Anesthesiology
V 41, No 2, Aug 1974

Responses of the Coronary Circulation to Physiologic Changes and Pharmacologic Agents

*George G. Rowe, M.D.**

AS THE GUARDIAN of the oxygen transport system through periods of almost unbelievable physiologic stress, and as medicine's most experienced practitioner of clinical pharmacology, it is imperative for the anesthesiologist to have detailed knowledge of the coronary circulation. This is so because the diseased coronary circulation system cannot manage its own affairs through the wide ranges of stress to which man is exposed. Thus, there are approximately 2,000 cardiovascular deaths per day in the United States,[1] and these deaths are not limited to the aged and infirm. Indeed, postmortem examination of Americans killed in the Korean War whose average age was 22 years revealed grossly visible coronary atherosclerosis in 77.3 per cent of hearts and 90 per cent or greater occlusion of a coronary artery in 8.3 per cent.[2] Hence, each adult male subject, even though without symptoms of cardiovascular disease, must be treated as though he has some coronary atherosclerosis, and those subjects with any symptoms of coronary insufficiency must be presumed to have extensive coronary disease indeed. This review attempts to cover briefly the control of the coronary circulation, its modification by physiologic stress and disease, and finally, the effects upon the coronary circulation of various therapeutic and pharmacologic interventions, especially those used during anesthesia and in patients with cardiovascular disease.

Physiologic Determinants of Coronary Flow

It is obvious that the "resting" heart is a working muscle and therefore its vascular bed must deal with special problems which include a wide arteriovenous oxygen difference and consequently a venous oxygen content in the range of 30 per cent saturated.[3] This means that any significant increase in myocardial oxygen consumption must be met by an increase in coronary blood flow. Under conditions of duress, the heart may increase its output manyfold,[3,4] and if accomplished against elevated arterial systolic pressure, as it usually is, the increase in left ventricular work and coronary blood flow is indeed impressive.[4–8] Since increases of 500 per cent in coronary blood flow have been reported,[5] obviously highly adjustable factors are involved in its control. These are reviewed below.

In its simplest terms, coronary flow is determined by the interplay of coronary vascular resistance and perfusion pressure,[9] since changes in blood viscosity, the other factor in the equation, are generally not sufficiently variable to be very important. Clearly the prime determinants of myocardial blood flow are the cardiac rate and the arterial blood pressure, with these two variables alone accounting for most of the changes seen.[10–12] This is apparently because of the close direct relation between these factors and myocardial metabolism, hence demand for flow. Coronary blood flow and rate are directly related over the wide range which has been explored both in animals[13,14] and in man.[15–17] Although there is a minimum arterial pressure below which no coronary flow can occur, and although increasing arterial pressure in the intact animal is accompanied by increased flow, coronary flow is not linearly related to perfusion pressure because of vasomotion and autoregulation.[9] Thus, in the perfused heart when arterial pressure is increased acutely, coronary flow increases transiently, the vascular bed then adapts itself to the increased

* Professor of Medicine and Director, Cardiovascular Research Laboratory, University of Wisconsin Medical School, 1300 University Avenue, Madison, Wisconsin 53706.

pressure, and flow tends to return to the level which existed prior to the pressure change.[9,18] Similarly, when perfusion pressure is suddenly decreased, coronary flow transiently decreases and then tends to increase again to the control level as the coronary resistance readjusts itself.[9,18] It has been postulated that the smooth muscle in the vessel walls of the coronary arteries effects autoregulation by maintaining a constant tension, adjusted by tension sensors in the walls.[9] Since tension in a vessel wall is related to its diameter, a smooth muscle will exert the same tension in a dilated vessel distended by a low pressure and in a constricted vessel whose intraluminal pressure is high. As with other contracting muscles,[19] myocardial blood flow is sharply reduced during strong contractions.[20,21] Thus, phasic measurements of coronary blood flow in the epicardial arteries supplying the left ventricle generally show a sharp systolic reduction and diastolic augmentation.[20,21] The idea that this pattern is due to compression of the intramyocardial arteries is supported by the observation in the dog that flow in the right coronary artery closely follows the arterial pressure,[22] presumably because it supplies chiefly the right ventricle and is not compressed so much in systole. These observations lend some credence to the idea that left ventricular intramyocardial pressure may exceed intravascular pressure and throttle systolic flow.[20-24] It is known, however, that during contraction of skeletal muscle interruption of blood flow tends to occur by kinking of larger arteries where they pass through muscle layers[19] and thus it is possible that a similar mechanism is more responsible for reduced myocardial systolic flow than is capillary compression. If perfusion pressure is sustained during cardiac arrest, in spite of markedly reduced myocardial metabolic demands, coronary flow increases sharply[21] and myocardial oxygen extraction is reduced.[25]

It is of considerable interest that the phasic pattern of coronary flow changes in passage through the myocardium, since in the epicardial vessels diastolic flow is greatest[20,21] and in the coronary sinus systolic flow is greatest.[26] Although, as already indicated, it is presumed that this change in phase is due to interruption of the arterial inflow by the intramyocardial systolic pressure, which simultaneously "wrings out" blood through compression of the cardiac venous tree, it must be conceded at the present time that no opinion concerning the timing of nutrient myocardial capillary flow is justified. It has been concluded that the systolic tissue pressure increases from the epicardium to the endocardium but does not significantly affect endocardial flow so long as normal coronary perfusion pressure and total coronary flow are maintained.[27,28] However, it cannot be predicted in the absence of data whether the capillaries placed in the interstices around the myocardial cells are compressed or dilated during cardiac contraction, because it is not known whether the change in shape of the myocardial cells as their rigidity increases in systole would tend to reduce or to increase pressure in the specific location of the capillary. The capillaries in skeletal muscle are known to remain open during contraction.[19] An analogy may be that delicate organisms live among the boulders at the bottom of a rockslide unaffected by the force distributed through the rigid structures which surround them but may be crushed quickly when a new slide occurs. Thus it would seem likely to this reviewer that at normal ventricular volumes relatively little myocardial capillary compression occurs, whereas if the end-diastolic volume were sharply reduced, considerable compression might occur. In line with this thesis, Gregg has pointed out that intravascular resistance appears to be more important than extravascular compression.[29]

As would be expected, delivery of oxygen to the myocardium is very important in regulating coronary flow. This, in acute[7] and chronic severe anemia, coronary flow per unit of left ventricular weight increases.[30,31] This would appear to be related to the reduced oxygen-carrying capacity of the blood, since flow varies inversely with the hemoglobin content of a solution perfusing the myocardium.[32] Furthermore, when dextran is infused, producing hemodilution, myocardial blood flow increases.[30] It has also been shown that when the hemoglobin content is raised by blood transfusion coronary flow in anemic

subjects falls toward the normal range.[30,31] This observation is confirmed further by the fact that coronary flow is reduced in subjects with polycythemia.[32] If the arterial blood oxygen content is reduced by administration of 10 per cent oxygen, cardiac output increases, left ventricular work increases, and coronary blood flow increases considerably.[33] Inhalation of 100 per cent oxygen or administration of hyperbaric oxygen usually causes diminution of coronary blood flow in the normal dog.[34,35]

Hyperventilation decreases P_{CO_2}, increases pH, and reduces coronary blood flow of experimental animals[36] and man,[37] and markedly decreases coronary sinus blood P_{O_2} in both.[37] On the other hand, sodium bicarbonate increases blood carbon dioxide content, cardiac output, left ventricular work, myocardial oxygen consumption, and coronary blood flow.[38] Similar changes in blood pH produced by administration of THAM did not significantly change coronary blood flow of the intact dog,[39] but unbuffered THAM with a pH of 10.2 or sodium carbonate infused directly into the coronary arteries of the open-chest dog did increase coronary flow.[40]

