MYOCARDIAL ISCHAEMIA ASSOCIATED WITH GENERAL ANAESTHESIA

A Review of Clinical Studies

S. REIZ

The incidence of perioperative myocardial ischaemia in patients with coronary artery disease, as reported in the literature, varies widely (tables I, II). Much of the confusion surrounding this issue can probably be related to differences in patient populations studied, study programmes and techniques used to establish ischaemia (table III). Until recently, efforts to avoid myocardial ischaemia concentrated primarily upon decreasing myocardial oxygen demand by controlling hypertension and tachycardia. It was accepted widely that a reduction of arterial pressure was safe in patients with coronary artery disease (CAD), provided the contractility of the heart, and hence oxygen consumption, were depressed proportionally by the anaesthetic agent [18]. More recently, it has been recognized that myocardial oxygenation may, under some circumstances, be impaired, despite apparently normal systemic haemodynamics. When the first reports of non-haemodynamically related myocardial ischaemia, associated with inhalation anaesthesia in man, appeared in 1983 [52], it was not surprising that these data stimulated many investigators [4,36–39] and created the impetus for intense research in the field.

In the years that followed, researchers focused their interest on three main areas:

(1) Clinical and laboratory studies on the coronary haemodynamic effects of anaesthetic agents and techniques and their relation to myocardial ischaemia.
(2) Development of more sensitive techniques for detecting ischaemia in the operating room.
(3) Epidemiological studies aimed at defining the intraoperative risk factors predicting perioperative myocardial injury.

This review deals mainly with the first of these areas, with special emphasis being placed on the role of ischaemia without associated haemodynamic abnormalities, for example myocardial oxygen deprivation related to vasomotion.

EFFECTS OF ANAESTHETIC AGENTS UPON THE CORONARY CIRCULATION AND MYOCARDIAL OXYGENATION IN PATIENTS WITH CORONARY ARTERY DISEASE

Short-Acting I.V. Induction Agents and Sedatives

Barbiturates

Although the effects that sedatives and induction agents have on systemic haemodynamics in patients with coronary artery disease are well documented, only a few studies exist of their action upon the coronary circulation and myocardial oxygenation. In unpremedicated vascular surgical patients studied by Reiz and co-workers [49], thiopentone 6 mg kg⁻¹ caused substantial declines in systemic arterial pressure (−27%) and systemic vascular resistance, with only a modest (10%) increase in heart rate. Coronary blood flow decreased in parallel with perfusion pressure. Myocardial oxygen consumption decreased (−39%) and myocardial oxygen balance was maintained, as judged from the ECG and lactate balance studies. These data contrast with findings by Sonntag and colleagues [62] in healthy subjects given thiopentone 5 mg kg⁻¹. They observed tachycardia, but little effect on arterial pressure or cardiac output. Myocardial blood flow increased to meet the increased demand for oxygen associated with the tachycardia. There are a number of possible reasons for the contrasting results when compared with those obtained in patients with coronary artery disease. Depressed baroreceptor function [6], beta-blockade and impaired left ventricular function with high endogenous sympathetic activity [14] are some of

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TABLE I. Incidence of pre-bypass myocardial ischaemia in coronary artery surgery

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
<th>Pre-induction</th>
<th>Total</th>
<th>Mode of detection</th>
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<tbody>
<tr>
<td>Wilkinson et al. (1981) [70]</td>
<td>26</td>
<td>27</td>
<td>62</td>
<td>2-lead ECG, lactate</td>
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<tr>
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<tr>
<td>Slogoff and Keats (1985) [60]</td>
<td>1023</td>
<td>18</td>
<td>37</td>
<td>2-lead ECG</td>
</tr>
<tr>
<td>Slogoff and Keats (1986) [61]</td>
<td>495</td>
<td>26</td>
<td>55</td>
<td>2-lead ECG</td>
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TABLE II. Incidence of myocardial ischaemia in vascular and other non-cardiac surgery

<table>
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<tr>
<th>Source</th>
<th>n</th>
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<th>Total</th>
<th>Mode of detection</th>
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</thead>
<tbody>
<tr>
<td>Roy, Edelist and Gilbert (1979) [55]</td>
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<td>NA</td>
<td>38</td>
<td>Multi-lead ECG</td>
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<tr>
<td>Coriat et al. (1982) [9]</td>
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<td>39</td>
<td>V5 ECG</td>
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<tr>
<td>Hägmark et al. (1987) [17]</td>
<td>61</td>
<td>13</td>
<td>74</td>
<td>12-lead ECG, CKG, lactate</td>
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</tbody>
</table>

TABLE III. Incidence of intra-operative myocardial ischaemia in vascular surgery in relation to mode of detection. Data from Hägmark and colleagues [17]

<table>
<thead>
<tr>
<th>Mode of detection</th>
<th>Incidence of ischaemia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiokymography (wall function)</td>
<td>53</td>
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<tr>
<td>12-lead ECG</td>
<td>34</td>
</tr>
<tr>
<td>Lactate balance</td>
<td>20</td>
</tr>
<tr>
<td>Increased PCWP and abnormal wave form</td>
<td>23</td>
</tr>
<tr>
<td>All modalities</td>
<td>74</td>
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the more obvious causes. These factors, alone or in combination, may explain why patients with cardiac disease have greater decreases in systemic arterial pressure and minimal reflex tachycardia.

