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ABSTRACT

Aims To test a method to predict the end-diastolic pressure—volume relationship (EDPVR) from a single beat in patients with heart failure.

Methods and results Patients (New York Heart Association class III—IV) scheduled for mitral annuloplasty (n=9) or ventricular restoration (n=10) and patients with normal left ventricular function undergoing coronary artery bypass grafting (n=12) were instrumented with pressure-conductance catheters to measure pressure—volume loops before and after surgery. Data obtained during vena cava occlusion provided directly measured EDPVRs. Baseline end-diastolic pressure (P_m) and volume (V_m) were used for single-beat prediction of EDPVRs. Root-mean-squared error (RMSE) between measured and predicted EDPVRs, was 2.79±0.21 mm Hg. Measured versus predicted end-diastolic volumes at pressure levels 5, 10, 15 and 20 mm Hg showed tight correlations (R^2=0.69—0.97). Bland—Altman analyses indicated overestimation at 5 mm Hg (bias: pre-surgery 44 ml (95% CI 29 to 58 ml); post-surgery 35 ml (23 to 47 ml)) and underestimation at 20 mm Hg (bias: pre-surgery −57 ml (−80 to −34 ml); post-surgery −13 ml (−20 to −7.0 ml)). End-diastolic volumes were significantly different between groups and between conditions, but these differences were not dependent on the method (ie, measured versus predicted). RMSEs were not different between groups or conditions, nor dependent on V_m or P_m, indicating that EDPVR prediction was equally accurate over a wide volume range.

Conclusions Single-beat EDPVRs obtained from hearts spanning a wide range of sizes and conditions accurately predicted directly measured EDPVRs with low RMSE. Single-beat EDPVR indices correlated well with directly measured values, but systematic biases were present at low and high pressures. The single-beat method facilitates less invasive EDPVR estimation, particularly when coupled with emerging non-invasive techniques to measure pressures and volumes.

INTRODUCTION

Diastolic left ventricular (LV) properties are divided into active and passive components.[1] Availability of a family of echocardiographic and Doppler-derived parameters has facilitated significant advances in basic understanding of many aspects of the active component of left ventricular relaxation.[2] Quantification of passive diastolic LV properties remains a challenge, even when invasive techniques are employed,[3] and it continues to be debated whether echocardiographic evaluation is sufficient to diagnose diastolic function and guide clinical care in patients with heart failure.[4] This issue has received renewed interest with the desire to better characterise pathophysiological entities which are currently acknowledged to have high clinical relevance such as heart failure with normal ejection fraction and diastolic heart failure,[1 3 5 6] and to understand the impact of treatments such as surgical ventricular reconstruction,[7–9] assist devices[10 11] and cell therapy[12 13] on ventricular function. It is widely accepted that the optimal way to characterise passive ventricular properties is via the relation between end-diastolic pressure and end-diastolic volume.[14] This end-diastolic pressure—volume relationship (EDPVR) uniquely describes the amount of volume required to achieve a specific pressure in the relaxed left ventricle and, vice versa, the diastolic filling that will occur for a specified filling pressure. This global relationship integrates the net effects of chamber geometry, myocardial wall thickness, and structure and composition of the myocardium. In patients with heart failure, each of these factors may be abnormal, either directly caused by the disease or as a compensatory response, typically resulting in a change in the global EDPVR.

An essential feature of the EDPVR is its non-linearity, reflecting the fact that diastolic stiffness, dP/dV, gradually increases with loading. This results in an EDPVR that is convex towards the volume axis and is typically well described by an exponential or power function. This property dictates that EDPVR quantification requires measurement of end-diastolic pressure and volume from multiple beats over a fairly wide range of end-diastolic pressures. Recently, Klotz *et al*[15 16] proposed a methodology to estimate the EDPVR from a single beat. This method was based on the observation that EDPVRs from patients with widely different heart sizes, and even EDPVRs from different species, all have a fairly common shape provided that ventricular volume is normalised with an appropriate scaling method. The authors tested their approach prospectively on a limited number of human subjects and concluded that the proposed scheme allowed a reasonably accurate prediction of the EDPVR, particularly when analysed at a group level.

Although this approach was validated to predict the EDPVR in human dilated cardiomyopathic hearts ex vivo (following their removal for heart transplant), the single-beat method has not yet been validated in vivo in patients with dilated

cardiomyopathy. Therefore, the purpose of our study was to assess prospectively the accuracy of the approach in patients with end-stage heart failure scheduled for surgery, using the conventional multibeat EDPVR obtained from pressure–volume loops acquired during gradual preload reduction by vena cava occlusion as the gold standard.

