Digital On-Line Computation of a Predictor of Cardiac Oxygen Consumption

Left Ventricular Systolic Pressure Volume Area

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SUMMARY

Left ventricular systolic pressure volume area (PVA) has been proposed as a reliable predictor of cardiac oxygen consumption per beat (VO_2). PVA is the area in the pressure-volume (P-V) diagram that is circumscribed by the end-systolic and end-diastolic P-V relation curves and the systolic segment of the P-V loop trajectory. It represents the total mechanical energy required for the ventricle to contract, to change its wall's elastic state from end diastole to end systole, and to eject blood against afterload. PVA has so far been measured manually with a planimeter applied to the P-V diagram. To measure PVA more accurately and on line during experiments, we devised a new method of computing PVA with a digital computer. The method consists of integrating during systole the infinitesimally narrow triangular pressure volume area swept by the straight line segment connecting Vd (ventricular volume at which peak isovolumic pressure is zero) and the instantaneously counter-clockwise moving P-V data point in the P-V plane, and adding a small area between the end-diastolic P-V relation curve and the line connecting Vd and the end-diastolic P-V point. This method has proved useful in our study of the relation between VO_2 and PVA to evaluate the PVA's ability to predict VO_2 .

Additional Indexing Words:

Heart Cardiac energetics Cardiac mechanics Pressure-
volume diagram End-systolic pressure-volume relation

A reliable method of predicting cardiac oxygen consumption from cardiodynamic parameters under given conditions of loading, heart rate and contractility has been needed. To this end, various cardiodynamic parameters and indices have been proposed as primary and secondary determinants of

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cardiac oxygen consumption by many investigators.^{1),2)} However, none of the techniques proposed thus far can serve as a reliable predictor of cardiac oxygen consumption under various combinations of cardiac loading, heart rate and contractility.

In a search for a more reliable predictor of cardiac oxygen consumption, we have found that left ventricular systolic pressure volume area (PVA) correlates linearly with cardiac oxygen consumption per beat (VO_2) regardless of changes in preloaded end-diastolic volume, afterloaded systolic pressure and heart rate of the left ventricle in a stable contractile state.^{3),4)} The PVA is a specific area that is circumscribed by the following three curves in the pressure-volume (P-V) diagram³⁾⁻⁵⁾: 1) the end-systolic P-V relation curve, which is practically linear, 2) the end-diastolic P-V relation curve, which is concave upwards, and 3) the systolic segment of the P-V loop trajectory.

PVA has so far been measured manually with a planimeter applied to a photographed P-V diagram.^{3),4)} The manual measurement of PVA is a tedious task which must be performed after each experiment. Although we recently devised an analog circuit to compute PVA, computation depends on a mathematical approximation of a trigonometric function and hence its accuracy has been limited.⁶⁾ In order to circumvent these problems, we now utilize a digital computer to accurately compute PVA on line. In the present paper, we summarize the new technique and discuss the results of using it in our recent experiments.

METHODS

Fig. 1A schematically depicts a left ventricular P-V loop trajectory in the P-V diagram, together with the end-systolic and end-diastolic P-V relation curves. V_d is the ventricular volume at which peak isovolumic pressure is zero. V_d is a constant (5–8 ml in 40–90 Gm left ventricles), practically independent of heart rate and contractility. V_d is virtually the same as the volume axis intercept of the end-systolic P-V relation line. The PVA is the area between the end-systolic and end-diastolic P-V relation curves on the left side of the systolic part of the P-V loop trajectory, as shown by the dotted area in Fig. 1A. PVA is an energy quantity by itself, consisting of stroke work within the P-V loop and the end-systolic potential energy on the left side of the loop. PVA has dimensions of mmHg ml or joules ($1 \text{ mmHg ml} = 1.33 \times 10^{-4} \text{ J}$). Further details of PVA have been described previously.³⁾⁻⁵⁾

PVA is mathematically an integration from end diastole to end systole of the infinitesimally narrow triangular area (ΔPVA) between the two straight lines connecting V_d and the two P-V data points at two infinitesimally close

Fig. 1. Panel A: Schematic illustration of a left ventricular pressure-volume loop trajectory (solid line) and systolic pressure volume area (PVA, dotted area) in the pressure-volume diagram. ES=end-systolic pressure-volume relation line; ED=end-diastolic pressure-volume relation curve; V_d =volume at which peak isovolumic pressure is zero.