Preliminary results from patients with CAD studied by the group headed by Reiz provide further information on the effects of thiopentone on myocardial oxygenation and blood flow distribution. Three groups of patients, all with stable CAD, were studied: group I had normal left ventricular (LV) function (ejection fraction (EF) > 0.50) and no hypertension; group II had hypertension and normal LV function; group III had depressed LV function (EF < 0.40), but no hypertension. Patients were premedicated with morphine 200 µg kg⁻¹ and anaesthesia was induced with fentanyl 3 µg kg⁻¹ followed by a dose of thiopentone 2–4 mg kg⁻¹, adjusted to keep mean arterial pressure within 70% of the awake value. Neuromuscular blockade for intubation was provided with suxamethonium 1.5 mg kg⁻¹. Patients were studied up to 10 min after tracheal intubation, at which time all the circulatory effects of laryngoscopy and intubation had passed. By this time, neuromuscular blockade had been achieved using pancuronium bromide and patients' lungs were ventilated with 30% oxygen–70% nitrous oxide to maintain normocapnia. Systemic and regional coronary haemodynamics were measured before induction, immediately before laryngoscopy and 2 and 10 min after intubation. Myocardial ischaemia was assessed from myocardial lactate balance studies at the same intervals.

Before induction, hypertensive patients had higher mean arterial pressures and patients with decreased LV function higher pulmonary capillary wedge pressures (fig. 1). Following induction, all three groups demonstrated a comparable decline in systemic arterial pressure. However, the responses in heart rate and filling pressure were different: while patients in groups I and III demonstrated an increase in heart rate, which was most pronounced in group III, no change was seen in group II, probably because 88% were receiving chronic medication with beta-blockers. Filling pressure increased in group I, remained unchanged in group II and decreased progressively in patients with depressed LV function (group III), probably because of unloading of the left ventricle by a decreased impedance to left ventricular ejection. With induction of anaesthesia, the proportion of total coronary blood flow directed to the left ventricle remained constant in group I and II, but decreased initially in group III. Left ventricular ischaemia, made evident by lactate production, was observed at this time in
approximately 33% of the patients in group III, compared with 7% and 6% in groups I and II, respectively. These observations emphasize the importance of preventing even a moderate increase in heart rate (+15%) and decline of coronary perfusion pressure (−17%) in patients with high coronary back pressures.

**Ketamine**

Ketamine 2 mg kg$^{-1}$ administered as the induction agent in patients with generalized atherosclerotic disease caused a transient increase in circulating plasma catecholamine concentrations, manifested by increases in systemic arterial pressure, heart rate, pulmonary capillary wedge pressure and systemic vascular resistance [3]. Both coronary blood flow and myocardial oxygen consumption increased by approximately 50%, and myocardial oxygenation was adequate as judged by myocardial lactate metabolism and ECG.

**Propofol**

Stephan and colleagues [65] studied the systemic and coronary haemodynamic effects of propofol, administered as a bolus (2 mg kg$^{-1}$) followed by a continuous infusion (200 μg kg$^{-1}$ min$^{-1}$) for induction of anaesthesia for coronary artery bypass grafting (CABG) in individuals with normal LV function. Before sternotomy, fentanyl 10 μg kg$^{-1}$ was administered and patients’ lungs were ventilated with 70% nitrous oxide in oxygen. Induction of anaesthesia produced a variable, and sometimes pronounced, decline in coronary perfusion pressure, previously described by other investigators in similar patients [47]. Cardiac output decreased by a moderate extent and there was a slight increase in heart rate. Myocardial blood flow decreased in proportion to myocardial oxygen consumption. Myocardial ischaemia, as indicated by lactate production, developed in one of 12 patients, probably as a result of hypotension. Sternotomy was followed by normalization of all systemic haemodynamic variables with the exception of cardiac output. Myocardial lactate production associated with coronary vasospasm was observed in another patient.

**Benzodiazepines**

A large number of studies report minor systemic haemodynamic effects of various benzodiazepines used for induction or maintenance of anaesthesia in patients with cardiac disease [2, 25, 31, 34, 54, 58]. Studies of the action of these drugs upon the coronary circulation and myocardial
oxygenation in such patients are, however, restricted to the cardiac catheterization laboratory. Diazepam produces minor changes in coronary blood flow. A slight coronary vasodilating action has been proposed [1, 10]. In patients with CAD, flunitrazepam 15 μg kg\(^{-1}\) produced decreases in coronary perfusion pressure and left ventricular end-diastolic pressure and increases in heart rate and left ventricular \(V_{\text{max}}\). Despite a reduction in myocardial oxygen consumption, coronary blood flow remained unchanged and myocardial oxygen extraction declined [45]. These findings demonstrate that flunitrazepam has a coronary vasodilating action unrelated to changes in myocardial oxygen demand. However, none of the patients studied had ECG or metabolic evidence of ischaemia.