In addition to physiological studies regarding mechanisms of diastolic dysfunction, the single-beat methodology has direct practical clinical utility because it allows more specific—that is, less load-dependent, quantification of diastolic function. As an example, it should allow a more detailed evaluation of surgical interventions which potentially have opposing effects on systolic and diastolic function.[17] Also, this method may enable more specific targeting of pharmacological support in intensive care.[18]

PATIENTS AND METHODS

Patients

The study groups consisted of patients with heart failure (New York Heart Association (NYHA) class III–IV, LV ejection fraction <40%) despite optimal medical treatment, scheduled for restrictive mitral annuloplasty (RMA group, n=9), or surgical ventricular restoration (SVR) with or without RMA (SVR group, n=10). A third group consisted of patients with normal LV function (ejection fraction >50%) undergoing elective coronary artery bypass grafting (CABG group, n=12). The sample size was based on the aim to detect differences between groups and conditions that would be considered physiologically relevant (>25%). Based on earlier studies we assumed a 20% within-group variability for the main parameters. The aim to detect differences >25% with type I error <5% and a power of 80% indicated that approximately 10 patients per group should be enrolled. In principle, all patients scheduled for CABG, RMA and/or SVR were considered eligible for the study. Potential enrolment in the study was left to the discretion of the surgeon who would operate on the patient. Three patients initially enrolled were not included in the analysis because ultimately no complete measurements were performed owing to time limitations or technical difficulties during the procedure.

Heart failure symptoms were quantified by NYHA classification, and baseline angiographic LVEFs were obtained during diagnostic catheterisation. In all patients LV pressure–volume loops (see below) were assessed in the operating room before (pre) and after (post) the surgical intervention. Thus, all measurements were obtained in anaesthetised conditions, with open chest and open pericardium, and either just before (pre) or after (post) cardiopulmonary bypass. All patients underwent normothermic heart operations as scheduled with intermittent antegrade warm, oxygenated blood cardioplegia.[19 20] The study protocol was approved by our local ethics committee, and all patients gave written informed consent.

Anaesthesia

Before surgery the patients received 2 mg of lorazepam as sublingual premedication. Subsequently, all patients received total intravenous anaesthesia with target-controlled infusion of propofol, remifentanil and sufentanil, as described previously.[8 21] We expected that some patients would need inotropic support and, therefore, to avoid bias, we provided the same (low dose) inotropic support in all patients with heart failure. Inotropic support was started directly after induction of anaesthesia, with a low loading dose of 0.25 mg/kg enoximone administered over 10 min, and thereafter we provided continuous infusion at a rate of 0.50 μg/kg/min, which was maintained during the whole operation.

Instrumentation

To acquire pressure–volume loops, we used a 7F pressure-conductance catheter (CD-Leycom, Zoetermeer, The Netherlands) incorporating a solid-state pressure sensor and 12 electrodes (10 mm spacing), which was connected to a Leycom Cardiac Function Lab signal processor (CD-Leycom). A multiplane transoesophageal echocardiography probe was inserted to monitor cardiac function and facilitate positioning of the conductance catheter intraoperatively. The conductance catheter was introduced via a sheath in the ascending aorta and positioned with the pigtail in the LV apex and the two most proximal electrodes just above the aortic valve to get an optimal match with the LV long axis.[21] The conductance signals were calibrated by thermodilution and hypertonic saline dilution.[21–23] To this end, a thermal filament catheter was placed with its tip in the pulmonary artery via the right internal jugular vein for semicontinuous thermodilution cardiac output measurements (Edwards Life Sciences, Uden, The Netherlands) and for hypertonic saline injections. A caval tourniquet was applied around the inferior cava to perform temporary preload reductions by caval occlusion. Epicardial pacing wires were placed on the right atrium.

EDPVR by caval occlusion and by single-beat estimation

The study protocol involved pressure–volume measurements at a fixed (paced) heart rate of 80 bpm during steady-state conditions and during gradual preload reduction by inferior vena caval occlusion (VCO). To avoid interference with respiration, all measurements were acquired after disconnecting the ventilator. The conventional EDPVRs were derived from the serial pressure–volume loops acquired during preload reduction as shown in figure 1. From each loop the end-diastolic pressure–volume point was identified, and the set of points were fit by least-squared regression analysis to a standard curve to characterise the EDPVR: $P=C_{ED}\cdot\exp(K_{ED}V)$.[14] This EDPVR was designated as the VCO-derived EDPVR ($EDPVR_{VCO}$). From the fit, we determined the volumes at end-diastolic pressures (EDPs) 5, 10, 15 and 20 mm Hg; EDV_5, EDV_{10}, EDV_{15} and EDV_{20}, respectively.

