Oxygen Consumption for Constant Work Is Minimal at Lowest Working Contractility in Normal Dog Hearts

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Abstract We tested whether minimal myocardial oxygen consumption (MV_{O_2}) for a given external work would exist in the middle of a normal contractility range as previously predicted theoretically. The left ventricle of the excised cross-circulated dog heart preparation was connected to a volume servo pump. Myocardial contractility in terms of ventricular end-systolic elastance (E_{max}) was gradually increased from control 8.9 ± 3.4 (mean $\pm$ SD) to 30.0 mmHg/(ml/100 g) by epinephrine and decreased to 1.8 mmHg/(ml/100 g) by propranolol while heart rate, end-systolic pressure and stroke work were kept constant. MV_{O_2} was determined as the product of total coronary flow and coronary arteriovenous oxygen content difference in each contractile state. We plotted MV_{O_2} values against E_{max} values in each heart. The MV_{O_2} - E_{max} relation for a constant cardiac work showed that MV_{O_2} was minimal at the low end of the covered E_{max} range. We conclude that minimal MV_{O_2} for a given cardiac work is generally obtained at the lowest working contractility in normal dog hearts. This conclusion might pose some problems in the previous theoretical prediction as to the contractility that achieves the minimal MV_{O_2} in a given external work.

Key words: cardiac energetics, optimality principle, contractility, external work, pressure-volume area.

Cardiotonic agents can sometimes decrease myocardial oxygen consumption (MV_{O_2}) for a given cardiac work in failing hearts [1-5]. This decrease in MV_{O_2} has been attributed to the following mechanisms: the decreased MV_{O_2} by the decreased cardiac size and myocardial tension (via Laplace law) associated with the enhanced

contractility exceeds the increased MV_{O_2} with the enhanced contractility per se [1, 5–7]. However, this concept has not satisfactorily been validated experimentally.

We have studied this concept theoretically and found a possibility that a minimal MV_{O_2} for a constant cardiac work would appear as a nadir of a parabolic MV_{O_2} -contractility curve within the normal contractility range [8]. We have however shown another possibility that the minimal MV_{O_2} would appear at or near the lowest contractility in a heart with a reduced end-diastolic ventricular compliance [8]. To examine the theoretical existence of a nadir MV_{O_2} in the middle of the normal contractility range, we previously carried out *in situ* heart experiments in dogs and found that the minimal MV_{O_2} for a given cardiac work appeared at or near the lowest contractility [7]. We then suspected a possibility that we did not enough depress contractility to show the nadir MV_{O_2} because pulmonary edema occurred by the increased end-diastolic pressure.

In the present experimental study, we reexamined the possible existence of the nadir MV_{O_2} for a constant cardiac work using the excised cross-circulated canine heart preparation instead of the previously used *in situ* heart preparation. The excised heart preparation circumvented the problem of pulmonary edema during depressing the ventricular contractility and elevating the ventricular end-diastolic pressure.

MATERIALS AND METHODS

Preparation. The excised, cross-circulated heart was prepared in the standard manner [9–11]. Briefly, sixteen pairs of mongrel dogs (10–15 kg body weight) were anesthetized with ketamine hydrochloride (5 mg/kg i.m.) followed by pentobarbital sodium (25 mg/kg i.v.). The larger dog of each pair was used as a metabolic supporter, and the smaller one was used as a heart donor. The cross-circulation tubes were cannulated into the common carotid arteries and right jugular vein of the support dog. Blood was heparinized in both dogs (500–750 U/kg i.v.). To prevent allergic hypotension, we gave diphenhydramine hydrochloride (30–60 mg i.m.) to the support dog. The heart donor dog was thoracotomized under artificial ventilation and its left brachiocephalic artery and right ventricle via the right atrium were cannulated with the other ends of the arterial and venous cross-circulation tubes. The descending aorta, superior and inferior venae cavae, azygos vein, and pulmonary hili were ligated in the heart donor dog, and the cross-circulation was started. The supported heart was excised from the chest.

We opened the left atrium of the excised heart and severed the chordae tendineae of the left ventricle (LV) to minimize the volume measurement error by the balloon method [12]. A 0.1 ml solution of 30% formalin was injected into the atrioventricular node to produce atrioventricular block and minimize unpaced beating rate [13]. A thin latex balloon with an unstressed volume of 50 ml was fitted in the LV cavity and connected to the custom-made volume servo pump [9–11, 14]. The balloon and the pump were primed with water. The volume servo

pump system enabled us to precisely control and accurately measure LV volume [9–11, 14]. LV pressure was measured with a Konigsberg P-7 pressure gauge placed inside the apical end of the balloon.

We paced the ventricle with a pair of electrodes screwed into the LV apex, except in two hearts with unsuccessful atrioventricular block and therefore paced atrially (#Ej2 and #Ej5 in Tables 1 and 2). LV surface ECG, which was detected by another pair of screw-in electrodes, was used to trigger the volume servo pump in synchrony with ventricular contraction and to count heart rate.

