Ouabain Effects on Oxygen Physiology in Anemic Lambs

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ABSTRACT. We studied the effects of anemia and ouabain administration on cardiac function, oxygen physiology, and blood catecholamine levels in nine newborn lambs. We measured oxygen consumption continuously, along with traditional hemodynamic variables. Oxygen transport was calculated. Following baseline measurements, lambs were made anemic (mean hematocrit = 12%) by isovolemic exchange transfusion with Plasmanate, and measurements were repeated. Thereafter ouabain was administered as a 75 µg/kg bolus, followed by 30 min of infusion at a rate of 0.05 µg/kg/min. Measurements were repeated at the conclusion of infusion. Anemia was associated with a heart rate related rise in left ventricular rate of pressure rise, a rise in oxygen consumption, an increase in cardiac output, a decrease in systemic vascular resistance, and a rise in fractional oxygen extraction (oxygen consumption/transport). Following ouabain administration, cardiac output, oxygen consumption, and stroke work fell, but left ventricular rate of pressure rise and the extraction ratio did not change. Serum levels of epinephrine and norepinephrine rose with sustained anemia and ouabain infusion. In this setting, ouabain effects are manifested primarily by alterations in oxygen transport and metabolism rather than by changes in traditional assessments of left ventricular contractile function. (*Pediatr Res* 21: 447–452, 1987)

Abbreviations

LV, left ventricle
dP/dt, rate of pressure rise
PEP, preejection period
ET, ejection time
VO_2, oxygen consumption
A-V, arterial-venous
SOT, systemic oxygen transport
SVR, systemic vascular resistance

Cardiac glycosides are used commonly to treat circulatory congestion in infants and children with congenital cardiac defects (1–3). Traditionally, the weight-related doses of digoxin used in immature subjects are higher than those used in adults (4, 5), although the reasons for that practice remain unclear (6–10). Moreover, because the high resting level of myocardial muscle function early in life may not be affected adversely by structural cardiac defects (11–14), some have questioned the appropriateness of inotropic therapy for this patient group. Nevertheless,

clinical impression and a few selected studies suggest that young subjects with structural cardiac defects benefit from cardiac glycoside therapy (15–17), although the precise mechanism of the effect has not been established (18–20).

Despite the presence of vigorous myocardial muscle function with many congenital cardiac defects, the congested circulatory state can perturb oxygen transport to the tissues (15, 21). It is possible that in this setting cardiac glycosides may exert their predominant influence on the peripheral supply and demand for oxygen through their effect on the energy requiring sodium-potassium ATPase pump enzyme system. In the present study we created circulatory conditions characterized by normal to increased myocardial function, yet compromised systemic oxygen transport by inducing anemia in conscious newborn lambs. It was our purpose to test the effects of ouabain on both myocardial function and systemic oxygen transport under these conditions.

METHODS

Studies were performed in 13 newborn lambs within the 1st wk of life. Animals were blindfolded, restrained in a sling, and given local anesthesia with 1% xylocaine to permit insertion of central venous and aortic polyvinyl catheters (OD 0.090 in, ID 0.050 in) via the right femoral vein and artery, a 5 French left ventricular manometric-tipped catheter inserted retrograde via the carotid artery, and ECG electrodes into the chest wall. Sedation and general anesthesia were not administered during the 3–4 h of study. Animals were kept normothermic (39° C) by the use of a heating pad. During the study, the following measurements were made: aortic, right atrial and LV pressure; arterial hematocrit and hemoglobin concentration; heart rate (via a Beckman 9857 cardiotachometer); ECG, LV dP/dt (via a Beckman 9879 differentiating circuit); LV PEP and LVET by methods described previously (11); right atrial and aortic oxygen saturations (Radiometer OMII, Copenhagen, Denmark) and blood gas tensions (at 37° C); VO_2, measured continuously by the flow through method (22); and serum levels of epinephrine and norepinephrine (CAT-A-KIT ASSAY, Upjohn Diagnostics, Kalamazoo, MI) (23). From the measured variables, the following data were calculated: mixed venous and arterial oxygen contents (as the sum of dissolved and hemoglobin-bound O_2); the A-V O_2 content difference; cardiac output (according to the Fick principle); SOT (cardiac output × arterial oxygen content); SVR (systemic perfusion pressure/cardiac output); the PEP/LVET ratio; the fractional oxygen extraction (VO_2/SOT); and base deficit.

