Review Article

Anaesthesia for coronary artery surgery - a plea for a goal-directed approach

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The purpose of the current literature review was to examine whether changes in current anaesthetic techniques are warranted for patients undergoing coronary artery surgery in light of recent information presented in the literature. The objectives of a cardiac anaesthetic technique are to maintain haemodynamic stability and myocardial oxygen balance, minimize the incidence and severity of ischaemic episodes, be aware of cardiopulmonary bypass-induced pharmacokinetic changes, and facilitate early tracheal extubation if appropriate. Many techniques have been utilized. Provided attention is paid to the details of managing myocardial oxygen supply and demand, none has emerged as superior in preventing intraoperative myocardial ischaemia. Silent myocardial ischaemia (i.e., ischaemia occurring in the absence of haemodynamic aberrations) is common throughout the perioperative period and may occur even in the presence of an appropriately used anaesthetic technique. The incidence and severity appear to be greatest in the postoperative period when the effects of anaesthesia are dissipating. The use of high-dose opioid anaesthesia may no longer be the most appropriate technique to facilitate the anaesthetic objectives. The role of pain management in altering the incidence of ischaemia requires further study. Increased waiting lists for cardiac surgery and ever-diminishing resources should prompt a re-evaluation of early extubation (i.e., within eight hours) as a method of improving utilization of scarce ICU resources. It is suggested that this should be possible with currently available agents to achieve the anaesthetic objectives. Future suggestions for research in this area are made.

Le but de cette revue de la littérature courante est de vérifier si, en chirurgie des artères coronaires, les modifications apportées aux techniques anesthésiques usuelles se justifient à la lumière des informations récentes de la littérature. Les objectifs de l'anesthésie cardiaque consistent à maintenir la stabilité hémodynamique et l'équilibre de l'oxygène myocardique, à abaisser l'incidence et la gravité des épisodes ischémiques, à reconnaître l'évolution pharmacocynétique pendant la chirurgie sous CEC et à effectuer l'extubation précocement lorsque nécessaire. On a utilisé plusieurs techniques anesthésiques. En autant qu'on prend bien soin de toutes les facettes de la gestion de l'apport et de la demande du myocarde en oxygène, aucune technique spécifique n'est considérée comme supérieure pour la prévention de l'ischémie myocardique peropératoire. L'ischémie coronarienne silencieuse (i.e., celle qui survient sans aberrations hémodynamiques) est fréquente pendant toute la période périopératoire et peut survenir même avec une technique anesthésique appropriée. Son incidence et sa gravité paraissent plus importantes à la période postopératoire lorsque les effets de l'anesthésie se dissipent. L'utilisation de doses élevées d'opiacés ne semble plus la technique la plus appropriée pour obtenir les meilleurs résultats. L'influence du traitement de la douleur sur l'incidence ischémique nécessite des études supplémentaires. L'augmentation des listes d'attente pour la chirurgie associée à une réduction des ressources nécessite une réévaluation de l'extubation précoce (en de-ça de huit heures) pour mieux utiliser les ressources trop peu abondantes des soins intensifs. On suggère que ceci soit possible avec les agents actuellement disponibles. Des suggestions sont proposées pour la recherche dans ce but.

Key words
ANAESTHESIA: cardiovascular.

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Contents

With ever-increasing demands for the provision of anaesthetic techniques which provide the maximum benefit to the patient at the least cost, increasing waiting lists for surgery, and a sicker operative population, re-examination of the current practice of anaesthesia for coronary artery surgery (CABG) is warranted.[1-3] In addition to the traditional requirements to maintain intraoperative myocardial oxygen balance, other factors must now be considered, especially in the postoperative period. These include early tracheal extubation, silent myocardial ischaemia, and new approaches to pain management. This review will examine the anaesthetic requirements for CABG surgery. The concept of tailoring intraoperative anaesthetic management to meet specific new objectives defined for the postoperative period, e.g., pain management, extubation, etc., will be introduced.

The ideal cardiac anaesthetic agent

The ideal single angent is not available. Consequently, combinations of agents are used to achieve the objectives (Table I).

Current practice

It is important to establish whether any anaesthetic technique for use during CABG surgery is superior to all others and should, therefore, be used exclusively. If such data exist, then experiments with different agents to produce desired effects in the postoperative period are misguided, since the primary focus must be to provide adequate anaesthesia for the procedure.

Studies carried out in the 1970's and early 1980's focused on control of factors determining myocardial oxygen balance (Table II).[4] Control of myocardial oxygen balance was difficult to achieve using a single agent. Volatile anaesthetic agents provided intraoperative haemodynamic control but were associated with the rapid development of unacceptable haemodynamic conditions, i.e., hypertension and tachycardia in the early postoperative period.[5,6] Opioids were associated with unpredictable episodes of hypertension and tachycardia,[7-10] and some patients had recall of perioperative stimuli.[11] Questions related to the potential of isoflurane to cause myocardial ischaemia by promoting coronary "steal"[5,12] and nitrous oxide by perhaps promoting coronary artery constriction were raised and debated.[13-16] In one review it was suggested that to meet the intraoperative objective of maintaining myocardial oxygen balance the ideal cardiac anaesthetic technique would consist of a combination of an opioid with a volatile anaesthetic agent.[4] This technique has proved to be extremely popular. However, its employment usually involves the use of high doses of potent opioids which lead to prolonged mechanical ventilation after surgery. Traditional reasons for admitting patients to intensive care units such as bleeding, haemodynamic instability, and underlying pathophysiology, have been abrogated due to the requirement for mechanical ventilation in *all* patients, as a result of the type of anaesthetic they received.

Provided the anaesthetist is cognizant of the principles involved in anaesthetizing patients for CABG surgery[17] and intervenes to interrupt adverse haemodynamic changes, it is my opinion that any anaesthetic agent can be used safely.[18-21] Factors such as severity of the patient's primary disease, primary errors in operative technique, operative judgement, and inadequate myocardial preservation are far more important determinants of outcome than the anaesthetic.[20] When compared with the properties of the ideal cardiac anaesthetic agent (Table I), the deficiencies of certain of the commonly employed agents become evident. For example, while fentanyl is cheap and commonly utilized as the primary anaesthetic adjuvant, the pharmacokinetic behaviour of fentanyl is considerably altered after cardiopulmonary bypass[22] with a prolongation of the elimination half-time. Depending on the dose and duration of administration, the time required for a decline in plasma concentrations to a point where resumption of spontaneous ventilation is likely may be substantially longer than for other high potency opioids (e.g., sufentanil, alfentanil).[23,24]

For the volatile agents the lack of residual analgesia, when combined with rapid emergence, may exacerbate postoperative hypertension and tachycardia with the potential for myocardial ischaemia and anastamotic suture disruption.[5,6]

Changes in clearance following cardiopulmonary bypass for agents such as diazepam and lorazepam, which

TABLE I Features of an ideal anaesthetic agent for coronary artery surgery

1 Unaltered haemodynamics
2 Lack of myocardial depression
3 Ease of administration
4 Lack of toxicity
5 Elimination independent of lungs, liver, and kidney
6 Rapid onset and offset of activity
7 Lack of coronary artery vasoconstriction
8 Residual analgesia
9 Titratable effect from hypnosis to anaesthesia

NB The suggested features are those which the author considers important and largely reflect personal experience.

