Myocardial ischaemia

Dilemma between information available and information demand

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SUMMARY The information available on the factors responsible for perioperative myocardial ischaemia justifies certain guidelines to the anaesthetist for preventive therapy. Contrary to present practice, the effect of different perturbations on myocardial oxygen consumption (MVO_2) should be considered per beat rather than per unit time, because recovery for the energy expended during systole must occur during each diastole. During pacing-induced tachycardia MVO_2/beat decreases as heart rate increases, suggesting that faster heart rates produce angina pectoris by a reduction in the duration of recovery, not an increase in oxygen demand. The effects of a change in heart rate induced by exercise are less obvious in this respect, but analysis shows that the MVO_2/beat may increase because of the raised aortic systolic pressure, not heart rate.

Clinical angina pectoris is preceded by a rise in left ventricular end-diastolic pressure because the chronically ischaemic left ventricle relaxes abnormally when challenged by an acute volume load imposed by an increase in venomotor tone and the associated increase in right ventricular over left ventricular stroke volume. This sequence suggests that an increase in left ventricular intracavitary pressure contributes to the regional reduction in coronary blood flow. Perioperative therapy, intended to prevent myocardial ischaemia, must include control of heart rate and scrupulous attention to the myocardial perfusion gradient. Occasionally, this requires the use of alpha-agonist drugs and venodilators (for example, phenylephrine and glyceryl trinitrate).

The right ventricle is very often the source of perioperative haemodynamic deterioration caused by ischaemia resulting from end-diastolic dilatation. Treatment of right ventricular ischaemia requires an increase in systemic vascular resistance to ensure appropriate perfusion of the right coronary artery especially when this artery is obstructed. Vasodilator therapy, when used, is intended to maintain right ventricular end-diastolic volume small.

This shortened version of the St Cyres lecture that had been given by the late Professor Laver on 8 December 1981 was kindly prepared by Professor Peter Harris, of the Cardiothoracic Institute, London.

Every cardiologist will find it necessary at one time or another to prepare a patient with angina pectoris for an operation. If the procedure is intended to relieve myocardial ischaemia, then the preoperative preparation will identify the site of the coronary artery lesion, and the revascularisation, once completed, will minimise the chances of postoperative infarction.

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Professor Laver died on 31 August 1982.

When, in the presence of angina pectoris, the operation involves other areas of the body, then the patient will leave the operating room with the potential for infarction unchanged. In the first case, ischaemia will have been relieved; in the latter, infarction can be prevented only if ischaemia is recognised early and treated aggressively by pharmacological means.

Close invasive monitoring and scrupulous protection of the myocardium during coronary artery bypass are the key factors held responsible for its low morbidity. With other operations, the risk of postoperative infarction appears to be increased, a fact generally assumed to reflect the influence of augmented sympathetic activity on the heart affected by coronary artery disease. The consequences of this stimulus on

myocardial oxygen demand, the distribution of myocardial blood flow, and shift in blood volume have been the subject of extensive study in the animal experiment; how these data should best be applied to the intact individual appears to be a source of confusion.

Myocardial ischaemia results from an imbalance between the demand for oxygen distal to the arterial stenosis and the supply provided by the chronic adjustments to the disease. The sequence of perioperative events leading to an imbalance is less than obvious, and the lack of clarity explains why we have not achieved adequate prophylaxis when a patient is operated upon within a few months after a myocardial infarct.^{1,2}

Although experimentally-induced stenosis or occlusion of a coronary artery causes ischaemia, this model is not equivalent to human angina pectoris because the background against which blood flow is reduced is radically different. In animal experiments acute ischaemia is induced in the presence of an otherwise normal myocardium, while in man ischaemia is a recurrent problem in a heart where histological studies have shown that the structure of the myocardium is abnormal.^{3,4}

The purpose of the present discussion is to show that angina pectoris and perioperative ischaemia result from the effect of sympathetic stimuli on capacitance vessel tone and heart rate imposed on a ventricle(s) whose structure characteristics make it unable to relax normally when stressed. Two crucial points underlie proof for these arguments. First, that the balance between myocardial oxygen demand and delivery must be considered per cardiac event or per beat, not per unit time. Second, that pulmonary blood volume, or left ventricular preload, increases before the appearance of angina pectoris. These will be considered in turn.

