Independence of Myocardial Oxygen Consumption from Pressure-Volume Trajectory during Diastole in Canine Left Ventricle

Hiroyuki Suga, Yoichi Goto, Osamu Yamada, and Yuichiro Igarashi
From the Department of Cardiovascular Dynamics, National Cardiovascular Center Research Institute, Fujishirodai, Suita, Osaka, Japan

SUMMARY. We have found that myocardial oxygen consumption is linearly correlated with the systolic pressure-volume area in the canine left ventricle. This pressure-volume area is a specific area in the pressure-volume diagram that is circumscribed by the end-systolic pressure-volume relation line, the end-diastolic pressure-volume relation curve, and the systolic segment of the pressure-volume trajectory. This area is equivalent to the total mechanical energy generated by ventricular contraction, consisting of the external mechanical work and the mechanical potential energy. In the present study, we specifically changed the course of the diastolic segment of the pressure-volume trajectory without changing the systolic segment of the pressure-volume trajectory and the systolic pressure-volume area. Although the fractions of external mechanical work and mechanical potential energy in the pressure-volume area were markedly changed, the simultaneously measured left ventricular oxygen consumption remained unchanged. This result indicates that the myocardial oxygen consumption is predominantly determined by the total mechanical energy generated during systole, or the systolic pressure-volume area, independent of how the total mechanical energy is converted effectively to external mechanical work during the cardiac cycle (Circ Res 55: 734-739, 1984)

WE have recently found that left ventricular oxygen consumption is closely correlated with the left ventricular systolic pressure-volume area (PVA) (Suga et al., 1981a). We defined PVA as a specific area in the pressure-volume (P-V) diagram that is circumscribed by the end-systolic P-V relation line, the end-diastolic P-V relation curve, and the systolic segment of the P-V trajectory (Suga, 1979b). As shown in Figure 1, PVA in a normal ejecting contraction consists of two areas: one is the rectangular area within the P-V trajectory, and the other is the triangular area between the end-systolic P-V line and the end-diastolic P-V curve on the left side of the P-V trajectory. The former area represents the external mechanical work, and the latter the mechanical potential energy. Thus, PVA represents the total mechanical energy generated by each ventricular contraction, of which external mechanical work is the effective stroke work output of the ventricular pump, and the potential energy is the remaining part unused for the pumping. The P-V trajectory during diastole divides PVA into these two parts. The potential energy will be eventually converted to heat unless it is further converted to an additional external mechanical work by afterload reduction during diastole (Suga, 1979a).

The purpose of the present study was to investigate whether left ventricular oxygen consumption was affected by a shift of the course of the P-V trajectory during diastole when there was no change of the course of the systolic segment of the P-V trajectory. This procedure was performed as a new method which variably reconverts the external mechanical work once performed during systole back into the mechanical potential energy during diastole. PVA was supposed to be unaffected by this procedure in a stable heart because the systolic segment of the P-V trajectory was kept unchanged with our servo control pump system.

We found that left ventricular oxygen consumption remained the same even when the external mechanical work performed during systole was variably reconverted to the mechanical potential energy during diastole. This finding indicates that ventricular oxygen consumption is determined exclusively by the cardiodynamic events during systole, independent of the events during diastole, and the external mechanical work and the mechanical potential energy are interchangeable during the cardiac cycle without any extra energy cost.

Method

The left ventricular preparation and the experimental setup we used were the same as described previously (Suga et al., 1981a, 1982, 1983a). Briefly, two dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv). The heart-lung section was isolated in one dog, and its left subclavian artery and the right ventricle via the right atrial appendage were connected via the cross-circulation tubing with the other dog's common carotid arteries and external jugular vein. The lung lobes were removed and the cross-circulated beating heart was excised from the chest.