Baseline measurements in nine study animals were made 1 h following instrumentation. Then animals were made anemic by phlebotomy and isovolemic, warmed Plasmanate replacement in 50-ml increments (total volume varied between 300 and 550 ml to achieve the desired level of anemia). VO_2 was measured continuously and hemodynamic data were recorded periodically

until the arterial hematocrit fell below 15%. Thirty min after completion of blood removal, measurements were repeated. Ouabain was then given as a bolus dose of 75 μg/kg followed by a continuous infusion of 0.05 μg/kg/min (19). Following a 30-min infusion period, measurements were repeated again. Animals were killed by pentobarbital overdose.

Additional studies were performed on four other lambs (mean age 5.2 ± 0.5 days, mean weight 5.8 ± 0.6 kg) for two reasons: *1)* to verify the stability of hemodynamic changes caused by a level of anemia comparable to that of the study animals and *2)* to determine the effects of progressive levels of anemia on hemodynamic and oxygen transport variables. One hour following instrumentation, baseline measurements were made. The animals were then made anemic over 30 min by phlebotomy with Plasmanate replacement in 50-ml increments. Thirty min and 2 h later, measurements were repeated. Additional blood removal with volume replacement was then performed to reduce arterial hematocrit below 10%. One h later measurements were repeated and the animals were killed. Data were compared by
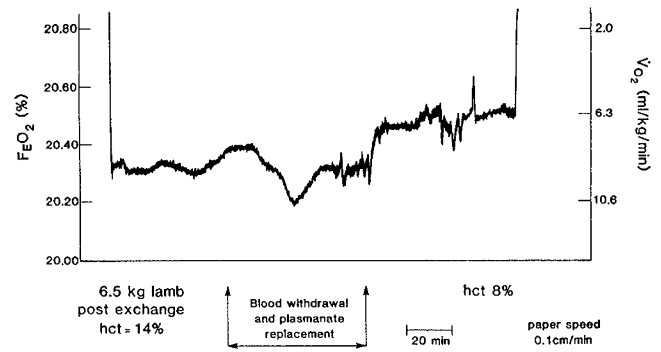

Fig. 1. Slow speed tracing of VO_2 during staged induction of anemia in one of four control group lambs. The ordinate scale is expressed both as percent expired oxygen (F_EO_2) and VO_2. The baseline VO_2 in this study was 9.2 ml/kg/min. The fall in VO_2 following reduction of the hematocrit (*hct*) from 14 to 8% is evident.

Table 1. *Physiologic effects of anemia (mean ± SD)**

	Baseline	Anemia × ½ h	Anemia × 2 h	Severe anemia × 1 h
Hematocrit (%)	32 ± 3	13 ± 1	13 ± 1	8 ± 0
Heart rate (beats/min)	245 ± 21	283 ± 18†	285 ± 18†	277 ± 17†
Arterial pH	7.42 ± 0.05		7.42 ± 0.04	7.45 ± 0.04
PO₂ (torr)	63 ± 4		62 ± 3	60 ± 6
PCO₂ (torr)	37 ± 5		33 ± 2	17 ± 2†‡
Arterial base excess (mEq/liter)	0 ± 5		−3 ± 3	−12 ± 2†‡
Ao (mm Hg)	85 ± 14	72 ± 2†	71 ± 3†	65 ± 1†‡
CVP (mm Hg)	3 ± 1	12 ± 1†	13 ± 1†	12 ± 4†
CO (ml/kg/min)	223 ± 33	322 ± 54	306 ± 59	247 ± 35
LV dP/dt (mm Hg/s)	4011 ± 508	5524 ± 637†	5618 ± 640†	5510 ± 432†
PEP/LVET	0.36 ± 0.04	0.29 ± 0.06†	0.28 ± 0.07†	0.28 ± 0.05†
SVR (mm Hg × kg × min/ml)	0.37 ± 0.06	0.19 ± 0.03†	0.19 ± 0.04†	0.21 ± 0.02†
SOT (ml/kg/min)	30.3 ± 5.4	17.6 ± 3.3†	18.0 ± 2.7†	9.0 ± 1.8†‡
VO₂ (ml/kg/min)	8.4 ± 1.7	11.4 ± 1.7†	11.8 ± 2.1†	6.9 ± 0.7‡
A-V O₂ (ml O₂/liter)	37.5 ± 4.5	36.1 ± 8.2	39.0 ± 7.9	28.0 ± 2.6
% Extraction (%)	28 ± 5	66 ± 16†	66 ± 13†	77 ± 8†

* Ao, mean aortic pressure; CVP, mean central venous pressure; CO, cardiac output; % extraction, % extraction of oxygen from arterial blood (VO_2/SOT); Hg, hemoglobin.
† Differs from baseline, $p < 0.05$.
‡ Differs from anemia × 2 h, $p < 0.05$.