We can begin our discussion by considering the three misconceptions responsible for the confusion surrounding the understanding of the causes for and the treatment of perioperative myocardial ischaemia. They are, first that angina pectoris occurring after an increase in heart rate is secondary to an increase in myocardial oxygen demand ($\dot{MVO}_2$) (at stake is the fundamental classification of heart rate on the demand side of the balance sheet)^{5,6}; secondly, that clinical angina pectoris is the cause rather than consequence of an increase in left ventricular end-diastolic pressure; and thirdly, that the left ventricle is exclusively responsible for angina pectoris.

I: Effect of changes in heart rate on $\dot{MVO}_2$

The ground rules for the relation between heart rate and myocardial oxygen consumption were established

by Rohde in 1912.⁷ He concluded from studies on the perfused isolated mammalian heart, that "... a relative close relationship exists between myocardial O_2 consumption and the product of heart rate times aortic pressure *as long as the initial heart volume remains constant.*" The last part of this statement appears to have been forgotten or lost in the translation and may explain why classification of a change in heart rate on the demand side qualifies as a major misconception.

Confusion associated with defining the contribution of heart rate to the appearance of ischaemia is related to the custom of expressing oxygen consumption per unit time rather than per contraction, a problem compounded further by the use of an index (that is the product of heart rate times the arterial systolic blood pressure or "double product").

Each contraction cycle must be regulated so that the energy required during systole must be restored during the subsequent diastole. If it is not, then the heart becomes ischaemic and the number of beats necessary to make it apparent depends on the energy level at which the heart performs.

Analysis of the numerous sources that have measured the changes in $\dot{MVO}_2$ associated with changes in heart rate caused by atrial pacing shows that in the intact animal or the isolated, supported mammalian heart, the myocardial oxygen consumption *per beat*, remains unchanged or decreases as the number of contractions per minute increases.⁸⁻¹⁰ The increase in $\dot{MVO}_2$ per minute seen with an increase in heart rate is generally attributed to an increase in "contractility," but the evidence for a direct relation between the change in value of the "contractility index" and the oxygen required per beat in the intact heart is tenuous at best. Boerth *et al.*¹¹ who analysed the effect of tachycardia on V_{max} and $\dot{MVO}_2$ showed that the added oxygen required per beat to account for the increase in V_{max} when wall tension is constant is of questionable significance.¹²

Weber and Janicki^{13,14} have studied the effect of changes in heart rate on wall force and $\dot{MVO}_2$. Again, at constant wall force, $\dot{MVO}_2$ per beat decreased as heart rate increased. The integral of total wall force also decreased with induced tachycardia despite the enhanced contractility calculated from the rate of change of force per unit time (dF/dt).¹⁵

An alternative correlation between mechanical activity and $\dot{MVO}_2$ has been proposed by Suga *et al.*¹⁶⁻¹⁹ According to these authors, oxygen consumption per beat correlated closely with the pressure-volume curve generated during contraction,¹⁶ a relation that appears to hold during isovolumic as well as ejecting contractions, and is allegedly independent of calculated peak systolic stress or wall force. Regardless of which measurement one chooses as valid, the critical contribution of ventricular volume cannot be

ignored, a crucial point missing in the tension-time index calculation of Sarnoff *et al.*²⁰

The available data on the effects of exercise on oxygen demand in normal non-trained individuals and athletes are in conflict. According to Gibbs and Chapman,²¹ who used data published by several sources, exercise was associated with a substantial rise in heart rate and $\dot{M}V\text{O}_2$ per minute. The calculated $\dot{M}V\text{O}_2$ per beat did not change, a phenomenon apparent in both untrained individuals and athletes. In contrast, the calculated heart rate times aortic systolic blood pressure product increased five or six times. In the study published by Nelson *et al.*,²² the highest $\dot{M}V\text{O}_2$ per minute and per beat occurred with a combination of dynamic and static effort. At equal heart rates, $\dot{M}V\text{O}_2$ per beat was significantly higher during combined as compared with static effort, and analysis of the data suggests that this difference may be attributable to the significantly higher systolic pressure (140 vs. 128 mmHg) elicited by a combination of dynamic and static effort. The authors' data, however, also show a discrepancy between $\dot{M}V\text{O}_2$ and the tension-time index, with tension-time index per beat unchanged at a time when the highest and lowest values of $\dot{M}V\text{O}_2$ per beat were recorded.

