Baseline Hemodynamic and Echocardiographic Indices in Anesthetized Calves

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The experimental calf model is used to assess mechanical circulatory support devices and prosthetic heart valves. Baseline indices of cardiac function have been established for the normal awake calf but not for the anesthetized calf. Therefore, we gathered hemodynamic and echocardiographic data from 16 healthy anesthetized calves (mean age, 189.0 ± 87.0 days; mean body weight, 106.9 ± 32.3 kg) by cardiac catheterization and noninvasive echocardiography, respectively. Baseline hemodynamic data included heart rate (65 ± 12 beats per minute), mean aortic pressure (113.5 ± 17.4 mm Hg), left ventricular end-diastolic pressure (16.3 ± 38.9 mm Hg), and mean pulmonary artery pressure (21.7 ± 8.3 mm Hg). Baseline two-dimensional echocardiographic data included left ventricular systolic dimension (3.5 ± 0.7 cm), left ventricular diastolic dimension (5.6 ± 0.8 cm), end-systolic intraventricular septal thickness (1.7 ± 0.2 cm), end-diastolic intraventricular septal thickness (1.2 ± 0.2 cm), ejection fraction (63 ± 10%), and fractional shortening (37 ± 10%). Doppler echocardiography revealed a maximum aortic valve velocity of 0.9 ± 0.5 m/s and a cardiac index of 3.7 ± 1.1 L/minute/m^2. The collected baseline data will be useful in assessing prosthetic heart valves, cardiac assist pumps, new cannulation techniques, and robotics applications in the anesthetized calf model and in developing calf models of various cardiovascular diseases. *ASAIO Journal* 2004; 50:267–271.

Because of their similarity to humans in size and cardiovascular anatomy, large animals are the models of choice for testing new cardiac assist systems, prosthetic valves, and novel surgical interventions. Traditionally, the juvenile calf has been preferred in the research setting over the pig and sheep because of its ease of restraint and the closer similarity of its hematologic properties to those of humans.[1,2] Moreover, the extreme hemodynamic conditions (*i.e.*, elevated intracardiac pressures and flow) and the fast calcium turnover rate that occur in juvenile bovine physiology make it an ideal model in which to simulate worst-case scenarios for device testing.

Device assessment, safety, and efficacy are routinely performed by measuring the hematologic effects caused by the presence of the device in the bloodstream and the hemodynamic impact of its operation within the cardiovascular system. Because any such effect must be measured as a deviation from baseline physiology, it is imperative that the baseline (*i.e.*, the situation before device implantation) be carefully accounted for and subtracted as background from the values measured after implantation. However, it is well known that anesthesia induces marked depression of hemodynamic values in addition to any fluctuations that it may cause in the coagulation or complement systems.[3] The necessity thus becomes one of accurately assessing baseline conditions under anesthesia rather than during the awake state.

Normalized indices of cardiac function have been reported for healthy, awake cows, but few data exist for anesthetized calves. In this study, we set out to establish a set of baseline hemodynamic indices derived from cardiac catheterization and echocardiography studies in anesthetized calves.

Materials and Methods

Animals

Corriente crossbred calves of either sex were used for this study. The body surface area of each calf was calculated using the following formula: $(10.5 \times [\text{body weight} \times 1000]^{2/3})/10{,}000$, where the body weight is given in kilograms and the surface area is given in square meters.[4] All calves received humane care in compliance with the *Principles of Laboratory Animal Care*, formulated by the National Society for Medical Research, and the *Guide for the Care and Use of Laboratory Animals* (National Institutes of Health Publication No. 85–23, revised 1996). The Institutional Animal Care and Use Committee at the authors' institution approved all experiments.

