総 説 (Review)

Anesthetic Effects on the Coronary Circulation

Richard F. Davis*

Control of Coronary Circulation

The coronary circulation is unique among the organ vascular beds in the body because it provides nutrient blood flow to the organ that itself generates the force that produces the flow of blood. Because of this, traditional consideration of the control of the coronary circulation has given major attention to the hemodynamic parameters that influence coronary blood flow. However it is cirtical to understand that regional myocardial blood flow (RMBF) is neither uniform throughout the myocardium nor constant in any region during the cardiac cycle (Fig. 1). For example, in the left ventricle where, normally, pressure is generated that is equal to aortic systolic pressure, only a small fraction of myocardial blood flow occurs during systole when aortic pressure is highest.[1] Aortic diastolic pressure is the motivating force for the majority of left ventricular (LV) blood flow. This is because even though the aortic pressure is less during diastole, the coronary perfusion pressure (CPP), which may de defined as difference between aortic pressure and LV intracaritary pressure, is greater during diastole because LV pressure is low. In contrast, the low pressures normally generated by the right ventricle and both atria allow a high CPP gradient even during systole, therefore right ventricular and atrial blood flow occurs throughout the cardiac cycle with little interference due to cardiac contraction. Neither is myocardial blood flow uniformly distributed across the thickness of the LV wall. During systole, compressive forces generated by muscle contraction produce virtual cessation of blood flow to suben-

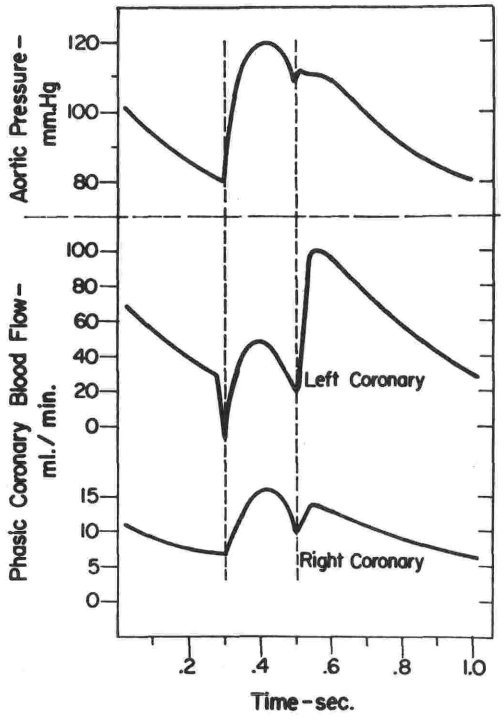

Fig. 1.A. Comparison of phasic coronary blood flow in the left and right coronary arteries with simultaneous aortic pressure measurement. The interval between the vertical dash lines represents systole. (Used with permission.)

*Department of Anesthesiology, Oregon Health Sciences University, Portland, Oregon, U. S. A.

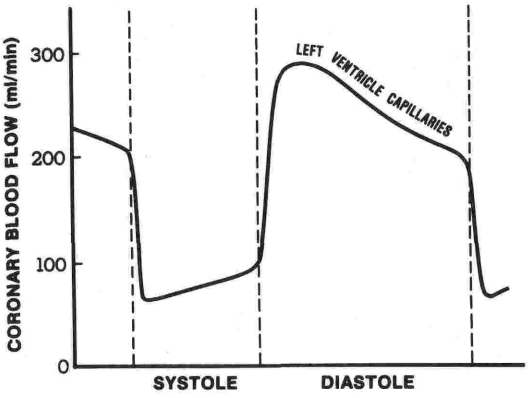

Fig. 1.B. Schematic representation of the phasic nature of the flow of blood through the human coronary capillary bed in the left ventricle. (Used with permission.)

docardial regions while flow may persist in subepicardial regions. Despite this systolic interruption of subendocardial RMBF in the LV, time averaged RMBF is 10 to 20 percent greater in subendo cardial regions, producing endocardial to epicardial blood flow rations normally of 1.1 or 1.2 to 1.[2)]

The relationship between LV intracavitary pressure and LV myocardial blood depends upon the compression of the coronary vasculative generated within the myocardium by myocardial contraction. In the LV, because tissue pressure exceeds coronary venous pressure during much of systole, a Starling resistor mechanism has been proposed to explain the relationship between LV blood flow and tissue pressure.[3)] By this mechanism, effective CPP is equal to aortic perfusion pressure minus myocardial pressure, and is not a constant but varies throughut the cardial cycle. In certain pathologic circumstances, such as aortic insufficiency, the markedly elevated LV cavitary pressure during diastole can significantly impair diastolic coronary blood flow (CBF). However, even in the normal setting, with a Starling resistor, blood flow would be independent of downstream (coronary venous) pressure. In the coronary circulation

