Anesthesiology
56:84-92, 1982

Myocardial Functional and Metabolic Responses to Ischemia in Swine during Halothane and Fentanyl Anesthesia

Robert G. Merin, M.D., Pieter D. Verdouw, Ph.D.,† Jan Willem de Jong, Ph.D.‡*

The effect of 60 per cent reduction in flow to the left anterior descending (LAD) coronary artery in young swine during N_2O–pancuronium anesthesia supplemented with either halothane (0.52 per cent end-tidal) or fentanyl (50 $\mu g \cdot kg^{-1}$ bolus, 100 $\mu g \cdot kg^{-1} \cdot h^{-1}$ infusion) was compared. The presence of ischemia was assessed from coronary arterial-venous (a-v) blood content differences of O_2, H^+, lactate, K^+, and inosine. Cardiac output and left ventricular pressure indices were used to estimate ventricular function. Before stenosis, mean aortic pressure (MAP), left ventricular systolic pressure, (LVSP) rate of rise of LVSP (dP/dt), peak contractile element velocity (V_{ce} Peak), and systemic vascular resistance (SVR) were higher during fentanyl (MAP = 137 mmHg; LVSP = 160 mmHg; LVdP/dt = 2230 $mmHg \cdot s^{-1}$; V_{ce} Peak = 67 $l \cdot s^{-1}$; SVR = 5,930 $dyne \cdot s \cdot cm^{-5}$) than during halothane (MAP = 80 mmHg; LVSP = 96 mmHg; LVdP/dt = 930 $mmHg \cdot s^{-1}$; V_{ce} Peak = 42 $l \cdot s^{-1}$; SVR = 2,945 $dyne \cdot s \cdot cm^{-5}$). Heart rate (HR), left ventricular end-diastolic pressure (LVEDP), cardiac output (CO) and stroke volume (SV) were not significantly different. LAD coronary blood flow (CBF) and regional myocardial oxygen consumption ($\dot{V}_{O_2}$) were also higher during fentanyl (CBF = 40 $ml \cdot min^{-1}$; $\dot{V}_{O_2}$ = 3.5 $ml \cdot min^{-1}$) than during halothane (CBF = 26 $ml \cdot min^{-1}$; $\dot{V}_{O_2}$ = 2.1 $ml \cdot min^{-1}$). Significant extraction of lactate without v-a differences of K^+ and inosine indicated that the hearts during both anesthetics were well-oxygenated. After 30 min of 60 per cent reduction in LADCBF, the metabolic and functional effects were similar during both anesthetics. Lactate extraction changed to production and coronary v-a differences of H^+, K^+, and inosine became positive or increased. In addition, O_2 extraction increased as well. There was little change in HR, SVR, MAP, LVdP/dt, or V_{ce} Peak with either anesthetic, but CO and SV decreased and LVEDP increased during both anesthetics indicating global pump dysfunction. Subsequent to 30 min of reperfusion, the metabolic indices returned towards control although lactate extraction was still lower than before stenosis with both anesthetics. CO and LVdP/dt did not recover with halothane and SV was still depressed with both halothane and fentanyl. MAP decreased further with both anesthetics and HR and SVR increased after reperfusion during fentanyl anesthesia. In summary, 60 per cent decrease in LADCBF resulted in equivalent depression in ventricular pump function and degree of ischemia during halothane or fentanyl supplemented N_2O–pancuronium anesthesia in young swine. There was partial recovery both functionally and metabolically with both agents. Thus, the effect of significant stenosis of the LADCA was equivalent whether the hearts had a high (fentanyl) or low (halothane) O_2 supply and demand before stenosis. (Key words: Anesthetics, intravenous: fentanyl. Anesthetics, volatile: halothane. Heart: blood flow, myocardial; cardiac output; coronary occlusion; myocardial function; oxygen consumption; vascular pressures. Metabolism: fatty acids; glucose; lactate; phosphate; inosine. Oxygen: consumption, heart.)

ANESTHETICS produce characteristic cardiovascular effects which may modify the response of the heart to ischemia. The halogenated inhaled anesthetics (halothane and enflurane) depress the cardiovascular system, decreasing myocardial function, oxygen supply and demand.[1,2] Balanced anesthetic techniques based on narcotic analgesics appear to produce minimal functional cardiac depression, but may be associated with arterial hypertension which would increase myocardial oxygen supply and demand. Although the normal coupling between supply and demand is not altered by anesthetics in normal hearts,[1-3] the response during ischemia may be different. In addition, ischemia itself results in decreased ventricular function which may be compounded by anesthetic depression.[4] In order to delineate the effects of two commonly used anesthetic regimens on the response of the heart to ischemia in the intact animal, we have utilized an ischemic porcine model developed in our laboratory for drug evaluation.[5,6] Swine were chosen because the response of the porcine heart to ischemia appears to resemble that of humans insofar as arrhythmias, metabolism and development of collateral flow are concerned.[7-9] The purpose of these experiments was to compare the functional and metabolic responses of the porcine heart to a 30-min period of 60 per cent reduction in left anterior descending coronary artery flow during halothane-supplemented nitrous oxide anesthesia (low myocardial function and perfusion) and fentanyl-supplemented nitrous oxide anesthesia (high myocardial function and perfusion).

Methods

The model has been described previously in detail (fig. 1).[5] Briefly, after an overnight fast, 20- to 30-kg Yorkshire piglets were anesthetized by mask with halothane

* Professor, Department of Anesthesiology, University of Rochester School of Medicine.

† Director, Laboratory for Experimental Cardiology.

‡ Director, Cardiochemistry Laboratory, Thoraxcenter, Erasmus University, Rotterdam, The Netherlands.

