Mechanisms causing myocardial ischaemia

Charles W. Buffington MD

Myocardial ischaemia can result from many processes in patients with coronary artery disease. Alterations in haemodynamics in patients with fixed-resistance coronary stenoses can upset the balance between oxygen supply and demand. A maldistribution of coronary flow can occur when a potent coronary dilator is given to a patient with "steal-prone" coronary anatomy. Primary reductions in coronary flow can result from coronary spasm or when the vessel is partially or totally occluded by thrombus.

It is important to understand how these various mechanisms operate in order to prevent or treat the underlying cause of ischaemia. What clues provide information about the likelihood of each mechanism in a given patient? What treatments are most likely to be effective? Are some treatments counter-productive when applied to the wrong situation?

Haemodynamic ischaemia

Much effort has gone into understanding how changes in blood pressure, heart rate, filling pressure, contractility, or ventricular volume can produce ischaemia in patients with stable coronary artery disease. Experimental studies have manipulated these factors and determined how each variable affects the balance between oxygen supply and demand, and thus the likelihood of ischaemia. Unfortunately, no good animal model of atherosclerosis exists, and so experimenters have used a variety of devices to limit coronary flow and mimic the restriction caused by a coronary stenosis. Each device affects flow in a slightly different manner, and so the results of studies must be interpreted in light of the device used.[1]

Studies in animal models of coronary stenosis indicate that tachycardia, hypotension,[2–4] ventricular failure[5] and anaemia[6] all upset the balance between supply and demand.

Attempts to validate these results in humans with coronary artery disease have been moderately successful,[7,8] but human coronary stenoses have additional dynamic properties that complicate the interpretation of clinical studies (see below).

Coronary steal

Data from animal studies have shown that isoflurane causes direct coronary arteriolar dilatation[9] and can induce coronary "steal" in a model of chronic occlusion.[10] Data from studies in humans indicate direct dilatation,[11] but whether or not steal is of clinical importance to the outcome of anaesthesia is not yet clear.

It is important to understand the *anatomy* required for intra-coronary steal, since not all patients with coronary artery disease are at risk. "Steal-prone" anatomy includes three elements: (1) a complete occlusion of one or more coronary arteries, (2) collateral blood flow into the zone previously supplied by the occluded vessel, and (3) a haemodynamically significant stenosis of the artery supplying the collaterals.[12] This anatomical arrangement occurs in 19–23 per cent of patients with coronary artery disease.[13]

It is also important to understand the *mechanism* by which arteriolar dilatation causes steal. Agents such as dipyridamole, adenosine, nitroprusside, and isoflurane dilate intramyocardial coronary arterioles preferentially over large epicardial coronary arteries. Arteriolar dilatation in the zone supplied by the stenosed artery leads to an increase in flow through the stenosis and a greater pressure drop across the stenosis. If aortic pressure stays constant, then the pressure distal to the stenosis decreases and flow through the "pressure-dependent" collateral vessels may decrease as well. While a stenosis of the supplying artery is not absolutely necessary for steal to occur, the stenosis magnifies the effect.[14,15]

The question of whether or not steal occurs in humans during anaesthesia and whether or not harm results is not settled. A study by Reiz *et al.* provides indirect evidence that the use of isoflurane can be associated with electrocardiographic evidence of myocardial ischaemia in the absence of haemodynamic changes.[11] Since myocardial oxygen extraction was decreased by isoflurane, these authors concluded that direct arteriolar dilatation was present and that this effect might explain, *via* a steal mechanism, the observed non-haemodynamic ischaemia. Unfortunately, current methods of measuring the distribution of myocardial blood flow in man are relatively crude and do not permit a direct test of the hypothesis that isoflurane can cause a maldistribution of flow. Statistical

Department of Anesthesiology and Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA.

outcome studies of large numbers of anaesthetized patients have, so far, found no "excess risk" associated with the use of isoflurane.

Dynamic coronary stenosis

Recent observations have challenged the notion that patients with coronary artery disease have lead pipes instead of coronary arteries.[16] While it is true that calcium and cholesterol *can* form a concentric narrowing of the vessel, and that these lesions behave as a fixed-resistance hindrance to flow, a surprisingly high proportion of coronary stenoses have eccentric atheroma.[17] These atheroma bulge into the lumen of the vessel but leave an arc of relatively normal vessel wall across from the atheroma. This arrangement allows both active and passive changes in lumen size and hence in stenosis resistance.

