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A Study of Cardiac Ventricle Performance Indices Estimated with Data from Single-Beat Pressure Volume Loops

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Abstract: Cardiac ventricle function can be measured from a multiple-beat pressure volume loop sequence, or estimated from a single beat of pressure volume loop data. In this study, the effectiveness of single-beat estimation is evaluated with functional markers defined by maximum elastance, isovolumic mode developed pressure, ejecting mode pressure volume area, and isovolumic mode pressure volume area. These estimates applied a linear regression model of chamber volume equilibrium as the calculation input. With data collected from 23 published pressure volume diagrams, estimates were assessed for percent differences to multi-beat outcomes. Results by method were: isovolumic pressure volume area (4 ± 4 %), isovolumic peak pressure (8 ± 6 %), ejecting pressure volume area (9 ± 6 %), and maximum elastance (22 ± 17%); $p<.0001$ one way ANOVA. The isovolumic pressure volume area estimates had the minimum overall error, and appeared to correlate with chamber volume variations through a measured range from 25 mL to 230 mL. This size correlation suggests the method is useful for interpreting normality of natural changes occurring during developmental stages of pediatric patient growth.

Keywords: Pressure Volume Loop, Single-Beat Estimates, Pressure Volume Area, Isovolumic Contracting Mode, Contractility Methods.

1. Introduction

The pressure volume loop (PV loop) is a graphic representation of the heart's cyclical pattern of chamber pressure (P) vs. chamber volume (V). Calculations which apply PV loop data can measure the intrinsic contracting performance of the heart. For this purpose, measures include time varying elastance, peak pressure development, hydraulic work provided for arterial consumption, and the development of structural elastic potential energy [1-2]. To calculate these indices, a hemodynamic response is typically recorded as the heart's filling volume (preload) or outflow impedance (afterload) is altered by an intervention. Yet, procedures which adjust preload or afterload are not always easy to perform for every subject, and load alterations may not yield recorded patterns leading to reliable functional measures. For these reasons, it is worthwhile to examine the effectiveness of estimation methods applied to PV loops measured at a natural load - with the goal to confidently assess chamber contracting function when load adjustments are not feasible or effective.

2. Methods

2.1. Physiological Basis of Measures

PV diagram measures to be studied for single-beat effectiveness are derivative properties of a cardiac

pressure volume relationship outlined in this mathematical form by Suga and Sagawa [1].

$$\text{PV relationship: } P(t) = E(t)\times(V(t)-Vo) \qquad (1)$$

The E(t) parameter defines 'time varying elastance', and functionally specifies the changing dP/dV elastic modulus of the chamber. E(t) changes reflect tissue structures becoming mechanically altered between flexible conditions conducive during filling, and conditions of increased rigidity to sustain structural integrity during ejecting intervals of pressurization. The Vo property of Eqn. (1) is a measure of the 'equilibrium volume'. From the pressure volume relationship, it is seen the Vo equilibrium volume effectively defines a hypothetical chamber size, if experimentally depressurized to P=0 and stress-free conditions.

Applying these properties from the pressure volume relationship, the performance functions to be measured and studied from the PV loop diagram are shown in Fig. 1, and are now described.

Maximum elastance (E_{max}): E_{max} is the maximum cardiac cycle value of E(t) elastance. The E_{max} measure functionally specifies a peak dP/dV structural modulus developed momentarily near the completion of the ejection interval. In this study, the E_{max} measure will be calculated with provided inputs of Vo equilibrium, and samples of V(t), P(t) data digitized from one PV loop measured at natural baseline function.

$$E_{max} = \text{maximum } P(t)/(V(t)-Vo) \qquad (2)$$

Peak Isovolumic Pressure (P_{iso}): The P_{iso} measure indicates a maximum pressure developed during isovolumic functional contraction, when an experimental clamping of the arterial conduit prevents the heart from ejecting, and the chamber is subsequently pressurized at a constant end-diastolic volume (EDV). Since human P_{iso} cannot be safely measured, P_{iso} is inferred from the PV relationship of Eqn. (1) with the fundamental assumption that E_{max} and Vo properties of natural ejecting conditions also remain in effect if the chamber is experimentally placed into an isovolumic condition [3].

