Noninvasive Pressure-Volume Analysis by Three-Dimensional Echocardiography: A Novel Powerful Method for Evaluating Left Ventricular Function

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Background: Pressure-volume (PV) analysis is the gold standard for evaluating left ventricular (LV) function but is rarely used clinically due to its invasiveness. We validated a noninvasive method for PV analysis by three-dimensional (3D) echocardiography against invasive reference measurements and a novel index of LV efficiency against LV efficiency derived from metabolism by positron emission tomography-computed tomography (PET-CT).

Methods: In 22 canines, LV volume was measured invasively using piezoelectric crystals and LV pressure by micromanometer. Echocardiography and peak pressure were used to obtain 3D LV volume traces and LV pressure trace estimates. Stroke work, single-beat contractility indices, arterial elastance, and an index of LV efficiency were derived from echocardiography and compared with their invasively measured counterparts at baseline and different interventions. In 12 sheep, the LV efficiency index was compared with efficiency calculated as stroke work divided by total LV glucose metabolism from PET-CT. The sheep underwent 8 weeks of rapid dyssynchronous pacing to induce heart failure (HF). Recordings were performed during synchronous and dyssynchronous electrical activation, at baseline, and after 8 weeks of pacing-induced HF.

Results: In canines, there was a very good correlation and agreement between noninvasive and invasive measurements of LV stroke work (r = 0.98, P < .0001; difference 237 $\pm$ 212 mm Hg $\times$ mL, mean $\pm$ SD). The noninvasive and invasive efficiency indices also showed very good agreement (r = 0.95, P < .0001; difference 0.4% $\pm$ 3.4%). The changes in LV function by the different interventions resulted in similar changes in the noninvasive and invasive PV indices (all P < .001). In sheep, the efficiency index showed similar decline compared to efficiency by PET-CT after induction of HF and after switching from synchronous to dyssynchronous electrical activation (r = 0.67, P < .001 for all interventions).

Conclusions: Noninvasive PV analysis by three-dimensional echocardiography is feasible and accurate, making PV loop parameters for evaluating LV function accessible for clinical use. Further studies should explore the clinical utility of this method. (J Am Soc Echocardiogr 2025;38:946-58.)

Keywords: Echocardiography, Pressure-volume analysis, Ventricular efficiency, Arterial elastance, Ventricular contractility

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Tweet: "A pioneering study shows pressure-volume analysis by 3D echocardiography accurately assesses left ventricular function. The method agrees well with invasive standards for stroke work, efficiency, and contractility, opening new possibilities for research and care."

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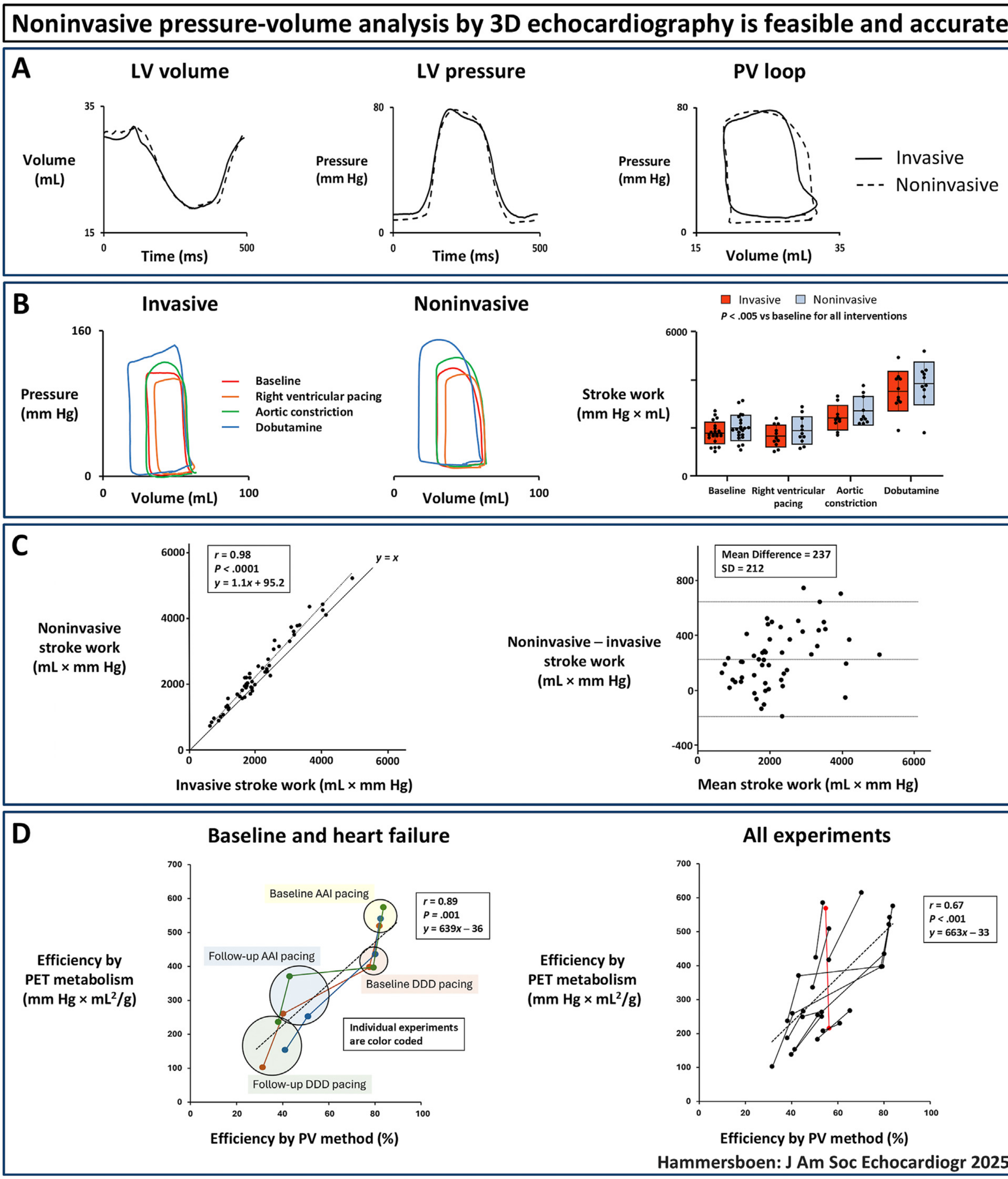

Central Illustration Validation of noninvasive PV analysis by 3D echocardiography. The estimated noninvasive and invasive volume and pressure traces, and the resulting PV loop, were similar, as shown in representative experiments **(A** and **B)**. The *box and dot plots* in panel B illustrate the average SW from the animals across different interventions, showing the similarities in value and changes between invasive and noninvasive SW. Consequently, there was a very good correlation as well as good agreement between the methods **(C)**. In a separate sheep study, the noninvasive LV efficiency index showed similar decline compared to efficiency by PET-CT following 8 weeks paced induced heart failure and after switching from AAI to dyssynchronous DDD pacing **(D)**. Overall correlation between the methods was good and very good in animals with longitudinal data. Student's *t*-test was used to compare means, while Pearson correlation coefficient and Bland-Altman analysis were used to assess agreement between the methods.