TABLE II Factors affecting myocardial oxygen balance

Decreased oxygen supply	*Increased oxygen demand*
1 Decreased coronary blood flow	1 Tachycardia
(a) Tachycardia	2 Increased wall tension
(b) Diastolic hypotension	(a) Increased preload
(c) Increased preload	(b) Increased afterload
(d) Hypocapnia	3 Increased contractility
(e) Coronary spasm	
2 Decreased oxygen delivery	
(a) Anaemia	
(b) Hypoxia	
(c) Decreased 2,3 diphsophoglycerate	

have long elimination half-times,[25] may produce prolonged residual effects in the postoperative period. Diazepam has active metabolites[25] and both lorazepam and diazepam depend on hepatic metabolism for their elimination. Liver blood flow is altered following cardiopulmonary bypass.[26]

The introduction of shorter-acting agents such as alfentanil, midazolam, etomidate, and propofol has prompted an evaluation of their role in the provision of anaesthesia for cardiac surgery.

In the presence of adequate premedication, alfentanil provided suitable anaesthetic conditions in some but not all patients,[9,27] and was not associated with earlier extubation.[27] Alfentanil kinetics are altered following CABG surgery[22] and alfentanil may no longer be a short-acting agent when given as an infusion during CABG surgery.[23,24]

Midazolam was not associated with an increased incidence of myocardial ischaemia in patients undergoing cardiac catheterization[28] or coronary artery revascularization,[29] but its haemodynamic effects, when combined with opioids, have been variable and include hypotension, and decreased cardiac index due to a reduction in stroke volume.[29-31] In part, these alterations may reflect the dosing sequence and technique employed.[31] Attempts to define a concentration-effect relationship for midazolam and fentanyl during CABG surgery have been reported in a preliminary fashion.[32]

Etomidate, while providing excellent haemodynamic intraoperative control, is associated with inhibition of adrenal steroidogenesis, and increased mortality in patients sedated with etomidate in the intensive care unit.[33-35] This agent is not available for use in Canada.

Propofol is the latest agent to be introduced. Its use in cardiac anaesthesia was delayed due to concerns that it may produce myocardial depression.[36,37] Changes in blood pressure after propofol administration are due to vasodilatation and mild myocardial depression.[38-40] Lack of heart rate change has been noted and has been attributed to resetting of baroreceptors, allowing a lower level of arterial pressure for a given heart rate.[41,42] Propofol also affects the autonomic nervous system - probably by a central sympatholytic action.[43]

Administration of propofol (as compared to a sufentanil-enflurane anaesthetic technique) during induction and maintenance of anaesthesia in patients with preserved ventricular function undergoing CABG surgery produced hypotension on induction of anaesthesia but was not otherwise associated with important haemodynamic aberrations (−33% vs −18%).[44] The incidence of myocardial ischaemia in the prebypass period was not different from sufentanil-enflurane. There was no increased requirement for inotropic support to terminate cardiopulmonary bypass in the propofol-treated patients. These data are in keeping with other reports of the use of propofol during induction and/or maintenance of cardiac anaesthesia in patients with preserved ventricular function.[45-50] Propofol has also been used with satisfactory results in patients with reduced ejection fraction.[51] Thus, despite the initial misgivings, propofol may find a place in the cardiac anaesthetist's armamentarium.

For each anaesthetic technique there is a learning curve which, once mastered, leads to fewer anaesthetic misadventures. Due to the invasive nature of the procedure and the extensive monitoring employed, cardiac surgical patients are often studied early in the development of a drug when the technique has not been well established. This may be a factor in some of the adverse reports cited in early studies describing the use of a drug for cardiac surgery. Examples of this phenomenon exist for sufentanil,[52] midazolam,[30] propofol,[44,53] and perhaps desflurane.[54]

Taken together, these studies support my bias that, provided the anaesthetist controls myocardial oxygen balance, understands the principles involved in anaesthetizing patients for CABG surgery, and intervenes early when adverse events occur, there is no ideal anaesthetic technique for CABG surgery. Certainly, the use of high doses of opioids as the primary anaesthetic technique could

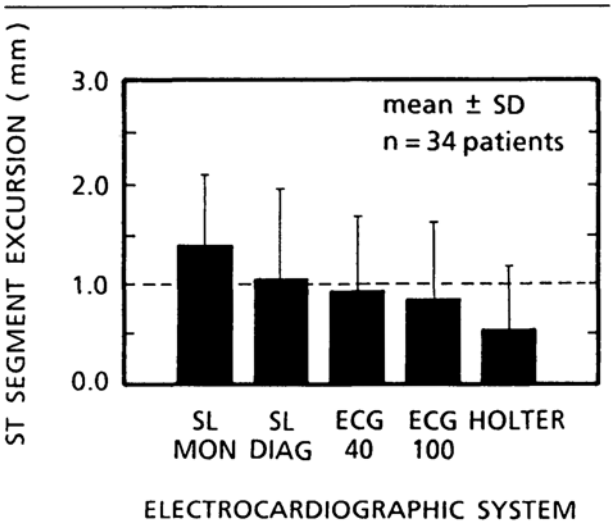

FIGURE 1 Mean ST segment excursion on each ECG system for 34 patients with new intraoperative myocardial ischaemia diagnosed by at least 1.0-mm ST segment displacement from preoperative ECG on at least one of the five ECG systems. Duration of displacement was ignored in calculating means. SLMON = Spacelab® Alpha 14 Model Series 3200 ECG Cardule in monitor mode; SLDIAG = Spacelabs® Alpha 14 Model Series 3200 ECG Cardule in Diagnostic Mode; ECG 40 = Marquette® MAC II ECG in the 9.05–40 Hz mode; ECG 100 = Marquette® MAC II ECG in the standard mode (0.05–100 Hz); Holter = DelMar® Model 453–A Holter monitor. (Reproduced with permission.[59])

be usefully and safely abandoned to permit certain objectives, e.g., early tracheal extubation, alternative pain management techniques, to be studied in the postoperative period.