$$P_{iso} = E_{max} \times (EDV-Vo) \qquad (3)$$

Ejecting Pressure Volume Area (PVA): PVA is a contracting work energy quantified by two regional PV diagram areas. These area measurements are shown in Fig. 1 as the stroke work (SW) defined by hydraulic energy ejected for arterial load consumption, and a residual elastic potential energy (EPE) remaining withheld by the chamber structure at the ejection interval's conclusion [2].

$$PVA = SW + EPE \qquad (4)$$

Isovolumic Pressure Volume Area (PVA_{iso}): PVA_{iso} is a measure obtained in the special-case when PVA energy is assessed in the isovolumic contracting mode. By definition, with an isovolumic function SW=0, and all measured PVA energy from Eqn. (4) is fully realized in the isovolumic mode as the elastic potential energy developed by the work of contracting mechanisms.

$$PVA_{iso} = \text{EPE of isovolumic mode when SW=0} \qquad (5)$$

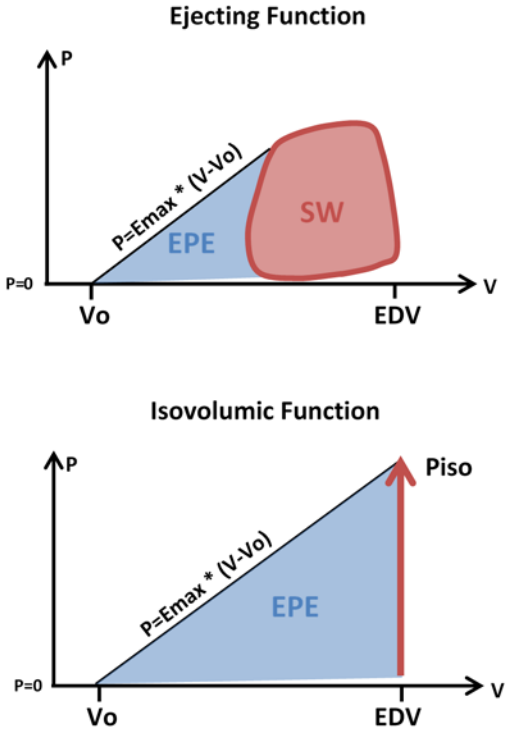


Fig. 1. In ejecting function, a PV loop is shown in red with a pressure volume relationship $P= E_{max}\times(V-Vo)$ defined by a line with slope Emax, and Vo volume intercept at P=0. The pressure volume area PVA = SW + EPE is the numerical sum of the red and blue region diagram areas.

With isovolumic function, the end-diastolic volume (EDV) is assumed to be maintained during pressurization to a maximum pressure P_{iso}. By definition since SW=0 in the isovolumic mode, PVA_{iso} = EPE is the large blue region area. In practice with human subjects, the P_{iso} and PVA_{iso} measures of isovolumic function are inferred from the pressure volume relationship, by assuming Emax and Vo properties measured from the ejecting condition remain in effect for isovolumic conditions.

2.2. Single-beat Estimations

The steps for calculating Emax, P_{iso}, PVA, and PVA_{iso} share a common reliance on Vo equilibrium volume as needed input. However with one beat of PV loop data, the Vo input cannot be measured and needs to be approximated. For this purpose, a regression model was developed to generate an approximation to the Vo input needed for single-beat processing.

The regression model implemented collected measures of ejected stroke volume (SV) as a predictor, and the dependent variable was assessed from 'effective preload' measures defined as EDV-Vo [4].

With 23 data sets of digitized [5] PV loops from right ventricle diagrams [6-21], this result of the regression model was obtained.