More recently, the same group of investigators [35] published data obtained under comparable conditions during cardiac catheterization in similar patients administered midazolam 0.2 μg kg\(^{-1}\) i.v. Five to 15 min after this drug, coronary blood flow had decreased in proportion to the decline in myocardial oxygen consumption. The investigators observed a slight increase in coronary venous oxygen saturation, indicating some coronary vasodilatation. As in their previous study on flunitrazepam, no ischaemia was observed following the administration of midazolam.

In summary, short-acting drugs used for induction of anaesthesia or sedation have little or no direct effect on coronary vascular tone. Myocardial oxygenation is adequate, provided coronary perfusion pressure is controlled and tachycardia can be avoided. Ischaemia related to stress-induced coronary vasomotion is probably not prevented by these drugs (for further data, see below).

Inhalation Agents

**Halothane**

In one of few randomized studies, Wilkinson and colleagues [70] investigated the effects of 0.2–1% end-tidal halothane or morphine 2 mg kg\(^{-1}\) i.v. plus 50% nitrous oxide in oxygen in patients undergoing CABG. Before surgical intervention, both techniques resulted in an approximately 20% reduction in myocardial oxygen consumption. Coronary perfusion pressure was preserved better with morphine than during halothane anaesthesia. Halothane, but not morphine anaesthesia, was associated with a reduction in myocardial oxygen extraction, suggesting coronary vasodilatation. One patient in the halothane group had myocardial lactate production before induction of anaesthesia, whereas lactate production was observed in three patients after intubation. Three morphine patients had myocardial lactate production before anaesthesia, which changed to lactate uptake after intubation. These coronary haemodynamic effects of halothane are in agreement with work in healthy individuals receiving halothane–air–oxygen [64], in vascular surgical patients with a history of congestive heart failure and who received halothane–air–oxygen [50] and in patients with CAD and normal LV function who were given halothane–oxygen with and without nitrous oxide [44]. All four studies demonstrate increased coronary venous saturation during administration of halothane. One additional study performed in patients with stable CAD has documented similar changes in coronary perfusion pressure and myocardial oxygen consumption, without evidence of coronary vasodilatation during halothane anaesthesia [22].

Halothane produces a similar degree of coronary vasodilatation in the experimental animal [12, 66, 67]. Other animal studies have demonstrated that myocardial ischaemia associated with halothane anaesthesia appears to be a hydraulic phenomenon produced by decreased perfusion pressure rather than impairment of coronary autoregulation [7, 13].

In summary, the possible mild coronary vasodilating action of halothane observed in humans appears to have little, if any, importance in the development of inadequate myocardial oxygenation, compared with the effects of altered systemic circulation.

**Enflurane**

Studies in the intact dog have demonstrated that enflurane dilates coronary vessels and that its vasodilating potency is greater than that of halothane [66, 67] (fig. 2). Heikkinä and co-workers [20] administered enflurane to patients during CABG. Induction of anaesthesia was accomplished with lorazepam–fentanyl–pancuronium and enflurane was delivered in 40% oxygen in air. Enflurane did not decrease coronary blood flow as much as was expected from the decline in myocardial oxygen consumption. Hence, myocardial oxygen extraction was reduced. Similar observations were made in comparable patients by Moffitt and colleagues [41] and in vascular
Fig. 2. Diastolic pressure–coronary flow relations in the awake and anaesthetized dog. Enflurane and isoflurane are more powerful coronary vasodilators than halothane, although none impairs coronary autoregulation comparably to adenosine. (Reproduced from Sybert and colleagues [66].)

surgical patients with CAD by Rydvall and associates [56]. These investigators also studied the regional coronary haemodynamic effects of enflurane by the use of the multiple thermistor, retrograde thermodilution coronary flow technique [48], allowing great cardiac venous blood flow (GCVF), which represents most of left ventricular blood flow, and total coronary sinus blood flow (CSF) to be assessed separately. The authors found a decline in the GCVF: CSF ratio from a mean of 0.70 to 0.54 following administration of 1 MAC enflurane. The results demonstrate a normal adjustment of the distribution of coronary blood flow to the decrease in regional myocardial oxygen consumption and thereby contradict the presence of any major regional maldistribution of coronary flow during enflurane anaesthesia.

Isoflurane

Animal experimentation has demonstrated that isoflurane, in common with adenosine and dipyridamole, dilates epicardial resistance vessels [59]. It is a weaker coronary vasodilator than adenosine (fig. 2) and dipyridamole, but has a considerably stronger coronary vasodilating action than halothane or enflurane [66,67]. A similar relationship appears to exist in patients with CAD.

Reiz and colleagues [52] studied unpremedicated vascular surgical patients administered 1 MAC isoflurane in oxygen-enriched air (30:70). The anaesthetic was associated with a 35% reduction in coronary perfusion pressure, unchanged pulmonary capillary wedge pressure and a small increase in heart rate (+5 beat min⁻¹).