Factors affecting the choice of anaesthesia

Anaesthesia and perioperative myocardial ischaemia

The supposed advantages of a particular anaesthetic technique are often based on the incidence of myocardial ischaemia.

DETECTION

Methods of detection include measurement of pulmonary artery occlusion pressure,[55] central venous pressure,[56] ST segment changes on the ECG (either single lead or multilead with or without trending),[57–60] biochemical markers such as lactate extraction,[44,51,61–64] continuous ECG recordings using Holter monitors for off-line analysis,[65,66] and regional wall motion abnormalities using transoesophageal echocardiography.[67–70] The sensitivity of these methods varies and must be kept in mind when comparing the reported incidence of ischaemia.[59,69,71–76] For example, Slogoff *et al.* in CABG patients, compared ECG lead V_5 recorded from a standard 12-lead ECG system at 40 or 100 Hz frequency response, a Spacelabs operating room ECG monitor in monitor mode, and a Del Mar Holter monitor.[59] The Holter was the least sensitive method of detecting ischaemia (Figure 1). This is important because several studies have employed this monitor as the basis for determining the incidence of myocardial ischaemia. Monitoring multiple leads increases the sensitivity of detection to 96% in non-cariac surgical patients.[60] Use of ST segment trends increases the ability to detect ischaemia beyond that provided by intermittent observation alone.[66] However, not all ST segment changes are due to ischaemia (Table III).

TABLE III Factors associated with changes in the ECT ST segment[66]

Ischaemia
Myocardial infarction
Left ventricular hypertrophy
Conduction disturbances
Electrolyte disturbances
Pharmacological agents
Body position changes
Postprandial changes
Filtering techniques of the recorder

Studies are needed to examine objectively the relative sensitivity and specificity of each of these monitors in detecting myocardial ischaemia. Studies reporting differences in the frequency of ischaemia among anaesthetic techniques must provide exact descriptions of the methods for detecting ischaemia to allow meaningful interpretations.

No matter how detected, however, the demonstration that myocardial ischaemia is present may have important prognostic implications.[65,67,77–81]

PERIOPERATIVE ISCHAEMIA

Factors associated with perioperative myocardial ischaemia and amenable to correction by the anaesthetist include maintenance of anti-ischaemic therapy in the preoperative period,[82–85] control of intraoperative haemodynamic abnormalities (primarily hypertension, hypotension and tachycardia)[79,86] and the provision of pain relief in the postoperative period.[87,88] However, studies have also determined that there is a high incidence of "silent" myocardial ischaemia during CABG surgery.[79,89] In awake patients this has usually been defined as ST segment deviation, detected using Holter monitoring, to a degree usually associated with myocardial ischaemia, occurring during activities of daily living, but not accompanied by chest pain.[81] Under these conditions, silent myocardial ischaemia is associated with an increased incidence of adverse outcomes including mortality.[81,90,91] By inference, in the anaesthetic context, silent myocardial ischaemia is said to be present when monitors of ischaemia (e.g., ECG, intraoperative transoesophageal echocardiogram, myocardial lactate extraction) indicate ischae-

mia to be present in the absence of haemodynamic aberrations, e.g., tachycardia, hypotension, hypertension.[65,67,72,79,80,83,89] The appearance of "silent" myocardial ischaemia, the value of its treatment and relationship to adverse outcome, e.g., MI for patients having CABG surgery is becoming less uncertain. It is apparent that a proportion of patients with intraoperative ischaemia go on to sustain an adverse outcome, e.g., MI. This was demonstrated by Slogoff and Keats who noted intraoperative ischaemia in 36.9% of patients of whom 6.9% developed myocardial infarction (vs 2.5% in patients without intraoperative ischaemia ($P < 0.005$)).[79]

A number of anaesthetic agents have been utilized in these studies, but the contribution of the anaesthetic technique to the development of ischaemia remains uncertain.[6,40,44,47,51,54,92] Indeed, the highest incidence of ischaemia occurred in the postoperative period (maximum at two hours) when the anaesthetic effects are dissipating.[80] This suggests that factors other than the anaesthetic agent are responsible. Studies comparing differences in the degree of ischaemia produced during CABG surgery employing different anaesthetic techniques show that intraoperative ischaemia is common and differences among anaesthetic agents can sometimes be demonstrated.[6,20,21,39,40,44,47,51,54,92] Very few studies have had sufficient power to detect differences between process variables (e.g., ischaemia) and outcome (e.g., MI or stroke). In those studies which did have sufficient power no differences in outcome were detected.[20,21] While needed, studies with sufficient power to detect a difference in the degree of ischaemia and outcome among anaesthetic techniques are difficult and costly to perform and usually require large numbers of patients. They are often contaminated by adjuvant agents which make extrapolation of the results to one's practice difficult. Multicentre trials designed to determine whether anaesthetic-induced ischaemia occurs, the significance relative to outcome, and with which agents are in process. At present there are no data to suggest that one anaesthetic regime is associated with a more severe outcome than another.[93] For the intraoperative phase it is not which drug is given but whether attention is paid to rigid control of haemodynamic aberrations, including those which are drug-induced, that seems to be important.[20,21,79,89] Even with a meticulous anaesthetic technique, however, a large proportion of ischaemia occurs unrelated to haemodynamic aberrations and probably reflects perturbations in the underlying disease process[89] and may or may not be amenable to intervention by the anaesthetist. When detected, ischaemia should be treated.[86]

PREVENTION

Based on the supposition that myocardial ischaemia leads to increased morbidity and mortality, that it occurs frequently in the postoperative period, and that previous studies had demonstrated elevations in stress-related hormones,[10,94-99] including catecholamines, in the postoperative period,[94-97] Mangano *et al.* treated a group of 106 cardiac patients with an intensive analgesic regimen in an effort to minimize episodes of ECG detected myocardial ischaemia.[100] Anaesthetic agents had been shown in some[101-106] but not all[10,95,96] studies to ameliorate the stress response to surgery. Compared with a group of patients receiving morphine 2 $mg \cdot hr^{-1}$, patients receiving sufentanil 1 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ for 18 hr in the ICU had fewer and less severe episodes of ischaemia.[100] The incidence of adverse outcomes was not different. Requirements for midazolam sedation were higher in the morphine-treated group and times to extubation and ICU discharge were not different. There was no difference between the groups with respect to haemodynamic changes. The authors postulated that the difference in the degree of ischaemia was due to suppression of sympathetic nervous system activity (not measured) and its effects on platelets, fibrinolysis, regional ventricular function, and coronary artery vasoconstriction.[107-110]