Received from the Thoraxcenter, Erasmus University, Rotterdam, The Netherlands. Accepted for publication July 10, 1981. The project was performed at the Thoraxcenter, Erasmus University, Rotterdam, The Netherlands, while Dr. Merin was a Senior Visiting Scientist. Supported in part by DHEW grants HL13257 and HL31750 (Research Career Development award to Dr. Merin). Dr. de Jong is a Dutch Heart Association Established Investigator. Presented in part at the 1977 annual meeting of the American Society of Anesthesiologists.

Address reprint requests to Dr. Merin: Department of Anesthesiology, University of Texas Health Science Center, 6431 Fannin, Room 5020, Houston, Texas 77030.

0003-3022/82/0200/0084 $00.95

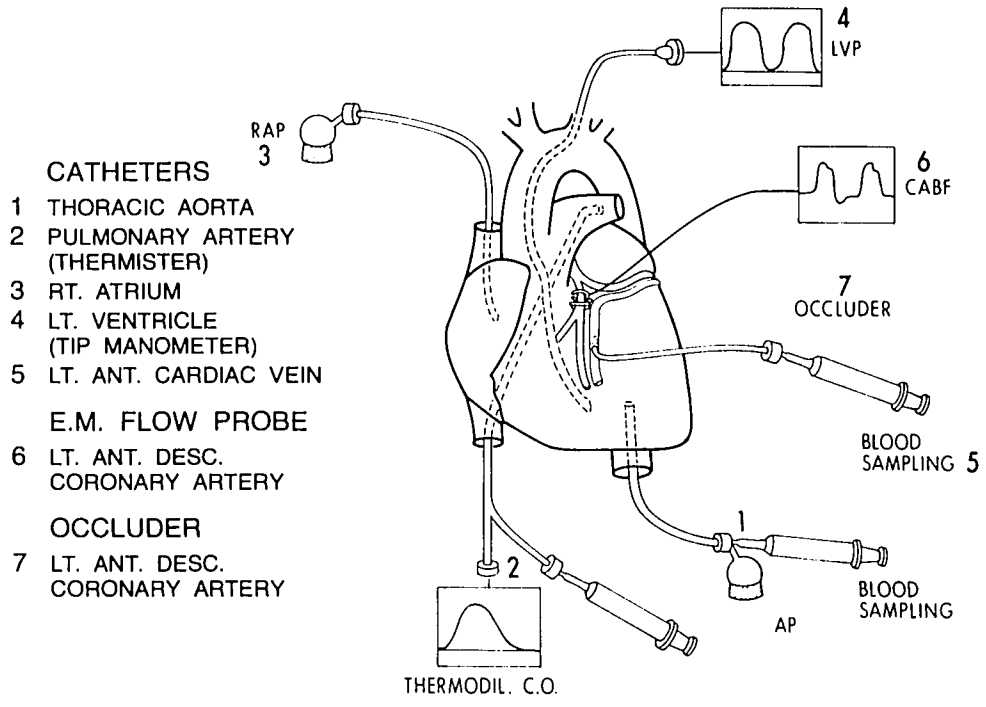

FIG. 1. Schematic of experimental model. EM = electromagnetic; AP = aortic pressure; thermodil. CO = thermodilution cardiac output, RAP = right atrial pressure; LVP = left ventricular pressure; CABF = coronary artery blood flow.

and nitrous oxide–oxygen. The tracheas were intubated with a cuffed tube and ventilation was controlled with a volume limited ventilator throughout the experiment in order to maintain arterial carbon dioxide tension at 35–40 mmHg. Sodium chloride (0.9 per cent) was infused through a catheter in an ear vein at 3–4 $ml \cdot kg^{-1} \cdot h^{-1}$. Blood temperature was monitored and controlled by external heating. With the aid of fluoroscopy, cardiac catheters were placed as follows: an 8F Cournand in the thoracic aorta; a 7F triple-lumen balloon-tipped thermal dilution catheter (Edward Laboratories) in the pulmonary artery; an 8MMC Dallons Telco manometer tipped catheter in the left ventricle; and an 8F Cournand in the right atrium. Through a modified median sternotomy, approximately 1 cm of the left anterior descending coronary artery (LAD) just distal to the circumflex branching was dissected. An electromagnetic flow probe (Skalar, Delft, Netherlands) and adjustable screw clamp were positioned around the artery. The probe was calibrated *in vitro* and zero adjusted at intervals throughout the experiment by occlusion of the LAD with an atraumatic clamp. The occlusion lasted less than 10 s and was never performed within 30 min of any measurements. A small catheter was inserted in the accompanying anterior ascending coronary vein so that the venous blood sampled was predominately from an area supplied by the LAD. Aortic and atrial pressures were transduced through Statham® p23 db transducers and recorded together with the electrocardiogram, the ventricular pressure and coronary flow on a Siemens Oscillomink B.® polygraph (frequency response flat to 1,200 Hz). The first derivative of the left ventricular pressure (LVdP/dt) was obtained using a differentiating network with a phase shift of less than 2 per cent at 100 Hz. Left ventricular contractile element velocity (V_{ce}) was calculated by the method of Brower *et al.*[10] Although there is general agreement that actual V_{ce} cannot be measured by this technique, there is good evidence that the calculation decreases the load (pre and after) dependence of the dP/dt measurement, and hence, is a reasonable estimate of *in vivo* contractile cardiac function.[11] Cardiac output measurements were made at least in duplicate using the thermal dilution technique with the injection of iced saline through the right atrial port of the thermal dilution catheter and sampling from the distal port in the main pulmonary artery. Duplication was ± 5 per cent.