Coronary blood flow remained unaltered, despite a 36% reduction in myocardial oxygen consumption. Myocardial oxygen extraction decreased from a mean of 68% to 48%. Similar systemic and coronary haemodynamic effects of isoflurane were observed in patients anaesthetized for CABG by Moffitt and colleagues [40]. Eleven of the 21 patients studied by Reiz had ECG or metabolic evidence of myocardial ischaemia. In 10 of the 21 patients, five of whom had evidence of ischaemia, coronary perfusion pressure was adjusted back to awake values by the use of i.v. infusions of phenylephrine and nitroglycerin. Heart rate was controlled to awake values using pacing electrodes incorporated in the coronary sinus catheter. Despite normalization of systemic haemodynamics, myocardial oxygen extraction remained profoundly decreased, providing evidence of persistent coronary vasodilatation. Ischaemia disappeared in two patients, but remained until isoflurane was discontinued in the remaining three. The authors suggested that maldistribution of coronary blood flow ("coronary steal"), produced by the coronary vasodilating effect of isoflurane, might be the mechanism for ischaemia in these three individuals. It was suggested also that isoflurane might decrease coronary vasodilating reserve and therefore arterial pressure, filling pressure and heart rate should be more rigorously controlled in patients with CAD who were anaesthetized with isoflurane. The study by Moffitt and associates [40] reported myocardial lactate production in three of 11 patients during an isoflurane-oxygen anaesthetic for CABG, deep enough to reduce systolic arterial pressure by 30%. Previously, the same group of investigators, using the same end-points in similar patients, observed no instance of myocardial lactate production during either halothane-oxygen or enflurane-oxygen anaesthesia.

Coronary arteriolar dilators have the potential for causing myocardial ischaemia by a steal syndrome or, in the case of a severe single vessel narrowing, by endo-to-epicardial flow maldistribution. The anatomical basis for coronary steal was proposed by Becker [5]. A territory behind a complete occlusion, perfused via collaterals from a stenosed artery may be subject to hypoperfusion if a small coronary vessel dilator is administered (fig. 3). This occurs because collaterals are less responsive to vasodilator stimuli than normal coronary vessels [57]. An area distal to a critical stenosis in which the vasculature is
maximally dilated and the autoregulatory reserve is exhausted may also be deprived of adequate blood flow when normal coronary vessels are dilated pharmacologically. Under these conditions, a small vessel coronary dilator may decrease flow through the collaterals or across the constriction, and flow may actually reverse from the area previously maximally dilated to the areas supplied by those vessels which are responsive to the vasodilator [69]. Intramyocardial blood flow maldistribution was demonstrated during exercise by Gallagher and colleagues [15] in dogs with chronic severe stenosis of a single coronary artery. Myocardial function and flow distribution were normal at rest but, during exercise, total flow to the stenotic segment remained unaltered instead of demonstrating the normal doubling. While flow to the subepicardium doubled normally, flow to the mid-myocardium remained unchanged and subendocardial blood flow approached zero. It has been proposed that an intervention which produces negative inotropy prevents maldistribution of myocardial blood flow in the presence of dilatation of both large and small coronary arteries [16]. This suggestion has to be considered when the possible role of isoflurane-associated myocardial ischaemia is discussed.

Larsen and colleagues [28] compared the systemic and coronary haemodynamic effects of enflurane and isoflurane administered in 50% nitrous oxide in oxygen for CABG in patients with normal LV function. Before sternotomy, the anaesthetic agents produced minimal and comparable systemic haemodynamic changes. Enflurane decreased myocardial blood flow more than isoflurane, and coronary sinus oxygen saturation was increased to the same degree. With sternotomy, important differences became apparent. In enflurane patients, myocardial blood flow increased and coronary sinus oxygen content decreased to meet the increased myocardial oxygen demand. In isoflurane patients, myocardial blood flow increased to the same degree as in enflurane patients, whereas coronary sinus oxygen saturation remained markedly increased, demonstrating persistent coronary vasodilatation and uncoupling of the normal autoregulatory response to increased demand for oxygen (fig. 4). None of the enflurane group exhibited evidence of myocardial ischaemia during the study period. Among isoflurane patients, one produced lactate before sternotomy and three thereafter.

Reiz and Östman [53] measured regional coronary blood flow during isoflurane–nitrous oxide anaesthesia for vascular surgery in patients with CAD. In approximately 50% of the patients, they found that isoflurane increased the GCVF:CSF ratio, despite markedly decreasing left ventricular oxygen consumption. A majority of these patients also had electrocardiographic or metabolic evidence of myocardial ischaemia. Khambatta and co-workers [26] compared the regional coronary haemodynamic effects of halothane and isoflurane in patients anaesthetized for CABG. They also measured the GCVF:CSF ratio, and found indications of coronary blood flow maldistribution in patients anaesthetized with isoflurane, but not with halothane. Four of 10 isoflurane patients, compared with none of the halothane patients, demonstrated metabolic evidence of ischaemia at comparable coronary perfusion pressures.

