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

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### **Citation**

Tulner, S. A. F. (2006, March 8). *Non-pharmacological heart failure therapies : evaluation by ventricular pressure-volume loops*. Retrieved from <https://hdl.handle.net/1887/4328>

Version: Corrected Publisher's Version

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**Note:** To cite this publication please use the final published version (if applicable).

# **CHAPTER 2**

## **Peri-operative assessment of left ventricular function by pressure-volume loops using the conductance catheter**

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**Anest Analg 2003; 19: 259-266**

**Poster presentation at Cardiac Techniques and Technologies, March 2003, Miami,  
Florida, USA**

## ABSTRACT

Interpretation of peri-operative measurements of cardiac function during cardiac surgery is complicated by changes in loading conditions induced by anesthesia, cardiopulmonary bypass (CPB) and the surgical procedure itself. Quantification of left ventricular (LV) function by pressure-volume relations as obtained by the conductance catheter would be advantageous because load-independent indices can be determined. Accordingly, we evaluated methodological aspects of the conductance catheter technique and documented LV function pre- and post-CPB in 8 patients undergoing CABG. LV pressure-volume loops by TEE-guided trans-aortic application of the conductance catheter were obtained at steady state and during preload reduction by temporary occlusion of the inferior caval vein. All patients remained hemodynamically stable and no complications occurred. Complete data were acquired within 15 minutes pre- and post-CPB. Cardiac output ( $5.2 \pm 1.3$  to  $6.0 \pm 1.4$  L/min) and LV ejection fraction ( $46 \pm 17$  to  $48 \pm 19\%$ ) did not change, but end-diastolic pressure increased significantly post-CPB ( $8 \pm 2$  to  $16 \pm 7$  mmHg,  $p < 0.05$ ). Load-independent systolic indices remained constant (end-systolic elastance:  $1.31 \pm 1.20$  to  $1.13 \pm 0.59$  mmHg/mL). Diastolic function changed significantly post-CPB, as Tau decreased from  $64 \pm 6$  to  $52 \pm 5$  ms ( $p < 0.05$ ) and the chamber stiffness constant increased from  $0.016 \pm 0.014$  to  $0.038 \pm 0.016$  mL ( $p < 0.05$ ). We conclude that the conductance catheter method provides detailed data on peri-operative myocardial function. Therefore, the conductance catheter method may be used to evaluate the effects of new surgical and anesthetic procedures for which the present data may serve as reference data.

## INTRODUCTION

Recently, several new approaches were introduced in cardiac surgery such as restrictive mitral annuloplasty, endoventricular circular patch plasty, and off-pump CABG. Generally, the efficacy of new techniques is assessed by long-term follow-up of patients. However, the acute effects on left ventricular (LV) function of these procedures are not well documented and may be predictive for long-term outcome. Peri-operative assessment of LV function may allow better evaluation of new surgical procedures and may help post-operative management by providing insight in the cardiac pathophysiology. During cardiac surgery cardiac output, aortic pressure, central venous

pressure and the pulmonary arterial wedge pressure usually assess hemodynamic status. In addition, transesophageal echocardiography (TEE) is used to assess regional contractile function. However, interpretation of all these parameters is complicated by their load-dependency. Therefore, given the substantial changes in loading conditions that may occur during the operation, these parameters may not reflect intrinsic myocardial function. Pressure-volume relations as obtained by the conductance catheter, have been shown to provide load-independent indices of systolic and diastolic function.<sup>1,2</sup> Accordingly, the aim of present study was twofold. Firstly, we described and evaluated the application of the conductance technique in the operating room including catheter placement, calibration procedures and heart rate-controlled measurement of systolic and diastolic pressure-volume relations. Secondly, we compared various indices of LV function before and after CPB in patients undergoing CABG. These data obtained in patients with relatively normal LV function may provide reference data for future studies in which more complex cardiac surgical procedures are evaluated.

## **METHODS**

The study protocol was approved by the Local Ethics Committee and all patients gave informed consent. Eight patients with multivessel coronary artery disease elected for CABG were included. Patients with severely depressed LV function (LVEF < 35%), unstable angina or atrial fibrillation were excluded.

### **Anesthesia**

After 2mg lorazepam as sublingual premedication two hours before surgery, all patients received total intravenous anesthesia with target-controlled infusion of propofol, remifentanil and sufentanil.<sup>3-5</sup> Hypnotic state was monitored with a Bispectral Index (BIS) monitor (Aspect medical systems, Newton, MA). Induction of anesthesia was started with targeted concentration of 1.5µg/ml propofol and 3ng/ml remifentanil. Before intubation the remifentanil-targeted concentration was increased to 9ng/ml and the targeted propofol concentration to 2µg/ml. A single dose of pancuronium bromide (0.1mg/kg) was given to facilitate intubation. During surgery the propofol concentration was adjusted between 1.5µg/ml and 2.0µg/ml to maintain a BIS value below 60. Remifentanil was titrated between 5 and 10ng/ml in response to the patient's

hemodynamic reaction on surgical stimuli. Sufentanil was started at a targeted concentration of 0.1ng/ml after start of surgery to allow smooth transition of the patient analgesic state from the operating room to the ICU. The patients were ventilated with an oxygen/air mixture ( $FiO_2=40\%$ ) at a ventilatory rate of 12-15/min and ventilatory volume was adjusted to maintain  $PaCO_2$  between 4.5 and 5.5kPa (34-41mmHg). A thermal filament catheter was placed in the pulmonary artery via the right internal jugular vein for semi-continuous cardiac output measurements (Edwards Lifesciences, Uden, The Netherlands). To monitor cardiac function and facilitate positioning of the conductance catheter peri-operatively a multiplane TEE-probe was inserted.