Arterial blood Pa_{O_2} , Pa_{CO_2} , and pH were measured (System IL-1303, Instrumentation Laboratory). Pa_{O_2} was kept > 100 mmHg by supplemental oxygen, Pa_{CO_2} 30–40 mmHg by changing ventilation frequency, and pH 7.28–7.45 by sodium bicarbonate. Temperature of the excised cross-circulated heart was kept at 35–37°C.

Oxygen consumption. We obtained myocardial oxygen consumption (MV_{O_2}) as the product of coronary flow and arteriovenous oxygen content difference (AVD_{O_2}). Coronary flow was measured with an electromagnetic flowmeter (MVF-2100, Nihon Kohden) by placing a 5 mm probe (FF-050T, Nihon Kohden) in the venous cross-circulation tube from the right ventricle. This tube hydrostatically drained total coronary venous blood except for a negligibly small thebesian coronary venous return into the LV [15]. The small amount of thebesian drainage was drained through small manifold tube stabbed into the LV apical dimple. This drainage made the latex balloon fit well the endocardium. Coronary AVD_{O_2} was continuously measured with an arteriovenous O_2 difference analyzer (A-VOX Systems, San Antonio, U.S.A.). The cuvettes of the A-VOX analyzer received parts of coronary arterial and venous blood (8–10 ml/min) [16]. The A-VOX analyzer was calibrated against a CO-oximeter (IL-282, Instrumentation Laboratory) in each experiment. MV_{O_2} was then calculated on-line using an NEC San-ei 7T18 signal processor (Tokyo) with a home-made software. MV_{O_2} was expressed in ml O_2 /min.

Data processing. ECG, LV volume, LV pressure, coronary flow, and AVD_{O_2} signals were on-line processed with the 7T18 signal processor to determine heart rate, stroke work, E_{max} (see below), PVA (see below), and MV_{O_2} . We stored the measured and calculated data on floppy diskettes and recorded the signals on a thermal printer. We continuously listed stroke work, peak systolic pressure and E_{max} values on a display.

E_{max} and pressure-volume area (PVA). Ventricular contractility was assessed by the end-systolic maximal elastance (E_{max}). E_{max} was obtained as the slope of the end-systolic pressure-volume line (ESPVL) of a steady-state contraction connecting the volume-axis intercept (V_0) of the ESPVL and the LV end-systolic pressure (P_{es})-volume (V_{es}) point [11, 14, 17, 18]. V_0 was determined directly as the LV volume at which P_{es} was zero in each experiment.

Ventricular mechanical energy was assessed by the systolic pressure-volume area (PVA). PVA was obtained as the area in the PV diagram that was

Table 1. Controlled cardiodynamic conditions.

DOG #	HR (beats/min)	Pes (mmHg)	SV (ml)	SW (mmHg·ml/beat)	PP (mmHg)	$E_{\max}$ range (mmHg/(ml/100 g))	$E_{\max}$ at control (mmHg/(ml/100 g))	Ped range (mmHg)
Ejection contraction								
Ej1 (Epi, Prop)	149	100.6±3.9 (3.9%)	4.8±0.3 (7.3%)	448±7 (1.7%)	78±12 (15.8%)	2.9-10.9	8.6	10.1-30.2
Ej2 (Epi, Prop)	120	71.1±3.8 (4.8%)	4.5±0.1 (5.9%)	334±5 (1.4%)	67±3 (4.1%)	6.6-14.5	6.6	-1.7-0.1
Ej3 (Epi, Prop)	149	77.5±2.7 (3.5%)	4.3±0.3 (7.2%)	326±10 (3.1%)	65±3 (4.7%)	4.0-11.4	11.4	2.7-17.9
Ej4 (Epi, Prop)	181	78.8±3.4 (4.4%)	4.0±0.6 (16.1%)	323±13 (4.1%)	84±3 (3.6%)	1.9-9.9	7.5	-0.8-38.2
Ej5 (Epi, Prop)	149	75.2±2.3 (3.0%)	3.3±0.1 (4.0%)	262±6 (2.3%)	74±4 (5.5%)	1.8-8.1	4.9	-5.1-6.7
Ej6 (Epi, Prop)	149	93.0±3.4 (3.6%)	3.2±0.6 (17.6%)	338±10 (2.9%)	73±7 (9.0%)	4.0-7.6	6.6	5.5-14.1
Ej7 (Epi, Prop)	158	79.1±1.7 (2.1%)	2.9±0.3 (9.7%)	341±9 (2.5%)	69±7 (10.1%)	3.2-9.1	7.5	-2.7-8.2
Ej7 (Ca, Ver)	158	77.9±2.2 (2.9%)	3.0±0.3 (8.7%)	344±7 (2.0%)	67±3 (4.5%)	3.4-6.7	7.5*	-1.4-5.8
Ej8 (Epi, Prop)	129	103.4±6.9 (6.7%)	5.1±0.3 (5.1%)	512±40 (7.8%)	66±3 (5.0%)	2.0-21.2	11.7	-1.7-34.2