A thin latex balloon was fitted via the mitral ring in the...
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FIGURE 1. Schematic illustration of systolic pressure-volume area
isovolumic contraction phase and the ejection phase. The diastolic
systolic segment of the P-V loop consists of the segments for the
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FIGURE 2. Time tracings of left ventricular pressure (P), volume (V),
and time-derivative of V (—dV/dt). The bottom row shows the con-
tours of left ventricular systolic pressure-volume area (PVA), external
mechanical work (EW), and mechanical potential energy (PE) in the
two differently loaded contractions shown above each. Note that the
course of the diastolic segment of the P-V loop is markedly shifted
and the fractions of EW and PE in PVA were changed.

left ventricle, and connected to the servo pump (Suga et
alkaline pressure was measured by the displacement of the piston of the pump, and
ventricular pressure, by a miniature gauge placed inside
the apical end of the intraventricular balloon. The servo
pump system enabled us to change the courses of the
P-V trajectory during systole and diastole and to have
end-diastolic volume, ejection pressure, and stroke volume
at our disposal.

Left ventricular pressure and volume signals were dis-
played on a storage oscilloscope and photographed. The
same signals were fed to an analog-to-digital converter,
and PVA and its two components, i.e., external mechanical
work and mechanical potential energy, were determined
with a digital computer (Suga et al., 1983b). PVA and its
two components were expressed in mm Hg ml/beat per
100 g of left ventricle. 1 mm Hg ml = 1.33 x 10^{-3} J.

The determination of PVA required the identification
of the end of systole as in our previous studies (Suga et
al., 1983b). Our definition of end systole was the same as
proposed previously (Suga et al., 1973, 1979). Briefly, we
first determined ventricular volume Vd where the peak
isovolumic pressure was zero. Then, the P-V ratio, namely,
the slope of the line connecting Vd and the instantaneous
P-V data point on the P-V trajectory, was calculated in
the computer. End-systole was identified as the time when
the P-V ratio became maximal, i.e., E_{max}.

Left ventricular oxygen consumption was determined
in the same way as described previously (Suga et al.,
the right heart was continuously drained out hydrostati-
cally through an electromagnetic flowmeter. Oxyhemoglo-in percent saturations of both coronary arterial and ve-
rous bloods were determined with an oximeter (Erma
Optical Works, PWA-200). Coronary arterial blood of a
known saturation was sampled, and its oxygen content
was determined with a Lex O2 Con oxygen content ana-
lyzer to obtain an oxygen saturation-to-content conversion
factor. Coronary arteriovenous oxygen content difference
was then determined from the coronary oxyhemoglobin
saturation difference and the saturation to content con-
version factor.

Because the right ventricle was maintained collapsed
by the continuous hydrostatic drainage of the coronary
venous return, the measured oxygen consumption of the
heart was assumed to be exclusively of the left ventricle.
Left ventricular oxygen consumption (\(V_{O_2}\) ) was expressed
in ml \(O_2/\)beat per 100 g of left ventricle; 1 ml \(O_2\) is
equivalent approximately to 20 J under normal aerobic
conditions.

We used the following experimental protocols. In a
given contractile state of the left ventricle without any
inotropic interventions to the cross-circulated heart prep-
paration, we produced steady state normal ejecting con-
tractions that had a rectangular P-V trajectory loop, as
shown in the leftmost column of Figure 2. Both \(V_{O_2}\) and
PVA were determined when ventricular pressure, coro-
nary flow, and coronary venous oxyhemoglobin saturation
reached steady state at 2–3 minutes after each specified
loading condition was imposed.

Then, the course of the diastolic segment of the P-V
trajectory was due to two to four different pathways by
appropriately advancing the onset of filling, as shown in
the middle and rightmost columns of Figure 2. This pro-
cedure did not affect the systolic segment of the P-V
trajectory, due to both the servo control pump system and
the stability of the ventricle preparation. \(V_{O_2}\) and PVA
were determined for these contractions with different
courses of the diastolic segment of the P-V trajectory.

Beside this main protocol, we produced isovolumic
contractions at different end-diastolic volumes, as shown
in Figure 3A, and produced ejecting contractions with a
constant stroke volume whose systolic segment of the
P-V trajectory was markedly shifted, by changing the onset of ejection (Figure 3B). In these ejecting contractions, the diastolic segment of the P-V trajectory was kept unchanged with the servo control pump system.

At the end of each experiment, the atria and the right ventricular free wall were trimmed off the heart, and the left ventricle was weighed. The mean left ventricular weight of eight hearts was 76 ± 9 (SD) g.