Keeping in mind that data obtained in animals with pacing-induced tachycardia in the presence of critical coronary stenosis show no change, or usually a decrease in $\dot{M}V\text{O}_2$ per beat; secondly that in the previously mentioned experiments performed by Boerth *et al.*¹¹ an increase in heart rate caused no significant rise of $\dot{M}V\text{O}_2$ per beat when wall stress was kept constant; and thirdly that a change in either filling left ventricular end-diastolic pressure or aortic pressure does change the energy requirement per contraction secondary to the change in baseline wall force, then one is justified in concluding that in the intact human, whether anaesthetised or not, an increase in heart rate causes ischaemia by limiting the time available for recovery from the consequences of contraction and not by increasing oxygen demand as usually stated.

The consequences for the patient in need of an operation are simple; drug treatment should be planned so that a critical abbreviation of diastole is prevented. The advantages of prophylactic beta blocker therapy are self evident. Whether the arterial hypertension which accompanies sympathetic stimulation is a contributing factor to the appearance of ischaemia over and above the simultaneous increase in filling pressure and reduction in duration of diastole is uncertain. In any event, the benefits accrued from beta blocker treatment appear to be the result primarily of a lengthening of diastolic recovery time, not a diminution in "contractility," a point also made by Boudoulas *et al.*²³

II: Angina pectoris and changes in end-diastolic pressure

The angina pectoris of left anterior descending or circumflex coronary artery disease is associated with an increase in left ventricular end-diastolic pressure. Whether the rise in filling pressure precedes or follows ischaemia is of more than academic interest because of the implications for peroperative drug treatment.

The timing between the onset of pacing-induced tachycardia, the increase in left ventricular end-diastolic pressure, and the appearance of angina pectoris is illustrated in Fig. 1 from data published by Parker *et al.*²⁴ Chest pain, produced by a progressive increase in heart rate, was not associated with a change in mean left ventricular end-diastolic pressure. At this time removal of an average of 400 ml whole blood, while pacing was continued, resulted in a distinct reduction in left ventricular end-diastolic pressure and disappearance of angina pectoris so that the higher heart rate was tolerated at a substantially lower intracavitary pressure. Reinfusion of the withdrawn blood caused left ventricular end-diastolic pressure to return to control values and led to reappearance of ischaemic pain.

An abnormal response to stress, caused by impaired myocardial relaxation, is a characteristic of coronary artery disease.^{25 26} This inability to cope with a physiological increase in pulmonary blood volume,

Fig. 1 The influence of left ventricular end-diastolic pressure on the presence of pacing-induced angina pectoris. Patients with known coronary artery disease were paced atrially until the appearance of angina pectoris. At this point an average of 400 ml whole blood was withdrawn while pacing was continued. Angina pectoris disappeared as left ventricular end-diastolic pressure decreased and reappeared upon reinfusion of the blood and return of left ventricular end-diastolic pressure to control values.

the focal point responsible for angina pectoris, appears to have been recognised in Brunton's paper on amyl nitrite²⁷ in which he stated that, for relief of pain, "small bleedings of three or four ounces, whether by cupping or venesection were, however, always beneficial".

In the initial phase of exercise, sympathetic stimuli cause heart rate to rise and modify both resistance and capacitance vessel tone in a manner equivalent to the infusion of an alpha agonist drug such as phenylephrine. Increased venomotor tone and a shift of blood volume to the right heart lead to an increase in pulmonary blood volume²⁸ because of an initial, albeit small, discrepancy between left ventricular and right ventricular stroke volumes. Cold- or pain-induced peripheral vasoconstriction have a similar effect. The discrepancy will be of brief duration if the left ventricle is normal; when left ventricular relaxation is impaired, then the stroke volume mismatch will be pronounced (if the right ventricle does not become ischaemic as well!) and the increase in pulmonary blood volume correspondingly greater. This challenge provided by (a) sympathetic stimulation, (b) a responsive right ventricle, and (c) an abnormal left ventricular relaxation causes left ventricular end-diastolic pressure to rise until the combination of an increase in heart rate and raised filling pressure with an associated diminution in subendocardial blood flow results in angina pectoris.