### Conductance catheter technique

We used a 7F integrated pressure-conductance catheter (CD-Leycom, Zoetermeer, The Netherlands) incorporating a solid-state pressure sensor and 12 electrodes with an inter-electrode spacing of 10mm. A pigtail facilitates placement through the aortic valve and positioning within the LV apex (Figure 1).

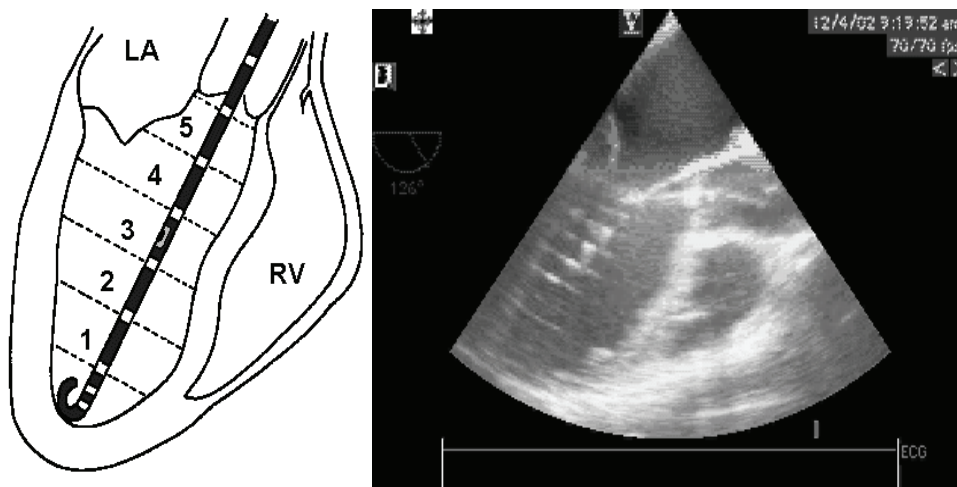


Figure 1. Left: The optimal position of the conductance catheter along the long-axis of the left ventricle. Right: the conductance catheter viewed by long-axis view by TEE peri-operatively

The catheter is connected to a Leycom Cardiac Function Lab (CFL) signal-processor. Between the two most proximal and two most distal electrodes a dual electric field (20kHz, 30 $\mu$ A) is generated.<sup>6</sup> The remaining 8 electrodes are used to measure 5 segmental volume signals. The user may select from three settings the best match with the LV long axis: by skipping electrodes one or two 1-cm segments may be converted to 2-cm segments thereby extending the effective length of the catheter. The optimal setting is selected based on inspection of the segmental volume signals. An aortic

volume signal is easily distinguished from a ventricular signal because it resembles an aortic pressure signal and is out-of-phase with the ventricular volume signals. The segmental conductance's are summed to yield total conductance  $G(t)$  and, taking into account the specific resistivity of blood and the electrode spacing, converted to a time-varying volume signal,  $V(t)$ , which follows through the equation:

$$V(t) = (1/\alpha) \cdot (\rho \cdot L^2) \cdot (G(t) - G^P)$$

where  $\alpha$  is a slope factor,  $L$  is the inter-electrode spacing,  $\rho$  is the specific resistivity of blood measured from a 5ml blood sample using a special 4-electrode cuvette connected to the CFL, and  $G^P$  is the parallel conductance.  $G(t)$  is the sum of the conductance of the blood in the LV and  $G^P$ . The latter results from the conductance of the ventricular wall, other cardiac chambers and to some extent all electrically conductive structures outside the LV cavity. Baan et al. devised a method to determine  $G^P$  by injecting a small bolus (7ml) of hypertonic saline solution (10%) in the distal port of the pulmonary artery catheter.<sup>1</sup> The highly conductive saline transiently changes blood conductivity, which is measured only in the LV. By analyzing the conductance signal registered during passage of the bolus through the LV,  $G^P$  can be determined.<sup>1</sup> The correction volume ( $V_c$ ) corresponding to  $G^P$  equals:

$$V_c = (\rho \cdot L^2) \cdot G^P$$

After correction for  $G^P$  the volume signal is directly proportional to actual ventricular volume, but generally underestimates true volume by a fixed factor. There are two main causes for this underestimation. First, there may be a mismatch between the measured segments and the LV long-axis. Secondly, the conversion of conductance to volume assumes that the electric field is homogeneous within the cavity. In reality this is not entirely the case resulting in underestimation. The development of dual field excitation has substantially improved electric field homogeneity, but some underestimation remains especially in large hearts.<sup>6</sup> To correct for this underestimation the factor  $\alpha$  was introduced, which is obtained by comparing conductance-derived stroke volume (SV) with an independent measure of SV. In most studies  $\alpha$  is calculated by dividing SV of the conductance catheter by SV obtained by thermodilution:  $\alpha = SV_{\text{conductance}}/SV_{\text{thermodilution}}$ . In the present study we used the 'stat' cardiac output

measurements recorded from a Vigilance® Continuous Cardiac Output Monitoring System (Edwards Lifesciences, Uden, The Netherlands).