Among substances commonly administered clinically, 50 per cent glucose[41] and molar sodium succinate[42] had relatively little effect on coronary blood flow of intact animals, whereas molar sodium lactate increased body oxygen consumption, cardiac output, cardiac work, and coronary blood flow.[43] Administration of calcium chloride intravenously to anesthetized dogs produced a marked slowing in cardiac rate with a considerably enhanced stroke volume but no change in cardiac output, while coronary blood flow decreased and coronary vascular resistance rose.[44] In the intact unanesthetized dog, similarly administered calcium was strongly inotropic and coronary flow increased, apparently secondary to its metabolic effects.[45] Hypertonic sodium chloride caused increased cardiac output and cardiac work without increasing arterial blood pressure, with a variable but not significant increase in coronary blood flow.[46] Administration of hypertonic contrast material produced hemodilution with an apparently increased blood volume, and elevated cardiac output, cardiac work and coronary blood flow.[47]

There is no doubt that neural and neurohumoral factors affect coronary blood flow, although relationships are complicated and the interplay of factors has been difficult to distinguish.[9] Thus, stimulation of the sympathetics increases cardiac output, augments the vigor of cardiac contraction, increases cardiac metabolic demands, and increases coronary blood flow,[48,49] whereas the best current evidence indicates that the direct effect of the sympathetics on the coronary vessels alone is probably that of constriction.[50-52] Contrariwise, stimulation of the vagus slows the heart, reduces the cardiac metabolic demands, and decreases coronary flow in the intact preparation. Yet it can be shown that vagal stimulation directly reduces coronary vascular resistance.[50-53] Carotid sinus nerve stimulation decreases arterial pressure, heart rate, and work, and has been utilized to relieve anginal pain.[54]

Effects of exercise on coronary flow, especially in those with cardiovascular disease, has long been of interest. It is agreed that coronary blood flow increases with exertion[3-7] as it does during excitement and sympathetic stimulation.[48,49] This is true in normal human subjects,[8,55] those with minimal heart disease,[55,56] subjects with aortic stenosis and insufficiency,[57] and patients in congestive heart failure.[58] In subjects with coronary disease, coronary flow has been found to be normal at rest,[59-63] with a tendency to be higher in those with more severe disease[63] and to increase with exercise[59,64] or pacing.[65] Recent data indicate a limited capacity of those with coronary disease to increase their myocardial flow with pacing,[65] Isuprel,[66] and drugs which increase coronary blood flow, although coronary flow increased normally during limited exercise in anginal subjects with aortic-valve disease.[57] However, in violently exercising Alaskan sled dogs, coronary flow increases roughly five times over resting values,[6] and in heavily exercised normal men flow is estimated to increase by at least three times.[8] This degree of exercise has not yet been approached in studies of subjects with angina pectoris, and it would

be predicted that such increases in myocardial blood flow could not occur in the heavily diseased coronary circulation.

Myocardial Metabolism

Clearly, myocardial blood flow is regulated in some way by myocardial metabolism, increasing and decreasing to supply myocardial metabolic demands.[7-14,48,67] It has been postulated that local release of adenosine within the heart controls coronary flow,[68] and there is much to support this hypothesis,[69,70] since it is a very active coronary vasodilator,[71-74] which is locally available and is destroyed in blood and even more rapidly inactivated in the lung.[75] Thus, it could produce the evanescent type of response required for rapid, profound adjustments. Whether or not the substance eventually proves to be adenosine, some compound or compounds formed in tissue during the metabolically active state must be important in local blood flow control. As reviewed by Berne,[9] potassium and other substances have been suggested as the controlling agent, but although they can increase coronary blood flow, the increase achieved is considerably less than that produced in response to physiologic stimuli or to the adenine nucleotides or adenosine; consequently, it seems unlikely that these agents are primary in controlling coronary flow.

Teleologically, it would be desirable for an organ so essential to life as the heart to be capable of metabolizing a wide variety of substances. It has been established that although the normal heart is predominantly aerobic, it is also capable of anaerobic metabolism, and that carbohydrates, proteins, and fats are consumed.[67] The oxygen consumption of the resting noncontracting heart is very low,[25,76-78] presumably only that required for maintenance of cellular viability.[76,77] If useless work such as fibrillation is permitted to occur, oxygen consumption is increased[76,78,79] but still does not approach the high cardiac oxygen consumption per unit of weight which is the hallmark of normally working myocardium.[25,78,79] As the amount of cardiac work increases above the resting level, cardiac oxygen consumption increases also.[7-11,25] However, it has been established that "pressure work" is metabolically more expensive to the heart than "volume work," with the increment added by increasing stroke volume being so small that in some situations it is scarcely measurable, whereas the increment added by increases in arterial pressure is very marked indeed.[10,11,25] It is well established that myocardial oxygen consumption is closely and directly related to cardiac rate over the wide ranges in which this has been measured both in experimental animals and in man.[13-17] The product of heart rate and systolic blood pressure, or the "time–tension index," is very closely related to myocardial oxygen consumption.[10,11,25] An additional important factor is the velocity at which contraction occurs; the faster the myocardial fibers shorten, the more oxygen is consumed per contraction.[25] Electrical depolarization and repolarization of the heart is a minor energy cost.[25] All additional factors are small compared with the overriding determinants of cardiac rate, velocity of shortening, and tension achieved,[25] and in practical terms, since these are the variables over which the clinician has most control, they are of the greatest clinical importance.

Although traditionally coronary flow is regarded as subservient to metabolic demands, it is clear that overperfusion of the left ventricle increases myocardial oxygen consumption[80-82] and even contractility.[83,84] Practical ramifications of this observation are not clear, but it should be remembered that a very considerable increase in oxygen consumption has been shown to occur with overperfusion,[80] especially in the non-working heart.[82] These observations may well apply to the heart during cardiopulmonary bypass, when myocardial perfusion is suddenly increased during induced arrest or fibrillation. Underperfusion has even more profound effects. Thus, during myocardial hypoxia, rapid dephosphorylation of the high-energy phosphate compounds occurs and there is considerable glycogenolysis.[67,85] The content of diphosphopyridine nucleotides in the heart diminishes with persistent hypoxia,[85] and myocardial metabolism tends to become

anaerobic, with production of lactate.[86,91] The concept of "excess lactate"[87] as a reliable indicator of hypoxia has been both supported[87–91] and questioned.[92]

Coronary Blood Flow and Disease

Great interest has centered on the determination of coronary blood flow in subjects with angina pectoris, but measurements utilizing many different methods have failed to differentiate subjects with atherosclerotic heart disease from normal individuals.[59–63,93] Although early data indicated that such subjects could not increase their myocardial blood flow with relatively mild exercise,[59] later data did not confirm these preliminary observations.[64,94] Recently, observations collected with new methods of measuring coronary flow and utilizing cardiac pacing or administration of Isuprel as the challenge have shown that when greater demands are made on the circulation, subjects with atherosclerotic heart disease are not capable of increasing their coronary blood flow to the same extent as normal subjects.[65,66,95] Inequality of flow in different regions of the heart has long been suspected to occur in subjects with angina pectoris, and has been confirmed by following the rate of clearance of radioactive material after its local injection in several areas of the heart.[96] After systemic injection of radioactive material, non-uniform perfusion has also been found by using multiple counters located in a regular lattice over the cardiac shadow.[97] It is not presently known whether the areas of reduced flow measured by these methods contain normal heart muscle, but it seems very probable that if there is inadequate blood flow to maintain normal resting myocardial metabolism, localized necrosis will result, with a fibrotic scar.[98] Presently it is clear that in most subjects with significant atherosclerotic heart disease the major epicardial coronary arteries are obstructed in localized areas. Apparently, in spite of the augmented collateral circulation, blood flow remains inadequate in certain myocardial areas during increased metabolic demands and produces angina. In time these areas may undergo diffuse fibrosis if ischemia is slowly progressive, or if outright myocardial infarction occurs, a scar results. The anginal attack has also undergone considerable study and it is widely agreed, although not yet proven, to be due to a discrepancy between demand and supply of blood flow to the myocardium. The ischemic attack may be accompanied by alteration in compliance of the left ventricle, with elevated pressure in the left ventricle at end-diastole,[90,99,100] in the systemic arteries,[101] and in the left atrium as reflected in the pulmonary arterial wedge pressure.[102] Such hemodynamic events are readily accepted as manifestations of acute left ventricular failure precipitated by ischemia. Relief of the anginal attack is frequently produced by nitrites. However, there is excellent evidence presently that this is not due to coronary vasodilatation, since administration of nitroglycerin into the coronary artery during an anginal attack does not relieve anginal pain even though an increase in coronary blood flow occurs.[103] On the other hand, systemic administration of nitrites decreases peripheral venous tone and return of blood to the heart,[104,106] reduces cardiac size,[105,107–109] lowers arterial blood pressure,[110–113] and diminishes cardiac work,[110–114] with relief of anginal pain. The hypothesis that nitrites are effective by reducing cardiac work is strengthened by the observation that angina is more easily produced after blood volume expansion with dextran,[115] and is less easily produced after phlebotomy.[116] Thus, our investigations would appear to have come full circle[114] from 100 years ago, when T. Lauder Brunton[117] introduced nitrites on the thesis that they reduced cardiac work and thereby relieved pain of cardiac ischemia. Furthermore, administration of coronary vasodilators, which increase coronary blood flow, generally does not relieve angina; indeed, it may precipitate such pain.[98] This is believed to be due to interference of vasodilators with the coronary vasoregulatory mechanisms, preventing optimal distribution of blood flow in the ischemic heart[3] and perhaps precipitating "coronary steal."[118] For the "steal syndrome" to occur, collateral vessels which supply an ischemic area must arise from an artery beyond a stenosis. In a partially obstructed artery there are two potential areas