Abbreviations

3D = Three-dimensional

CMR = Cardiac magnetic resonance

EDV = End-diastolic volume

EF = Ejection fraction

ES = End-systolic

ESPVR = End-systolic pressure-volume relation

ESV = End-systolic volume

LV = Left ventricular

MAP = Mean arterial pressure

PE = Potential energy

PET-CT = Positron emission tomography-computed tomography

PV = Pressure-volume

SW = Stroke work

TME = Total mechanical energy

INTRODUCTION

In the late 19th century, Otto Frank proposed pressure-volume (PV) analysis for evaluating cardiac function.[1] Suga and colleagues[2] later refined the PV method into a powerful framework for understanding cardiac mechanics and energetics, which has since reigned supreme as the gold standard for assessing left ventricular (LV) function. Technological advancements, notably the development of the conductance catheter, enabled PV analysis in human hearts in vivo, providing detailed assessment of LV function including stroke work (SW), contractility (E_{ES}) and efficiency, and systemic arterial elastance (E_a).[3] However, despite its considerable clinical potential, PV analysis has remained confined to specialized research settings due to its invasive nature and associated risks.[4]

Russell *et al.*'s[5] echocardiographic method for pressure-strain analysis, which integrates LV pressure curve estimation and strain for myocardial work, saw widespread adaptation in clinical research after it was introduced. A limitation of this method is the inability to account for differences in ventricular size, which is known to alter O_2 consumption.[6] This implies that a normal sized heart and a dilated heart may have the same estimated LV pressure-strain loop using the current method, even though O_2 is higher in the dilated heart. Furthermore, in PV analysis, a rightward shift of the PV loop is associated with decreased efficiency. However, as strain is calculated relative to end-diastolic dimension with the starting point fixed at 0%, there will not be a similar rightward shift to reflect the reduced efficiency. Hence, PV analysis may complement pressure-strain analysis by providing alternative functional indices. Recent advancements in three-dimensional (3D) echocardiography over the past decades have now made it possible to accurately measure the LV volume time trace.[7] Together with the ability to estimate the LV pressure curve noninvasively, this should make noninvasive PV analysis by echocardiography feasible.

The aim of the present study was to validate noninvasive PV analysis using 3D echocardiography by comparing it to an invasive gold standard in our well-established canine model under normal conditions and during reduced and increased LV function and increased afterload.[8] Additionally, a novel PV efficiency index was validated using positron emission tomography-computed tomography (PET-CT) and cardiac magnetic resonance (CMR) data from a dyssynchronous heart failure model in sheep.[9]

MATERIAL AND METHODS

Canine Model

Animal Preparation. Twenty-two open-chest mongrel canines (either sex, average weight 33 ± 4 kg, and age 12-24 months) were sedated with methadone (0.3-0.4 mg/kg) and subsequently anesthetized with a propofol bolus (5-10 mg/kg). Anesthesia and analgesia were maintained

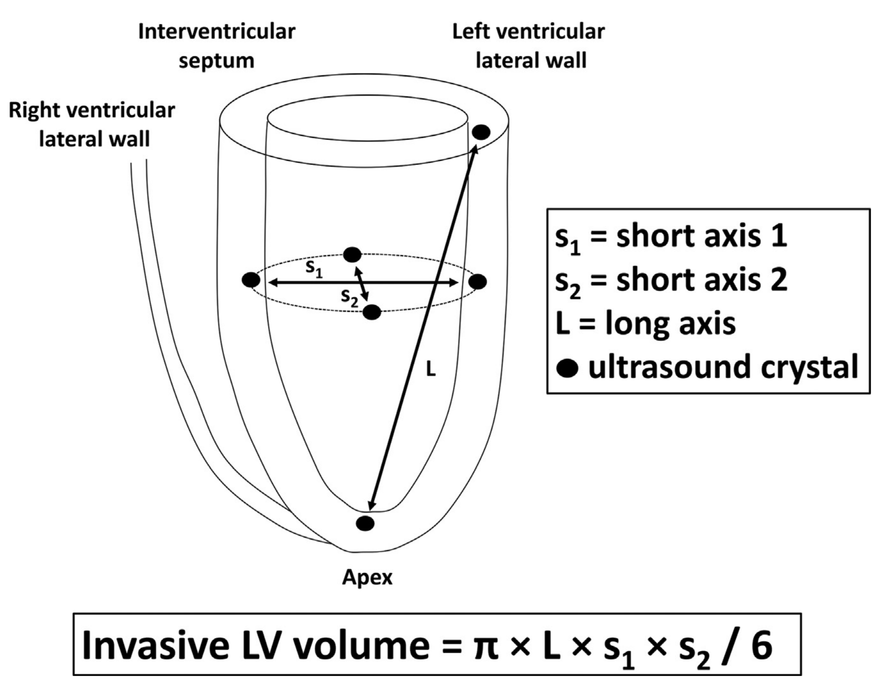

Figure 1 Schematic of ultrasound crystal placements. Six ultrasound crystals were implanted in the subendocardium to enable invasive measurement of left ventricular (LV) volume. LV long axis was defined by crystals at the apex and base. Short axis 1 was defined by crystals in the interventricular septum and LV lateral wall, and short axis 2 by crystals in the LV anterior and posterior walls. An ellipsoid model was used to calculate LV volume as ($\pi \times$ long axis $\times$ short axis 1 $\times$ short axis 2)/6.

HIGHLIGHTS

- PV analysis by 3D echocardiography enables accurate PV loops.
- LV SW, efficiency, and contractility agree well with invasive metrics.
- The efficiency index correlates well with efficiency derived by PET-CT metabolism.
- Arterial elastance can be accurately estimated by 3D echocardiography.
- PV analysis by 3D echocardiography is ready for widespread clinical testing.

with continuous infusions of propofol (1.3 mg/kg/hour) and fentanyl (0.8 mg/kg/hour). The animals were ventilated through an endotracheal tube and monitored by electrocardiogram. Median sternotomy and pericardiotomy were performed followed by implantation of 6 sonomicrometric crystals measuring 2 to 3 mm (Sonometrics) in the LV subendocardium: 1 in the apex, 1 in the base, and 4 in the short-axis plane (Figure 1). Septal and lateral wall crystals were paired with electrodes for electromyographic measurements. The pericardium was loosely resutured after instrumentation. Rubber bands were placed around the venae cavae, and a pneumatic occluder was positioned around the ascending aorta. The common carotid artery was cannulated, and a micromanometer (MPC-500, Millar Instruments) introduced into the LV chamber. Another micromanometer and a fluid-filled pressure catheter were placed in the left atrium via the left atrial appendage. Jugular veins were cannulated for fluid, anesthesia, and dobutamine infusion. A pacing lead was sutured on the right ventricular free wall. The canines were placed in a supine position during the recordings. Ethical approval for the animal protocols was obtained from the Norwegian Food Safety Authority (FOTS ID: 22863 and 29818). All experiments were conducted in compliance with the ARRIVE guidelines. The experiments were terminal where the animals were ventilated and surgically prepared under full anesthesia. Animals were supplied by the Center for Comparative Medicine (Oslo University Hospital, Rikshospitalet).