### **Instrumentation and surgical technique**

After harvesting bypass material, the pericardium was opened and epicardial pacemaker leads were placed on the right atrium. A caval tourniquet was applied around the inferior caval vein to perform temporary preload reductions by caval vein occlusion. After systemic heparinization, a sheath (F8, Cordis, Roden, The Netherlands) was introduced in the ascending aorta for placement of the conductance catheter. Subsequently the conductance catheter was inserted into the LV and positioned along the long axis toward the LV apex. Catheter introduction and positioning was guided and verified by TEE and inspection of the segmental conductance signals. Positioning was aimed at locating the pigtail in the apex while the most proximal electrodes should be located just above the aortic valve. Measurements were started if 5 segmental LV volume signals were obtained.

### **Measurement protocol and data acquisition**

The protocol included measurements at a paced heart rate of 80bpm pre- and post-CPB. If intrinsic rate was above 80bpm the pacemaker was set slightly above the intrinsic rate. Pressure-volume loops were measured at steady state and during transient caval vein occlusion (typical pressure drop of 20mmHg within 5-10s) in order to obtain systolic and diastolic pressure-volume relationships. The ventilator was turned off to exclude the effects of respiration. Rho was measured just before data acquisition, both before and after CPB. Additional acquisitions (before and after CPB) were done for determination of  $G^P$  after injection of 7ml 10% hypertonic saline solution through the distal port of the pulmonary artery catheter. Independent cardiac output measurements by thermodilution were obtained during steady state. The thermodilution catheter provides update measurements approximately every minute indicating average cardiac output over the preceding period. An analog signal reflecting the 'stat' signal was recorded simultaneously with the pressure-volume signals for off-line calculation of  $\alpha$ .

### **Data analysis**

Baseline hemodynamic data were calculated from steady state pressure-volume loops: heart rate (HR), end-systolic volume (ESV), end-diastolic volume (EDV), end-systolic pressure (ESP), end-diastolic pressure (EDP), cardiac output (CO), stroke volume (SV),

stroke work (SW), maximal and minimal rate of LV pressure change ( $dP/dt_{MAX}$ ,  $dP/dt_{MIN}$ ), ejection fraction (EF) and the relaxation time constant (Tau). Tau, reflecting the early active relaxation process, was calculated as the time constant of mono-exponential pressure decay during isovolumic relaxation. The isovolumic period was defined as the period between the time-point of  $dP/dt_{MIN}$  and the time-point at which  $dP/dt$  reached 10% of the  $dP/dt_{MIN}$  value. From pressure-volume loops during caval vein occlusion indices of systolic and diastolic function were derived. For systolic function, the end-systolic pressure-volume relation (ESPVR), the  $dP/dt_{MAX}$ -EDV relation and the preload recruitable stroke work relation (PRSW: SW versus EDV) were determined as for diastolic function the chamber stiffness constant (CS) was determined. The systolic relationships were characterized by their slope and volume intercept. The slope of the ESPVR ( $E_{es}$ ) as well as its volume intercept, at a fixed systolic pressure of 75mmHg ( $V_{75}$ ) have been shown to be indices of contractility, largely independent of loading conditions.<sup>7,8</sup> The ESPVR was determined by linear regression of end-systolic pressure-volume points obtained during caval vein occlusion. Similarly, the PRSW slope (S-PRSW) was determined by plotting SW against EDV and the same was done for the slope of the  $dP/dt_{MAX}$ -EDV relation (S- $dP/dt$ ). The slopes of these two relationships have also been shown to reflect contractility.<sup>9,10</sup> The chamber stiffness constant (CS) was determined by exponential regression of the end-diastolic pressure-volume relation (EDPVR) by means of the following equation:

$$EDP = y_0 + A \cdot e^{CS \cdot EDV}$$

where  $y_0$  is the pressure asymptote and A is a constant.

### **Statistical analysis**

Pre- and post-CPB data were compared with paired t-tests. Statistical significance was assumed at  $p < 0.05$ . All data are presented as the mean  $\pm$  SD.

