Critical Evaluation of Left Ventricular Systolic Pressure Volume Area as Predictor of Oxygen Consumption Rate

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Abstract Left ventricular systolic pressure volume area (PVA) has been reported to be a reliable predictor of cardiac oxygen consumption rate per beat ($\dot{V}_{O_2}$) in a given heart with a stable inotropic background. PVA has been defined as the specific area in the pressure-volume (P - V) plane that is bounded by the end-systolic and end-diastolic P - V relationship lines and the systolic segment of the P - V loop trajectory. In the present experimental study, we separated PVA into two parts: EW and PE. EW is the area surrounded by the P - V loop, corresponding to the external mechanical work. PE is the area surrounded by the end-systolic and end-diastolic P - V lines and the relaxation segment of the P - V loop, corresponding to what is considered the end-systolic elastic potential energy in terms of a time-varying elastance model of the ventricle. We attempted to find an optimal weighting coefficient K of PE for the best correlation between $\dot{V}_{O_2}$ and $PVA_w = EW + K \cdot PE$, changing K from 0 to infinity. Results in 7 canine excised cross-circulated hearts showed that PVA_w best correlated with $\dot{V}_{O_2}$ at $K = 1.03 \pm 0.03$ (SE). Since PVA_w at $K=1$ is identical with the original PVA, we concluded that PVA could serve as a reliable predictor of $\dot{V}_{O_2}$. PVA is concluded to be physiologically significant in the coupling between cardiac mechanics and energetics.

Although many cardiodynamic parameters have been proposed as determinants of cardiac oxygen consumption, none of them alone nor appropriately combined is unanimously accepted (GIBBS, 1978; GIBBS and CHAPMAN, 1979). Recently, left ventricular systolic pressure volume area (PVA) has been reported to be a promising candidate for a reliable predictor of cardiac oxygen consumption rate per beat ($\dot{V}_{O_2}$) (SUGA, 1979b, c; KHALAFBEIGUI *et al.*, 1979; SUGA *et al.*, 1980).

PVA as originally proposed is the specific area in the left ventricular pressure-

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Fig. 1. Schematic illustrations of PVA and its two separated parts: EW and PE. Panel A shows a pressure-volume loop (LOOP) of an ejecting contraction and the end-diastolic (ED) and end-systolic (ES) pressure-volume relationship lines. V_d is the volume axis intercept of the end-systolic P - V line. Panel B shows PVA as the shaded area surrounded by the end-systolic and end-diastolic P - V lines and the systolic segment of the P - V loop. Panel C shows the external mechanical work (EW) as the shaded rectangular area within the P - V loop. Panel D shows area PE as the shaded triangular area bounded by the end-systolic and end-diastolic P - V lines and the relaxation segment of the P - V loop. In all the panels, the V axis indicates intraventricular volume from zero volume and the P axis intraventricular pressure from the atmospheric pressure.

volume (P - V) diagram that is bounded by the end-systolic and end-diastolic P - V relationship lines and the systolic segment of the P - V loop trajectory, as schematically shown in Fig. 1. It is the sum of area EW for the external mechanical work and area PE for what is considered the end-systolic elastic potential energy in terms of the time-varying elastance model of the left ventricle (SUGA, 1979b; SUGA *et al.*, 1973; SUGA and SAGAWA, 1974).

Previously, EW and PE were not separately measured, and PVA as a whole was correlated with V_{O_2} . Although V_{O_2} was highly linearly correlated with PVA in a given heart with a stable inotropic background, there was some scatter of V_{O_2} -PVA data points around the regression line (SUGA, 1979b; KHALAFBEIGUI *et al.*, 1979; SUGA *et al.*, 1980). It remained to be elucidated whether PVA was truly the best predictor of V_{O_2} among differently weighted sums of EW and PE.

In this new series of experiments, we measured the two parts of PVA separately and attempted to find an optimal weighting coefficient K of PE for the best correlation between V_{O_2} and the weighted sum of EW and $K \cdot PE$. To minimize technical errors in the assessment of V_{O_2} , we improved the methods of measurements of coronary arterial and venous oxygen contents.

METHODS

Heart preparation. A pair of mongrel dogs of about 12 kg body weight were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) in each experiment.

