THE PHYSIOLOGY OF THE CORONARY CIRCULATION *†

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MANY factors influencing coronary blood flow are directly or indirectly affected by the course of an anesthesia. The anesthesiologist should, therefore, be familiar with the physiology of the coronary circulation in order to evaluate the effects of anesthesia and its possible complications upon coronary blood flow. Only by the anesthetist possessing such information can he anticipate and prevent sudden coronary occlusion or insufficiency in the anesthetized patient. This report is a presentation of recently obtained data pertaining to the physiology of the coronary circulation and contains as well an interpretation of those data from the viewpoint of the anesthesiologist.

Wearn (1) has demonstrated that every myocardial fiber is accompanied by one or more capillaries. The capillary density of the heart (1) is five times greater than that of the brain (2). Through this abundant circulation about 65 to 85 cc. of blood per 100 gm. of myocardium flows per minute, equivalent in the adult man to 200 cc. of blood for the whole heart. There has been, however, no general agreement as to the mechanisms regulating this flow of blood. The influence of the vasomotor nerves in controlling coronary arterial tone has been a source of debate (3, 4, 5) and data to substantiate other theories of control (e.g., 6) have not appeared. It has been recognized that the rise and fall of arterial blood pressure is accompanied by a similar directional change in coronary blood flow but again definitive data have been lacking.

The coronary circulation, however it be controlled, supplies blood to a working muscular organ which should reasonably be expected to require a large amount of oxygen. Twelve years ago it was demonstrated that coronary venous blood contained far less oxygen than systemic venous blood (7), yet this important observation did not receive the attention it deserved. This report will, therefore, attempt

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to indicate the importance of this observation as well as to offer answers to the problems already mentioned.

METHODS UTILIZED

Much of the investigative work which has been done on the coronary circulation has been on preparations far removed from the normal (isolated heart preparation and the heart-lung preparation) and by methods that are of questionable accuracy (coronary sinus outflow, 4, and the thermostrohmuhr of Rein, 8). In an attempt to obtain a preparation more closely approximating the normal and yet use a reliable instrument for measuring blood flow, the author and his coworkers have utilized the anesthetized, spontaneously breathing dog, measuring the coronary blood flow by the bubble flowmeter technic. The details of this method are available elsewhere (9, 10) but, in brief, dogs were lightly anesthetized with pentobarbital sodium, following which heparinized blood was circuited from a cannulated right carotid artery through a bubble flowmeter and thence into a cannulated anterior descending or circumflex branch of the left coronary artery. Coronary venous blood was obtained from a cannulated branch of the great cardiac vein. The chest was closed during the experiments.

In a further attempt to develop a method of measuring coronary blow flow in the intact dog and possibly ultimately in man, the author and his co-workers (11) in collaboration with Goodale and associates (12) and Bing and co-workers (13) have applied the nitrous oxide method of measuring blood flow (14, 15) to the coronary circulation. The underlying principle is that the amount of nitrous oxide taken up by the myocardium during a specified time, divided by the difference in nitrous oxide content between arterial and coronary venous blood, must equal the volume of blood that flowed through the coronary circulation during that period. This method briefly consisted of lightly anesthetizing large dogs with pentobarbital and then obtaining coronary venous blood by means of a catheter placed into the coronary sinus under fluoroscopic vision. Arterial blood was obtained from a femoral artery and coronary blood flow estimated from the arteriovenous nitrous oxide difference while the animal inhaled a 15 per cent nitrous oxide mixture for ten minutes (11, 12). This method has now been used repeatedly to measure the coronary blood flow of man (13).

RESUME OF DATA OBTAINED AND PHYSIOLOGIC PRINCIPLES DEDUCED

A. *Volume of coronary blood flow.*—By both of the methods described above, values for coronary blood flow were obtained which closely approximated those estimated by Wiggers (16), namely, 65 to 85 cc. per 100 Gm. per minute. Under our standard conditions, this volume of flow for the entire heart amounted to 4 to 5 per cent of the cardiac output (9).