Several observations can be made regarding this study. No difference in adverse outcomes was appreciated, likely due to a small sample size (106 patients); and larger studies need to determine if intensive analgesia leads to reductions in morbidity and mortality. The role of sedation in combination with analgesia is uncertain but potentially important, since the morphine-treated group required more sedation and the degree of sedation provided was not quantified. The postulation that intensive analgesia is effective because it alters the degree of sympathetic activity can be tested by quantifying differences in catecholamine concentrations, and by demonstrating similar benefits from the use of other sympatholytic agents, e.g., beta or alpha adrenergic blocking drugs. This would be important since the use of high-dose opioids can mandate prolonged mechanical ventilation and delay discharge from the ICU, at least in some patients. Prolonged mechanical ventilation is not without its complications.[111] Which opioid should be used to provide analgesia requires further study.[24] Age-related differences in response to stress[112-118] and the role of stress in altering organ function[119-122] are only beginning to be studied. Finally, which of the ECG changes were related to ischaemia is unknown. Factors contributing to ST changes were not controlled (Table III).

Early vs late extubation of the trachea

The resurgence of normothermic cardiopulmonary bypass, increasing waiting lists for cardiac surgery, and reductions in already scarce resources have prompted a reexamination of the practice of delayed tracheal extubation for cardiac surgical patients. The arguments for and

TABLE IV Criteria for early extubation[111]

Preoperative status
- Adequate ventricular function
- No heart failure
- Age <70 yr
- Elective procedure
- No important valvular heart disease
- No clinically important extracardiac vascular disease
- Preoperative serum creatinine <1.9 mg% (200 mmol · L^{-1})
Operative events
- Single uncomplicated bypass run <2.5 hr
- Low dose or no inotropes required for separation from CPB
- Technically satisfactory revascularization
- Surgeon in agreement
Condition at extubation
- Awake and responsive to commands
- Adequate gag reflex and ability to protect airway
- pH >7.35 on spontaneous ventilation
- Haemodynamically stable without dysrhythmias
- Well-perfused with adequate urine output
- Mediastinal bleeding <100 ml · hr^{-1} for ≥2 hr
- Fully rewarmed (37° with no shivering)

TABLE V Reasons for recommending early vs delayed tracheal extubation

Early extubation	*Delayed extubation*
1 Avoids patient discomfort[125,126]	1 Patient comfort
- Use of neuromuscular relaxants and inadequate sedation	- Higher analgesic doses permitted
- Inadequate analgesia	2 Observation
2 Reduces risk of pulmonary barotrauma[127]	- Blood loss
3 Reduces ICU stay[128]	- Haemodynamics
4 Improves ventricular performance[129]	3 Reduced work of breathing*
5 Improves renal function[127,130]	4 Reduce postoperative bleeding using PEEP†
6 Reduces complications 2° to endotracheal tube[125,127]	5 Allows control of stress response by permitting higher doses of analgesics and sedatives[100]
- Lobar collapse[131,132]	6 Prevention of ARDS‡
- Cough[132]	
- Accidental extubation	
7 Earlier mobilization[128,133]	
8 Improved resource utilization[133]	

*Not supported by recent studies.[134,135]
†Not supported by recent study.[136]
‡Not supported by recent studies.[106,137,138]

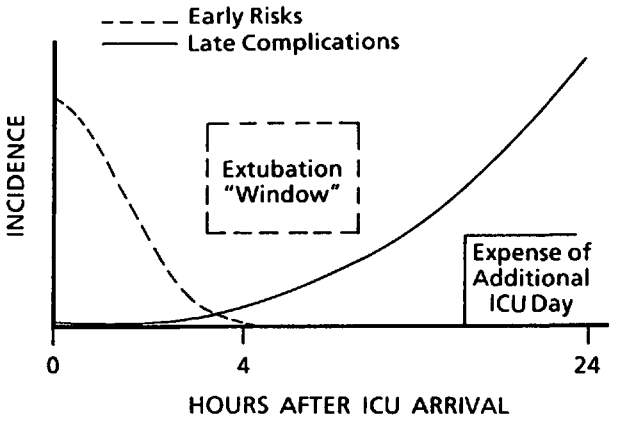

FIGURE 2 Complications related to early vs delayed tracheal extubation. Early risks include haemodynamic instability, hypermetabolism, shivering, and mediastinal bleeding. Late complications encompass ciliary dysfunction, inability to cough and clear secretions, and patient discomfort. Costs escalate markedly if late extubation delays ICU discharge for an additional day. (Reproduced with permission.[111])

against the procedure have been well examined in two recent reviews.[111,123] Early extubation, by definition, is performed within eight hours of the end of surgery.

In general, three groups of patients comprise the ICU population following CABG surgery.[124] The first, the majority, have had uneventful surgery, and have little or no requirement for ongoing inotropic or ventilatory support. Early extubation is most appropriately performed in this group. The second large group consists of individuals who require sustained support with inotropes, vasodilators, or mechanical circulatory support. Finally, there is a small group in whom attempts at weaning from ventilatory support have failed. Table IV lists criteria which might be considered when early extubation is contemplated.

Arguments for early vs delayed extubation are presented in Table V. The question of when to perform early extubation is important. Myocardial function after cardiopulmonary bypass is impaired both functionally and metabolically with the nadir at approximately four hours.[107,110,139-143] Increased sympathetic nervous system activity leads to alterations in coagulability and in particular to platelet activation[144-146] and may be the mechanism for the tachycardia which is commonly observed. Platelets may play an important role in the development of myocardial ischaemia.[147]

Recovery from hypothermia increases myocardial oxygen consumption and demand and there is an increased risk for cardiac dysfunction during this period.[148-150] The peak incidence of postoperative ischaemia is within the first two to four hours after bypass during which rewarming is accomplished.[80] Optimally rewarming is complete before extubation to prevent excessive work for the cardiopulmonary system with the possibility that respiratory failure might necessitate reintubation of the trachea (Figure 2). Effective analgesia must be ensured.