Coronary vessels contain elastic fibres in the wall that elongate when stretched and shorten when tension is reduced. The circumferential tension applied to these fibres is determined by the distending pressure within the lumen. This pressure is determined by aortic pressure, the velocity of blood as it passes the stenosis, and the pressure downstream from the stenosis.[18] Increases in aortic pressure and *arteriolar* constriction increase the distending pressure, passively dilate the vessel and thus reduce stenosis severity.[19,20] Conversely, decreases in aortic pressure or *arteriolar* dilatation reduce the distending pressure, and stenosis resistance increases because of inward collapse.[21,22]

Coronary vessels also contain smooth muscle cells that respond to vasoactive drugs and substances.[23] Because of the geometry of the stenosis, even small changes in smooth muscle tone can have profound effects on stenosis resistance.[24] Large coronary vessels constrict in response to alpha-adrenergic, serotonergic and muscarinic cholinergic stimulation.[25] Dilatation of vessels occurs in response to prostaglandin El, nitroglycerine and nitroprusside. Calcium channel blocking drugs abolish the response to adrenergic stimulation.

Endothelial cells lining the vessels play an important role in the reponse to circulating vasoactive substances such as epinephrine and histamine and to substances such as serotonin, thromboxane A2 and ADP that are released by platelets when they degranulate.[26,27] A substance known as endothelium-derived relaxing factor (EDRF) and currently thought to be nitric oxide is released in response to these and other circulating biogenic amines. EDRF diffuses into vascular smooth muscle cells where it increases the concentration of cyclic GMP and causes relaxation. Of importance, many substances that produce vasodilatation *via* EDRF when the endothelium is intact, produce direct constriction when the endothelium is damaged or removed. Histological examination of coronary arteries at the site of stenoses frequently shows endothelial disruption. Loss of EDRF response at these sites may explain the apparent hyperreactivity of diseased sections of coronary vessels in response to constrictor agents.[28]

Coronary thrombosis

Coronary thrombosis is the major cause of myocardial infarction.[29–32] Evidence supporting this concept comes from acute intervention studies in which coronary occlusion by thrombus has been observed both directly during surgery or angiography, and from studies in which acute thrombolysis has been used to salvage myocardium at risk of necrosis. Partial occlusion of the vessel by thrombus is almost certainly the cause of the clinical syndrome of unstable angina.[33–35]

Interactions between the atheroma, the vessel and blood form the basis for coronary thrombus formation. Although it seems logical that thrombus should form in the most severe stenosis, this is not always the case, and occasionally thrombus forms in a vessel without significant stenosis. The initiating event for thrombus formation appears to be rupture of the atheromatous plaque. For reasons that are not well-understood, plaques develop fissures and may extrude a very thrombogenic mixture of cholesterol, lipid, and necrotic material into the lumen of the vessel. The mechanisms by which anaesthesia and surgery might influence this process remain speculative. Acute, short-term hypertension has been shown to damage endothelium[36] and enhance platelet aggregation. Tachycardia in the presence of a stenosis has also been shown to cause platelet aggregation on the endothelium downstream from the stenosis.[37] Surgery and anaesthesia are associated with a hyper-coagulable state that features diminished fibrinolysis and enhanced factor VII release.[38,39] Platelet aggregation *in vivo* is enhanced by epinephrine, and such an effect seems possible during surgery or the postoperative period.

Relevance to anaesthesia

Patients with coronary stenoses are at risk of myocardial ischaemia and infarction during anaesthesia. Uncontrolled haemodynamics can upset the balance between oxygen delivery and demand in the setting of a fixed-resistance coronary stenosis. Sympathetic activation that frequently accompanies intubation and surgery in an inadequately anaesthetized patient may dramatically reduce coronary flow by direct coronary constriction at the site of an eccentric stenosis. Hypotension may reduce the distending pressure for flexible stenoses and permit passive collapse; arteriolar dilatation may have the same

effect. Anaesthesia and surgery have complex effects on the tendency for a thrombus to form and dissolve.