B. *Vasomotor control.*—According to our data (9) the coronary arteries did not follow the general pattern of many peripheral vessels in that neither the parasympathetic nor the sympathetic nerves had apparent significant influence over coronary arterial tone. Particularly, we were unable to find supportive evidence for the often mentioned (17, 18, 19) theory of coronary constriction caused by parasympathetic stimulation. Furthermore, the chemical mediators by which autonomic nerves are generally accepted to act were both coronary dilators as indicated in figure 1. The intra-arterial injection of minute amounts of either acetylcholine or of epinephrine led to prompt and marked increases in coronary flow, independent of changes in heart rate and of blood pressure. These observations therefore placed the coronary vessels in the same category with the cerebral vessels which have been demonstrated not to be significantly affected directly by vasomotor action (20, 21).

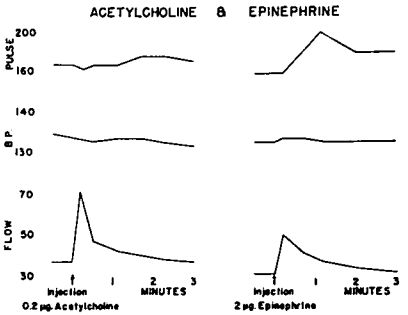

FIG. 1. Pulse = beats/min. B.P. = mean arterial blood pressure. Flow = coronary flow in cc./100 Gm. myocardium/min. Injections were intra-arterial. (Reproduced from: Am. J. Physiol. 148: 590, 1947.)

C. *The effect of systemic circulatory changes.*—1. Blood pressure: The volume of coronary blood flow more or less parallels mean arterial blood pressure so that a given percentile fall in blood pressure results in a corresponding decrease in coronary blood flow (9). This fact has been demonstrated in other laboratories (e.g., 22) and is recognized by the anesthesiologist and surgeon who have seen cardiac pain or even coronary occlusion develop in patients during periods of low blood pressure.

2. Cardiac output: With diminished cardiac output due to blood loss, the relative proportion of the cardiac output going through the coronary arteries increases (9). Figure 2 demonstrates that under conditions in which the cardiac output was reduced to 500 cc. per minute, the relative proportion of that output diverted to the coronary arteries

was increased to as much as 14 per cent. The actual coronary flow, however, was always reduced.

D. *The effect of arterial gas content upon coronary flow.*—1. Carbon dioxide: In the dog, increasing the carbon dioxide content of arterial blood did not have a significant effect on the volume of coronary flow (9). This may not be true in man, however, since carbon dioxide was found to be a potent cerebral vasodilator in man (23) after experiments on the monkey were essentially negative (20). Changing the hydrogen ion concentration of arterial blood apparently does have an effect on coronary flow since a raising of the hydrogen ion concentration always produced a slight but consistent acceleration of coronary flow.

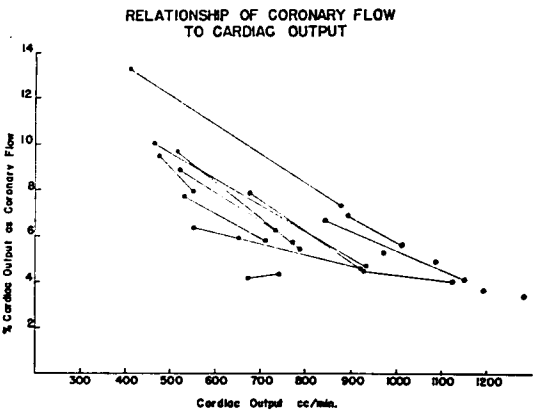

FIG. 2. Relationship of coronary flow to cardiac output. Dots connected by lines indicate observations in the same experiment. Dots unconnected indicate experiments in which only one determination of cardiac output was made.