Table 2. *Hemodynamic effects of intervention (mean ± SD)**

	Baseline	Anemia	Anemia + ouabain
Hematocrit (%)	38 ± 4	12 ± 2†	12 ± 2†
Heart rate (beats/min)	225 ± 25	270 ± 28	255 ± 37
Arterial pH	7.41 ± 0.02	7.44 ± 0.03	7.39 ± 0.03‡
PO₂ (torr)	67 ± 3	69 ± 2	61 ± 2†‡
PCO₂ (torr)	35 ± 2	32 ± 2†	34 ± 3‡
Arterial base excess (mEq/liter)	−2 ± 2	−3 ± 2	−4 ± 2
Ao (mm Hg)	97 ± 18	87 ± 13	83 ± 14
CVP (mm Hg)	4 ± 1	10 ± 5†	10 ± 5†
CO (ml/kg/min)	226 ± 69	398 ± 140†	290 ± 126‡
LV dP/dt (mm Hg/s)	4061 ± 602	5689 ± 667†	5711 ± 757†
SW (mm Hg × liter/kg/min)	22.4 ± 9.6	36.6 ± 16.2†	24.7 ± 12.7‡
PEP/LVET	0.36 ± 0.04	0.29 ± 0.06†	0.27 ± 0.02†
SVR (mm Hg × kg × min/ml)	0.45 ± 0.18	0.23 ± 0.12†	0.30 ± 0.17†
SOT (ml/kg/min)	32.7 ± 12.9	19.6 ± 4.0†	13.9 ± 4.3†
VO₂ (ml/kg/min)	9.28 ± 1.22	12.86 ± 2.12†	8.40 ± 1.39‡
A-V O₂ (ml O₂/liter)	42.0 ± 11.8	35.0 ± 10.3	33.7 ± 9.4
% Extraction (%)	32 ± 11	65 ± 14†	62 ± 16†
Serum epi (pg/ml)	38 ± 12	56 ± 9	166 ± 38†‡
Serum n-epi (pg/ml)	474 ± 209	841 ± 340†	1617 ± 232†‡

*Ao, mean aortic pressure; CVP, mean central venous pressure; CO, cardiac output; SW, stroke work; % extraction, % extraction of oxygen from arterial blood; epi, epinephrine; n-epi, norepinephrine; Hg, hemoglobin.
† Differs from baseline, $p < 0.05$.
‡ Differs from anemia, $p < 0.05$.

an analysis of variance and the Scheffé test of significance (24). $p < 0.05$ was considered statistically significant.

RESULTS

Anemia to hematocrit levels of 12–15% produced stable hemodynamic alterations in the four control animals over a 2-hr observation period (Table 1). Both 30 and 120 min following completion of blood removal and isovolemic Plasmanate replacement, heart rate, cardiac output, central venous pressure, and oxygen consumption rose; systemic oxygen transport, aortic mean pressure, and systemic vascular resistance fell. Although the A-V oxygen content difference did not change from control levels, the fractional extraction of oxygen from arterial blood (VO_2/SOT) rose markedly. The subsequent reduction of hematocrit to levels less than 10% (mean 8%) resulted in a marked fall in oxygen consumption, oxygen transport, and base buffering capacity and a further rise in percent oxygen extraction (Table 1, Fig. 1).

The nine study lambs weighed 5.4 ± 1.0 kg when studied at 5.1 ± 1.9 days of age. Baseline hemodynamic data are shown in Table 2. Following phlebotomy, mean arterial hematocrit fell from 38 to 12%. As with the control lambs during anemia, mean cardiac output rose (from 226 to 398 ml/kg/min). There was a heart rate-related rise in LV dP/dt and a fall in the PEP/LVET ratio. VO_2, the fractional oxygen extraction (VO_2/SOT), and stroke work rose; systemic oxygen transport and vascular resistance fell. Serum levels of norepinephrine rose, but serum epinephrine levels were not significantly altered. Figure 2 shows the effects of anemia on VO_2, LV dP/dt, and oxygen extraction in the nine study and four control lambs.