of resistance, one at the site of the partial obstruction, the other at the normal site of most vascular resistance in the arterioles. The arterioles are so dominant in flow control that a non-critical proximal epicardial arterial stenosis usually does not interfere with their autonomy. However, if the arterioles dilate widely, the partial obstruction may become flow limiting. Then pressure will be reduced at the source of collateral vessels which arise distal to the partial occlusion and they will fail to deliver blood as they normally do. Thus, the normal arteriolar bed "steals" the blood which should have been supplied to the ischemic area.[118] Recently, it has been recognized that during angina the hemoglobin in the coronary sinus blood has less affinity for oxygen and therefore, at any given saturation, delivers oxygen at a higher P_{O_2}.[119]

There have been several reviews of the metabolism of the heart during congestive heart failure.[67,120,121] Although cardiac output is low, and coronary sinus oxygen content reduced,[122] coronary blood flow is within the broad limits of normal.[123] Cardiac efficiency is reduced, however, because of the increased oxygen consumption per unit of work done.[123] When strophanthidin is given to human subjects with heart failure, cardiac output improves[124] but left ventricular oxygen consumption is unchanged, and therefore efficiency improves.[123] In the non-working left ventricle, strophanthidin transiently decreases and then increases coronary blood flow, whether or not there is ganglionic blockade, cardiac denervation, or adrenalectomy.[125] Subsequent to strophanthidin, potassium is lost from the myocardium of man,[124] and in the normal dog potassium is lost and sodium is taken up.[126] Lanatocide C produced little change in cardiac metabolism,[127] and it was concluded in a study of the dinitrophenol-poisoned dog heart that this glycoside restored the initial work performance of the heart without changing its oxygen consumption.[128]

Coronary blood flow has been studied in several states commonly associated with hypotension. During hemorrhagic shock, coronary blood flow and cardiac output are sharply reduced.[129] It appears highly unlikely, however, that the reduction in coronary flow contributes much to the circulatory decay, except late in the course of the syndrome, when the heart, as well as many other organs, is damaged by prolonged hypoperfusion. Thus, in the terminal states of shock, when the heart dilates and left atrial pressure rises, augmenting left coronary flow, even while maintaining the same degree of hypotension, will reduce left atrial pressure to normal and improve myocardial contraction.[130] Hyperbaric oxygen administration normally decreases coronary blood flow, but in hemorrhagic hypotension it causes no change in flow, only an increase in myocardial oxygen consumption.[35] When hyperbaric oxygen is given to dogs in shock from myocardial infarction induced by microsphere embolization, arterial pressure rises and, in at least some animals, there is a transient increase in coronary blood flow with a marked increase in coronary sinus blood oxygen content and a significant decrease in lactate production.[131] Beta-adrenergic receptor blockade ameliorates the systolic reduction in coronary flow seen in hemorrhagic hypotension,[132] improves myocardial blood flow,[132] and reduces the myocardial lesions which result from prolonged shock.[133] These results are believed to be due to relief from the intense sympathetic inotropic stimulation of the heart in hemorrhagic shock.[133] During cardiac tamponade coronary flow decreases, as do cardiac output and left ventricular work.[134] However, with the increase in rate produced by tamponade, left ventricular oxygen consumption remains unchanged, so cardiac efficiency is markedly reduced.[134] During pulmonary embolization, in the dog, coronary flow through the left ventricle is reported to be unchanged,[135] while coronary flow to the hypertensive right ventricle increased markedly.[136] When a large arteriovenous fistula is opened, coronary flow increases in spite of the low diastolic perfusion pressure,[137] indicating marked capacity of normal vessels to adapt to this stressful situation.

When cardiac work is increased by disease, coronary flow also increases. Thus, in subjects with thyrotoxicosis, cardiac output and coronary blood flow increase, accompanied by

reduced coronary and peripheral vascular resistance.[138,139] Treatment of such subjects with ^{131}I and restoration of euthyroidism also restores normal coronary blood flow.[138] Coronary blood flow per unit of left ventricular weight is normal in hypertensive subjects[140,141]; however, allowing for the increased left ventricular mass and reduced output in Grade III and IV hypertensive subjects, total coronary flow is considerably increased and cardiac efficiency reduced.[141]

Anesthesia and Coronary Blood Flow

Extensive studies of the effects of anesthetics on coronary blood flow do not appear to have been made; most studies are done in alert human subjects or already anesthetized animals, and there is reason to doubt that the effect of an additional anesthetic in a sleeping animal is comparable to inducing anesthesia. It is well known that anesthetic doses of pentobarbital produce considerable increases in cardiac rate, cardiac output, and coronary blood flow. If the dose of barbiturates is increased progressively, cardiac depression occurs and failure is induced.[142,143] Administration of ketamine is accompanied by increased systemic arterial pressure, cardiac output, and coronary blood flow.[144] When given to alert animals, some of this "ketamine effect" may be due to the excitement phase.[144] The systemic and coronary hemodynamic effects of many drugs, including some which may be used during anesthesia, has been summarized in tabular form for those who wish to have a ready reference to this material.[145] Further data on some agents of special interest are included here.

Administration of atropine is associated with a marked increase in coronary blood flow parallel to the increase in cardiac rate.[15] It is reasonable to anticipate that most of the sympathomimetic agents which produce increases in cardiac rate would have a similar effect. Studies of catecholamines confirm that this is the case for isoproterenol in dogs[146] and in man,[66,147,148] as well as for epinephrine and norepinephrine.[149,150] Although the latter drugs are direct coronary vasoconstrictors, their metabolic effects quickly overcome constriction and result in overall coronary vasodilatation.[149] If there is myocardial infarction through coronary embolization, the increased flow achieved by Isuprel is reported not to be sustained.[151] Under circumstances of infarction with shock, norepinephrine was thought to be superior to isoproterenol.[152] The increase in coronary blood flow which occurs with increases in cardiac rate is presumed to be directly related to the myocardial metabolic demand. It is known that subjects with coronary-artery disease may have ischemia induced by pacing the heart,[65,99] so it is reasonable to expect that inducing tachycardia by other means may have a similar effect.

Vasoconstricting nerves are blocked by a wide variety of hypotensive drugs. Among these, the ganglion-blocking drugs tend to reduce cardiac output, coronary blood flow, and left ventricular oxygen consumption, as shown by studies of hexamethonium,[153] pentolinium,[154] mecamylamine,[155] trimethidinium,[156] and trimethapan.[157] Much of this effect seems clearly related to reduced arterial blood pressure and cardiac work. There are, of course, limits to how far the blood pressure can be lowered safely with vasodepressor agents, since coronary blood flow is heavily dependent on perfusion pressure and falls off rapidly when excessively low blood pressures are reached. These limits are presumed to be even more critical in the presence of coronary arterial obstructive disease. Acute systemic and coronary vasodilatation occurs with diazoxide[158,159] and is not blocked to any great extent by pretreatment with reserpine.[158] When release of catecholamines from peripheral nerves is blocked, the effects are similar to ganglionic blockade.[160] Pericoronary neurectomy with phenolization of the proximal coronary arteries, hence presumably localized denervation, caused an increase in coronary blood flow and a decrease in arteriovenous oxygen difference.[161] When hypotension is induced acutely by guanethidine, cardiac output and coronary blood flow increase unless there has been prior reserpinization.[162] Presumably this acute effect is due to acute catecholamine release.

