Regulation of coronary blood flow

Richard Gorlin

From the Cardiovascular Division, Department of Medicine, Peter Bent Brigham Hospital and Harvard Medical School, Boston, Massachusetts, U.S.A.

Coronary blood flow is dependent upon arterial pressure, diastolic time, and small vessel resistance. The system is regulated to achieve a low flow high oxygen extraction and low myocardial Po2. This setting is sensitive to change in oxygen needs. Regulation of blood flow occurs primarily through local intrinsic regulation, most likely through production of vasodilating metabolites in response to minimal degrees of ischaemia. Local regulation appears to dominate over remote regulation in most circumstances. Blood flow distribution to the myocardium is depth dependent as well as regional in variation. Both types of distribution of blood flow are profoundly disturbed in the presence of obstructive coronary atherosclerosis. This results in either concentric myocardial shells or patchy transmural zones of selective ischaemia with clear-cut but local abnormalities in metabolism and performance.

Experimental studies during the last decade have provided a better understanding of the operation of the coronary circulation than was possible before. The types of vascular effector receptors, the relative importance of local versus remote control of blood flow, the difference between deep and superficial myocardial blood flow, and the relationship between local blood flow, metabolism, and contractile state all deserve discussion. The purposes of this paper are to describe the unique characteristics of the normal coronary circulation; to elucidate the above mentioned areas of new knowledge; and to describe the mechanism of blood flow delivery when there is intrinsic obstructive disease of the large coronary arteries – that is, atherosclerosis.

Normal coronary circulation

Coronary blood flow as in any other vascular bed is a direct function of blood pressure and an inverse function of the degree of small vessel resistance (Fig. 1). Blood pressure is a primary variable, but because coronary flow occurs mainly in diastole the diastolic level of pressure and the duration of diastole (heart rate effect) become important modifying factors. Similarly, as will be discussed below, intramyocardial resistance will add to or subtract from resistance forces intrinsic to the small vessels per se. Small vessel resistance is a function of a variety of neurogenic and chemical effects on its smooth muscle cells. Small changes in the diameter of resistance vessels result in profound changes in blood flow for any given pressure.

The energy requirement of the human heart in relation to its size is the greatest of any tissue in the body. The heart consumes approximately 0.1 ml. of oxygen per gramme of muscle per minute. Under normal conditions high energy phosphate is derived almost exclusively via aerobic pathways. Energy requirements may double or triple with applied cardiovascular stress.

The oxygen delivery system is essentially a high extraction low flow system. The myocardium removes approximately 120 ml. oxygen per litre of coronary blood flow (Fig. 2). As a result, coronary venous oxygen content is about 50 to 60 ml. per litre and venous Po2 is in the range of 20 mm. Hg. Thus myocardial fluid Po2 must be lower, a condition unique to the heart and to exercising skeletal muscle. Basal myocardial flow is less than 1 ml. per gramme of muscle or about 250 ml. per minute. This is in sharp contrast to other organs such as liver, kidney, or brain, in which tissue Po2 is much higher, arteriovenous oxygen extraction less, and blood flow per unit mass the same or even greater.

1 Supported by USPHS and Heart Research Foundation, Boston, Massachusetts. Dr. Gorlin is an investigator of the Howard Hughes Medical Institute.
Local versus remote control of coronary flow

It is necessary at this point to consider the relative importance of local versus remote mechanisms in the regulation of myocardial flow. The pattern of blood flow and energy need described above provides the first insight into local control within the myocardium itself.

Chemical regulation The ‘set’ of the coronary system is one of relative underperfusion as a result of high basal vascular tone. This forces the myocardial cells to operate at a low Po2. It has been suggested that this marginally ‘hypoxic’ state provides a mechanism for sensitive local auto regulation of blood flow. Even the slightest decrease in tissue Po2 from 20 mm. Hg may be enough to render the cell hypoxic. The cell may release chemical byproducts as a result. Shea and co-workers (1962), for example, have shown that glycolysis with profuse lactate production occurs in the dog heart when coronary venous Po2 drops to 10 mm. Hg or less. Berne (1963) has promulgated the theory that intracellular high energy phosphate compounds are exquisitely sensitive to intracellular oxygen conditions. These moieties readily break down to adenosine which diffuses out of the cell into the surrounding extracellular fluid. Most members of this class of compounds are potent vasodilators. After biochemical analysis of recovery products during induced hypoxia in various preparations, Rubio and Berne (1969) believe that adenosine, in particular, acts on the smooth muscle in the walls of arterioles adjacent to the cardiac muscle cells. This causes vasodilatation (Fig. 3). Thus, a feedback mechanism directly related to intracellular oxygen availability would exist which could regulate flow either to general or to regional myocardial needs. Whether or not adenosine is the true effector, this autoregulation occurs both with and without cardiac nerves and in both intact and isolated preparations.

