Coronary Flow and Myocardial Oxygen Metabolism in the Newborn Lamb

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Analysis of factors which may influence oxygen metabolism of the heart has received much attention since the early part of this century (1). Quantitative measurements of coronary blood flow and myocardial oxygen consumption (MVO₂) have been accumulated from both human and animal studies (2, 3). These studies were uniformly concerned with adults, however, and virtually no information is available from newborn or young mammals. This may, in part, be related to difficulties in measuring coronary flow by conventional techniques and to problems in collecting representative coronary venous samples from hearts of newborns.

Recently an approach has been developed in our laboratory using the newborn lamb which has yielded consistent and reproducible data. It is based on the particular anatomical arrangement in this species in which the hemiazygous vein drains into the coronary sinus (4). It has permitted us to design a system involving cannulation of the sinus through this tributary. Blood flow measurements and collection of coronary sinus samples for study of oxygen consumption and substrate metabolism could be readily achieved by this approach. The purpose of the present study was to investigate the relative influence of individual hemodynamic factors on those measurements. A preliminary report on these findings has appeared (5).

METHODS

Seventeen newborn Dorset lambs of both sexes varying in age from 5 hr to 5 days, in weight from 2.9 to 6.0 kg were used in this study. Each lamb was anesthetized with sodium pentobarbital (20 mg/kg, iv). The trachea was exposed and intubated. The chest was opened in the midline and ventilation was maintained with a Harvard constant-volume, positive-pressure pump.

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The ductus arteriosus was ligated with umbilical tape. The brachiocephalic artery was ligated to abolish cephalic blood flow and eliminate reflex factors. The internal mammary vessels were also ligated and transected. Heparin (1000 units) was given intravenously to prevent clotting in the recording catheters and extracorporeal system. The descending thoracic aorta was cannulated, and systemic blood flow (cardiac output—coronary blood flow) was measured with a Statham 6.0-mm o.d. extracorporeal flow transducer and a Medicon K-2000 electromagnetic flowmeter. The flow transducer was calibrated in vitro with saline. Calibration curves were found to be linear for the entire flow range used. Zero flow was frequently checked during the experiment by switching the instrument to "base-line" position. This compared closely with mechanical zero obtained by cross-clamping the aorta at the end of the experiment. The systemic flow was passed through a Sarns heat exchanger to the descending aorta. Blood flow could be varied over a broad range by varying the speed of the Sarns roller pump in the extracorporeal circuit. An adjustable constant-pressure blood reservoir was employed in the extracorporeal circuit to control mean aortic pressure (Fig. 1).

Pressures were measured with Sanborn 267 AC (aorta) or 267 B (left ventricle) transducers filled with freshly boiled saline. The midlevel of the heart was used as the zero reference. Full left-ventricular pressure contours as well as an amplified left ventricular end-diastolic pressure trace were recorded.

Heparinized maternal donor blood (5 mg/100 ml) was used for the reservoir, heat exchanger, and extracorporeal tubing. Blood temperature was maintained at 38 ± 1°C with the heat-exchange system (Fig. 1) and continuously monitored with a Yellow Springs probe and telemeter. Arterial pH, PO₂, and PCO₂ were continuously monitored with a Jewett flowthrough electrode assembly (Fig. 1) using three Beckman 160 physiological gas analyzers, and frequently checked with an Instrumentation Laboratories blood-gas analyzer and pH system. During the experiment arterial PO₂ and pH were kept within normal limits by the addition of oxygen or NaHCO₃ if necessary.

Heart rate was controlled by pacing the left atrium with a Grass SD-5 stimulator and recorded with a Sanborn cardiograph triggered by the ventricular pressure wave. The pressures, systemic blood flow, heart rate, and ventricular dP/dt were recorded simultaneously on a multichannel oscillograph (Sanborn model 358) at a chart speed of 0.25 or 100 mm/sec. This preparation permitted the independent control of cardiac output, aortic pressure, and heart rate.

Coronary blood flow was measured by retrograde cannulation of the coronary sinus through the hemiazygous vein with a polyethylene catheter (PE 205). The coronary sinus was then closed by stitch ligation 1–2 mm from its orifice in the right atrium. Flow from the cannulated coronary sinus was diverted through Tygon tubing (⅛ in. i.d.) to the external jugular vein. A T connector was placed in the tubing to permit temporary diversion of coronary sinus flow into a graduated cylinder for timed collections for flow measurements (Fig. 1). The tip of the drainage tube was 8 cm below the level of the coronary sinus. This source was also used for sampling sinus blood.

