Heart-Rate-Proportional Oxygen Consumption for Constant Cardiac Work in Dog Heart

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Abstract We studied whether there is an optimal heart rate (HR) that would minimize myocardial oxygen consumption (MV_{O_2}) per min for a constant minute cardiac work. We measured minute MV_{O_2} (mlO_2/min) of the left ventricle paced at increasing rates (100–200 beats/min) in 10 right-heart-bypassed dogs. In each experiment, cardiac output was kept constant with a constant-flow bypass pump, and mean aortic pressure was also kept constant by inflation or deflation of an intra-aortic balloon. Minute cardiac work was thus kept constant. Minute MV_{O_2} was obtained as the product of mean coronary arteriovenous O_2 difference and mean coronary blood flow drained from the collapsed right ventricle. Both left ventricular $E_{max}$ (contractility index defined as the slope of the left ventricular end-systolic pressure-volume relation) and PVA (pressure-volume area as a measure of total mechanical energy of contraction) were obtained by an abrupt aortic occlusion method. The obtained minute MV_{O_2}-HR relationship showed a good linear positive correlation ($r=0.824-0.995$) in every heart. We accounted for this relationship by the changes in PVA and $E_{max}$ that we had proposed as primary determinants of MV_{O_2}. We conclude that minute MV_{O_2} for a constant minute cardiac work increased monotonically with increases in HR from 100 to 200 beats/min, being minimum at the lowest HR, and that this relation was ascribable to the HR-proportional increase in the MV_{O_2} component for the excitation-contraction coupling.

Key words: external work, pressure-volume area, PVA, $E_{max}$, optimality.

Heart rate (HR) is one of the major determinants of myocardial oxygen consumption (MV_{O_2}) per min besides myocardial wall tension and myocardial contractility (Braunwald, 1971). An individual animal requires certain levels of

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minute cardiac output (CO) and mean arterial pressure (mAoP) and hence a certain cardiac external work per min for a given level of physical activity. When the heart at a given contractility performs a required minute cardiac work, different combinations of HR and stroke work are possible. For example, in a given set of mAoP, CO, and contractility index $E_{\text{max}}$ (SUGA and SAGAWA, 1974), one of the following three combinations of HR and stroke work exists: a low HR and a large stroke work, or a high HR and a small stroke work, or a middle HR and a middle stroke work.

When we assume constant $E_{\text{max}}$ and mAoP, a given left ventricle (LV) has a constant end-systolic volume (SUGA et al., 1973) and a larger stroke work is produced from a larger end-diastolic volume, which is accompanied by a higher systolic myocardial wall tension according to Laplace's relation (BRAUNWALD et al., 1976). Then, $\text{MV}_{\text{O}_2}$ fraction for myocardial wall tension is higher, though HR is low. On the other hand, a smaller stroke work is produced from a smaller end-diastolic volume, which is accompanied by a lower myocardial wall tension. Then $\text{MV}_{\text{O}_2}$ fraction for myocardial wall tension is lower, though HR is high. Therefore, as the net effect of both HR and myocardial wall tension affected by cardiac size on $\text{MV}_{\text{O}_2}$ per min, there may be an intermediate HR that minimizes minute $\text{MV}_{\text{O}_2}$ under the condition of constant minute cardiac work.

We examined in this study whether such an optimal HR exists under the condition of constant CO and mAoP and hence a constant minute cardiac work. To this end, we carried out experiments in 10 right-heart-bypassed dog preparations, and attempted to account for the results by a combination of left ventricular PVA (pressure-volume area, a measure of total mechanical energy of the ventricle) and $E_{\text{max}}$ (a ventricular contractility index) which we had proposed as two primary determinants of $\text{MV}_{\text{O}_2}$ per beat (SUGA et al., 1983a; TANAKA et al., 1988; SUGA, 1990).