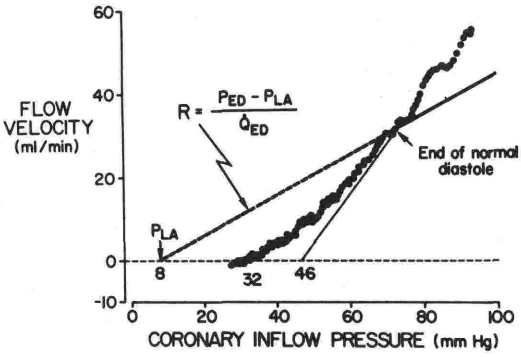

Fig. 2. Comparison of pressure and flow velocity values obtained during the initial portion of a diastole with predicted values from a calculation of resistance in which the zero flow pressure is taken as left atrial pressure. The solid circles represent measured values of pressure and flow obtained during a single long diastole; the measured zero flow pressure intercept is 32 mmHg. If data for the normal diastolic period are linearly extrapolated to the zero flow intercept the resultant pressure is 46 mmHg. The heavy dash line represents the predicted values for the pressure flow relationship based on a resistance calculation from the end diastolic data when the driving pressure is taken to be the difference between end diastolic circumflex coronary artery pressure (Ped) and left atrial pressure (Pla). (Used with permission.)

increments in coronary venous pressure change the diastolic pressure flow relationship to produce less coronary blood flow for any given CPP.[4)] The CPP at zero flow (P_{ZF}) has been used to quantify this relationship (Fig. 2). P_{ZF} increases as coronary venous back pressure increases. Thus it may be appropriate to calculate CPP as aortic diastolic pressure minus P_{ZF} and coronary vascular resistance (CVR) as this value of CPP divided by CBF.

Since blood flow to the LV is greatest during diastole when CPP is greatest, the diastolic interval is an important hemodynamic determinant of LV blood flow. The longer the

diastolic interval, the greater the opportunity for LV blood flow. Because of this, rapid heart rates, which produce a disproportionate decrease in diastolic interval, tend to interfere with coronary blood flow. Fortunately, under normal physiologic circumstances, such as vigorous exercise, this hemodynamic effect is more than offset by another primary coronary vascular control mechanism, namely the increase in CBF produced by the increase in myocardial demand for oxygen and nutrients.

Myocardial metabolism plays a key role in controlling resistance to blood flow in the coronary circulation. An increase in myocardial minute oxygen consumption ($M\dot{V}O_2$) produces a decrease in CVR. This vasodilation results in an increased CBF provided that CPP is maintained. The biochemical linkage for this metabolically induced coronary vasodilation has not been precisely determined. Arterial hypoxemia produces a decrease in CVR while hyperroxia increases CVR, decreses CBF and at the same time tends to decrease $M\dot{V}O_2$.[5] The coronary circulation is sensitive to carbon dioxide tension with hypocapnia producing an increase in CVR and hypercapnia having the opposite effect.[6] The CO_2 effects are proportional to changes in hydrogen ion concentration. Although glucose and nonesterified fatty acids are primary foodstuffs of myocardial metabolism, there is apparently no direct linkage between the blood concentration of these metabolites and CVR.

Adenosine, the major breakdown product of adenosine triphosphate, is a potent coronary vasodilator and may be the major metabolic regulator of coronary blood flow. In the heart, in addition to producing coronary vasodilation, adenosine depresses electrical activity in sinoatrial and atrioventricular nodes, decreases contractility, decreases ventricular automaticity and decreases the augmentation of contractility produced by catecholamines.[7] In 1963, Berne stated the hypothesis that adenosine functions as the mediator of metabolically induced coronary vasomotor activity, providing the linkage between coronary vasodilation and myocardial metabolism.[8] According to this hypothesis, increased myocardial metabolism or tissue hypoxia produces a decrease of high energy phosphate stores (ATP and phosphocreatine) and an increse of the degradation products ADP, AMP and adenosine. Because adenosine is freely disffusible across cell membranes while ATP, ADP and AMP are not, it becomes a major candidate for the role of a transmitter of the vasodilatory signal during hypoxia or ischemia. Because the coronary circulation responds to a variety of substances and conditions as partially noted above, adenosine is clearly not the only mediator of local coronary vasomotor activity. As concluded by Feigl "The adenosine hypothesis remains a hypothesis".[9]