In a randomized trial, Hohner and colleagues [24] compared the effects of fentanyl 10 μg kg⁻¹, halothane and isoflurane in 60% nitrous oxide in oxygen, after induction of anaesthesia using fentanyl 3 μg kg⁻¹–thiopentone 2–4 mg kg⁻¹, on
Fig. 4. Effects of anaesthesia and sternotomy on haemodynamics, myocardial blood flow (MBF) and lactate uptake and coronary venous oxygen saturation ($Scv_O_2$) in patients with coronary artery disease during inhalation of enflurane (—) or isoflurane (—–) with 50% nitrous oxide ($n = 10$ in each group). Note the difference in coronary venous oxygen saturation during surgery, suggesting persistent coronary vasodilatation in isoflurane-anaesthetized patients. (Plotted from data by Larsen and colleagues [28], with permission.)

Fig. 5. Effects of halothane(○), isoflurane(△) and fentanyl(□)-nitrous oxide-oxygen anaesthesia on mean arterial pressure (MAP), heart rate (HR), pulmonary capillary wedge pressure (PCWP) and stroke volume index (SVI) before (C) and during anaesthesia for major vascular surgical procedures. A = Steady state anaesthesia; 10 and 30 = 10 and 30 min after abdominal incision. Vasopressors and vasodilators were used to control systemic haemodynamics. With the exception of PCWP, which was significantly higher in the inhalation groups during surgery, haemodynamics in the three groups were indistinguishable. *$P < 0.05$. (Replotted from data by Hohner and colleagues [24].)
systemic and regional coronary haemodynamics and myocardial oxygenation. Pancuronium bromide was used for neuromuscular blockade. Halothane and isoflurane were administered according to a double-blind procedure. Systemic haemodynamics were maintained by adjustment of anaesthetic dose, pharmacological intervention, or both, to avoid hypotension, hypertension, tachycardia and failure. With the inclusion of the pharmacological intervention agents (phenylephrine and nitroglycerin), the effects of the three anaesthetics as regards to mean arterial pressure, heart rate and stroke volume were indistinguishable. Filling pressure during surgery was significantly less in fentanyl patients (fig. 5). Fentanyl did not affect coronary vascular tone, whereas halothane produced slight, and isoflurane more powerful and progressive, coronary vasodilatation despite comparable changes in myocardial oxygen consumption in the three groups (figs 6, 7). Myocardial ischaemia was assessed by a 12-lead ECG, cardiokymography, recording anterior left ventricular wall motion and myocardial lactate balance studies. Patients were ischaemic significantly more frequently in the inhalation groups (table IV). The total number of ischaemic episodes was greater in isoflurane-anaesthetized patients than in the halothane or fentanyl patients. This difference could partly be attributed to the increased coronary back pressure (e.g. pulmonary capillary wedge pressure) in the inhalation groups, and partly to significantly more ischaemic episodes without associated haemodynamic abnormalities in the isoflurane group (table IV). Six of the 14 isoflurane patients demonstrated one ischaemic episode each, which was not associated with tachycardia, hypertension, hypotension or failure. In a majority of these observations, and in contrast to patients anaesthetized with fentanyl or halothane, regional coronary blood flow measurements demonstrated uncoupling between coronary flow distribution and oxygen consumption in the corresponding territory (fig. 8).

All six clinical studies reported above support the concept of an isoflurane-associated redistribution of coronary blood flow as a cause of ischaemia. Three other studies in patients with CAD obtained data which have been interpreted to be in conflict with this suggestion. Hess and co-workers [21] used isoflurane to treat two patients with ischaemia which developed during sternotomy as a result of insufficient fentanyl–flunim-
BRITISH JOURNAL OF ANAESTHESIA

TABLE IV. Incidence of myocardial ischaemia in relation to haemodynamic abnormalities in patients anaesthetized with fentanyl-, halothane- or isoflurane–nitrous oxide for major vascular surgical procedures. Data from Hohner and colleagues [24]. *P < 0.05 compared with isoflurane if coronary vasospasm is excluded; **P < 0.02 compared with halothane and isoflurane; ***P < 0.01 compared with isoflurane

<table>
<thead>
<tr>
<th></th>
<th>Fentanyl (n = 10)</th>
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<th>Isoflurane (n = 14)</th>
</tr>
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<tbody>
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<td>2**</td>
<td>9</td>
<td>10</td>
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<tr>
<td>No. of ischaemic events</td>
<td>4****</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>With haemodynamic abnormalities</td>
<td>4</td>
<td>10</td>
<td>13</td>
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<tr>
<td>Without haemodynamic abnormalities</td>
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<td>Coronary vasospasm</td>
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</tr>
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<td>No. of ischaemic patients without haemodynamic abnormalities</td>
<td>0*</td>
<td>2*</td>
<td>6</td>
</tr>
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</table>