METHODS

Preparation. Ten mongrel dogs weighing 11–15 kg were anesthetized with ketamine hydrochloride (5 mg/kg i.m.) followed by pentobarbital sodium (25 mg/kg i.v.). Blood was heparinized (500–750 U/kg i.v.). The dog was artificially ventilated through an endotracheal tube with a positive pressure respirator. The chest was opened by median sternotomy. The pericardium was cut open, and a pericardial cradle was formed. An electromagnetic flow probe (10–14 mm in internal diameter; model FB-10T, 12T, or 14T, Nihon Kohden, Japan) was placed on the ascending aorta to monitor the aortic flow (AoF) and to obtain LV volume changes during ejection period, as described below in Data analysis.

A right-heart-bypassed preparation was then established as described previously (NOZAWA et al., 1987). Briefly, the azygos vein was ligated, the superior and inferior venae cavae were cannulated via the right atrium, and the venous return was directed into a reservoir. The superior and inferior venae cavae were tied on the cannulae. Fresh blood obtained from a second dog (anesthetized in the same way as the
preparation dog) and lactate Ringer solution containing 5% glucose were mixed to prime the reservoir and tubing. The venous blood was returned with a roller pump (RP-LVS, Furure Science, Japan) into a cannula passed via the right ventricular conus into the main pulmonary artery. Pulmonary valvular regurgitation was stopped by tying the pulmonary arterial trunk on the cannula. A heating tape was wrapped around the tubing between the reservoir and the pulmonary artery to keep blood temperature at ~37°C. Another cannula was placed in the right ventricle to drain the entire coronary venous return (except for LV Thebesian flow) for flow and oxyhemoglobin content measurements.

A 7F micromanometer-tipped catheter with a fluid-filled lumen (Miller PC-470) was inserted into the LV cavity through the apical dimple to measure LV pressure (LVP). It was calibrated with a Statham pressure transducer (Model P23 ID).

Aortic flow (AoF) was measured at the aortic root with an electromagnetic flowmeter (MVF-2100, Nihon Kohden, Japan). The gain calibration factor was set on the flowmeter. Zero flow balance was carefully adjusted so that the diastolic flow level was zero.

Mean aortic pressure (mAoP) was also measured with another Statham pressure transducer through a water-filled catheter introduced from the left carotid artery. If necessary, mAoP was controlled by inflation or deflation of a Fogarty balloon catheter (model 32-080-8/10 F) which had been introduced into the thoracic aorta via the right femoral artery.

The sinus node was destroyed by a subepicardial injection of 0.1 ml of 30% formalin. Then, HR was controlled by artificial left auricular pacing.

Aortic occlusion. The ascending aorta between the flow probe and the brachiocephalic artery was abruptly clamped in diastole with Satinsky vascular forceps. The occlusion was maintained over a few isovolumic contractions, of which the first single beat was used for analysis. We expected that the LV end-diastolic volume of the first transient isovolumic contraction was the same as that of the last steady-state ejecting contraction (IGARASHI and SUGA, 1986; NOZAWA et al., 1987). In fact, LV end-diastolic pressures were the same in these two contractions, as seen in Fig. 1. We considered the aortic occlusion to be successful when it was associated with 1) no ejection in aortic flow and its time integral tracings, 2) a monotonic fall of the aortic pressure, and 3) a smooth sinusoidal LV pressure contour, as previously described (IGARASHI and SUGA, 1986).

Myocardial $O_2$ consumption. Coronary blood flow was continuously measured with another electromagnetic flowmeter (MVF-2100, Nihon Kohden, Japan) in the coronary venous return tubing draining the right ventricle. Zero-flow balance was adjusted to the zero flow produced by the complete occlusion of the coronary venous return tube. We neglected the LV Thebesian flow because it is known to be less than a small percentage of the total coronary flow (SUGA et al., 1986a).

Coronary arteriovenous $O_2$ content difference (AVDO$_2$) was continuously measured with an arteriovenous $O_2$ difference analyzer (A-VOX Systems, San Antonio, Texas, U.S.A.) (SHEPHERD and BURGAR, 1977). The cuvettes of the A-VOX
Fig. 1. Representative analog data tracings. From the top down, electrocardiogram (ECG), left ventricular pressure (LVP), left ventricular end-diastolic pressure (LVEDP) as magnified LVP, mean aortic pressure (mAoP), aortic flow (AoF), coronary flow, and coronary arteriovenous O\textsubscript{2} content difference (AVDO\textsubscript{2}). A: heart rate (HR) was 120 beats/min. During aortic occlusion, AoF was zero and LVP tracing showed smooth sinusoidal wave. B: HR was 160 beats/min.