Results

Figure 3 shows representative scatter diagrams of VO2-PVA data points obtained in one left ventricle. Panel A of Figure 3 shows a set of data of isovolumic contractions in a stable contractile state. There was a high and linear correlation between VO2 and PVA over the physiological range. All other left ventricles showed similar findings (Suga et al., 1981a).

Panel B of Figure 3 shows the data of the contractions whose PVA was changed by shifting the systolic segment of the P-V trajectory, as seen in the inset P-V diagram. The linear regression line fitted to the VO2-PVA data points of these contractions plus one unloaded contraction was close to that fitted to the isovolumic contractions of the same left ventricle in panel A.

Panel C of Figure 3 shows the results obtained in the main protocol. This panel shows one set of VO2-PVA data of contractions, whose diastolic segment of the P-V trajectory was widely shifted without any changes in its systolic segment, as seen in the inset P-V diagram. In spite of these changes and the resulting significant decreases in the external mechanical work and increases in the mechanical potential energy, VO2, as well as PVA, remained unchanged. The linear regression line of these data, together with one unloaded contraction, was close to those of the same left ventricle in panels A and B.

Panel D of Figure 3 pooled all those data points in panels A through C. The correlation coefficient was close to 1, and the scatter of the data points around the linear regression line was small. The three solid circles are identical with those data points in panel C in the main protocol. These three data points are within the 95% confidence range of the sampled data, indicating that the VO2-PVA point was not affected by the marked shift of the diastolic segment of the P-V trajectory. We observed similar results in all eight left ventricles.

Figure 4 shows more explicitly the independence of VO2 from the relative magnitude of external mechanical work (EW) in PVA. This figure plots VO2 against EW:PVA ratio in the main protocol in all eight left ventricles. PVA in each left ventricle was set to a constant in the range between 1000 and 2500 mm Hg ml/beat per 100 g. The coefficient of variation (Snedecor and Cochran, 1971) of PVA around each mean PVA in each left ventricle was computed. The mean coefficient of variation across all eight hearts was only 4.0 ± 1.6%, indicating the constancy of a given PVA. The EW:PVA ratio therefore indicates the fraction of external mechanical work in a constant PVA. This ratio is dimensionless, and can vary between 0 and 1. The greatest EW:PVA...
Figure 4. Constancy of left ventricular oxygen consumption (Vo2) in spite of the marked changes in the ratio of external mechanical work (EW) to a constant PVA in each of eight hearts. Each set of connected symbols corresponds to an individual heart.

ratio in each run was obtained in the contraction whose diastolic segment of the P-V trajectory was vertical in the P-V diagram, as in normal contractions in situ. EW:PVA decreased as the course of the diastolic segment of the P-V trajectory was shifted to the right by advancing the onset of ventricular filling, as seen in the bottom PVA patterns (from left to right) in Figure 2.

As seen in Figure 4, Vo2 did not change, or changed only little, with the wide changes in EW:PVA ratio between 0 and 0.8. The mean coefficient of variation of Vo2 around each mean Vo2 was only 3.9 ± 1.8%, indicating the constancy of Vo2 despite the marked changes in EW:PVA ratio. These results indicate that, when PVA remained unchanged, Vo2 also remained constant, in spite of the marked changes in the fraction of external mechanical work in PVA by the shift of the diastolic segment of the P-V trajectory.

Discussion

The present results have indicated that myocardial oxygen consumption is virtually independent of the cardiodynamic events during diastole. The diastolic cardiodynamic events are represented by the course of the diastolic segment of the P-V trajectory. This independence of myocardial oxygen consumption from diastolic cardiodynamic events is consistent with the concept of PVA.

The physical and physiological significance of PVA was first derived from the time-varying elastance model of the canine left ventricle (Suga et al., 1973; Suga, 1979b). PVA was equivalent to the total mechanical energy generated in the model during the gradual increment in the time-varying elastance from the end-diastolic compliant level to the end-systolic stiff level (Suga, 1979b; Piene and Sund, 1982).