## **RESULTS**

### **Patients**

Patient characteristics are shown in table 1. All patients underwent normothermic CPB and received intermittently antegrade warm oxygenated blood cardioplegia. The surgical procedure and postoperative intensive care stay were uncomplicated. Peri-operative and post-operative ECGs did not show signs of ischemia. Furthermore



troponin T levels were measured at least up to 12 hours post-surgery and did not exceed 0.6  $\mu\text{g/L}$  at any time point indicating that in none of the patients peri-operative myocardial infarction occurred.<sup>11</sup>

Table 1. Patient-characteristics

Variable	Mean $\pm$ SD	Range
Age (yr.)	63 $\pm$ 11	42-75
Male sex (%)	88	-
EF (%)	58 $\pm$ 9	40-68
CPB-time (min)	100 $\pm$ 31	60-162
Aox-time (min)	70 $\pm$ 22	49-80
Duration of surgery (min)	301 $\pm$ 72	200-381
Grafts (number)	4 $\pm$ 1	2-5

EF = Ejection fraction; CPB = Cardiopulmonary bypass; Aox = Aortic cross clamp

### Technical considerations

In all patients complete pressure-volume data were acquired before and after CPB. Preparation of the pacemaker wires, application of the caval tourniquet and introduction of the sheath were uncomplicated. The introduction of the conductance catheter through the aortic valve and catheter placement required careful monitoring by use of TEE (figure 1) to reduce the risks of perforation and to obtain an optimal catheter position.

The optimal transesophageal long-axis view was obtained with the multiplane TEE-probe from the midesophageal transducer position with the array at 135 ° of rotation. Occasionally, placement of the catheter within the apex caused ventricular extrasystolic beats, but a stable catheter position without arrhythmias could always be obtained. After the pre-CPB measurements the conductance catheter was withdrawn, rinsed with normal saline, and placed on a sterile table to be re-used post-CPB. During the CPB, the introducer sheath on the ascending aorta was used to infuse cardioplegia. Catheter placement and measurements before and after CPB were completed within approximately 15 minutes.

### Calibration of the conductance measurements

Rho measurements, assessment of  $V_c$  and  $\alpha$  were performed in each patient before and after CPB. Results are summarized in table 2. Rho decreased significantly post-CPB as

expected due to hemodilution. On the average,  $V_c$  and  $\alpha$  were not significantly altered post-CPB but showed a substantial interindividual variability.

Table 2. Conductance catheter calibration factor, hemoglobin and hematocrit, pre- and post CPB

Variable	Pre-CPB	Post-CPB	P
$V_c$ (ml)	129 ± 54	139 ± 50	0.696
$\alpha$	0.54 ± 0.24	0.67 ± 0.21	0.267
Rho (ohm·cm)	129 ± 23	105 ± 9	0.015
Hemoglobin (mmol/L)	7.5 ± 1.1	5.3 ± 0.7	<0.001
Hematocrit (%)	0.40 ± 0.05	0.26 ± 0.03	<0.001

$V_c$  = Parallel conductance correction volume;  $\alpha$  = slope factor; rho = blood resistivity

### Hemodynamic data

Measurements were obtained in each patient before and after CPB. Figure 2 shows typical steady state volume, pressure and dP/dt signals and pressure-volume loops.

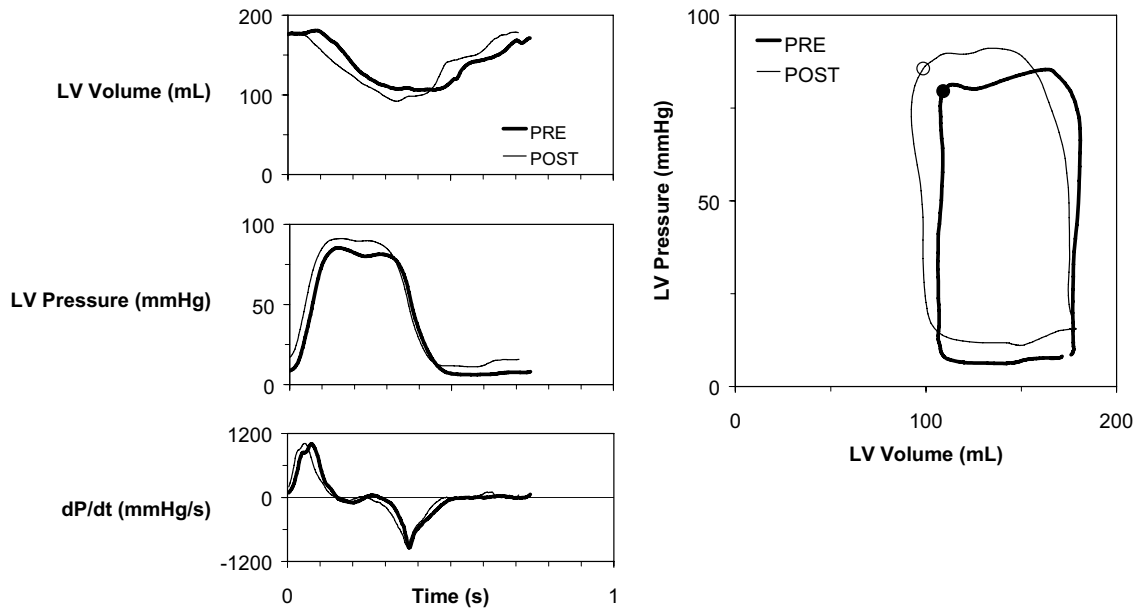


Figure 2. Typical steady state volume, pressure and dP/dt signals, and corresponding pressure-volume loops before (PRE: thick lines) and after (POST: thin lines) cardiopulmonary bypass (CPB). As shown by the open and closed circles marking the end-systolic pressure-volume points on the pressure-volume loops, ESP increased and ESV decreased after CPB indicating increased systolic function. Diastolic function, however, appears decreased since diastolic pressure is higher at any given diastolic volume. However, while the average values for the whole group showed the same trend, the changes in ESV and ESP did not reach statistical significance

Systolic and diastolic pressure-volume relations (ESPVR, EDPVR, PRSW and  $dP/dt_{MAX}$ -EDV) in the same patient derived from pressure-volume loops during caval vein occlusion are shown in Figure 3.