Simultaneous samples of arterial and coronary venous blood were withdrawn from the aorta and coronary sinus for determinations of oxygen content by the method of Roughton and Scholander (6), pyruvate concentration (7), pH, PO₂, PCO₂, and hematocrit. Myocardial oxygen consumption (MVO₂) was calculated as the product of coronary sinus flow and coronary arteriovenous oxygen difference.
Fig. 1. Preparation for control and measurement of left ventricular performance and measurement of coronary sinus (great cardiac vein) blood flow. Brachiocephalic artery and ductus arteriosus ligated. Coronary sinus closed by stitch ligation 1 mm proximal to right atrial (RA) orifice. Inset shows posterior view of lamb heart with principal veins and cannula in place.
and expressed as milliliters per minute per 100 grams of left ventricle (wet weight). The coefficient of myocardial oxygen extraction (A–V/A), and pyruvate utilization (A–V × coronary sinus flow) and extraction (A–V/A) were also calculated. Cardiac output was obtained by summing systemic blood flow and coronary sinus flow. Left-ventricular minute and stroke work were calculated in kilograms-M/min and grams-M, respectively. Myocardial efficiency was computed as the ratio of left ventricular minute work and myocardial oxygen consumption per minute and expressed as percent. The “true” arteriovenous pressure gradient was not determined, since the coronary sinus was opened to atmospheric pressure during the flow measurement. Therefore, coronary resistance was estimated as the ratio of mean aortic pressure (mm Hg) and coronary sinus flow (ml/min) and was expressed in terms of peripheral resistance units (PRU).

At the termination of each experiment the sinus was checked for leaks and the hearts were excised, cleaned, and dissected. All portions of the heart were weighed separately. The maximum horizontal and vertical dimensions of the left ventricular cavity were measured. A prolate spheroid model was used for calculating left-ventricular volume from these measurements (8). Myocardial wall tension was estimated from the formulations of Rodbard and associates (9,10).

In three animals both the left and right coronary arteries were cannulated postmortem with PE 240 tubing and attached to the calibrated pressure reservoir. Fourteen simultaneous determinations were made of either right or left coronary artery inflow and sinus outflow. A constant fraction of 65–70% of left coronary flow was recovered from the sinus in each animal. None of the right coronary flow entered the sinus but passed into the right atrium through separate ostia (11).

The distribution of coronary venous drainage into the cannulated coronary sinus was assessed by retrograde injection of monastral blue gelation mass with barperse2 immediately postmorten in four lambs. The injection pressure was 40 mm Hg. When the mass had “set” (30–45 min) the chambers walls were dissected and weighed. Those portions containing blue pigment were identified, further dissected, and weighed. This approach indicated that 85 (%1.5 SE)% of the cardiac mass which contained injected vessels was from the left ventricle and septum, 8% from the left atrium, 7% from the right ventricular free wall, and none from the right atrium. Thus, 93% of the postcapillary vessels in communication with the coronary sinus were located in the left heart mass.

For statistical evaluation of the results, the means, standard errors of the mean, Student’s t, correlation coefficients, linear regression, and the significance of the difference between regression coefficients were calculated according to standard methods (12). The differences were considered significant when the P value was less than 5%.

RESULTS

Effects of Changing Aortic Pressure on Coronary Flow and Resistance

In all experiments increasing aortic pressure was associated with an increase of coronary sinus flow. As shown in the left panel of Fig. 2, this was a nearly linear relationship for most animals. The calculated linear regression line is shown and the correlation coefficient of 0.81 is highly significant (P < 0.001).

Evidence for autoregulation in the coronary vascular bed was not obtained in

* Kindly supplied by Dr. Charles B. Carrington.
FIG. 2. Left panel. Relationship between coronary sinus flow and aortic pressure in 10 lambs. Calculated regression line is shown and regression data are indicated. Most individual lambs show a nearly straight line relationship in the steady state. This impression is confirmed by the correlation coefficient (0.81). Right panel. Mean values for coronary resistance (mm Hg/ml/min) and aortic pressure. Horizontal and vertical brackets indicate standard errors of the respective measurements. Coronary resistance is significantly higher at the higher aortic pressures.

this group because flow was not continuously measured. However, coronary resistance was calculated as the ratio of aortic pressure to coronary flow for three pressure ranges as illustrated in the right panel of Fig. 2. Resistance was significantly higher at a mean aortic pressure of 105 (range 85–125) mm Hg than when the mean aortic pressure averaged 38 (range 30–50) mm Hg.