Anesthesia

A standard anesthesia protocol was followed. Food was withheld for at least 12 hours before induction of general anesthesia. On the morning of examination, each calf was premedicated with intramuscular glycopyrrolate (0.02 mg/kg) and xylazine (0.2–0.7 mg/kg). A 12-Fr triple-lumen venous catheter was then inserted percutaneously into the right external jugular vein. Intravenous fluid replacement was initiated and administered as needed throughout examination. Ketamine (10–20 mg/kg) was administered intravenously to induce anesthesia. A cuffed endotracheal tube was inserted under direct visualization. General anesthesia was maintained with isoflurane (1.0–1.5%) in oxygen (40–100%). An orogastric tube was inserted to decompress the lumen. After standard

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surgical preparation, each calf was transported to the operating room, placed on the operating table in a right lateral decubitus position, and connected to electrocardiographic leads. Hemodynamic and echocardiographic studies were performed while the calf was anesthetized.

Hemodynamic Studies

An 8-Fr Swan-Ganz catheter was passed via the left external jugular vein into the pulmonary artery to measure pulmonary artery pressure and pulmonary artery wedge pressure. Hemodynamic data were averaged at 1-minute intervals by a continuous cardiac output monitor. A special catheter fitted with a high-fidelity micromanometer tip (Millar Mikro-Tip Catheter; Millar Instruments, Houston, TX) was passed via the left carotid artery into the left ventricle to measure left ventricular pressure. Heart rate, aortic pressure, left ventricular pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and central venous pressure were recorded every 5 seconds by a 16-channel data acquisition system (Ponemah system version 3.3; Gould Instrument System Inc., Valley View, OH).

Echocardiographic Studies

All echocardiographic and Doppler examinations were performed by a cardiologist experienced in echocardiography, using a Hewlett Packard Sonos 2000 ultrasound system equipped with a 2.5-MHz phased-array transducer, according to the method described by Braun *et al*.[5] and according to the guidelines of the American Society of Echocardiography.[6] The results were interpreted independently at a later time by a second experienced echocardiographer who was not present during the initial period of hemodynamic and echocardiographic data collection. To image the caudal long axis of the left and right ventricles, the transducer was held parallel to the ribs in the fourth intercostal space and then slightly rotated caudodorsally to obtain sharper images. Examination of the caudal long axis of the heart from the left side revealed the left and right ventricles and the left ventricular outflow tract. In this position, the left ventricle, mitral valve, and part of the left atrium were imaged. Further medially, the interventricular septum, right ventricle, right atrium, and tricuspid valve were visible. To image the left ventricular outflow tract, including the aortic valve and ascending aorta, the transducer was first positioned to image the left and right ventricles on the left side but then turned slightly cranially and rotated 10° counterclockwise. To image the right ventricular outflow tract (*i.e.*, the pulmonary artery and valve) in the cranial long axis of the heart, the transducer was held parallel to the ribs in the third intercostal space, 3–6 cm dorsal to the level of the olecranon. The left foreleg was abducted to make the position more accessible. Doppler echocardiographic data were collected for the aortic and mitral valves and, when possible, for the tricuspid and pulmonary valves.

Statistics

All hemodynamic and echocardiographic data were described as means and estimates of distribution (standard deviation, standard error of the mean, and 95% confidence interval). Previously published normal human values[7–12] were normalized using an average body surface area of 1.94 ± 0.8[13] and using the sums of squares of deviations where applicable.[14]

Results

Sixteen Corriente crossbred calves (mean age, 189.0 ± 87.0 days; mean body weight, 106.9 ± 32.3 kg) of either sex were used for this study. Of these, nine calves were catheterized and studied echocardiographically. The remaining seven calves were studied echocardiographically but were not catheterized. Physical examination and auscultation showed all calves to be healthy and free of detectable cardiovascular disease. All calves survived the protocols and were ultimately transferred to the experiments for which they were originally slated. The

Table 1. Hemodynamic Data (n = 9)