Biochemical Measurements

End-tidal halothane concentrations were measured by means of gas chromatography. Plasma glucose, potassium, and inorganic phosphate were assayed by autoanalyzer techniques, as was blood lactate.[5] Serum free fatty acids were measured by the Trout modification of the Dole technique.[12] Blood inosine was measured as described previously.[5] Blood gases were determined on a standard electrode system. Oxygen content was calculated from measured O_2 saturation, O_2 tension, and hemoglobin concentration using 1.3 ml of oxygen per gram of hemoglobin as the value for 100 per cent oxyhemoglobin saturation.

TABLE 1. Myocardial Oxygen Supply

	Control	Stenosis	Release
Ca_{O_2}			
Halothane	16.3 ± 0.5*	16.1 ± 0.4*	16.0 ± 0.2*
Fentanyl	18.6 ± 0.6	18.5 ± 0.4	18.4 ± 0.6
CBF			
Halothane	26.5 ± 2.5*	11.5 ± 1.0*†	23.9 ± 2.9*
Fentanyl	40.2 ± 3.6	17.3 ± 1.7†	34.6 ± 6.1
Ca_{O_2} × CBF			
Halothane	4.3 ± 0.4*	2.0 ± 0.2*†	4.1 ± 0.5
Fentanyl	7.5 ± 0.8	3.2 ± 0.3†	6.6 ± 1.2

Values are means ± SEM.
* $P < 0.05$ *vs.* fentanyl.
† $P < 0.05$ *vs.* control.
Ca_{O_2} = arterial O_2 content, $ml \cdot dl^{-1}$. CBF = left anterior descending coronary artery blood flow, $ml \cdot min^{-1}$. Ca_{O_2} × CBF, $ml \cdot min^{-1}$.

CALCULATIONS

Stroke volume was calculated as the quotient of cardiac output and heart rate. Systemic vascular resistance was calculated as the quotient of mean aortic blood pressure minus right atrial blood pressure and cardiac output. The results were converted to $dyne \cdot s \cdot cm^{-5}$. Coronary vascular resistance was calculated as the quotient of mean aortic blood pressure minus right atrial pressure and coronary blood flow. Per cent oxygen or substrate extraction was calculated as the quotient of the respective arterial-coronary venous plasma or blood content difference and the arterial plasma or blood concentration × 100. Regional oxygen or substrate uptake was calculated as the product of the respective arterial-coronary venous plasma or blood content difference and LAD coronary blood flow.

EXPERIMENTAL PROTOCOL

After completion of the surgical preparation, 60-min stabilization time was allowed while an infusion of 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$ pancuronium bromide was begun and continued for the remainder of the experiment. In the animals where fentanyl was to be studied, halothane was discontinued. Nitrous oxide was continued at a 60–65 per cent concentration. At the end of the 60 min of stabilization, 50 μg/kg fentanyl was given intravenously as a bolus dose followed by 100 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (12 animals). In 13 animals, the halothane concentration was adjusted to maintain aortic systolic pressure above 90 mmHg (mean end-tidal concentration 0.52 per cent) and kept at that concentration throughout the remainder of the experiment. In previous experiments, 0.46 per cent (end-tidal) halothane in 60 per cent nitrous oxide was just sufficient to keep swine from responding to noxious stimuli.[3] Thirty minutes after the bolus injection of fentanyl or the maintenance of a constant halothane concentration, control hemodynamics and coronary blood flow measurements were made and aortic and coronary venous blood were sampled. The adjustable screw clamp on the left anterior descending coronary artery was tightened to produce 40–50 per cent of the control coronary blood flow and adjusted as necessary to keep this flow constant for 30 min. At the end of that time, all hemodynamic measurements and blood sampling were repeated. In some animals epicardial ST segment changes were analyzed, using the method of Maroko *et al.*[13] The clamp was then released gradually over 5 min, and reperfusion allowed for another 25 min at which time a third set of measurements were made and blood samples were withdrawn. A two-tailed Student's *t* test for paired and unpaired samples was used for statistical analysis.

Results

Body temperature and arterial blood gases were within physiological limits, unchanged throughout the experiment, and not different for the two anesthetics. Hemoglobin concentration was higher during fentanyl (13.8 ± 0.4 $g \cdot dl^{-1}$) than during halothane (12.0 ± 0.3 $g \cdot dl^{-1}$).

There are two major areas of importance to be considered and the data will be presented accordingly. First, the interaction between the anesthetics, ischemia and myocardial oxygen balance will be analyzed. Secondly, the effect of ischemia on global ventricular function during the two anesthetics will be compared.

MYOCARDIAL OXYGEN BALANCE: SUPPLY *VS.* DEMAND

Myocardial oxygen supply is the product of coronary blood flow and arterial oxygen content. Inasmuch as both coronary blood flow and arterial oxygen content (as a result of the higher hemoglobin concentration) were higher during fentanyl anesthesia, the product was also significantly higher and remained so during the course of the experiment (table 1).