Administration of the beta-adrenergic receptor blocker, propranolol, produces a significant decrease in coronary blood flow and an

increase in coronary vascular resistance, accompanied by reduced cardiac output and cardiac work.[163] Cardiac contractile force is sharply reduced,[164] as is the cardiovascular response to exercise.[163] These actions may explain its efficacy in angina. Since propranolol increases coronary vascular resistance in reserpinized dogs which are catecholamine-depleted, at least part of the change is due primarily to propranolol itself.[164] Isolated helical strips of smooth muscle from small coronary arteries and isolated perfused small coronary arteries relax when exposed to small concentrations of epinephrine and norepinephrine. This response is blocked by the beta-adrenergic blocker, nethalide.[165] The response of similar smooth muscle preparations from large coronary arteries was variable.[165]

Various "biological products" or closely related compounds which have important coronary hemodynamic effects may be administered or released during anesthesia. Among these, dopamine has long been known to be a very active coronary vasodilator which increases cardiac output and cardiac work.[166] In the closed-chest dog the coronary sinus oxygen content rises markedly, since coronary flow exceeds demand,[166] but in the open-chest dog coronary flow and myocardial oxygen consumption increase together.[167] Propranolol blocks the cardiovascular effects of dopamine.[167] Serotonin also causes coronary vasodilatation,[168] but is much less active than dopamine[166] or adenosine.[71–74] Systemically administered bradykinin is a still less potent coronary vasodilator[169,170]; however, any of these compounds which may be synthesized in tissue could be very important in local adjustments of blood flow.

Among the so-called "coronary vasodilators" there are few which are indeed active in altering coronary blood flow. Thus, intravenous administration of papaverine decreases coronary resistance and increases coronary blood flow,[171] but aminophylline does not.[172] Administration of nitrites other than directly into the coronary circulation is now generally agreed to be associated with no significant change in coronary blood flow or to produce a slight decrease.[111–114] Nitrites are well known by coronary arteriographers to dilate the major epicardial coronary arteries and to relieve catheter-induced large coronary-artery spasm. It is not known whether spasm occurs spontaneously in normal or diseased coronary arteries or whether it is a significant problem in producing myocardial ischemia, but many suspect that it can occur. Consequently, the use of nitrites to sustain adequate coronary blood flow during surgery on subjects with atherosclerotic coronary-artery disease is neither unreasonable nor well founded. If used, it must be recognized that nitrites usually reduce the cardiac filling pressure, and reduce the systemic arterial pressure against which the ventricle must empty, as their major effects.[114] They may improve coronary blood flow distribution.

The effects of thermal changes have been carefully studied, and it is established that during hypothermia from total-body cooling there is a sharp initial decrease in coronary flow, while the decline in arterial pressure is small.[173] This is presumably due to the reduced metabolic demand of the body, the diminished cardiac output, and the bradycardia.[174] In spite of the reduced coronary resistance[175] and extravascular myocardial compression, during total-body hypothermia perfusion pressure tends to decrease sufficiently that actual coronary flow in ml/min is reduced.[173,174] After cooling is achieved, even though there is prolongation of systole,[173] coronary vascular resistance remains low because elevation of the perfusion pressure results in considerable increase in flow.[173] When cardiac cooling is achieved through perfusion with cold blood, coronary vascular resistance is reduced, but when warmed blood is diverted through the coronary circuit, resistance falls acutely and then returns again toward the control level.[175] It is concluded that the dilatation from cold blood might result from a direct temperature effect upon the vascular smooth muscle. Part of the reduced coronary resistance may also be due to slowing of the heart rate, but in general the duration of systole per cycle is prolonged enough to increase the period of extravascular compression.[175] The hypothermic heart is capable of extracting oxygen very effectively,[176] but fibrillates readily, especially if underperfused.[177] When epinephrine is administered to the cold heart, heart rate, blood

pressure, and coronary blood flow increase, but ventricular fibrillation is prone to occur.[173] Although there is considerable reduction in coronary flow during hypothermia, the reduction in cardiac output is greater, so that the fraction of cardiac output perfusing the coronary arteries is increased.[174] The reduction in left ventricular work during hypothermia exceeds the decrease in left ventricular metabolism, suggesting a failure of cardiac efficiency during the cold state.[178] On the contrary, during hyperthermia induced by external warming, there are marked increases in heart rate, cardiac output, left ventricular work, coronary blood flow, and myocardial oxygen consumption.[179] Coronary blood flow was also increased during drug-induced hyperpyrexia.[180]

The repeated use of cardiac arrest during heart surgery has increased the practical value of knowledge of its physiology. Studies of the arrested or non-working perfused heart indicate reduction in oxygen consumption to 20–30 per cent of that of the naturally perfused working heart *in situ*.[76,78,79] There is only slightly less oxygen consumption in the arrested heart than in the fibrillating organ,[77] and there is little evidence of uptake of glucose, lactate, or ketones during the arrested state.[78] In cyanotic children, the myocardium tolerates longer ischemic periods with less anaerobic glycolysis and less lactate production than in the noncyanotic child.[181] This coincides with data indicating that the heart of the altitude-acclimatized rat tolerates coronary-artery ligation better than does that of the control rat.[182] During anesthesia for heart surgery on cyanotic and noncyanotic children, the coronary sinus blood oxygen content increases, as does coronary sinus blood *p*H, with P_{CO_2} remaining high.[183] The predominant myocardial substrate during anesthesia is nonesterified fatty acids, whereas consumption of glucose is sharply reduced.[181,183] There is a marked fall in *p*H of the blood contained in the coronary circulation during cardiac arrest, but this takes place only slowly, with a minor change in the first ten minutes of acute ischemia.[184]

Considerable reduction in left ventricular work may be produced by withdrawing blood—or volume—from the arterial system during systole and replacing it during diastole. This may be effected by the process known as "counterpulsation."[185] It has been shown to decrease left ventricular oxygen consumption in normotensive dogs, but in the dog with a deteriorating heart, an increase in coronary flow occurs, accompanied by an increase in cardiac oxygen consumption.[185] No attempt is made here to review the extensive literature on this process or its clinical promise in supporting subjects with acute infarction and shock, in acute coronary care, or through emergency myocardial revascularization.

Summary and Conclusion

The flow of blood through the coronary circulation is heavily dependent on myocardial metabolic demands which are determined chiefly by cardiac rate, the systolic blood pressure and the velocity of contraction achieved by the ventricle. Other factors, such as the length of shortening (stroke volume), the maintenance of cellular viability, and the production of electrical activity, are relatively minor energy costs. The coronary circulation autoregulates so that changes in perfusion pressure meet a variable local vascular resistance determined chiefly by myocardial metabolic needs. Various coronary vasodilators interfere with this autoregulatory process, but there is little evidence that they improve the distribution of blood flow in the myocardium, which seems to be the fundamental problem in coronary-artery disease; indeed, they are apt to make it worse. Those agents most effective in treating ischemia secondary to coronary-artery disease probably produce their effect by reducing cardiac work. It is not established presently whether vasodilatation in the large epicardial coronary arteries insures better flow through collateral vessels or partial coronary arterial obstructions, but it seems probable that it does, and that it produces better distribution of flow. Present evidence indicates that myocardial perfusion is best insured by maintaining near-normal cardiac rate and blood pressure.

It is clear that further information concerning the effects of anesthetics on systemic and coronary hemodynamics is needed. Current techniques of chronic instrumentation in

trained animals should make it feasible to do a systematic study of the effects of premedication and anesthesia on intact animals during the crucial transition from the alert state through the successive planes of anesthesia. Although the question of "species specificity" will always be directed against such studies, past experience has shown that insofar as they are available, data concerning the coronary circulation obtained from animals and from man are essentially interchangeable. It is suspected that when such information has been obtained, it will follow a pattern which already can be predicted closely from what is known about the determinants of myocardial metabolism and coronary flow. Thus, the knowledgeable anesthesiologist, applying that information which is already available to unfamiliar situations and drugs, will probably not be seriously misled very often by assuming that the interplay of cardiac work, coronary blood flow, and cardiac metabolism will remain closely related, as they have been shown to be in a wide variety of experiments.