	Calf			
Parameter	Mean ± SD (SEM)	95% CI	Absolute Range	Human*
HR (bpm)	65 ± 12 (4)	57–73	46–80	60–100[7]
SAP (mm Hg)	129.7 ± 19.3 (6.4)	117.2–142.2	105–161	100–140[7]
DAP (mm Hg)	96.5 ± 15.5 (5.2)	86.4–106.6	80–127	60–90[7]
MAP (mm Hg)	113.5 ± 17.4 (5.8)	102.1–130.9	92–144	70–105[7]
LVSP (mm Hg)	131.8 ± 13.8 (4.6)	122.8–140.8	104–145	100–140[7]
LVEDP (mm Hg)	16.3 ± 8.9 (3)	10.5–22.1	6–26	3–12[7]
dP/dt + (mm Hg/s)	1,750.2 ± 669.2 (223.1)	1,313.0–2,187.4	1,068–3,035	1,500–2,500[8]
dP/dt– (mm Hg/s)	2,864.9 ± 1,081.8 (360.6)	2,158.9–3,570.9	1,597–4,855	800–1200[8]
SPAP (mm Hg)	25.6 ± 8.6 (2.9)	19.9–31.3	15.2–45.6	16–30[7]
DPAP (mm Hg)	17.7 ± 7.9 (2.6)	12.5–22.9	8.1–34.7	0–8[7]
MPAP (mm Hg)	21.7 ± 8.3 (2.8)	16.3–27.1	11.7–41	10–16[7]
CVP (mm Hg)	9.4 ± 6.8 (2.3)	5.0–13.8	0–16.5	0–8[7]
PCWP (mm Hg)	13 ± 3.0 (1)	11.0–15.0	8–16	1–10[7]

* Values shown are normal ranges reported in previous studies.

CI, confidence interval; HR, heart rate; SAP, systolic aortic pressure; DAP, diastolic aortic pressure; MAP, mean aortic pressure; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; dP/dt, rate of change in pressure over time; SPAP, systolic pulmonary arterial pressure; DPAP, diastolic pulmonary arterial pressure; MPAP, mean pulmonary arterial pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; SD, standard deviation; SEM, standard error of mean.

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Table 2. Echocardiographic Data (n = 16)