Interventions and Experimental Protocol. To reduce the total number of animals, they were also utilized in other studies; hence, not all interventions could be performed in all experiments. Right ventricular free-wall pacing was performed to induce LV mechanical dyssynchrony similar to left bundle branch block ($n = 11$). Left ventricular septal and lateral wall electromyographic activation pattern and LV contraction pattern by sonomicrometry were assessed to confirm successful capture. Afterload was increased by inflating the pneumatic vascular occluder around the ascending aorta, maintaining elevated peak systolic LV pressure constant throughout data collection ($n = 10$). Finally, dobutamine was infused to increase contractility, as indicated by at least a twofold increase in dP/dt_{max} from baseline ($n = 10$).

Acquiring Invasive Pressure and Volume Traces. Invasive LV volume was measured by sonomicrometry, and invasive LV pressure by micromanometry. Data were digitized at 200 Hz. Micromanometers were calibrated before use and drift adjusted to pressure measured by a fluid-filled catheter in the left atrium during long diastasis, induced by a ventricular extrasystole via epicardial pacing.

An ellipsoid model was used to calculate LV volume as ($\pi \times$ long axis $\times$ short axis 1 $\times$ short axis 2)/6 using the crystals shown in Figure 1. Subsequently, the invasive volume traces were calibrated to end-diastolic volume (EDV) and end-systolic volume (ESV) measured by 3D echocardiography.

Calculating Invasive PV Parameters. Invasive pressure and volume traces were combined to create PV loops. Stroke work was calculated as the area of the PV loop from mitral valve closure to the next closure. This corresponds to the red area in the left diagram in Figure 2. Mitral valve closure was identified at peak LV volume after QRS onset in the electrocardiogram.

As shown in Figure 2 (left panel), invasive E_{ES}, potential energy (PE), total mechanical energy (TME), and efficiency were derived from multiple PV loops during preload reduction by constriction of the venae cavae. The end-systolic (ES) point on each loop was identified as the longest normalized distance from the center of the PV loop. These loop points were used for least-squares regression to calculate the ES PV relation (ESPVR) line and its volume axis intercept, V_0. The value of invasive E_{ES} was defined as the slope of this line. We also extracted the single-beat contractility indices P_{ES}/EDV and P_{max}/EDV, where P_{ES} was the pressure at the ES point described above and P_{max} was peak pressure.[10] The E_a was calculated as P_{ES} divided by the difference between EDV and volume at the ES point. Potential energy was calculated as half the product of P_{ES} and the difference between volume at the ES point and V_0 (blue area in left panel of Figure 2). Total mechanical energy was calculated as the sum of SW and PE, and, finally, LV efficiency was determined as the ratio of SW to TME.

Acquiring Noninvasive Pressure and Volume Traces. A Vivid 95 ultrasound scanner with a 4Vc probe (GE Vingmed Ultrasound AS) was used to measure mitral and aortic valve event timings and 3D volumes. The probe was placed at the heart's apex with a gel standoff. Transducer frequency, sampling rate, and sample volume were optimized. The LV pressure curve was estimated by adjusting the phases of a reference pressure curve to mitral and aortic valve events in the echocardiographic apical 3-chamber view and its amplitude to peak LV pressure by micromanometer.[5] To ensure adequate frame rate and image quality, up to 6 consecutive beats were stitched. A frame rate of at least half of heart rate was considered necessary to meet the requirements of the Nyquist sampling theorem.[11] Each 3D volume image loop was recorded just before invasive LV volume measurements to avoid interference of the echocardiographic and sonomicrometric ultrasound signals. Invasive data were continuously monitored to make sure no significant hemodynamic changes occurred between recordings. Noninvasive LV volume traces were synchronized with invasive traces and resampled to match the sample rate of the LV pressure curves.

Calculating Noninvasive PV Parameters. Figure 2 (right panel) shows how the noninvasive PV loop parameters were calculated using 3D echocardiography. Since the estimated LV pressure curve does not provide estimates for pressure during filling, SW was calculated as the area under the PV curve from mitral valve closure to opening determined by echocardiography in the apical 3-chamber view (illustrated by the red area). As seen in the figure, this slightly overestimates SW relative to a closed loop as the work done on the LV during filling is not subtracted (i.e., the area under the closed loop).

Stroke work was also estimated as stroke volume times mean arterial pressure (MAP) for comparison with this clinical approach. Here, MAP was calculated as the $0.67 \times$ LV pressure at aortic valve opening (time of maximum LV dP/dt) $+ 0.33 \times$ peak LV pressure to mimic diastolic and systolic cuff pressure values.

A simplified 1-beat approach was used to calculate E_{ES}, PE, TME, and an index of LV efficiency. The ESPVR line was approximated as a

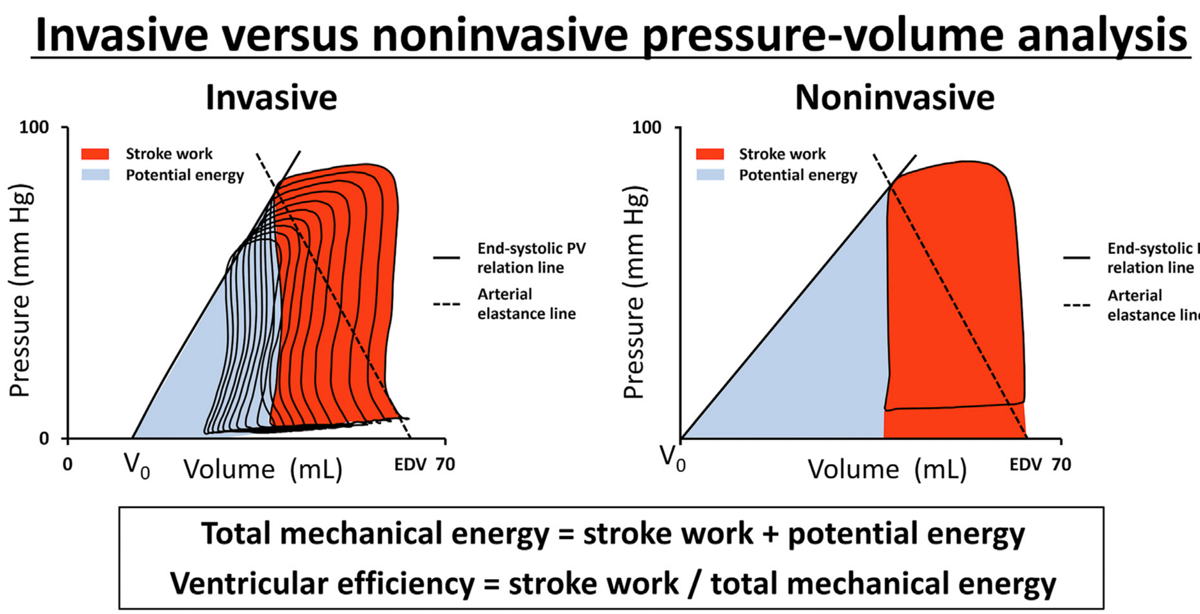

Figure 2 Invasive versus noninvasive PV analysis. The figure shows invasive *(left)* and noninvasive *(right)* PV loop parameters. Noninvasive parameters set V_0 to the origin and filling pressure to zero. Invasive SW *(red area, left)* is the PV loop area; noninvasive SW includes the PV loop area plus the area between the loop and volume axis *(red area, right)*. E_{ES} is the slope of the ESPVR from V_0 to the PV loop point furthest from the normalized loop center, and E_a the slope of the line from this point to the volume axis intercept at the EDV. Potential energy is the *blue area* between the volume axis, ESPVR line, and PV loop. Efficiency is SW/(PE + SW).

line from the origin to the ES PV curve point identified as above. The value of noninvasive E_{ES} was defined as the slope of this line. The variables P_{max}/EDV, P_{ES}/EDV, and E_a were defined as above. Potential energy was calculated as half the product of pressure and volume at the ES PV curve point (blue triangle, right panel in Figure 2). Total mechanical energy was calculated as the sum of SW and PE, and the LV efficiency index as the ratio of SW to TME. The noninvasive PV indices were compared with their invasively obtained counterparts.

