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Cardiac dimensions fetus
cardiac function newborn
cardiac output ventricular compliance

Limited Left Ventricular Response to Volume Overload in the Neonatal Period: a Comparative Study with the Adult Animal

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Summary

The unique fragility of the neonatal circulation in response to disease states and various physiologic stimuli is apparent clinically, although underlying mechanisms have not been explored. Accordingly, this report examines and compares the influence on cardiac performance of changes in left ventricular (LV) filling pressure in six conscious, unsedated newborn lambs studied serially at 1 and 3 weeks of age and five adult sheep. All animals were instrumented chronically to assess LV internal dimensions and pressures and cardiac output. At constant heart rate, infusion of saline to comparably high LV end diastolic pressure was associated in the younger newborns with significantly elevated mean arterial pressures (MAP), reduced LV stroke volume, stroke work, and mean fiber shortening when compared to older newborns or adults. A separate analysis of the LV pressure-dimension relationships showed lowest LV compliance in the youngest animals with a progressive increase with age. Thus, these results suggest that the youngest newborns have limited preload reserve related to reduced LV compliance. With volume infusion, sacromeres are stretched fully; the rise in peripheral resistance creates a mismatch between afterload and the level of inotropic state. These findings provide a framework for viewing cardiocirculatory adaptation to left-to-right shunt lesions in the human newborn and support the contention that age-dependent, disadvantageous myocardial mechanical factors play a critical role in their clinical course.

Speculation

The determinants of LV performance can best be described in terms of preload, afterload, and contractile state. The dynamic transition after birth from a single, parallel fetal circulation into separate, independent pulmonary and systemic circuits imposes marked loading alterations on the left ventricle of the newborn. Thus, preload increases dramatically in parallel with a 3-to 4-fold augmentation in pulmonary blood flow; systemic vascular resistance rises when clamping the umbilical cord removes the low resistance placental circulation, and when constriction of the ductus arteriosus occurs. Of course, the presence of a cardiac malformation may further accentuate either preload or afterload.

A paucity of studies exist concerning the mechanics of contraction of the newborn left ventricle and none have examined left ventricular function in the intact, conscious animal or made direct comparisons with the adult. Accordingly, the present investigation was designed to examine and compare the influence on cardiac performance of changes in LV filling pressure in the conscious, unsedated newborn lamb and adult sheep.

MATERIALS AND METHODS

Techniques developed by others (1, 11, 12, 31, 34) and adapted in this laboratory for the present investigation (13, 27, 28) and, subsequently, for fetal cardiac instrumentation were employed (16, 17).

Six newborn lambs in their first hr of life (2–12 hr) and five adult sheep, weighing 29–50 kg, underwent a left lateral thoracotomy using general anesthesia (sodium thiamytal, 5 mg/kg iv). The experimental model is depicted in Figure 1. Polyvinyl catheters were implanted into the left ventricle and thoracic aorta, and in the inferior vena cava through a peripheral vein. Miniature piezoelectric crystals (diameter 2.5 mm for the newborn lambs and 5 mm for the adult sheep) with a resonant frequency of 5 mHz were implanted into the left ventricle in a subendocardial position, perpendicular to the longitudinal axis of this chamber, and across its estimated maximal internal diameter. Pacing wires were sutured to the left atrial appendage. Catheters and wires were exteriorized and buried subcutaneously on the back of the animals.

Experiments began 7 days after operation. All newborns and three adult sheep were studied again 3–4 weeks later. The animals were studied undisturbed in fabricated cages without sedation. The heart rate from a standard EKG was utilized as an indicator of steady state. No experimental maneuvers were performed until the heart rate was stable and the animal appeared quiet and comfortable. The heart rate was then kept constant by atrial pacing at a rate 10–15% greater than the control rate.