Myocardial oxygen demand is not quantitated so easily as myocardial oxygen supply. If there is no restriction on coronary blood flow, then myocardial oxygen consumption is a reasonable measure. However, with coronary stenosis, as in this study, the coronary blood flow may not be able to adjust to myocardial oxygen demand and myocardial oxygen consumption may not be a good estimate. Tabulation of the determinants of myocardial oxygen demand[14] may help to indicate the state of myocardial oxygen demand. *Heart rate* tended to be higher during fentanyl anesthesia although the difference was significant only during reperfusion (table 2). We used the isovolumic left ventricular pressure indices to estimate *contractile function*. Both LVdP/dt and the con-

tractile element velocity estimate, V_{ce} Peak, were higher during fentanyl than halothane (table 2). *Wall tension* is the most difficult estimate of all. It is a function of intraventricular pressure, diameter, and wall thickness, predominantly during systole.[14] Consequently left ventricular systolic pressure or better, the integral of left ventricular systolic pressure, the systolic pressure time index (SPTI) and end-diastolic pressure (if compliance does not change) should be at least proportional to wall tension. Both left ventricular systolic pressure and systolic pressure time index were greater during fentanyl than during halothane, and there was no difference in left ventricular end-diastolic pressure (table 2). Hence, there can be little doubt that myocardial oxygen demand (and in fact myocardial oxygen consumption) was markedly greater during fentanyl (table 2).

The crucial factor is whether or not oxygen supply is adequate for oxygen demand. Our experimental design utilized two methods for assessing this balance. Epicardial ST segment analysis proved to be qualitative only in this study. Although there were always ST segment changes during the period of stenosis verifying that there was indeed ischemia, both depression and elevation of the ST segment occurred. Measurement of the degree was difficult and finally abandoned. These observations may be a reflection of the fact that the classic ST segment changes have been documented during coronary occlusion rather than stenosis. In addition, factors other than tissue hypoxia, such as hydrogen ion and potassium imbalance, may also produce changes.[15,16] The major indicator of ischemia in this experiment was metabolic.[17] During stenosis, myocardial extraction of lactate changed from positive to negative and coronary venous blood concentrations of inosine, hydrogen ion and potassium increased (table 3). Arterial-coronary venous blood oxygen content difference and extraction increased. In addition, myocardial plasma glucose extraction and uptake increased markedly (table 4). Significant free fatty acid uptake also continued and extraction actually increased during fentanyl anesthesia. Although the changes in metabolism generally reverted back towards control after reperfusion, lactate extraction was still depressed with both anesthetics (tables 3 and 4).

TABLE 2. Myocardial Oxygen Demand

	Control	Stenosis	Release
HR			
Halothane	118 ± 7	124 ± 2	126 ± 9*
Fentanyl	133 ± 7	148 ± 10	158 ± 9*
Contractility			
LVdP/dt			
Halothane	930 ± 60*	825 ± 80*†	760 ± 70*‡
Fentanyl	2230 ± 190	2010 ± 130	2020 ± 180
V_{ce} Peak			
Halothane	42.1 ± 2.3*	39.2 ± 5.2*	36.6 ± 3*
Fentanyl	66.7 ± 5	62 ± 7.5	65 ± 6
Wall Tension			
LVSP			
Halothane	96 ± 1.7*	86 ± 1.8†*	87 ± 3.6*†
Fentanyl	160 ± 10	147 ± 8	140 ± 7†
SPTI			
Halothane	1440 ± 35*	1390 ± 50*	1270 ± 60
Fentanyl	2080 ± 130	1780 ± 170	1680 ± 240†
LVEDP			
Halothane	7.0 ± 0.4	10.5 ± 2.0	13.3 ± 5
Fentanyl	6.3 ± 1.2	9.1 ± 1.6†	7.8 ± 1.4
$\dot{V}_{O_2}$			
Halothane	2.1 ± 0.2*	1.2 ± 0.2*†	1.8 ± 0.2*†‡
Fentanyl	3.5 ± 0.3	1.9 ± 0.3*	2.9 ± 0.5†‡

Values are means ± SEM.
* $P < 0.05$ *vs.* fentanyl.
† $P < 0.05$ *vs.* control.
‡ $P < 0.05$ *vs.* stenosis.
LVdP/dt = maximum rate of rise of left ventricular pressure, mmHg · s^{-1}. V_{ce} Peak = *in vivo* peak left ventricular contractile element velocity, $l \cdot s^{-1}$. LVSP = left ventricular systolic pressure, mmHg. SPTI = Systolic pressure time index mmHg · s^{-1} · min^{-1}. LVEDP = left ventricular end diastolic pressure, mmHg. HR = heart rate, beats · min^{-1}. $\dot{V}_{O_2}$ = myocardial O_2 consumption, ml · min^{-1} (left anterior descending coronary artery).

VENTRICULAR FUNCTION

Two aspects of ventricular function will be considered, together with the factors that modify these estimates. Left ventricular pressure indices provide measurement of isovolumic function before the aortic valve opens and may be considered to be analogous to isometric tension development in isolated muscle. In the intact heart, increases in rate, diastolic pressure, and aortic pressure all increase the rate of rise of left ventricular pressure (LVdP/dt) without a change in the actual inotropic state of the heart. By relating the dP/dt to the instantaneous pressure in the ventricles, the effect of diastolic and aortic pressure can be lessened, especially the latter.[11] V_{ce} is such a relationship.[10] The pumping function of the heart was evaluated using cardiac output measurements and calculating stroke volume. As with the isovolumic indices, heart rate and diastolic pressure increase the pumping function of the heart without a change in intrinsic contractile function. However, increased aortic pressure, or more precisely, systemic vascular resistance, decreases cardiac output and stroke volume in contrast to the effect on left ventricular pressure development.