Regression result: EDV-Vo= 1.91×SV, R^2=.966 (6)

For simplification, the 1.91 slope result was rounded to the whole number of 2, and formed this input provided to the single-beat processing.

Vo input to estimates: Vo = EDV– 2×SV (7)

The calculations from this approximation to single-beat Vo, were compared to results when the Vo input could be directly measured from multi-beat data. In Fig. 2, the calculations for both types of input (measured or approximated) are shown to follow identical steps. Emax was first calculated from Eqn. (2), and the P_{iso} calculation followed from Eqn. (3). Ejecting pressure volume area PVA = SW + EPE was calculated based on diagram area measures. The isovolumic pressure volume area was inferred from PVA and a supplemental ΔPVA diagram area as PVA_{iso}= PVA + ΔPVA.

3. Results

3.1. Estimation Effectiveness

To gauge the effectiveness of single-beat estimates, percent differences were compiled between calculation results from approximated Vo input, and paired results from calculations applying Vo input measured from multi-beat data. A summary of the percent differences is shown in Table 1, with differences ranging from 4 ± 4 % for the PVA_{iso} method to 22 ± 17 % for the Emax method. One way ANOVA with repeated measures yielded a p<.0001 result across method defined groups.

Table 1. Percent differences and regression slopes between single-beat (sb) and multi-beat (mb) calculations.

Method	% Difference	Slope	R^2
E_{max}	22 ± 17 %	sb = 1.189 × mb	.904
P_{iso}	8 ± 6 %	sb = 1.002 × mb	.924
PVA	9 ± 6 %	sb = 1.047 × mb	.991
PVA_{iso}	4 ± 4 %	sb = 1.015 × mb	.999

3.2. Interpretation of Percent Differences

An interpretation of the results from Table 1 is provided with a PV loop schematic in Fig. 3, showing an offset factor ΔVo = ε × SV introduced to alter Vo and facilitate error sensitivity analysis for each calculation. The offset's effect on each method's result is also catalogued in Fig. 2 to demonstrate similarities with the measures from Table 1. These include: 1) A direct sensitivity of the Emax calculation to ΔVo; 2) A fractional offset dependence by PVA and P_{iso} calculation results, and 3) a limited sensitivity to ΔVo by the PVA_{iso} method, which reflects the method's estimation accuracy.

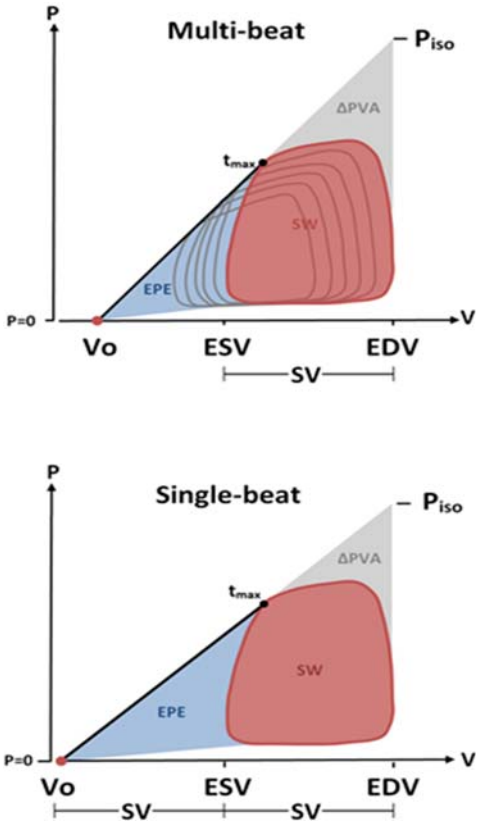
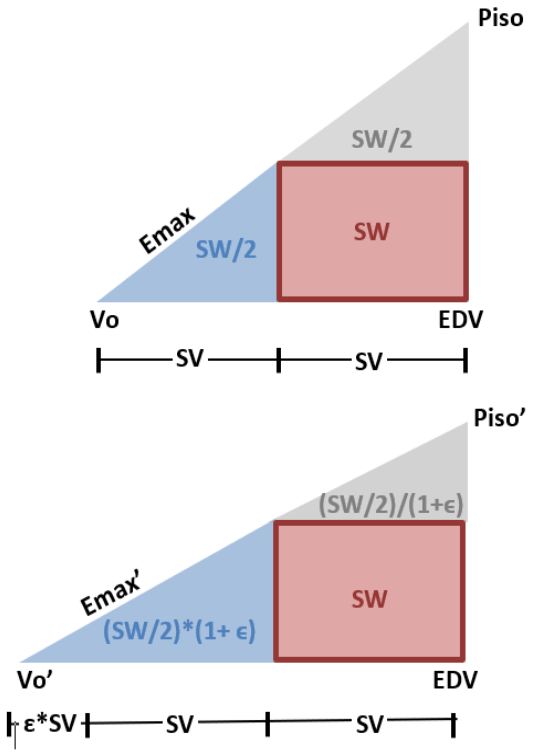