Relative Influence of Aortic Pressure and Cardiac Output on Myocardial Oxygen Metabolism

The effects of independently varying aortic pressure (pressure run) while cardiac output was held constant or varying cardiac output (flow run) while aortic pressure was held constant were examined while the heart rate was controlled by electrical pacing. Figure 3 illustrates an experiment with a 5-day-old lamb. The left portion shows data from the pressure run and the right portion data obtained shortly thereafter during the flow run. In the former, cardiac output was held nearly constant at approximately 400 ml/min and aortic pressure was increased incrementally from 35 to 75 to 100 mm Hg. This was associated with an increase of coronary sinus flow and a progressive reduction in myocardial oxygen extraction coefficient. Oxygen consumption increased from 5.04 to 6.29 to 6.66 ml/min/100 g LV.

The above findings may be compared with those resulting from increasing the flow load. With aortic pressure held constant at 75 mm Hg (Fig. 3, right panel) increasing the cardiac output from 300 to 600 to 900 ml/min produced a smaller increase of coronary sinus flow. But oxygen extraction increased progressively in
Fig. 3. Influence of changing aortic pressure (pressure run, left panel) and cardiac output (flow run, right panel) in a 5-day-old lamb on coronary flow and myocardial oxygen metabolism. Heart rate held constant at 222 beats per minute by electrical pacing. Increasing aortic pressure with cardiac output held constant was characterized by an increase of coronary sinus flow, reduced oxygen extraction, and increased MVO₂. Increasing cardiac output with aortic pressure held constant produced a smaller increase of coronary flow, increased oxygen extraction, and increased oxygen consumption.

contrast with the decrease observed with the pressure run. Hence, oxygen consumption of the myocardium increased substantially from 6.69 to 8.20 to 10.34 ml/min/100 g LV.

The data from individual experiments showing the effects of changing aortic pressure on coronary flow and myocardial oxygen extraction and utilization are presented in Table 1. Similar data showing the responses to changing cardiac output while mean aortic pressure and heart rate were constant are shown in Table 2. It is evident that changes in either hemodynamic variable were uniformly associated with directionally similar changes in MVO₂. The increased O₂ demands with increasing aortic pressure were met primarily by increments of coronary flow, and oxygen extraction diminished in most experiments (Table 1). On the other hand, the increased myocardial oxygen requirements associated with increasing cardiac output were met either by increasing coronary flow or oxygen extraction, or a combination of these factors (Table 2).

The oxygen cost of changing calculated left ventricular external work by independently varying either the afterload or preload are illustrated in Fig. 4. The expected scatter for individual animals is evident in the upper panel. The data suggest
TABLE 1