References

1. Favaloro RG: Surgical treatment of coronary arteriosclerosis by the saphenous vein graft technique. Am J Cardiol 28:493–495, 1971
2. Enos WF, Holmes RH, Beyer J: Coronary artery disease among United States soldiers killed in action in Korea. JAMA 152:1090–1093, 1953
3. McGregor M, Fam WM: Regulation of coronary blood flow. Bull NY Acad Med 42: 940–950, 1966
4. Lamb LE, Smith WL, Kelly RJ, et al: Cardiac output and coronary blood flow during progressive recumbent exercise. Aerosp Med 40:1238–1243, 1969
5. Khouri EM, Gregg DE, Rayford CR: Effect of exercise on cardiac output, left coronary flow and myocardial metabolism in the unanesthetized dog. Circ Res 17:427–437, 1965
6. Van Citters RL, Franklin DL: Cardiovascular performance of Alaska sled dogs during exercise. Circ Res 24:33–42, 1969
7. Vatner SF, Higgins CB, Franklin D: Regional circulatory adjustments to moderate and severe chronic anemia in conscious dogs at rest and during exercise. Circ Res 30:731–740, 1972
8. Kitamura K, Jorgensen CR, Gobel FL, et al: Hemodynamic correlates of myocardial oxygen consumption during upright exercise. J Appl Physiol 32:516–521, 1972
9. Berne RM: Regulation of coronary blood flow. Physiol Rev 44:1–29, 1964
10. Sarnoff SJ, Braunwald E, Welch CH Jr, et al: Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension–time index. Am J Physiol 192:148–156, 1958
11. Braunwald E, Sarnoff SJ, Case RB, et al: Hemodynamic determinants of coronary flow: Effect of changes in aortic pressure and cardiac output on the relationship between myocardial oxygen consumption and coronary flow. Am J Physiol 192:157–163, 1958
12. Gregg DE, Shipley RE: Augmentation of left coronary inflow with elevation of left ventricular pressure and observations on the mechanism for increased coronary inflow with increased cardiac load. Am J Physiol 142:44–51, 1944
13. Maxwell GM, Castillo CA, White DH Jr, et al: Induced tachycardia: Its effects upon the coronary hemodynamics, myocardial metabolism and cardiac efficiency of the intact dog. J Clin Invest 37:1413–1418, 1958
14. Boerth RC, Covell JW, Pool PE, et al: Increased myocardial oxygen consumption and contractile state associated with increased heart rate in dogs. Circ Res 24: 725–734, 1969
15. Gorlin R: Studies of the regulation of the coronary circulation in man. Am J Med 25:37–42, 1958
16. Rowe GG, Stenlund RR, Thomsen JH, et al: Coronary and systemic hemodynamic effects of cardiac pacing in man with complete heart block. Circulation 40:839–845, 1969
17. Holmberg S, Varnauskas E: Coronary circulation during pacing-induced tachycardia. Acta Med Scand 190:481–490, 1971
18. Eckel RR, Eckstein RW, Stroud M, et al: Effect of over and under perfusion upon coronary arterial blood flow. Fed Proc 8: 38, 1949
19. Gray SD, Carlsson E, Staub NC: Site of increased vascular resistance during isometric muscular contraction. Am J Physiol 213:683–689, 1967
20. Gregg DE, Khouri EM, Rayford CR: Systemic and coronary energetics in the resting unanesthetized dog. Circ Res 16:102–113, 1965
21. Sabiston DC Jr, Gregg DE: Effect of cardiac contraction on coronary blood flow. Circulation 15:14–20, 1967
22. Gregg DE: Phasic blood flow and its determinants in the right coronary artery. Am J Physiol 119:580–588, 1937
23. Gregg DE, Eckstein RW: Measurement of intramyocardial pressure. Am J Physiol 132: 781–790, 1941
24. Eckstein RW, Moir TW, Driscoll TE: Phasic mean blood flow in the canine septal artery and an estimate of systolic resistance in deep myocardial vessels. Circ Res 12: 203–211, 1963

25. Braunwald E: Control of myocardial oxygen consumption: Physiologic and clinical considerations. Am J Cardiol 27:416–432, 1971
26. Stein PD, Badeer HS, Schuette WH, et al: Pulsatile aspects of coronary sinus blood flow in closed-chest dogs. Am Heart J 78: 331–337, 1969
27. Moir TW, DeBra DW: Effect of left ventricular hypertension, ischemia and vasoactive drugs on the myocardial distribution of coronary flow. Circ Res 21:65–74, 1967
28. Moir TW: Coronary vascular adjustments to acute myocardial ischemia. Arch Intern Med 129:799–807, 1972
29. Lewis FB, Coffman JD, Gregg DE: Effect of heart rate and intracoronary isoproterenol, levarterenol, and epinephrine on coronary flow and resistance. Circ Res 9:89–95, 1961
30. Regan TJ, Frank MJ, Lehan PH, et al: Influence on red cell mass on myocardial blood flow and oxygen uptake. Clin Res 8:367, 1960
31. Bhatia ML, Manchanda SC, Roy SB: Coronary haemodynamic studies in chronic severe anaemia. Brit Heart J 31:365–374, 1969
32. Guz A, Kurland GS, Freedberg AS: Relation of coronary flow to oxygen supply. Am J Physiol 199:179–182, 1969
33. Hellems HK, Ord JW, Talmers FN, et al: The effects of hypoxia on coronary blood flow and myocardial metabolism in normal human subjects. Circulation 16:893, 1957
34. Sobol BJ, Wanless SA, Joseph EB, et al: Alteration of coronary blood flow in the dog by inhalation of 100% oxygen. Circ Res 11:797–802, 1962
35. Ratliff NB, Hackel DB, Mikat E: Myocardial oxygen metabolism and myocardial blood flow in dogs in hemorrhagic shock: Effects of hyperbaric oxygen. Circ Res 24:901–909, 1969
36. McArthur WJ: Coronary flow response to hypocapnia induced by hyperventilation. Aerosp Med 36:5–8, 1965
37. Rowe GG, Castillo CA, Crumpton CW: Effects of hyperventilation on systemic and coronary hemodynamics. Am Heart J 63:67–77, 1962
38. Rowe GG, McKenna DH, Jaramillo CV, et al: The systemic and coronary hemodynamic effect of sodium bicarbonate. Am J Med Sci 248:424–428, 1964
39. Rowe GG, Afonso S, Lugo JE, et al: The systemic and coronary hemodynamics of Tromethamine (THAM) in the anesthetized dog. ANESTHESIOLOGY 25:317–320, 1964
40. Wang H, Katz RL: Effects of changes in coronary blood pH on the heart. Circ Res 17:114–122, 1965
41. Rowe GG, Afonso S, Castillo CA, et al: The systemic and coronary hemodynamic effects of intravenous administration of 50% glucose. Am J Med Sci 244:186–190, 1962
42. Rowe GG, Castillo CA, Afonso S, et al: The systemic and coronary hemodynamic effects of molar sodium succinate. Am J Med Sci 246:180–183, 1963
43. Rowe GG, Maxwell GM, Castillo CA, et al: Systemic and coronary hemodynamic effects of sodium lactate. J Lab Clin Med 56: 874–878, 1960
44. Sialer S, McKenna DH, Corliss RJ, et al: Systemic and coronary hemodynamic effects of intravenous administration of calcium chloride. Arch Int Pharmacodyn Ther 169: 177–184, 1967
45. Pitt B, Sugishita Y, Gregg DE: Coronary hemodynamic effects of calcium in the unanesthetized dog. Am J Physiol 216:1456–1459, 1969
46. Rowe GG, McKenna DH, Corliss RJ, et al: Hemodynamic effects of hypertonic sodium chloride. J Appl Physiol 32:182–184, 1972
47. Friesinger GC, Schaffer J, Criley JM, et al: Hemodynamic consequences of the injection of radiopaque material. Circulation 31:730–740, 1965
48. Shipley RE, Gregg DE: The cardiac response to stimulation of the stellate ganglia and cardiac nerves. Am J Physiol 143:396–401, 1945
49. Denison AB Jr, Green HD: Effects of autonomic nerves and their mediators on the coronary circulation and myocardial contraction. Circ Res 6:633–643, 1958
50. Berne RM, DeGeest H, Levy MN: Influence of the cardiac nerves on coronary resistance. Am J Physiol 208:763–769, 1965
51. Feigl EO: Sympathetic control of coronary circulation. Circ Res 20:262–271, 1971
52. Hackett JG, Abboud FM, Mark AL, et al: Coronary vascular responses to stimulation of chemoreceptors and baroreceptors—Evidence for reflex activation of vagal cholinergic innervation. Circ Res 31:8–17, 1972
53. Feigl EO: Parasympathetic control of coronary blood flow in dogs. Circ Res 25:509–519, 1969
54. Braunwald E, Epstein SE, Glick G, et al: Relief of angina pectoris by electrical stimulation of the carotid sinus nerves. N Engl J Med 277:1278–1283, 1967
55. Gorlin R, Cohen LS, Elliott WC, et al: Effect of supine exercise on left ventricular volume and oxygen consumption in man. Circulation 32:361–371, 1965
56. Gorlin R, Krasnow N, Levine HJ, et al: Effect of exercise on cardiac performance in human subjects with minimal heart disease. Am J Cardiol 13:293–300, 1964
57. Rowe GG, Afonso A, Lugo JE, et al: Coronary blood flow and myocardial oxidative metabolism at rest and during exercise in subjects with severe aortic valve disease. Circulation 32:251–257, 1965
58. Levine HJ, Messer JV, Neill WA, et al: The effect of exercise on cardiac performance in human subjects with congestive heart failure. Am Heart J 66:731–740, 1963