In a given contractile state, PVA is explicitly determined by the systolic segment of the P-V trajectory because both the end-systolic P-V relation line and the end-diastolic P-V relation curve are considered to be constant for any given left ventricle (Suga et al., 1973, 1979). Thus, the course of the diastolic segment of the P-V trajectory is not related to the determination of PVA when the contractile state remains unchanged.

PVA consists of the external mechanical work and the mechanical potential energy (Suga, 1979b). The diastolic segment of the P-V trajectory is directly related to the division of PVA into these two energy components. In normal ejecting contractions, the diastolic segment of the P-V trajectory during the isovolumic relaxation phase is vertical. In the present study, the diastolic segment of the P-V trajectory was variably shifted so that the isovolumic relaxation phase was curtailed and the fraction of PVA contributed to the external mechanical work in one cardiac cycle was reduced.

We interpreted the shift of the diastolic segment of the P-V trajectory as follows. The external mechanical work performed during systole is equal to the area under the systolic segment of the P-V trajectory. This is the work that was performed by the left ventricle on the outside environment. The area under the diastolic segment of the P-V trajectory is equivalent to the mechanical work performed by the environment on the ventricle during diastole. The net external mechanical work output is therefore equal to the external mechanical work performed during systole, minus the mechanical work paid back from outside to the ventricle during diastole. This net work is represented by the area within the P-V trajectory during one cardiac cycle. The area for the mechanical potential energy is therefore increased by the amount of the mechanical work returned to the ventricle from outside. Thus, in the present main protocol, the fraction of external work in PVA once determined by the end of systole was decreased during diastole. Therefore, the present results indicate the total myocardial oxygen consumption is determined by the total mechanical energy generated during systole, independent of how much of this total mechanical energy is converted to effective pump work output during the entire cardiac cycle.

Although our present finding may appear to be consistent with Monroe's (1964) finding that as much as 90% of myocardial oxygen consumption was determined during systole, we consider that there is a substantial difference between Monroe's experiments and ours. Monroe's experiment was
limited to quasi-isovolumic contractions whose volume was rapidly reduced to zero at different times during cardiac cycle. These were quick volume-released contractions. Thus, there was no return of mechanical work to the left ventricle from outside during diastole. Instead, the mechanical potential energy generated during systole was partially converted to external mechanical work during the quick volume release in early diastole. In this sense, Monroe's type of contraction is opposite to ours in the direction of external mechanical work performed during diastole.

Our present results, together with Monroe's (1964), therefore would indicate that, whether the relaxing ventricle performs mechanical work on the environment or has work performed on it from outside, the oxygen consumption of the ventricle is determined predominantly by the cardiodynamic events during systole, and is affected little by the cardiodynamic events during diastole.

In the isolated cat papillary muscle, Cooper (1979) found that a significant proportion (36%) of myocardial oxygen consumption was saved by a quick release of force and length of isometrically contracting muscle at the peak of force. This curtailment of VO₂ is greater than Monroe's (1964) 9% in the canine left ventricle. Besides the difference in species, Monroe's (1964) preparation was blood perfused at 37°C, whereas Cooper's preparation was superfused with a non-blood perfusate at 29°C. These differences in experimental conditions might be related to the marked disparity between the two results.

Cooper's (1979) speculative mechanism for the difference between his own observation and Monroe's deserves mention. Cooper's papillary muscle preparation remained isometric until the length release, whereas Monroe's ventricle had compressed intraventricular air before the volume release, and the ventricular contraction was not purely isovolumic. This quasi-isovolumic contraction had experienced the shortening deactivation (Brutsaert and Paulus, 1977) by the time of the release, and the oxygen consumption was largely terminated by the end of systole. This situation did not occur in Cooper's purely isometric muscle. If this speculation is reasonable, our present finding of the independence of oxygen consumption from diastolic cardiodynamic events may also be related to the shortening deactivation during systolic ejection phase.

However, we consider that shortening deactivation was small in our present ejecting contractions, according to our previous observations (Suga et al., 1979). We had observed that the amount of end-systolic pressure deficit from the peak isovolumic pressure at the same volume due to shortening deactivation was only a few percent in ejecting contractions with ejection fractions between 0 and 50%, although it amounted to 10-15% at an ejection fraction of 75%. Therefore, we consider that shortening deactivation may not be the sole mechanism underlying the present independence of myocardial oxygen consumption from the diastolic cardiodynamic events.