Following ouabain infusion, hematocrit, heart rate, the A-V O_2 content difference, LV dP/dt, the PEP/LVET ratio, and SVR did not change significantly. VO_2, cardiac output, and stroke work fell. Neither Oxygen extraction nor base deficit changed significantly. The serum levels of epinephrine and norepinephrine rose. Serum pH fell slightly, but significantly.

Figure 3 shows tracings from a 6-day-old, 4.5-kg lamb. Rhythmic variations in tracings with anemia and anemia plus ouabain are due to the increased respiratory efforts of the anemic animals (25). The anemia-related rise in heart rate, LV dP/dt, and VO_2, as well as the ouabain related fall in VO_2, are seen
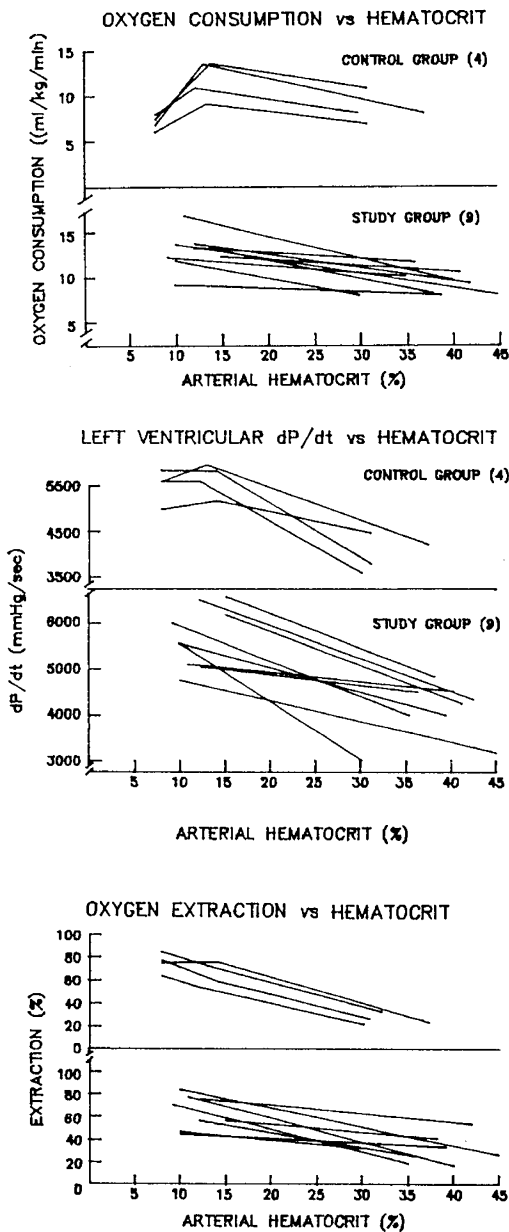