59. Brachfeld N, Corlin R: Physiologic evaluation of angina pectoris. Dis Chest 38:1–8, 1960
60. Rowe GG, Thomsen JH, Stenlund RR, et al: A study of hemodynamics in man with coronary artery disease. Circulation 39:139–148, 1969
61. Holmberg S, Paulin S, Prerovsky I, et al: Coronary blood flow in man and its relation to the coronary arteriogram. Am J Cardiol 19:486–491, 1967
62. Ganz W, Tamura K, Marcus HS, et al: Measurement of coronary sinus blood flow by continuous thermodilution in man. Circulation 44:181–195, 1971
63. Rowe GG: Observation on coronary blood flow with the nitrous oxide method in man with coronary artery disease, Myocardial Blood Flow in Man—Methods and Significance in Coronary Disease. Edited by A Maseri. Torino, Italy, Minerva Medica, 1972, pp 297–307
64. Bing RJ: The anoxic heart, Lecture at Henry Ford Symposium on Coronary Artery Disease, Henry Ford Hospital, Detroit, Michigan, November 1961
65. Yoshida S, Ganz W, Donoso R, et al: Coronary hemodynamics during successive elevation of heart rate by pacing in subjects with angina pectoris. Circulation 44:1062–1071, 1971
66. Knoebel SB, McHenry PL, Phillips JF, et al: Coronary collateral circulation and myocardial blood flow reserve. Circulation 46: 84–94, 1972
67. Bing RJ: Cardiac metabolism. Physiol Rev 45:171–213, 1965
68. Berne RM: Cardiac nucleotides in hypoxia: Possible role in regulation of coronary blood flow. Am J Physiol 204:317–322, 1963
69. Rubio R, Berne RM: Release of adenosine by the normal myocardium in dogs and its relationship to the regulation of coronary resistance. Circ Res 25:407–415, 1969
70. Kator M, Berne RM: Release of adenosine from anoxic hearts: Relationship to coronary flow. Circ Res 19:420–425, 1966
71. Wedd AM: The action of adenosine and certain related compounds on coronary flow of the perfused heart of the rabbit. J Pharmacol Exp Ther 41:355–366, 1931
72. Wedd AM, Drury AN: The action of certain nucleic acid derivatives on the coronary flow in the dog. J Pharmacol Exp Ther 50:157–164, 1934
73. Winbury MM, Papierski DH, Hemmer ML, et al: Coronary dilator action of the adenine-ATP series. J Pharmacol Exp Ther 109: 255–260, 1953
74. Rowe GG, Afonso S, Gurtner HP, et al: The systemic and coronary hemodynamic effects of adenosine triphosphate and adenosine. Am Heart J 64:228–234, 1962
75. Afonso S, O'Brien GS: Mechanism of enhancement of adenosine action by dipyridamole and lidoflazine, in dogs. Arch Int Pharmacodyn Ther 194:181–196, 1971
76. McKeever WP, Gregg DE, Canney PC: Oxygen uptake of the nonworking left ventricle. Circ Res 6:612–623, 1958
77. Castèn GG, Marsh JB: Metabolic studies on cardiac tissue obtained by needle biopsy in the intact unanesthetized dog. Circ Res 1:226–229, 1953
78. Beuren A, Sparks C, Bing RJ: Metabolic studies on the arrested and fibrillating perfused heart. Am J Cardiol 1:103–112, 1958
79. Paul MH, Theilen EO, Gregg DE, et al: Cardiac metabolism in experimental ventricular fibrillation. Circ Res 2:573–578, 1954
80. Gregg DE: Effect of coronary perfusion pressure or coronary flow on oxygen usage of the myocardium. Circ Res 13:497–500, 1963
81. Kahler RL, Braunwald E, Kelminson LL, et al: Effects of alterations of coronary blood flow on the oxygen consumption of the non-working heart. Circ Res 13:501–509, 1963
82. Ross J Jr, Klocke F, Kaiser G, et al: Effect of alterations of coronary blood flow on the oxygen consumption of the working heart. Circ Res 13:510–513, 1963
83. Weisberg H, Katz LN, Boyd E: Influence of coronary flow upon oxygen consumption and cardiac performance. Circ Res 13:522–528, 1963
84. Abel RM, Reis RL: Effects of coronary blood flow and perfusion pressure on left ventricular contractility in dogs. Circ Res 27:961–971, 1970
85. Michal G, Naegle S, Danforth WH, et al: Metabolic changes in heart muscle during anoxia. Am J Physiol 197:1147–1151, 1959
86. Michal G, Beuren A, Hogancamp CW, et al: Effect of interruption of coronary circulation on metabolism of the arrested heart. Am J Physiol 195:417–423, 1958
87. Huckabee WE: Relationship of pyruvate and lactate during anaerobic metabolism. V: Coronary adequacy. Am J Physiol 200:1169–1176, 1961
88. Krasnow N, Neill WA, Messer JV, et al: Myocardial lactate and pyruvate metabolism. J Clin Invest 41:2075–2085, 1962
89. Krasnow N, Gorlin R: Myocardial lactate metabolism in coronary insufficiency. Ann Intern Med 59:781–787, 1963
90. Cohen LS, Elliott WC, Rolett EL, et al: Hemodynamic studies during angina pectoris. Circulation 31:409–416, 1965
91. Herman MV, Elliott WC, Gorlin R: An electrocardiographic, anatomic and metabolic study of zonal myocardial ischemia in coronary heart disease. Circulation 35:834–846, 1947
92. Olson RE: "Excess lactate" and anaerobiosis. Ann Intern Med 59:960–963, 1963
93. Bing RJ, Hellberg K: Coronary blood flow in relation to angina pectoris. Circulation 46:1146–1154, 1972