Normal saline, 5 ml/kg/min, was injected through the catheter implanted in the inferior vena cava until the left ventricular end diastolic pressure (LVEDP) was raised to 21–25 mm Hg. Generally, 2–3 min infusion were sufficient to obtain the desired changes in LVEDP. The aortic pressure and left ventricular pressure (LVP) were monitored through fluid-filled catheters connected to Statham P 23 Db gauges. These catheters were square wave tested and found to be 3 Db attenuated at 25 Hz (flat to 5 Hz). The LVP was recorded at full scale and at high gain for accurate measurement of LVEDP. The maximum rate of left ventricular pressure development (dp/dt) was obtained using an R-C electronic circuit constructed to function as a differentiator. The LV internal diameter was monitored continously by an ultrasonic transit time dimension gauge. In brief, this device activates one of the piezoelectric crystals and then measures the transit time of the acoustic impulses traveling at sonic velocity between the two crystals on opposing endocardial surfaces of the left ventricle. A voltage proportional to transit time was recorded and calibrated in terms of crystal separation. The operating cycle is repeated often enough (5,000 times/sec) to obtain an essentially continuous display of the crystal separation throughout the cardiac cycle. This gauge was calibrated by substituting signals of known time duration from a calibrated pulse generator. At constant temperature, the base line drift was less than 0.15 mm/hr. The maximal and

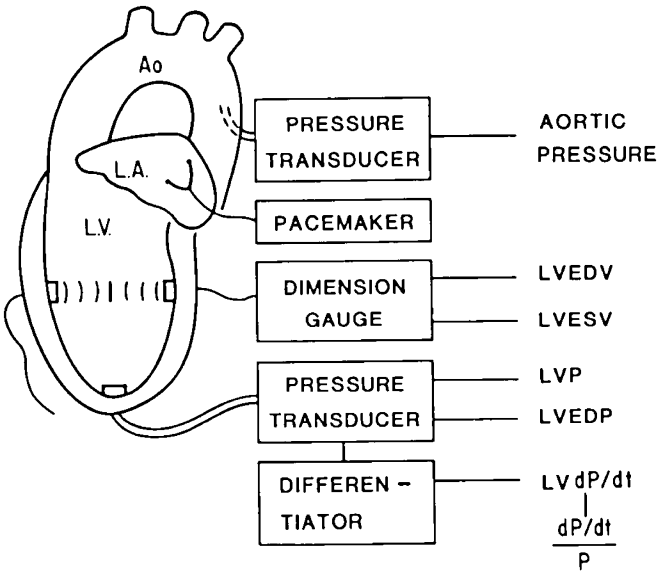

Fig. 1. The experimental model is described in the text. LVEDD = left ventricular end diastolic volume. LVESV = left ventricular and systolic volume. LVP = left ventricular pressure. LVEDP = left ventricular end diastolic pressure. dP/dt/P = the rate of change of left ventricular pressure/left ventricular developed pressure of peak dP/dt.

minimal crystal separation in a single beat were measured as end diastolic and end systolic dimension (EDD, ESD) respectively.

The EKG, LV systolic and end diastolic pressures, LV dp/dt, and LV internal dimension were recorded on a multichannel oscillograph and stored on magnetic tape. A beat-to-beat analysis was made of the above parameters before, and during, the infusion of saline.

LV volume (V) was calculated, employing the expression $V = \frac{\pi}{3} \times D^3$, where D = LV internal dimension. End diastolic and end systolic volumes (EDV and ESV, respectively) were derived from the corresponding D values. Stroke volume was obtained as EDV-ESV. Cardiac output was calculated as stroke volume × heart rate and expressed in ml/kg/min. In order to determine the validity of the latter calculation, cardiac output was measured in duplicate by indicator-dilution technique in a group of 10 lambs, 1–14 wk old, instrumented similarly (including the animals of the present study). Indocyanine green 0.5–1.0 ml was injected through polyvinyl tubing (0.065 mm outer diameter) positioned within the inferior vena cava with sampling from the aorta. Only dye-dilution outputs with less than 5% discrepancy between the duplicates were considered for comparison. A highly significant correlation existed between both techniques ($r = 0.95$; $P < 0.001$, stroke volume (dye) = 0.91 stroke volume (sonomicrometer) + 0.11).