In addition, the EDPVR was determined by the single-beat method.[15] The computational method has been explained in detail elsewhere.[16] Briefly, Klotz *et al* proposed that after appropriate normalisation of volumes to account for heart size, the EDPVR is approximately invariant between subjects and even between species. Specifically, normalised volume (V_n) is based on estimates of the volume at which pressure is ~0 mm Hg (V_0) and the volume at which pressure equals 30 mm Hg (V_{30}), so that $V_n=(V-V_0)/(V_{30}-V_0)$. The EDPVR based on V_n is designated as $EDPVR_n$. Based on measurements in ex vivo isolated human hearts, this volume-normalised curve was found to be well represented by the equation $P=A_nV_n^{Bn}$ with $A_n=27.78$ mm Hg and $B_n=2.76$. The authors also derived an empirical relationship to estimate V_0: $V_0=EDV\ (0.6–0.006\ EDP)$. Based on these relations the EPDVR in an individual subject can be predicted (ie, specified analytically) from a single measured end-diastolic pressure–volume point (V_m, P_m) by calculating V_{30} as: $V_{30}=V_0+(V_m-V_0)/(P_m/A_n)^{(1/Bn)}$, and subsequently represented as $P=\alpha V^{\beta}$, with $\beta=\log(P_m/30)/\log(V_m/V_{30})$ and $\alpha=30/V_{30}^{\beta}$. Thus, α and β are directly calculated from the V_m and P_m values and define the single-beat derived EDPVR ($EDPVR_{SB}$). In our study we used the first beat of the VCO dataset to determine the $EDPVR_{SB}$ as illustrated in figure 1. In analogy with the $EDPVR_{VCO}$ we also calculated the values of volumes on the $EDPVR_{SB}$ at the pressure levels 5, 10, 15 and 20 mm Hg. Comparisons between $EDPVR_{VCO}$ and $EDPVR_{SB}$ were performed in individual patients and also analysed at the group level by

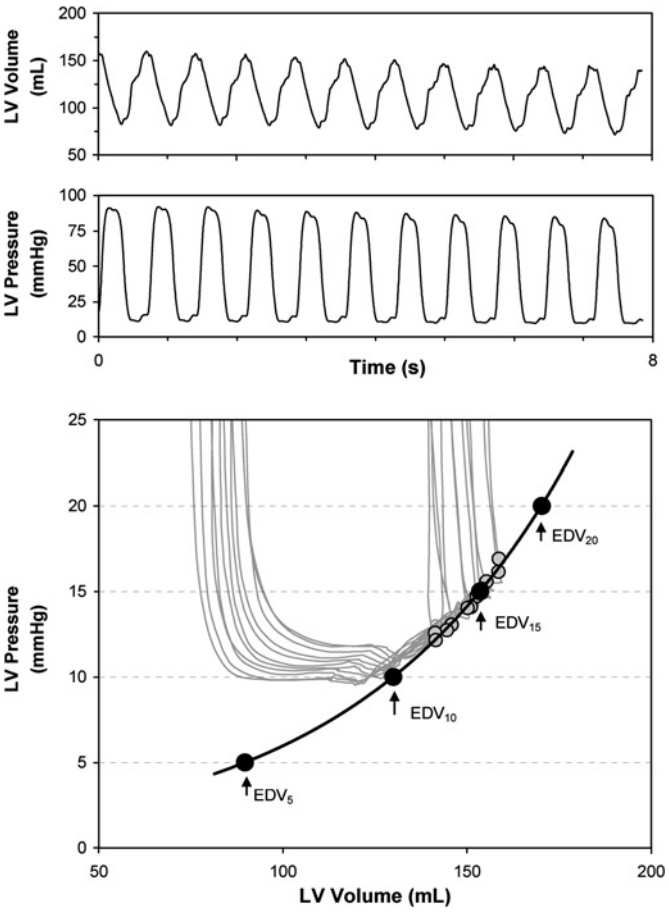

Figure 1 Left ventricular (LV) pressure and volume signals during gradual preload reduction obtained by vena cava occlusion. End-diastolic pressure–volume points were fitted with an exponential curve and the intercepts at 5, 10, 15 and 20 mm Hg are indicated (EDV_5, EVD_{10}, EDV_{15}, and EDV_{20}).

considering six groups: the patients with CABG before and after surgery (CABG-pre, CABG-post), the patients with RMA before and after surgery (RMA-pre, RMA-post), and the patients with SVR before and after surgery (SVR-pre, SVR-post).

Data analysis and statistical methods

To determine the predictive accuracy of the $EDPVR_{SB}$ in individual patients we calculated the root-mean-squared error (RMSE) between actual and estimated pressure (ie, based on $EDPVR_{SB}$) at the same end-diastolic volume. RMSE quantifies the average difference between the estimated and the actual values including both bias and variance of the estimator. All data points (ie, beats) acquired during a VCO were included in the calculation. Thus, $RMSE=\sqrt{[(1/n)\sum(P_{m,i}-P_{p,i})^2]}$, in which "n" equals the number of data points, $\sum$ indicates the summation over all n data points (i=1 to n), $P_{m,i}$ represents the measured pressures for an individual data point and $P_{p,i}$ the corresponding predicted pressure.