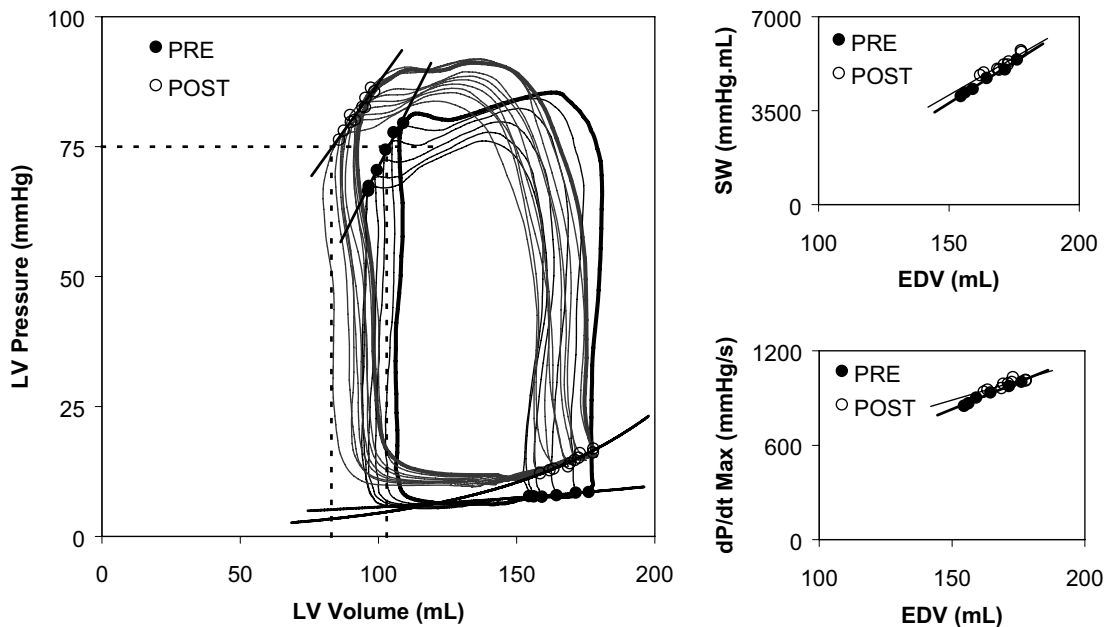


Figure 3. Example of pressure-volume relations derived by caval vein occlusion before and after CPB. The ESPVRs (left panel) show the increased contractile performance after CPB in this patient: although Ees is slightly decreased, the position of all end-systolic P-V points to the left and above the pre-CPB ESPVR suggests higher contractility. The dotted lines indicate the position of the ESPVR at 75-mmHg (V75). The same holds for the PRSW relation (upper-right panel) and the  $dP/dt_{MAX}$ -EDV relation (lower-right panel) although the differences are much less pronounced. The EDPVRs (left panel) provide clear evidence for substantial increase in chamber stiffness after CPB, as observed in all patients. As shown in table 3, the average position and slope of the ESPVR were not significantly altered after CPB in this group of patients

All patients had sinus rhythm and were paced at 80-90bpm during measurements. Hemodynamic data are summarized in table 3: Only EDP, Tau and CS changed significantly post-CPB

## DISCUSSION

Assessment of peri-operative ventricular function during cardiac surgery is complicated by the fact that substantial changes in loading conditions may occur. Therefore the quantification of systolic and diastolic function requires load-independent indices, which can be determined from ventricular pressure-volume relations as obtained by the

conductance catheter. Accordingly, the purpose of this study was twofold: we evaluated methodological aspects of peri-operative application of the conductance catheter and documented changes of various indices of LV function pre- and post-CPB in patients undergoing CABG.