Throughout the experiment, both left ventricular pressure indices, dP/dt and V_{ce} Peak, were markedly higher during fentanyl anesthesia (table 5). In addition, LVdP/dt was significantly lower during ischemia with halothane and did not recover with perfusion (table 5). However, this may have been influenced by the simultaneous

TABLE 3. Metabolic Myocardial Ischemic Indices

	Control	Stenosis	Release
O_2a-cv(ml·dl^{-1})			
Halothane	8.4 ± 0.9*	10.7 ± 0.9*†	8.2 ± 0.9*‡
Fentanyl	8.7 ± 0.4*	11.0 ± 9.8*†	8.7 ± 0.9*‡
O_2 per cent extraction			
Halothane	50.6 ± 4.1*	62 ± 3.3*†	47.4 ± 4.5*‡
Fentanyl	46.8 ± 2.7*	59.4 ± 3.7*†	46.8 ± 3.4*‡
Lactate (mmol·l^{-1})			
Art.			
Halothane	1.12 ± 0.1	1.03 ± 0.10	1.11 ± 0.16
Fentanyl	0.93 ± 0.13	0.86 ± 0.1	0.84 ± 0.1
a-cv			
Halothane	0.38 ± 0.9*	−0.6 ± 0.2*†	0.13 ± 0.06*‡§
Fentanyl	0.25 ± 0.07*	−0.52 ± 0.13*†	0.05 ± 0.05*‡
Per cent extraction			
Halothane	34 ± 4*	−75 ± 25*†	14 ± 4*†‡
Fentanyl	28 ± 6*	−60 ± 15*†	7 ± 6†‡
Inosine (mmol·l^{-1})			
Art.			
Halothane	5.6 ± 0.6	5.4 ± 0.7	7.1 ± 0.6
Fentanyl	7.1 ± 0.6	7.1 ± 0.7	6.5 ± 0.6
a-cv			
Halothane	−0.2 ± 0.7	−18 ± 5*†	0.2 ± 1‡
Fentanyl	−0.7 ± 1.1	−11 ± 3*†	1.2 ± 0.6‡
H^+(nEq·l^{-1})			
Art.			
Halothane	35.2 ± 0.3	36.4 ± 0.4	37.1 ± 0.4
Fentanyl	38.9 ± 0.4	37.9 ± 0.7	36.5 ± 0.3
a-cv			
Halothane	−4.1 ± 0.5*	−12.2 ± 0.7*†	−5.1 ± 0.2*‡
Fentanyl	−4.4 ± 0.6*	−10.2 ± 0.8*†	−6.3 ± 0.3*‡
Potassium (mmol·l^{-1})			
Art.			
Halothane	4.9 ± 0.16	5.2 ± 0.2	5.3 ± 0.2
Fentanyl	4.8 ± 0.2	5.0 ± 0.2	5.2 ± 0.1
a-cv			
Halothane	−0.08 ± 0.04	−0.28 ± 0.07*†	0.16 ± 0.07*†‡
Fentanyl	−0.09 ± 0.06	−0.30 ± 0.13*†	0.12 ± 0.06‡

Values are means ± SEM.
* $P < 0.05$ a-cv difference or extraction.
† $P < 0.05$ *vs.* control.
‡ $P < 0.05$ *vs.* stenosis.
§ $P < 0.05$ *vs.* fentanyl.
Art. = arterial concentration. a-cv = arterial coronary venous concentration difference. Per cent extract. = a-cv/art.

decrease in aortic pressure, as V_{ce} Peak was unchanged by ischemia. Cardiac output and stroke volume were similar during fentanyl and halothane anesthesia and both decreased significantly during ischemia (table 5); however, the etiology appeared to be different. Systemic vascular resistance (SVR) which was already high in the control state during fentanyl anesthesia, increased further during ischemia probably resulting in decreased cardiac output and stroke volume. SVR was significantly lower during halothane and did not change through the course of ischemia and reperfusion. LVEDP increased during ischemia with both anesthetics (although the variability during halothane precluded statistical significance). Thus, the combination of increased LVEDP and decreased cardiac output and stroke volume strongly suggests that ischemia resulted in decreased pump function of the heart during both anesthetics.

After reperfusion there was little recovery of pumping function. The slight increase in cardiac output during fentanyl anesthesia was a result of an increase in heart

TABLE 4. Myocardial Metabolism

	Control	Stenosis	Release
Glucose (mmol·l^{-1})			
Art.			
Halothane	4.8 ± 0.6	5.0 ± 0.6	5.2 ± 0.6
Fentanyl	5.2 ± 0.5	4.9 ± 0.6	5.2 ± 0.9
Per cent extraction			
Halothane	−13 ± 15	22 ± 5*†	10 ± 4*‡
Fentanyl	0 ± 3	18 ± 4*†	6 ± 3*
Uptake (mmol·min)			
Halothane	1 ± 8	11 ± 3*†	9 ± 4
Fentanyl	1 ± 9	14 ± 3*†	11 ± 7
Free Fatty Acids (mmol)			
Art.			
Halothane	0.56 ± 0.12§	0.77 ± 0.16§	0.62 ± 0.15§
Fentanyl	1.6 ± 0.3	1.7 ± 0.3	1.5 ± 0.2
Per cent extraction			
Halothane	37 ± 9*	27 ± 6*	15 ± 9
Fentanyl	3 ± 15	17 ± 6*	19 ± 5*
Uptake (mmol·min)			
Halothane	5.6 ± 1.3*	2.2 ± 0.5*†	1.9 ± 1.4
Fentanyl	11 ± 10	6 ± 2*	6.2 ± 2.0*

Values are means ± SEM.
* $P < 0.05$ per cent extraction or uptake.
† $P < 0.05$ *vs.* control.
‡ $P < 0.05$ *vs.* stenosis.
§ $P < 0.05$ *vs.* fentanyl.
Art. = arterial concentration. a-cv = arterial coronary venous concentration. Per cent extraction = a-cv/art. Uptake = a-cv x coronary blood flow.

rate. Stroke volume remained decreased with both anesthetics. LVEDP was variable and no significant changes were seen although it tended to be higher during halothane. Again, this could be related to a significantly lower heart rate as compared to fentanyl.