Both major components of the autonomic nervous system (cholinergic and adrenergic) exert significant influence on the coronary vaculature. Parasympathetic stimulation produces coronary vasodilation while sympathetic stimulation intrinsically produces coronary vasoconstriction.[10] The increased chronotropic and inotropic effects of sympathetic stimulation increase $M\dot{V}O_2$ and produce a net coronary vasodilation, however, the direct effect of alpha adrenergic stimulation on the coronary circulation is vasoconstriction.[11] This vasoconstriction is present in both larger epicardial coronary arteries and small endomyocardial vessels. The adrenergic vasoconstriction limits maximum metabolic vasodilation by approximately 30%.[12] The apparent paradox of alpha adrenergically mediated coronary vasoconstriction may have a significant role in the adaptation of the coronary circulation to exercise stress. In a chronically instrumented canine preparation, Chilian has shown that exercise produces an epicardial vasoconstriction that is mediated by alpha adrenergic receptors.[13]

This alpha adrenergic constriction serves to prevent transmural redistribution of blood away from subendocardial regions during exercise, thereby preserving subendocardial CBF. Coronary artery beta adrenergic receptors are of the beta-2 subtype and mediate coronary vasodilation.

Recently much attention has been given to local endothelial control of vascular smooth muscle tone. In 1980 endothelial derived relaxant factor (EDRF) was identified that mediates vascular smooth muscle relaxation.[14] Chemically, EDRF appears to be nitric oxide.[15,16] Some vasodilation, for example that due to acetylcholine, is due to release of EDRF, while other vasodilators, for example adenosine and nitroprusside, are not EDRF dependent. However, in the case of nitroprusside, the vasodilation may result from release of nitric oxide as the nitroprusside molecule is metabolized. Recently, an endothelial derived constricting factor, endothelin, has been described, although its importance in the coronary circulation is not known.[17]

Coronary steal is a phenomenon in which blood flow to an area of myocardium that is dependent on collateral vascular channels for blood flow is decreased when a vasodilation is forced in the collateral vascular bed.[18] An important component of the physiologic setting for coronary steal is a critical or flow limiting stenosis (or a functional equivalent) in the supply vessel perfusing the collateral vascular bed. Because of the proximal flow limiting stenosis, any vasodilation distal to the stenosis produces a decreased distal coronary pressure. Hence the effective perfusion pressure to the collateral vascular bed is decresed. When the collateral vascullar bed is operating at the limit of its vasodilatory reserve, then the decreased pressure results in a decreased collateral blood flow and a redistribution of flow occurs, away from the collateral dependent areas of myocardium to other regions. In order to demonstrate exogenous vasodilator induced coronary steal, proximal perfusion pressure must be held constant.[18] This is because a decreased proximal pressure will produce an autoregulation-mediated decrease in CVR in the distal coronary circulation that results in the same sequence of events in the collateral dependent areas as that produced by an exogenously administered vasodilator.

Myocardial Metabolism

The heart is capable of metabolizing a variety of foodstuffs through normal aerobic pathways. Free fatty acids and glucose are the primary metabolites under normal circumstances. Metabolism of fatty acids proceeds by beta-oxidation and that for glucose by aerobic glycolysis. Both share the Kreb's cycle as the final common pathway (Fig. 3). Lactate is consumed by the heart in proportion to its concentration. Under anaerobic conditions, such as during myocardial ischemia, glucose breakdown proceeds to pyruvate but excess pyruvate cannot be further metabolized via aerobic mechanisms and is therefore converted to excess lactate (Fig 4). Hence, during ischemia the usual state of lactate consumption by the heart is replaced by net lactate production, and this apparent lactate production is due, at least in part, to actual synthesis of lactate from the pyruvate produced during glycolysis. The use of the calculated lactate extraction (coronary A-V lactate concentration difference divided by arterial lactate concentration) to quantify the degree of aerobic metabolism is however problematic. Rather one should quantify the actual amount of lactate that is produced (or consumed) by the heart by including blood flow in the calculation. This value, lactate flux, is the AV lactate difference multiplied coronary blood flow and relates closely to the change in coronary blood flow during ischemia.[19]

During normal aerobic conditions, glycolysis

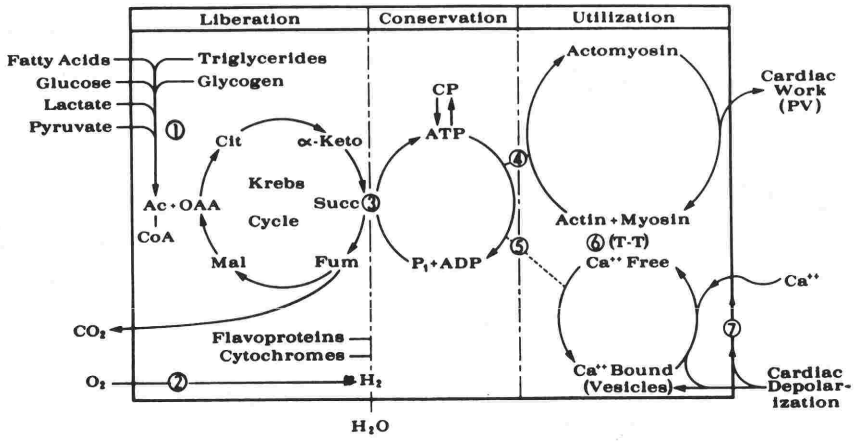

Fig. 3. Schematic representation of the aerobic metabolic processes within cardiac muscle. (Used with permission.)