2. Oxygen: Coronary venous blood is characteristically almost black in color and when analyzed it is found to contain only 4 to 6 volumes per cent of oxygen as compared with 14 to 16 volumes per cent found in mixed venous blood in the right ventricle (7, 24, 10). This means that, under normal circumstances, the heart removes 75 to 80 per cent of the oxygen delivered to it, thus placing this organ in the same category with working striated muscle which likewise may show a venous blood almost devoid of oxygen (25).

When the oxygen content of coronary arterial blood is reduced, an acceleration in the volume of coronary flow occurs. In an attempt to gather more precise information on the nature of the effect of anox-

emia, we allowed animals to breathe gradually decreasing concentrations of oxygen, meanwhile measuring the volume of coronary flow as well as changes in cardiac work and cardiac efficiency (10). The results of one of a series of these experiments are shown in table 1. Coronary flow increased fivefold as the arterial oxygen content decreased from 18 to 4 volumes per cent. This occurred without any great change in cardiac work.

Thesis of control of coronary blood flow.—The inability to demonstrate a significant effect of either the sympathetic or parasympathetic nerves over coronary blood flow excludes a nervous mechanism of regulating the volume of coronary flow. However, some mechanism of control must exist. In an attempt to determine the nature of this regulation the following facts appeared to be important: (a) Under conditions in which cardiac work was increased, either by increasing arterial blood pressure or by increasing cardiac output, coronary blood flow increased. (b) When cardiac work was reduced, coronary flow declined. (c) When the oxygen supply was decreased by reducing the arterial oxygen content, the oxygen demands of the heart were met

TABLE 1

EFFECT OF ANOXEMIA ON THE CORONARY CIRCULATION

Experiment No. 0-10 Dog—16.3 Kg.

Oxygen Mixture Inhaled (per cent)	100	21	16	12	8
Arterial Oxygen Content (vol. per cent)	19.5	15.7	11.2	7.9	4.0
Coronary Blood Flow (cc./100 Gm./min.)	54	82	106	176	264
Cardiac Oxygen Consumption (cc./100 Gm./min.)	8.5	9.0	9.9	12.0	9.0

by an acceleration of coronary flow. (d) There was an excellent correlation ($r = 0.85$) between myocardial oxygen consumption and coronary blood flow. These facts caused us to conclude that the metabolic demands of the heart, of which oxygen may be the most important, is the regulating device of coronary flow. The exact mechanism by which this control is exerted has not been elucidated although Katz (6) has postulated the presence of a dilator substance inactivated in the presence of adequate oxygen.

Actually, one might look on coronary flow as being determined by an additional factor, namely the driving pressure supplied by arterial blood pressure. These two factors can be considered as a "coarse" and a "fine" adjustment comparable to those of a microscope; the "coarse" adjustment is the alteration of coronary blood flow occurring with sudden changes in blood pressure, after which the "fine" adjustment regulates the flow exactly to the needs of the heart. In brief, the metabolic demands keep the blood supply in "sharp focus" for the heart.

CLINICAL INFERENCES

There are many practical aspects of the data presented above. One of the most interesting to the anesthesiologist is the effect of hypotension upon coronary flow. If the thesis of control of coronary flow mentioned previously is acceptable, then the following should be true: during a period of hypotension such as commonly accompanies spinal anesthesia, reduction of cardiac work with a simultaneous diminution in oxygen demand occurs and thus a decrease in the volume of coronary blood flow should normally follow. Since it has been assumed that a reduction in coronary flow was undesirable under these conditions, we conducted a series of experiments on dogs to determine the importance of the reduced coronary flow occurring in a hypotension produced by spinal anesthesia (26). We found that the fall in blood pressure so produced led to a 56 per cent reduction in cardiac work with coronary blood flow diminishing only 25 per cent; therefore, coronary blood flow became more abundant relative to the cardiac needs.