Fig. 8. Relation between oxygen consumption (\(\dot{V}m_{O_2}\)) in the LAD territory, drained by the great cardiac vein (GCV) (right panel) and the relative distribution of total coronary blood flow (CSF) to this area (GCVF:CSF) (left panel) in six isoflurane-anaesthetized patients with evidence of myocardial ischaemia without associated haemodynamic abnormalities. Decreased (patients Nos 3, 5, 6) or slightly increased (patient No. 1) oxygen consumption in four of the patients was not accompanied by proportional changes in blood flow distribution, indicating uncoupling of the association between flow and oxygen consumption and, probably, maldistribution of coronary blood flow. (Replotted from data by Hohner and colleagues [24].)

trazepam anaesthesia. Since coronary vasodilatation was probably maximal in the ischaemic area, the reduction in myocardial oxygen demand induced by isoflurane under these conditions must clearly have outweighed any adverse coronary redistributive effect of the anaesthetic agent. The data, however, do not permit any conclusions as regards the action of isoflurane upon coronary autoregulation.

O’Young and co-workers [46] investigated the regional coronary haemodynamic effects of isoflurane used to treat hypertension produced by sternotomy under high-dose sufentanil anaesthesia. Significant reductions of heart rate (−5%), mean arterial pressure (−25%), pulmonary capillary wedge pressure (−30%), systemic vascular resistance (−15%) and total and left ventricular oxygen consumption (−10% and −25%, respectively) were observed. The blood flow through the territories in which oxygen consumption was measured, however, was not significantly altered. Although the authors interpreted their data to indicate that autoregulation was not affected adversely by isoflurane, their results clearly demonstrate that the agent produced substantial coronary vasodilatation unrelated to changes in myocardial oxygen demand.

Tarnow and associates [68] investigated the effects of atrial pacing on the ECG V5 ST-segment before and during isoflurane–nitrous oxide anaesthesia in patients with CAD and normal LV function. When patients were paced during anaesthesia to the same heart rate that produced angina and significant ST-depression while awake, they had significantly less ST-
Fig. 9. Changes in rate-pressure product vs. ST-segments with coronary artery disease awake (○) and anaesthetized with isoflurane-nitrous oxide (●). Anginal threshold was determined by atrial pacing while awake. The heart was then paced to the same heart rate during anaesthesia, at which time arterial pressure and filling pressures were lower than awake. Of 13 patients, three had unchanged ST-segments and one had more severe depression, despite decreased and unchanged oxygen demand respectively (broken lines). (Replotted from data by Tarnow and colleagues [68].)

depression. Furthermore, mean arterial pressure, pulmonary capillary wedge pressure and rate-pressure product (RPP) were lower than awake values. Although RPP has been demonstrated to be a poor indicator of myocardial oxygen consumption during anaesthesia [43], it is likely that myocardial oxygen consumption was reduced. This may explain the lesser ST-segment depression, provided that the degree of ST-depression was proportional to the metabolic severity of ischaemia. When individual data were analysed, isoflurane improved the tolerance to pacing-induced ischaemia in nine of 13 patients. However, three patients had unaltered ST-segment depression, despite pronounced reductions in RPP and one patient demonstrated further ST-depression with unaltered RPP (fig. 9). In these four patients with signs of impaired oxygen supply:demand ratio, we cannot exclude isoflurane-induced redistribution of myocardial blood flow as a factor contributing to worsening ischaemia.

Recent data collected by Hohner and colleagues [23] in vascular surgical patients with CAD suggest that isoflurane-associated coronary vasodilatation is dose-dependent. Coronary perfusion pressure and heart rate were controlled at near-awake values by pharmacological interventions for each dose range. When isoflurane was administered in concentrations less than 0.75%, coronary vasodilatation was not observed. With increasing doses in the ranges 0.75–1.25% and 1.5–2.0%, there was a proportional decline in myocardial oxygen extraction, consistent with increasing coronary vasodilatation (fig. 10). It remains to be clarified if the incidence of isoflurane-associated myocardial ischaemia is also dose-related. The observations may explain why investigators who have used low doses of isoflurane as an adjunct to high-dose opioid anaesthesia in patients with CAD have been unable to document an increased incidence of ischaemia [46].

Evidence confirming the role of redistribution of coronary blood flow during isoflurane anaesthesia has been obtained more recently in animal models. Buffington and associates [8], in chronically instrumented dogs with the appropriate anatomical basis for a steal syndrome, demonstrated that 1% isoflurane shifted myocardial blood flow from collateralized to normal myocardium. The maldistribution affected primarily the subendocardial zone and was associated with impaired wall function in the territory perfused by the collaterals. In comparison, halothane did not produce either redistribution of blood flow or impairment of wall function, despite a comparable effect on contractility.