Total peripheral resistance was calculated as mean aortic pressure (mm Hg)/cardiac output (ml/min/kg). Stroke work was computed in g M as mean aortic pressure (mm Hg) − LVEDP (mm Hg) × stroke volume (ml) × 1.36/100.

The mean velocity of LV circumferential fiber shortening (circumferences/sec) was calculated as $\frac{EDD - ESD}{EDD \times \text{ejection time}}$. The ejection time was obtained directly from the aortic pressure tracing. The isovolumic phase determination $\frac{dp/dt}{p}$ was used as an index of contractility, where dp/dt = the first derivative of LV pressure development, and p = LV pressure at peak dp/dt.

In order to calculate LV chamber compliance, the LVEDP − diameter data points were fitted by least-squares to an exponential relationship in every experiment (6, 7, 8). The pressure (LVEDP) − diameter relations were defined as $P = A + be^{C \cdot d}$ where P = LVEDP in mm Hg, d = diameter in cm, and A, b, and C are constants. Thus, the slope of the pressure-diameter curve depends primarily on the magnitude of the exponential constant C.

RESULTS

Resting values for each animal studied are provided in Table 1. Little variation existed within each age group in heart rate, hemodynamic variables, cardiac dimensions, and isovolumetric ejection indices of LV function. As expected, heart rate, LVEDP, cardiac index, and mean velocity of circumferential fiber shortening rate (VCF) declined and mean aortic pressure, cardiac dimensions, stroke volume, total peripheral resistance, and stroke work increased progressively with age.

Figure 2 describes the hemodynamic alterations induced by saline infusion at constant heart rate. When compared to the adult, mean aortic pressure rose to significantly higher levels in the 7-day-old animals ($P < 0.05$) and to intermediate, but not significantly higher, levels in the 3-wk-old animals as LVEDP rose progressively. Directionally opposite differences were observed in total peripheral resistance, which fell in the adult and older newborn, but not in the youngest animals. Whereas EDD and ESD increased significantly with saline infusion in all groups, stroke volume increased progressively in only the adult and older newborns, but not in the 7-day-old lambs. In the latter, a plateau was achieved beyond end diastolic pressures of 6–10 mm Hg. Parallel changes occurred in stroke work when comparing the adult to the older newborn. In striking contrast, significantly reduced values of stroke work were observed at all elevated levels of LVEDP in the 7-day-old animals ($P < 0.01$); stroke work in the latter group actually declined beyond an LVEDP of 11–15 mm Hg.

No changes were observed in dp/dT/P in any of the 3 groups as LVEDP rose as the result of saline infusion (Fig. 3). However, mean VCF fell progressively in the 7-day-old lambs beyond end diastolic pressures of 6–10 mm Hg ($P < 0.01$); no significant changes were observed in circumferential fiber shortening in either the adult or 3-to 4-wk-old lambs (Fig. 3). The fall in the youngest animals in mean VCF paralleled the increase in mean aortic pressure in that group (Fig. 3).

Table 2 provides the data describing the pressure-dimension relationships in the three groups of animals studied. The statistical comparison of the exponential constant C describing the slopes of the pressure-diameter curve for each animal and group is provided in Table 3. Significantly lower values for the exponent C were observed in the 7-day-old lambs when compared to the adult; the 3-to 4-wk-old newborns falling in an intermediate position. Thus, LV compliance was lowest in the youngest animals and appeared to increase progressively with age.

DISCUSSION

The results of the present study indicate that LV performance in the unsedated, conscious newborn animal is limited early in the neonatal period in response to a volume load by at least two factors. These are a lower LV compliance and an age-related, disproportionate increase in afterload.