| Age | AP (mm Hg) | MŶO₂ (ml/min/100 g LV) | CF (ml/min) | Art. cont. (Vol %) | A-V (Vol %) | C. ext. (%) | LVEDP (cm H₂O) |
|-----|------------|------------------------|-------------|-------------------|-------------|------------|----------------|
| 5 Hr | 50         | 8.13                   | 14.0        | 11.24             | 8.72        | 77.38      | 1.5            |
|      | 75         | 9.53                   | 18.0        | 12.50             | 7.96        | 63.68      | 3.5            |
|      | 100        | 12.53                  | 37.0        | 12.45             | 6.97        | 53.98      | 6.5            |
| 1 Day | 35         | 8.74                   | 14.0        | 10.96             | 8.91        | 52.33      | 3.0            |
|      | 60         | 10.55                  | 22.0        | 10.83             | 6.87        | 40.81      | 6.0            |
|      | 85         | 12.16                  | 35.0        | 17.29             | 4.98        | 28.95      | 6.0            |
| 1 Day | 40         | 8.77                   | 22.5        | 9.26              | 6.35        | 68.57      | 7.5            |
|      | 65         | 10.98                  | 29.0        | 10.26             | 6.17        | 60.13      | 8.0            |
|      | 90         | 12.82                  | 35.0        | 12.98             | 5.97        | 43.99      | 10.0           |
| 1 Day | 30         | 7.15                   | 11.5        | 13.24             | 10.25       | 77.41      | 3.5            |
|      | 70         | 8.60                   | 21.0        | 12.94             | 6.70        | 51.77      | 5.5            |
|      | 100        | 11.21                  | 33.0        | 13.64             | 5.60        | 41.05      | 8.0            |
| 1 Day | 40         | 6.25                   | 14.5        | 9.69              | 8.39        | 88.64      | 6.5            |
|      | 75         | 7.15                   | 21.5        | 9.91              | 6.64        | 67.00      | 10.0           |
|      | 115        | 10.30                  | 31.5        | 10.36             | 6.54        | 63.12      | 15.0           |
| 2 Days | 40        | 5.55                   | 17.0        | 16.10             | 6.20        | 38.50      | 4.0            |
|      | 70         | 6.40                   | 33.5        | 15.29             | 3.62        | 23.68      | 6.0            |
|      | 100        | 9.10                   | 44.0        | 15.43             | 3.90        | 25.28      | 9.0            |
| 3 Days | 40        | 7.61                   | 17.0        | 12.54             | 11.62       | 92.66      | 4.0            |
|      | 70         | 9.15                   | 23.0        | 13.27             | 10.34       | 77.92      | 4.0            |
|      | 100        | 9.19                   | 27.5        | 14.00             | 8.69        | 62.07      | 7.0            |
|      | 125        | 14.15                  | 41.0        | 14.37             | 8.97        | 62.42      | 9.0            |
| 3 Days | 40        | 10.47                  | 15.0        | 12.26             | 10.32       | 84.18      | 8.5            |
|      | 75         | 12.70                  | 25.5        | 11.53             | 7.38        | 64.00      | 9.0            |
|      | 100        | 15.81                  | 31.0        | 11.71             | 7.56        | 64.56      | 10.5           |
| 4 Days | 50        | 5.75                   | 18.0        | 14.00             | 8.18        | 58.43      | 5.0            |
|      | 75         | 6.30                   | 22.0        | 14.06             | 7.80        | 55.47      | 6.0            |
|      | 100        | 8.27                   | 29.0        | 14.15             | 7.44        | 52.52      | 8.5            |
| 5 Days | 35        | 5.04                   | 23.0        | 11.99             | 7.69        | 64.13      | 5.0            |
|      | 75         | 6.29                   | 35.0        | 11.50             | 6.30        | 54.78      | 6.0            |
|      | 100        | 6.66                   | 40.0        | 11.60             | 5.85        | 50.05      | 7.0            |

*AP = aortic pressure; A-V = arterial minus venous oxygen content; Art. cont. = arterial oxygen content; C. ext. = coefficient of extraction; CF = coronary flow; LVEDP = left ventricular end-diastolic pressure.

that there was no greater increment of oxygen usage whether calculated work was increased by elevating aortic pressure (closed circles) or by increasing cardiac output (open circles). This impression is borne out by the regression calculations indicated in the lower panel. Both regression lines are highly significant (P < 0.001). The slope for increasing aortic pressure does not differ significantly from that for increasing cardiac output.

The data were further analyzed by comparing calculated left ventricular efficiency in terms of percentage changes in going from low-to-middle and low-to-high levels of work. A 94% increase of left ventricular minute work produced by increasing aortic pressure resulted in a 19% increase of myocardial oxygen consumption and a 64% increase of efficiency. This may be compared with an 83% increase of work produced by increasing cardiac output which led to a 21% increase
of O₂ consumption and a 53% increase of efficiency. Similarly, when work was increased 182% by increasing aortic pressure or 173% by increasing cardiac output the percentage increments for oxygen consumption were 48% and 65%, respectively and for efficiency 92% and 72%, respectively. Hence, the percentage increments were entirely comparable and did not differ significantly when analyzed statistically.

From Tables 1 and 2 it can be seen that there is a directional relationship between MVO₂ and the end-diastolic pressure of the left ventricle in both the pressure-run and flow-run studies. These findings are compared in Fig. 5. The individual data shown in the left panel indicate that there is a nearly uniform increase of MVO₂/100 g LV with increasing LVEDP whether this was accomplished by increasing aortic pressure (closed circles) or increasing cardiac output (open circles). The respective regression lines are shown in the right panel. Both slopes are highly significant and virtually identical so that only a single line could be drawn.