Validation of the LV Efficiency Index With PET-CT in Sheep

Twelve female Swifter-Charolais sheep (average age, 12 months; body weight, 44 ± 4 kg) were implanted with a right atrial and right ventricular free-wall pacemaker under general anesthesia and mechanical ventilation as previously described.[9] The study was approved by the animal ethical committee of the KU Leuven (project Number P146/2012) and complied with the European Commission Directive 2010/63/EU for protection of animals used for scientific purposes.

Left ventricular pressures and volumes were acquired using a micromanometer tipped PV catheter (Ventri-Cath 507; Millar Instruments) with volumes calibrated using CMR images.[9]

The sheep underwent 8 weeks of rapid DDD pacing at 180 bpm, resulting in LV systolic dysfunction and dilatation in all animals. Pacemaker settings during recordings included both AAI (synchrony) and DDD (dyssynchrony) pacing at baseline and after 8 weeks pacing-induced heart failure and were performed at 110 bpm.

Fluorodeoxyglucose PET-CT scans were performed on a Biograph 16 HireZ scanner (Siemens Healthcare). The standard glucose-insulin clamping technique was used to ensure that myocardial metabolism was dominated by glucose. Positron emission tomography reconstructions and total myocardial glucose uptake calculations were performed as previously described.[9] The PET-CT scans were performed in 3 animals at baseline and in all 12 animals at 8 weeks.

Left ventricular efficiency by PET-CT was defined as the ratio between SW and LV total energy consumption (i.e., LV glucose metabolism) and compared with the LV efficiency index as defined above (Figure 2, right panel).

Statistical Analysis

Values are presented as mean ± SD. Changes from baseline during interventions were evaluated using a paired Student's *t*-test, applied only to the animals undergoing the specific intervention. Invasive and noninvasive measurements were compared using least-squares linear regression and the Bland-Altman method. All statistical analyses were performed using IBM SPSS Statistics (Windows, ver. 26.0, IBM Corp.). The first author had access to all the data in the study and takes responsibility for its integrity and the data analysis.

RESULTS

Canine Model Results

In canines, aortic constriction increased peak systolic pressure, dobutamine infusion increased peak dP/dt_{max}, and right ventricular pacing decreased dP/dt_{max} and increased EDV and ESV ($P < .005$ for all; Table 1).

Invasive Versus Noninvasive PV Loops and Estimated LV Stroke Work. The noninvasive pressure and volume traces closely mirrored their invasive counterparts, leading to PV loops that exhibited a high degree of similarity not only throughout the baseline measurements but also across all interventions. Notably, alterations in LV function and loading conditions during interventions were reflected in changes in noninvasive PV loop area and morphology in a similar manner as compared to the invasive method, indicating good agreement (panel A and left and mid-diagram in panel B, Central Illustration).

Table 1 Standard values at baseline and interventions

Parameter	Baseline (n = 22)	Right ventricular pacing (n = 11)	Aortic constriction (n = 10)	Dobutamine (n = 10)
EDV, mL	55 ± 10	59 ± 6	59 ± 9	56 ± 9
ESV, mL	31 ± 9	35 ± 5*	33 ± 8	20 ± 6*
Stroke volume, mL	25 ± 5	24 ± 4†	26 ± 5	36 ± 7*
EF, %	45 ± 8	41 ± 6*	45 ± 8	64 ± 9*
Peak LV pressure, mm Hg	94 ± 13	92 ± 14†	119 ± 8*	128 ± 10*
LV dp/dt_{max}, mm Hg/sec	1,424 ± 287	1,131 ± 245*	1,613 ± 466	3,509 ± 617*
Heart rate, bpm	112 ± 19	114 ± 13	116 ± 20	113 ± 26

*P < .005 vs baseline.
†P < .05 vs baseline.

The similarity between noninvasive and invasive PV loops resulted in close concordance in SW calculated from the 2 methods when analyses from all experiments were pooled together (right diagram, panel B, Central Illustration). Noninvasive SW was similar to invasive SW in terms of both absolute values and changes in value across all interventions. The correlation between invasive and noninvasive SW was very good (r = 0.98, P < .0001; left panel C, Central Illustration). However, there was a minor overestimation as noninvasive SW was calculated from mitral valve closure to opening, excluding the work done on the ventricle by filling (right panel C, Central Illustration). The noninvasive SW estimated from the PV loops agreed very well with MAP × SV (r = 0.98, P < .001; difference = 73 ± 210 mL × mm Hg).

Invasive Versus Noninvasive LV Contractility. Both noninvasive and invasive E_{ES} demonstrated increased contractility with dobutamine (panels A and B in Figure 3), and there was a good correlation between E_{ES} derived from the 2 methods (r = 0.63, P = .003). Because V_0 was set to zero in the noninvasive method, noninvasive E_{ES} understimated invasive E_{ES}, as shown in panel C in Figure 3.

Noninvasive P_{ES}/EDV increased from 1.6 ± 0.3 to 2.2 ± 0.4 mm Hg/mL (P < .001), similar to invasive P_{ES}/EDV, which increased from 1.6 ± 0.4 to 2.0 ± 0.3 mm Hg/mL (P < .001). The difference in the increase between the 2 methods was not significant (P = .31). Noninvasive and invasive P_{max}/EDV were identical as the 2 methods used the same peak pressure and EDV and changed from 1.8 ± 0.4 to 2.4 ± 0.4 mm Hg/mL (P < .005). Correlations between P_{max}/EDV and noninvasive P_{ES}/EDV versus invasive E_{ES} were good for both parameters (r = 0.77, P < .001 and r = 0.79, P < .001, respectively; Figure 4).

Invasive Versus Noninvasive Systemic Arterial Elastance. Noninvasive and invasive E_a showed good agreement (Figure 5). When increasing LV afterload by constricting the ascending aorta, both increased in a similar manner. Furthermore, the correlation between noninvasive and invasive E_a was very good (r = 0.92, P < .001), with only minor bias in the noninvasive estimates (Figure 5C).

Invasive Versus Noninvasive LV Efficiency and Efficiency Index. In canines, the single-beat efficiency index estimated by 3D echocardiography was calculated using a larger PE area and larger SW area compared to the original invasive method by Suga *et al.*[2] derived from multiple PV loops during preload reduction (left vs right panel, Figure 2). Still, the correlation between the methods was good (r = 0.63, P < .001) with difference −1.6% ± 2.4% (mean ± SD). However, when PE and SW of the invasive pressure and volume measurements were also calculated as in the right panel of Figure 2, there was a very good correlation (r = 0.95, P < .001) and good agreement (difference 0.4% ± 3.4%) with the noninvasive estimated index (Figure 6).