Fig. 2. The relationship of arterial hematocrit to VO_2, LV dP/dt, and arterial oxygen extraction in four control and nine study group animals. The anemia related rise in LV dP/dt and oxygen extraction is in contrast to the rise and subsequent fall of VO_2 following reduction of hematocrit to values under 10% in the four control group lambs.
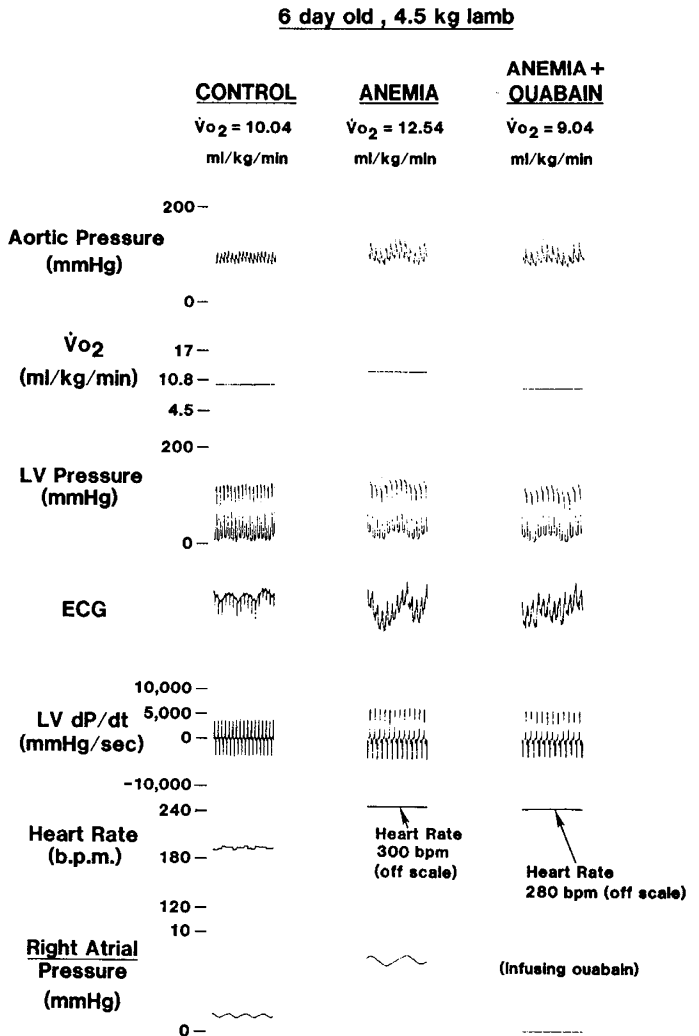

Fig. 3. Tracings from a 6-day-old lamb prior to intervention (control), following isovolemic Plasmanate exchange (anemia), and finally following ouabain infusion (anemia + ouabain). Heart rates during anemia and ouabain plus anemia were calculated manually, as the tracings are off scale. Although heart rate and LV dP/dt max remain high following induction of anemia, the anemia-associated rise in VO_2 is abolished following ouabain infusion.

clearly. Ouabain infusion reduced oxygen consumption, cardiac output, and SOT without changing LV dP/dt or the oxygen extraction ratio significantly (Table 2).

Figure 4 displays trends of VO$_2$, arterial oxygen extraction, and LV dP/dt in the nine study animals under baseline conditions, during anemia, and with anemia following ouabain infusion. The ouabain-related fall in oxygen consumption is not accompanied by a further increase in oxygen extraction from the anemic state or with a change in LV myocardial function, as reflected by the dP/dt value; the fall in VO$_2$ is unaccompanied by a change in oxygen extraction because of a parallel fall in oxygen transport during the ouabain infusion—a reflection of the reduced cardiac output during that state.

Figure 5 relates oxygen transport to oxygen consumption in all animals studied. Points recorded during ouabain administration are cross-hatched. The reduction in oxygen consumption at low levels of oxygen transport is evident.

DISCUSSION

This study was undertaken to pursue cardiac glycoside actions, other than inotropic stimulation, which might account for beneficial drug effects in infants and children with circulatory failure. Previous studies in animals (19, 20) and man (15) have emphasized the difficulties of evaluating glycoside effects on the myocardial contractile state in some circumstances. Moreover, because clinical benefit does not always coincide with a demonstrable improvement in myocardial function (15), the possibility of a salutary noninotropic mechanism was pursued.

Our studies showed a consistent pattern of change in hemodynamic and oxygen transport variables with anemia. With hematocrit reductions from control values to levels between 10–15%, cardiac output increased, LV dP/dt and heart rate increased, and SVR decreased. Oxygen transport declined as a consequence of the reduction in arterial oxygen content.