Thus there is overwhelming experimental and clinical evidence that isoflurane, in common with other dilators of coronary resistance vessels, may cause ischaemia by maldistribution of myocardial blood flow, despite decreasing inotropy. Small coronary vessel dilators also reduce the tolerance to haemodynamic aberrations. It therefore appears prudent to maintain systemic haemodynamic values close to normal in patients with CAD if isoflurane is used in doses producing coronary vasodilatation. Nevertheless, it is likely that isoflurane at such doses could cause ischaemia by redistributing myocardial blood flow in patients with the appropriate anatomical basis for "coronary steal". Most probably, coronary vaso-
FIG. 10. Relation between changes in myocardial oxygen consumption (\(\Delta V_{\text{mo}_2}\)) and flow (\(\Delta \text{GCVF}\)) in the corresponding territory with increasing isoflurane doses during anaesthesia for major vascular surgery. Regression lines: (1) 0.25–0.5% Isoflurane: \(y = 0.90x + 2.8, r = 0.957, n = 30\). (2) 0.75–1.25% Isoflurane: \(y = 1.03x + 19.1, r = 0.962, n = 33\). (3) 1.5–2.0% Isoflurane: \(y = 0.92x + 35.8, r = 0.925, n = 24\). The left-ward shift of the regression lines demonstrates greater coronary vasodilatation with higher doses of the anaesthetic agent. Isoflurane in concentrations less than 0.75% does not produce coronary vasodilatation, since the regression line for the low concentration range (1) is not significantly different from the line of identity. (Data from Hohner and colleagues [23].)

Opioids Used in Anaesthesia

Since high-dose opioid anaesthesia has become increasingly popular for heart surgery, many data on coronary haemodynamics and myocardial oxygenation with this technique have become available during recent years. Sonntag and co-workers studied patients with normal LV function during high-dose fentanyl anaesthesia for CABG [63]. After 10 \(\mu\)g kg\(^{-1}\), minimal systemic haemodynamic changes were observed. After another 90 \(\mu\)g kg\(^{-1}\), systemic haemodynamics were only marginally affected. Nevertheless, five of nine patients demonstrated myocardial lactate production. With sternotomy, mean heart rate increased by 22 beat min\(^{-1}\) and myocardial oxygen consumption by approximately 40%. There was evidence of coronary vasodilatation and eight of the nine patients had metabolic evidence of myocardial ischaemia. In similar patients anaesthetized with a comparable total dose of fentanyl (75 \(\mu\)g kg\(^{-1}\) at induction and 25 \(\mu\)g kg\(^{-1}\) before sternotomy), Heikkilä and associates [20] found evidence of

Nitrous oxide

Nitrous oxide constricts epicardial coronary arteries without affecting the resistance vessels in the intact dog [71]. In vascular surgical patients anaesthetized with enflurane, part exchange of enflurane for 70% nitrous oxide, keeping MAC constant, resulted in further haemodynamic depression and distribution of regional coronary blood flow to awake patterns, despite a further decline in myocardial oxygen consumption [56]. Haemodynamic depression and increased myocardial oxygen extraction were noted also when 50% nitrous oxide was added to enflurane or halothane anaesthesia for CABG [42, 44]. All these clinical data suggest that nitrous oxide may produce some coronary vasoconstriction. It remains to be clarified if this may modify the risk for myocardial ischaemia associated with coronary vasodilatation.

dilatating doses of isoflurane should therefore be avoided in patients with CAD.
ischaemia after sternotomy in only one of 12 patients. In contrast to the patients investigated by Sonntag’s group, surgery induced coronary vasoconstriction, as demonstrated by increased myocardial oxygen extraction and coronary vascular resistance. In another study by the same group of investigators [19], administration of droperidol before sternotomy inhibited the surgically induced coronary vasoconstriction without affecting the incidence of myocardial ischaemia. Part of the conflicting results in the studies by Sonntag and Heikkilä can probably be attributed to differences in the design of the studies. At the time of surgery, plasma concentrations of fentanyl were probably considerably higher in Heikkilä’s patients, resulting in better systemic haemodynamic stability, and hence lower incidence of ischaemia.

Data from vascular surgical patients with CAD who received lower doses of fentanyl (10–15 μg kg⁻¹) with nitrous oxide after thiopentone induction [24, 51] have demonstrated that coronary autoregulation is well maintained. Surgical stimulation may produce coronary vasoconstriction and associated ischaemia. The incidence of myocardial ischaemia is comparable to that reported during high-dose fentanyl anaesthesia for CABG by Heikkilä and colleagues [19, 20].

### OTHER FACTORS

#### Effects of interventions during anaesthesia

Laryngoscopy, endotracheal intubation and major surgical stimulation appear to have profound coronary flow limiting effects, thereby threatening myocardial oxygen delivery.

The group headed by Maseri has been at the forefront in establishing coronary vasospasm as an important mechanism of ischaemia in stable angina pectoris. Unlike classical variant angina, which presents with ST-segment elevation, coronary spasm may be associated also with pseudo-normalization or depression of the ST-segments. Deanfield and associates [11] documented ST-depressions and temporally related impairment of coronary perfusion by scintigraphy after mental arithmetic in the absence of haemodynamic changes in patients with CAD. Frequently, these ischaemic episodes were not accompanied by angina pectoris.