Validation of the LV Efficiency Index in Sheep

In sheep, following 8 weeks of rapid pacing–induced heart failure, ejection fraction (EF) and SW were reduced and EDV and ESV were increased (Table 2). During heart failure, switching from synchronous AAI to dyssynchronous DDD pacing significantly increased ESV and numerically increased EDV and decreased EF. Similar changes were observed at baseline (Table 2). In all 3 animals with baseline PET-CT data, there was a marked decline in efficiency after 8 weeks both by PET-CT and by the PV efficiency index (left panel D, Central Illustration). The figure also shows a subtle reduction in efficiency by both methods when shifting from AAI to DDD pacing. In all 12 animals at 8 weeks, DDD pacing exhibited reduced efficiency by PET-CT and in 11 of the animals with the PV efficiency index (right panel D, Central Illustration). Pooling data from all experiments and interventions together, the correlation between the PET- and PV-based methods was good (r = 0.67, P < .001). In a pooled analysis using data from animals with recordings at both baseline and follow-up, the correlation between the methods was very good (r = 0.89, P = .001; panel D, Central Illustration).

DISCUSSION

Our findings show that PV analysis by 3D echocardiography is feasible and accurate. The noninvasive PV loops were robust and comparable to invasive PV loops across various hemodynamic conditions, including pacing-induced dyssynchrony, increased afterload, and increased contractility. By combining simple echocardiographic measures with peak LV pressure, the estimated PV indices of LV mechanics and energetics showed good agreement with invasive

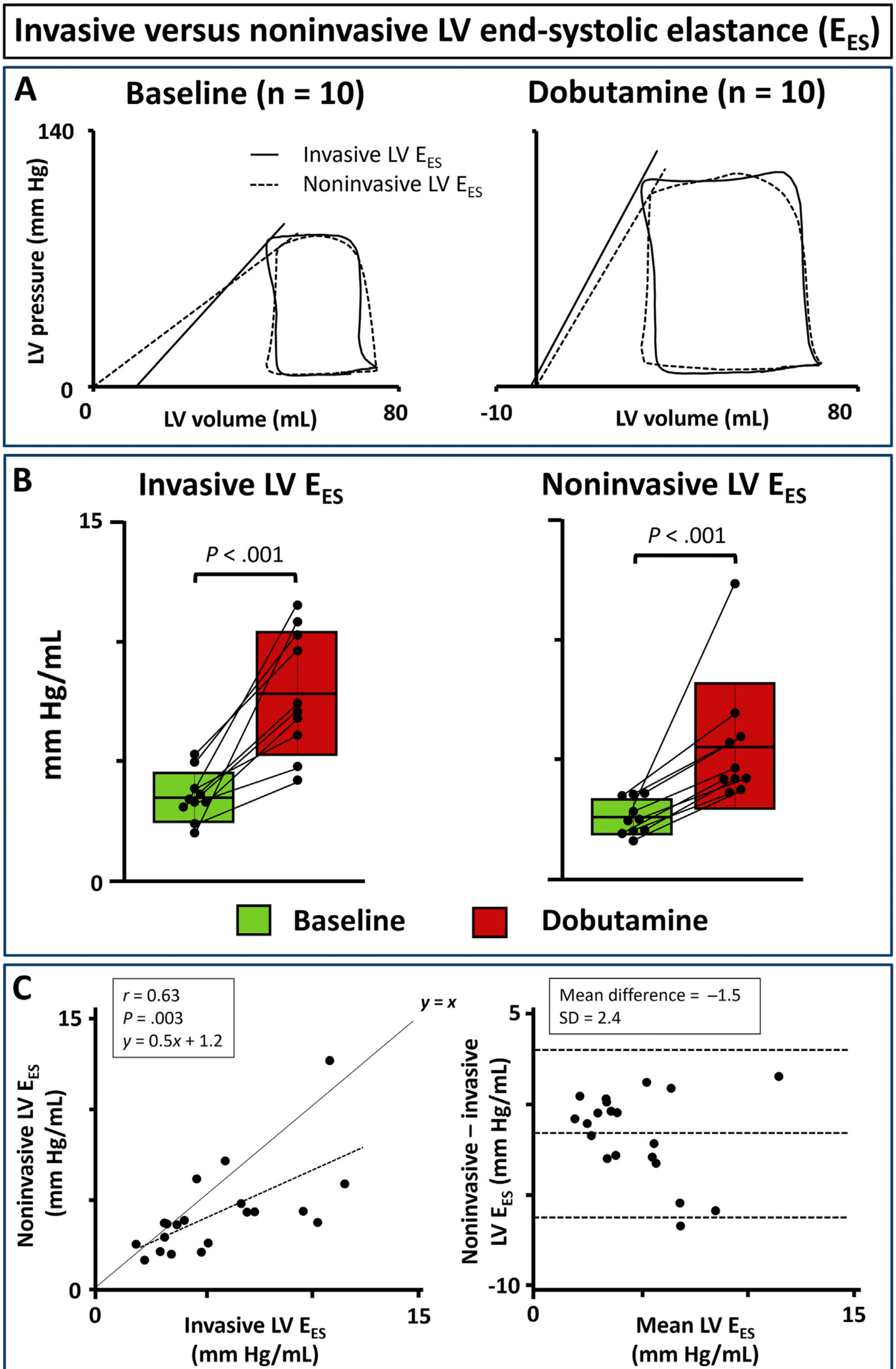

Figure 3 Invasive versus noninvasive E_{ES}. **(A)** Invasive *(solid line)* and noninvasive *(dashed line)* E_{ES} at baseline and during dobutamine infusion. **(B)** *Box and dot plots* with the mean data and SDs showing similarities between invasive and noninvasive E_{ES}. **(C)** Correlation and Bland-Altman plots showing good correlation and agreement between methods. Student's *t*-test was used to compare means, while Pearson correlation coefficient and Bland-Altman analysis were used to assess agreement between the methods.