Table 3. Hemodynamic measurements before and after CPB

Variable		PRE-CPB	POST-CPB	t-test
		Mean $\pm$ SD	Mean $\pm$ SD	p
HR	bpm	82 $\pm$ 3	85 $\pm$ 4	0.024
CO	L/min	5.2 $\pm$ 1.3	6.0 $\pm$ 1.4	0.293
EF	%	46 $\pm$ 17	48 $\pm$ 19	0.521
SV	mL	64 $\pm$ 14	72 $\pm$ 18	0.402
SW	mmHg-L	4.5 $\pm$ 0.9	5.1 $\pm$ 1.4	0.364
ESV	mL	109 $\pm$ 93	99 $\pm$ 57	0.625
EDV	mL	169 $\pm$ 104	164 $\pm$ 51	0.845
ESP	mmHg	73 $\pm$ 9	83 $\pm$ 15	0.198
EDP	mmHg	8 $\pm$ 2	16 $\pm$ 7	0.004
dP/dt <sub>MAX</sub>	mmHg/s	926 $\pm$ 224	1016 $\pm$ 183	0.226
dP/dt <sub>MIN</sub>	mmHg/s	-825 $\pm$ 127	-958 $\pm$ 147	0.093
Tau	ms	64 $\pm$ 6	52 $\pm$ 5	0.001
V75	mL	104 $\pm$ 10	87 $\pm$ 13	0.216
Ees	mmHg/mL	1.31 $\pm$ 1.20	1.13 $\pm$ 0.59	0.496
S-dP/dt	mmHg/s/mL	6.9 $\pm$ 3.7	6.3 $\pm$ 3.7	0.524
S-PRSW	mmHg	62 $\pm$ 35	59 $\pm$ 24	0.822
CS	1/mL	0.016 $\pm$ 0.014	0.038 $\pm$ 0.016	0.017

CO: cardiac output; EF: ejection fraction; SV: stroke volume; SW: stroke work; ESV: end-systolic volume (mL); EDV: end-diastolic volume (mL); ESP: end-systolic pressure; EDP: end-diastolic pressure (mmHg); Tau: relaxation time constant, V75: ESPVR volume intercept (at ESP=75 mmHg); Ees: end-systolic elastance; S-dP/dt: slope of dP/dt<sub>MAX</sub> – EDV relation; slope of the PRSW relation; CS: chamber stiffness constant

### Methodological aspects

Previous studies have extensively shown that the conductance catheter can be applied to obtain pressure-volume relationships. Although most patient studies were performed in

the catheterization laboratory, several groups have demonstrated feasibility of the technique in the operating room under various conditions.<sup>12-14</sup> Consistent with these previous studies, our study demonstrates that peri-operative pressure-volume measurements by the conductance catheter can be used to quantify detailed intrinsic systolic and diastolic function within an acceptable time-window. Measurements were uncomplicated and no technical difficulties during instrumentation; catheter placement and loading interventions were encountered. New technical aspects of our study were the use of retrograde insertion of the conductance catheter using TEE guidance compared to the trans-mitral approach used in previous studies in the operating room. Both approaches may have theoretical advantages and disadvantages: The trans-aortic approach provides a better match of the catheter position with the LV long axis. Compared with the anterograde placement this gives a better registration especially of the volume changes in the basal segments. In contrast anterograde placement through the mitral valve may complicate interpretation of segmental volume signals because of changes in the mitral valve plane during ejection and filling. On the other hand with retrograde placement eccentric (antero-medial) displacement of the catheter at the base of the heart may occur but the electric field is such that the measurement electrodes will move approximately parallel to the equipotential planes field and thus the eccentric movement is unlikely to strongly influence the conductance signal. Another reason for using the trans-aortic approach is that we aim to apply this methodology in future studies to evaluate the effects of mitral valve surgery, in which case placement through the aortic valve is clearly preferable. Furthermore we analyzed the changes in the calibration factors. As a disadvantage, substantial between-patient variability was found for calibration factors ( $\rho$ ,  $\alpha$  and  $V_c$ ) indicating the need for careful assessment of these factors in each individual patient. In addition, after CPB calibration factors  $\rho$  and, to a lesser extent  $\alpha$  and  $V_c$ , were changed due to reduced hematocrit, fluid shifts and possibly altered catheter position with re-insertion. Although the average  $\alpha$  and  $V_c$  were not significantly changed, substantial differences were present in individual patients indicating that re-assessment is required at the various stages of surgery. Besides influencing between and within-patient variability, the calibration factors importantly determine the absolute accuracy of the conductance-derived volumes. Calibration factors  $\alpha$  and  $V_c$  are both obtained by means of indicator-dilution methods: thermodilution and, respectively, saline dilution. Thermodilution is widely used in the surgical setting and the accuracy is generally found to be acceptable.<sup>15</sup> In the present study we used 'stat' continuous cardiac output measurements using a thermal filament

catheter which has been shown to have accuracy comparable to the bolus injection method.<sup>16,17</sup> The saline dilution method has been used extensively to obtain parallel conductance and was found to be accurate with a slight tendency to underestimate parallel conductance obtained by alternative methods.<sup>18</sup> An important advantage of these indicator-dilution methods compared to imaging modalities such as TEE is that they do not require assumptions regarding the geometry of the ventricle. This may be relevant especially when comparing conditions in which geometrical changes would be anticipated such as after ventricular reconstruction or mitral valve surgery. Furthermore the inter- and intra-observer variability of indicator-dilution methods is very limited.