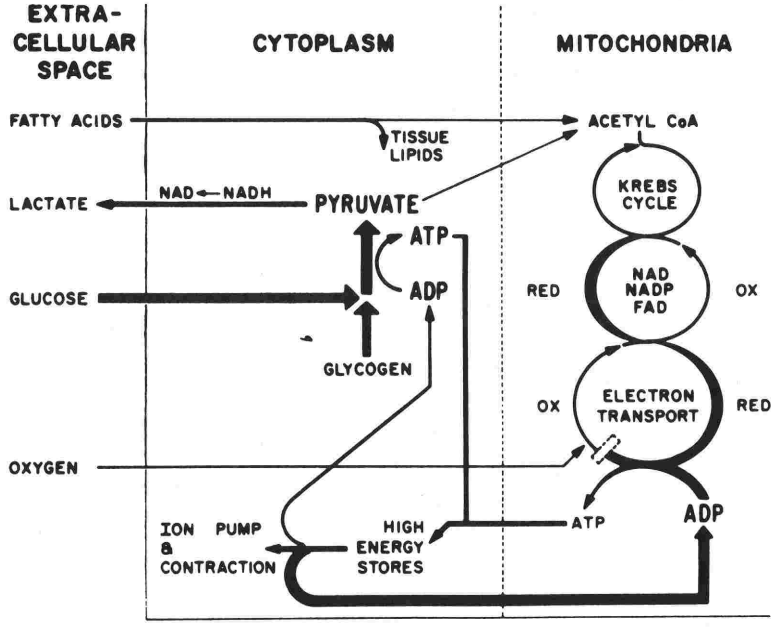

Fig. 4. Schematic representation of anaerobic metabolic processes in myocardial muscle. (Used with permission.)

yields approximately 36 millimoles of ATP per millimole of glucose metabolized and metabolism of free fatty acids has a similar energy production. During ischemic states, there is initially an enhancement of glycolysis but this is insufficient to meet metabolic needs.[20] Lactate accumulation and tissue acidosis subsequently impair anaerobic glycolysis and high energy phosphate production further declines to levels insufficient to support the contractile electrical work of the myocardium.[21]

Anesthetic Effects on Coronary Circulation

Experimental study of the effects of anesthetics on the coronary circulation involves both normal and stenotic coronary vasculature

using direct measurements of CBF and measurements based on the functional, electrophysiologic, or metabolic effects of alterations in CBF. Direct CBF measurement techniques include electromagnetic and ultrasound transit time flow meters and indicator techniques such as redionuclide labeled microspheres.[22] Measurement of ST segment deviation from baseline is the classic electrophysiologic method for detecting myocardial ischemia.[23] Functional measurements that correlate with deficient CBF include the regional wall motion abnormalities of delayed or decreased systolic segment shortening or wall thickening, detected by sonomicrometry or echocardiography, and overall hemodynamic function.[24] Metabolic correlates of decreased CBF include oxidative enzyme (myocardial CK and LDH isoenzyme) depletion from myocardium and the net production of lactate by the myocardium.[25] Finally, myocardial infarct size is often measured to determine the net effect of an intervention on the experimental outcome of ischemic myocardium.[26] Infarct size is most commonly measured using a macroscopic histologic stain, tetrazolium, that selectively bonds to oxidative enzymes and so does not stain infarcted (enzyme depleted) myocardium. Tetrazolium, therefore, produces a negative image of the area of myocardial infarction.[27]

The effects of anesthetics on myocardial function are widely appreciated. In general, all anesthetic drugs produce does dependent decreases of the contractile properties of the myocardium. However in the context of ischemic heart disease, the specific coronary vascular effects of anesthetic drugs, are also of fundamental importance. Numerous studies have investigated the effects of anesthetic durgs and techniques including volatile agents, narcotics, major tranquilizers, sedative hypnotics, and regional anesthetics on the coronary circulation in normal and pathologic states.