The foregoing findings imply that a close relation between MVO₂ and minute work can be expected only in circumstances in which there is also a close relation between external work and EDP. This point is demonstrated by the experiment shown in Fig. 6. Elevation of AP to 120 mm Hg caused an increase in EDP to 16 cm H₂O, while at a comparable work level produced by elevating the cardiac

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**TABLE 2**

**EFFECTS OF CARDIAC OUTPUT ON CORONARY SINUS FLOW AND MYOCARDIAL OXYGEN METABOLISM (AORTIC PRESSURE CONSTANT)***

| Age  | CO (ml/min/100 g LV) | MVO₂ (ml/min) | CF (ml/min) | Art. cont. (Vol %) | A-V (Vol %) | C. ext. (%) | LVEDP (cm H₂O) |
|------|---------------------|--------------|--------------|--------------------|-------------|------------|---------------|
| 5 Hr | 309.0              | 5.86         | 11.0         | 13.40              | 8.01        | 59.27      | 3.5           |
| 1 Day| 430.2              | 8.39         | 13.0         | 19.55              | 9.23        | 47.21      | 5.0           |
| 1 Day| 536.6              | 8.34         | 33.5         | 7.06               | 4.06        | 57.50      | 5.0           |
| 3 Days| 404.4             | 7.07         | 17.0         | 13.70              | 6.33        | 46.10      | 4.0           |
| 4 Days| 602.6             | 7.45         | 21.5         | 10.00              | 6.91        | 69.10      | 9.5           |
| 5 Days| 917.5             | 11.75        | 23.5         | 0.00               | 10.00       | 83.33      | 12.5          |
| 905.7 | 10.34             | 41.0         |              | 13.33              | 8.86        | 66.46      | 9.0           |

* Symbols same as Table 1.
output with the AP at 75 mm Hg, the EDP was about 5 cm H₂O. The MVO₂ was substantially higher under the former conditions (Fig. 6, left panel). The relationship between wall tension and MVO₂ was unchanged, however (Fig. 6, right panel).

The interrelations of MVO₂ and calculated myocardial wall tension were assessed from 79 observations in 10 lambs and are shown in Fig. 7. The data include those from both pressure and flow runs, and changes in cardiac frequency while aortic pressure and cardiac output were held constant. These showed no tendency for separation into subgroups by inspection or mathematically. The calculated linear regression line is shown and the correlation coefficient (0.719) indicates a highly significant relationship (P < 0.001).

**Left Ventricular Pyruvate Metabolism and Oxygen Consumption**

The relationship between pyruvate utilization and MVO₂ is summarized for six animals 1–5 days of age in Fig. 8. When the mean aortic pressure was increased from 38 to 105 mm Hg, MVO₂ increased from 6.7 to 10.7 ml/min/100 g LV and pyruvate utilization increased from 1.3 to 3.4 mg/min/100 g LV. These incre-
Fig. 5. Left ventricular end-diastolic pressure (LVEDP) and left ventricular oxygen consumption with changing aortic pressure (closed circles) and changing cardiac output (open circles). Although the expected scatter for individual animals is present (left panel) an increase of LVEDP was uniformly accompanied by an increase of M\textsubscript{VO\textsubscript{2}}. The linear regression lines for each relationship are virtually identical (right panel) and the coefficients are highly significant. Average of values of different heart rates (HR) (200–292 beats/min) while minute work was held constant was calculated and found to lie on the same regression lines (right panel). Horizontal and vertical brackets indicate respective standard errors.

Fig. 6. Relationship between left ventricular oxygen consumption and work (left panel) or wall tension (right panel) with incremental increases of cardiac output (open circles) or aortic pressure (closed circles). Figures in () are end-diastolic pressure cm H\textsubscript{2}O. Maximum flow work (open circles) at EDP 5 CM H\textsubscript{2}O. Same work level achieved by progressive afterloading (closed circles )increased EDP to 16 cm H\textsubscript{2}O). Right panel shows nearly linear relationship between tension and M\textsubscript{VO\textsubscript{2}} plotted from same data as left panel.
Fig. 7. Relationship of estimated left ventricular wall tension to oxygen consumption with changes in aortic pressure (closed circles), cardiac output (open circles), and cardiac frequency (squares). Calculated linear regression line is shown.

Relationships are both significant ($P < 0.005$). They may be compared with increasing cardiac output from 334 to 854 ml/min while aortic pressure was held constant. The MVO$_2$ increased from 7.2 to 10.4 ml/min/100 g LV, while pyruvate utilization increased from 0.5 to 3.1 mg/min/100 g LV. Increasing heart rate in these lambs from 208 ($\pm$12 SE) to 282 ($\pm$11 SE) beats/min led to a small increase of MVO$_2$ which was of marginal significance ($0.05 < P < 0.1$). Correspondingly, pyruvate utilization was 1.8 at the lower heart rate and 2.0 mg/min/100 g LV at the higher rate and this difference was not significant.