Panel B: Schematic illustration of the infinitesimally narrow triangular area (ΔPVA , dotted) swept by the line segment connecting V_d and the instantaneously moving pressure-volume point ($V(t)$, $P(t)$) during an infinitesimally short time. The crescentic area (dark) above the curvilinear end-diastolic pressure-volume curve (ED) is the small additional area to be included in PVA. Details of this area are described in the Methods.

instants of time, as schematically shown in Fig. 1B. Since the interior angle of the narrow triangle at V_d , $\Delta\theta$, is infinitesimally small, the two sides of the narrow triangle can be considered to be of the same length of $\sqrt{[V(t)-V_d]^2 + P(t)^2}$. Therefore, the area of this narrow triangle is given as $0.5 \cdot \{[V(t)-V_d]^2 + P(t)^2\} \cdot \Delta\theta$. Integration of this narrow area from end diastole to end systole gives PVA. Namely, given θ_{ed} =end-diastolic θ and θ_{es} =end-systolic θ with respect to the volume axis,

$$PVA = 0.5 \int_{\theta_{ed}}^{\theta_{es}} \{[V(t)-V_d]^2 + P(t)^2\} \cdot d\theta$$

where $\theta = \arctan \{P(t)/[V(t)-V_d]\}$.

An additional area to be included in PVA is the small area between the straight line connecting V_d and the end-distolic P-V point and the curvilinear end-diastolic P-V relation curve, as shown by the dark crescentic area in Fig. 1B. The end-diastolic P-V relation curve has conventionally been approximated by an exponential function $P=a \cdot \exp(V/b)$. Although the exponential stress-strain relation seems reasonable for biological materials in general, exponential function does not always fit observed end-diastolic P-V curves.⁷⁾ Moreover, determination of the two coefficients a and b of the exponential equation requires at least two different end-diastolic P-V data points. There-

Fig. 2. Log-log plot of end-diastolic pressure-volume data points (solid circles) and their regression line (solid slant line). The inner pair of the dashed curves indicate the 95% confidence range of the regression line, whereas the outer pair of the dashed curves the 95% confidence range of the sampled data points. The abscissa shows log (end-diastolic volume- V_d) and the ordinate log (end-diastolic pressure). The covered ranges of the pressure and volume were 5–75 mmHg and 17–40 ml, respectively, in the left ventricle (62 Gm in a 9 Kg dog) of a canine excised cross-circulated heart. The correlation coefficient is 0.997. The slope of the regression line is 3.12 and its standard deviation is 0.08 in this case. The slope value is practically equal to 3, indicating the end-diastolic pressure-volume relation can be approximated by $P = a \cdot (V - V_d)^3$.

fore, in the present study, we examined whether or not the end-diastolic P-V relation of the left ventricle of the canine excised cross-circulated heart could be approximated by a power function.

We plotted end-diastolic P-V data points of each left ventricle in a log-log plane, covering an end-diastolic pressure range from 5 to as high as 75 mmHg, as shown in Fig. 2. We avoided including data below an end-diastolic pressure of 5 mmHg for the following two reasons. The first one is that the relative accuracy of pressure reading near 0 mmHg is relatively low and a slight error in P near 0 mmHg influences log(P) value markedly. The second one is that the additional area of a contraction becomes negligibly small as its end-diastolic pressure approaches 0 mmHg. As a result of the analysis, the slope of the regression line in the log-log plane was 3.1 ± 0.5 (SD, N=5 left ventricles). Therefore we concluded that the end-diastolic P-V relation can reasonably be approximated by a power function $P = a \cdot (V - V_d)^3$ over an end-diastolic pressure range from 5 to as high as 75 mmHg.

The additional area is the difference of the area under the line connecting V_d and the end-diastolic P-V data point minus the area under the non-linear P-V curve approximated by the third power function. The former is $0.5 \cdot P_{ed} \cdot (V_{ed} - V_d)$ where P_{ed} =end-diastolic P and V_{ed} =end-diastolic volume, whereas the latter is $0.25 \cdot P_{ed} \cdot (V_{ed} - V_d)$ irrespective of the value for the coefficient a in the power equation. Therefore, the additional area is equal to $0.25 \cdot P_{ed} \cdot (V_{ed} - V_d)$ and can be calculated from P_{ed} and V_{ed} data of a given contraction alone.