	Calf						Human	
				Index*				
Parameter	Mean ± SD (SEM)	95% CI	Absolute Range	Mean ± SD (SEM)	95% CI	Absolute Range	Normal (mean ± SD)	Index (mean ± SD)†
				Echocardiography				
BSA (m^2)	2.2 ± 0.7 (0.2)	1.8–2.6	1.5–3	—	—	—	—	1.94 ± 0.8[13]
HR (bpm)	73.3 ± 14.6 (3.7)	65.9–80.7	46–80	—	—	—	67.0 ± 9.1[9]	N/A
LVIDd (cm)	5.6 ± 0.8 (0.2)	5.2–6.0	4–6.5	2.5 ± 0.5 (0.1)	2.2–2.8	1.6–3.6	4.9 ± 0.3[9]	2.5 ± 1.4
LVIDs (cm)	3.5 ± 0.7 (0.2)	3.3–3.8	2.5–4.5	1.6 ± 0.4 (0.1)	1.4–1.8	0.8–2.1	3.2 ± 0.2[9]	1.6 ± 0.2
IVSd (cm)	1.2 ± 0.2 (0.1)	1.1–1.3	1–1.7	0.5 ± 0.1 (0.1)	0.4–0.6	0.4–0.8	0.8 ± 0.1[9]	0.4 ± 0.1
IVSs (cm)	1.7 ± 0.2 (0.1)	1.6–1.8	1.4–2.2	0.8 ± 0.1 (0.1)	0.7–0.9	0.5–0.9	1.3 ± 0.2[10]	0.7 ± 0.2
PWd (cm)	1.2 ± 0.2 (0.1)	1.1–1.3	0.8–1.5	0.5 ± 0.1 (0.1)	0.4–0.6	0.4–0.7	0.8 ± 0.1[9]	0.4 ± 0.1
PWs (cm)	1.7 ± 0.3 (0.1)	1.6–1.8	0.9–2	0.7 ± 0.1 (0.1)	0.6–0.8	0.4–1	1.3 ± 0.2[10]	0.7 ± 0.2
LVEDV (mL)	168 ± 41.3 (10.3)	147.9–188.1	106.1–224.8	72.8 ± 20.8 (5.2)	62.7–82.9	40.3–100.1	71.0 ± 24[11]	N/A
LVESV (mL)	66.5 ± 22.4 (5.6)	55.1–77.9	27.8–99.7	29.2 ± 11.6 (2.9)	18.6–40.8	8.9–48.7	23.0 ± 11[11]	N/A
RVIDd (cm)	3.2 ± 0.5 (0.1)	3.0–3.4	2.3–3.6	1.4 ± 0.3 (0.1)	1.3–1.5	1–1.8	2.1 ± 0.4[10]	1.1 ± 0.2
RVIDs (cm)	1.9 ± 0.3 (0.1)	1.7–2.1	1.3–2.5	0.8 ± 0.3 (0.1)	0.7–0.9	0.6–1.2	1.8 ± 0.4[10]	0.9 ± 0.2
LA (cm)	3.9 ± 0.5 (0.1)	3.6–4.2	3.2–5.4	1.7 ± 0.4 (0.1)	1.5–1.9	1.1–2.5	3.3 ± 0.5[10]	1.7 ± 0.2
MV E/A	1.4 ± 0.3 (0.1)	1.2–1.6	1.1–1.9	0.6 ± 0.2 (0.1)	0.5–0.7	0.4–1.1	2.0 ± 0.5[12]	1.0 ± 0.2
Ao (cm)	2.6 ± 0.4 (0.1)	2.4–2.8	1.9–3.2	1.2 ± 0.2 (0.1)	1.1–1.3	0.6–1.6	2.9 ± 0.4[10]	1.5 ± 0.2
PA (cm)	2.6 ± 0.3 (0.1)	2.4–2.8	2.1–3	1.1 ± 0.3 (0.1)	1.0–1.2	0.8–1.5	1.8 ± 0.2[10]	0.9 ± 0.2
EF (%)‡	63 ± 10 (2.5)	55.5–70.5	51–82	—	—	—	68.0 ± 11[11]	N/A
FS (%)	37 ± 10 (2.5)	31.9–42.1	25–59	—	—	—	32.0 ± 0.4[9]	N/A
				Doppler Echocardiography				
Ao Vmax (m/s)	0.9 ± 0.5 (0.1)	0.6–1.2	0.5–1.6	0.4 ± 0.2 (0.1)	0.3–0.5	0.2–0.9	1.4 ± 0.35[37]	0.7 ± 0.2
Ao TVI (cm)	24.1 ± 12.1 (3.2)	17.2–31.0	12–59.3	10.6 ± 5.7 (1.4)	7.6–13.6	5.7–25.8	22 ± 4[38]	11.3 ± 0.2
PV Vmax (m/s)	0.7 ± 0.1 (0.1)	0.6–0.8	0.6–0.8	0.3 ± 0.1 (0.1)	0.2–0.4	0.2–0.4	0.75 ± 0.15[37]	0.4 ± 0.1
PV TVI (cm)	15.3 ± 2.0 (0.5)	14.2–16.4	14.2–17.6	5.8 ± 1.1 (0.3)	5.1–6.5	4.9–6.9	20 ± 0.4[38]	10.3 ± 0.2
TV Vmax (m/s)	0.8 ± 0.2 (0.1)	0.7–0.9	0.5–1	0.3 ± 0.1 (0.1)	0.2–0.4	0.2–0.4	0.5 ± 0.2[37]	0.3 ± 0.1
EF (%)§	63 ± 10 (2.5)	58.3–67.7	43–71	28.0 ± 5.8 (1.5)	25.5–30.5	17.3–38.8	50–60[34]	N/A
CO (L/min)§	8.0 ± 1.9 (0.5)	7.0–9.0	4.5–11.5	3.6 ± 1.1 (0.3)	3.0–4.2	2–6.3	5–7[37]	—
Cardiac index (L/min/m^2)	3.6 ± 1.1 (0.3)	3.0–4.2	—	—	—	—	2.5–3.5‖	—

* Each calf index was calculated as dimension divided by body surface area.

† Each human index was normalized using a mean body surface area of 1.94 ± 0.8 m^2 for an adult male[13] and using the sums of squares of deviations where applicable.[14]

‡ In two dimensional echocardiographic studies, ejection fraction was determined by stroke volume.