The volatile agents in particular have been extensively tested for their effects on coronary circulation. In general, the negative inotropic effects of these drugs lead to decreased $M\dot{V}O_2$ and to a reduction in CBF. This decreased CBF is largely in proportion to the decreased $M\dot{V}O_2$ so that in the absence of gross changes in perfusion pressure, CBF remains adequately linked to myocardial metabolic needs. The volatile agents do produce some direct coronary vasodilation (isoflurane > enflurane > halothane) but the magnitude of vasodilation is far less than that produced by adenosine (Fig. 5).[28] The myocardial contractile depression and coronary vasomotor changes produced by the volatile agents are of theoretical importance especially in the setting of myocarial ischemia and this is where most work has been done.

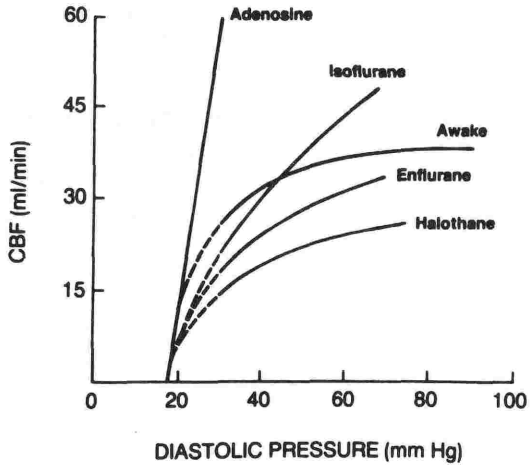

Fig. 5. Schematic representation of the effects of the volatile anesthetic isoflurane, enflurane, and halothane and the vasodilator adenosine on the coronary pressure flow relationship. All three anesthetics tend to increase the slope of the coronary pressure flow relationship. The coronary pressure flow relationship during maximal coronary vasodilation is indicated by the line labeled adenosine. During maximal coronary vasodilation coronary blood flow is completely pressure dependent. (Used with permission.)

Early studies showed that coronary venous oxygen content in areas of myocardial ischemia increased during halothane administration.[29] These observations led to the hypothesis that halothane would produce a decreased myocardial infarct size. In anesthetized dogs, halothane was found to decrease the number of epicardial site showing ST segment elevation and to decrease the total magnitude of ST elevation following coronary artery occulusion.[30] In dogs anesthetized with halothane, the size of myocardial infarction produced by coronary artery ligation is less than in control animals despite a significant decrease in aortic perfusion pressure (Fig. 6).[31] A similar investigation has demonstrated a decreased infarct size, with preserved LV stroke volume when the volatile anesthetic, isoflurane is administered after coronary artery ligation.[32]

In the case of isoflurane, controversy exists regarding its coronary vasodilating properties and the production of coronary steal. In one carefully controlled canite study with collateral dependent myocardium, CBF to the collateral dependent areas was decreased when isoflurane was administered, to a similar extent as when adenosine was administered.[33] A very recent

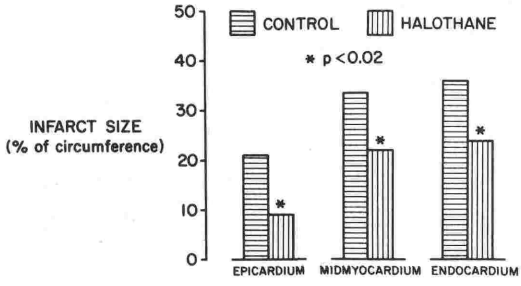

Fig. 6. Comparison of infarct size between halothane treated and control dogs. Data are expressed as a percentage of the circumference occupied by infarction in the epicardium, midmyocardium, and endocardium. Asterisk indicates P value less than 0.05 when compared with corresponding control value. (Used with permission.)

study using a similar experimental model was used to investigate the effects of isoflurane on CBF distribution.[34] These investigators demonstrated that isoflurane (up to approximately 1.8 and 2.5% inspired) did not redistribute blood flow away from a zone of ischemic myocardium. Moreover the CBF decrease that was observed with isoflurane was reversed by restoration of heart rate and CPP to conscious levels. Virtually all clinical studies discussing coronary steal in association with isoflurane have permitted a decreased aortic pressure and therefore are unable to distinguish blood flow redistribution due to vasodilation produced by isoflurane from that due to vasodilation produced by autoregulation.