Fig 2. A multi-beat PV loop dataset illustrates preload reduction from a baseline function PV loop shown in red. The resulting depressurization trend is characterized by a line, which defines the linear slope Emax and Vo equilibrium volume at the red circle intercept to P=0. With single-beat data, Vo equilibrium cannot be measured and is approximated as Vo= EDV – 2×SV. With either the approximated or measured Vo input, E_{max} is determined to occur at a sample 't_{max}', when E(t) = P(t)/(V(t)-Vo) is a maximum. The P_{iso} calculation follows from Eqn. (3). The diagram areas indicate the SW energy (red region area) and EPE energy (blue region area) which combine to form the PVA=SW+EPE energy sum. The gray region area specifies a ΔPVA energy difference between the ejecting mode PVA measure, and the PVA_{iso} of inferred isovolumic pressurization to P_{iso}. By definition, PVA_{iso}= PVA + ΔPVA= =SW + EPE +ΔPVA. The figure is adapted from Bellofiore and Chesler [22] with permission from Springer Nature.

3.3. Correlations to Chamber Size

The study data consisted of measures from mammalian species with ventricle sizes quantified by end-diastolic volume (EDV). The EDV measures ranged from 25 mL to 230 mL, and reflected the order-of-magnitude size growth of a normal human ventricle into adulthood [23]. The effects of EDV size variations on the measured indices can be seen from the results

of correlation between measures and EDV in Table 2. These results illustrated the PVA and PVA_{iso} energy measures increased in step with EDV size, Emax measures were inversely size correlated, and P_{iso} results were uncorrelated to EDV.



Calculations	First-order Ratio
Emax = SW/SV^2 **Emax'** = $(SW/SV^2) / (1+ \epsilon)$	**Emax'/ Emax** ≈ $(1- \epsilon)$
P_{iso} = 2*SW/SV P_{iso} ' = SW/SV * (1 + 1 / (1+ ϵ))	P_{iso} ' / P_{iso} ≈ $(1- \epsilon/2)$
PVA = 3*SW/2 **PVA'** = SW + (SW/2) * (1+ ϵ)	**PVA' / PVA** ≈ $(1+ \epsilon/3)$
PVA_{iso} = 2*SW PVA_{iso} ' = SW + (SW/2) * (1+ ϵ) + (SW/2) / (1+ ϵ)	PVA_{iso} '/ PVA_{iso} ≈ 1

Fig 3. A rectangular PV loop is applied to examine the effects of Vo approximation error. Top panel calculations are provided with representative Vo =EDV-2×SV input from Eqn. 7. The bottom panel adds the Vo offset factor ΔVo = ε×SV to generate altered results shown with a primed notation. The ratios between results with and without the offset, predict the PVA_{iso} assessment has no first-order sensitivity to ϵ.