Several studies have attempted to address the issue of safe early tracheal extubation.[128,129,131,151-161] Attempts to reverse the respiratory depression attendant upon the use of high doses of opioids with partial agonists such as

nalbuphine have not been successful and cannot be recommended.[151,152]

The criteria developed in Table IV arose out of the results of a number of studies, mostly non-randomized, which looked at consecutive attempts at early extubation.[153-160] The majority of studies have demonstrated the practice to be safe.

To determine whether extubation led to myocardial ischaemia, Elia *et al.* examined the haemodynamic and myocardial metabolic effects of extubation in seven patients after aortocoronary artery bypass surgery, utilizing a high-dose sufentanil anaesthetic technique.[162] Extubation was performed 14–18 hr postoperatively. The duration of anaesthesia and surgery was not specified. Extubation was associated with an increase in cardiac index due to an increase in stroke index with no change in heart rate, mean arterial pressure, or pulmonary capillary wedge pressure. Myocardial oxygen consumption and coronary blood flow ($n = 5$ patients) increased. Two patients experienced myocardial lactate production (i.e., ischaemia) without haemodynamic or ECG alterations. The authors concluded that extubation of the trachea was not associated with the same degree of adverse systemic or coronary haemodynamic responses in cardiac surgical patients as was seen with intubation. However, despite revascularization, the myocardium was still at risk for ischaemia in the immediate postoperative period.

In a follow-up study, 17 patients were examined for global and regional myocardial ischaemia during the weaning process following aortocoronary artery bypass surgery under high-dose fentanyl or sufentanil anaesthesia.[163] Eight of 17 patients had myocardial lactate production during at least one of the weaning phases without ECG evidence of ischaemia. Comparison of patients who had myocardial lactate production with those who did not showed that the group with lactate production had greater increases in mean arterial pressure and systemic vascular resistance during the weaning process (Figure 3). The authors concluded that myocardial ischaemia occurs commonly during weaning from mechanical ventilation.

Haemodynamic changes at the time of extubation were examined by Paulissian *et al.*[164] They noted increases in heart rate, mean arterial pressure, cardiac index, right atrial pressure, and mean pulmonary artery pressure at the time of suctioning and extubation which resolved within five minutes. There was no ECG or enzymatic evidence of myocardial ischaemia. The authors concluded that, compared with haemodynamic changes associated with intubation, extubation was associated with much less pronounced effects.

To summarize, early extubation is feasible in a selected group of cardiac surgical patients, although complications

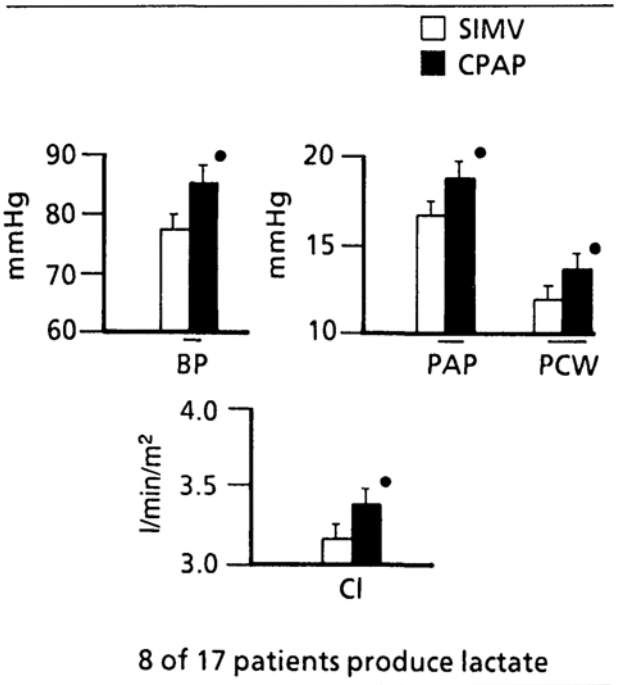

FIGURE 3 Mean arterial pressure (BP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCW) and cardiac index (CI) during weaning from synchronized intermittent mandatory ventilation (SIMV) to continuous positive airway pressure (CPAP) (*$P < 0.05$; error bars represent SEM). (Reproduced with permission.[163])

related to pulmonary and cardiovascular system deterioration can occur. Studies to date suggest that some patients (as high as 10%)[131] will require tracheal reintubation if strict criteria for extubation are not employed. The majority of the studies have few patients, were retrospective, and not randomized. In adults, patients had preserved ventricular function, were otherwise healthy, and underwent surgery employing hypothermic cardiopulmonary bypass. Extubation may represent a period of stress for patients and some will have myocardial ischaemia at this time. Studies involving patients with impaired ventricular function (likely to have altered haemodynamic responses to extubation) or undergoing normothermic cardiopulmonary bypass (thus avoiding the adverse effects of hypothermia) are required.

Pharmacokinetics

Cardiopulmonary bypass alters both the pharmacokinetic and pharmacodynamic behaviour of drugs administered during CABG surgery.[22,165-168] Alterations in liver blood flow lead to reductions in clearance for drugs such as the opioids, benzodiazepines, and propofol.[26,169,170] This is reflected in an increased elimination half-time following bypass and the potential for drug accumulation and prolongation of effect if drug administration occurs at rates

usually employed in the absence of cardiopulmonary bypass. Changes in protein binding due to haemodilution may lead to enhanced effect of drugs since the free, unbound fraction may be elevated.[171] Alterations in cardiac function and systemic vascular resistance may change the volume of distribution and this is likely to be highly variable among patients.[169]

Data in dogs suggests that, independent of any pharmacokinetic changes, there may also be pharmacodynamic changes in drug effect.[165,168]

Taken together, the most rational way to administer drugs, particularly infusions, following cardiopulmonary bypass is to titrate the drug to a desired effect. This may be guided by target plasma concentrations[169] but will likely require adjustment (usually a reduction) as the drug's effect becomes manifest. Caution is urged with the use of bolus administration of drugs such as propofol which may have a significant haemodynamic effect.[172]

Current options

Since the ideal cardiac anaesthetic agent is not available, we must continue to use combinations of agents to achieve the desired effect. Not only must the ability to control myocardial oxygen balance be considered, but also new objectives including the provision of analgesia (and sedation?) in the postoperative period to ameliorate ischaemic changes, and consideration for early extubation should be considered. While each of these objectives requires further study (and in particular studies of sufficient power to detect real changes in outcome (MI, stroke) as opposed to process variables (e.g., ischaemic changes on the ECG)), changes in our current practice to enable us to study the utility of these objectives can be effected now. The following provides some background on the strengths and limitations of each of the classes of drug available with particular reference to the objectives of providing residual analgesia/sedation and the possibility for early extubation. Recommendations based on the previous considerations are provided.