To detect possible differences in RMSE values between groups (CABG, RMA and SVR) or between conditions (pre-surgery, post-surgery) we performed a univariate analysis of variance using a general linear model with patients as random factor and groups and conditions as fixed factors, including all interactive effects. Similar analyses were performed for V_m and P_m. We also determined VCO-derived and single-beat-derived EDV_5, EDV_{10}, EDV_{15} and EDV_{20}. To compare these values between the two methods (single-beat vs VCO), VCO-derived and single-beat derived EDV_5, EDV_{10}, EDV_{15} and EDV_{20} values were correlated with linear regression, and biases and limits of agreement were determined with Bland–Altman analyses. Pre- and post-surgery data were analysed separately to obtain a cross-sectional (ie, one data point per patient) design. Precisions of biases and limits of agreement were quantified by 95% CIs.[24]

To assess possible differences between groups, conditions and methods, the data were subjected to a univariate analysis of variance using a general linear model with patients as random factor, and groups, conditions and methods as fixed factors. All interactive effects between fixed factors were included in the model, in particular to assess whether the detected differences were dependent on the method. This approach takes into account that each group consisted of a different set of patients, but within each group each patient was measured in two conditions (ie, a repeated measures design). Statistical analyses were performed with commercially available software (SPSS 12.0). Results are expressed as means±SD, all tests were two sided and a probability value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the patients are summarised in table 1. Representative EDPVRs from five patients spanning a wide range of volumes are shown in figure 2. On average, end-diastolic volume decreased by 37±17 ml and end-diastolic pressure decreased by 5.8±4.0 mm Hg during a VCO. These loading changes corresponded to 22±12% of baseline end-diastolic volume (V_m) and 41±18% of baseline end-diastolic pressure (P_m), which allowed an accurate determination of VCO-derived EDPVR. Relative changes were similar in all groups (CABG group: 25±12% and 45±17%; RMA group: 19±13% and 36±18%; SVR group: 19±13% and 36±18%, respectively, for end-diastolic volume and end-diastolic pressure). The RMSEs for these examples are indicated in the figure. The overall mean RMSE obtained by pooling data from all patients was 2.79±0.21 mm Hg. Table 2 provides the mean RMSEs for each of the groups in both conditions. Statistical analysis (ANOVA) showed that the RMSE was not significantly different between groups or between conditions, indicating that the predictive accuracy of the single-beat method was similar in all cases.

Table 2 also shows mean EDV_5, EDV_{10}, EDV_{15} and EDV_{20} obtained by the single-beat method and by VCO for all groups and conditions. Differences between groups, conditions and methods, and their interactions were tested by ANOVA. The results indicated the presence of significant differences in EDVs between *groups* at each pressure and also between *conditions*, except at 5 mm Hg. Significant differences between *methods* for EDV_5 and EDV_{20} were also noted, indicating that the single-beat

Table 1 Baseline patient characteristics

	CABG group	RMA group	SVR group
No of patients (n)	12	9	10
Male/female (n)	10/2	4/5	8/2
Age (y)	63±9	55±17	66±8
NYHA class		2.5±0.8	3.3±0.5
LVEF (%)	59±9	29±8	25±10
MR grade		3.0±0.5	2.0±1.1

Data are presented as number of patients, or as mean±SD.
CABG, coronary artery bypass grafting; LVEF, angiographic left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; RMA, restrictive mitral annuloplasty; SVR, surgical ventricular restoration.