The excised cross-circulated heart preparation was instituted and a thin latex balloon was fitted in the left ventricle in the same way as previously described (SUGA *et al.*, 1979; KHALAFBEIGUI *et al.*, 1979). Briefly, the heart-lung section was isolated in the heart donor dog and connected to the support dog's common carotid artery and jugular vein. A cross circulation was started and the lungs were removed. The supported heart was excised from the chest. The left atrium was opened and all the chordae tendineae were cut. A thin balloon with an unstressed volume of 50 ml, mounted on a plastic connector, was placed within the left ventricle and secured at the mitral annulus. A plastic plate, placed underneath the aortic valve and tied on the mitral annulus, prevented the balloon from herniating into the aorta. A small manifold tube was placed between the balloon and the endocardium to drain the thebesian blood and thereby facilitate the fitting of the balloon on the endocardium (SUGA and SAGAWA, 1979). A miniature pressure gauge (Konigsberg, P-22) was placed inside the apical end of the balloon to measure left ventricular pressure.

The coronary perfusion pressure was equal to the support dog's arterial pressure, which was relatively constant in each experiment and ranged from 75 to 120 mmHg (mean=92) among preparations. The temperature of the heart was maintained constant in each experiment, but ranged between 35 and 37°C among hearts.

ECG was recorded from the left ventricular surface and its R wave was used to trigger the volume servo pump in synchrony with the cardiac cycle. Heart rate was a stable sinus rhythm in each heart, ranging between 90 and 150 beats/min among hearts.

The support dog was ventilated artificially with room air appropriately mixed with O₂. Coronary perfusion arterial blood pH, P_{O_2} and P_{CO_2} were occasionally measured and reasonably stable in each experiment. Their ranges among preparations were 7.13–7.50 for pH, 73–133 mmHg for P_{O_2} , and 22–33 mmHg for P_{CO_2} .

The right ventricle was mechanically unloaded by continuous drainage of the coronary venous return to maintain its oxygen consumption at a minimal level.

Volume servo pump. The left ventricle was connected to the volume servo pump via a balloon connector, as shown in Fig. 2. For details of the pump, the reader is referred to the original description (SUGA and SAGAWA, 1977). The balloon and the water housing of the pump were primed with water. The pump enabled us to precisely control and accurately measure instantaneous left ventricular volume. Isovolumic contractions were produced by fixing the position of the plunger at various levels with constant command voltages. Ejecting contractions were produced by changing the position of the plunger during systole and appropriately changing command voltages in synchrony with the cardiac cycle.

Cardiac oxygen consumption. Coronary perfusion blood flow was continuously measured with an electromagnetic flowmeter (Narcomatic RT-510 and K-2 probe) in the coronary venous tubing draining the right ventricle. This flow

Fig. 2. Schematic diagram of experimental setup. A=coronary arterial tubing from the common carotid artery. B=box for the heart preparation. BC=Bellofram (rolling seal diaphragm) cylinder. DOG=support dog. ECG=ventricular electrocardiogram. EDV and ESV=volume command signal for end-diastolic and end-systolic volumes. F=electromagnetic flow meter for total coronary perfusion flow. H=excised, cross-circulated heart. HE=heat exchanger for coronary perfusion arterial blood. O_2 =oxymeter to measure coronary arterial or venous oxyhemoglobin percent saturation. V=coronary venous tubing to the external jugular vein. VP=miniature pressure gauge for intraventricular pressure. W=tap water priming the intraventricular balloon and the water housing of the pump.

was considered equal to the total coronary perfusion flow except for the minute thebesian flow into the left ventricle. The thebesian flow drained from the left ventricular vent was as small as 1–2 ml/min.

Coronary arterial and venous blood flows were partially bypassed at a flow rate of about 4 ml/min through the cuvettes of the two carefully calibrated oximeters (Waters 600A) and their oxyhemoglobin percent saturations were continuously recorded. This method assured the reliability of V_{O_2} data by allowing us to read a stabilized venous oxyhemoglobin saturation under each ventricular loading condition. Coronary arterial blood of a known saturation was occasionally sampled and its oxygen content in volume % was determined with a Lex- O_2 -Con-TL oxygen content analyser to obtain a conversion factor from oxyhemoglobin percent saturation to oxygen content. With this conversion factor, coronary arteriovenous oxyhemoglobin percent saturation differences under different ventricular loading conditions were converted into coronary arteriovenous oxygen content differences in each experiment. The ranges among preparations of coronary flow, arterial and venous oxyhemoglobin saturations, and saturation to content conversion factor were 21–96 ml/min, 92–98%, 25–

83%, and 14.1–19.0 volume % per 100% saturation, respectively.