Ej9	160	80.2±3.3 (4.2%)	7.1±0.5 (7.3%)	522±6 (1.2%)	87±5 (5.8%)	4.8-11.0	10.7	2.6-23.5
(Epi, Prop)								
Ej10	149	56.2±2.0 (3.6%)	5.5±0.3 (5.5%)	298±10 (3.2%)	63±5 (7.5%)	1.4-13.0	6.4	-0.9-15.3
(Epi, Prop)								
Isovolumic contraction								
Iso1	120	74.9±1.3 (1.8%)	0	0	68±4 (5.5%)	4.5-13.4	5.8	-1.5-5.7
(Epi, Prop)								
Iso2	140	101.5±1.3 (1.3%)	0	0	74±4 (5.5%)	9.5-28.1	9.5	-10.2--5.7
(Epi, Prop)								
Iso3	120	104.0±1.4 (1.3%)	0	0	69±4 (6.4%)	2.1-6.1	4.1	2.1-31.5
(Epi, Prop)								
Iso4	149	99.3±1.8 (1.8%)	0	0	65±3 (5.1%)	2.1-26.9	16.2	-9.4-36.1
(Epi, Prop)								
Iso5	139	101.4±1.7 (1.7%)	0	0	82±2 (2.4%)	2.2-30.0	12.7	-18.6-29.8
(Epi, Prop)								
Iso6	149	104.1±1.2 (1.1%)	0	0	89±7 (7.8%)	3.1-15.6	12.6	-5.3-22.6
(Epi, Prop)								

Numerical data are expressed as mean±SD. Numerical data in parentheses are percent coefficients of variance (SD/mean×100 (%)). HR, heart rate; Pes, end-systolic pressure; SV, stroke volume; SW, stroke work; PP, perfusion pressure as mean arterial pressure; Ped, end-diastolic pressure; Epi, epinephrine; Prop, propranolol; Ca, calcium chloride; Ver, verapamil. * E_{max} at control in Ej7 (Ca, Ver) is the same as Ej7 (Epi, Prop).

Table 2. Nonlinear fitting curves for MV_{O_2} per minute- $\dot{E}_{max}$ relationships.

DOG #	Empirical and best-fitted						Theoretically predicted							
	p	q	r	Sig of $r \cdot \dot{E}_{\max}^{-1}$	Nadir MV_{O_2}	Optim $\dot{E}_{\max}$	A	B	C	p'	q'	r'	Nadir MV_{O_2}	Optim $\dot{E}_{\max}$
Ejection contraction														
Ej1 (Epi, Prop)	0.18	13.40	-0.54	NS	—	—	—	—	—	0.36	3.45	14.33	7.98	6.33
Ej2 (Epi, Prop)	0.23	3.48	-0.62	NS	—	—	—	—	—	0.29	2.41	5.76	4.99	4.47
Ej3 (Epi, Prop)	0.77	-2.91	10.82	$p < 0.01$	2.87	3.74	2.4	5.1	-2.7	0.36	3.03	8.50	6.52	4.88
Ej4 (Epi, Prop)	0.53	6.97	-0.73	$p < 0.05$	—	—	—	—	—	0.43	3.62	10.68	7.93	4.96
Ej5 (Epi, Prop)	0.42	4.36	1.25	NS	5.82	1.72	0.3	2.8	2.9	0.36	2.79	8.01	6.17	4.73
Ej6 (Epi, Prop)	6.64	-45.92	125.91	$p < 0.05$	11.89	4.36	20	44.5	-36.6	0.36	2.93	12.2	7.11	5.85
Ej7 (Epi, Prop)	1.42	-2.59	12.37	NS	5.80	2.95	2.5	90	-2.2	0.38	2.90	9.39	6.67	4.98
Ej7 (Ca, Ver)	2.01	-7.06	21.18	$p < 0.01$	6.00	3.24	4.4	12.7	-5.5	0.38	2.91	9.11	6.63	4.90
Ej8 (Epi, Prop)	0.051	7.63	-0.55	NS	—	—	—	—	—	0.31	3.10	13.10	7.13	6.51
Ej9 (Epi, Prop)	0.47	1.81	15.07	NS	7.15	5.64	2.9	2.9	-0.5	0.38	3.97	9.78	7.85	5.05
Ej10 (Epi, Prop)	0.32	5.65	-1.97	$p < 0.01$	—	—	—	—	—	0.36	2.96	4.47	5.49	3.54
Mean $\pm$ SD	1.19	-1.33	16.56											
	± 1.90	± 15.88	± 37.13											

circumscribed by the ESPVL, end-diastolic PV curve and systolic PV trajectory [11, 19, 20]. We have shown that PVA closely correlates with MV_{O_2} in a stable contractile state and that a change in $E_{\max}$ shifts the MV_{O_2} -PVA relation in a parallel manner [9, 11, 14, 19, 21].