Discussion

There can be no doubt that the 60 per cent reduction in left anterior descending coronary artery blood flow produced during this experiment resulted in ischemia of the cardiac muscle supplied by that vessel. In addition to the qualitative effects on the epicardial electrocardiogram, analysis of the constituents of the venous blood draining from that area of the heart compared with the arterial blood provide conclusive evidence for this statement. The most commonly accepted metabolic index of cardiac muscle ischemia is that of lactate production.[17] However, during this experiment not only was there production of lactate, but there was also a marked and significant increase in coronary venous concentrations of hydrogen ion, potassium, and inosine. Inosine is a metabolite of ATP and an increase in coronary venous concentration has been shown to reflect cardiac muscle ischemia and ATP depletion.[5,18] Further evidence of the insufficiency of coronary oxygen supply was the consistent increase in myocardial oxygen extraction. Finally, in the presence of insufficient oxygen, cardiac muscle attempts to compensate for the insufficient production of energy through aerobic pathways by an increase in anaerobically mediated glycolysis. The significant increase in plasma glucose extraction was final confirmation of the ischemia produced.[17]

The major objective of this study was to compare the effect of ischemia in animals anesthetized with halothane and fentanyl supplemented nitrous oxide anesthesia. There appeared to be little difference in the degree of ischemia estimated by the metabolic indices referred to previously. Consequently, we must conclude that the decrease in oxygen supply produced by the coronary stenosis was no more deleterious to metabolic function when the initial oxygen supply and demand were high as during fentanyl anesthesia or when the supply-demand indices were low as during halothane anesthesia.

The major difference in ventricular function and hemodynamics between the two anesthetics lay in the high ventricular and aortic pressures and systemic vascular resistance during fentanyl anesthesia. As a result of this markedly increased afterload, although the isovolumic contractile function of the heart during fentanyl was markedly greater than during halothane anesthesia, pumping function of the heart was not significantly different. With both anesthetics this degree of coronary stenosis produced definite evidence of decrease in global pump function. Cardiac output and stroke volume were decreased during both anesthetics together with an in-

TABLE 5. Ventricular Function

	Control	Stenosis	Release
Modifying Factors			
Heart rate			
Halothane	118 ± 7	124 ± 2	126 ± 9†
Fentanyl	133 ± 7	148 ± 10	158 ± 9*
LVEDP			
Halothane	7.0 ± 0.4	10.5 ± 2	13.3 ± 5
Fentanyl	6.3 ± 1.2	9.1 ± 1.6*	7.8 ± 1.4
MAP			
Halothane	79.7 ± 2.5†	69.9 ± 1.3*†	71 ± 2.9*†
Fentanyl	137.2 ± 7	128.8 ± 7.7	112.2 ± 6.9*‡
SVR			
Halothane	2945 ± 145†	2980 ± 170†	3160 ± 300†
Fentanyl	5930 ± 540	6630 ± 750	6190 ± 660‡
Isovolumic LVdP/dt			
Halothane	930 ± 60†	825 ± 80*†	760 ± 70†‡
Fentanyl	2230 ± 190	2010 ± 130	2020 ± 180
V_{ce} Peak			
Halothane	42.1 ± 2.3†	39.2 ± 5.2†	36.6 ± 3†
Fentanyl	66.7 ± 5	62 ± 7.5	65 ± 6
Pump			
CO			
Halothane	2.10 ± 0.08	1.85 ± 0.1*	1.84 ± 0.12*
Fentanyl	1.94 ± 0.15	1.66 ± 0.13*	1.77 ± 0.13
SV			
Halothane	18.5 ± 1.4	15.6 ± 1.4*	15.8 ± 1.6*†
Fentanyl	15.3 ± 1.7	11.9 ± 1.4*	11.3 ± 0.9*

Values are means ± SEM.
* $P < 0.05$ *vs.* control.
† $P < 0.05$ *vs.* fentanyl.
‡ $P < 0.05$ *vs.* stenosis.
LVEDP = left ventricular end diastolic pressure, mmHg. MAP = mean arterial pressure, mmHg. SVR = systemic vascular resistance, dyne·s·cm^{-5}. LVdP/dt = maximum rate of rise of left ventricular pressure, mmHg·s^{-1}. V_{ce} Peak = *in vivo* peak left ventricular contractile element velocity, l·s^{-1}. CO = cardiac output, l·min^{-1}. SV = stroke volume, ml.

crease in left ventricular filling pressure indicating significant pump dysfunction.

Reperfusion of coronary arteries totally occluded for more than 15 min in pigs has been reported to result in no metabolic improvement.[19] Fifty per cent flow reduction of the left anterior descending coronary artery in dogs for one hour with reperfusion for two hours was followed by partial functional recovery.[20] Consequently, we reasoned that reperfusion after a 50–60 per cent decrease in left anterior descending coronary artery blood flow in the pig would result in recovery and might allow for further differentiation between the effects of anesthetics. After 30 min of reperfusion, left anterior descending coronary artery blood flow and regional oxygen consumption and extraction had returned to control values, and lactate was no longer being produced. However, lactate extraction was less than before occlusion, suggesting that some ischemia persisted. Inosine, potassium, and hydrogen ion concentration in coronary venous blood had also returned to pre-stenosis values with no difference between anesthetics. The indices of left ventricular contractile performance remained higher with fentanyl anesthesia after reperfusion although this may well be related to the increased heart rate and afterload. Although cardiac output recovered with fentanyl to a greater extent than with halothane, this was a function of heart rate as stroke volume remained depressed with both anesthetics.