The product of total coronary flow in ml/min and coronary AVDO\textsubscript{2} in % of arterial blood from the left carotid artery and coronary venous blood from the right ventricle. The A-VOX analyzer was calibrated against a Lex-O\textsubscript{2}-Con O\textsubscript{2} content meter in each experiment.
HEART RATE AND MV$_{O_2}$

volume divided by 100 gives O$_2$ consumption rate in ml/min (MV$_{O_2}$). It was normalized with respect to left ventricular wet weight to give MV$_{O_2}$ in ml of consumed O$_2$/(min·100 g of LV). Since the right heart was bypassed and collapsed, we assumed that the right ventricular O$_2$ consumption was minimal and negligible (NOZAWA et al., 1987).

Data analysis. All data (electrocardiogram (ECG), LVP, LV end-diastolic pressure (LVEDP), mAOA, AoF, mean coronary perfusion flow, and AVDO$_2$) were recorded on a multichannel thermal recorder (Polygraph 36, NEC San-ei, Japan; Fig. 1). Their signals were digitized at 2 ms intervals (500 Hz) and analyzed with a signal processing computer system (7T18, NEC San-ei, Japan).

HR and stroke volume (SV) were obtained as mean values of a series of three steady-state ejecting contractions just before the first transient isovolumic contraction by the aortic occlusion method. The AoF signal was time-integrated to obtain instantaneous volume changes with the signal processing computer. The integrated volume signals were reset to zero in synchrony with every R wave of ECG (Fig. 2A, C) to obtain the pressure-volume (PV) trajectories in a PV diagram (Fig. 2B, D).

An end-systolic PV relation (ESPVR) line was obtained from the last steady-state ejecting contraction and the first transient isovolumic contraction in the same way as described previously (IGARASHI and SUGA, 1986; NOZAWA et al., 1987). Briefly, the PV trajectories of the ejecting and isovolumic contractions were superimposed in the same PV diagram so that their end-diastolic volumes were equalized on the relative volume coordinate. We then computed a straight line from the peak isovolumic pressure point through the left upper corner of the PV trajectory of the ejecting contraction to the volume axis. We identified this line with the ESPVR line and its slope with $E_{max}$ (SUGA and SAGAWA, 1974; SAGAWA, 1978) in the same way as before (IGARASHI and SUGA, 1986; NOZAWA et al., 1987) (Fig. 2B, D). The volume-axis intercept of the ESPVR line was identified with $V_0$. We repeated the abrupt occlusion 2 or 3 times and obtained reasonably reproducible $E_{max}$ values.

Cardiac external work (EW) per beat (mmHg·ml/beat), i.e., stroke work, was also obtained as the mean of EW values of the three consecutive ejecting beats just before the abrupt aortic occlusion: EW of each ejecting contraction was obtained by calculating the area circumscribed by the PV trajectory in the PV diagram throughout one cardiac cycle with the 7T18 signal processor. The diastolic PV segment was assumed to be a straight line connecting $V_0$ and the end-diastolic PV point (Fig. 2B, D) because we could not directly determine the diastolic PV trajectory by the present method. The linearized diastolic PV segment may have been slightly different from the true end-diastolic PV trajectory, but we considered the difference to be a negligibly small fraction of EW in the present study. EW of each ejection contraction corresponds to the shaded area in Fig. 2B and D. Then, minute EW was obtained as the product of mean EW per beat and HR.