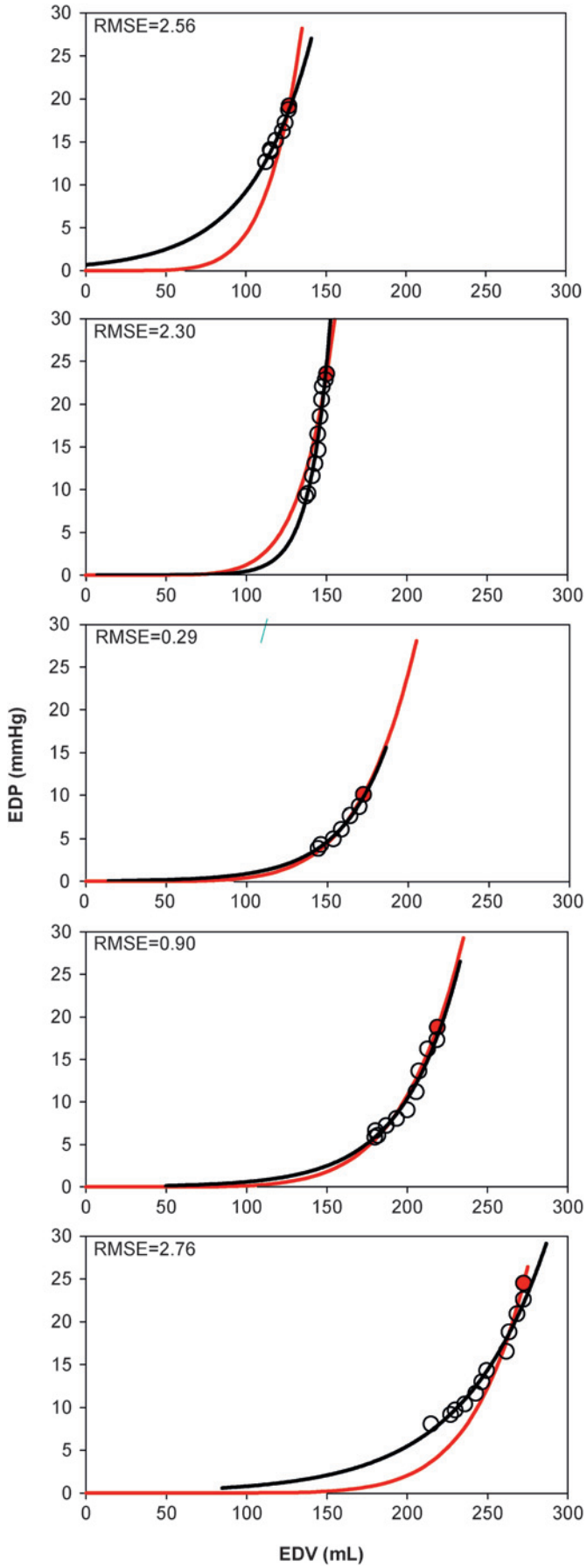

Figure 2 Illustration of the wide range of end-diastolic volumes covered in the various patients groups. Representative examples of end-diastolic pressure–volume points during preload reduction (vena cava occlusion, VCO) and corresponding single-beat derived EDPVRs are shown. The measured data were fitted with an exponential curve (black lines indicate $EDPVR_{VCO}$: $P=C_{ED}\cdot\exp(K_{ED}V)$). The predicted single-beat-derived EDPVR (shown in red) was based on the end-diastolic pressure–volume points of the baseline pressure–volume point (marked in red): P_m, V_m. Root-mean-squared errors (RMSEs) were calculated including all data points obtained during preload reduction.

method overestimated EDV_5 and underestimated EDV_{20}. Interestingly, ANOVA did not show any significant interaction effects, indicating that the observed differences between groups and between conditions (main effects) were not dependent on the method (or, vice versa, that the observed differences between methods were not dependent on the group or on the condition).

The relations between single-beat-derived and VCO-derived EDV_5, EDV_{10}, EDV_{15} and EDV_{20} were also analysed by linear regression and by Bland–Altman analyses (figure 3). These plots show a good correlation between the two methods (R^2=0.69–0.97) and confirm the overestimation of EDV_5 and underestimation of EDV_{20} as quantified by the biases in the Bland–Altman plots.

To investigate a possible dependence of the goodness of the fit on baseline end-diastolic pressure or volume, we performed linear regressions between RMSE and P_m and V_m, respectively, for all pooled data. The results indicated no significant correlations: $RMSE=2.1+0.053\cdot P_m$ (R^2=0.031, p=0.180) and $RMSE=3.4-0.0035\cdot V_m$ (R^2=0.023, p=0.246). To further illustrate this, figure 4 shows RMSE in relation to P_m and V_m for all groups. Figure 5 shows mean (V_m,P_m) and the mean $EDPVR_{SB}$ based on these values for each group. The figure shows the larger volumes and higher end-diastolic pressures in the patients with heart failure (RMA and SVR groups) compared with the patients with relatively normal LV function (CABG groups). In all patients, EDP increased and EDV decreased, or at least tended to do so, after surgery. As expected this effect was particularly evident in the patients undergoing ventricular reshaping (SVR group). Note that the change (comparing pre- versus post-surgery) in $EDPVR_{SB}$ was also most pronounced in this group.

DISCUSSION

This study assessed the accuracy of a method to estimate the EDPVR from EDP and end-diastolic volume measured on a single steady-state beat.[15 16] Several recent studies have applied this concept, but in vivo validation in patients with dilated cardiomyopathy was still lacking.[25–27] The EDPVR is the most comprehensive and specific means of characterising passive diastolic properties of the left ventricle and thus provides essential information on ventricular remodelling in heart failure. This relation enables accurate determination of the effects of disease and of treatments on ventricular remodelling and reverse remodelling. Unfortunately, assessment of the EDPVR is complicated because it requires continuous LV pressure and volume measurements obtained during a change in loading to achieve the required variation in pressures and volumes. This typically involves the use of a conductance catheter combined with, for example, a vena cava balloon catheter to induce a preload reduction. The required invasive instrumentation has limited the employment of the EDPVR concepts in routine clinical practice. The proposed computational method avoids the need for a load intervention and, particularly when combined with evolving non-invasive techniques to estimate ventricular pressure and volume, would provide an attractive alternative for assessing the EDPVR. Non-invasive methods for measurements

Table 2 End-diastolic pressure–volume relation (EDPVR) indices in all groups and conditions obtained by the single-beat (SB) and the vena cava occlusion (VCO) methods