Volatile anaesthetic agents

These agents provide sedation/amnesia and reduced requirements for analgesic agents.[133,173] Their action can be adjusted and/or terminated relatively quickly and they have been the agents most frequently used when a trial of early extubation is contemplated.[133,173] Disadvantages include myocardial depression, haemodynamic instability, lack of analgesia, and the requirement for an anaesthetic circuit for administration. While isoflurane has been used for ICU sedation,[174,175] unfamiliarity of nursing personnel with its properties and mode of administration, environmental pollution during tracheal suctioning and other respiratory manoeuvres, and cost are severe limitations to its use as an ICU sedating agent.[174] If used as the primary anaesthetic agent, consideration should be given to the early provision of analgesia to avoid hypertension and tachycardia postoperatively.[173]

TABLE VI Opioid target plasma concentrations for adult patients[175]

	Meperidine ($ng \cdot ml^{-1}$)	*Fentanyl* ($ng \cdot ml^{-1}$)	*Sufentanil* ($ng \cdot ml^{-1}$)	*Alfentanil* ($\mu g \cdot ml^{-1}$)
During surgery with N_2O/O_2	300–2000	2.5–10	0.25–1.0	2–8
During surgery with O_2		15–60	2–8	10–40
Adequate post-operative ventilation	150(?)	1.5	0.25	1.25

Opioids

In North America, these agents form the major component of most cardiac anaesthetics. Much is known about their pharmacokinetics[22–24] and given a set of pharmacokinetic variables, models and simulations of changes in blood concentrations and effect site concentration over time with differing durations of infusions have been described.[23,24] Target concentrations for intraoperative and postoperative control of noxious stimuli are being defined[176] (Table VI). Cardiopulmonary bypass may be expected to alter clearance mechanisms and therefore reduce requirements following termination of cardiopulmonary bypass.[22] Substantial variability in drug effect should be anticipated. Intravenous administration of opioids following cardiopulmonary bypass should, therefore, be titrated to specific end points, e.g., pain relief until rapid assay methods that allow for prompt determination of plasma opioid concentrations are developed. Alternatively, the approach employed by Mangano *et al.*[100] of utilizing a fixed dose of opioid known to produce reductions in patient responses to noxious stimuli can be employed. The plasma levels achieved by this technique are likely to be above those which allow for spontaneous ventilation, at least in some patients. This will therefore necessitate prolonged mechanical support and obviate the possibility of early extubation unless antagonists are employed. The latter approach has not been demonstrated to be satisfactory.[151,152]

If early extubation is a consideration, one could consider employing other measures to control the stress response besides intensive analgesia (e.g., beta adrenergic blocking agents, clonidine[177]) thus permitting reductions in systemic opioid concentrations. Alternative routes of administration of analgesia could also be considered, e.g., epidural.[160,178] Clearly, much work remains to be done in this area.

However, based on its pharmacokinetic behaviour and the concept of a context-sensitive half-life, for infusions lasting less than ten hours, sufentanil would appear to be the agent with the most rapid offset of action so as to permit a reduction in plasma levels leading to extubation in as timely a fashion as possible.[23,24] This would theoretically be the agent of choice were early extubation to be considered. For more prolonged infusions, the pharmacokinetics of alfentanil suggest that it should be considered. Here cost may be an issue. The role of sedation in combination with an analgesic in altering requirements for analgesia following cardiopulmonary bypass remains to be examined.

Hypnotics

The current theory that activation of the sympathetic nervous system is responsible for many of the adverse events occurring after cardiopulmonary bypass suggests a role for continuing sedation into the postoperative period. Opioids, alone, do not blunt the sympathetic response during cardiac surgery[10,179] and their requirements for control of adverse haemodynamic responses are reduced by the addition of hypnotic agents.[32,180] The ideal agent would sedate the patient with no effect on the respiratory or cardiovascular systems or on the clearance of other drugs, would be cleared by mechanisms independent of renal, pulmonary, or hepatic function, should be short-acting even after prolonged infusions,[23,181-183] and tolerance should not occur. The ideal sedative does not exist.

BARBITURATES

These agents accumulate, are relatively long-acting, and produce myocardial depression. They have been employed for neuroprotection, but their use entails an increased requirement for inotropic agents at the end of cardiopulmonary bypass and a prolonged time to extubation.[184,185] Their use in combination with an opioid by infusion in the postoperative period would likely result in a considerable prolongation of the time to extubation.

BENZODIAZEPINES

Of the benzodiazepines, midazolam with its short elimination half-time (2.4 hr)[186] and lack of active metabolites has the most favourable pharmacokinetic profile.[23] It is water soluble, short acting, and capable of delivery by continuous infusion.[187] Variability in patient pharmacokinetic behaviour may occur.[169,188] Its pharmacokinetics have been determined in a group of cardiac surgical patients postoperatively.[189] The elimination half-time was increased (10.6 hr) and clearance reduced in this group of patients. Depending on the duration of infusion, the potential for accumulation and prolonged effect exists.

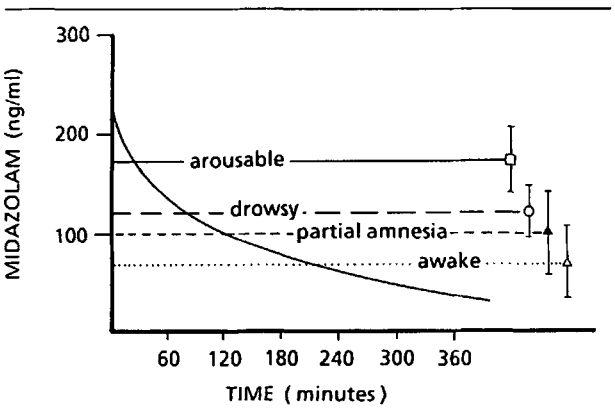

FIGURE 4 The concentration-time profile of midazolam after extubation. The mean (±SD) concentrations associated with various pharmacodynamic end points are shown. (Reproduced with permission.[191])

Concentration vs effect relationships have been determined, including the observation that combination with alfentanil shifts the dose-response curve to the right (i.e., increased sedation for any given plasma level of midazolam)[186,190,191] (Figure 4). These data make it possible to design infusion regimens permitting effective sedation with a short time to extubation.[23,169,192]

ETOMIDATE

Studies demonstrating that the cortisol response to surgery was obtunded and that the use of etomidate for prolonged infusions was associated with increased mortality suggest that its use as a sedative in the routine post-cardiopulmonary bypass patient would require careful scrutiny.[34,35] Unfortunately, etomidate is not available for use in Canada, although it provides superb control of intraoperative myocardial oxygen balance.[33]

PROPOFOL

The pharmacokinetic variables for propofol during and following cardiac surgery have been determined.[48,170,193,194] After cardiopulmonary bypass, elimination half-time was prolonged and clearance reduced[193] or unchanged.[194] Its use for sedation in the intensive care unit has been described and cumulative effects and tachyphylaxis did not occur. Reductions in mean arterial pressure were noted.[191-197] Rapid recovery from sedation was apparent when infusions were discontinued.[197] Concentration vs effect relationships have been determined[48,197-202] (Figure 5). It should be possible for it to be administered by infusion to permit early tracheal extubation.