Pressure-volume area (PVA) per beat (mmHg·ml/beat) (SUGA et al., 1983a) was calculated as the area circumscribed by the ESPVR line, the linearized
Fig. 2. Determination of $E_{\text{max}}$ and systolic pressure-volume area (PVA). A: digitized tracings of ECG, LVP, AoF, and stroke volume at 120 beats/min of HR. Stroke volume was time-integrated AoF, reset at every end diastole. During aortic occlusion, AoF was zero and LVP showed smooth sinusoidal wave. B: pressure-volume (PV) trajectories of the last ejection beat and the first isovolumic contraction at HR = 120 beats/min. Upper and lower broken lines indicate end-systolic and end-diastolic PV lines. Shaded area shows stroke work of the heart. Triangular area between end-systolic and end-diastolic PV lines on the origin side of the shaded area means potential energy. The sum of this potential energy and stroke work is the systolic pressure-volume area. C: digitized tracings of ECG, LVP, AoF, and stroke volume at HR = 160 beats/min. D: PV trajectories of the last ejection beat and the first isovolumic contraction at HR = 160 beats/min. Note that stroke volume and stroke work were smaller at 160 beats/min but $E_{\text{max}}$ and the potential energy were nearly constant.
Fig. 3. $E_{max}$-HR relation at constant minute external work. $E_{max}$ did not correlate with HR in all hearts except three (#4, #5, #8). In these exceptional hearts, $E_{max}$ positively correlated with HR. Dashed lines and equations indicate the regression line of $E_{max}$ (ordinate) on HR (abscissa). Dog#, experimental number; n, number of sampled data; p, significance level of correlation; NS, not significant.

end-diastolic PV relation, and the systolic PV trajectory. Then we obtained PVA per min per 100 g of LV (mmHg ml min$^{-1}$ 100 g LV$^{-1}$). Elastic potential energy (PE), the triangular area under ESPVR on the PV origin side of the PV trajectory, was derived by subtracting EW from PVA (SUGA et al., 1983a).

Experimental protocols. We attempted to fix CO and mAoP, and hence minute
Fig. 4. Minute MV\textsubscript{O}_2-HR relation at constant minute external work. Minute MV\textsubscript{O}_2 significantly correlated with HR in all hearts except one (#10). Dashed lines and equations indicate the regression line of minute MV\textsubscript{O}_2 (ordinate) on HR (abscissa). Dog#, experimental number; n, number of sampled data; r, significance level of correlation; NS, not significant.

EW as much as possible. We also expected that E\textsubscript{max} would also be stable because of the constant mAoP. Then, we changed HR alone in steps of about 20 beats/min from the lowest possible setting (100–138 beats/min) to the highest possible setting (179–201 beats/min) that were attainable without frequent arrhythmias and alternans.
**HEART RATE AND MV$_{O_2}$**

![Graphs showing heart rate and MV$_{O_2}$](image)

Fig. 5. Beat MV$_{O_2}$-HR relation at constant minute external work. Beat MV$_{O_2}$ correlated negatively with HR, but statistical significance was observed in only 3 hearts (#2, #3, and #9). Dashed lines and equations indicate the regression line of beat MV$_{O_2}$ (ordinate) on HR (abscissa). Dog#, experimental number; n, number of sampled data; p, significance level of correlation; NS, not significant.

We obtained data at least 3 min after we changed the pacing rate. This period was enough for the heart to reach new steady state contractions. Then we studied the $E_{max}$-HR (Fig. 3), minute MV$_{O_2}$-HR (Fig. 4), beat MV$_{O_2}$-HR (Fig. 5), minute mechanical energy-HR (Fig. 6), beat mechanical energy-HR (Fig. 7), and minute
Fig. 6. Minute mechanical energy and HR. Minute PVA (pressure-volume area)-HR (○), minute EW (external work)-HR (□), and minute PE (potential energy)-HR (△) were plotted with their regression lines. Minute EW was kept nearly constant \( (p>0.05) \) in all hearts as designed, except in one heart (19, \( p<0.01 \)). Minute PE did not significantly \( (p>0.05) \) increase with HR in all hearts except one (5, \( p<0.05 \)). Minute PVA did not significantly \( (p>0.05) \) changed with HR in all hearts, except it slightly decreased in two hearts (7 and 8).

MV\( \text{O}_2 \)-minute PVA (Fig. 8) relations.

**Statistical analysis.** Hemodynamic data were presented as mean\( \pm \) S.D. Variation from the mean was expressed as the percent coefficient of variation (CV = 100 \cdot S.D./mean) (Table 1).

