A novel method to derive pressure-volume (PV) loops noninvasively from cardiac magnetic resonance images has recently been developed. The aim of this study was to evaluate inter- and intraobserver variability of hemodynamic parameters obtained from noninvasive PV loops in healthy controls, subclinical diastolic dysfunction (SDD), and patients with heart failure with preserved ejection fraction, mildly reduced ejection fraction, and reduced ejection fraction. We included 75 subjects, of whom 15 were healthy controls, 15 subjects with SDD (defined as fulfilling 1 to 2 echocardiographic criteria for diastolic dysfunction), and 15 patients with preserved ejection fraction, 15 with mildly reduced ejection fraction, and 15 with reduced ejection fraction. PV loops were computed using time-resolved left ventricular volumes from cardiac magnetic resonance images and a brachial blood pressure. Inter- and intraobserver variability and intergroup differences of PV loop-derived hemodynamic parameters were assessed. Bias was low and limits of agreement were narrow for all hemodynamic parameters in the inter- and intraobserver comparisons. Interobserver difference for stroke work was 2 ± 9%, potential energy was 4 ± 11%, and maximal ventricular elastance was −4 ± 7%. Intraobserver for stroke work was −1 ± 7%, potential energy was 3 ± 4%, and maximal ventricular elastance was 1 ± 5%. In conclusion, this study presents a fully noninvasive left ventricular PV loop analysis across healthy controls, subjects with SDD, and patients with heart failure with preserved or impaired systolic function. In conclusion, the method for PV loop computation from clinical-standard manual left ventricular segmentation was rapid and robust, bridging the gap between clinical and research settings.

Methods

This study was approved by the regional ethical review board in Lund, Sweden (permit 2005/269 and 2013/891) and follows the Declaration of Helsinki. Written informed consent was obtained from all research participants before recruiting. There is currently a lack of clinically available, safe, and reliable diagnostic tools with sufficient granularity to meaningfully investigate the hemodynamics of patients under suspicion of heart failure.\(^1\) Left ventricular (LV) pressure-volume (PV) loop analysis provides unique physiologic insight into hemodynamic parameters and may support clinical decision making based on ventricular function, energy consumption, and stroke work.\(^2\) A newly developed and validated method for calculating PV loops noninvasively using cardiac magnetic resonance (CMR) images and brachial blood pressure makes PV loop analysis more clinically available and safer than invasive methods.\(^3,4\) The aim of this study was to evaluate inter- and intraobserver variability of noninvasive PV loops in healthy controls, subclinical diastolic dysfunction (SDD), and patients with heart failure with preserved ejection fraction (HFrEF), mildly reduced ejection fraction (HfmrEF), and reduced ejection fraction (HFrEF). In addition, we aimed to evaluate a new method designed to accelerate the workflow of computing PV loops.

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Table 1
Population characteristics, cardiac parameters and medications

<table>
<thead>
<tr>
<th>Participant characteristics</th>
<th>Healthy controls (n=15)</th>
<th>SDD (n=15)</th>
<th>HFpEF (n=15)</th>
<th>HFmrEF (n=15)</th>
<th>HFrEF (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>9/6</td>
<td>5/10</td>
<td>4/11</td>
<td>5/10</td>
<td>3/12</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.76 [1.72 – 2.09]</td>
<td>2.06 [1.74 – 2.21]</td>
<td>2.07 [1.64 – 2.26]</td>
<td>2.13 [1.94 – 2.21]</td>
<td>1.99 [1.79 – 2.11]</td>
</tr>
<tr>
<td>Cardiac parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>6.0 [5.7 – 6.7]</td>
<td>6.3 [5.1 – 7.2]</td>
<td>7.0 [6.2 – 7.3]</td>
<td>6.5 [5.1 – 8.0]</td>
<td>5.5 [4.5 – 6.6]</td>
</tr>
</tbody>
</table>

HFpEF = heart failure with preserved ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFrEF = heart failure with reduced ejection fraction; SDD = subclinical diastolic dysfunction; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor-neprilysin inhibitor.

Values are presented as median [IQR].