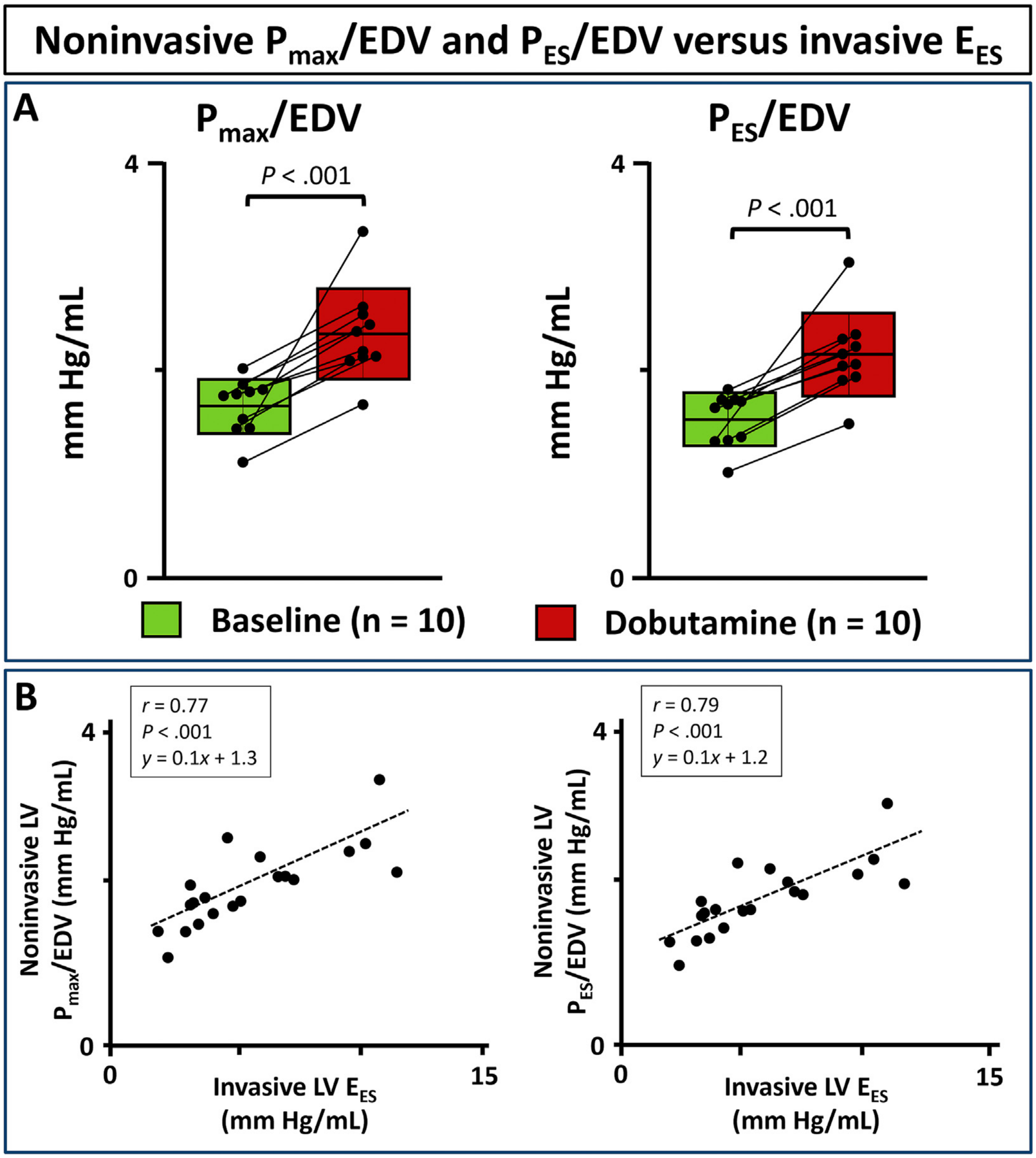

Figure 4 Invasive versus noninvasive indices of LV contractility. The response of noninvasively obtained P_{max}/EDV and P_{ES}/EDV to dobutamine infusion is shown in panel **(A)**. These noninvasive indices captured changes in LV contractility similarly to the invasive gold standard, E_{ES} **(B)**. Student's *t*-test was used to compare means, while Pearson correlation coefficient and Bland-Altman analysis were used to assess agreement between the methods.

gold standards. As these measurements can also be accurately obtained noninvasively in patients,[5,7] it is herein implicit that noninvasive PV analysis by 3D echocardiography is ready for widespread clinical testing with a potential wealth of utility.

Left Ventricular Energetics by 3D Echocardiography Versus Ejection Fraction

As demonstrated in this study, acquiring a 3D volume trace along with the timing of valvular events and peak LV pressure enables noninvasive PV loop analysis that provides a comprehensive assessment of cardiac function. This method can account for both SW and total oxygen consumption of the left ventricle. Thereby, it allows for estimation of an LV efficiency index that captures similar changes as PET-CT from baseline to dilated heart failure and from synchronous to dyssynchronous contractions, both at baseline and with dilated heart failure. It has previously been shown that EF by 3D echocardiography performs better as a predictor of adverse events compared to two-dimensional EF by the biplane Simpson's method.[12,13] Efficiency index contains information comparable to EF, as shown recently by Seeman *et al.*,[14] who demonstrated a very good correlation between LV 3D EF and efficiency from PV loops in normotensive heart failure patients. Thus, the information efficiency index adds to 3D EF when LV afterload is unchanged may be of limited value. However, in conditions like aortic stenosis and hypertension, patients may have increased energy consumption and reduced efficiency that can be captured by efficiency index but not EF.