The quantity of blood redistributed from the periphery to the lung is dependent upon the position the patient is in when exercise is performed. When the patient is upright, more effort is needed to elicit ischaemic pain (and a lesser increase in heart rate) than in the supine position because gravity will minimise the blood volume displacement. Unfortunately, the anaesthetised patient is invariably supine and particularly likely to respond unfavourably when stimulated.

It is surprising that the role of blood volume redistribution and its contribution to the appearance of ischaemia has received little or no attention, particularly as the phenomenon was described 50 years ago by Hochrein and Matthes,²⁹ and its role for the production of pulmonary oedema was discussed in remarkable detail 104 years ago by Welch.³⁰ Its importance to the patient with coronary artery disease, when operated upon, must not be minimised.

That the conditions described actually apply is supported by studies using radionuclide techniques in patients with coronary artery disease.³¹⁻³³ They confirm the presence of redistribution described for normal subjects³⁴ and support the concept that during exercise an increase in left ventricular end-diastolic pressure precedes the appearance of ischaemia (Fig. 2). According to Nichols *et al.*,³² who

Fig. 2 Changes in left ventricular end-diastolic pressure left ventricular end-diastolic pressure were recorded during changes in heart rate associated with exercise in patients with coronary artery disease. Except for one patient, left ventricular end-diastolic pressure rose progressively before the appearance of chest pain.

measured pulmonary blood volume by coincidence counting positron-emission tomography after inhalation of ¹¹CO, patients with ischaemic heart disease showed a progressive increase in pulmonary blood volume followed by the appearance of angina pectoris. The symptoms disappeared when exercise stopped, and this coincided with a return of pulmonary blood volume to control values. Okada *et al.*³³ followed the changes in pulmonary blood volume with the gamma camera subsequent to the intravenous administration of technetium-99m and found that the exercise-induced increase was inversely proportional to the diminution in left ventricular ejection fraction. In other words, progressive deterioration of left ventricular function was associated with a correspondingly greater accumulation of blood in the lung. In all subjects, exercise was terminated by the appearance of angina pectoris, not the dyspnoea of pulmonary oedema.

Redistribution of preload is an important sequence responsible for angina pectoris in the unanaesthetised patient and for the appearance of ischaemia in the anaesthetised patient. In the anaesthetised patient, the autotransfusion promoted by raising the legs causes ischaemia by an increase in either right or left ventricular filling pressures and respective wall forces. Where the ischaemia comes from will depend on the site of the coronary artery stenosis. In the development of left ventricular ischaemia, an increase in left ventricular end-diastolic pressure arises secondary to an increased lung blood volume caused by a transiently augmented right ventricular contraction

superimposed on inappropriate relaxation of the malperfused ventricle. The higher intramyocardial pressure leads to a diminished perfusion gradient across the stenosis (aortic diastolic pressure being constant), and ischaemia appears once coronary blood flow is reduced to a critical value. In this way the principal effect of sympathetic stimulation is a primary decrease in blood flow, not an increase in regional myocardial oxygen demand.

How well the intramural coronary arteries can fill during diastole will also depend on the influence exercised by the anaesthetic on intrinsic coronary vascular tone and myocardial relaxation. This problem has not been the object of active investigation; recently published data³⁵ suggest, however, that halothane may enhance myocardial stiffness of the animal heart subjected to extracorporeal bypass. The degree of emptying during systole (that is the so-called "massaging" effect originally described by Wiggers³⁶) is also important. According to Verrier *et al.*³⁷ halothane shifts the canine coronary autoregulation pressure flow curve to the left of control and decreases the perfusion pressure at the zero flow intercept. This shift is opposite to that found with alpha receptor stimulation and suggests that the anaesthetic blocks alpha mediated vasoconstriction. Diminished diastolic vascular tone, less complete relaxation, and reduced forcefulness of contraction all affect the supply side of the oxygen balance equation, while the direct effect of the anaesthetic on the beta receptors could modify translation of sympathetic stimulation into energy demand. We do not know which mechanism dominates nor have we enough information to decide how useful the anaesthetic drugs can be vis-à-vis an ischaemia-inducing stimulus.