Previous studies from our laboratory have demonstrated that isometric force development and the extent and velocity of shortening at any load are reduced in the fetal lamb heart when compared to the adult (7, 8). Moreover, fetal ventricular passive, but not active, compliance is reduced when compared to the adult (7, 17, 18). It would appear that ultrastructural and geometric considerations are responsible for the age-dependent differences in ventricular distensibility (7, 17, 31). In the fetal lamb, it is clear that changing fiber length is a fundamental determinant of cardiac output within the physiologic range of ventricular EDD and pressures (14). With respect to the newborn lamb, Downing *et al.* (4) have evaluated the function of the left ventricle by constructing ventricular function curves. These studies did not permit a quan-

Table 1. *Resting Values*

Group 1: (Newborn lambs 7 days old)	Age	Body wt (kg)	Heart rate (beats/min)	MAP (mm Hg)	dp/dt max (mm Hg/sec)	LVEDP (mm Hg)	ESD (cm)	EDD (cm)	SV (ml)	CO (ml/min/kg)	TPR (mm Hg/ml/min/kg)	VCF mean (circ/sec)	$\frac{dp/dt}{P}$ (sec)	SW (g)
1-a	7 days	4.5	170	78.5	2,700	2.5	1.5	2.1	5.88	222.9	0.349	1.90	45.0	6.07
2-a	7 days	5.0	172	83	3,100	4.5	1.9	2.42	7.31	251.1	0.331	1.26	49.5	7.8
3-a	7 days	5.2	151	87	2,600	3.2	2.0	2.62	9.98	287.5	0.301	1.48	39.1	11.37
4-a	7 days	3.1	176	85	2,330	5	1.21	1.75	3.59	203.8	0.419	2.03	36.2	3.91
5-a	7 days	4.9	165	82	2,420	3.5	2.15	2.65	8.67	292.0	0.82	1.26	39.0	9.26
6-a	7 days	4.8	174	84	2,680	3.5	1.88	2.35	6.33	229.5	0.348	1.25	41.9	6.94
Average		4.6	168	83.2	2,638	3.7	1.77	2.32	6.96	247.8	0.338	1.53	41.8	7.55
SEM		(±.2)	(±6.2)	(±1.8)	(±42)	(±0.4)	(±0.2)	(±0.1)	(±0.83)	(±13.1)	(±0.02)	(±0.4)	(±0.7)	(±0.98)
Group 2: (Newborn lambs 21–30 days old)														
1-b	26 days	7.8	136	80	2.550	5	2.1	2.75	11.54	201.2	0.398	1.31	42.1	11.77
2-b	23 days	6.8	160	87.5	2.380	3	2.0	2.58	9.17	215.8	0.405	1.18	35.5	10.5
3-b	22 days	8.5	156	95	2.730	2	2.0	2.82	14.43	264.8	0.359	1.22	36.7	18.3
5-b	24 days	7.8	145	92.5	2,700	3.8	2.2	2.87	12.99	241.5	0.353	1.37	37.3	15.67
6-b	22 days	7.6	147	96	2,580	2	2.17	2.82	12.21	236.2	0.406	1.27	34.0	15.60
Average		7.7	148.8	90.2	2,588	3.16	2.09	2.76	12.06	231.9	0.390	1.27	37.1	14.37
SEM		(±0.3)	(±5.9)	(±2.7	(±25)	(±0.6)	(±0.01)	(±0.05)	(±0.87)	(±9.8)	(±0.01)	(±0.2)	(±0.6)	(±1.15)
Group 3: (Adult sheep)														
7	18 months	50	95	97	2,450	2.7	3.25	4.27	43.52	82.7	1.173	1.13	31.8	55.8
8	12 months	40	112	110	2,830	2.5	3.0	3.94	34.16	102.5	1.073	1.41	31.4	49.94
9	9 months	36	118	95	2,950	3	2.3	3.40	26.7	87.5	1.086	1.55	39.3	33.41
10	7 months	26	100	95	3,060	2.0	2.3	3.15	27.1	104.2	0.912	1.33	40.8	34.28
11	6 months	29	130	98.5	2,380	3.0	2.5	3.2	17.16	77.0	1.279	1.16	34.5	22.29
Average		36.2	111	99.1	2,734	2.64	2.67	3.59	29.73	90.8	1.105	1.32	35.6	39.16
SEM		(±4.2)	(±4.4)	(±2.8)	(±2.8)	(±54)	(±0.2)	(±0.2)	(±2.19)	(±4.8)	(±0.04)	(±0.3)	(±1.1)	(±4.8)