		CABG		RMA		SVR		Main effects			Interaction effects		
		Pre	Post	Pre	Post	Pre	Post	Group	Condition	Method	Group–condition	Group–method	Condition–method
RMSE (mm Hg)		2.6±1.5	2.6±1.7	3.3±1.6	2.2±1.0	2.7±1.2	3.5±2.1	0.524	0.854	NA	0.163	NA	NA
V_m (ml)		140±45	140±39	232±94	225±55	210±55	186±60	<0.001	0.484	NA	0.778	NA	NA
P_m (mm Hg)		8.7±2.2	13.7±5.0	13.0±5.2	14.2±3.1	11.9±5.6	18.3±4.6	0.014	<0.001	NA	0.182	NA	NA
EDV_5 (ml)	SB	127±40	120±34	201±83	190±50	186±50	154±51	<0.001	0.212	<0.001	0.479	0.562	0.695
	VCO	96±40	101±47	149±99	145±41	137±66	110±62						
EDV_{10} (ml)	SB	143±45	135±38	226±94	214±55	208±56	171±53	<0.001	0.010	0.916	0.323	0.950	0.404
	VCO	154±44	132±43	229±98	204±53	219±88	153±54						
EDV_{15} (ml)	SB	154±48	144±41	242±101	229±59	223±60	181±55	<0.001	0.002	0.095	0.300	0.997	0.177
	VCO	187±55	150±42	276±114	238±68	267±110	178±52						
EDV_{20} (ml)	SB	162±50	151±43	254±106	240±62	234±62	189±56	<0.001	0.001	0.010	0.299	0.966	0.106
	VCO	212±65	163±42	310±129	262±80	300±127	196±51						

Values are mean±SD. Indices were analysed by univariate analysis of variance to assess the effects of group, condition, and method (if applicable) and all interactive effects (the group–condition–method interaction was tested and non-significant at $p>0.90$ in all cases).
CABG, coronary artery bypass grafting; EDV, end-diastolic volume; NA, not applicable; RMA, restrictive mitral annuloplasty; RMSE, root-mean-squared error; SVR, surgical ventricular restoration; VCO, vena caval occlusion.

of LV volume include MRI, echocardiography and radionuclide ventriculography, whereas end-diastolic pressure may be estimated from pulmonary vein velocity by Doppler-echocardiographic techniques or by combining transmitral early diastolic velocity (E) with either tissue-Doppler mitral velocity (E′) or two-dimensional echocardiographic global diastolic strain or strain rate measurements.[28 29]

Development and prior validation of the single-beat method was mainly based on pressure–volume measurements in ex vivo hearts. While these measurements are highly accurate, they may not reflect in vivo conditions, in part because of the influences of the pericardium, atria and the right ventricles on the LV EDPVR. In this study, we tested this single-beat approach versus the EDPVR obtained by VCO in patients with ventricular volumes spanning from normal to severely dilated. We included the three surgical groups at two conditions to obtain a wide range of EDPVRs. As expected, differences in diastolic pressures and volumes were highly significant between groups and between conditions. The low overall RMSE values that characterises the difference between measured (VCO-derived) and predicted (single-beat-derived) EDPVRs indicated good predictive accuracy of the single-beat method. Although heart size (end-diastolic volume) and pressure were substantially different between groups, the mean RMSE was similar (~3 mm Hg) in each group and essentially the same as determined for the in vivo hearts in the original validation study.[15 16] Data from the ex vivo human hearts examined in that original study suggested that predicted EDPVRs based on measured pressure–volume points at lower pressures (~10 mm Hg) would be less accurate than those at higher pressures (~20 mm Hg). This limitation was not encountered in our study, which did not show a correlation between either measured end-diastolic pressure or volume and the accuracy as indicated by the RMSE of the predicted EDPVR.

The current analysis focused on testing the accuracy of the single-beat method to predict end-diastolic volume over a range of end-diastolic pressures from 5 to 20 mm Hg. The analysis of pooled data showed a tight correlation between measured and predicted end-diastolic volume at each pressure level. The best correspondence between the single-beat and VCO methods was obtained at the 10 mm Hg level, which was partly predictable because the estimated EDPVR is anchored to the baseline end-diastolic pressure–volume point and the overall mean end-diastolic pressure was 13±5 mm Hg.

We observed a statistically significant overestimation of end-diastolic volume at the 5 mm Hg pressure level and an underestimation at 20 mm Hg. There are at least two possible explanations for these systematic errors. First, the values of A_n and B_n on which the predication is based were determined from direct, highly reliable volume measurements made with intraventricular balloons in explanted hearts. A systematic difference in volume determination by conductance catheter compared with the balloon method would impact on the optimal values of A_n and B_n. Second, as implied above, optimal values of A_n and B_n may be influenced by the effects of the pericardium, the atria and the right ventricle on the LV EDPVR. However, the highly linear correlation between measured and predicted volumes at each pressure level, and the fact that these relations are independent of heart size and underlying clinical condition suggest that it is possible to correct the prediction method with a linear transformation using the equations shown in figure 3 for the different pressure levels.