§ In Doppler echocardiographic studies, ejection fraction was determined by planimetry, and cardiac output was determined by aortic flow measurement.

‖ Texas Heart Institute experience.

CI, confidence interval; BSA, body surface area; HR, heart rate; LVIDd, end-diastolic left ventricular internal dimension; LVIDs, end-systolic left ventricular internal dimension; IVSd, end-diastolic intraventricular septal thickness; IVSs, end-systolic intraventricular septal thickness; PWd, end-diastolic left ventricular posterior wall thickness; PWs, end-systolic left ventricular posterior wall thickness; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; RVIDd, end-diastolic right ventricular internal dimension; RVIDs, end-systolic right ventricular internal dimension; LA, left atrial dimension; MV E/A, mitral valve E/A ratio; E/A, Ao, aortic diameter; PA, pulmonary artery diameter; EF, ejection fraction; FS, fractional shortening; Ao Vmax, maximum velocity of aortic valve; Ao TVI, aortic valve time velocity index; PV Vmax, maximum velocity of pulmonary valve; PV TVI, pulmonary valve time velocity index; TV Vmax, maximum velocity of tricuspid valve; CO, cardiac output; N/A = not applicable; SD, standard deviation; SEM, standard error of mean.

Table 3. Comparison of Baseline Hemodynamic Indices in Awake *versus* Anesthetized Calves

	Awake						Anesthetized	
Parameter	Kuida *et al.*[28]	Weber *et al.*[29]	Buss *et al.*[30]	Lin *et al.*[25]	Stowe *et al.*[16]	Inman *et al.*[31]	Current Study	Stowe *et al.*[16]
BSA (m^2)	2.2	2.4	1.66	1.6	2.04		2.3	1.69
HR (bpm)	109	101	79–82	82	—		65	
MAP (mm Hg)	131	134/94	110–116	123	—		114	
MPAP (mm Hg)	22	—	18–23	19	—		22	
CO (L/min)					10.6	6.0–9.0		7.5
Cardiac index (L/min/m^2)	7.10	3.9	4.8–5.6	4.9	5.2	3.0–3.9	3.7	4.5
LVEDP (mm Hg)	—	9	9–13	—	—		14	
dP/dt + (mm Hg/s)	—	1719	2055–2076	—	—		1751	
PCWP (mm Hg)	—	—	6–7	11	—		13	

BSA, body surface area; HR, heart rate; bpm, beats per minute; MAP, mean aortic pressure; MPAP, mean pulmonary arterial pressure; CO, cardiac output; LVEDP, left ventricular end-diastolic pressure; dP/dt, rate of change in pressure over time; PCWP, pulmonary capillary wedge pressure.

hemodynamic and echocardiographic data are summarized in **Tables 1 and 2**.

Discussion

The accurate preclinical assessment of mechanical circulatory support devices and prosthetic valves in the calf model requires hemodynamic monitoring during the anesthetized state. Several baseline hemodynamic and echocardiographic indices have been reported for normal awake calves,[15] but only one study has reported them for anesthetized calves.[16] In the current study, a set of baseline hemodynamic and echocardiographic values for the anesthetized calf model was established. Although anesthesia is a dynamic state that causes fluctuations in hemodynamic values, the indices compiled in this study should serve as a reliable reference and a general guideline. These results also may be useful for simulating a disease state in the calf model for preclinical studies of cardioactive medications, cardiac assist devices, and various systemic prostheses.