### **Physiological aspects**

Our main physiological findings were that systolic function was unchanged after CPB in these patients undergoing CABG, whereas early relaxation was improved and diastolic stiffness was increased. Previous pressure-volume studies comparing pre- and post-CPB cardiac function in patients undergoing CABG have shown conflicting data. Schreuder et al. reported unchanged systolic function and increased diastolic stiffness, while Wallace et al. found a decrease in systolic function, but no changes in relaxation or diastolic stiffness.<sup>13,14</sup> Both studies used cold cardioplegia whereas our study was performed with warm blood cardioplegic arrest, which may explain the preserved systolic function in our study as compared to the decrease found by Wallace et al. The unchanged systolic function found by Schreuder et al. may be explained by the fact that during their pre-CPB measurement the temperature was lowered below 35°C, which according to a recent study significantly reduces Ees by approximately 50%.<sup>19</sup> Since the post-CPB measurements in Schreuder's study were done at 37°C this may have masked an actual reduction in systolic function. With regard to diastolic function all studies report an increase in diastolic stiffness although in Wallace's study this effect did not reach statistical significance.<sup>14</sup> Also in Schreuder's study the increase was less pronounced as compared to our study (39% increase vs. 138%).<sup>13</sup> However, Schreuder et al. described the end-diastolic pressure-volume relation as linear, whereas we derived the diastolic stiffness constant from an exponential relation. The increase is most likely due to myocardial edema post-CPB as myocardial lymph flow has been shown to almost cease during cardioplegic arrest.<sup>20</sup> De Hert et al. have shown that a more rapid normalization of diastolic stiffness may be obtained by optimizing preload conditions prior to weaning from CPB.<sup>21</sup> Furthermore, Allen et al. demonstrated that increasing contractility by dobutamine infusion enhanced myocardial lymphatic function, thus

speeding edema removal post-CPB.<sup>22</sup> Thus, for patients who are difficult to wean from CPB due to increased diastolic stiffness, inotropic support could be considered. However it should be used with caution because it may adversely affect energetics, raise heart rate, and induce ischemia.<sup>23</sup> In addition several pharmacological substances added to the cardioplegia composition have been shown to be associated with reduced edema formation.<sup>24-26</sup> Remarkably, although diastolic stiffness was increased, early relaxation was improved in our study as shown by the significantly reduced Tau. After revascularization, enhanced oxygen dependent re-uptake of calcium into the sarcoplasmic reticulum would indeed be expected to improve active relaxation.<sup>27</sup> Our findings are consistent with the results of Humphrey et al. who demonstrated a reduced Tau post-CPB in patients undergoing CABG.<sup>28</sup> In contrast, De Hert et al. found an increased Tau in a similar patient group.<sup>21</sup> Differences may be due to the applied anesthetic and cardioplegic protocol which influence post-CPB relaxation directly or indirectly via changes in contractility or loading, which are tightly coupled with relaxation.<sup>23,29</sup> Thus unchanged or even increased Tau as found in some studies may be related to post-CPB changes in systolic function and/or loading conditions. In our study EDV, ESP,  $dP/dt_{MAX}$  and Ees were not significantly altered after CPB, whereas De Hert et al. report a reduced  $dP/dt_{MAX}$  indicating reduced contractile state.<sup>21</sup>

### **Comparison with TEE**

As an alternative to invasive volume measurements several groups have used TEE to obtain on-line area determination.<sup>30-33</sup> This method is less invasive but when used to construct pressure-area loops it still requires a LV catheter for pressure measurements, and a loading intervention. Schmidlin et al. tested whether pressure-area relations may be used as a surrogate for pressure-volume relations to detect changes in contractile state and they concluded that pressure-area analysis provides the same changes as pressure-volume analysis.<sup>33</sup> However the calculations derived from area estimates have several limitations. During the cardiac cycle the through-plane motion of the LV complicates volume calculations by short axis area estimates. This effect is even more prominent during acute loading interventions. On the contrary, the intraventricular placement of the conductance catheter provides on-line volume measurements of almost the whole ventricle unaffected by translations or rotations of the heart within the thorax. In general, on-line area determination by TEE requires optimal image quality and the stability and reproducibility of measurements is more successful at higher preload conditions by minimizing effects of tracing errors.<sup>31</sup> Area estimates derived during caval

vein occlusion could become very small thereby decreasing precision of the digital echocardiographic quantification method for calculation of pressure-area relations. In addition the precision is reduced in the presence of regional wall motion abnormalities.<sup>30</sup> Conventional assessment of diastolic function by TEE (i.e. without simultaneous LV pressure measurement) has two disadvantages compared with the conductance catheter method. First, assessment of both active and passive components requires two separate TEE views, being the midpapillary esophageal long-axis and transgastric short-axis view, respectively.<sup>32</sup> Second, the active diastolic relaxation measured by mitral Doppler flow analysis is heart-rate and load-dependent.

In conclusion, despite the above limitations, the limitations of TEE are outweighed by its proven clinical value to visualize the endoventricular wall and to quantify segmental wall motion. On the other hand, the important value of the conductance catheter is that it yields accurate, load-independent quantitative data on basic systolic and diastolic function. The possibility to measure these fundamental quantities in addition to the data provided by TEE may prove to be important in selected patient-groups and is ideal to evaluate e.g. new surgical techniques or anesthetic agents or procedures. The physiological effects on systolic and diastolic function reported in this study will be useful reference data for future studies in patients with depressed LV function undergoing cardiac surgery.