As seen in the top tracings in Figure 2, neither peak pressure nor its time integral, i.e., tension time index (Sarnoff et al., 1958), changed much despite large changes in diastolic conditions. The constancy of these two measures cannot, however, be the cause of the constancy of oxygen consumption in our main protocol (see Fig. 4). The reason is that neither peak pressure nor tension time index proved to be a good correlate of ventricular oxygen consumption in our previous study (Suga et al., 1981b).

Although we conclude that myocardial oxygen consumption is independent of the diastolic cardiodynamic events, we are not concluding that the relaxation is a passive process during which the myocardium is not utilizing energy. Relaxation of muscle is known to be the process of detachment of crossbridges by ATP following the sequestration of calcium by sarcoplasmic reticulum using ATP (Katz, 1977). Thus, the relaxation phase is an energetically active period during which myocardium utilizes ATP. Moreover, unlike the relaxation phase of the ventricle, the crossbridge breaking and the calcium reuptake are known to start in the contraction phase before the start of the relaxation phase (Brutsaert et al., 1978; Allen and Kurihara, 1982). Therefore, we conclude, simply, that the total energy utilization during one cardiac cycle is not influenced by the mechanical events that occur during ventricular relaxation.

The following speculation would be possible for the mechanism underlying the observed independence of the left ventricular oxygen consumption from the P-V trajectory during diastole. Myocardial oxygen consumption is primarily utilized for the basal metabolism, the excitation-contraction coupling, and the mechanical contraction (Gibbs, 1978; Suga et al., 1983b). The basal metabolic oxygen consumption is assumed to be constant despite the changes in the diastolic segment of the P-V trajectory (Monroe and French, 1960). Because PVA remains unchanged despite the changes of the diastolic P-V trajectory, the total mechanical energy generated by the contractile machinery remains the same by the definition of PVA (Suga, 1979b). In addition, excitation-contraction coupling is assumed to be unaffected by the change in diastolic P-V trajectory because the total amount of calcium ions released from the sarcoplasmic reticulum is determined by the end of systole (Allen and Kurihara, 1981), and, therefore, the energy needed to uptake the same amount of calcium ions will be the same. It seems unlikely that the diastolic events affect the calcium level in the next systole, because we did not observe any change in the ventricular contractile state in terms of the end-systolic pressure at a given end-systolic volume when the diastolic P-V trajectory was markedly shifted. Thus, the change of the...
diastolic P-V trajectory does not seem to have affected the primary determinants of \( \text{VO}_2 \) in the present study.

Our present finding indicates that external mechanical work and mechanical potential energy are interchangeable during diastole without any change in myocardial oxygen consumption. This finding is consistent with our previous finding that the oxygen cost of external mechanical work and that of potential energy are the same (Suga et al., 1980). If the oxygen cost of the work and that of the potential energy were different, the present interchangeability without any change in myocardial oxygen consumption would not have been observed.

To summarize, we specifically shifted the diastolic segment of the P-V trajectory in the P-V diagram without changing the systolic segment of the P-V trajectory and PVA. Although the fraction of external mechanical work in the total mechanical energy generated during systole was markedly changed by the shift of the diastolic segment of the P-V trajectory, oxygen consumption of the left ventricle remained unchanged. The result suggests for the first time that the external mechanical work and the mechanical potential energy of the left ventricle are interchangeable in one cardiac cycle without any change in myocardial oxygen consumption. The result also corroborates the concept that the myocardial oxygen consumption of the left ventricle is primarily determined by the systolic cardiodynamic events independent of the diastolic cardiodynamic events.

Received April 16, 1984; accepted for publication August 14, 1984.

References


INDEX TERMS: Heart • Cardiac mechanics • Cardiac energetics • Systole • Relaxation
Independence of myocardial oxygen consumption from pressure-volume trajectory during diastole in canine left ventricle.
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Circ Res. 1984;55:734-739
doi: 10.1161/01.RES.55.6.734

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