Single-beat estimation of the left ventricular end-diastolic pressure–volume relationship in patients with heart failure


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Single-beat estimation of the left ventricular end-diastolic pressure—volume relationship in patients with heart failure

Ellen A ten Brinke,1 Daniel Burkhoff,2 Robert J Klatz,3 Carsten Tschöpe,4 Martin J Schalij,1 Jeroen J Bax,1 Ernst E van der Wall,1 Robert A Dion,3 Paul Steendijk1

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 veno cava occlusion provided directly measured EDPVRs. Baseline end-diastolic pressure (P\textsubscript{m}) and volume (V\textsubscript{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\textsuperscript{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\textsubscript{m} or P\textsubscript{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 devices10 11 and cell therapy12 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 al15 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.11 Also, this method may enable more specific targeting of pharmacological support in intensive care.10

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 LV EFs 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. Continuous volumetric 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 enoximine 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 transesophageal 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.22 23 24 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 fitted by least-squared regression analysis to a standard curve to characterise the EDPVR: P=CEP·exp(KEDV).14 This EDPVR was designated as the VCO-derived EDPVR (EDPVRVCO). From the fit, we determined the volumes at end-diastolic pressures (EDPs) 5, 10, 15 and 20 mm Hg: EDV5, EDV10, EDV15 and EDV20, respectively.

In addition, the EDPVR was determined by the single-beat method.15 The computational method has been explained in detail elsewhere.18 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 (Vn) is based on estimates of the volume at which pressure is ~0 mm Hg (V0) and the volume at which pressure equals 50 mm Hg (V50), so that Vn=(V−V0)/(V50−V0). The EDPVR based on Vn is designated as EDPVRn. Based on measurements in ex vivo isolated human hearts, this volume-normalised curve was found to be well represented by the equation P=ANVnβ with AN=27.78 mm Hg and βn=2.76. The authors also derived an empirical relationship to estimate V0: V0=EDV (0.60–0.006 EDP). Based on these relations the EDPVR in an individual subject can be predicted (ie, specified analytically) from a single measured end-diastolic pressure—volume point (Vn, Pn) by calculating V50 as: V50=V0+[(V−V0)/(Pn/ANb)]1/β, and subsequently represented as P=αVnβ, with β=log(P50/log(V50)/V0) and α=V0/V50β. Thus, α and β are directly calculated from the Vn and Pn values and define the single-beat derived EDPVR (EDPVRn).

In our study we used the first beat of the VCO dataset to determine the EDPVRn and EDPVRVCO as illustrated in figure 1. In analogy with the EDPVRn we also calculated the values of volumes on the EDPVRn at the pressure levels 5, 10, 15 and 20 mm Hg. Comparisons between EDPVRVCO and EDPVRn were performed in individual patients and also analysed at the group level by...
methods (single-beat vs VCO), VCO-derived and single-beat derived EDV5, EDV10, EDV15 and EDV20 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.

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 (V̄m) and 41±18% of baseline end-diastolic pressure (P̄m), 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 EDV5, EDV10, EDV15 and EDV20 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 EDV5 and EDV20 were also noted, indicating that the single-beat

Table 1 Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>CABG group</th>
<th>RMA group</th>
<th>SVR group</th>
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<tbody>
<tr>
<td>No of patients (n)</td>
<td>12</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Male/female (n)</td>
<td>10/2</td>
<td>4/5</td>
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<td>Age (y)</td>
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<td>55±17</td>
<td>66±8</td>
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<td>NYHA class</td>
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<td>3.3±0.5</td>
<td>3.3±0.5</td>
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<td>LVEF (%)</td>
<td>59±9</td>
<td>29±8</td>
<td>25±10</td>
</tr>
<tr>
<td>MR grade</td>
<td>3.0±0.5</td>
<td>2.0±1.1</td>
<td>2.0±1.1</td>
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</tbody>
</table>

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.
method overestimated EDV5 and underestimated EDV20. 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 EDV5, EDV10, EDV15 and EDV20 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 EDV5 and underestimation of EDV20 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: $\text{RMSE} = 2.1 + 0.053 \cdot P_m$ ($R^2 = 0.031$, $p = 0.180$) and $\text{RMSE} = 3.4 + 0.0035 \cdot V_m$ ($R^2 = 0.023$, $p = 0.246$). 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_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_based 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.2527 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 of 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: $P = C_{E0} \cdot \exp(K_{E0} \cdot V)$). 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.
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 transmural early diastolic velocity (E) with either tissue-Doppler mitral velocity (E') or two-dimensional echocardiographic global diastolic strain or strain rate measurements.1620

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 characterise 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 (∼5 mm Hg) in each group and essentially the same as determined for the in vivo hearts in the original validation study.1516 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 An and Bn on which the prediction 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 An and Bn. Second, as implied above, optimal values of An and Bn 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 (SVCO) and single-beat derived stiffness (SSB) as

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**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

<table>
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<td>SVR</td>
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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<0.001 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.
the local slopes of the corresponding EDPVRs at the measured baseline end-diastolic pressure (Pm). Linear regression indicated a significant but limited correlation and the relation showed a substantial offset, indicating overestimation by the single-beat method (SVCO = 0.977SSB + 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 3  The relations between single-beat-derived and vena cava occlusion (VCO)-derived EDV5, EDV10, EDV15 and EDV20 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).

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 (Pm) and volume (Vm) for all groups. The horizontal error bars represent the SD for Pm (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.
Although our analysis
The present results obtained in
in the catheterisation laboratory.
acutely improve diastolic function
anaesthesia, in patients with dilated heart failure the relatively
indicated that the single-beat method was equally accurate over
volumes improve, this method may
patients with heart failure provide a critical independent vali-
diastolic pressure—volume relations: in addition to the effects of
anaesthesia, in patients with dilated heart failure the relatively
case improves stiffness and hamper
filling even in resting conditions and thus pericardectomy may
case improve diastolic function
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 were
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. The
present results obtained in
patients with heart failure provide a critical independent vali-
dation of the single-beat estimation of the EDFVR. 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 remod-
eling of the failing heart and in helping to understand the
pathophysiology of diastolic heart failure.

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**Competing interests** None.

**Ethics approval** This study was conducted with the approval of the ethics committee Leiden University Medical Centre.

**Patient consent** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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