Cardiac oxygen consumption rate was calculated as the product of the coronary perfusion flow rate in ml/min and the arteriovenous oxygen content difference in volume % of O_2 . The product in ml O_2 /min was divided by heart rate in beats/min to yield oxygen consumption rate per beat, V_{O_2} , in ml O_2 /beat.

Experimental protocol and data collection. First of all, a set of isovolumic contractions at several different volumes were produced in a stable inotropic state and their steady-state P - V trajectories were recorded on a storage oscilloscope. A linear regression line was drawn through the peak isovolumic pressure points. This line is the end-systolic P - V relationship line (SUGA and SAGAWA, 1974). The volume axis intercept of this line was determined as V_d (SUGA *et al.*, 1973; SUGA and SAGAWA, 1974). V_d was occasionally determined during each experiment, but it changed little. This V_d point in the P - V diagram was used later in the assessment of area PE of different contractions under variously changed loading conditions in the same ventricle.

As a main protocol, isovolumic contractions at different volumes (5–40 ml) and ejecting contractions with various stroke volumes (5–20 ml) from different end-diastolic volumes (10–40 ml) were produced in various sequences and volume steps in each heart with a stable inotropic background. When transient changes in ventricular pressure, coronary flow and coronary venous oxyhemoglobin saturation disappeared a few minutes after each step change in ventricular loading and ejecting conditions, steady-state P - V loop trajectories were recorded on the storage oscilloscope and photographed for the assessment of the two parts of PVA.

Assessment of two parts of PVA. Area EW was determined as the area bounded by the P - V loop trajectory. In isovolumic contractions, EW was zero.

Area PE of either an isovolumic or an ejecting contraction was assessed in the P - V diagram in the following manner according to its definition (SUGA, 1979b). A line was drawn from the predetermined V_d point to the end-systolic point of the P - V loop trajectory. The latter was either the peak pressure point of an isovolumic contraction or the left upper corner of the loop in an ejecting contraction (SUGA *et al.*, 1979). This line was the end-systolic P - V line of the contraction whose PE was to be assessed. The end-diastolic P - V relationship line was drawn through multiple end-diastolic P - V points of other contractions between the predetermined V_d and the end-diastolic point of the contraction concerned. The area between these two end-systolic and end-diastolic lines and on the left side of the relaxation segment of the P - V loop was area PE.

We measured the two areas of PVA of each contraction with a compensating planimeter (Koizumi KP 21). The areas were expressed in mmHg ml.

Optimal weighting. The originally defined PVA consists of the simple sum of EW and PE (SUGA, 1979b) and was found to be highly linearly correlated with V_{O_2} (SUGA, 1979b; KHALAFBEIGUI *et al.*, 1979). In the present study, we treated

EW and PE separately, and attempted to find an optimal weighting coefficient K of PE for the best correlation between V_{O_2} and the weighted sum of EW and $K \cdot PE$: $PVA_w = EW + K \cdot PE$. Note that PVA_w for $K=1$ is identical with the original PVA.

We computed correlation coefficients between V_{O_2} and PVA_w of a set of many isovolumic and ejecting contractions in each heart with a stable inotropic background while K was varied from 0 to infinity. The K value that produced the highest correlation coefficient from a given set of contractions in a given heart was identified as the optimal weighting coefficient of PE. The computation was done with a digital computer (DEC Minc-11).