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## LETTER TO THE EDITOR

### **Left ventricular function after cardiopulmonary bypass is related to the length-dependent regulation of myocardial function**

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**Anesth Analg 2004; 99: 311-312**

We read with interest the paper of Tulner and colleagues, in which they reported, in eight coronary surgery patients, the use of the conductance catheter method for the peri-operative assessment of left ventricular (LV) function.<sup>1</sup> After cardiopulmonary bypass (CPB), the authors observed a preserved systolic function, an acceleration of LV pressure fall, and an increase in end-diastolic pressure (EDP). They suggested that these data may constitute useful reference values for further studies in patients undergoing cardiac surgery. We think that some caution is indicated with respect to this statement.

Recovery of LV function after CPB is a complex phenomenon and various patterns have been described over the years, most of them reporting a transient decrease in cardiac function. Different factors may be responsible for this variability. Apart from differences in patient population and cardioprotective strategies, specific weaning procedures and the choice of the anesthetic regimen may also influence post-CPB myocardial recovery. For instance, early restoration of preload conditions can prevent the transient depression of both systolic and diastolic dysfunction after weaning from CPB (ref. 30 in the article by Tulner et al.).<sup>2</sup> Similarly, the use of a volatile anesthetic regimen was associated with a better early recovery of myocardial function than a total intravenous regimen.<sup>3,4</sup>

More important however is the individual variability in cardiac functional reserve. It has been shown in coronary surgery patients that an increase in cardiac load resulted in a variable hemodynamic response that could not be explained by differences in preoperative variables. Some patients showed an improvement, whereas other patients showed either no change or even an impairment of LV function. These patients developed a decrease in maximal rate of pressure development ( $dp/dt_{max}$ ), a delayed myocardial relaxation (increase in tau) with enhanced load dependence of LV pressure fall, and a major increase in EDP. These patients showed systolic and diastolic

dysfunction post-CPB, and necessitated inotropic support to be weaned from CPB.<sup>5</sup> This latter response has been attributed to a deficient length-dependent regulation of myocardial function.<sup>6</sup> On the other hand, patients who developed improvement of myocardial function with an increase in cardiac load (manifested by an increase in  $dP/dt_{max}$ , an acceleration of LV pressure fall with a decrease in tau, less load dependence of LV pressure fall and a minor change in EDP), typically showed no (or only minor) decrease in myocardial function post-CPB.<sup>5</sup>

In view of these data, it seems that the results reported by Tulner et al. concern a subgroup of patients with good cardiac functional reserve and an adequate length-dependent regulation of myocardial function, resulting in a preserved myocardial function post-CPB. Therefore, this particular response, although present in some patients, cannot be withheld as the sole reference for the patient population undergoing coronary surgery with CPB.

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## IN RESPONSE

We thank De Hert and Van der Linden for their insightful comments on our paper and we would like to respond on some of the issues brought forward.<sup>1</sup> The aim of our study was two-fold: First to describe our approach to quantify peri-operative LV function, and second to obtain a reference data set for future studies in patients undergoing cardiac surgery. The comments of De Hert and Van der Linden focus on the latter aspect of our study.

We fully agree that the published literature indicates a substantial variability in recovery of LV function after cardiopulmonary bypass and we acknowledge the extensive list of possible factors influencing this variable outcome. In fact, this is exactly the reason why we felt it was necessary to generate a data set that would be applicable to the anesthetic and cardioprotective approach followed in our institute. Specifically, we use low-dose target-controlled infusion of propofol, remifentanyl and sufentanil, and intermittent antegrade warm-blood cardioplegic arrest during normothermic cardiopulmonary bypass. The metabolic advantages of this approach have already been published, but few data are available on the acute hemodynamic effects. Our study was performed in patients with relatively preserved LV function undergoing elective CABG, to ensure that the possible changes in LV function could be contributed mainly to the effects of anesthesia and cardioplegic arrest, rather than to the surgical intervention. This selection may partly explain the preserved post-operative systolic function in our patient group. However, De Hert et al. studied a similar patient group and reported a more variable outcome that could not be explained by pre-operative LV function.<sup>2</sup> Therefore differences in anesthesia and cardioplegic approaches between our study and the studies by De Hert et al. may need to be considered. One such difference is the use of normothermic arrest with blood cardioplegia in our study, whereas the studies of de Hert et al. included the use of hypothermia and crystalloid cardioplegia. This may be important because recent studies indicate less myocardial cell damage after normothermic blood cardioplegia.<sup>3</sup> Furthermore, the use of propofol in both studies may not be comparable because hypothermia has an important influence on propofol pharmacokinetics.<sup>4</sup> However, we certainly agree that extrapolation of our findings to patients with poor baseline LV function and prolonged cardiac arrest should be done with caution. But despite this, we would still conclude that the new data provided by our study constitute valuable background information when interpreting the acute

hemodynamic effects of complex surgical interventions such as LV reconstruction in heart failure patients in whom the same anesthesia and cardioplegia approach is used.

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