A rational clinical approach is to base anaesthesia care on the *activity* of coronary artery disease as well as the severity. A careful history of anginal symptoms is useful: patients with stable, effort-related angina that has not changed in character or medication requirements and is not associated with congestive heart failure are best handled by avoiding tachycardia and hypotension, and by providing adequate anaesthesia and analgesia during the perioperative period. Those patients who are severely disabled due to stable angina are more likely to have ischaemia during the operation than those patients with only mininal symptoms.[40] Patients who give a history of a change in anginal pattern such that angina occurs more frequently or with less effort may have mural thrombus or spasm as a contributing factor and should be treated aggressively with nitrates and calcium channel-blocking drugs. The role of mini-dose aspirin in preventing myocardial infarction during anaesthesia needs to be evaluated in this population. Finally, the symptoms of unstable angina, especially chest pain at rest, are a warning of significant potential morbidity. Gottlieb and co-workers have shown a high incidence of progression to infarction or coronary artery bypass surgery in this population.[41] Elective surgery should be cancelled in patients with unstable angina. Urgent surgery should be undertaken with haemodynamic monitoring, intravenous nitroglycerin and lots of care.

References

1 *Föex P.* Experimental models of myocardial ischaemia. Br J Anaesth 1988; 61: 44–55.

2 *Buffington CW.* Hemodynamic determinants of ischemic myocardial dysfunction in the presence of coronary stenosis in dogs. Anesthesiology 1985; 63: 651–62.

3 *Szekeres L, Udvary E.* Haemodynamic factors influencing myocardial ischaemia in a canine model of coronary artery stenosis: the effects of nitroglycerine. Br J Pharmac 1983; 79: 337-45.

4 *Watanabe J, Maruyama Y, Ashikawa K et al.* The changes in ECG ST segment and mechanical function of regional ischemia myocardium during afterload reduction in isolated dog hearts with coronary stenosis. Jap Circul J 1986; 50:248–57.

5 *Satoh S, Maruyama Y, Ashikawa K et al.* Effects of preload alteration on the degree of ischemia and function of ischemic myocardium under constant mean aortic pressure, coronary perfusion pressure and heart rate in isolated perfused canine heart. Jap Circul J 1986; 50: 1100–12.

6 *Hagl S, Heimisch W, Meisner H, Erben R, Baum M, Mendler N.* The effect of hemodilution on regional myocardial function in the presence of coronary stenosis. Basic Res Cardiol 1977; 72: 344–64.

7 *Lieberman RW, Orkin FK, Jobes DR, Schwartz AJ.* Hemodynamic predictors of myocardial ischemia during halothane anesthesia for coronary-artery revascularization. Anesthesiology 1983; 59: 36–41.

8 *Loeb HS, Saudye A, Croke RP, Talano JV, Klodnysky ML, Gunnar RM.* Effects of pharmacologically-induced hypertension on myocardial ischemia and coronary hemodynamics in patients with fixed coronary obstruction. Circulation 1978, 57: 42–6.

9 *Gelman S, Fowler KC, Smith LR.* Regional blood flow during isoflurane and halothane anesthesia. Anesth Analg 1983; 63: 557–65.

10 *Buffington CW, Romson JL, Levine A, Duttlinger NC, Huang AH.* Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. Anesthesiology 1987; 66: 280–92.

11 *Reiz S, Balfors E, Sorensen MB, Airola S Jr, Friedman A, Truedsson H.* Isoflurane – a powerful coronary vasodilator in patients with coronary artery disease. Anesthesiology 1983; 59: 91–7.

12 *Becker LC.* Conditions for vasodilator-induced coronary steal in experimental myocardial ischemia. Circulation 1978; 57: 1103–10.

13 *Buffington CW, Davis KB.* The prevalence of steal-prone coronary anatomy in patients with coronary artery disease: an analysis of the CASS registry. Anesthesiology 1988; 69: 721–7.

14 *Patterson RE, Kirk ES.* Coronary steal mechanisms in dogs with one-vessel and other arteries normal. Circulation 1983; 67: 1009–15.

15 *Gross GJ, Warltier DC.* Coronary steal in four models of single or multiple vessel obstruction in dogs. Am J Cardiol 1981; 48: 84–92.

16 *Brown BG, Bolson EL, Dodge HT.* Dynamic mechanisms in human coronary stenosis. Circulation 1984; 70: 917–22.

17 *Freudenberg H, Lichtlen PR.* Das normale wandsegment bei koronarstenosen – Eine postmortale studie (The normal wall segment in coronary stenoses – a postmortal study). Z Kardiol 1981; 70: 863–9.