* p < 0.05 compared to healthy controls.

data acquisition. All examinations were performed in accordance with current guidelines and regulations at Skane University Hospital Lund, Sweden. The study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology criteria for observational cohort studies.5

We prospectively recruited 75 participants from 1 of 5 groups: healthy controls (n = 15) and participants with SDD (n = 15) from the population-based Swedish CArdioPulmonary BioImage Study (SCAPIS)6 and patients with heart failure (HFpEF n = 15, HFmrEF n = 15, HFrEF n = 15) from clinical referrals or the prospective HeARt and brain Studies.5 Cardiac magnetic resonance imaging was performed using a 1.5T scanner (Siemens Aera, Siemens Healthcare, Erlangen, Germany). Balanced steady-state free precession cine images were acquired in the 2-, 3-, and 4-chamber views, as well as the short-axis view covering the left ventricle. Typical short-axis imaging parameters: slice thickness 8 mm, in-plane spatial resolution 1.0 × 1.0 mm, no slice gap, flip angle 70°, TE/TR 1.1/41 ms. Retrospective electrocardiogram-gating was used, and data were reconstructed to 25 timeframes per cardiac cycle. Brachial blood pressure was measured by an automatic brachial cuff in conjunction with CMR image acquisition.

We developed and validated a semiautomated LV segmentation technique using spline interpolation for time-resolved segmentation. This technique was first evaluated in 12 datasets chosen at random from healthy controls and patients with heart failure. For this initial evaluation, the LV endocardial border was segmented manually over the entire cardiac cycle by 2 observers with 3 (observer 1, JE) and 10 (observer 2, PA) years of experience in CMR
research. Next, we used a spline interpolation approach (Figure 1) for LV segmentation, based solely on end-systolic, end-diastolic, and mid-diastasis (when applicable) timeframes, segmented manually by the more experienced observer. The spline interpolation method deforms the segmentation in each short-axis slice separately, allowing corrections if desirable. For this evaluation, we used only minor manual corrections in the most basal slices. Interobserver variability between observers 1 and 2, as well as intraobserver variability between manual and spline interpolation segmentation performed by observer 2, was assessed for hemodynamic parameters derived from the PV loop analysis, based on this initial dataset.

Bias and limits of agreement were lower comparing manual with spline interpolation than interobserver variability (Supplementary Figure 1, Supplementary Table 1). Thus, we chose the spline interpolation method for segmenting the remaining datasets of the study. An observer (observer 1, JE) performed interpolation based on manual delineations in end-systolic and end-diastolic timeframes by 2 observers with 10 (observer 2, PA) and 15 (observer 3, KSE) years of CMR experience, respectively. All image and PV loop analysis was performed using Segment 3.3 R9405e (http://segment.heiberg.se).10

PV loop parameters were computed using a plug-in for Segment, as described in a previous work, where the method was validated against invasively obtained parameters.3,4 Briefly, heart rate and time-resolved volumetric data from cardiovascular magnetic resonance imaging, as well as brachial blood pressure, were used as model input. These data are used to scale a time-varying elastance model to calculate ventricular pressure over the cardiac cycle.11 Maximal ventricular pressure is approximated from brachial pressure,12 whereas the user is prompted to estimate the end-diastolic pressure used to scale the time-varying elastance curve. For this study, we used a fixed value of 7.5 mm Hg, which is likely an underestimation of the true filling pressures in some of the patients. However, a sensitivity analysis performed by Seemann et al3 showed minimal impact on derived hemodynamic parameters when varying peak diastolic LV pressure between 0 and 15 mm Hg, and later, validation using invasive PV experiments confirmed that values between 3 and 30 mm Hg have a small impact on the loop parameters (unpublished data). Figure 2 shows an example of a PV loop indicating the analyzed parameters: stroke work, potential energy, PV area (PVA), ventricular efficiency, energy per ejected volume, mean external power, maximal ventricular elastance (E_{max}), and effective arterial elastance (E_A). Ventricular-arterial (VA) coupling was calculated as E_A/E_{max}.