To calculate PVA according to the above formula, we used a digital computer (Digital, PDP 11/60) and FORTRAN IV-plus language. The program consisted of 1) digitizing ventricular pressure and volume signals at every 2 msec with an LPA 11 K analog-to-digital converter, 2) storing the digitized values for one stable cardiac cycle in computer memories, 3) calculating each narrow pressure volume area for every consecutive 2 msec interval using a predetermined V_d value, 4) summing all the pressure volume areas from end diastole to end systole, and 5) adding the additional PVA explained above.

In addition, the digital computer was used to calculate many other cardiodynamic parameters such as peak wall force, time integral of wall force, tension time index, and stroke work from pressure and volume signals, together with cardiac oxygen consumption per min and pre beat from coronary flow and arteriovenous oxygen saturation difference signals. However, in the present report, we will not refer to those parameters other than PVA and VO_2 .

RESULTS

We have been using the new method of digital computation of PVA in recent experiments on canine excised cross-circulated heart preparations to study the relations between cardiac oxygen consumption (VO_2) and left ventricular systolic pressure volume area (PVA). The method has proved to be useful in evaluating with ease the VO_2 -PVA regression and correlation from a larger number of VO_2 -PVA data under each chosen experimental condition as compared to previous studies.^{3),4)} The method has definitely reduced the technical errors that previously existed in measuring PVA manually with a planimeter on a Polaroid picture or electronically with an analog computer. The on-line display of PVA values during actual experiments has aided in carrying out studies more efficiently.

Fig. 3A depicts an example of the computed data of cardiodynamic parameters including PVA and VO_2 , displayed on a graphic terminal. The computations and display take as short as 2 sec after a 1 sec sampling of ventricular

Fig. 3. Panel A: Hard copy of the computed PVA, VO_2 , and other data on the graphic display. Panel B: Hard copy of the VO_2 -PVA data plot on the display. The abscissa is PVA (0-3,000 mmHg ml/beat) and the ordinate is VO_2 (0-0.1 ml O_2 /beat). These 16 points were obtained in a canine left ventricle with a stable contractility, but under different loading conditions.

pressure and volume, coronary arteriovenous oxygen saturation difference, coronary flow, and ECG in a steady state.

Fig. 3B depicts an example of the scatter diagram plotting VO_2 -PVA data points (PVA on the abscissa), displayed on the same graphic terminal. These data were obtained in a canine left ventricle (46 Gm in an 11 Kg dog) while the pre- and afterloading conditions were widely varied in a constant contractile state. Looking at the scatter diagram, we can immediately determine with ease the ranges of PVA to be covered additionally in the same experimental run.

Fig. 4A is the scatter diagram of the same VO_2 -PVA data points shown in Fig. 3B, processed with the computer and copied on a plotter after the experiment. The statistical results of correlation and regression analyses are

Fig. 4. Panel A: Scatter diagram of the VO₂-PVA data points, plotted after the experiment. These 16 data are identical to those shown in the previous figure. Both VO₂ and PVA are normalized for 100 Gm left ventricle. The solid diagonal line is the regression line. The inner pair of dashed curves indicates the 95% confidence range of the regression line, and the outer pair of dashed curves the 95% confidence range of the sampled data points. The correlation coefficient (R) and the regression equation are shown in the graph. Panel B: Comparison of the scatter diagrams of the VO₂-PVA data points in a control contractility (solid circles) and an epinephrine-enhanced contractility (open circles) in another left ventricle.

also shown on the scatter diagram. The correlation coefficient is very close to 1. The diagonal solid line is the linear regression line. The inner pair of dashed lines around the regression line indicate the 95% confidence zone of the linear regression line. The outer pair of dashed lines indicate the 95% confidence range of the sampled data points. These results indicate that PVA linearly correlates with VO₂ regardless of changes in ventricular loading conditions in a constant contractile state, confirming our previous observation.³⁾

Fig. 4B is another example of the scatter diagram of the VO₂-PVA data obtained in another left ventricle (48 Gm in a 10 Kg dog) in a control and an enhanced contractile state with epinephrine infused into the coronary circulation at a rate of 2 μ g/min. Heart rate was maintained constant at 150 beats/min by atrial pacing. The correlation and regression analyses indicate that the VO₂-PVA regression in the enhanced as well as control contractile state is linear. Analysis of covariance⁸⁾ indicates that the slope of the VO₂-PVA regression line did not change but the regression line was significantly shifted upward with epinephrine.