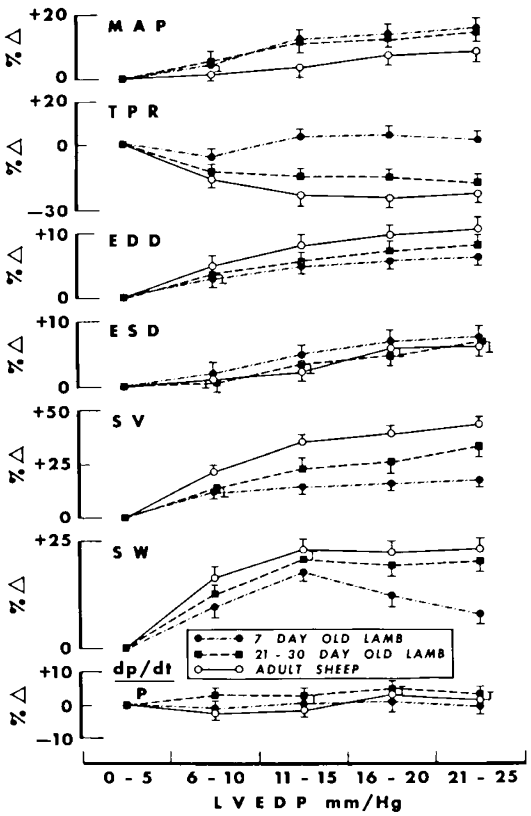

Fig. 2. Changes induced by saline infusion at constant heart rate. Each point and the vertical bar = the mean ± SE MAP = mean arterial pressure. TPR = total peripheral resistance. EDD = end diastolic diameter. ESD = end systolic diameter. SV = stroke volume. SW = stroke work. dP/dt/P = rate of change of pressure development/developed pressure at peak dP/dt.

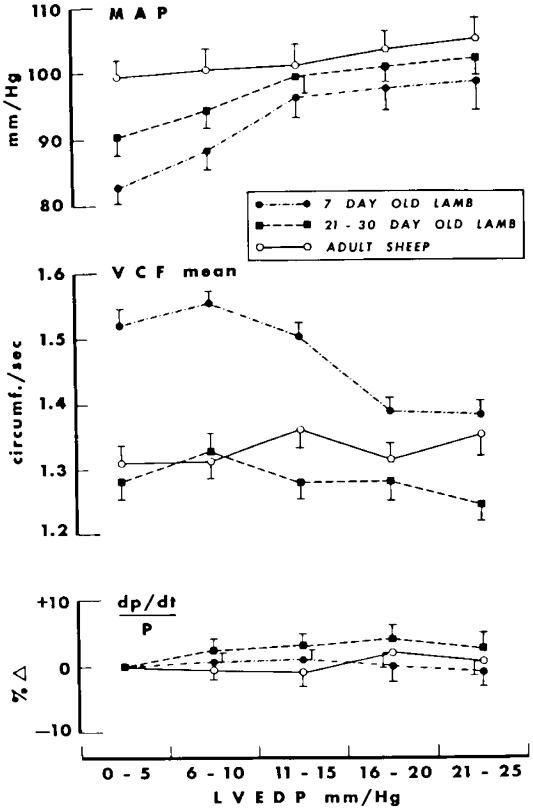

Fig. 3. Changes associated with saline infusion at constant heart rate in mean arterial pressure (MAP) mean circumferential of fiber shortening (VCF mean) and dP/dt/P. Each point and the vertical bars represents the mean ± SE.