Fig. 3. Representative set of tracings of coronary perfusion pressure (CP), ventricular pressure (P), ventricular volume (V), coronary perfusion flow (CF), and coronary venous oxyhemoglobin percent saturation (Sv), from top to bottom, of one heart with a stable inotropic background under different loading conditions. The inset shows the pressure-volume loops of those ejecting contractions. The last loading condition was identical to the first one in the tracing. The black arrow heads on the CF tracing indicate the instants of changes in the ventricular loading condition. The horizontal bars on the CF and Sv tracings indicate our readings of the stabilized mean CF and Sv values. The CF and Sv tracings were recorded much slower than the other top three tracings. The connecting lines between the V and the CF tracings indicate the instants of recording of the top three tracings in the bottom two tracings. Evidently, the CF and Sv tracings were stabilized within a few minutes after step changes in ventricular loading conditions. Two areas EW and PE were planimetered on the pressure-volume diagram shown in the inset. V_d is the volume axis intercept of the end-systolic pressure-volume relationship line. The end-systolic pressure-volume line bordering area PE was drawn, though not shown, as a rectilinear line between the predetermined V_d and the left upper corner of each pressure-volume loop.

RESULTS

Figure 3 shows representative tracings of ventricular pressure and volume, and coronary perfusion pressure, flow, and venous oxyhemoglobin percent saturation. The figure also shows the *P-V* loop trajectories of these ejecting contractions. The heavy bars in the coronary flow and venous saturation tracings indicate our readings of their values. The first and the last loading conditions in the figure were the same, and the reproducibility of the coronary flow and venous oxyhemoglobin saturation as well as ventricular pressure and volume was confirmed.

Table 1 lists V_{O_2} , EW, PE and other related data of multiple isovolumic and ejecting contractions in one heart with a stable inotropic background. Coronary flow, venous oxyhemoglobin saturation, arteriovenous oxygen content difference, and V_{O_2} changed with changes in EW and PE. Similar sets of data were obtained

Table 1. V_{O_2} , EW and PE data in one heart.

Cor flow (ml/min)	SaO ₂ (%)	SvO ₂ (%)	(A-V)O ₂		V_{O_2}		EW (mmHg ml)	PE (mmHg ml)
			S (%)	C (vol %)	/min	/beat		
72	94	64	30	5.70	4.10	0.0357	416	495
72	94	58	36	6.84	4.92	0.0428	794	495
76	94	53	41	7.79	5.93	0.0502	661	1,079
73	94	75	19	3.61	2.64	0.0223	292	167
77	94	74	20	3.80	2.93	0.0259	357	317
80	94	70	24	4.56	3.65	0.0323	578	317
76	94	60	34	6.45	4.91	0.0434	627	1,173
92	94	75	19	3.61	3.32	0.0288	433	172
88	94	75	19	3.61	3.18	0.0276	0	614
83	94	63	31	5.89	4.89	0.0425	0	1,250
82	94	80	14	2.66	2.18	0.0189	0	150
81	94	82	12	2.28	1.85	0.0161	0	0
86	94	83	11	2.09	1.79	0.0163	0	0
78	94	82	12	2.28	1.78	0.0162	0	153
78	94	78	16	3.04	2.37	0.0216	0	413
70	94	72	22	4.18	2.93	0.0287	0	690
60	94	63	31	5.89	3.53	0.0336	0	1,123
62	94	45	49	9.31	5.77	0.0548	0	1,720
67	94	61	33	6.27	4.20	0.0400	639	590
70	94	74	20	3.80	2.66	0.0253	300	185
65	94	73	21	3.99	2.59	0.0254	0	570
64	94	78	16	3.04	1.95	0.0244	0	268
60	94	79	15	2.85	1.71	0.0166	0	74
57	94	79	15	2.85	1.62	0.0158	0	0

This heart is #3 in Table 2. Cor=coronary. SaO₂, SvO₂=coronary arterial and venous oxyhemoglobin percent saturations. (A-V)O₂=arteriovenous difference in saturation (S) and oxygen content (C).

Fig. 4. Graph showing the relationship between the correlation coefficient (R) and the weighting coefficient (K) in 7 hearts. R was calculated between V_{O_2} and $PVA_w = EW + K \cdot PE$ for K varied between 0 and 4 at a step of 0.01.

in all hearts, and subjected to the following analyses.

Figure 4 graphically shows how correlation coefficient R between V_{O_2} and PVA_w (i.e., $EW + K \cdot PE$) changed with K in all 7 hearts. K was changed by a step of 0.01 over the range of 0–4. R monotonically increased as K increased from 0 to near 1, reached a maximal for $K \simeq 1$, and then monotonically decreased as K increased from near 1 to infinity. The optimal K values were nearly equal to 1 in all hearts. The correlation coefficient R at the optimal K was very close to unity in all the hearts.