The bovine model has been used for cardiovascular research since the 1960s,[17,18] when Larson *et al.* first conducted aortic valve surgery in this species. It has since become the conventional model for testing the preclinical safety and efficacy of cardiac assist devices and mechanical heart valves. For more than 20 years, we have used juvenile calves in the research laboratory for this purpose.[19–24] Compared with other animal models, the juvenile calf has the advantages of a faster growth rate, stronger myocardial contractility, higher blood velocities, and higher pressure differentials. Further, the calf has an accelerated calcium turnover rate that makes it an excellent model for the rigorous testing of bioprosthetic valves.[20]

It is known that the hemodynamics of the awake calf differ from those of the anesthetized calf.[25] In this study, standard methods were used to anesthetize calves before gathering the hemodynamic and echocardiographic data. The standard anesthesia protocol calls for a combination of glycopyrrolate and xylazine to premedicate the calves, ketamine to induce anesthesia, and isoflurane to maintain anesthesia. Although this protocol is safe,[26] previous studies have shown that these drugs may have prolonged side effects that continue even after anesthesia is discontinued.[27] These effects include bradycardia, elevated systemic blood pressures, and decreased cardiac output.

In 1960, Stowe measured cardiac output in awake and anesthetized calves using the dye method and Fick oxygen techniques (**Table 3**).[16] Several groups subsequently studied baseline hemodynamic parameters in the awake calf model.[16,25,28–30] Our group previously reported on the resting cardiac index in conscious cows.[31] Unfortunately, statistical comparisons between the data from these studies are impossible because of variations in methods of measurement, bovine species, and body size. However, several general conclusions can still be drawn: heart rate, mean arterial pressure, and cardiac index are lower and mean pulmonary capillary wedge pressure and mean pulmonary arterial pressure are higher in anesthetized calves than in awake calves.

Echocardiography has already been used successfully to assess cardiac function in other species. Studies in the cat and the mouse have established that fractional shortening is decreased after anesthesia is induced.[32,33] In two-dimensional echocardiographic studies in humans, Schnittger *et al.* established a simple normalized method for estimating intracardiac dimensions in humans.[34] As shown in **Table 2**, the human baseline indices compiled from reports by Schnittger *et al.* and others are comparable to those established here for anesthetized calves. This similarity suggests that the calf model may be useful for deducing human cardiac function, particularly the physiologic reaction to various modalities of mechanical circulatory support.[35] Echocardiography also has been established as a feasible technique in the bovine.[5,35,36] In echocardiographic studies of awake calves, Amory *et al.* established functional indices comparable to those for other species;[36] however, their indices were consistently higher than those found for anesthetized calves in the current study (**Table 4**). Altogether, these findings emphasize the need to clarify the effect of anesthesia on cardiac function and morphology in the anesthetized calf.

Furthermore, the indices compiled in this study may be useful in developing various models of cardiovascular disease in the calf. For example, we are currently developing a calf model of chronic heart failure to test cardiac assist/recovery systems. Baseline hemodynamics are measured using cardiac catheterization and echocardiography. These indices will help investigators validate the accuracy of these baseline hemodynamic measurements.

One limitation of this study was that it did not include echocardiographic studies of the right heart. This may limit the

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Table 4. Comparison of Baseline Echocardiographic Indices in Awake *versus* Anesthetized Calves

Index	Calculation	Awake (Amory *et al.*[36])	Anesthetized (Current study)
ΔIVS (%)	(IVSs–IVSd)/IVSd × 100	60	44
ΔPW (%)	(PWs–PWd)/PWd × 100	76	41
FS (%)	(LVIDd–LVIDs)/LVIDd × 100	43	37

ΔIVS, change in intraventricular septal thickness; IVSs, end-systolic intraventricular septal thickness; IVSd, end-diastolic intraventricular septal thickness; ΔPW, change in left ventricular posterior wall thickness; PWs, end-systolic left ventricular posterior wall thickness; PWd, end-diastolic left ventricular posterior wall thickness; FS, fractional shortening; LVIDd = end-diastolic left ventricular internal dimension; LVIDs, end-systolic left ventricular internal dimension.

general applicability of these results. However, in restricting the studies to the left heart, we were able to take advantage of the ability to produce and refine stable echocardiographic images in anesthetized animals. Another limitation of the study was that it did not compare closed-chest and open-chest data. Such comparisons will be made in future studies.

In summary, the results of the current study provide baseline hemodynamic and echocardiographic indices for anesthetized calves that may be useful for future preclinical studies of cardiac assist devices and prosthetic heart valves in the calf model. These indices also may be useful in developing various models of cardiovascular disease in the calf.

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