Nitrous oxide when administered in 50% or greater concentrations to patients undergoing aortocoronary bypass surgery is associated with significant hemodynamic depression.[35,36] In these studies, nitrous oxide also produced a decreased coronary sinus blood flow and an increased myocardial oxygen and lactate extraction. An increased myocardial lactate extraction without a corresponding change in arterial lactate concentration suggests the occurrence of anaerobic glycolysis. In another experimental model, nitrous oxide, when administered to dogs with a critical coronary stenosis produced decreased systolic segment length shortening without overt hemodynamic altercation.[37] This occurrence is, at least consistent with, nitrous oxide induced ischemia. From a mechanistic standpoint, quantitative coronary angiography studies in dogs and pigs have shown significant epicardial coronary artery constriction in association with nitrous oxide that is (in pigs) apparently endothelial mediated.[38,39,40] Thus by an as yet undetermined mechanism, nitrous oxide may be able to produce sufficient coronary vasoconstriction to result in anaerobic metabolism (ischemia) in some clinical and experimental states.

The newest volatile anesthetic agent,

desflurane, has hemodynamic properties in most ways similar to isoflurane. In a recent clinical study comparing isoflurane to desflurane in aortocoronay bypass patients, 1 MAC desflurane was associated with a transiently greater pulmonary capillary wedge pressure than isoflurane.[41] However another similar clinical study found no such difference.[42] In a chronically instrumented canine study, no significant difference between desflurane and isoflurane were seen with regard to CBF, CVR or regional wall thickening.[43]

Narcotic anesthetics are often used in the clinical setting of ischemic heart disease because of their relative lack of cardiovascular effects. One of the early myocardial infarct size studies using a narcotic showed a decreased infarct size in association with the "Lytic cocktail" of morphine, phenergan and thorazine.[44] The mechanism of this effect has not been determined. In a comparison of isoflurane and sufentanil, an infarct size reduction with isoflurane was apparent while sufentanil had no similar effect.[45] However, experimental mortality was higher with sufentanil due to a higher frequency of ventricular fibrillation. Little information is available regarding the direct coronary vascular effects of other tranquilizer and sedative hypnotic anesthetic drugs.

The reported beneficial influence of cardiac sympathectomy during myocardial ischemia led to the hypothesis that sympathetic blockade using a regional anesthetic could decrease myocardial infarct size.[46] In one study, cardiac sympathectomy produced by thoracic epidural injection of lidocaine was associated with an improved endocardial to epicardial blood flow ratio in ischemic areas of myocardium.[47] In another study, myocardial infarct size was reduced by a thoracic epidural anesthetic using lidocaine (Fig. 7).[48] In that study, regional myocardial blood flow to subendocardial areas of the infarct zone was increased as well. The hypothesis that these effects were specifically due to selective cardiac sympathectomy is currently being tested.

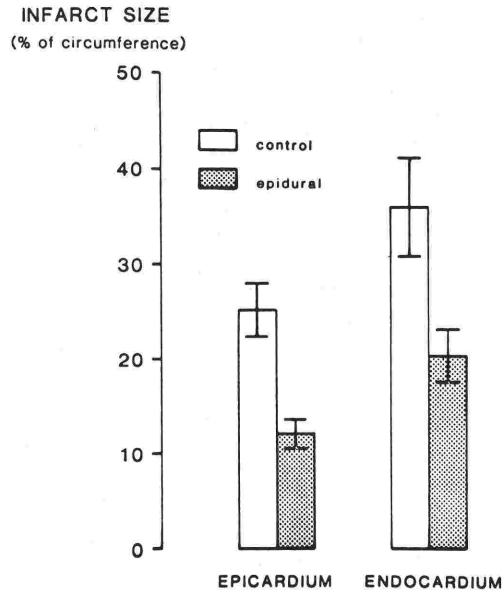

Fig. 7. The percent of the circumference of endocardial surface occupied by infarction in control animals was 36.2±5% (n=7) and in thoracic epidural animals was 20.2±3.0% (n=7). For the epicardial surface corresponding data are 25.2±2.6% for control and 12.2±1.8% for thoracic epidural animals ($p<0.05$, for both comparisons). (Used with permission.)

Conclusion

A full understanding of the effects of anesthetics on the coronary circulation must be based on an understanding of the physiological controls of coronary blood flow coupled with knowledge of myocardial metabolism. Anesthetic agents and techniques have major effects on myocardial contractile function (depression) which decrease $M\dot{V}O_2$ and generally decrease coronary blood flow also. This is often countered by direct depressant effects on vascular smooth muscle (vasodilation) such as is the case with isoflurane and probably

desflurane. Regional anesthetic techniques can decrease sympathetic neural stimulation of myocardium leading to both decreased $M\dot{V}O_2$ (decreased heart rate and contractility) and coronary vasodilation. In some experimental circumstances such induced vasodilation can lead to improved coronary perfusion. However in the presence of collateral flow depedent myocardium and proximal conductance vessel fixed stenosis, a forced distal coronary vasodilation can lead to an adverse redistribution of flow away from the collateral dependent area, the coronary steal. The complex interplay of these, at times conflicting, effects makes it often difficult to predict the net effect of a specific anesthetic agent or technique a CBF and its distribution in a specific clinical situation.