All the relations including the minute MV\( \text{O}_2 \)-HR relation were first analyzed
Fig. 7. Beat mechanical energy and HR. Beat PVA-HR (○), beat EW-HR (□), and beat PE-HR (△) were plotted with their regression lines. Because minute EW was kept nearly constant, beat EW negatively correlated with HR with significance in every dog. Beat PVA also negatively correlated with HR with significance in all 10 dogs. Beat PE was nearly constant except for in dogs #3, #7, and #8. In these exceptional dogs, PE negatively correlated with HR with significance.

by linear regression analysis. When a parabolic fitting was suspected to be better in the minute MV_{O2}-HR relation, we fitted \( y = a \cdot HR^2 + b \cdot HR + c \) and tested statistical significance of coefficient \( a \) of squared HR (Snedecor and Cochran, 1971).

\( p \) values smaller than 0.05 were assumed to be statistically significant.
Fig. 8. Minute MV\textsubscript{O\textsubscript{2}}-minute PVA relation. Minute MV\textsubscript{O\textsubscript{2}} increased with increases in minute PVA in dogs #1, #2, and #5, though statistical significance was not recognized in these dogs. In the other dogs, minute MV\textsubscript{O\textsubscript{2}} decreased with increases in minute PVA, though statistical significance was recognized only in dog #8.

RESULTS

Figure 1 shows representative tracings (ECG, LVP, LVEDP, mAoP, AoF, coronary flow, and AVDO\textsubscript{2}). Figure 1A is the case of HR = 120 beats/min, and Fig. 1B is the case of HR = 160 beats/min. Although peak AoF values were different between the two panels, CO was unchanged between both panels. Note the zero AoF and monotonic falls of the mAoP during aortic occlusion and also the smooth

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<th>Heart No.</th>
<th>HR range (beats/min)</th>
<th>$P_{\text{peak}}$ (mmHg)</th>
<th>$P_{es}$ (mmHg)</th>
<th>CO (l/min)</th>
<th>EW ($\times 10^5$ mmHg·ml/min)</th>
<th>$E_{\text{max}}$ (mmHg/(ml/100 g))</th>
<th>mAoP (mmHg)</th>
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Data are expressed as mean ± S.D. Numerical data in parentheses are coefficients of variation (= 100·S.D./mean). HR, heart rate; $P_{\text{peak}}$, peak left ventricular pressure; $P_{es}$, end-systolic left ventricular pressure; CO, cardiac output; EW, external work; mAoP, mean aortic pressure.
sinusoidal LVP waves of the first isovolumic contractions. Figure 2 shows LVP, AoFP, and stroke volume tracings and PV trajectories before and during an abrupt aortic occlusion at two different HR.

Table 1 summarizes hemodynamic conditions in 10 dogs. HR ranges in 10 dogs were 100–201 beats/min. The minimum heart rate attained was 121 ± 10 (S.D.) beats/min despite the destruction of the sinus. Although the bypass pump flow was kept constant, CO slightly varied in each dog. Because we calculated CO as SV·HR, the minor changes in CO may be due to the exclusion of coronary flow from SV measured with the aortic flowmeter.

$E_{\text{max}}$ did not correlate with HR except in 3 of the 10 dogs (#4, #5, #8) as shown in Fig. 3. This means that $E_{\text{max}}$ was not significantly affected by HR in general. In those three exceptional dogs, $E_{\text{max}}$ positively correlated with HR for no explicit reason.

As shown in Fig. 4, minute $MV_{O_2}$ for a nearly constant minute EW increased with increases in HR in all 10 hearts. The correlation coefficients of these relations were 0.824–0.995, all statistically significant. The regression lines of minute $MV_{O_2}$ on HR are also shown in Fig. 4. Although the second data points from the lowest HR had lower minute $MV_{O_2}$ than the data points at the lowest HR in dogs #3, 4, and 7, a parabolic function ($y = a\cdot HR^2 + b\cdot HR + c$) did not better fit the data than a linear regression line because coefficient $a$ of $HR^2$ term was not statistically significant ($p > 0.05$). Thus, there were no nadirs on the minute $MV_{O_2}$-HR relations within the tested HR ranges. This is the first main experimental result of the present study.

