BACKGROUND AND METHODS

We recently presented and validated a clinically available, non-invasive method for generation of pressure–volume (PV) loops from time-resolved ventricular volumes and brachial pressure (Seemann et al., 2019). The method is based on estimation of left ventricular pressure as the product of elastance from a mathematical model and volume from cardiovascular magnetic resonance imaging. While the previous method produced valid data at resting heart rates, its performance was impaired at high heart rates, such as in children or during exercise. To address this limitation, we present an improved method. This new method takes into account the heart rate–dependent relative duration of systolic and diastolic phases of the cardiac cycle (Chung et al., 2004). The aim of the present study was to develop the model into allowing for higher heart rates when the diastolic fraction of the cardiac cycle shortens and to...
validate it in a porcine model at rest and at varied heart rates in healthy human volunteers. Furthermore, since ventricular-arterial coupling increase the understanding of cardiac pathophysiology and has been shown to have prognostic value in cardiac disease (Ikonomidis et al., 2019; Ky et al., 2013), we also added this feature to the method.

Given that the model-derived pressure is the product of elastance and the measured volume, it is critical that the timing of these curves is accurate. In the original model (Seemann et al., 2019), elastance was defined from the double-Hill equation (Stergiopulos et al., 1996). To accommodate different heart rates while achieving physiological scaling of the elastance function, we replaced the double-Hill equation with the digitalized a normalized elastance curve presented by Senzaki et al (Senzaki et al., 1996). This elastance curve was scaled in amplitude and in time so that the end-systolic point (defined as minimal left ventricular volume) corresponded to the middle of the downslope of the elastance curve. The point on the PV loop that defines the end systolic pressure volume relation (ESPVR) is the point of maximal elastance and the corresponding volume at the same instance in time (Zhong et al., 2005).

Contractility is defined as the slope between V₀ and the point on the PV loop where the elastance is maximal (Eₘₐₓ). In the literature, Eₘₐₓ is sometimes referred to as systolic elastance (Eₛₑ); however, we prefer the usage of Eₘₐₓ since maximal elastance may not occur exactly at volumetric end systole. In fact, maximal elastance occurs slightly before minimal ventricular volume and the isovolumetric relaxation. In the previous version of the non-invasive PV loop method (Seemann et al., 2019), contractility was defined as the slope from V₀ to and to the point of pressure at maximal elastance and the pressure at the smallest volume, and thus theoretically there will be a small difference. Effective arterial elastance (Eₐ) was added in the new model and is defined as the slope from the point on the PV loop where elastance is maximal to the point of end-diastolic volume and zero pressure.

1.1 | Statistical analysis

Statistical analysis was performed using GraphPad (v9.1.0). Continuous variables are presented as mean ± standard deviation (SD). The paired t-test was used to assess differences in controls before and after stress. If the p-value <0.05 the result was considered significant.

2 | RESULTS

2.1 | Animals

Validation was performed with invasive pressure loops registered in either pigs (Figure 1a,b). The difference between non-invasive and invasive PV loops were for stroke work 0.00 ± 0.03 J, ventricular efficiency 0.1 ± 0.4%, and contractility 0.1 ± 0.1 mmHg/ml.

![Figure 1](image_url) (a) Validation of non-invasive stroke work against invasive pressure volume (PV) loops in 8 animals. (b) Representative non-invasive PV loops derived from the original and improved models in one pig experiment, showing improved agreement with the invasive PV loops for end-systolic elastance (Eₘₐₓ), corresponding to contractility and the arterial elastance (Eₐ). (c) Representative PV loops in one human participant at rest with heart rate 55 beats per minute and during stress with heart rate 120 beats per minute, comparing the original and improved methods showing the more pronounced effect on contractility at stress. (d) Detail from the PV loop at stress in c showing the point of end-systolic pressure-volume relations, Eₘₐₓ with the original and the improved method, marked with red dots.
2.2 | Humans