III: Right ventricular versus left ventricular ischaemia; where does the angina come from?

It has been generally assumed that angina pectoris arises from the body of the left ventricle. Though most often true, there is no reason to preclude its origin from the septum of the right ventricle. The right coronary artery is frequently involved in multiple vessel coronary artery disease. Isolated right coronary artery obstruction, angina pectoris, and a diminished right ventricular free wall thallium uptake during exercise represent a known combination. If the left ventricle shows good uptake of thallium with exercise and the electrocardiogram gives evidence for an inferior infarct, are we justified in assuming that the ischaemia resides in the left ventricle? Pulmonary hypertension and right ventricular hypertrophy when present may provide a substrate for ischaemia even in the absence of right coronary artery obstruction. It

would be a more rational explanation for the pain of pulmonary hypertension than acute distension of the pulmonary artery. The increase in intracavitary diameter associated with mitral regurgitation must lead to a substantial increase in right ventricular free wall stress and the likelihood of ischaemia when impedance to outflow is raised acutely. Pulmonary embolism is a dramatic example of this phenomenon; acute respiratory failure and the associated pulmonary hypertension run a similar course.³⁸ In both instances, the impediment of right ventricular function induced by ischaemia can be substantial whenever poor function caused by added resistance to outflow is treated with expansion of intravascular volume, particularly in the presence of right coronary artery stenosis. What remains unexplained is why right ventricular free wall infarction is rare despite the massive increase in wall force produced by acute obstruction of the pulmonary artery and subsequent intravascular volume replacement therapy.

The importance of identifying the site of ischaemia lies in the implications for appropriate treatment. Narrowing of the pulmonary artery in the dog is associated with an acute increase in right ventricular systolic pressure and eventual haemodynamic failure similar to the sequence found with massive pulmonary embolism.³⁹ When it happens, an increase in right coronary artery perfusion pressure will allow the right ventricle to recover because of improved right ventricular myocardial blood flow (Fig. 3). This is particularly applicable in man when an increase in pulmonary artery pressure appears in the presence of known coronary artery disease, especially an inferior infarct. In these patients, progressive haemodynamic deterioration with or without supraventricular tachyarrhythmias, secondary to right ventricular ischaemia, is likely if an adequate aortic diastolic pressure cannot be maintained. Therapy guided according to pulmonary capillary wedge pressure readings will reflect upon performance of the left ventricle but provide little else in the way of useful information. In such cases, vasodilators are likely to be effective leading, as they do, to a decrease in right ventricular rather than left ventricular afterload^{40 41} or, as with glyceryl trinitrate, to a reduction in right ventricular end-diastolic size. The need for a decrease in size of the ischaemic right ventricle faced with an acutely raised impedance to flow must not be confused with the conditions associated with right ventricular infarction, where a high filling pressure can restore adequate haemodynamic function but only if the pulmonary vasculature is normal. There is little if any evidence to suggest that volume loading is effective treatment for a massive pulmonary embolism even in the presence of a previously normal right ventricle.

The problem for the anaesthetist is compounded

Fig. 3 Right ventricular failure was produced in the experimental animal by progressive occlusion of the main pulmonary artery. This resulted in a low aortic pressure, a diminution of right ventricular systolic pressure, and an increase in right ventricular end-diastolic pressure (lower panel). Injection of phenylephrine (an alpha-agonist) into the aortic root caused aortic diastolic pressure to rise and improved coronary blood flow sufficiently to allow the right ventricle to generate a systolic pressure in excess of 100 mmHg.

because recognition of right ventricular ischaemia is always difficult. Since the electrocardiogram is not always helpful, a high level of suspicion is necessary; in rare cases, a gamma camera can be used at the bedside and the diagnosis facilitated with a gated 99m technetium scan; occasionally the pulmonary artery catheter will show the presence of pulsus alternans (Fig. 4). Peroperative concern with left ventricular function alone in the critically ill has little except tradition to support its pursuit. The two ventricles act both in series and in parallel; it is unlikely that significant prevention of peroperative ischaemia will be possible unless function of each is evaluated and treatment guided according to the specific problem.