Theoretical background for MV_{O_2} - $E_{\max}$ relation. Based on our previous studies [8, 11, 14, 20], we have obtained a theoretical MV_{O_2} - $E_{\max}$ relation for constant cardiac work as shown in APPENDIX. The theoretical relation predicts that MV_{O_2} will be minimized for a given work within the physiological range of $E_{\max}$ [7, 8].

Protocol. Ejecting run: In 10 hearts, we studied the MV_{O_2} - $E_{\max}$ relation in ejecting contractions. At a mid-range end-diastolic volume, we specified heart rate, end-systolic pressure, and stroke work to obtain control data in steady state. We then increased $E_{\max}$ by gradually increasing the infusion rate of epinephrine (0.1–10 $\mu\text{g}/\text{min}$ into coronary artery) while keeping the same end-systolic pressure and stroke work by appropriately decreasing end-diastolic volume. When stroke work increased due to decreases in end-diastolic pressure as $E_{\max}$ increased, we appropriately decreased stroke volume by decreasing end-diastolic volume to keep stroke work as constant as possible. Otherwise, stroke work would have increased as $E_{\max}$ increased and end-diastolic pressure decreased.

Next, we stopped epinephrine infusion and gradually increased the infusion rate of propranolol (1–120 $\mu\text{g}/\text{min}$ into coronary artery) to decrease $E_{\max}$. We appropriately increased end-diastolic volume so as to keep the same end-systolic pressure and stroke work. In one heart (DOG#Ej7), calcium chloride (4.2×10^{-5} – 1.3×10^{-3} mEq/min, into coronary artery) and verapamil (4.1×10^{-3} – 3.3×10^{-2} mg/min, into coronary artery) were used to change $E_{\max}$ after epinephrine and propranolol. A representative set of PV loops in the ejecting run is shown in Fig. 1A.

Isovolumic run: In additional 6 hearts, we studied the MV_{O_2} - $E_{\max}$ relation in isovolumic contractions. We added this run because our previous report suggested that contractions with a smaller stroke volume could more easily manifest $E_{\max}$ for minimal MV_{O_2} within the physiological $E_{\max}$ range [8]. After obtaining control data at a mid-range end-diastolic volume, we increased and decreased $E_{\max}$ with epinephrine and propranolol, respectively, in the same way as in the ejecting run while keeping the same end-systolic pressure by adjusting isovolumic ventricular volume. A representative set of PV trajectories in this run is shown in Fig. 1B.

Data analysis and statistics. Cardiodynamic data were expressed as mean $\pm$ SD. Percent coefficients of variation ($100 \times \text{SD}/\text{mean}$) were also obtained. We used these data to evaluate the constancy of cardiodynamic conditions. All MV_{O_2} , PVA, and $E_{\max}$ values were normalized for 100 g LV.

MV_{O_2} - $E_{\max}$ data in each heart were fitted by both linear regression ($MV_{O_2} = p \cdot E_{\max} + q$) and nonlinear regression ($MV_{O_2} = p \cdot E_{\max} + q + r \cdot E_{\max}^{-1}$; Eq. (A6) in APPENDIX) using the least square method [7, 22].

Statistical significance was given for $p < 0.05$. Significance of the nonlinear

Fig. 1. Representative pressure-volume loops with a constant stroke work. A: Ejection contractions. B: Isovolumic contractions (stroke work=0). Arrows indicate directions of changes in contractility, E_{max} .

term ($r \cdot E_{max}^{-1}$) in the nonlinear regression equation was tested by analysis of variance [7,22].

RESULTS

Cardiodynamics

Representative ejecting PV loops in one heart are shown in Fig. 1A. E_{max} was changed widely with constant heart rate, end-systolic pressure, and stroke work. Stroke volume was gradually increased with decreases in E_{max} and increases in end-diastolic pressure. Representative isovolumic PV trajectories are also shown in Fig. 1B. E_{max} was widely changed while heart rate and end-systolic pressure were kept constant.

Cardiodynamic parameters in both ejecting and isovolumic runs in all hearts

are summarized in Table 1. Small percent coefficients of variation show that end-systolic pressure was kept reasonably constant in each experiment. Stroke volume was slightly varied because we adjusted it to keep stroke work constant at a constant end-systolic pressure. Since heart rate was constant, constant stroke work means constant minute work throughout this study.

Coronary perfusion pressure which was equal to the mean aortic pressure of the support dog was also reasonably constant and no myocardial ischemia was suspected [23] in each experiment (Table 1).