Sixteen human controls (age 35 years [28–42], 13 men) were examined with cardiovascular magnetic resonance and a non-invasive brachial cuff pressure at rest and during dobutamine stress. The heart rate increased from 65±10 at rest to 134±12 bpm during stress, systolic blood pressure from 122±11 to 158±22 mmHg and diastolic pressure from 74±10 to 87±10 mmHg. End-diastolic volume decreased from 186±28 to 162±26 ml, and ejection fraction (EF) increased from 56±5 to 69±4%. Representative PV loops from one human participant at rest and stress are shown in Figure 1c. Stroke work increased from 1.3±0.3 to 1.7±0.4 J, ventricular efficiency from 70±4 to 82±4%, contractility from 1.1±0.2 to 2.0±0.5 mmHg/ml, and the ratio of effective arterial elastance (E a) to maximal ventricular elastance (E max) decreased from 0.96 to 0.56. At rest, the improved method, in comparison to the original, generated higher stroke work (1.3±0.3 vs 1.2±0.2, p<0.01) but similar contractility (1.1±0.2 vs 1.1±0.2 mmHg/ml, p<0.13). The impact of the improved model was more pronounced at stress for stroke work (1.7±0.4 vs 1.6±0.4, p<0.0001) and contractility (2.0±0.5 vs 1.9±0.5 mmHg/ml, p<0.05). At higher heart rates during dobutamine stress, the model-derived PV loops increased in amplitude, moved leftward to decreased volumes and maintained the physiological shape (Figure 1c).

3 | DISCUSSION

This study contributes with further development of a non-invasive method for quantification of pressure–volume loops from brachial pressure and cardiovascular magnetic resonance to accommodate the higher heart rates seen during exercise or pharmacological stress, as well as in children. The improved model also offers estimation of arterial elastance and thereby the ventricular-arterial coupling expressed as the ratio E a/E max.

Ventricular-arterial coupling has been suggested as a prognostic marker in cardiac disease (Godfrey et al., 2018; Ikonomidis et al., 2019; Ky et al., 2013). The E a/E max ratio in healthy controls at rest was in the range of earlier reports, 0.6–1.2 (Borlaug & Kass, 2008). A ratio around 1 is thought to be optimal balance between mechanical and energetic efficiency (Chantler et al., 2008; Chirinos, 2013) and means that EF would be 50%, since EF = E max/(E max+E a). The E a/E max ratio decreased in our study to 0.56 at stress as ventricular contractility increases more than the afterload to augment cardiac output. Maximal mechanical efficiency is when the ratio is 0.5 (Burkhoff & Sagawa, 1986) which would suggest an EF of 67% (Robotham et al., 1991), which is close to the 69% found at stress in this study.

Pressure volume loops have been utilized to diagnose heart failure with preserved ejection fraction in patients with unexplained chronic dyspnea (Penicka et al., 2010), and Wong et al. used load-independent measurement of ventricular function to explain exercise intolerance in patients with congenital heart disease (Wong et al., 2017). Those studies, however, used catheterization which restricts utility in clinical routine. In contrast, our method is clinically applicable at no added risk, enabling clinicians to detect early signs of deteriorating ventricular function and to monitor disease progression or response to interventions.

3.1 | Limitations

A limitation is that the method uses brachial pressure to estimate left-ventricular systolic pressure and will therefore underestimate the true PV area in cases with a stenotic aorta. Moreover, the method requires the user to estimate left ventricular end-diastolic pressure, a potential limitation in patients with heart failure. Sensitivity analysis, however, found the impact of changes in end-diastolic pressure to be small (Seemann et al., 2019). In addition, end-diastolic pressure does not affect estimates of contractility (E max), or E a. The measure of contractility requires a correct measure of V 0 and in this method V 0 is approximated with zero that might vary between individuals. The present study did not evaluate PV loops during varying loading conditions, motivating further enquiry.

4 | CONCLUSION

This improved method for non-invasive PV loops provides a new diagnostic tool for cardiac disease states in a wider range of study cohorts than previously attainable and at both rest and during stress. It facilitates the clinical use of PV loops for diagnosis and monitoring of heart failure patients and might improve prognostic assessments.

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CONFLICT OF INTEREST

Dr Heiberg is the founder of Medviso AB, Lund, Sweden, producer of the software Segment. The other authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

Patient data cannot be made available due to data privacy concerns. Other data will be made available upon reasonable request.

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