Physical control The blood flow distribution to cardiac muscle is governed in part by anatomical and physical factors. It has been known for many years that the subendocardium of the left ventricle is uniquely prone to develop ischaemia. Intramural blood supply particularly of the thick-walled left ventricle takes place through two separate types of blood vessels (Fig. 4). Estes and co-workers (1966) have termed these ‘A’ and ‘B’ vessels. The A vessels leave the epicardial arteries at a shallow angle, and branch within and supply the outer one-half of the myocardium.1 The inner aspects of the myocardium (except for the endocardium), however, are supplied by the B vessel, a ‘perforator’ arising at right angles and plunging directly through the myocardial substance to ramify in the subendocardial plexus.

The B vessel by its very anatomical course is susceptible to change in the balance between intramyocardial compressive forces and coronary perfusion pressure. As a result, change in blood pressure or myocardial contractile state

**FIG. 1** Hydraulic factors affecting coronary flow (C.F.). Diastolic blood pressure (BPd) and time act in concert with resistance factors to deliver coronary flow. There are multiple points of resistance to blood flow.

**FIG. 2** Systemic and regional arteriovenous oxygen extraction. qO2 = oxygen consumption per minute. Exercising skeletal muscle extracts an increasing but varying amount of O2 during effort (arrow). Cardiac muscle extraction remains relatively constant and exceeds that of other organs.

1 The right ventricular myocardium has only A vessels.
per se can selectively alter deep as opposed to superficial myocardial blood flow. Thus there emerges the concept of 'shells' of blood flow capacity, all depth-dependent in nature (Kirk and Honig, 1964). Some investigators have attributed certain differences in biochemical composition of the deep and superficial myocardial layers to the differences in blood flow (Griggs, Tchokoev, and De Clue, 1969).

Topographic as distinct from transmural differences in regional perfusion will be discussed later.

Remote regulation Thus far mechanisms for autoregulation of blood supply have been described. The coronary system like other vascular beds is under central nervous and circulating humoral control as well.

Adrenergic mechanisms Evolution of the pharmacological concept of alpha and beta receptors within the vascular bed has given new insights into circulatory regulation. Selective receptor stimulators and inhibitors have helped to define the characteristics of the coronary small vessels. Both alpha and beta receptors are present. In the normal basal state there is a mild alpha or vasoconstrictor 'set' to the system with no apparent beta activity (Brachfeld, Monroe, and Gorlin, 1969). In the presence of chronic recurrent ischaemia, however, the system generally exhibits an overall beta-stimulated or vasodilated state (Wolfson and Gorlin, 1969).

Infused catecholamines have characteristic primary effects on the coronary circulation. Methoxamine, an alpha stimulator, constricts while isoproterenol, a beta stimulator, dilates. The naturally occurring catecholamine nor-epinephrine is a primary coronary constrictor (Yurchak et al., 1964).

Cholinergic stimulators appear to cause coronary vasodilatation. There are certain other humoral substances which influence the coronary vessels, in particular vasopressin, which leads to vasoconstriction.

Integration of control mechanisms
The primacy of local over remote regulation seems to be established in most circumstances. For example, certain catecholamines which stimulate myocardial activity and therefore create a need for increased coronary blood flow, at the same time also stimulate alpha receptors in the coronary arterioles which promote vasoconstriction. The pattern seen is an initial coronary constriction followed by coronary vasodilatation, suggesting that local biochemical or other influences are more
Factors influencing coronary flow

Fig. 5 represents a schema of factors known to influence coronary blood flow. These are exclusive of factors which are mechanically responsible for the actual delivery of coronary flow (Fig. 1).

Basal coronary flow will depend in part on the available oxygen per litre of blood flow. Therefore, arterial anoxaemia or anaemia will result in increased coronary flow to keep venous \( P_{O_2} \) and corresponding tissue \( P_{O_2} \) constant. There may be minor effects of \( p\text{H} \) on the haemoglobin oxygen dissociation curve.

Coronary flow will also depend on myocardial oxygen requirements, both acute and chronic. Energy needs are dependent in turn on mechanical activity of the heart. Thus increases or decreases in systemic arterial pressure, heart rate, heart size, and in intrinsic contractile state (speed of muscle shortening) all profoundly influence the need for or create a deficiency of coronary flow. Neurogenic influences are usually superseded by changes in local metabolic factors if the two occur simultaneously as with adrenergic stimulation.

Effect of coronary atherosclerosis on myocardial blood flow

The prevalence and importance of coronary artery disease justify a separate analysis of its effect on regulation of blood flow. Coronary atherosclerosis is a heterogeneous disease in all respects: distribution and severity of obstruction and the extent and uniformity of collateral compensation exhibit major and unpredictable variation.

Two heterogeneities in blood flow distribution have resulted from coronary atherosclerosis: deep versus superficial myocardial blood flow differences, and topographic or regional blood flow differences.