Fig. 2. Linear fitting of MV_{O_2} - $E_{\max}$ data in ejecting contractions. n , number of data points; r , correlation coefficient; p , significance level. Equations show linear regression equations.

MV_{O₂}-E_{max} relation

Ejecting run. Figure 2 shows that MV_{O₂} linearly and positively correlated with E_{max} in ejecting contraction in all the 10 dogs. #Ej7 and #Ej7C were obtained in one heart: the former with epinephrine and propranolol and the latter with calcium and verapamil. Correlation coefficients were above 0.940 except in two hearts with 0.846 and 0.722. All these coefficients were significant. Their mean correlation coefficient after z-transformation was 0.953. Mean slope and intercept were 0.658 ± 0.718 (ml O₂·mmHg⁻¹·ml·100 g LV⁻²·min⁻¹) and 4.65 ± 3.74 (ml O₂·100 g LV⁻¹·min⁻¹), respectively.

Fig. 3. Curvilinear fitting of MV_{O₂}-E_{max} data in ejecting contractions. Fitting equations and the statistical significance of the nonlinear terms are listed in Table 2.

Table 3. Cardiodynamic parameters at minimal MV_{O_2} .

DOG #	$E_{\max}$ (mmHg/(ml/100 g))	mCP (mmHg)	Pes (mmHg)	CO (l/min)	EW (mmHg·ml/100 g/min)	min MV_{O_2} (ml O_2 /100 g/min)	Eff (%)	Ped (mmHg)
Ejection contraction								
Ej1 (Epi, Prop)	2.9	58	98.2	0.79	150713	13.79	7.3	30.2
Ej2 (Epi, Prop)	7.2	64	75.0	0.54	61735	4.86	8.4	0.1
Ej3 (Epi, Prop)	4.0	63	79.1	0.73	64366	2.96	14.5	17.9
Ej4 (Epi, Prop)	2.0	83	76.9	0.85	89358	7.50	7.9	16.8
Ej5 (Epi, Prop)	2.3	71	74.5	0.49	69783	5.72	8.1	0.9
Ej6 (Epi, Prop)	4.5	60	90.9	0.57	84938	11.05	5.1	14.1
Ej7 (Epi, Prop)	3.2	68	79.3	0.52	100768	5.64	11.9	8.2
Ej7 (Ca, Ver)	3.4	66	81.8	0.44	96406	5.92	10.8	5.5
Ej8 (Epi, Prop)	2.0	69	106.1	0.72	91798	6.77	9.0	34.2
Ej9 (Epi, Prop)	4.8	81	81.8	1.28	95346	6.84	9.2	23.5
Ej10 (Epi, Prop)	1.4	54	54.8	0.98	74375	4.92	10.1	15.3
Isovolumic contraction								
Iso1 (Epi, Prop)	4.5	68	75.0	0	0	3.29	0	7.4
Iso2 (Epi, Prop)	11.1	71	101.3	0	0	6.08	0	-7.3
Iso3 (Epi, Prop)	2.1	67	104.0	0	0	5.93	0	31.5
Iso4 (Epi, Prop)	2.1	71	100.2	0	0	4.36	0	36.1
Iso5 (Epi, Prop)	2.2	80	100.0	0	0	5.24	0	29.8
Iso6 (Epi, Prop)	3.1	78	104.5	0	0	4.28	0	22.6

DOG #, dog number from Ej1 to Ej10 and Iso1 to Iso6; mCP, mean coronary perfusion pressure as mean aortic pressure; CO, cardiac output; min MV_{O_2} , minimum myocardial oxygen consumption; Eff, efficiency from MV_{O_2} to external work; Ped, end-diastolic pressure.

Figure 3 shows that $MV_{O_2}-E_{max}$ data were also reasonably fitted by the nonlinear regression curve (Eq. (A6) in APPENDIX). Five hearts showed downward convexity as expected whereas five others showed upward convexity unexpectedly. The downward convex curves show that all the data points fell on the nadir and ascending limb of the curves; no data points fell on the descending limb of the curve.

Table 2 shows nonlinear regression coefficients (p , q , and r). The nonlinear term ($r \cdot E_{max}^{-1}$) was significant in five hearts, which showed either downward or upward convex curves in Fig. 3. The $MV_{O_2}-E_{max}$ curves in only three hearts (#Ej3, Ej6, and Ej7C) were downward convex and their nonlinear terms were statistically significant. Table 3 lists cardiodynamic data at minimal MV_{O_2} in all the ten hearts.

Isovolumic run. Figure 4 shows similar $MV_{O_2}-E_{max}$ relations in isovolumic contractions. All the six hearts showed linear correlation between MV_{O_2} and E_{max} in the same way as in ejecting runs. Mean correlation coefficient after z-transformation was 0.948. Mean slope and intercept were 0.849 ± 0.525 (ml O₂ · mmHg⁻¹ · ml · 100 g LV⁻² · min⁻¹) and 4.23 ± 1.74 (ml O₂ · 100 g LV⁻¹ · min⁻¹), respectively.