#### Ischaemia before and during induction

The incidence of non-haemodynamically related new ischaemic ECG changes upon arrival in the operating room is reported to be of the order of 25% in patients scheduled for CABG (table I) [60, 61, 70]. Most commonly, the ischaemia was

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**Fig. 11.** Haemodynamics and coronary sinus blood flow (CSF) before, during and after laryngoscopy and intubation in 30 patients who became ischaemic (●—●) and 20 matched, non-ischaemic patients (O—O). Note the similarity of haemodynamic changes, but the transient decline in coronary sinus blood flow in patients who developed ischaemia. The data suggest that coronary vasospasm is involved. I = Awake; II = 5 s before laryngoscopy; III = laryngoscopy; IV = intubation ended; V = maximum haemodynamic changes. ***P < 0.001 compared with non-ischaemic patients from II to III. (Data from Lowenstein and Reiz [33], reproduced with permission.)
silent, that is, not associated with chest pain. During anaesthesia, the incidence of ischaemia reported in these patients was of the order of 20–40%. At least 50% of the ischaemic episodes were unrelated temporally to haemodynamic abnormalities, suggesting that disturbed vaso-motion might have limited or maldistributed oxygen delivery.

Kleinman and associates [27] studied patients during tracheal intubation before CABG. Anaesthesia was induced with either halothane or high-dose fentanyl. Thallium scintigraphy revealed new myocardial perfusion defects in approximately 45% of patients in either group. These signs of relative, regional hypoperfusion were not associated with haemodynamic abnormalities and were accompanied only occasionally by ECG evidence of ischaemia. They suggest that tracheal intubation may elicit coronary vasospasm.

Similar results have been documented in vascular surgical patients with CAD, with the trachea intubated after induction with fentanyl–thiopentone, followed by either enflurane– or isoflurane–oxygen anaesthesia [33]. Thirty patients who developed electrocardiographic evidence of myocardial ischaemia following intubation were compared with 20 matched patients without ECG documented ischaemia at this time. Both groups had similar changes in systemic arterial pressure, heart rate and pulmonary capillary wedge pressure. Strikingly, patients with ischaemia had a transient decline in coronary blood flow immediately following laryngoscopy (fig. 11). The reduction in coronary blood flow preceded the changes in systemic haemodynamics (fig. 12). All these data suggest that coronary vasospasm might initiate myocardial ischaemia during laryngoscopy and tracheal intubation. The rapid decline of coronary blood flow, preceding the systemic haemodynamic changes suggests a neurogenic, rather than a humoral, mechanism of action.

Surgical stimulation

Several studies report coronary haemodynamic changes during surgical stimulation. The same lack of agreement between studies noted previously exists. The study by Wilkinson [70], comparing morphine– with halothane–nitrous oxide anaesthesia, found significant haemodynamic changes following sternotomy in both groups. Myocardial oxygenation was inadequate, as judged by lactate production or abnormalities...
in the ECG, in four of 12 morphine patients and in nine of 14 patients given halothane. Hilfiker and colleagues [22] investigated similar patients using halothane–nitrous oxide anaesthesia, but did not record any systemic or coronary haemodynamic changes following sternotomy, nor was ischaemia diagnosed in any patient.

The coronary haemodynamic effects of abdominal incision were also different between vascular surgical patients receiving halothane–, isoflurane– or fentanyl–nitrous oxide in oxygen anaesthesia in a randomized, partly double-blind study [24]. Pharmacological interventions were performed to counteract hypotension, hypertension and tachycardia. At 10 and 30 min after the incision, mean arterial pressure, heart rate and stroke volume index were comparable in the three groups. Pulmonary capillary wedge pressure was significantly higher in patients administered inhalation agents when compared with those receiving fentanyl (fig. 5). In fentanyl and halothane patients, coronary blood flow followed changes in myocardial oxygen consumption and myocardial oxygen extraction approached control values. In patients administered isoflurane, left ventricular oxygen extraction remained profoundly depressed during surgery, despite increasing demand for oxygen (figs 6,7). These findings agree closely with those reported by Larsen and co-workers [29,30], who studied the effects of enflurane–compared with isoflurane–nitrous oxide in oxygen anaesthesia in patients during myocardial revascularization (fig. 4). In patients anaesthetized with isoflurane, myocardial blood flow and coronary sinus oxygen saturation decreased to meet the increased demand for oxygen induced by sternotomy. Patients anaesthetized with isoflurane demonstrated increased myocardial blood flow, whereas coronary venous oxygen saturation remained markedly increased with sternotomy. In the study of Hohner and colleagues [24], patients receiving fentanyl or halothane had a GCVF:CSF ratio which varied predictably with alterations in left ventricular oxygen consumption. In contrast, patients anaesthetized with isoflurane did not exhibit a change in this flow ratio, indicating uncoupling between coronary blood flow and myocardial oxygen consumption (table V).

In summary, vasoactive drugs administered as adjuncts to anaesthesia appear to interfere little with the action of general anaesthetic agents upon the coronary circulation. In contrast, laryngoscopy, tracheal intubation and the stress of surgery may elicit profoundly flow-limiting reactions in patients with CAD. During isoflurane anaesthesia, signs of coronary vasodilatation persist during surgery, despite clear evidence of myocardial oxygen deprivation. This indicates that hyper- and hypoperfusion may coexist during isoflurane anaesthesia.

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