we investigate patients before pacemaker implantation and after 6 months of CRT. The example shown in Figure 8 illustrates reversed remodeling with improved systolic and diastolic function and reduction in mitral regurgitation. Analysis of the segmental conductance signals yielded improved systolic and diastolic mechanical synchrony and reduced internal flow.[61]

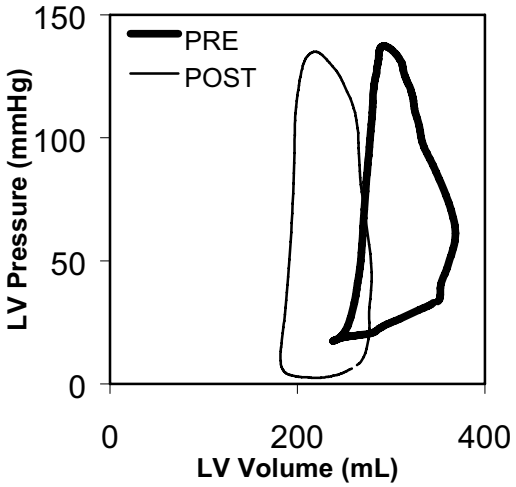

Figure 8. Effects of chronic CRT. Pressure-volume loops at baseline (PRE) and after 6 months of chronic CRT (POST). Note the left ward shift of the pressure-volume loop indicating substantial reversed remodeling. Diastolic pressure decreased and the diastolic part of the pressure-volume loop indicates improved diastolic compliance

CONCLUSION

We conclude that, in the context of CRT, pressure-volume measurements by conductance catheter have been mainly applied to study the basic mechanisms of dyssynchronous and resynchronized cardiac contraction. In this field important new insights were obtained from pressure-volume measurements. There are certainly possibilities and distinct advantages in the field of patient selection but this application will remain limited by the invasive character of the conductance method. Currently, ongoing studies apply pressure-volume measurements to optimize CRT in individual patients and evaluate the long-term hemodynamic effects of CRT. The possibility to assess cardiac function and mechanical dyssynchrony during implantation and study the immediate effects of changes in lead position, AV and VV-delay, in an on-line and quantitative fashion makes this a promising tool to optimize CRT. Load-independent quantitative parameters of systolic and diastolic function derived from pressure-volume relations should provide more insight in the working mechanisms of chronic CRT.

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