The data obtained in these experiments have been from dogs with presumably normal coronary vasculature. In such animals, adjustments of vascular tone are apparently made easily. The reactivity of abnormal or sclerotic arteries is probably entirely different. If the vessels are fixed in caliber, their tonus cannot change so that the "fine" adjustment is removed and only the "coarse" adjustment remains. Under such circumstances a sudden fall in arterial blood pressure leads to an immediate decrease in coronary flow; if the decreased flow is adequate for the altered metabolic needs of the myocardium, no harm is done but if the flow is inadequate, relative coronary insufficiency occurs.

Blood pressure is not always elevated in situations in which there is an increase in cardiac oxygen demand (that is, in exercise or under emotional stress, 27). Here again, if the arteries are unable to change their internal diameter, not enough oxygen is delivered and coronary insufficiency results. With either circumstance symptoms of coronary occlusion and death can occur, yet at autopsy the arteries are found to be patent and, to the unsuspecting, quite adequate.

It might be argued that when coronary blood flow is limited, more oxygen can be removed from the arterial blood, leaving the venous blood completely desaturated. It is important to remember that coronary venous blood normally contains only 4 to 6 volumes per cent of oxygen. This means that no significant extra amount of oxygen can be obtained from coronary arterial blood. Cytrochrome C has been advocated to increase the oxygen removed from coronary blood in coronary occlusion and angina pectoris, but in a series of experiments we were unable to demonstrate that this drug had any such effect (30).

The patient's reaction to a fall in blood pressure would apparently be the best guide to therapy. Marked falls in blood pressure may appear in younger individuals yet not be accompanied by any signs of

discomfort or distress. Vasopressor drugs are not necessarily indicated in such instances. On the other hand, slight decreases in blood pressure may in some individuals be accompanied by pallor, sweating, dyspnea, tachycardia and even pain in the chest. This is suggestive of coronary insufficiency and an attempt should be made immediately to return the patient's blood pressure to its former levels. In such instances, vasopressor drugs should be given intravenously in small amounts so that the pressure is not spiked to a high level to be followed by a subsequent depression. Vasopressor agents which exert their principal effect upon the peripheral vessels rather than upon the heart itself (that is, neosynephrine) should be used.

Patients with hypertension do not always show evidence of coronary insufficiency if their blood pressure is reduced (28). This is particularly true of those individuals who have hypertention without coronary arteriosclerosis. This suggests that the coronary arteries of these people can diminish their tone when the blood pressure is lowered. Of course, during such a period of lowered blood pressure these same individuals may develop symptoms of cerebral anoxia or anuria or both due to a diminished oxygen supply to the brain and kidney respectively. In these patients it is necessary to maintain blood pressure at or near hypertensive levels during anesthesia to prevent postanesthetic cerebral and renal complications. A dilute intravenous infusion of a pressor drug may be needed throughout the anesthesia for this purpose. In the hypertensive patient with coronary sclerosis, blood pressure must be maintained by the same means to prevent coronary insufficiency since only the "coarse" mechanism is functioning.

When confronted by a patient with prolonged hypotension, such as in shock, the compensating mechanisms that serve to keep coronary flow adequate for the myocardial needs should be kept in mind. As mentioned previously, one of the major compensating mechanisms in hypotension from a reduced blood volume is a redistribution of the circulating blood so that a relatively greater proportion goes to the coronary bed. Constriction of the peripheral vessels in those areas supplied by sympathetic efferents assists in this redistribution. Increasing body temperature rapidly leads to vasodilation of the skin and skeletal muscles (29) which may cause an undesirable reapportionment of cardiac output to the detriment of the heart. External heat should not be applied in shock until the blood volume has been augmented.