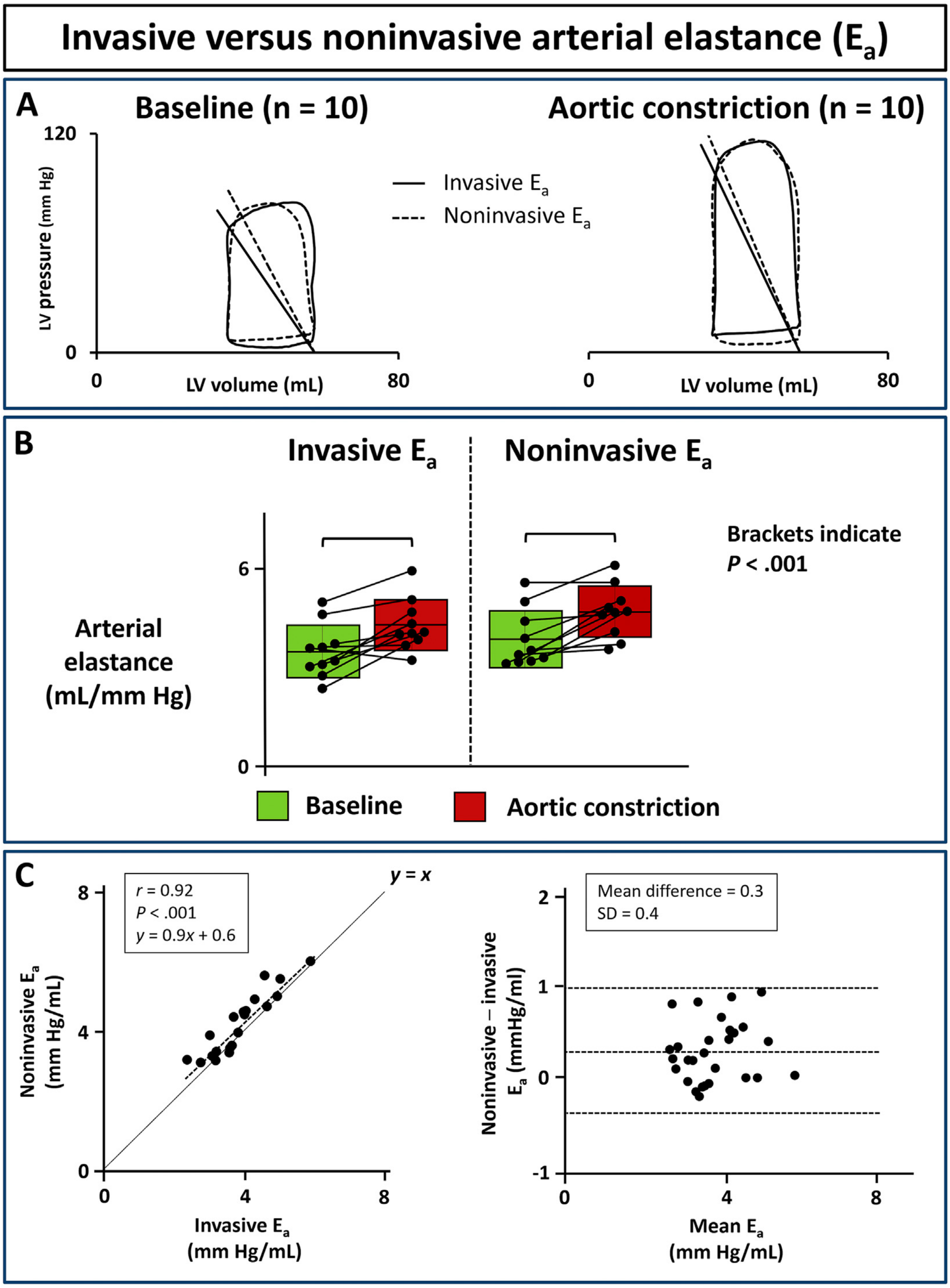

Figure 5 Invasive versus noninvasive systemic arterial elastance. **(A)** Invasive *(continuous line)* and noninvasive *(dashed line)* E_a at baseline and during aortic constriction. **(B)** *Box and dot plots* with the mean data and SDs showing the similarities in response to aortic constriction between the methods. **(C)** Correlation and Bland-Altman plot indicate very good correlation and good agreement between invasive and noninvasive E_a. Student's *t*-test was used to compare means, while Pearson correlation coefficient and Bland-Altman analysis were used to assess agreement between the methods.

In canines, the correlation between the efficiency index by 3D echocardiography and invasive efficiency calculated from multiple loops during preload reductions according to the method of Suga *et al.* was only $r = 0.63$. However, the Suga method for estimating TME and oxygen consumption was validated in a highly specialized setting using a dual canine setup with balloon instrumentation of the LV cavity for volume measurements.[2] Additionally, Suga's experiments involved controlled laboratory conditions with anesthesia, open-chest procedures, and external pacing, which significantly differ from the physiological conditions.[2] Consequently,

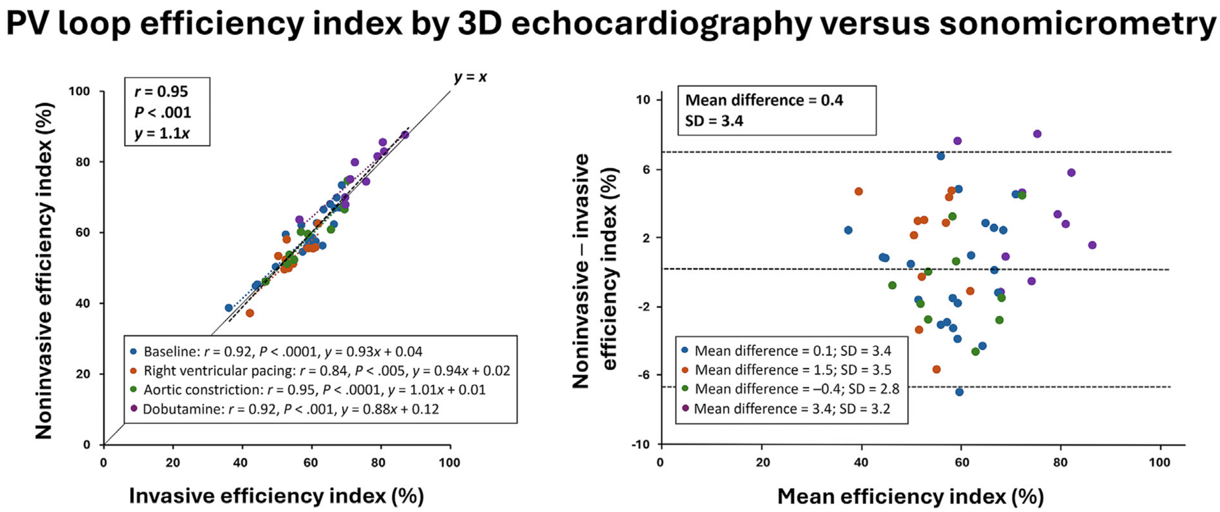

Figure 6 Validation of the noninvasive efficiency index. In canines, the noninvasive efficiency index by 3D echocardiography showed very good agreement with the invasively obtained efficiency index. Student's *t*-test was used to compare means, while Pearson correlation coefficient and Bland-Altman analysis were used to assess agreement between the methods.

these results may not be directly translatable to human hearts in vivo and therefore may not serve as a reliable gold standard for efficiency in the present context. In contrast, our closed-chest chronic heart failure sheep model is better suited for this purpose, and we found a very good correlation between efficiency measured by PET-CT and the efficiency index. Therefore, we believe that it may be of value to assess the efficiency index from 3D echocardiography in patients.

Left Ventricular Contractility and Arterial Elastance by 3D Echocardiography

The E_{ES} derived from invasive PV loops during preload reductions is a load-independent measure of LV contractility, but it is not feasible to obtain from our noninvasive PV method. Instead, we estimated E_{ES} by using a simplified single-beat approach where E_{ES} was defined as the slope of a line from the origin to the coordinate in the upper left corner of the PV loop. Similar approaches have previously been used to approximate ventricular elastance,[15] and Heerdt *et al.*[16] recently showed that a simulation model using fixed V_0 agreed well with experimentally measured elastance. Furthermore, a recent study by Ahmadian *et al.*[10] showed that the contractility indices P_{max}/EDV and P_{ES}/EDV agreed fairly well with gold standard invasive E_{ES}. In accordance, in the present study we show that E_{ES}, P_{max}/EDV, and P_{ES}/EDV derived from noninvasive PV analysis by 3D echocardiography capture increased LV contractility with dobutamine infusion in a manner similar to invasive E_{ES}.

Arterial elastance E_a showed very good correlation and agreement between the noninvasive and invasive methods. Hence, PV analysis by 3D echocardiography provides an accurate estimate of arterial stiffness that integrates both the resistance and compliance of the arterial system. This parameter can be used to assess the ability of the arterial bed to accommodate the volumetric output of the LV, which is of high interest in the diagnosis and management of conditions like hypertension, heart failure, and aortic stenosis.

Pressure-Volume Method by 3D Echocardiography Potential Clinical Utility

Our noninvasive method provides accurate PV loop–derived indices comparable to invasive measurements. Its potential clinical utility should be similar to that of invasive PV analysis.[4,17] PV analysis may be useful by providing a more comprehensive assessment of cardiac function. EF, which is the most used parameter of systolic function, is influenced not only by contractility but also by afterload and preload, all of which can alter EF directly. Myocardial strain is another echocardiographic parameter suggested to be superior to EF, but it is also influenced by many of the same factors as EF. Pressure-volume-derived parameters can aid in this respect by integrating the influences of preload, afterload, and contractility.

In the setting of heart failure, which is currently classified based on EF, the PV-derived efficiency index may offer superior prognostic value compared to conventional load-dependent measures.[18]

As noninvasive PV analysis becomes more accessible for clinical use, future multicenter trials should investigate the prognostic value of PV indices across diverse patient populations (e.g., heart failure, valvular heart disease, cardiac oncology, hypertension). Randomized trails are needed to assess whether treatment guided by PV-derived measures of LV function and arterial elastance can improve outcomes. The PV analysis–derived E_{ES}, E_a, and efficiency may aid in determining the etiology of heart failure and guide treatment. PV analysis in valvular heart disease may also be useful. For example, in acute evaluation of transcatheter-based aortic valve replacement, an immediate reduction in systolic pressure allows contraction to a lower ESV, so the PV loop would be lower in height and shifted leftward. Such a leftward shift will presumably not be seen in pressure-strain loops where end-diastolic strain is fixed to 0.