Figure 5 shows that five of the six hearts had upward convex curves unexpectedly. Only one heart (#Iso2) had a downward convex curve but the minimal MV_{O_2} did not fall on the nadir of the curve.

Fig. 4. Linear fitting of $MV_{O_2}-E_{max}$ data in isovolumic contractions. n , number of data points; r , correlation coefficient; p , significance level. Equations show linear regression equations.

Fig. 5. Curvilinear fitting of MV_{O_2} - E_{max} data in isovolumic contractions. Fitting equations and the statistical significance of the nonlinear terms are listed in Table 2.

Table 2 shows nonlinear regression coefficients. The nonlinear term of the downward convexity in heart #Iso2 was not statistically significant. Table 3 lists cardiodynamic data at minimal MV_{O_2} in all the six hearts.

PVA- E_{max} relation

Figure 6 shows that PVA steeply increased with decreases in E_{max} under a condition of constant external work in ejecting contractions in each heart. This increase in PVA with a decrease in E_{max} was due to the increase in the elastic potential energy fraction of PVA because the stroke work fraction of PVA was kept constant. Figure 7 shows similar PVA- E_{max} relations in isovolumic contractions, in which any changes in PVA mean corresponding changes in the elastic potential energy because of no external work.

DISCUSSION

The present results have shown that MV_{O_2} for a given cardiac work is minimal at or near the lowest working contractility in normal dog hearts. Our previous theoretical analysis has suggested existence of a minimal MV_{O_2} at a nadir of a downward convex MV_{O_2} - E_{max} relation within a normal contractility range [5, 8]. However, the present study has proved that the theoretically predicted existence

Fig. 6. PVA- $E_{\max}$ relations in ejecting contraction hearts. Under the experimental conditions as constant external work, the total mechanical energy (PVA) increased with decreases in $E_{\max}$ in all excised hearts.

does not hold as such in the cross-circulated excised normal dog hearts.

The present finding is similar to our previous result on the right-heart-bypassed dog heart preparation [7]. In the previous study, we could not decrease $E_{\max}$ to the extent that end-diastolic pressure stably rose above 14 mmHg because any higher end-diastolic pressure was accompanied by acute pulmonary edema. To circumvent the problem of pulmonary edema, we used in this study the excised supported heart preparation and could raise left ventricular end-diastolic pressure above 15 mmHg in ten hearts and above 30 mmHg in five hearts. Although this heart preparation has allowed downward convex $\dot{M}V_{O_2}$ - $E_{\max}$ curves in a slightly greater

Fig. 7. PVA- $E_{\max}$ relations in isovolumic contraction hearts. Under the experimental conditions as constant external work, the total mechanical energy (PVA) increased with decreases in $E_{\max}$ in all excised hearts. In isovolumic contracting hearts, the increase in PVA strictly means the increase in "potential energy."

number (4 hearts) of hearts than before, minimal MV_{O_2} for a given cardiac work did not yet appear as an explicit nadir of a downward convex curve against our expectation. Therefore, we would conclude that normal dog hearts have minimal MV_{O_2} at or near the lowest working contractility, not as a nadir at a middle working contractility.

The obtained MV_{O_2} - $E_{\max}$ curves are always increasing functions of $E_{\max}$ as seen in Fig. 2-5 whereas the PVA- $E_{\max}$ curves are always decreasing functions of $E_{\max}$ as seen in Figs. 6 and 7. Since PVA is the primary determinant of the mechanical fraction of MV_{O_2} ($HR \cdot A \cdot PVA$ in APPENDIX), the present result indicates that the increasing MV_{O_2} with $E_{\max}$ is primarily determined by the non-mechanical fraction of MV_{O_2} ($HR \cdot (B \cdot E_{\max} + C)$ in APPENDIX) which increases with $E_{\max}$.

Let us speculate about why we could not see a minimal MV_{O_2} at a nadir of a downward convex MV_{O_2} - $E_{\max}$ curve. One possibility would be that our theoretical MV_{O_2} - $E_{\max}$ relation is not capable of predicting actual MV_{O_2} in an extremely low $E_{\max}$ range. In fact, we have not experimentally confirmed constancy of A , B , and C values (see APPENDIX) at high end-diastolic pressures in the extremely low $E_{\max}$ range as covered in the present study [7, 11, 14, 20]. If A , B , and C changed in an extremely low $E_{\max}$ range, the experimental result may deviate from the theoretical prediction.