titative comparison of myocardial function in different aged animals, but did suggest that important age-related differences may exist in the LV response to increased afterload. The latter studies employed a paced heart rate, anesthetized, open-chest lamb preparation which demonstrated an almost linear relationship between cardiac output and LVEDP (6.0–12.5 mm Hg) when MAP was maintained constant at 77 mm Hg. Elevations in MAP beyond the latter value caused a progressive decline in LV stroke volume and stroke work. These results may be contrasted with those obtained in adult cat experiments in which MAP over the wide range of 50–125 mm Hg had little influence on LV stroke volume (32). Moreover, newborn lambs reportedly show a marked increase in left atrial pressure and a transient increase in MAP after large blood transfusion (45 ml/kg during 30 min). These observations suggest that the newborn circulation has a reduced capacity to accommodate to relatively rapid expansion of the blood volume (5) because adult animals transfused similarly show no changes in those parameters (24, 25, 35). Thus, all of these findings suggest that the fetal and newborn left ventricle may be limited substantially, in the face of increased preload or afterload, in its ability to increase its extent of shortening at high end diastolic fiber length. The results of the present study provide strong evidence in support of the latter concept.

In the conscious adult dog, rapid expansion of the vascular volume results in an increase in both stroke volume and mean aortic pressure in the range of 30–80% and 15–22%, respectively, indicating a substantial reduction in total peripheral resistance (2, 11, 21). Teleologically, this reduction in peripheral resistance may be interpreted as a mechanism to improve LV performance in response to circulatory volume overload. The results of the present study indicate that the young newborn animal is impaired in its ability to alter peripheral vascular resistance acutely, thus disallowing augmentation of the extent of LV shortening. The reasons for this are unclear. Baroreceptor reflexes have been shown to be present and active in the full term newborn infant (19, 22, 23). Moreover, the peak discharge rate of the baroreceptors appears to be similar at any given MAP at all ages (3). Whether the newborns' failure to lower total peripheral resistance in the current study in the face of volume overload of the circulation is related to mechanical, autonomic, or autoregulatory factors remains conjectural.

Supportive evidence exists from other investigations that the 7-day-old lambs in the current study were, indeed, unique in their cardiocirculatory responses. Thus, the maximal changes in LV internal dimensions (10.1 and 5.6% in end diastole and end systole, respectively) in the adult sheep in the present study are similar to changes induced in conscious adult dogs instrumented and infused similarly (14.3 and 7.9%) (29). In the latter experiments, the mean aortic pressure increased 10–15 mm Hg with no appreciable decrement in LV function. Furthermore, it was noted that after LV internal diameter and stroke volume reached a plateau, cardiac output increased further as heart rate continued to rise. In this regard, preliminary experiments from our laboratory suggest that further increases beyond the high heart rates in the newborn period may be ineffective in augmenting cardiac output (27).

The pressure-dimension relationships observed at the various ages in this study indicate that LV compliance increases with advancing development postnatally. These findings appear to be independent of geometrical differences in LV shape, because past studies have sought, but not found, age-related geometries for the left ventricle (26). However, it should be recognized that our experimental technique for evaluating LV diastolic stiffness provides an analysis of the elastic behavior of the entire LV chamber, and not the specific elastic properties of the materials of which

Table 2. *Left ventricular end diastolic pressure (P) and internal diameter (d). Exponential fitting of data obtained in conscious animals*