Several studies have compared propofol with midazolam for sedation in the intensive care unit following cardiac surgery. After a thiopentone, high-dose fentanyl, ni-

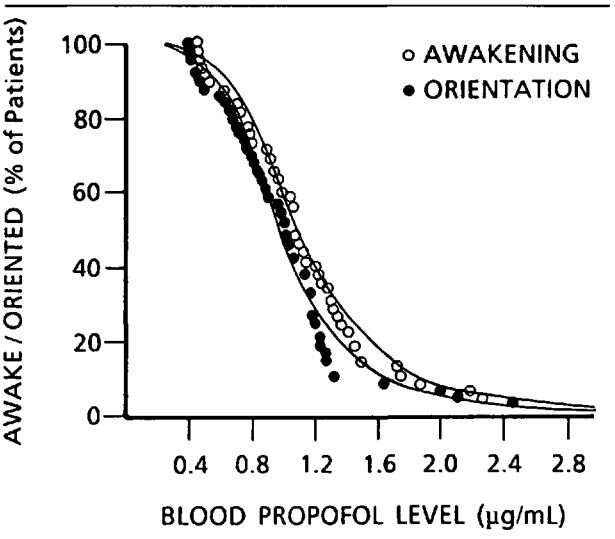

FIGURE 5 Concentration-response curves for awakening and orientation as a function of blood propofol level ($\mu g \cdot ml^{-1}$). The cumulative percent of patients who awoke (O) or were oriented (●) at various blood propofol levels are shown. (Reproduced with permission.[198])

trous oxide anaesthetic, Grounds *et al.* studied 60 patients randomly allocated to receive propofol by continuous infusion or intermittent midazolam.[195] Analgesia was provided by intermittent papaveretum. Sedation was titrated according to a scale,[203] in order to maintain patients at a level where they responded only to commands. Tracheal extubation was performed when patients were considered ready. Patients in the propofol-treated group required less analgesia, were more easily maintained at the desired sedation level, and extubation occurred earlier (6.5 vs 10 hr). There were no haemodynamic differences between the groups.

McMurray *et al.* studied 100 patients randomized to receive either a continuous infusion of propofol or intermittent midazolam.[193] Anaesthesia was standardized and included high-dose fentanyl with supplemental halothane. Analgesia in the postoperative period was provided with intermittent morphine *iv.* Sedation was titrated to produce a level at which the patient responded to commands. Pharmacokinetic variables were determined in ten patients in each group. Patients in the propofol-treated group required less morphine analgesia, and were more easily maintained at the target sedation level. Patients received the sedative drugs for approximately 17 hr. The time from discontinuation of propofol to extubation was 7.6 min (95% CI 2.9–19.1 min) compared with 125 min (73.6–208.5 min) in the midazolam group. No haemodynamic differences were detected. While the redistribution half-time for propofol was shorter than for midazolam (13.4 ± 2.8 vs 30.1 ± 2.6 min), the elimination half-time was longer (470.2 ± 60.5 vs 403.6 ± 73.3 min). These pharmacokinetic variables were longer than values obtained in patients not undergoing hypothermic cardiopulmonary bypass.[204,205]

Snellen *et al.* studied 40 patients randomized to receive continuous infusions of either midazolam or propofol.[172] Anaesthesia was standardized and consisted of an induction dose of thiopentone, and high-dose sufentanil supplemented by halothane. Patients were sedated postoperatively for 12 hr and analgesia was maintained by a variable rate infusion of piritramide. A level of sedation of 2–4 on the Ramsey scale[203] was targeted. The time from stopping the infusion to spontaneous ventilation was shorter in the propofol-treated group and less attempts at weaning from mechanical support were required. However, time to extubation was not different (propofol 154 ± 33 vs midazolam 243 ± 44 min; P = NS). In both groups, administration of bolus doses of the agent resulted in reductions in blood pressure.

Taken together, these results suggest that the use of propofol for sedation following cardiopulmonary bypass would seem reasonable. The pharmacokinetic profiles of sufentanil by infusion and propofol are closely matched[23] and this combination would appear to be optimal. It would allow reductions in analgesic requirement and permit trials of early extubation. Determination of the effects on catecholamine levels is required to determine if the stress response is altered. Further studies on the optimum combination of analgesia/sedation in terms of ameliorating ischaemia are required.

Conclusions

Requirements for cardiac anaesthesia must keep in perspective the ongoing requirements for anaesthesia for cardiac surgery including amnesia/analgesia and haemodynamic control. During surgery, no specific anaesthetic technique has been clearly demonstrated to be superior and it is suggested that a more goal-oriented approach be employed. This would involve abandoning the current practice of high-dose opioid anaesthesia in favour of reduced doses of opioids and increased use of other anaesthetic agents. New concepts of silent myocardial ischaemia and resultant postoperative morbidity and mortality, together with the role of anaesthetic agents in limiting the process, require further study. The feasibility and safety of early tracheal extubation needs further investigation. However, based on pharmacokinetic principles, it should be possible to design and implement studies to examine these questions with agents currently available. We must resist the temptation to become complacent in the use of any anaesthetic technique and begin to explore the use of anaesthetic agents providing safe, effective cardiac anaesthesia in the most cost-effective manner. The postoperative course of the patient should not be man-

dated by the anaesthetic they received intraoperatively. Rather, goal-directed therapy with targeted objectives, e.g., reduction in ischaemia, haemodynamic control, and early extubation should be the anaesthetic objective for the 1990's.

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References

1 *Higginson LAJ, Cairns JA, Keon WJ, Smith ER.* Rates of cardiac catheterisation, coronary angioplasty and open-heart surgery in adults in Canada. Can Med Assoc J 1992; 146: 921–5.