As shown in Fig. 5, beat $MV_{O_2}$ decreased with increases in HR except for one heart (#5), although the statistical significance of the negative correlation was recognized in only 3 of the 10 hearts (#2, #3, and #9). In the other 7 hearts, beat $MV_{O_2}$ did not significantly correlate with HR.

Figure 6 shows the relations between minute cardiac mechanical energy (EW, PE, and PVA, individually) and HR. Minute EW ($= EW \cdot HR$, □) was kept nearly constant with intention as described in Experimental protocols. Only heart #9, however, showed a statistically significant negative correlation between minute EW and HR. Minute PE (△) did not significantly change with HR, except for only one significantly positive correlation in heart #5. Minute PVA (○) neither significantly changed with HR, except for only two significantly negative correlations in hearts #7 and #8. This generally unchanged minute PVA with HR is the second main experimental result of this study.

Figure 7 shows the relations between beat cardiac mechanical energy (EW, PE, and PVA, individually) and HR. Beat EW (□) decreased with increases in HR in all hearts. The negative correlation between beat EW and HR was statistically significant in all hearts. This decrease in beat EW with HR was reasonably expected from the attempted constancy of minute EW. Beat PVA (○) also decreased with increases in HR. The negative correlation between beat PVA and HR was also significant in all hearts. Beat PE (△) was nearly constant in all hearts except #3, #7,
and #8 in which beat PE significantly decreased with increases in HR.

Figure 8 shows the minute MV_{O_2}-minute PVA relations. Minute MV_{O_2} tended to increase sharply with increases in minute PVA in hearts #1, #2, and #5, though they did not show statistical significance. In the other hearts, minute MV_{O_2} rather decreased with increases in minute PVA, though only heart #8 showed statistical significance. That there was generally no correlation between minute MV_{O_2} and minute PVA is the third main experimental result of this study.

DISCUSSION

We studied whether there is any optimal HR that minimizes minute MV_{O_2} for a given minute EW. However, within the tested HR range of 100–200 beats/min, minute MV_{O_2} monotonically increased with increases in HR. In other words, we found such an optimal HR, if we may call it so, only at the lowest tested HR.

We started this study with the hypothesis that the myocardial wall tension would increase when HR is decreased and in turn end-diastolic volume is increased at constant CO, mAoP, and E_{max}. However, minute MV_{O_2} increased monotonically with HR and we could not confirm the expected increases in minute MV_{O_2} with decreases in HR. Since we could not obtain MV_{O_2} data in a HR range less than 100 beats/min in the present preparation, we can neither discuss the minute MV_{O_2}-HR relation over the full physiological HR range (e.g., 50–250 beat/min), nor can we know whether the optimal HR which manifests the nadir of the minute MV_{O_2}-HR relationship exists at a HR lower than 100 beats/min.

We designed the study to keep minute EW constant as an experimental condition by keeping both minute CO and mean arterial pressure constant. Although there are some reports on the relation between MV_{O_2} and HR (Laurent et al., 1956; Maxwell et al., 1958; Van Der Veen and Willebrands, 1967; Boerth et al., 1968), only Laurent et al. (1956) changed HR widely while keeping minute EW constant. Although they observed monotonic increases in MV_{O_2} with HR similar to our result, they did not analyze simultaneous changes in determinants of MV_{O_2} as we did. Therefore, they were not successful in explicitly explaining this monotonic increases in MV_{O_2} with HR at a constant minute EW.