Comparing the statistical results of the VO₂-PVA relation in a stable contractile state, we found that VO₂-PVA correlation coefficients become

closer to unity and the 95% confidence zone of the VO_2 -PVA data became narrower in our recent experiments with the digital computation of PVA than in our previous ones without it.³⁾⁻⁵⁾ We would interpret this improvement to indicate that the relation between VO_2 and PVA is essentially unique and load-independent in a constant contractile state. Thus, we conclude that the new method of accurate on-line computation of PVA is very useful in our study of the VO_2 -PVA relation of the left ventricle of our excised canine heart preparation.

DISCUSSION

The unique point of the new digital method of computing PVA exists in that it requires instantaneous ventricular pressure and volume signals of a single contraction of interest. PVA can be computed without computing end-diastolic and end-systolic P-V relation curves, once Vd is predetermined. This feature originates on one hand from using Vd as a pivot of the moving line segment connecting Vd and the instantaneously moving P-V data point, and on the other hand from approximating the nonlinear end-diastolic P-V relation curve by the power function.

The analog method that we reported previously⁶⁾ is based partly on the same principle. However, its accuracy is limited because it cannot directly compute $\theta = \arctan \{P(t)/[V(t) - Vd]\}$ which is necessary for accurate calculation of PVA (see Methods). The analog circuit computes PVA by substituting $\theta \cong P(t)/\sqrt{[V(t) - Vd]^2 + P(t)^2}$ for $\theta = \arctan \{P(t)/[V(t) - Vd]\}$. In addition, the analog circuit cannot compute the additional area below the line connecting Vd and the end-diastolic P-V point. The present digital method is therefore much superior in accuracy to the previous analog method.

In the present study, we approximated the nonlinear end-diastolic P-V relation curve by the third power function based on the empirical equation. This approximation is also feasible mathematically because an exponential function can be replaced by a power series: $e = 1 + x + x^2/2 + x^3/6 + x^4/24 + x^5/120 + \dots$. As x increases from 0, a higher power term becomes dominant. Therefore, although we used the third power function for an end-diastolic pressure range from 5 to 75 mmHg, the second power (i.e., parabolic) function or even the first power (i.e., linear) function can reasonably approximate the exponential end-diastolic P-V curve in a lower range of end-diastolic pressure.

The ability of PVA to predict VO_2 will be briefly discussed based on our previous studies.^{3),4)} Under a given stable inotropic background, as high as 92% of a change in VO_2 is ascribable to a change in PVA regardless of changes in pre- and afterloading conditions.³⁾ Changes in heart rate do not affect

the VO_2 -PVA relationship (unpublished). The standard deviation of sampled data points is of the order of as small as 0.006 ml O_2 /beat/100 Gm left ventricle, considerably smaller than the working level of VO_2 . However, there is some variation of the VO_2 -PVA relationship among different hearts, which is often greater than the standard deviation of sampled data in a given heart.³⁾ For example, the slope of the VO_2 -PVA regression line is $1.64 \times 10^{-5} \pm 0.38 \times 10^{-5}$ (SD) ml O_2 /(mmHg ml), and the VO_2 -axis intercept of the line is 0.015 ± 0.009 (SD) ml O_2 /beat/100 Gm LV. Moreover, as shown in the Results, changes in contractility shift the VO_2 -PVA regression line markedly, and the sensitivity of the shift to a given change in contractility seems to be variable among hearts. For these reasons, it seems still difficult to predict precisely the absolute value for VO_2 from PVA alone in a given heart.

In terms of predictability of VO_2 , PVA seems superior to many other so-called determinants of VO_2 . Our previous results⁴⁾ show that PVA is superior in VO_2 predictability to tension time index⁹⁾ and peak ventricular wall force. PVA has higher correlation coefficients with VO_2 than do stroke volume, stroke work, systolic ventricular pressure, and end-diastolic ventricular volume.⁴⁾ Contractile element work¹⁰⁾ and ventricular wall force integral over systole¹¹⁾ have lower correlation coefficients with VO_2 than PVA has. Thus, our present contention is that PVA is worth studying as a strong candidate for the primary determinant of VO_2 . The present digital method of computing left ventricular systolic pressure volume area (PVA) is very useful in the study of the capability and limitation of PVA as a reliable predictor of cardiac oxygen consumption.

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