18 *Santamore WP, Kent RL, Carey RA, Bove AA.* Synergistic effects of pressure, distal resistance, and vasoconstriction on stenosis. Am J Physiol 1982; 243: H236–42.

19 *Schwartz JS, Carlyle PF, Cohn JN.* Effect of coronary arterial pressure on coronary stenosis resistance. Circulation 1980; 61: 70–6.

20 *Schwartz JS.* Effect of distal coronary pressure on rigid and compliant coronary stenoses. Am J Physiol 1983; 245: H1054–60.

21 *Schwartz JS, Carlyle PF, Cohn JN.* Effect of dilation of the distal coronary bed on flow and resistance in

severely stenotic coronary arteries in the dog. Am J Cardiol 1979; 43: 219–24.

22 *Walinsky P, Santamore WP, Wiener L, Brest AN.* Dynamic changes in the haemodynamic severity of coronary artery stenosis in a canine model. Cardiovasc Res 1979; 13: 113–8.

23 *Brown BG.* Response of normal and diseased epicardial coronary arteries to vasoactive drugs: quantitative arteriographic studies. Am J Cardiol 1985; 56: 23E–29E.

24 *MacAlpin RN.* Contribution of dynamic vascular wall thickening to luminal narrowing during coronary arterial constriction. Circulation 1980; 60: 296–300.

25 *Young MA, Vatner SF.* Regulation of large coronary arteries. Cir Res 1986; 59: 579–96.

26 *Shepherd JT, Vanhoutte PM.* Spasm of the coronary arteries: causes and consequences (the scientist's viewpoint). Mayo Clin Proc 1985; 60: 33–46.

27 *Bassenge E, Busse R.* Endothelial modulation of coronary tone. Prog Cardiovasc Dis 1988; 30: 349–80.

28 *Ginsburg R, Bristow MR, Davis K, Dibiase A, Billinham ME.* Quantitative pharmacologic responses of normal and atheroschlerotic isolated human epicardial coronary arteries. Circulation 1984; 69: 430–40.

29 *Fuster V, Badimon L, Cohen M, Ambrose JA, Badimon JJ, Chesbro J.* Insights into the pathogenesis of acute ischemic syndromes. Circulation 1988; 77: 1213–20.

30 *Gorlin R, Fuster V, Ambrose JA.* Anatomic-physiologic links between acute coronary syndromes. Circulation 1986; 74: 6–9.

31 *Forrester JS, Litvack F, Grundfest W, Hickey A.* A perspective of coronary disease seen through the arteries of living man. Circulation 1987; 75: 505–13.

32 *Mehta JL* (Ed.). Thrombosis and platelets in myocardial ischemia. Philadelphia: F.A. Davis, 1987.

33 *Bashour TT, Myler RK, Andreae GE et al.* Current concepts in unstable myocardial ischemia. Am Heart J 1988; 115: 850–61.

34 *Sherman CT, Litvack F, Grundfest W et al.* Coronary angioscopy in patients with unstable angina pectoris. N Engl J Med 1986; 315: 913–9.

35 *Willerson JT, Hillis LD, Winniford M, Buja M.* Speculation regarding mechanisms responsible for acute ischemic heart disease syndromes. J Am Coll Cardiol 1986, 8: 245–50.

36 *Lamping KG, Dole WP.* Acute hypertension selectively potentiates constrictor responses of large coronary arteries to serotonin by altering endothelial function in vivo. Circ Res 1987; 61: 904–13.

37 *Modig J, Borg T, Bagge L, Saldeen T.* Role of extradural and of general anaesthesia in fibrinolysis and coagulation after total hip replacement. Br J Anaesth 1983; 55: 625–9.

38 *Walinsky P, Lefer AM, Frasca P, Santamore W.* Potentiation of coronary vascular platelet adhesion by atrial pacing in the presence of arterial stenosis in dogs. JACC 1984; 3: 1252–5.

39 *Borg T, Modig J.* Potential anti-thrombotic effects of local anaesthetics due to their inhibition of platelet aggregation. Acta Anaesthesiol Scand 1985; 29: 739–42.

40 *Coriat P, Harari A, Daloz M, Viars P.* Clinical predictors of intraoperative myocardial ischemia in patients with coronary artery disease undergoing non-cardiac surgery. Acta Anaesth Scand 1982; 26: 287–90.

41 *Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G.* Silent ischemia as a marker for early unfavorable outcomes in patients with unstable angina. N Engl J Med 1986; 314: 1214–9.