Taking advantage of both PVA and E_{max}, minute MV_{O_2} is predictable by the following empirical equation (Suga et al., 1987; Tanaka et al., 1988; Suga, 1990):

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\text{Minute } MV_{O_2} = \text{HR} \cdot (\text{beat } MV_{O_2}) = \text{HR} \cdot (A \cdot \text{PVA} + B \cdot E_{max}) + \text{BM} = \text{HR} \cdot \{A \cdot (\text{EW} + \text{PE}) + B \cdot E_{max}\} + \text{BM} = \text{HR} \cdot (\text{PVA-dependent beat } MV_{O_2}) + \text{HR} \cdot (\text{PVA-independent beat } MV_{O_2}), \tag{1}
\]

where \(A\) and \(B\) are empirical constants and BM is basal metabolic MV_{O_2} per min.
(SUGA et al., 1987). As for the PVA-independent and PVA-independent beat MV_{O_2}, see below. The constancy of coefficients \( A \) and \( B \) in a given heart have been shown previously (SUGA et al., 1986b; BURKHOFF et al., 1987). The increases in minute MV_{O_2} with increases in HR in the present study can therefore be accounted for by the following factors: 1) increases in HR per se, 2) changes in contractility in terms of \( E_{\text{max}} \), 3) total cardiac mechanical energy or PVA (especially, PE which is a component of PVA, because the other component of PVA, EW, was kept constant in this study), and 4) BM.

Beat MV_{O_2} (in the first line of Eq. (1)) generally decreased with increases in HR as shown in Fig. 5, whereas minute MV_{O_2} increased with increases in HR as seen in Fig. 4. Similar to beat MV_{O_2}, both beat PVA and beat EW (in the second and third lines of Eq. (1)) decreased with increases in HR, although beat PE (in the third line of Eq. (1)) either decreased slightly or remained unchanged, as seen in Fig. 7. BM per min (in Eq. (1)) is unlikely to change with HR (GIBBS et al., 1980). Thus, HR is the only term that can increase minute MV_{O_2} with HR despite the decrease in beat MV_{O_2} with HR. Therefore, HR must be the primary factor to have monotonically increased minute MV_{O_2} as a function of HR.

Minute PVA (=HR·PVA), minute EW, and minute PE did not significantly change with HR in almost all hearts despite the HR-proportional increase in minute MV_{O_2} as seen in Figs. 4 and 6. Therefore, none of HR·A·PVA, HR·A·EW, and HR·A·PE in Eq. (1) alone can account for the increase in minute MV_{O_2} with HR. The fraction of MV_{O_2} related to these mechanical terms can be called PVA-dependent MV_{O_2} (SUGA, 1990). This fraction of MV_{O_2} is considered to be related to ATP hydrolysis by myosin ATPase (GIBBS, 1978; SUGA, 1990). Since BM is unlikely to be changed by HR and ventricular loading conditions (GIBBS et al., 1980; NOZAWA et al., 1988), the remaining term that could account for the HR-proportional increase in minute MV_{O_2} must be HR·B·E_{max} in Eq. (1).

Although we designed to keep minute EW constant over the tested range of HR, minute EW tended to decrease with increases in HR in seven hearts, #3, #4, and #6 through #10, where the decrease was statistically insignificant except in heart #9 (\( p < 0.01 \)). If minute EW had been kept rigorously constant over the tested range of HR in these hearts as in the three hearts #1, #2, and #5, the decreasing tendency of minute PVA with HR would have been smaller and minute MV_{O_2} would have more steeply increased with HR than in Fig. 4. Nevertheless, minute PVA, and hence HR·A·PVA, cannot yet account for the HR-proportional increase in minute MV_{O_2}.

The HR·B·E_{max} term, which is suspected above to be the most responsible to the HR-proportional increase in minute MV_{O_2}, means the minute MV_{O_2} fraction for the excitation-contraction (E-C) coupling (SUGA et al., 1983b, 1985, 1987). This term increases with increases in HR·E_{max} because B has been shown to be constant in a given LV (BURKHOFF et al., 1987; OHGOSHI et al., 1990). In the present study, E_{max} significantly increased with HR in hearts #4, #5, and #8. It is obvious in these hearts that HR·B·E_{max} is primarily responsible for the increases in minute MV_{O_2}.
with HR. Even in the other seven hearts where \( E_{\text{max}} \) did not significantly change, \( HR \cdot B \cdot E_{\text{max}} \) also increased with HR. Therefore, we would conclude that the factor most responsible for the monotonically increased \( MV_O_2 \) with HR is the minute \( MV_O_2 \) component for the E-C coupling in all hearts.