Estimated SW using the PV method was practically identical to the clinical approach multiplying MAP with stroke volume in our data, which indicates the more complex PV procedure is not required for this purpose. This may not apply to cases of mitral and aortic

Table 2 Characteristics and hemodynamics of sheep population

Parameter	Normal LV AAI (n = 3)	Normal LV DDD (n = 3)	Remodeled LV AAI (n = 12)	Remodeled LV DDD (n = 12)
EDV, mL			111 ± 21	116 ± 23
n_1	71	82	130	125
n_2	83	96	112	137
n_3	83	99	119	129
ESV, mL			69 ± 21	74 ± 22*
n_1	25	31	83	83
n_2	25	30	72	85
n_3	31	35	73	83
Stroke volume, mL			41 ± 9	42 ± 11
n_1	45	61	47	42
n_2	58	66	40	54
n_3	52	64	46	46
EF, %			38 ± 8	36 ± 8
n_1	64	63	36	33
n_2	70	69	36	38
n_3	63	64	39	35
SW, mm Hg × mL			2,210 ± 635	1,746 ± 461†
n_1	4,118	3,803	2,581	1,698
n_2	3,966	3,231	1,817	1,644
n_3	4,732	3,672	1,526	1,033
PET-CT efficiency, mm Hg × mL/g			370 ± 153	238 ± 104†
n_1	543	435	255	154
n_2	576	398	371	238
n_3	522	397	260	103
PV loop efficiency index, %			54 ± 9	46 ± 8†
n_1	82	80	51	41
n_2	84	79	43	38
n_3	82	79	40	31

LV, left ventricle.
All measurements were performed at 110 bpm. Mean and SD values are provided for all 12 animals after LV remodeling and heart failure occurred. Additionally, data for the 3 animals with baseline measurements are presented separately and labeled as *n*1–*n*3. For each of these animals, values across all interventions are included in the table.
**P* < .01 vs AAI.
†*P* < .001 vs AAI.

insufficiency where volume changes occur during the isovolumic phases. Also note the comparison was performed using stroke volume measured by 3D echocardiography, which is more accurate than two-dimensional echocardiography.[12,13] Therefore, if volume is assessed using 3D echocardiography regardless, the difference in complexity will be minimal.

Feasibility of Implementing PV Analysis by 3D Echocardiography in Clinical Practice

The LV volume signal is a low-frequency content wave and can therefore be sampled at relatively low sample rates. Sampling approximately 30 harmonics above the heart rate frequency is typically sufficient in most cases.[11] A frame rate of at least 20 frames/sec can usually be obtained in 1-beat 3D volume acquisitions in adults. Therefore, noninvasive PV analysis should require stitching of 2 or 3 consecutive beats in patients with normal heart rate in the range of 60 to 90 bpm. Unstable rhythm, for example, in atrial fibrillation, or if frequent extrasystoles occur, will consequently limit the applicability of our method. However, as frame rate and image quality improve in the future, PV analysis by 1 beat will probably become feasible. This will eliminate the need for stitching of beats and, furthermore, potentially enable real-time PV analysis. Brachial systolic and diastolic pressures are measured routinely at every echocardiographic examination, and methods to detect valvular events have improved in recent years so that they now can be detected automatically from standard apical views, with manual adjustments when needed.[19] Hence, acquiring noninvasive PV loop–derived parameters validated in the present study will likely be no more time-consuming than just measuring regular 3D volumes, which, according to guidelines, should be performed in all labs with the necessary experience.[7]

Recent advances in AI suggest that automatic detection of valve events and measurements of LV volume trace may be feasible.[19,20]

These methods could enable fully automated assessment of the PV loop and associated indices of LV function, which could be integrated directly into 3D echocardiographic analysis systems.

Limitations

The estimated SW did not include the work done during filling due to the lack of a proper method to estimate pressure during filling. However, the area under the PV loop is small relative to the loop area, and recent observations indicate that filling pressures have low influence on PV parameters.[21] Nevertheless, in a situation with high filling pressure and low systolic pressure, this simplification will presumably have higher impact. A recent proof-of-concept study suggests a method to estimate the LV diastolic pressure curve using echocardiography and simple clinical parameters, which if successfully validated will mitigate this limitation in the future.[22]

Least-squares linear regression was used to obtain a reference ESPVR; hence the inherent nonlinearity of ESPVR could have influenced results. Special care was taken to exclude beats deviating from linearity. However, we cannot rule out the possibility that nonlinearity of ESPVR may have affected our results.

The variable V_0 represents the theoretical volume in the ventricle at peak contraction against zero pressure and will be larger than 0 mL as fiber shortening is limited by myocardial incompressibility and limited stretch in cross-fiber directions. Assessment of the ESPVR from multiple loops during a preload reduction is challenging. Extrapolation of the ES points frequently results in negative values for V_0.[23-25] This has been attributed to the ESPVR relation being actually nonlinear. Although setting V_0 to 0 mL contradicts theoretical principles, it is a pragmatic approach to ensure the method's feasibility in clinical practice. The slope of this line, noninvasive E_{ES}, should therefore be viewed as a different index of contractility. This index increased in all animals following infusion of dobutamine. Also, the resulting efficiency index captured similar changes as efficiency measured by PET-CT. Thus, despite that these indices differing from the original theory, they may still be useful for functional classification of patients and for monitoring progression of disease and response to treatment. As for all parameters, there will likely be situations and limitations where these indices fail, and future studies will have to identify these cases and evaluate how the efficiency index and the other noninvasive parameters can enhance diagnosis, prognosis, and guiding of treatment.

In this study we adjusted the magnitude of the noninvasive pressure waveform to measured invasive peak LV pressure, which may have produced somewhat idealized results as in clinical practice it would be adjusted to brachial systolic cuff pressure. We have previously validated the noninvasive pressure curve estimate using cuff pressure in patients against invasively measured pressures and found very good correlation and agreement.[5] The percentage sensitivity of the estimated SW to an error in the estimated peak LV pressure from brachial systolic cuff pressure is equal to the percentage error in pressure.

The PET-CT method reflects glucose metabolism, not overall oxidative metabolism. An 11C-acetate tracer would have been optimal but was not available when the experiments were conducted.

CONCLUSION

Noninvasive PV analysis by 3D echocardiography is feasible and accurate, making powerful PV loop parameters for evaluating LV function easily available for clinical use. This includes a novel index of LV efficiency, which correlated well with reference measurements, and appears to be a particularly interesting marker of cardiac function. Further studies should explore the clinical utility of noninvasive PV analysis by 3D echocardiography.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT and Microsoft Copilot in order to improve specific sentences in the manuscript, aiding in the clear and consistent presentation of complex concepts. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

CONFLICTS OF INTEREST

Otto A. Smiseth is co-inventor of "Method for myocardial segment work analysis," has a patent on "Estimation of blood pressure in the heart" and has received a speaker honorarium from GE Healthcare. The remaining authors have nothing to disclose.

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