Figure 8 suggests this possibility. We first divided MV_{O₂} into mechanical and non-mechanical fractions. The former is $HR \cdot A \cdot PVA$ and the latter is $HR \cdot (B \cdot E_{\max} + C)$ in Eq. (A1) in APPENDIX. According to our previous studies [11, 14, 20, 24], coefficient A is a constant with a mean value of 1.9×10^{-5} ml O₂/(mmHg·ml). Using this A value, the mechanical fraction of MV_{O₂} is calculated to be 1.9×10^{-5} .

Fig. 8. MV_{O_2} and its mechanical and non-mechanical fractions plotted against $E_{\max}$ in representative ejecting and isovolumic contracting hearts. A (Ej10): Coefficient A is assumed to be constant (1.9×10^{-5} ml O₂/(mmHg·ml)). MV_{O_2} (○) is measured value. Mechanical fraction of MV_{O_2} (Mech; ×) is obtained by $A \cdot PVA \cdot HR$. Non-mechanical fraction (Non-mech; +) is obtained as [measured MV_{O_2} (○) - $A \cdot PVA \cdot HR$ (×)]. As the non-mechanical fraction is not a linear function of $E_{\max}$, coefficient B may not be constant in extremely low $E_{\max}$ ranges. B (Ej10): Coefficient B is assumed to be constant as well as coefficient A even in extremely low $E_{\max}$ range. Mechanical fraction (×) is transcription from panel A. Non-mechanical fractions (+) is assumed a completely linear function of $E_{\max}$ as the extrapolation of the linear portions ($E_{\max} > 8$ in #Ej10) in panel A. The MV_{O_2} (○) is not measured value but obtained as the sum of the mechanical (× in Panel B) and non-mechanical fractions (+ in panel B). Under these assumptions, MV_{O_2} - $E_{\max}$ relation (○) have a nadir. C (Iso4): This panel is obtained as panel A in Iso4 heart. D: This panel is obtained as panel B in Iso4 heart. The linear non-mechanical fraction (+) is the extrapolation of the linear portion ($E_{\max} > 10$ in #Iso4) in panel C. The MV_{O_2} - $E_{\max}$ relation (○) obviously has a nadir.

HR·PVA and the non-mechanical fraction to be $[MV_{O_2} - 1.9 \times 10^{-5} \cdot \text{HR} \cdot \text{PVA}]$. Figure 8A and C show examples of this result in two hearts (#Ej10 and #Iso4) which have shown upward convex MV_{O_2} - $E_{\max}$ curves in Fig. 3 and 5. The resultant non-mechanical fraction of MV_{O_2} decreases nonlinearly in a low $E_{\max}$ range in these hearts. This may mean that coefficient B was not constant and did increase as $E_{\max}$ decreased. Since B means the oxygen cost of $E_{\max}$ and reflects the amount of total calcium ions handled in the excitation-contraction coupling [8, 20], the decrease in B suggests a disproportionately more suppressed calcium handling in a lower $E_{\max}$ range.

If we assume that B is constant over the entire $E_{\max}$ range as in our previous theoretical study [8], MV_{O_2} estimated as the sum of the mechanical and non-mechanical fractions would show a nadir in either ejecting and isovolumic contractions as seen in Fig. 8B and D. Similar differences between the reality and the theory were seen in all the other cases. This difference suggests that our theory [8] based on physiological studies cannot always be linearly extrapolated to the extremely low contractility. This phenomenon may also be related to the fact that it was not always easy to obtain stable contractions at a very low $E_{\max}$.

A minimal MV_{O_2} for a constant cardiac work has not always been seen as a nadir of an MV_{O_2} -contractility curve even in previous studies [1, 4, 7]. Sarnoff *et al.* [4] used an isolated supported heart preparation similar to our present one. They first raised left ventricular end-diastolic pressure to 24 ± 9 mmHg. Of these 15 cases, 6 cases showed slight decreases in MV_{O_2} for a constant cardiac work with increase in contractility by epinephrine. Covell *et al.* [1] used *in situ* dog hearts and observed only 2 cases which showed a decrease in MV_{O_2} for a constant cardiac work with an increase in contractility by acetylcholine. Covell *et al.* [1] could not find any decrease in MV_{O_2} for a constant cardiac work with increases in contractility when the initial end-diastolic pressure was below 8 mmHg. The range of left ventricular end-diastolic pressure where minimal MV_{O_2} was observed in these previous studies correspond to the range covered in the present study.

In relation to this aspect, our previous theoretical study [8] has shown that the MV_{O_2} - $E_{\max}$ curve tends to show a nadir more easily in the middle of the normal working $E_{\max}$ range as ventricular end-diastolic compliance increases (F value in Eq. (A2) in APPENDIX). Since a chronically failing ventricle has a greater end-diastolic compliance than an acutely failing heart, our failure in finding a nadir MV_{O_2} may be due to the normal end-diastolic compliance in acute failing hearts. Testing of the nadir MV_{O_2} hypothesis in chronic failing hearts seems needed.