**Relationships Between Body Weight, Heart Weight, and Calculated Left Ventricular Volume**

Cardiac chamber weights were obtained from eight of the 10 lambs and left ventricular volume was estimated from postmortem measurements using a prolate spheroid model (8). The free portion of the left ventricle averaged 14.4 $\pm$ 1.1 SE g, nearly twice the weight of the right ventricle (8.1 $\pm$ 0.6 g), and if the septum were included in the LV weight it exceeded that of the RV by a factor of 2 in all animals. The relationships among left ventricular weight and volume compared with body weight and age were examined. A linear relationship between LV volume and LV weight was evident and the correlation coefficient was 0.93 ($P < 0.001$). There was also a linear relationship between these values and body weight. Furthermore, the relationship between left ventricular volume and weight remained constant for this age span (5 hr to 5 days).
Fig. 8. Left ventricular oxygen consumption and pyruvate utilization with changing aortic pressure (PRESSURE RUN), cardiac output (FLOW RUN), and heart rate (FREQUENCY RUN) in six lambs 1–5 days of age. Vertical brackets indicate standard error of the mean. Increases of $\text{MV}_2$ are accompanied by increases of pyruvate utilization in both the pressure and flow runs. Marginally significant change of $\text{MV}_2$ during frequency run was associated with no significant change in pyruvate utilization.

**DISCUSSION**

Myocardial oxygen metabolism has not been previously studied in the neonate. Extrapolation from findings in mature subjects may be less than satisfactory when it is recognized that important structural and biochemical differences, presumably representing developmental changes, are now being uncovered (13–15). With this in mind, the present investigation was undertaken to obtain information on coronary flow and myocardial metabolism in the newborn lamb under various carefully defined hemodynamic conditions.

Determination of myocardial oxygen consumption was based on calculation of the product of coronary sinus flow and the difference in oxygen content between arterial and coronary sinus blood, and expressed as ml/min/100 g of left ventricular wet weight. Coronary sinus blood was assumed to be representative of mixed left ventricular coronary venous flow. Validity of this relationship for measuring oxygen consumption of the left ventricle has been established by various investigators (16, 17). It should be pointed out that in the lambs 65–70% of left coronary flow was recovered in the sinus. The remainder likely entered tributaries of the
middle cardiac vein which drains separately into the right atrium (11). Presumably, then, the true values for coronary flow and MVO₂ per 100 g LV are greater than those recorded. Proportional changes would be accurately reflected, however.

The findings indicate that all of the coronary sinus flow in the Dorset lamb is derived from the left coronary artery. In order to estimate those segments of the heart which were perfused from this source and ultimately drained by branches of the great cardiac vein (coronary sinus) a pigmented gelatin mass was introduced in a retrograde manner using the methods of Hales and Carrington (18). This mass has been shown to fill primarily to the level of venules and a few capillaries. This approach suggests that 93% (range 90–96%) of the left cardiac mass (including the left atrium and ventricular septum) is drained through this system. Only 7% of injected cardiac mass was from the right heart (ventricle). This would imply that the coronary venous samples were largely representative of postcapillary blood from the left heart, principally the left ventricle. Flow per gram of tissue can not, of course, be determined by this approach. It would seem unlikely that differences which may exist would be sufficient to alter these proportions importantly.

It might appear that a right heart bypass preparation would have offered some advantage by providing a measure of total coronary venous return. Anatomic patency of the foramen ovale in this age group, with potential admixture of left atrial blood, would render this an unreliable approach, however.

This study demonstrates that in lambs from a few hours to 5 days of age myocardial oxygen metabolism and coronary flow are closely and predictably regulated in relation to the performance of the heart. Our findings further indicate that within the range of aortic pressure, cardiac output, and LVEDP that may be encountered in the normal newborn lamb the energy cost for a given increment in left ventricular work does not differ whether the work increment is consequent to changing the afterloading or preloading conditions (Fig. 4).