Table 2 lists those optimal K values and correlation coefficients. On the average in 7 hearts, the optimal K was 1.03 and not statistically different from 1 ($P > 0.2$). The attained R at the optimal K was 0.978, very close to 1.

Figure 5 shows scatter diagrams of V_{O_2} - PVA_w data points of the same set of contractions with different K values including the optimal K and $K=1$. The scatter was minimized at the optimal K , and virtually the same minimized scatter was observed at $K=1$. Table 2 also lists the correlation coefficients R for $K=1$ in all hearts. These correlation coefficients were identical (to 2 or 3 places of decimals) to the corresponding correlation coefficients for optimal K . The table also lists the sample standard deviation of V_{O_2} from regression on PVA_w for $K=1$. These values were very small as compared to V_{O_2} .

Figure 6 shows the V_{O_2} - PVA (i.e., PVA_w for $K=1$) regression lines of all hearts. The 95% confidence zone of each regression line was also shown by the shade. Virtually the same regression lines and confidence zone were obtained for V_{O_2} - PVA_w data at optimal K , although not shown here.

The results so far indicated that the predictability of V_{O_2} from $PVA_w = EW + K \cdot PE$ was highest at optimal K near 1. We have used all available data sets in each heart under a stable inotropic background. To reconfirm the above results, we gradually reduced the number of data sets used for the analysis and examined the reproducibility of the results. Figure 7 shows how the optimal K values changed with changes in the number of data sets used. Evidently, the optimal K converged approximately to 1 with an increased number of data sets.

Table 2. Optimal coefficient K , correlation and regression.

Heart #	LV (g)	N			Optimal K	R	R ²	R for K=1	Slope of regression line $\times 10^{-5}$ $\left(\frac{\text{ml O}_2}{\text{mmHgml}}\right)$	SD from regression $\left(\frac{\text{ml O}_2}{\text{beat}}\right)$
		Total								
		I	E	U						
1	65	20	7	11	2	0.98	0.994	0.988	1.74	0.0014
2	60	23	17	3	3	1.01	0.971	0.943	2.18	0.0023
3	75	24	11	10	3	1.09	0.973	0.947	1.95	0.0027
4	52	21	9	8	4	0.90	0.964	0.929	1.11	0.0015
5	50	11	5	5	1	1.10	0.988	0.976	2.28	0.0026
6	55	18	11	6	1	1.02	0.984	0.968	1.20	0.0015
7	60	20	16	4	0	1.10	0.975	0.949	1.53	0.0020
Mean	60				1.03		0.978	0.957	1.71	0.0020
SD	9				0.07		0.011	0.021	0.46	0.0005
SE	3				0.03		0.004	0.008	0.17	0.0002

LV=left ventricle. N=number of contractions used for analysis. I=isovolumic. E=ejecting. U=unloaded, i.e., ventricular volume is V_d and therefore, PVA is zero. R=correlation coefficient between V_{O_2} and PVA_w for optimal K. R^2 =square of R. R for $K=1$ is the correlation coefficient between V_{O_2} and PVA. SD=standard deviation. SE=standard error of mean.

Fig. 5. Scatter diagrams of V_{O_2} - PVA_W data with different K values in one heart (#6). Solid circles indicate isovolumic contractions and open circles ejecting contractions. Unloaded contractions are on the ordinates except in the case of $K=0$ where all isovolumic points are on the ordinate. The same sets of data were used for all K 's. R =correlation coefficient. The solid line through the data points is the linear regression line. The inner dashed lines indicate the 95% confidence zone of the regression line. The outer dotted lines the 95% confidence zone of the data points *per se*. At K =optimal (1.02) and 1, R was highest and the two 95% confidence zones were narrowest, indicating the highest predictability of V_{O_2} from PVA . Similar results were obtained in all other hearts.

Fig. 6. V_{O_2} - PVA regression lines with their 95% confidence zones of 7 hearts. The solid lines are the regression lines of V_{O_2} on PVA , and the dotted zones indicate the 95% confidence zones of the regression lines.