OXYGEN THERAPY AND HYPOTENSION

The therapy of paramount importance in shock or in prolonged hypotension, particularly if it be associated with a damaged myocardium, is the administration of oxygen. While it is generally accepted that in such instances oxygen is of benefit by increasing the oxygen tension of arterial blood, thus supplying more oxygen to the periphery of the damaged area, a second and possibly more important

mechanism must not be overlooked. Anoxia, either of the body, of an organ or of a part of an organ, amounts to a disproportion between the oxygen supply and the oxygen requirement. In the case of the heart this disproportion can be produced by an increase in cardiac work without an increase in oxygen supply just as surely and with the same consequences as by a decrease in arterial oxygen content. Inhalation of 100 per cent oxygen produces a fall in cardiac output in normal individuals primarily because of a decrease in cardiac rate (31, 32). When a heart is laboring under a strain with an elevated heart rate and possibly an added suboxygenation of the arterial blood, the reduction in cardiac output following administration of 100 per cent oxygen may exceed the 10 per cent found in normal individuals. The reduction in cardiac work plus the increase in arterial oxygen tension would thus be additive in minimizing or preventing permanent myocardial damage by simultaneously decreasing oxygen demands and increasing oxygen supply.

THE EFFECT OF DRUGS ON THE CORONARY CIRCULATION

The choice of drugs for improving coronary blood flow may be influenced by the following factors: (a) are the coronary arteries and the heart normal, (b) is there evidence of coronary arteriosclerosis, and (c) is there evidence of cardiac damage or is the exercise tolerance low? If the coronary arteries are normal, the latitude in choice of drugs to increase coronary blood flow is relatively great. Most drugs which will lead to an elevated blood pressure will also increase coronary flow. Although total cardiac work may be increased at the same time, the ability to regulate coronary vascular tone will permit an accurate adjustment of the flow to oxygen needs. Drugs which could be utilized for this purpose would include all of the commonly used pressor substances such as ephedrine, methedrine, neosynephrine and so forth. Pitressin is contraindicated since it is one of the few drugs which will produce coronary constriction. In one of our experiments a small amount of this drug injected into the coronary arteries caused complete cessation of coronary blood flow.

In the presence of coronary arteriosclerosis, the vessels of the heart have partially or completely lost their ability to change their vascular tone and coronary blood flow is determined primarily by the arterial blood pressure. To increase coronary flow under these conditions, one should use preferably a drug having primarily a pressor action with a minimum of cardiac effect. Epinephrine and ephedrine are not desirable because of their stimulation of cardiac work. Carefully administered small amounts of neosynephrine or allied drugs are advantageous but must be given in such a manner as to avoid "peaking" of the blood pressure.

In the presence of cardiac damage or decreased exercise tolerance, the ideal drug as far as the coronary circulation is concerned is one which would increase coronary flow and thus the oxygen supply without

increasing cardiac work or oxygen demand. Papaverine has been found to do this best in animals (33, 34). Aminophylline increases coronary flow but usually also increases cardiac work. Nikethamide (coramine) is commonly used clinically in this type of case but it increases coronary flow at the expense of increased cardiac work and decreased cardiac efficiency (33, 35), and then only when used in excessive dosage. In our experimental work, nitroglycerine has not increased coronary flow consistently, a fact which leads one to suspect that much of the benefit derived from this drug in angina pectoris may be explained by a decreased oxygen demand by the heart consequent on the hypotension.

The recent development of the nitrous oxide method of measuring coronary blood flow in man offers a possibility of measuring the effects of these drugs on the coronary circulation of man. The method is in its early stages of development at present and may never prove to be practicable for such studies in man. However, it offers the closest approach to the problem.

SUMMARY

A resume of previously reported data pertaining to the physiology of the coronary circulation has been presented and used to support the thesis of regulation of the coronary blood flow by the metabolic demands of the heart. Practical applications of these data of interest to the anesthesiologist have been stressed. The hypotension occurring with spinal anesthesia has been shown not to be of great consequence from the cardiac standpoint in the presence of normal coronary arteries. The use of vasopressor and cardiac drugs to facilitate coronary flow in the normal and abnormal patient has been presented.

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