It is noteworthy that oxygen consumption increased consistently even though the SOT decreased by approximately 40% when hematocrit was reduced to 10–15% (see Tables 1 and 2). Under most physiologic conditions in which SOT is independently reduced, oxygen consumption initially remains unchanged and then is decreased by further, more severe limitations in oxygen transport (26–28). With the decline in oxygen transport and consumption there is metabolic evidence of tissue hypoxia, reflected by an increase in arterial blood lactate concentration (27–29). For oxygen consumption to increase as it did in the present study suggests that metabolic demands were increasing with moderate anemia. The findings herein are most easily explained by the fall in oxygen transport and attendant rise in oxygen extraction stimulating the release of catecholamines which, in turn, increase cardiac output, LV dP/dt, and heart rate. The decrease in viscosity with anemia also may have contributed to the augmented cardiac output and LV dP/dt. The association of elevated levels of catecholamines with congested circulatory states has been shown in adult patients by a number of authors (30–33). In addition, catecholamines may have other extracardiac effects that stimulate calorigenesis and increase the systemic metabolic rate (34, 35); these extracardiac effects may contribute substantially to the initial elevation in oxygen consumption seen in the animals made anemic in this study and seen previously in a study of anesthetized adult dogs made progressively anemic (see Fig. 2, Ref. 36). Using estimates of myocardial oxygen consumption at rest, it is clear that the increase in cardiac work during anemia could not account for
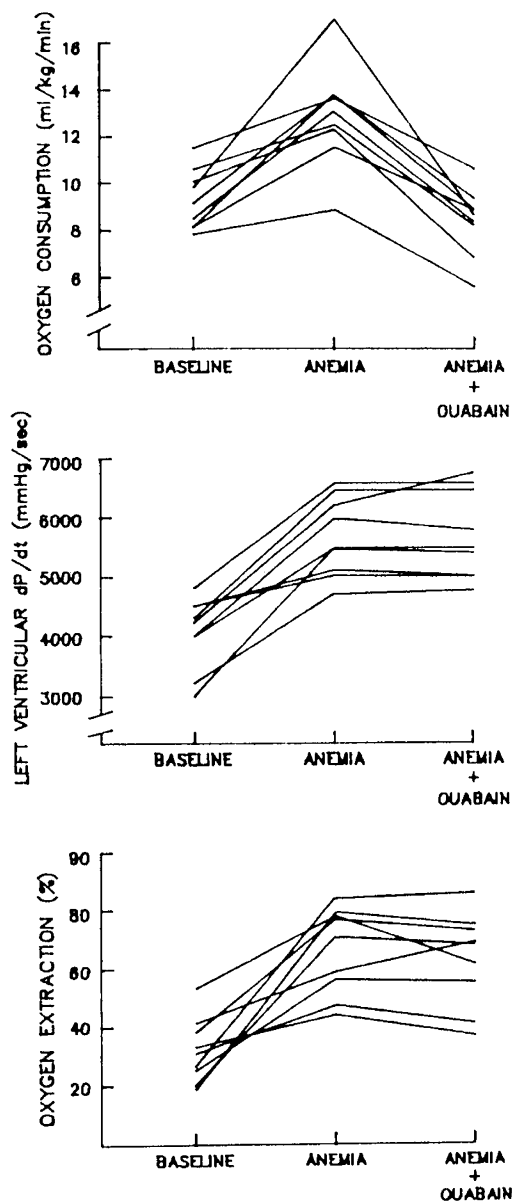

Fig. 4. Patterns of change of oxygen consumption, LV dP/dt, and arterial oxygen extraction in the nine study animals during the three experimental conditions: baseline, anemia alone, and anemia during ouabain administration.
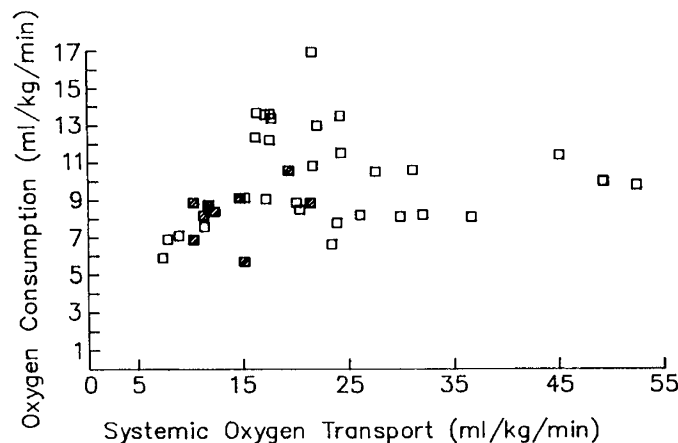

Fig. 5. The relationship of oxygen transport to consumption in all animals. The 39 points represent 27 points from nine study animals (baseline, anemia, anemia + ouabain) and 12 points from the four control animals (baseline, anemia × 2 h, severe anemia). The *points* representing animals receiving ouabain infusion are *cross-hatched*.

the 3 ml O_2/kg min increase in whole body oxygen consumption.[1]

With hematocrit reductions below 10% produced in the four control group lambs reviewed in this study, cardiac function as manifested by LV dP/dt and heart rate was maintained, but cardiac output fell slightly. There is no apparent explanation for this reduction in cardiac output. The further reduction of oxygen transport with profound levels of anemia, however, is associated with reduced oxygen consumption, a further increase in the fractional oxygen extraction, and evidence of tissue hypoxia, evidenced by the significant change in base deficit (Table 1).