Newborn lambs (7 days old)	Adult sheep	Newborn lambs (21–30 days)
1 $P = -14.8 + 0.0001e^{6.8d}$	7 $P = -34.6 + 0.09e^{2.05d}$	1 $P = -12.5 + 0.01e^{5.1d}$
2 $P = -35.6 + 0.07e^{2.65d}$	8 $P = -35.0 + 0.23e^{1.29d}$	2 $P = -36.1 + 0.1e^{1.9d}$
3 $P = -35.3 + 0.13e^{3.05d}$	9 $P = -35.9 + 2.09e^{0.75d}$	3 $P = -34.3 + 0.1e^{3.1d}$
4 $P = -35.3 + 0.16e^{3.51d}$	10 $P = -35.0 + 0.11e^{1.93d}$	5 $P = -32.8 + 0.2e^{2.5d}$
5 $P = -34.9 + 0.01e^{2.98d}$	11 $P = -34.2 + 0.13e^{1.86d}$	6 $P = -31.8 + 0.96e^{1.33d}$
6 $P = -35.1 + 0.11e^{2.64d}$		

Table 3. *Values for 'C' in pressure-diameter exponential equations*

Newborn lambs (Age = 7 days)	1 = 6.8			
	2 = 2.65			
	3 = 3.05			
	4 = 3.51			
	5 = 2.98			
	6 = 2.64			
	3.61			
	(±0.58)			
Newborn lambs (Age = 20–30 days)	1 = 5.1			
	2 = 1.9			
	3 = 3.1	N.S. ($t = 0.79$)		
	5 = 2.5			
	6 = 1.33			
	2.79			$P < 0.01$ ($t = 3.625$)
	(±0.56)			
Adult sheep	1 = 2.05			
	2 = 1.29			
	3 = 0.75	N.S. ($t = 1.74$)		
	4 = 1.93			
	5 = 1.86			
	1.58			
	(±0.21			

that chamber is constructed. Thus, the former is composite function of many factors, including the material properties of the heart, wall thickness, pericardial properties, extent of ventricular relaxation, and the postsystolic residual volume (9, 10, 18, 20). Moreover, previous studies from our laboratory suggest that under the present conditions of acute volume loading, the volume load on the right ventricle would be expected to disproportionately diminish LV chamber compliance in the youngest animals when compared to the older newborns and adults (26).

The results of the present investigation may be viewed conceptually within the framework proposed by Ross (29), of preload and afterload reserve in which a mismatch may occur between afterload and the intrinsic contractile ability of the heart in the face of a fully utilized preload reserve.

Indices of LV function are sensitive to acute afterload changes, responses that in turn are modulated by variations in preload and contractile state (6, 16, 30, 33). In the open-chest dog, at very high LV filling pressures (over 33 mm Hg), when the sarcomeres are extended maximally and the Frank-Starling reserve is minimal or nil, the stroke volume becomes highly dependent on the afterload, dropping markedly with further increases in aortic pressure (16, 29, 36). During acute volume loading in the intact, unanesthetized dog, there is some increase in the aortic pressure, yet the VCF and wall shortening remain unchanged (15). These findings are similar to those in the adult sheep in the present investigation in whom it is likely that any effects due to augmented afterload (increased systolic heart size and aortic pressure) were counterbalanced by the use of the Frank-Starling mechanism. Hence, no afterload mismatch was apparent with acute volume overload in the adult animal.

In contrast to the adult, the young newborn lamb has limited preload reserve, related most likely to reduced LV compliance at that age. Volume infusion stretches the sarcomeres fully and the rise in peripheral resistance creates a mismatch between afterload and the level of inotropic state identified by the fall in the young newborn of mean velocity of wall shortening and the reduced augmentation in stroke volume and work. Because the postnatal ventricle should resemble the late gestation fetus in its intrinsic physiologic properties and ultrastructural appearance, it is likely that a relative paucity of contractile material within the wall of the left ventricle contributes importantly to its mechanical disadvantage when compared to the adult (8, 31).

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