Continuous data are presented as median and interquartile range, unless otherwise stated. Intergroup differences were evaluated using Kruskal-Wallis H test with Dunn post hoc test, with significance assigned at p <0.05. Interobserver and intraobserver variability was evaluated using Bland-Altman plots and Pearson correlation coefficients. Statistical analysis was conducted using GraphPad Prism 8.4.1 (GraphPad Software, San Diego, California) and SPSS Statistics 27.0 (IBM Corp, Armonk, New York).

Figure 2. Example of a noninvasive pressure-volume loop derived from cardiovascular magnetic resonance imaging and brachial cuff blood pressure, with hemodynamic parameters indicated. Additional pressure-volume loop derived hemodynamic parameters include ventricular efficiency (VE) defined as SW/(SW+PE), PVA as SW+PE, energy per ejected volume as PVA/(EDV-ESV), mean external power as SW*(heart rate/60), and ventricular-arterial coupling as E_A/E_{max}.

ESV = end-systolic volume; EDV = end-diastolic volume; PE= potential energy; SW = stroke work.
Results

Participant biometric characteristics, basic cardiac parameters, and medication are presented in Table 1. Interobserver variability of LV volumes and interobserver and intraobserver variability of hemodynamic parameters derived from PV loop analysis is presented Figure 3, Supplementary Table 1. Bias was low and limits of agreement were narrow for all hemodynamic parameters in the interobserver and intraobserver comparisons.

Hemodynamic parameters derived from PV loop analysis for all groups are presented in Table 2. Figure 4 shows noninvasive PV loop analysis of ventricular energetics and Figure 5 shows noninvasive PV loop analysis of ventricular and arterial elastance.

Figure 3. Comparison of manual left ventricular segmentation and spline interpolation for PV loop derived hemodynamics. Pearson correlation (left column) and Bland-Altman plots for the inter- and intraobserver evaluation when comparing manual left ventricular segmentation and spline interpolation. Bias was lower and limits of agreement narrower when comparing manual to interpolated (right column) compared to the interobserver evaluation (center column). In the scatter plots, the solid line is a line of identity. In the Bland-Altman plots, the dashed line denotes the bias and the dotted lines the limits of agreement (defined as bias ± 1.96 SD).
Discussion

In this study, we present the first experience with a fully noninvasive LV PV loop analysis across healthy controls, subjects with SDD, and patients with heart failure with preserved or impaired systolic function. Bias was low and limits of agreement were narrow for all hemodynamic parameters in the inter- and intraobserver comparisons. Furthermore, the presented new method for PV loop analysis based on the interpolation of clinical routine LV segmentation shows results comparable to completely manual segmentation but with vastly reduced workload. This makes noninvasive PV loops derived from CMR feasible to implement clinically.

Our finding that systolic heart failure groups display differences in PV parameters affected by impaired contractility and larger cardiac volumes is in line with previous results from invasive PV loop studies. It has previously been suggested that noninvasive PV loops may be a useful tool to characterize energetic efficiency in patients with HFrEF. Although there were no statistical differences between healthy controls and patients with HFrEF for any of the variables in the present study, noninvasive PV loops at rest may add incremental information when following up patients over time to detect subtle changes in function. Bastos et al suggested that assessment of PV loops at rest and exercise can help diagnose HFrEF. Because brachial blood pressure and cardiac volumes can be assessed during exercise using exercise CMR, PV loops during exercise can be obtained and potentially unmask early symptoms of heart failure, both systolic and diastolic. This was, however, beyond the scope of this study.

The described method of using CMR to calculate PV loops is not the first noninvasive approach of assessing myocardial energetics. Pressure-strain loops derived from echocardiography have previously been shown by Russel et al to provide a noninvasive index of myocardial work. There are, however, several key differences between the methods. Using echocardiography, isovolumetric contraction, ejection, and isovolumetric relaxation are normalized by stretching or compressing the curve to the same duration; whereas in CMR, volumetric data, time-resolved through spline interpolation, provide empiric and non-normalized volumes and durations. In echocardiography, in the place of volumetric data, regional wall longitudinal 2-dimensional strain data are adjusted to the timings of the cardiac events. This is different from CMR, where the actual time-resolved volumetric data are used. Pressure-strain analysis provides the added benefit of assessing regional LV function and information regarding constructive versus wasted work, but a limitation of the pressure-strain index lies in the size of the ventricle affecting strain estimation, where a dilated ventricle results in an underestimation of strain. Although the CMR method would minimize such errors using non-normalized volumetric data, no regional information is provided.