From control studies presented herein, it is apparent that the effects of anemia are sustained and reproducible over a 2-h period of observation; this is evidenced by the anemia-induced alterations being similar at 30-min and 2-h observation points (Table 1). However, the addition of ouabain infusion to the anemic preparation causes several changes in this model. Myocardial function, as evidenced by LV dP/dt, heart rate, and central venous pressure, is affected little. VO_2, cardiac output, and stroke work fall. SOT remains low. The pattern of reduced SOT in the presence of preserved LV function is similar to findings of clinical studies in patients with anatomic congenital cardiac lesions (such as ventricular septal defect or a large patent ductus arteriosus) associated with normal left ventricular pump function but reduced levels of systemic blood flow and, therefore, SOT (15, 21). These similarities reinforce the notion that cardiac glycosides may exert a portion of their beneficial effect on the circulation through sites other than the myocardium itself. Because of this possibility, the extracardiac effects of ouabain were examined in our data analysis.

There are several possible explanations for the reduction in oxygen consumption and cardiac output following ouabain infusion. 1) Circulatory function may have been reduced. We have no evidence for this as the indices we used to estimate myocardial function did not change following ouabain infusion; there were no significant changes in arterial blood gases or base buffering capacity following ouabain infusion; oxygen extraction did not rise further following ouabain infusion; and no animal underwent hemodynamic deterioration or died during the infusion period. 2) There may have been a reduction in metabolic demands to account for the ouabain-related fall in oxygen consumption. Although cardiac work was reduced by 32% following ouabain administration, the change is not high enough to account for the 35% reduction in total systemic oxygen consumption following ouabain infusion (see prior calculations in the footnote). Moreover, there is no evidence from animal observation or arterial blood gas analysis that the work of respiration changed significantly following ouabain infusion. 3) The fall in oxygen consumption could be related to altered effects of the demonstrated high levels of circulating catecholamines. In fact, catecholamine levels continued to rise following ouabain infusion to the anemic animals, but the tissue effects of the catecholamines may have been modified by the presence of ouabain. Cardiac glycosides are known to inhibit the energy requiring membrane-bound sodium-potassium ATPase pump system, an enzyme complex which is stimulated by circulating catecholamines (38). Ouabain may have acted in this case by antagonism of the peripheral catecholamine effects, thereby reducing systemic oxygen consumption, but leaving peripheral catecholamine levels elevated. This mechanism would be in concert with observations on cardiac glycoside effects in hypovolemic dogs

(39) and in adults with respiratory distress (40). Alternatively ouabain may act through a central mechanism to reduce oxygen consumption to achievable levels of oxygen transport. The site or mechanism of this proposed central regulatory system is beyond conjecture at this time. 4) Systemic blood flow redistribution may have diverted flow from metabolically active tissues, such as brown fat. Because the flow measurements we made were global rather than regional, we cannot test this possibility with the data collected.

In summary, anemic circulatory stress in lambs increased heart rate, LV dP/dt, cardiac output, central venous pressure, arterial oxygen extraction, and systemic oxygen consumption. Ouabain infusion to anemic lambs did not change oxygen extraction or alter the balance between oxygen transport and consumption, but reduced VO_2, cardiac output, and stroke work. Circulating catecholamine levels rose during the period of anemia and ouabain infusion. These studies confirm an effect of cardiac glycosides that is not inotropic, but may be of benefit to subjects in high output hemodynamic states.

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[1] $\dfrac{5-8 \text{ g}}{\text{kg}} \text{ heart} \times \dfrac{0.8 \text{ mmol } O_2}{\text{min} \times 100 \text{ g}} \text{ (37)} \times \dfrac{22.4 \text{ ml } O_2}{\text{mmol } O_2} =$

$\dfrac{0.9 - 1.4 \text{ ml } O_2}{\text{kg} \times \text{min}} \text{ myocardial } VO_2 \text{ at rest}$

This value would have to increase about 3-fold to account for the increase in whole body oxygen consumption.

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