Interest in the interaction between anesthetics and the ischemic heart has increased in the last five years. The initial study of Bland and Lowenstein[21] suggested that halothane improved the balance of oxygen supply and demand in an ischemic dog heart model. Several other investigators have come to this same conclusion using halothane (table 6).[22–26] However, in most instances, halothane was administered to animals already basally anesthetized and with markedly increased heart rates and arterial pressures. When the administration of anesthetic resulted in a decrease in these determinants of oxygen demand, then there appeared to be a beneficial effect on the oxygen supply and demand relationship. This was most clearly illustrated by the study of van der Vusse *et al.*[27] who investigated the effect of fentanyl, 25 μg·kg^{-1} iv bolus dose, on a dog model with reversible coronary stenosis. With heart rate uncontrolled, the administration of fentanyl resulted in appreciably less ischemia (judged by metabolic indices) than during the same degree of coronary stenosis in the basally anesthetized animals. This was accompanied, however, by decreases in heart rate, arterial pressure, and left ventricular pressure indices. When the same experiment was conducted with heart rate fixed by atrial pacing, there was little effect of fentanyl on the metabolic ischemic markers. In a preliminary study reported at the end of their publication, Verrier *et al.*[22] also indicated that the decrease in heart rate produced by halothane in their preparation was responsible for the more favorable coronary blood flow pattern and distribution seen in their model. Tinker and Harrison[23] noted that extraction *decreased* markedly in their right heart bypass model of ischemia when anesthetizing concentrations of halothane were compared to nitrous oxide and 0.2 per cent halothane. Although there was a marked decrease in arterial pressure under these circumstances, heart rate remained unchanged. Utilizing a study protocol similar to ours, Hickey *et al.*[24] saw no hemodynamic electrocardiographic or metabolic effect of a 40 per cent decrease in left anterior descending coronary artery blood flow in a dog model during 1.2 MAC halothane anesthesia. Only with high concentrations of halothane (2.1 × MAC) and low arterial pressures was

TABLE 6. Anesthetic—IHD Dog Models

	Anesthetic	Model	Control	Anesthetic Effect	
				O_2 Demand	Ischemia
Bland and Lowenstein[21]	Halothane, 0.75 per cent	CL-R	Hyper	−−	++
Gerson *et al.*+	Halothane, 1.1 per cent	CL-R	Hyper	−−	++
van der Vusse *et al.*[27]	Fentanyl, 25 μg/kg	CS	Hyper	−−	++
Verrier *et al.*[22]	Halothane, 0.8 per cent	CS	Hyper	−−	++
Smith *et al.*[26]	Halothane, 1.0 per cent	CL-I	Hyper	−	++
Tinker and Harrison[23]	Halothane, 0.9 per cent	CS	Hyper	±	±
Hickey *et al.*[24]	Halothane, 1.0 per cent	CS	±	±	±
Prys-Roberts *et al.*[25]	Halothane, 1.0 per cent N_2O 66 per cent	CL-I	↑HR*	±	±

CL-R = coronary ligation, reversible. CL-I = coronary ligation, irreversible. CS = coronary stenosis. Hyper = tachycardia and hypertension in basally anesthetized control state.

* = awake

− → −− = decreased myocardial O_2 demand.

± = no significant change.

+ → ++ = more pronounced decrease in signs of ischemia.

+ = Gerson, J. I., Hickey, R. F., Bainton, C. R. Treatment of myocardial ischemia with either halothane or nitroprusside-propranolol. Abstracts Scientific Papers, American Society of Anesthesiologists, annual meeting, 1978, p. 521–522.

Whenever anesthesia has resulted in improvement in the signs of myocardial ischemia in the dog, significant decreases in the indices of myocardial O_2 demand have also occurred.

there evidence of ischemia in this model. Heart rate was unchanged throughout the experiment although cardiac output declined progressively. In the only study where the interaction of anesthesia and ischemic heart disease in a chronically instrumented animal was reported, Prys-Roberts *et al.*[25] saw a similar cardiodepressant effect of halothane in animals one week after a left anterior descending artery ligation compared to the results before the myocardial infarction. However, there was no indication that anesthesia had a beneficial effect on these ischemic hearts. Thus, the studies reported thus far suggest that the influence of anesthesia on the ischemic heart is related to the effect that the drugs have on myocardial oxygen supply/demand relationships. If a high cardiac oxygen demand can be decreased without markedly interfering with oxygen supply (especially by decreasing heart rate) then the result has universally been improvement in the electrical, functional, and/or metabolic indices of ischemia. Where there has been no such effect, or where myocardial supply has decreased to a greater extent than demand, especially with marked decreases in arterial pressure, then the result has been no effect or worsening of the ischemia. The results of the present study suggest that significant interference in coronary artery blood flow results in an equivalent degree of ischemia whether the oxygen supply and demand levels are high or low at the time of the production of the ischemia.

Although coronary physiology in the swine appears to resemble that of humans to a greater degree than does the dog, clinical application of these results must await confirmation for several reasons. In the first place, fentanyl even in doses larger than those used in this study, rarely results in such marked hypertension, tachycardia, and increased systemic vascular resistance in humans. Secondly, the model employs stenosis of one coronary artery in an otherwise healthy heart. Most patients with coronary artery disease have more than one vessel involved so that the functional response may be different. Many patients with ischemic heart disease may have some degree of ventricular dysfunction. Considering the marked difference in the contractile function of the hearts anesthetized with fentanyl and halothane, it seems likely that the latter might produce deleterious effects in such hearts.