The fraction of \( MV_O_2 \) related to the E-C coupling and BM can be called PVA-independent \( MV_O_2 \) (SUGA, 1990). The PVA-independent \( MV_O_2 \) in excess of BM is considered to be related to ATP hydrolysis by Ca-ATPase to uptake cytosolic Ca\(^{2+}\) and Na-K-ATPase to restore intracellular Na\(^+\) and K\(^+\) balance (CHAPMAN, 1983). \( HR \cdot B \cdot E_{\text{max}} \) is related to this PVA-independent \( MV_O_2 \): \( B \cdot E_{\text{max}} \) means beat \( MV_O_2 \) used for handling Ca\(^{2+}\), Na\(^+\), and K\(^+\) in each beat, and \( HR \cdot B \cdot E_{\text{max}} \) means minute \( MV_O_2 \) for handling Ca\(^{2+}\), Na\(^+\), and K\(^+\) in all beats per min. Stoichiometry has been shown to be 2 mol of Ca\(^{2+}\) per 1 mol of ATP for the Ca-pump and 3 mol of Na\(^+\) per 1 mol of ATP for the Na-K pump (CHAPMAN, 1983). The amounts of Ca\(^{2+}\) and Na\(^+\) involved in the E-C coupling seem to increase with contractility (LANGER, 1974; GIBBS, 1978; SUGA, 1990). Therefore, the amounts of these ions and hence the beat \( MV_O_2 \) fraction for handling these ions (i.e., \( B \cdot E_{\text{max}} \)) may have been largely unchanged when \( E_{\text{max}} \) was unchanged in most of the hearts in this study. Then, \( HR \cdot B \cdot E_{\text{max}} \) increased in proportion to HR.

There is a possibility that our \( E_{\text{max}} \) obtained by the abrupt aortic occlusion method was somewhat overestimated in the small stroke volume range (high HR in our protocol) and was underestimated in the large stroke volume range (low HR in our protocol) (IGARASHI et al., 1987; SUGIURA et al., 1989). We wonder whether the increased \( E_{\text{max}} \) with increases in HR in hearts \#4, \#5, and \#8 (Fig. 3) were true increments or only overestimations. Even if ventricular contractility remained unchanged in these hearts, the increases in \( HR \cdot B \cdot E_{\text{max}} \) with HR could account for the increases in minute \( MV_O_2 \) with HR in these hearts. BM is considered to be virtually unchanged with \( E_{\text{max}} \) (NOZAWA et al., 1988).

Can we expect a nadir of minute \( MV_O_2 \) if we extend the tested HR range to lower than 100 beats/min? MAUGHAN et al. (1985) reported that \( E_{\text{max}} \) increased with increases in HR over the range of 60–100 beats/min in excised hearts. The HR-proportional increase in \( E_{\text{max}} \) below 100 beats/min would be accompanied with increases in minute \( MV_O_2 \). Therefore, it is unlikely that we could obtain a nadir of minute \( MV_O_2 \) even if we change HR to below 100 beats/min.

We fixed minute EW in each heart. Would the HR-proportional minute \( MV_O_2 \) change when the level of minute EW is changed? A separate study is needed to answer this question. Minute EW ranged from \((0.64-1.8) \times 10^5\) mmHg \( \cdot \) ml/min among ten hearts, and all these hearts yielded essentially the same results. Therefore, we would speculate that qualitatively the same results will be obtained at different levels of minute EW.

In summary, minute \( MV_O_2 \) increased with increases in HR from 100 to 200 beats/min under the conditions of constant minute CO and mean arterial pressure and hence minute EW. The HR to minimize minute \( MV_O_2 \) for a constant minute EW existed at the lower end of the minute \( MV_O_2 \)-HR relationship within the tested
HR range. The result was reasonably explained by the concepts of PVA and $E_{\text{max}}$ in addition to HR changes. We conclude that the HR-proportionally increased minute $MV_O_2$ component for the E-C coupling is the factor most responsible for the monotonically increased minute $MV_O_2$ with HR.

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REFERENCES