In addition to estimating the volumes on the EDPVR at specific pressures, which can be used to index changes in ventricular capacitance in individual patients, or differences between groups, in a relatively load-independent fashion, other important parameters used to characterise diastolic properties are myocardial stiffness and ventricular chamber stiffness, which are both related to the local slope of the EDPVR at different pressures.[14] In the prior study it was determined that the prediction of the EDPVR provided by the single-beat method was not sufficiently accurate to allow quantification of the EDPVR slope, therefore this method was not recommended for assessment of diastolic stiffness. To test whether this limitation was also found in our dataset we determined conventional VCO-derived stiffness (S_{VCO}) and single-beat derived stiffness (S_{SB}) as

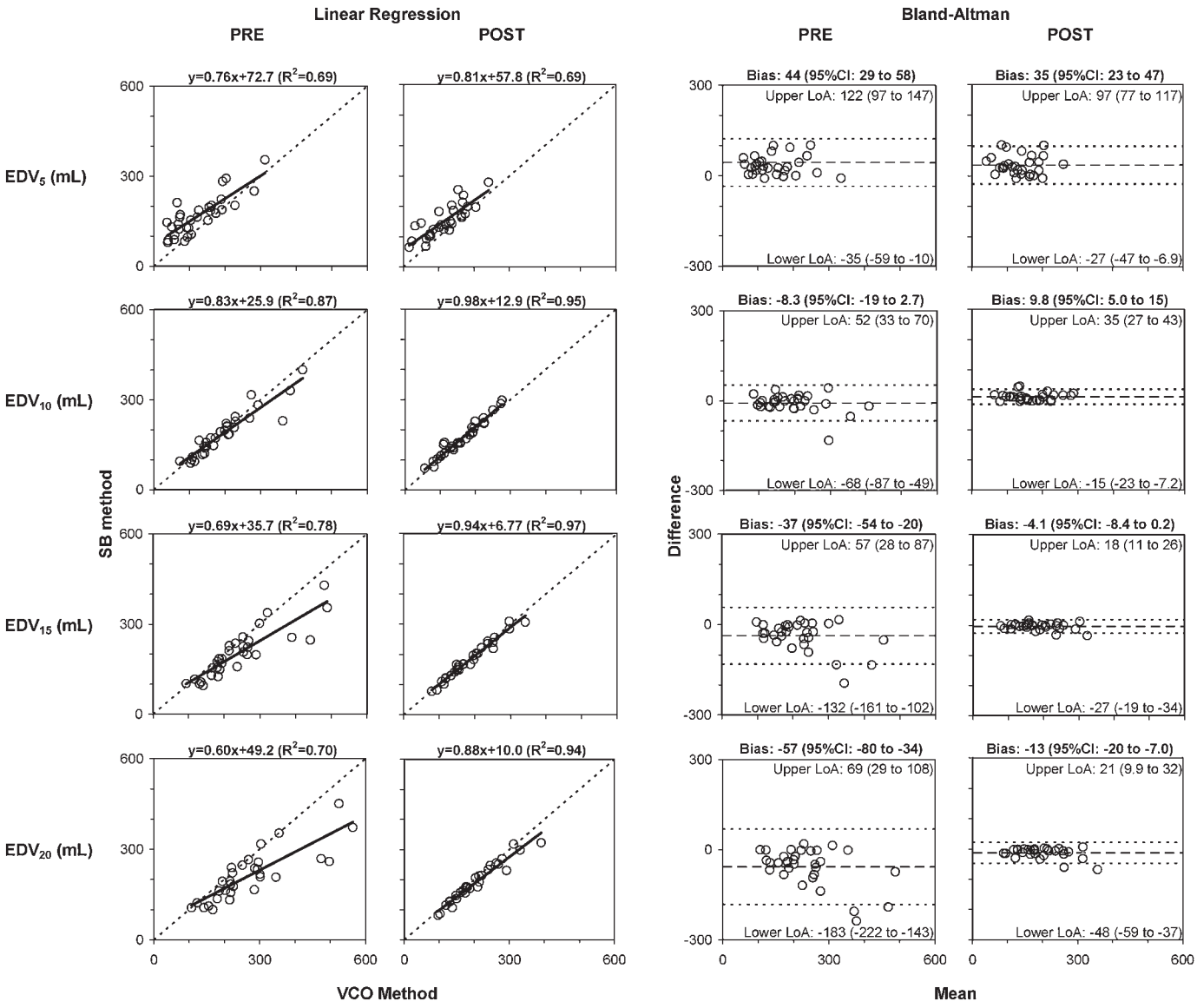

Figure 3 The relations between single-beat-derived and vena cava occlusion (VCO)-derived EDV_5, EDV_{10}, EDV_{15} and EDV_{20} were analysed for pre-surgery (PRE) and post-surgery (POST) data by linear regression (left panels) and by Bland–Altman analyses (right panels). In the regression plots, the full lines give the linear fits, the dotted lines represent the lines-of-identity. In the Bland–Altman plots, the biases and the limits of agreement (LoA=bias±1.96 SDs) are indicated by horizontal dotted lines. CIs (95%) for biases and limits of agreement are given in the figures (values between brackets).