VA coupling ($E_A/E_{max}$) in the present study differed between controls and systolic heart failure. However, there was no difference between controls and SDD or HFrEF. Although these findings can be explained by similar $E_A$ between groups and lower $E_{max}$ only in HFrEF and HFrEF, previous studies show conflicting results regarding VA coupling in HFrEF. If there is a proportional increase in both $E_{ss}$ and $E_A$, there will be no difference in the VA coupling. This proportional increase was shown by Lam et al. However, Kawaguchi et al found VA coupling to be lower in HFrEF, which is explained by a disproportionate increase in end-systolic elastance ($E_{es}$) compared with $E_A$. Furthermore, Maurer et al showed both $E_{es}$ and $E_A$ in normotensive HFrEF to not differ from healthy controls who are normotensive, which is similar to the findings in the present study, where blood pressure did not differ between groups. However, Chan et al showed an increase in LV work measured by pressure-strain echocardiography in patients with hypertension. Discrepancies in the findings regarding hemodynamic parameters in HFrEF could thus result from differences in control group characteristics or the heterogeneity of patients with HFrEF, such as presence or absence of hypertension.

In addition and not limited to the HFrEF group, heart failure medication could affect hemodynamic parameters. For example, contractility ($E_{max}$) could be decreased by $\beta$-blockers, or $E_A$ could be decreased by a lower heart rate or a decreased systemic vascular resistance caused by $\beta$-blockers or blood pressure medication. Finally,
ventricular energetics could be affected by changes in ventricular loading conditions resulting from the aforementioned medications. The differences between groups in this study could thus potentially be underestimated, owing to the high degree of medication of all 3 heart failure groups.

A potential benefit of using PV analysis compared with evaluation of EF and blood pressure separately is the added information regarding ventricular energetics. For example, PVA is proportional to cardiac oxygen consumption. In our study, HFrEF had increased potential energy and PVA, and although we did not find a statistically significant difference comparing HFrEF with healthy controls, a visual trend was seen toward increased stroke work and PVA in this group. This suggests both systolic and diastolic heart failure to increase cardiac oxygen consumption but through differing mechanisms. Thus, PV analysis could provide unique hemodynamic insights into the stages between the very basal metabolism of the myocytes and the end-product

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**Figure 4.** Noninvasive pressure-volume loop analysis of ventricular energetics. (A) No difference was found for stroke work and (E) external power. (B) Significant differences were seen in pressure-volume, (C) PVA, (D) ventricular efficiency and (F) energy per ejected volume. Horizontal bars denote median values.

CTL = healthy controls; SDD = subclinical diastolic dysfunction.
of cardiac output, moving a step closer to phenotyping cardiac metabolism on an individual basis.

Further PV loop analysis of heart failure is needed to assess the prognostic importance and potential role in guiding specific therapies. Furthermore, as described previously, PV loop analysis during physical exercise may unmask hemodynamic irregularities not evident at rest. Finally, non-invasive PV analysis may be useful in longitudinal studies looking at the individual patient rather than comparing between heterogeneous groups of heart failure.

In conclusion, to the best of our knowledge, this study is the first experience with a fully noninvasive LV PV loop analysis across healthy controls, subjects with SDD, and patients with heart failure with preserved or impaired systolic function. Bias was low and limits of agreement were narrow for all hemodynamic parameters in the inter- and intraobserver comparisons. The proposed new method for PV loop computation from clinical-standard manual LV segmentation was rapid and robust, bridging the gap between clinical and research settings.

Disclosures

Katarina Steding-Ehrenborg reports a relation with Bayer Medical that includes speaking and lecture fees. Einar Heiberg is the founder of Medviso AB, Lund, Sweden, which sells a commercial version of Segment. The other authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.09.001.