Deep versus superficial blood flow Owing to the peculiar architecture of the B vessels only minor reductions in epicardial perfusion pressure can lead to profound changes in deep blood supply. Downey and Kirk (1970, unpublished observations) have shown that, given even a 'noncritical' arterial stenosis, tachycardia can induce subendocardial ischaemia. Furthermore, this type of ischaemia leads to a subendocardial 'shell' of poor contractility at a time when epicardial contractility remains normal (Kirk et al., 1970). Thus, even mild degrees of coronary obstruction may under appropriate mechanical circumstances lead to deep myocardial ischaemia. This, of course, is recognized clinically in ST segment depression in the electrocardiogram recorded during an attack of angina pectoris.
Regional differences in blood flow  It has been demonstrated in man with coronary atherosclerosis that myocardial flow is regionally non-uniform (Sullivan et al., 1967; Liedtke et al., 1970) (Fig. 6). The degree of non-uniformity is dependent not only on the degree of local arterial obstruction but also on the extent of compensating collateral vessels. The region of low flow is supplied almost invariably at a greatly reduced arterial perfusion pressure (Fig. 7). It is probable that local blood supply is maintained through constant generation of local metabolites which effect local vasodilatation. This in no way, however, assures participation of the surrounding normal coronary vascular tree in the highly localized chemical feedback response. Evidence that local blood supply may yet be improved, presumably by effects on the surrounding vascular tissue, has been derived from studies with nitroglycerin, a powerful dilator of smooth muscle. This agent given sublingually causes little or no effect on overall coronary blood flow in patients with coronary disease. Yet it does increase local myocardial flow in zones of potential ischaemia (Horwitz et al., 1970) (Fig. 8). This selective action is not well understood, but may represent recruitment and dilatation of resistance vessels or collaterals lying outside the local area of production of vasodilating metabolites.

How much flow can occur via collateral pathways is unknown. This depends in part on the type, size, route, and site of origin of the collateral. A collateral arising from the proximal part of an artery which runs epicardially to another epicardial artery will deliver more flow than a distally arising vessel which runs via an intramyocardial course to an adjacent artery. Regulation of all these vessels is believed to occur via local mechanisms.

The level of blood pressure becomes all important when there are obstructions in the large coronary arteries. The pressure drop across the stenosis can be as great as 50 to 70 mm. Hg (Fig. 7). Even a minor decrease in arterial pressure can so lower postobstructive pressure that flow reaches intoleraibly low levels. The resulting flow per mm. Hg pressure is a function of degree of small vessel (arteriole and collateral) dilatation in response to hypoxia. Again, it would appear that local regulation dominates in redistribution of blood supply in coronary artery disease. It is currently unknown whether systemic mechanisms of control play a significant part in the adjustment to this disease, except that there appears to be a mild chronic beta adrenergic stimulation (Wolfson and Gorlin, 1969).

FIG. 6 Coronary arterial indicator dilution curves in a normal subject (above) and a patient with coronary artery disease (CAD) (below). Indocyanine green was injected selectively into each of the right coronary arteries shown and the curve sampled from coronary sinus. The wide spread of the lower curve is indicative of the heterogeneous blood flow pattern in coronary artery disease. (Liedtke et al., 1970.)

FIG. 7 Arterial pressures recorded during direct coronary artery surgery. The panel to the left indicates pressures in radial artery (RA) and postobstructive right coronary artery (RCA). Note the mean pressure difference of about 50 mm. Hg. This was restored to normal after vein bypass surgery. (S. Smith, W. J. Taylor, and R. Gorlin, 1970, unpublished observations.)
Similar to the relationship between shals of ischaemia causing shells of subnormal con-tractility, regional zones of ischaemic myocardium exhibit disordered or absent contraction during systole. The result is that patients with coronary artery disease often develop cardiac failure based solely on asynogy of contraction (Herman et al., 1967). This is accentuated by any state which induces local ischaemia. This can be through increased local stimulation, such as tachycardia or adrenergic activity, or through reduction in perfusion pressure so that the local supply of blood cannot match the cellular demand for energy. The ease with which the local myocardium ceases to contract against the load shows how close to the threshold of hypoxia is the state of otherwise normal cardiac muscle. Anaerobic glycolysis can in no way supply energy in sufficient amount for the mammalian heart under normal operating conditions (Krasnow et al., 1962).

Thus it can be appreciated that ‘normal’ blood supply in coronary artery disease is in part relative to and dependent on the applied load. For example, cardiac load can be minimized or check-reined by the use of beta adrenergic blocking agents. These drugs are capable of inhibiting adrenergic increases in heart rate, blood pressure, and contractile state. Under these conditions coronary blood flow is reduced. Evidence of myocardial ischaemia, if formerly present, is eliminated, and myocardial flow may be autoregulated to achieve nearly normal values despite widespread disparities in the pathways of blood flow in the diseased myocardium.

References
tion.
Herman, M. V., Heinle, R. A., Klein, M. D., and Gorlin, R. (1967). Localized disorders in myocar-
dial contraction. New England Journal of Medicine, 277, 222.
Rubio, R., and Berne, R. M. (1966). Release of adeno-
yology, 263, 463.

FIG. 8 Intramyocardial 133Xe clearance curves before and after sublingual nitroglycerin (0.3 mg.). Studies were done during revascul-
arization surgery at a myocardial site distal to a known severe obstruction in the left anterior descending artery. Praecordial gamma scintillation counting revealed an increase in both fast and slow components of myocardial flow after nitroglycerin administration (CPM = counts per minute). (Horwitz et al., 1970.)