94. Gorlin R: Physiologic studies in coronary atherosclerosis. Fed Proc 21:(part II, suppl 11)93–97, 1962
95. Knoebel SB, Elliott WC, McHenry PL, et al: Myocardial blood flow in coronary artery disease. Am J Cardiol 27:51–58, 1971
96. Hollander W, Madoff IM, Chobanian AV: Local myocardial blood flow as indicated by the disappearance of NaI^{131} from the heart muscle: Studies at rest, during exercise and following nitrite administration. J Pharmacol Exp Ther 139:53–59, 1963
97. Cannon PJ, Dell RB, Dwyer EM Jr: Regional myocardial perfusion rates in patients with coronary artery disease. J Clin Invest 51: 978–994, 1972
98. Rowe GG: Coronary vasodilator therapy for angina pectoris. Am Heart J 68:691–696, 1964
99. Parker JO, Chiong MA, West RO, et al: Sequential alterations in myocardial lactate metabolism, S-T segments, and left ventricular function during angina induced by atrial pacing. Circulation 40:113–131, 1969
100. Ross RS, Schwartz N, Gaertner RA, et al: Electrocardiographic and hemodynamic observations during selective coronary cineangiocardiography. J Clin Invest 41:1395, 1962
101. Roughgarden JW: Circulatory changes associated with spontaneous angina pectoris. Am J Med 41:947–961, 1966
102. Muller O, Rørvik K: Haemodynamic consequences of coronary heart disease with observations during anginal pain and on the effect of nitroglycerin. Br Heart J 20:302–310, 1958
103. Ganz W, Marcus HS: Failure of intracoronary nitroglycerin to alleviate pacing-induced angina. Circulation 46:880–889, 1972
104. Mason DT, Braunwald E: The effects of nitroglycerin and amyl nitrite on arteriolar and venous tone in the human forearm. Circulation 32:755–766, 1965
105. Winsor T: Effects of nitrates on the peripheral circulation, The Study of the Systemic, Coronary and Myocardial Effects of Nitrates. Edited by GG Gensini. Springfield, Ill., Charles C Thomas, 1972, pp 267–273
106. Mason DT, Zelis R, Amsterdam EA: Nitroglycerin and the peripheral circulation, The Study of the Systemic, Coronary and Myocardial Effects of Nitrates. Edited by GG Gensini. Springfield, Ill., Charles C Thomas, 1972, pp 274–291
107. Brandt JL, Caccese A, Dock W: Slit-kymographic evidence that nitroglycerin decreases heart volume and stroke volume—while increasing the amplitude of ballistocardiographic waves. Am J Med 12:650–658, 1952
108. Katzilambros L: Die veränderung des herz- und lungenschattens nach einatmung von amylnitrit. Fortschr Roentgenstr 48:338–339, 1933
109. Williams JF Jr, Glick G, Braunwald E: Studies on cardiac dimensions in intact unanesthetized man. V. The effect of nitroglycerin. Circulation 32:767–771, 1965
110. Brachfeld N, Bozer J, Gorlin R: Action of nitroglycerin on the coronary circulation in normal and in mild cardiac subjects. Circulation 19:697–704, 1959
111. Gorlin R, Brachfeld N, MacLeod C, et al: Effect of nitroglycerin on the coronary circulation in patients with coronary artery disease or increased left ventricular work. Circulation 19:705–718, 1959
112. Rowe GG, Chelius CJ, Afonso S, et al: Systemic and coronary hemodynamic effects of erythrol tetranitrate. J Clin Invest 40: 1217–1222, 1961
113. Afonso S, Rowe GG, Lowe WC, et al: Systemic and coronary hemodynamic effects of isosorbide dinitrate. Am J Med Sci 246: 584–589, 1963
114. Rowe GG: The nitrates as antianginal drugs, The Study of the Systemic, Coronary and Myocardial Effects of Nitrates. Edited by GG Gensini. Springfield, Ill., Charles C Thomas, 1972, pp 258–273
115. Khaja F, Sanghvi V, Mark A, et al: Effect of volume expansion on the angina threshold. Circulation 43:824–835, 1971
116. Parker JO, Case RB, Khaja F, et al: The influence of changes in blood volume on angina pectoris: A study of the effect of phlebotomy. Circulation 41:593–604, 1970
117. Brunton TL: On the use of nitrite of amyl in angina pectoris. Lancet 2:97–98, 1867
118. Rowe GG: Inequalities of myocardial perfusion in coronary artery disease ("coronary steal"). Circulation 42:193–194, 1970
119. Shappell SD, Murray JA, Nasser MG, et al: Acute changes in hemoglobin affinity for oxygen during angina pectoris. N Engl J Med 282:1219–1224, 1970
120. Olson RE: Myocardial metabolism in congestive heart failure. J Chronic Dis 9:442–464, 1959
121. Danforth WH, Ballard FB, Kako K, et al: Metabolism of the heart in failure. Circulation 21:112–123, 1960
122. Bing RJ: Metabolic activity of the intact heart. Am J Med 30:679–691, 1961
123. Bing RJ, Maraist FM, Dammann JF Jr, et al: Effect of strophanthus on coronary blood flow and cardiac oxygen consumption of normal and failing human hearts. Circulation 2:513–516, 1950
124. Regan TJ, Christensen RC, Wada T, et al: Myocardial response to acetyl strophanthidin in congestive heart failure: A study of electrolytes and carbohydrate substrates. J Clin Invest 38:306–316, 1959
125. Waldhausen JA, Kilman JW, Herendeen TL, et al: Effects of acetylstrophanthidin on coronary vascular resistance and myocardial oxygen consumption. Circ Res 16:203–209, 1965

126. Regan TJ, Talmers FN, Hellems HK: Myocardial transfer of sodium and potassium: Effect of acetyl strophanthidin in normal dogs. J Clin Invest 35:1220–1228, 1956
127. Blain JM, Eddleman EE, Siegel AL, et al: Studies on myocardial metabolism. V. The effects of lanatoside-C on the metabolism of the human heart. J Clin Invest 35:314–321, 1956
128. Rothlin E, Taeschler M, Cerletti A: Action of dinitrophenol and lanatocide-C on the canine heart lung preparation. Circ Res 3:32–38, 1955
129. Gregg DE, Fisher LC: Blood supply to the heart. Handbook of Physiology, Section 2: Circulation, Vol II. Baltimore, Williams and Wilkins, 1963, pp 158–159
130. Sarnoff SJ, Case RB, Waithe PE, et al: Insufficient coronary flow and myocardial failure as a complicating factor in late hemorrhagic shock. Am J Physiol 176:439–444, 1954
131. Kline HJ, Marano AJ, Johnson CD, et al: Hemodynamic and metabolic effects of hyperbaric oxygenation in myocardial infarction. J Appl Physiol 28:256–263, 1970
132. Entman ML, Martin AM Jr, Mikat E, et al: Phasic myocardial blood flow in hemorrhagic hypotension: Effect of beta sympathetic blockade. Am J Cardiol 21:881–885, 1968
133. Entman ML, Hackel DB, Martin AM, et al: Prevention of myocardial lesions during hemorrhagic shock in dogs by pronethalol. Arch Pathol 83:392–395, 1967
134. O'Rourke RA, Fischer DP, Escobar ED, et al: Effect of acute pericardial tamponade on coronary blood flow. Am J Physiol 212: 549–552, 1967
135. Hackel DB, Kinney TD, Goodale WT: Cardiovascular effects of pulmonary embolization in intact dogs studied by venous catheterization of the coronary sinus. Am J Physiol 176:135–138, 1954
136. Stein PD, Alshabkhoun S, Hawlins HF, et al: Right coronary blood flow in acute pulmonary embolism. Am Heart J 77:356–362, 1969
137. Rowe GG, Castillo CA, Afonso S, et al: The systemic and coronary hemodynamic effects of arteriovenous fistulas. Am Heart J 64:44–49, 1962
138. Rowe GG, Huston JH, Weinstein AB, et al: The hemodynamics of thyrotoxicosis in man with special reference to coronary blood flow and myocardial oxygen metabolism. J Clin Invest 35:272–276, 1956
139. Leight L, DeFazio V, Talmers FN, et al: Coronary blood flow, myocardial oxygen consumption, and myocardial metabolism in normal and hyperthyroid human subjects. Circulation 14:90–99, 1956
140. Bing RJ: The coronary circulation in health and disease as studied by coronary sinus catheterization. Bull NY Acad Med 27:405–424, 1951
141. Rowe GG, Castillo CA, Maxwell MM, et al: A hemodynamic study of hypertension including observations on coronary blood flow. Ann Intern Med 54:405–412, 1961
142. Brody TM, Palmer JF, Bennett DR: Phosphorylation in cardiac muscle from failing and unfailing heart–lung preparations. Proc Soc Exp Biol Med 86:739–741, 1954
143. Frommer PL, Robinson BF, Braunwald E: Paired electrical stimulation, a comparison of the effects on performance of the failing and non failing heart. Am J Cardiol 18: 738–744, 1966
144. Folts JD, Afonso S, Rowe GG: Systemic and coronary hemodynamic effects of ketamine in intact anesthetized and unanesthetized dogs (submitted to Anesth Analg)
145. Rowe GG: Myocardial perfusion and measurement of coronary blood flow, Clinical Cardiopulmonary Physiology. Third edition. New York, Grune and Stratton, 1969, pp 80–90
146. McKenna DH, Afonso S, Jaramillo CV, et al: Systemic and coronary hemodynamic effects of isoproterenol in control animals and those pretreated with a MAO inhibitor (pargyline hydrochloride). Arch Int Pharmacodyn Ther 162:275–282, 1966
147. Krasnow N, Rolett EL, Yurchak PM, et al: Isoproterenol and cardiovascular performance. Am J Med 37:514–525, 1964
148. Bertranou E, Ekestrom S, Giraudo N, et al: Effet de l'isoproterenol sur le debit des pontages aorto-coronaires chez l'-humain (rapport preliminaire). TOME 101:871–873, 1972
149. Berne RM: Effect of epinephrine and norepinephrine on coronary circulation. Circ Res 6:644–655, 1958
150. Marchetti PG, Maccari M, Merlo L: Recherches experimentales sur les effets de la l-adrenaline et de la l-noradrenaline sur la circulation coronarienne. Cardiologia 42: 1–26, 1963
151. Kuhn LA, Kline HJ, Goodman P, et al: Effects of isoproterenol on hemodynamic alterations, myocardial netabolism and coronary flow in experimental acute myocardial infarction with shock. Am Heart J 77:772–783, 1969
152. Mueller H, Ayres SM, Gregory JJ, et al: Hemodynamics, coronary blood flow, and myocardial metabolism in coronary shock: response to l-norepinephrine and isoproterenol. J Clin Invest 49:1885–1902, 1970
153. Crumpton CW, Rowe GG, O'Brien GS, et al: The effect of hexamethonium bromide upon coronary flow, cardiac work and cardiac efficiency in normotensive and renal hypertensive dogs. Circ Res 2:79–83, 1951
154. Crosley AP Jr, Brown JF, Tuchman H, et al: The acute hemodynamic and metabolic response of hypertensive patients to pentolinium tartrate. Circulation 14:584–592, 1956
155. Rowe GG, Castillo CA, Maxwell GM Jr,