the local slopes of the corresponding EDPVRs at the measured baseline end-diastolic pressure (P_m). Linear regression indicated a significant but limited correlation and the relation showed a substantial offset, indicating overestimation by the single-beat method ($S_{VCO}=0.977S_{SB}+0.299$, $R^2=0.390$, $p<0.0001$). Therefore, the same conclusion may be drawn from the present study and further work is needed to investigate if a single-beat model can be developed that more accurately predicts this specific aspect of diastolic function. In general, although EDPVR-derived indices are widely used in experimental physiological studies, their clinical utility and accuracy needs to be further investigated.

It should be noted that this study tested the single-beat method in anaesthetised, open-chest, open-pericardium, surgical patients. The intraoperative conditions may have affected the

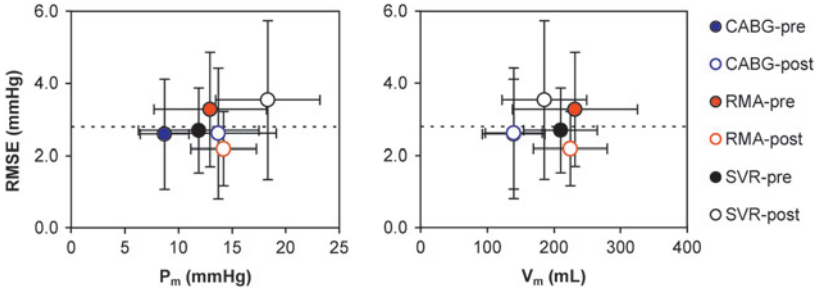

Figure 4 Root-mean-squared error (RMSE) between measured (ie, using the vena cava occlusion method) and predicted (single-beat method) pressure as a function of baseline pressure (P_m) and volume (V_m) for all groups. The horizontal error bars represent the SD for P_m (left panel) and Vm (right panel) and the vertical error bars represent the SD for RMSE. No correlations were present (see text for details). The overall RMSE (2.79±0.21 mm Hg) is indicated by the dotted lines. CABG, coronary artery bypass grafting; RMA, restrictive mitral annuloplasty; SVR, surgical ventricular restoration.

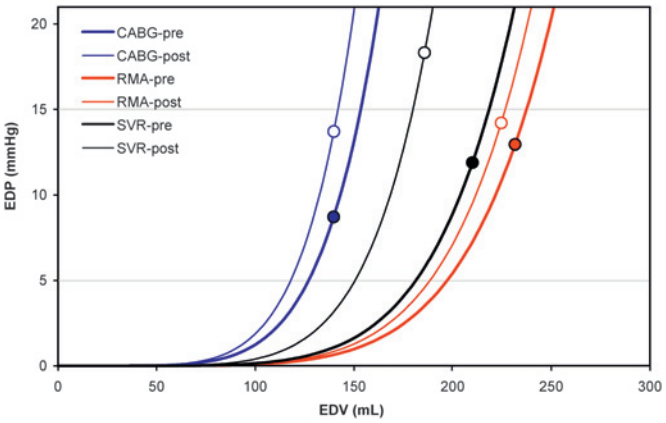

Figure 5 Mean end-diastolic pressure-volume points (P_m, V_m) for all groups and corresponding single-beat-derived end-diastolic pressure—volume relations. CABG, coronary artery bypass grafting; EDP, end-diastolic pressure; EDV, end-diastolic volume; RMA, restrictive mitral annuloplasty; SVR, surgical ventricular restoration.

diastolic pressure—volume relations: in addition to the effects of anaesthesia, in patients with dilated heart failure the relatively non-distensible pericardium may increase stiffness and hamper filling even in resting conditions and thus pericardectomy may acutely improve diastolic function[30 31] Although our analysis indicated that the single-beat method was equally accurate over a wide range of volumes and conditions, strictly speaking further research is needed to investigate whether the findings can be extrapolated to conditions such as encountered in awake patients in the catheterisation laboratory.

In summary, direct measurements of the EDPVRs from 31 patients with heart failure before and after surgical interventions using invasive methods correlated well with those predicted by a previously proposed single-beat method indicated by low RMSEs. Single-beat-derived indices showed tight correlations with corresponding VCO-derived indices, but systematic biases were present at low and high pressures. The findings were quantitatively similar to those obtained in prior isolated heart studies and in in vivo studies in a small number of patients with relatively normal heart sizes.[16] The present results obtained in patients with heart failure provide a critical independent validation of the single-beat estimation of the EDPVR. As (non-invasive) techniques to estimate end-diastolic pressures and volumes improve, this method may find an increasing number of applications in quantifying the effect of treatments on remodelling of the failing heart and in helping to understand the pathophysiology of diastolic heart failure.

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