Although we could have fitted a more complex nonlinear regression equation (Eq. (A4) in APPENDIX) to the MV_{O_2} - $E_{\max}$ data, the departure of the data from linear regression was not always significant and was practically negligible. Therefore, our simple nonlinear equation (Eq. (A6) in APPENDIX) may not be the cause of no detection of minimal MV_{O_2} as a nadir of a downward convex MV_{O_2} - $E_{\max}$ curve.

Another possibility is the following. If the curvilinearity of ESPVL is exaggerated as we changed myocardial contractility over a wide range, the result of

the previous theoretical prediction may be affected. Burkhoff *et al.* [25] have expressed the ESPVL as

$$Pes = a \cdot Ves^2 + b \cdot Ves + c$$

where Ves is end-systolic volume; a , b , and c are parameters. Then, ventricular contractile state can be assessed by the slope $E'_{\max}$ of the ESPVL in a low-volume range. From the above equation [25],

$$E'_{\max} = (b^2 - 4ac)^{1/2}.$$

Using $E'_{\max}$ instead of $E_{\max}$, the theoretically predicted MV_{O_2} may be underestimated by the underestimated contractility [25] and PVA [26] when the contractility was enhanced. On the other hand, when the contractility was depressed, the theoretically predicted MV_{O_2} may be overestimated by the overestimated contractility and PVA. As the result, the theoretical MV_{O_2} - $E_{\max}$ relation tends to hide the nadir point from us.

In conclusion, we studied the MV_{O_2} - $E_{\max}$ relationship for a constant external work in excised cross-circulated normal dog hearts in acute experiments. The MV_{O_2} - $E_{\max}$ relation was always monotonically increasing over almost the entire working $E_{\max}$ range, and the minimal MV_{O_2} did not appear as a nadir although $E_{\max}$ was considerably decreased. The minimal MV_{O_2} for a constant external work seems to occur at the lowest working contractility in normal dog hearts.

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APPENDIX

We considered the theoretical MV_{O₂}-E_{max} relationship at a constant external work of the heart. The general relation among MV_{O₂}, PVA, and E_{max} is given by

$$MV_{O_2} = HR \cdot (A \cdot PVA + B \cdot E_{max} + C), \quad (A1)$$

where HR is heart rate, *A* and *B* are coefficients and *C* is constant [14, 24]. HR · *A* · PVA is the mechanical fraction of MV_{O₂}. HR · (*B* · E_{max} + *C*) is the non-mechanical fraction of MV_{O₂}.

We have shown that the end-diastolic PV curve is reasonably approximated by [8, 24]

$$Ped = F \cdot (Ved - V_o)^3, \quad (A2)$$

where *Ped*, end-diastolic pressure; *Ved*, end-diastolic volume; *F*, coefficient; *V_o*, volume-axis intercept of end-diastolic PV curve.

PVA can then be expressed as [8, 24]

$$PVA = (1/2) \cdot Pes^2/E_{max} + SV \cdot Pes - (F/4) \cdot (Ved - V_o)^4, \quad (A3)$$

where SV, stroke volume; *Pes*, end-systolic pressure, which was assumed to be nearly equal to mean ejection pressure.

Substituting *Ved* = *Ves* + SV and *Ves* = *Pes*/E_{max} + *V_o* into Eq. (A3) yields

$$PVA = (1/2) \cdot Pes^2/E_{max} + SV \cdot Pes - (F/4) \cdot \{(Pes/E_{max}) + SV\}^4. \quad (A4)$$

When we neglect the third term of the right side of Eq. (A4), it reduces to

$$PVA = (1/2) \cdot Pes^2/E_{max} + SV \cdot Pes. \quad (A5)$$

Substituting Eq. A5 to Eq. A1 yields

$$MV_{O_2} \text{ per min} = p \cdot E_{max} + q + r \cdot E_{max}^{-1}, \quad (A6)$$

where *p* = *B* · HR (>0); *q* = (*A* · *Pes* · SV + *C*) · HR (>0); and *r* = (1/2) · *A* · *Pes*² · HR (>0).

Equation (A6) was used as a nonlinear regression curve for MV_{O₂}-E_{max} data in this study as well as in our previous study [7]. Equation (A6) is approximately linear in a higher E_{max} range and becomes hyperbolic in a lower E_{max} range.

When considerably high end-diastolic pressures are dealt with as in this study, more nonlinear terms in Eq. (A4), namely, -(*F*/4) · {(*Pes*/E_{max}) + SV}⁴ had better be included. However, we used Eq. (A5) rather than Eq. (A4) because the

deviation of the data points from linear regression was negligibly small.

The PVA- $E_{\max}$ relation under constant P_{es} and SV condition can be predicted by Eq. (A4) or (A5) as functions of $E_{\max}$, namely, PVA decreases nearly hyperbolically in a wide $E_{\max}$ range.