Table 2. Single-beat estimate variations with end-diastolic volume.

Regression	R^2
E_{max} = - 0.013 × EDV + 2.03	.400
P_{iso} = 0.070 × EDV + 41.49	.033
PVA = 25.50 × EDV - 653.06	.798
PVA_{iso} = 33.92 × EDV - 966.69	.778

Details of the PVA_{iso} estimations are shown in Fig. 4, with individual data points sorted into categories based on EDV. This graph demonstrated PVA_{iso} energy generally increased with ventricle size, and that estimation effectiveness by PVA_{iso} was maintained through the studied EDV and energy ranges.

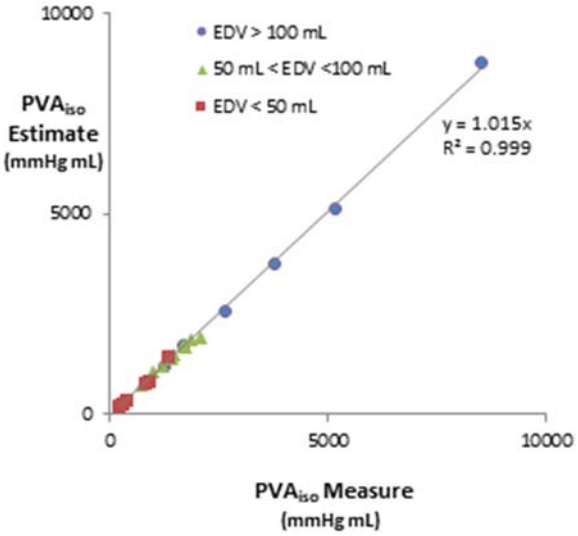


Fig 4. Paired PVA_{iso} single-beat estimates and multi-beat measures illustrate estimates were effective over the studied ranges of EDV size and chamber energy output.

4. Discussion

Estimation accuracy is one factor to consider when clinical measures seek to quantify function. A second challenging step in patient care, is to assess whether obtained measures falls within (or outside) of a range considered to be normal for the patient's age, height, weight or gender. In the setting of pediatric care, some understanding of normal value progressions anticipated during physical development [23] becomes a vital consideration to successfully interpret the meaning of a measure, and its implication for effective treatment pathways.

From results of this study, and based on the important need to interpret measures in the context of patient growth, there are two benefits realized by implementing the PVA_{iso} functional assessment. First, the PVA_{iso} estimates from single-beat data are accurately reflecting multi-beat results. As the PVA_{iso} measure is EDV correlated, there is also a compelling indication the measure can effectively be applied to formulate normal range charts useful in pediatric applications.

These computing benefits suggest there could be underlying physiological factors influencing the reliability of the PVA_{iso} assessment. By indicating potential energy developed from contractile mechanism work, the PVA_{iso} number reflects a maximum work capability potentially measured from

the PV diagram. The PVA_{iso} energy is also a constraining limit, which in a given contractile state effectively regulates the partition of energy into mechanisms of ejection work, elastic potentials, and other avenues of activated energy consumption.

An energy limit which effectively regulates function is also suggested from the results of this study, and specifically by this regression model result from Eqn. (7).

$$\text{EDV-Vo} = 2 \times \text{SV (regression result)} \quad (8)$$

To interpret this result, it is noted that an energy model first proposed by Sunagawa [4], describes an arterial load optimization of ejected stroke work (SW), and the arterial model specifies this condition will also optimize SW to be a maximum.

$$\text{EDV-Vo} = 2 \times \text{SV (SW is a maximum)} \quad (9)$$

With arterial considerations leading to Eqn. (9), it is interesting to note a complementary optimization is based on the ventricle's function. This ventricle result is realized from the analysis of Vo offsets in Fig. 3 and offset effects on the PVA_{iso} measure. From the Fig. 3 results of PVA_{iso}, in Appendix A it is demonstrated the PVA_{iso} measure of cardiac workload is optimized to be a minimum, when the effective preload condition described by Eqn. (8) and Eqn. (9) is in effect.