In summary, neither fentanyl nor halothane protected against ischemia produced by a 60 per cent decrease in left anterior descending coronary artery blood flow for 30 min in swine. The degree of ischemia and depression of ventricular function was not different. Thirty minutes of reperfusion of the artery resulted in partial but not complete recovery of both metabolic and functional indices. No advantage was seen for either anesthetic regimen in the acute ischemic, non-failing heart.

The authors thank Sally Basch, H. Marita Rutteman, Rob Van Bremen and Liesbeth Eijsbroeck-Sipman for their technical assistance. Janssen Laboratories provided the fentanyl base and ICI Holland donated the halothane. The gas chromatography of the halothane was performed by J. W. Meilink, Ph.D.

References

1. Merin RG, Kumazawa T, Luka NL: Myocardial function and metabolism in the conscious dog and during halothane anesthesia. ANESTHESIOLOGY 44:402–415, 1976
2. Merin RG, Kumazawa T, Luka NL: Enflurane depresses myocardial function, perfusion and metabolism in the dog. ANESTHESIOLOGY 45:501–507, 1976
3. Merin RG, Verdouw PD, de Jong JW: Dose-dependent depression of cardiac function and metabolism by halothane in swine (Sus Scrofa). ANESTHESIOLOGY 46:417–423, 1977
4. Katz AM: Effects of ischemia on contractile processes of heart muscle. Am J Cardiol 32:456–460, 1973
5. de Jong JW, Verdouw PD, Remme WJ: Myocardial nucleotide

and carbohydrate metabolism and hemodynamics during partial occlusion and reperfusion of pig coronary artery. J Mol Cell Cardiol 9:297–312, 1977
6. Verdouw PD, Schamhardt HC, Remme WJ, et al: Antiarrhythmic, metabolic and hemodynamic effects of Org 6001 (3 α-amino-5 α-androstan-2β-0l-17-one-HC1) after coronary flow reduction in pigs. J Pharmacol Exp Ther 204:634–644, 1978
7. Eckstein RW: Coronary intra-arterial anastamosis in young pigs and mongrel dogs. Circ Res 2:460–465, 1954
8. Christensen GC, Campeti FL: Anatomic and functional studies of coronary circulation in the dog and pig. Am J Vet Res 20:18–26, 1959
9. Brooks H, Al-Sadir J, Schwartz JH, et al: Biventricular dynamics during quantitated anteroseptal infarction in the procine heart. Am J Cardiol 36:765–775, 1975
10. Brower RW, Roelandt J, Meester GT: A device for calculation of dP/dt/P with internal calibration. IEEE Trans Biomed Eng 21:56–60, 1974
11. Mason DT: Usefulness and limitations of the rate of rise of intraventricular pressure (dP/dt) on the evaluation of myocardial contractility in man. Am J Cardiol 23:516–527, 1969
12. Trout DL, Estes EH, Freidberg SJ: Titration of free fatty acids of plasma cholinase. Study of current methods and a new modification. J Lipid Res 1:199–202, 1960
13. Maroko PR, Kjekshus JK, Sobel BE, et al: Factors influencing infarct size following experimental coronary artery occlusion. Circulation 43:67–82, 1971
14. Braunwald E: Control of myocardial oxygen consumption. Am J Cardiol 27:416–432, 1971
15. Kloner RA, Braunwald E: Observations on experimental myocardial ischemia. Cardiovasc Res 14:371–395, 1980
16. Holland RP, Brooks H: TQ-ST segment mapping: A critical review and analysis of current concepts. Am J Cardiol 40:110–129, 1977
17. de Jong JW: Biochemistry of acutely ischemic myocardium, Pathophysiology of Myocardial Perfusion. Edited by Schaper W. Amsterdam, Elsevier/North Holland, 1979, pp 719–750
18. Golstein S, de Jong JW: Changes in coronary venous inosine concentration and myocardial wall thinkening during regional ischemia in the pig. Circ Res 35:111–116, 1974
19. Althaus U, Gurtner HP, Baur H, et al: Consequences of myocardial reperfusion following temporary coronary occlusion in pigs: Effects on morphologic biochemical and hemodynamic findings. Eur J Clin Invest 7:437–443, 1977
20. Ramanathan KB, Raina S, Banka VA, et al: Effects of reperfusion on regional contraction of ischemic and non-ischemic myocardium following partial coronary occlusion. Circulation 57:47–52, 1978
21. Bland JHL, Lowenstein E: Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. ANESTHESIOLOGY 45:287–293, 1976
22. Verrier ED, Edelist G, Consigny PM, et al: Greater coronary vascular reserve in dogs anesthetized with halothane. ANESTHESIOLOGY 53:445–459, 1980
23. Tinker JH, Harrison CE: Protection from myocardial ischemia: Role of anesthetics. ANESTHESIOLOGY 51:S58, 1979
24. Hickey RF, Verrier ED, Baer RW, et al: Does deliberate hypotension produce myocardial ischemia when the coronary artery is stenotic? ANESTHESIOLOGY 53:S89, 1980
25. Prys-Roberts C, Roberts, JG, Föex P, et al: Interaction of anesthesia beta-receptor blockade and blood loss in dogs with induced myocardial infarction. ANESTHESIOLOGY 45:327–339, 1976
26. Smith G, Rodgers K, Thorburn J: Halothane improves the balance of oxygen supply to demand in acute experimental myocardial ischemia. Br J Anaesth 52:577–583, 1980
27. van der Vusse GJ, van Belle H, van Gerven W, et al: Acute effect of fentanyl on hemodynamics and myocardial carbohydrate utilization and phosphate release during ischemia. Br J Anaesth 51:927–935, 1979