et al: The effect of mecamylamine on coronary flow, cardiac work, and cardiac efficiency in normotensive dogs. J Lab Clin Med 52: 883–887, 1958
156. Afonso S, Rowe GG, Chelius CJ, et al: Acute systemic and coronary hemodynamic effects of trimethidinium methosulfate. Proc Soc Exp Biol Med 110:74–77, 1962
157. Rowe GG, Afonso S, Lugo JE, et al: Systemic and coronary hemodynamic effects of trimethaphan camphorsulfonate (Arfonad) in the dog. ANESTHESIOLOGY 25:156–160, 1964
158. Rowe GG, Leicht TR, Boake WC, et al: The systemic and coronary hemodynamic effects of diazoxide. Am Heart J 66:636–643, 1963
159. Scott JC, Cowley AW Jr: The effect of diazoxide on coronary blood flow. Am J Cardiol 24:865–869, 1969
160. Rowe GG, Maxwell GM, Castillo CA, et al: Hemodynamic effects of B methyl 2,6-dimethylphenyl-ether of choline (SKF 6890) on the systemic and coronary circulation. J Lab Clin Med 56:409–412, 1960
161. Brachfeld N, Monroe RG, Gorlin R: Effect of pericoronary denervation on coronary hemodynamics. Am J Physiol 199:174–178, 1960
162. Rowe GG, Afonso S, Chelius CJ, et al: The systemic and coronary hemodynamic effects of guanethidine. Am Heart J 62: 542–548, 1961
163. McKenna DH, Corliss RJ, Sialer S, et al: Effect of propranolol on systemic and coronary hemodynamics at rest and during simulated exercise. Circ Res 19:520–527, 1966
164. Whitsitt LS, Lucchesi BR: Effects of propranolol and its stereoisomers upon coronary vascular resistance. Circ Res 21:305–317, 1967
165. Zuberbuhler RC, Bohr DF: Responses of coronary smooth muscle to catecholamines. Circ Res 16:431–440, 1965
166. Maxwell GM, Rowe GG, Castillo CA, et al: The effect of dopamine (3-hydroxytyramine), upon the systemic, pulmonary, and cardiac haemodynamics and metabolism of intact dog. Arch Int Pharmacodyn Ther 129:62–70, 1960
167. Brooks HL, Stein PD, Matson JL, et al: Dopamine-induced alterations in coronary hemodynamics in dogs. Circ Res 24:699–704, 1969
168. Maxwell GM, Castillo CA, Clifford JE, et al: Effect of serotonin (5-hydroxytryptamine) on the systemic and coronary vascular bed of the dog. Am J Physiol 197:736–738, 1959
169. Maxwell GM, Elliott RB, Kneebone GM: Effects of bradykinin on the systemic and coronary vascular bed of the intact dog. Circ Res 10:359–363, 1962
170. Rowe GG, Afonso S, Castillo CA, et al: The systemic and coronary hemodynamic effects of synthetic bradykinin. Am Heart J 65:656–663, 1963
171. Fronek A, Ganz V: The effect of papaverine on coronary and systemic haemodynamics and on the oxygen metabolism of the myocardium. Cor Vasa 3:120–128, 1961
172. Maxwell GM, Crumpton CW, Rowe GG, et al: The effects of theophylline ethylenediamine (aminophylline) on the coronary hemodynamics of normal and diseased hearts. J Lab Clin Med 54:88–95, 1959
173. Berne RM: The effect of immersion hypothermia on coronary blood flow. Circ Res 2:236–242, 1954
174. Sabiston DC Jr, Theilen EO, Gregg DE: The relationship of coronary blood flow and hypothermia. Surgery 38:498–505, 1955
175. Hardin RA, Scott JB, Haddy FJ: Effect of cardiac cooling on coronary vascular resistance in normothermic dogs. Am J Physiol 199:163–166, 1960
176. Penrod KE: Cardiac oxygenation during severe hypothermia in dog. Am J Physiol 164: 79–85, 1951
177. Edwards WS, Simmons E, Lombardo CR, et al: Coronary blood flow in hypothermia. Arch Surg 71:853–858, 1955
178. Edwards WS, Tuluy S, Reber WE, et al: Coronary blood flow and myocardial metabolism in hypothermia. Ann Surg 139:275–281, 1954
179. Maxwell GM, Castillo CA, Crumpton CW, et al: Hyperthermia: Systemic and coronary circulatory changes in the intact dog. Am Heart J 58:854–862, 1959
180. Walton RP, Goldberg LI, Gazes PC, et al: Effects of hyperpyrexia on the heart *in situ*: Studies with dicumarol, dinitrophenol and external heat. Am J Physiol 169:78–93, 1952
181. Moffitt EA, Rosevear JW, McGoon DC: Myocardial metabolism in children having open-heart surgery. JAMA 211:1518–1524, 1970
182. Meerson FZ, Gomzakov OA, Shimkovich MV: Adaptation to high altitude hypoxia as a factor preventing development of myocardial ischemic necrosis. Am J Cardiol 31:30–34, 1973
183. Moffitt EA, Rosevear JW, Townsend CH, et al: Myocardial metabolism in patients having aortic valve replacement. ANESTHESIOLOGY 31:310–320, 1969
184. Winterscheid LC, Vetto RR, Merendino KA: Myocardial carbohydrate metabolism during induced cardiac arrest and post-arrest perfusion. Ann Surg 148:481–487, 1958
185. Hirsch LJ, Lluch S, Katz LN: Counterpulsation effects on coronary blood flow and cardiac oxygen utilization. Circ Res 19:1031–1040, 1966