$$\text{EDV–Vo} = 2 \times \text{SV} \ (PVA_{iso} \text{ is a minimum}) \quad (10)$$

The concept of a characteristic EDV-Vo effective preload, as a prevalent and shared feature of different PV loops is supported in three ways: First, from collected measures leading to the regression result of Vo input applied by this study, secondly by a model of arterial load which optimizes ejected stroke work, and finally with the observation that PVA_{iso} measures of contracting workload are optimally minimum when $\text{EDV-Vo} = 2 \times \text{SV}$.

These results raise a fundamental question, whether it is necessary to infer PVA_{iso} as a measure of contractile mechanism work, or whether the PVA measure from ejecting data is a more direct indication of the contracting workload. To address this question, it is noted the PVA measure from an ejecting chamber may be unable to detect all the energy dissipating mechanisms activated by contractility. For example, ejecting ventricles have pronounced structural motions which introduce viscous energy losses that cannot be measured by PVA [2]. With this ejecting motion, some contractile work will also be diverted into the kinetic energy required for tissue movement and blood flow. With measures obtained from the ejecting function, these lossy mechanisms will be more prevalent than for the isovolumic function, and it is hypothesized *some* amount of energy is missing from the ejecting PVA measure. Without a detailed knowledge of these lossy mechanisms, this presumed missing energy can be denoted as a generic ΔPVA energy quantity. The extent of ΔPVA as a full indication of the contractile work that cannot be detected by the ejecting PVA measure is considered to be a key topic of future research.

If energy optimization is a guiding principal of the PV loop function, new sensors and instrumentation systems might introduce capabilities to highlight the mechanisms activated by contractile work. These systems would provide a pathway towards safer techniques to measure ventricle function. By developing non-invasive methods to facilitate measuring the mechanisms activated by contractility (such as arterial flow), there is a possibility that reasonable estimates of ventricle energy development can be inferred from arterial energy dissipation measures. A practical benefit realized by this approach, would follow from a capability to measure arterial flow non-invasively, and provide alternatives to the invasive catheterization needed to measure pressure data components of the PV loop.

One of this study's intrinsic limitations follows from manually digitizing collected PV diagram charts, with some error potentially introduced to the calculation results from digitizing inaccuracy. While digitizing errors are a factor, these errors were limited in comparison the offsets introduced by a designed approximation to Vo input, and the larger influences these approximations had on results.

In summary, the PVA_{iso} energy of a right ventricle is reliably estimated from single-beat PV loop data. The estimate is accurate over a range of chamber energies, and is positively correlated to chamber size. These versatile features can assist future efforts to simplify PV loop assessment, and to reliably interpret longitudinal functional changes recorded during pediatric patient growth.

Appendix A

From the Vo sensitivity analysis of Fig. 3, it was shown the PVA_{iso} energy quantity is this function of $\varepsilon \times \text{SV}$ offset from a characteristic equilibrium volume $\text{Vo} = \text{EDV-2} \times \text{SV}$.

$$PVA_{iso} = \text{SW} + (\text{SW}/2) \times (1+\epsilon) + (\text{SW}/2)/(1+\epsilon) \quad (A1)$$

For simplification, a variable substitution is introduced.

$$\beta = (1+\epsilon) \quad (A2)$$

The energy calculation becomes a function of SW and β.

$$PVA_{iso} = \text{SW} + (\text{SW}/2) \times (\beta + 1/\beta) \quad (A3)$$

The PVA_{iso} energy will be a minimum when $\beta=1$ and $\varepsilon = 0$ to indicate the characteristic effective preload

$$\text{EDV–Vo} = 2 \times \text{SV} \quad (A4)$$

minimizes the PVA_{iso} measure of contractile mechanism work.

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