The biochemical findings provide further support for the observations with oxygen metabolism. In the flow runs the heart extracted and utilized at least as much pyruvate as in the pressure runs, despite a somewhat smaller increase of stroke work (Fig. 8). Pyruvate, a prime substrate for cardiac muscle in vitro and in vivo, is the final intermediate of carbohydrate metabolism before entering the Krebs cycle to be degraded to CO₂ and H₂O. The importance of this substrate is emphasized by the suggestion that carbohydrate is the main energy source of heart muscle in the early postnatal period (19). Since the arterial concentrations were nearly constant throughout each experiment, the observed pyruvate extraction and utilization increments during the pressure and flow runs would not have been influenced by this factor (20).

While these findings appear to be consistent with the early work of Starling and Visscher (21) most investigators have found that external cardiac work performed against a high pressure load results in a substantially greater oxygen consumption than similar levels of work consequent to an elevated flow load (1, 2, 22, 23). It is of interest that in the study reported by Braunwald et al. (22), this was true in circumstances in which the left atrial mean pressure exceeded 12 cm H₂O. In the more normal range, however, the difference was less evident. A similar pattern was reported by Evans and Matsouka (1) who showed that curves relating O₂ consumption to external work produced by flow or pressure loading crossed at a mean arterial pressure of about 100 mm Hg (see their text Fig. 4). This study
supports the view that the apparent conflict between these findings may be a function of the range of ventricular performance examined (fig. 6).

As in the adult, one of the primary mechanisms by which the newborn heart adapts to large variations of venous return under differing afterloading conditions is by utilization of the Frank–Starling mechanism (24). It was, therefore, of interest to find that, regardless of the hemodynamic changes examined, MVO₂ correlated well with LVEDP. As shown in Fig. 5, with either pressure or flow changes, the MVO₂ and LVEDP regression lines are almost identical and the slopes are highly significant. Moreover, the average of values obtained at different cardiac rates also fit precisely on the same regression lines. This observation is consistent with the results of several earlier adult heart studies relating MVO₂ to ventricular end-diastolic fiber length or diastolic volume (21, 25, 26). Others have found a poor relationship (22).

Perhaps a more important consideration is that, as in the adult, myocardial wall tension is the principal determinant of oxygen consumption in the absence of chronotropic or inotropic changes. The excellent correlation between calculated wall tension and MVO₂ (Figs. 6, 7) supports this view. Evidence from isolated muscle studies indicates that the work performed in stretching the series elastic component during tension development is more costly in terms of oxygen than is the work performed in shortening the muscle (27, 28). Cat papillary muscle studies have also emphasized that high-energy phosphate usage (creatine phosphate and ATP) is greater during tension development (internal contractile work) than when shortening against a load (external contractile work) (29). For reasons that are not readily apparent, increasing the stroke volume in the newborn may require generation of relatively greater increments of myocardial wall tension at more normal levels of ventricular performance. Such factors as smaller fiber diameter, a smaller portion of contractile filaments, and a greater myocardial water content in the newborn may contribute to differences in wall tension and oxygen utilization (13), but these could not be distinguished in the present study.

**SUMMARY**

Myocardial oxygen consumption (MVO₂) and pyruvate utilization (Py U) were studied in 10 newborn lambs ranging in age from 5 hr to 5 days, using a preparation which permitted independent control of cardiac output (CO), aortic pressure (AP), and heart rate (HR). Coronary flow (CF) was measured by timed collections from the cannulated coronary sinus (CS). MVO₂ was calculated as the product of CF and coronary arteriovenous oxygen difference, and expressed as milliliters per minute per 100 grams of left ventricle (wet weight). There was a linear relationship between AP and CF (r = .81). In all lambs incremental increases of AP and CO were associated with increments of CF and MVO₂. In the ranges studied in most animals there were no significant differences in energy cost as reflected by MVO₂ for a given change of cardiac work produced by increasing CO or augmenting AP. While there was good correlation between MVO₂ and end-diastolic pressure (EDP), a uniform and highly significant relationship was demonstrated between ventricular wall tension (T) and MVO₂. Generally, there were small increases of MVO₂ as HR was increased by electrical pacing. Py U increased with AP and CO, but not HR, paralleling changes in MVO₂. It is concluded that within the ranges examined there are no important differences in myocardial oxygen metabolism in the newborn which may be attributed to a relatively greater oxygen require-
ment during pressure loading. This appears consistent with previous findings in the adult dog under comparable hemodynamic conditions. In circumstances where pressure loading produces a large elevation of EDP, the MVO₂ for a given work level is enhanced, but the relation of T to MVO₂ remains unchanged.

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