Fig. 7. Variation of the optimal K values with decreases in the number of data sets for analysis in 7 hearts. The optimal K value obtained from the total number of data sets as shown in Table 2 is shown by an open circle for each heart. The number of data sets was reduced by randomly choosing a decremental number (N) of data sets from the total number of data sets in each heart. The randomization was done with the digital computer. The optimal K 's were calculated with a resolution of 0.1. Evidently, the optimal K tended to converge into 1 with increases in the number of data sets in any heart. Although the optimal K 's from a smaller number of data sets tended to scatter widely around 1, their mean value at each N seems near 1.

DISCUSSION

The present results evidently show that the simple sum of the two parts of PVA, identical with the originally defined PVA (SUGA, 1979b), correlates with cardiac oxygen consumption rate per beat practically best of all with regard to sums of external mechanical work (EW) and the differently weighted PE. Therefore, we conclude that the original PVA can reliably predict V_{O_2} in a given heart with a stable inotropic background.

The correlation coefficient R between V_{O_2} and PVA was as high as 0.978 on the average, which was much closer to unity than 0.92 obtained in the previous study (KHALAFBEIGUI *et al.*, 1979). We consider this owes to the improved reliability of V_{O_2} data in the present study. Since the square of R indicates the fraction of the variance of V_{O_2} attributable to the regression on PVA (SNEDECOR and COCHRAN, 1971), the present R^2 value of 0.957 on the average (see Table 2) indicates that as high as 96% of the variance of V_{O_2} is explainable by PVA. The other 4% remains to be attributed to other factors which may reasonably be technical errors in the measurements of V_{O_2} and PVA. Using the same improved method of the measurement of V_{O_2} , we have reexamined the correlation between V_{O_2} and PVA in many isovolumic and ejecting contractions in the left ventricle of canine excised cross-circulated hearts (SUGA *et al.*, 1980). The results have confirmed the earlier ones by KHALAFBEIGUI *et al.* (1979), and moreover, the correlation coefficient between V_{O_2} and PVA was 0.959 on the average, much higher than the previous 0.92 and very close to the present 0.978.

We are not concluding that PVA is the best predictor or V_{O_2} among all pre-

viously proposed determinants of $\dot{V}_{O_2}$ such as ventricular wall force (McDONALD *et al.*, 1966), tension-time index (SARNOFF *et al.*, 1958), contractile element work (BRITMAN and LEVINE, 1964), total integral of systolic force (WEBER and JANICKI, 1977), *etc.* New experiments specifically designed for the comparison seem indispensable.

From the present results, we would consider that area PE of the real ventricle does have a physiological significance in cardiac energetics. It seems very unlikely that PE has no physiological significance and yet PVA is always highly correlated with $\dot{V}_{O_2}$.

As previously reported (SUGA, 1979a), part of area PE of the real ventricle was actually converted into external mechanical work when an appropriate ejection was allowed during relaxation. Moreover, the maximal amount of this work during relaxation was greater than what was expected from the elastic potential energy of the series elasticity in the Hill model (SUGA, 1980). These results imply that a kind of potential energy does exist in the ventricle at end systole, which is actually convertible into external mechanical work and not entirely attributable to the series elasticity of the Hill model. In the time-varying elastance model of the ventricle, PE is the end-systolic elastic potential energy and is convertible to external mechanical work (SUGA, 1979b). The nature of area PE in the real ventricle still remains to be revealed.

With regard to the elastic potential energy of muscle, one may be reminded of the classic elastic body concept of skeletal muscle (HILL, 1913, 1925). However, the concept is essentially different from the present time-varying elastance model of the ventricle in that the increment in muscle elastance is instantaneous in the elastic body whereas it is gradual in the time-varying elastance (SUGA *et al.*, 1973; SUGA and SAGAWA, 1974). This difference is highly critical in energetics because a stepwise increment in the elastic potential energy of a given amount occurs at the onset of contraction and part of the constant potential energy is converted into external mechanical work regardless of the amount of shortening. This situation does not hold in the heart, where the sum of potential energy and external work is variable depending on ejection during systole. The elastic body concept of skeletal muscle was discarded because of its contradiction with the Fenn effect (FENN, 1923), whereas the time-varying elastance model of ventricle seems compatible with the cardiac version of the Fenn effect (COLEMAN *et al.*, 1969).

We conclude from the present results and discussion that left ventricular systolic pressure volume area (PVA) is a reliable predictor of cardiac oxygen consumption and is a promising candidate for the primary determinant of cardiac oxygen consumption.

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