(This paper was in part presented at the 11th Annual Meeting of Japanese Society of Circulation Control in Medicine, in Sapporo, 1990)

References

1) Textbook of Medical Physiology, Seventh Edition, Arthur C. Guyden, M. D., Pg. 296, W. B. Saunders Co., 1986.
2) Feigl, E. O.: Coronary Physiology. Physiol Rev **63**:39, 1983.
3) Downey, J. M., Kirk, E. S.: Inhibition of coronary blood flow by a vascular water fall mechanism. Circ Res **36**:753-760, 1975.
4) Bellamy, R. F., Lowensohn, H. S., Ehrich, W., et al.: Effective coronary sinus occulusion on coronary pressure flow relations. Am J Physiol **239**: H57-H64, 1980.
5) Feigl. E. O.: Coronary Physiology. Physiol Rev **63**:60, 1983.
6) Feigl, E. O.: Coronary Physiology. Physiol Rev **63**:60-68, 1983.
7) Belardinelli, L., Linden, J., Berne, R. M.: The cardiac effects of adenosine. Prog Cardiovasc Dis **32**:73-97, 1989.
8) Berne, R. M.: Cardiac neucleotides in hypoxia: possible role in regulation of coronary blood flow. Am J Physiol **204**:317-322, 1963.
9) Feigl, E. O.: Coronary Physiology. Physiol Rev **63**:95, 1983.
10) Tiedt, N., Religa, A.: Vagal control of coronary blood flow in dogs. Basic Res Cardiol **74**: 267-276, 1979.
11) Ross, G.: Adrenergic responses of the coronary vessels. Circ Res **36**:461-465, 1976.
12) Mohrman, D. E., Feigl, E. O.: Competition between sympathetic vasoconstriction and metabolic vasodilation in the canine coronary circulation. Circ Res **42**:79-86, 1978.
13) Chilian. W. M., Ackell, P. H.: Transmural differences in sympathetic coronary vasoconstriction during exercise in the presence of coronary stenoses. Circ Res **62**:216-225, 1988.
14) Furchgott, R. F., Zawadzki, J. V.: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature **288**:373-376, 1980.
15) Palmer, R. J., Ferrige, A. G., Moncada, S.: Nitric oxide accounts for the biological activity of endothelium-derived relaxing factor. Nature **327**: 524-526, 1987.
16) Ignarro, L. J., Byrns, R. E., Buga, G. M., et al.: Endothelium-derived relaxing factor from a pulmonary artery and vein possesses pharmacologic and chemical properties identical to those of nitric oxide radical. Circ Res **61**: 866-879, 1987.
17) Yanagisawa, M., Kurihara H., Kimura, S., et al.: A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature **332**: 411-415, 1988.
18) Becker, L. C.: Conditions for vasodilator-induced coronary steal in experimental myocardial ischemia. Circulation **57**:1103-1110, 1978.
19) Davis, R. F., Sidi, A.: Lactate extraction fails to accurately reflect regional lactate production in ischemic myocardium. J Cardiothoracic Anes **3**: 321-328, 1989.
20) Apstein, C. S., Gravion, F., Hood, W. B. Jr.: Limitations of lactate production as an index of myocardial ischemia. Circulation **60**:877-888, 1979.
21) Brachfeld, N.: Characterization of the ischemic process by regional metabolism. Am J Cardiol **37**:467-473, 1976.
22) Heymann, M. A., Payne, B. D., Hoffman, J. I. E., et al.: Blood flow measurements with radionuclide-labeled particles. Prog Cardiovasc Dis **20**:55-79, 1977.
23) Maroko, P. R., Kjekshus, J. K., Sobel, B. E.: Factors influencing infarct size following experimental coronary artery occlusions. Circulation **43**: 67-82, 1971.
24) Lowenstein, E., Foex, P., Francis, C. N., et al.: Regional ischemic ventricular dysfunction in myocarium supplied by a narrowed coronary artery with increasing halothane concentration in a dog. Anesthesiology **55**:349-359, 1981.
25) Maroko, P. R., DeBoer, L. W. L., Davis, R. F.: Infarct size reduction: a critical review. Adv Cardiol **27**:289-316, 1979.
26) Maroko, P. R., Braunwald, E.: Modification of myocardial infarct size after coronary occlusion. Ann Intern Med **79**:720-733, 1973.
27) Lie, J. T., Paiolero, P. C., Holley, K. E., et al.:

Macroscopic enzyme mapping verification of large homogenious experimental myocardial infarcts of predictable size and location in dogs. J Thorac Cardiovasc Surg **69**:599-605, 1975.
28) Hickey, R. F., Sybert, P. E., Verrier, E. D., et al.: Effects of halothane, enflurane, and isoflurane on coronary blood flow, autoregulation and coronary vascular reserve in the canine heart. Anesthesiology **68**:21-30, 1988.
29) Smith, G., Rogers, K., Thorburn, J.: Halothane improves the balance of oxygen supplied to demand in acute myocardial ischemia. Br J Anaesth **52**:577-583, 1980.
30) Bland, J. H. L., Lowenstein, E.: Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. Anesthesiology **45**:287-293, 1976.
31) Davis, R. F., DeBoer, L. W. V., Rude, R. E., et al.: The effect of halothane anesthesia on myocardial necrosis the hemodynamic performance and regional myocardial blood flow in dogs following coronary artery occlusion. Anesthesiology **59**: 402-411, 1983.
32) Davis, R. F., Sidi, A.: Effect of isoflurane on the extent of myocardial necrosis and on systemic hemodynamics, regional myocardial blood flow, and regional myocardial metabolism in dogs after coronary artery occlusion. Anes Analg **69**: 575-586, 1989.
33) Buffington, C. W., Romson, J. L., Levine, A., et al.: Isoflurane induces coronary steal in a canine model of chronic occlusion. Anesthesiology **66**: 280-292, 1987.
34) Hartman, J. C., Kampine, J. P., Schmeling, W., et al.: Alterations in collateral blood flow produced by isoflurane in a chronically instrumented caine model of multivessel coronary artery disease. Anesthesiology **74**:120-133, 1991.
35) Moffitt, E. A., Scovill, J. E., Barker, R. A.: The effects of nitrous oxide on myocardial metabolism and hemodynamics during fentanyl and enflurane anesthesia in patients with coronary artery disease. Anes Analg **63**:1071-1075, 1984.
36) Moffitt, E. A., Sethna, D. H., Gray, R. J.: Nitrous oxide added to halothane reduces coronary flow and myocardial oxygen consumption in patients with coronary artery disease. Can Anaesth Soc J **30**:5-9, 1983.
37) Philbin, D. M., Foex, P., Drummond, G., et al.: Post-systolic shortening of canine left ventricle supplied by a stenotic coronary artery when nitrous oxide is added in the presence of narcotics. Anesthesiology **62**:166-174, 1985.
38) Wilkowski, D. A. W., Sill, J. C., Bonta, W., et al.: Nitrous oxide constrics epicardial coronary arteries without effect on coronary arterials. Anesthesiology **66**:659-665, 1987.
39) Pettis, M. S., Witzeling. T. M., Sill, J. C., et al.: Nitrous oxide constricts coronary arteries in pigs via an endothelium dependent mechanism. Anesthesiology **71**:A533, 1989.
40) Pettis, M. S., Sill, J. C., Bertha, B., et al.: Nitrous oxide and coronary artery constriction in pigs. Anesthesiology **73**:A553, 1990.
41) Ross, A., Gomez, M., Lemmer, J., et al.: Hemodynamic effects of desflurane vs isoflurane in patients undergoing coronary bypass graft surgery. Anesthesiology **73**:A165, 1990.
42) Bowering, J. B., Thomson, I. R., Hudson, R. J., et al.: A comparison of desflurane and isoflurane for coronary artery surgery. Anesthesiology **73**: A321, 1990.
43) Merin, R. J., Bernard, J. M., Doursout, M. F., et al.: The effects of desflurane and isoflurane on cardiovascular and coronary dynamics in the chronically instrumented dog. Anesthesiology **73**: A552, 1990.
44) Ribiero, L. G. T., Yasuda, T., Lowenstein, E., et al.: Comparative effects on anatomic infarct size of verapamil, ibuprofen, and morphine-promethazine-chlorpromazine. (Abstract) Am J Cardiol **43**:396, 1979.
45) Davis, R. F., Sidi, I., MacCallum, P. S., et al.: Isoflurane vs sufentanyl: effects on experimental myocardial infarction. Anesthesiology **67**:A99, 1987.
46) Epidural Analgesia, Philip R. Bromage, W. B. Saunders Co. 1978, PP 347～442.
47) Klassen, G. A., Bramwell, R. S., Bromage, P. R., et al.: Effect of acute sympathectomy by epidural anesthesia on the canine coronary circulation. Anesthesiology **528**-15, 1980.
48) Davis, R. F., DeBoer, L. W. V., Maroko, P. R.: Thoracic epidural analgesia reduces myocardial infarct size after coronary artery occlusion in dogs. Anes Analg **65**:711-717, 1986.

(Circ Cont 12(1): 59～68, 1991)