IV: Peroperative prevention and treatment of myocardial ischaemia

Guidelines for treatment presuppose diagnosis of the malady; unfortunately, except for the precordial elec-

Fig. 4 Pronounced pulmonary artery pulsus alternans was evident in this patient (a 64 year old man with mitral stenosis) during operation, but before extracorporeal bypass, for mitral valve replacement. A 3 mm ST segment depression was also present in limb lead II. These changes suggest the presence of right ventricular ischaemia.

trocardiogram, the techniques available for consistent detection of intraoperative myocardial ischaemia are limited in number. The sleeping patient cannot complain of angina pectoris.

The monitoring available in the operating room is still at a level we might have considered adequate several decades ago. Even cardiac surgery, despite the possibilities for measuring pressure, flow, and the precordial electrocardiogram lacks the level of sophistication we can consider state-of-the-art for detection of myocardial ischaemia. The need here remains great.

Irrespective of anaesthetic technique or drug, intraoperative and postoperative changes in resistance and capacitance vessel tone can be expected. Glyceryl trinitrate, because of its predominant effect on venomotor tone at low infusion rates, is effective for control of preload while aortic diastolic pressure can be maintained with an alpha agonist drug (for example phenylephrine or methoxamine). This combination

was proposed originally by Epstein and colleagues^{34 42 43}; it does not enjoy the popularity it deserves. Phenylephrine as a bolus or a constant infusion causes arteriolar and venoconstriction, and the haemodynamic result is an autotransfusion superimposed on an increase in systemic vascular resistance. Combination therapy for acute ischaemia is intended to maintain an optimal gradient for myocardial perfusion with the alpha agonist effective in treating aortic-diastolic pressure while trinitroglycerin deadens the alpha agonist action on the venous side.⁴⁴

Most experiments in animals and studies in patients intended to examine the myocardial effects of phenylephrine-induced hypertension have ignored this dual effect of phenylephrine and attributed the resultant rise in left ventricular pressure to the increased afterload.⁴⁵⁻⁴⁸ Such conclusions can be misleading especially when applied to the ischaemic myocardium.

Independent manipulation of preload and afterload, which is possible in the isolated muscle preparation, is not feasible in the intact heart. A low peak systolic wall force can, however, be achieved despite a high aortic pressure if the end-systolic volume is small. This can be accomplished by maintaining aortic pressure with phenylephrine if adequate quantities of glyceryl trinitrate are given as well. No treatment of perioperative myocardial ischaemia is likely to be successful unless these goals are kept in mind. Drugs that alter inotropy while increasing heart rate are less likely to be useful because tachycardia can lead to ischaemia.⁴⁹

Effectiveness of prophylactic treatment is not likely to be demonstrable unless the influence of variables that initiate ischaemia can be documented by measurement. That coronary artery bypass surgery can be performed with a low mortality and infarction rate should persuade those involved in this procedure to evaluate closely the results of treatment. The same cannot be said for the patient with angina pectoris undergoing other types of operation where the anaesthetic management may fall into the hands of those less well informed about the details of the disease. It is here that complications in the need for postoperative intensive care can develop. Data on the frequency of perioperative myocardial ischaemia, its prevention, its treatment, and its contribution to postoperative haemodynamic problems are lacking. Relief of this condition requires tools for detection of altered myocardial perfusion which go beyond those now available in the operating room.

Treatment for established perioperative myocardial ischaemia requires little over and above the measures known to be effective in the treatment of chronic angina pectoris. We have failed, however, in our ability to detect perioperative ischaemia early to prevent

subsequent infarction. The information needed exceeds the information available.

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