2 *Jones EL, Weintraub WS, Craver JM, Guyton RA, Cohen CI.* Coronary bypass surgery: is the operation different today? J Thorac Cardiovasc Surg 1991; 101: 108–15.

3 *Naunheim KS, Fiore AC, Wadley JJ, et al.* The changing profile of the patient undergoing coronary artery bypass surgery. J Am Coll Cardiol 1988; 11: 494–8.

4 *Moffitt EA, Sethna DH.* The coronary circulation and myocardial oxygenation in coronary artery disease: effects of anesthesia. Anesth Analg 1986; 65: 395–410.

5 *Moffitt EA, Barker RA, Glenn JJ, et al.* Myocardial metabolism and hemodynamic responses with isoflurane anesthesia for coronary arterial surgery. Anesth Analg 1986; 65: 53–61.

6 *Moffitt EA, Imrie DD, Scovil JE, et al.* Myocardial metabolism and haemodynamic responses with enflurane anaesthesia for coronary artery surgery. Can Anaesth Soc J 1984; 31: 604–10.

7 *Wynands JE, Townsend GE, Wong P, Whalley DG, Srikant CB, Patel YC.* Blood pressure response and plasma fentanyl concentrations during high- and very high-dose fentanyl anesthesia for coronary artery surgery. Anesth Analg 1983; 62: 661–5.

8 *Edde RR.* Hemodynamic changes prior to and after sternotomy in patients anesthetized with high-dose fentanyl. Anesthesiology 1981; 55: 444–6.

9 *Hug CC Jr, Hall RI, Angert KC, Reeder DA, Moldenhauer CC.* Alfentanil plasma concentration v. effect relationships in cardiac surgical patients. Br J Anaesth 1988; 61: 435–40.

10 *Philbin DM, Rosow CE, Schneider RC, Koski G, D'Ambre MN.* Fentanyl and sufentanil anesthesia revisited: how much is enough? Anesthesiology 1990; 73: 5–11.

11 *Hilgenberg JC.* Intraoperative awareness during high-dose fentanyl-oxygen anesthesia. Anesthesiology 1981; 54: 341–3.

12 *Reiz S, Bålfors E, Sørenson MB, Ariola S Jr, Truedsson H.* Isoflurane – a powerful coronary vasodilator in patients with coronary artery disease. Anesthesiology 1983; 59: 91–7.

13 *Moffitt EA, Scovil JE, Barker RA, et al.* The effects of nitrous oxide on myocardial metabolism and hemodynamics during fentanyl or enflurane anesthesia in patients with coronary disease. Anesth Analg 1984; 63: 1071–5.

14 *Wilkowski DAW, Sill JC, Bonta W, Owen R, Bove AA.* Nitrous oxide constricts epicardial coronary arteries without effect on coronary arterioles. Anesthesiology 1987; 66: 659–65.

15 *Mitchell MM, Prakash O, Rulf ENR, Van Dale ME, Cahalan MK, Roelandt JR.* Nitrous oxide does not induce myocardial ischemia in patients with ischemic heart disease and poor ventricular function. Anesthesiology 1989; 71: 526–34.

16 *Becker LC.* Is isoflurane dangerous for the patient with coronary artery disease? (Editorial) Anesthesiology 1987; 66: 259–61.

17 *O'Connor JP, Ramsay JG, Wynands JE, Kaplan JA.* Anesthesia for myocardial revascularization. *In*: Kaplan JA (Ed.). Cardiac Anesthesia, 3rd ed. Philadelphia: WB Saunders Co., 1993; 587–628.

18 *Forrest JB, Rehder K, Goldsmith CH, et al.* Multicenter study of general anesthesia. I. Design and patient demography. Anesthesiology 1990; 72: 252–61.

19 *Forrest JB, Cahalan MK, Rehder K, et al.* Multicenter study of general anesthesia. II. Results. Anesthesiology 1990; 72: 262–8.

20 *Tuman KJ, McCarthy RJ, Spiess BD, De Valle M, Dabir R, Ivankovich AD.* Does choice of anesthetic agent significantly affect outcome after coronary artery surgery? Anesthesiology 1989; 70: 189–98.

21 *Slogoff S, Keats AS.* Randomized trial of primary anesthetic agents on outcome of coronary artery bypass operations. Anesthesiology 1989; 70: 179–88.

22 *Hall R.* The pharmacokinetic behaviour of opioids administered during cardiac surgery. Can J Anaesth 1991; 38: 747–56.

23 *Hughes MA, Glass PSA, Jacobs JR.* Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. Anesthesiology 1992; 76: 334–41.

24 *Shafer SL, Varvel JR.* Pharmacokinetics, pharmacodynamics, and rational opioid selection. Anesthesiology 1991; 74: 53–63.

25 *Stoelting RK.* Pharmacology and Physiology in Anesthetic Practice, 2nd ed. New York: JB Lippincott Co. 1991, 118–33.

26 *Koska AJ III, Romagnoli A, Kramer WG.* Effect of cardiopulmonary bypass on fentanyl distribution and elimination. Clin Pharmacol Ther 1981; 29: 100–5.

27 *Hynynen M, Takkunen O, Salmenperä M, Haataja H,*

Heinoven J. Continuous infusion of fentanyl or alfentanil for coronary artery surgery. Br J Anaesth 1986; 58: 1252–9.

28 *Marty J, Nitenberg A, Blanchet F, Zouioueche S, Desmonts JM.* Effects of midazolam on the coronary circulation in patients with coronary artery disease. Anesthesiology 1986; 64: 206–10.

29 *Murphy JT, Hall RI, Moffitt EA, et al.* Effects of midazolam or sufentanil on coronary haemodynamics after induction and endotracheal intubation in patients undergoing coronary artery bypass graft surgery. Can J Anaesth 1991; 38: A22.

30 *Heikkilä H, Jalonen J, Arola M, Kanto J, Laaksonen V.* Midazolam as adjunct to high-dose fentanyl anaesthesia for coronary artery bypass grafting operation. Acta Anaesthesiol Scand 1984; 28: 683–9.

31 *Raza SMA, Masters RW, Vasireddy AR, Zsigmond EK.* Haemodynamic stability with midazolam-sufentanil analgesia in cardiac surgical patients. Can J Anaesth 1988; 35: 518–25.

32 *Schwieger I, Bailey J, Hug CC Jr.* Anesthetic interaction of computer controlled and constant infusions of fentanyl and midazolam for cardiac surgery. Anesthesiology 1989; 71: A305.

33 *Gooding JM, Weng J-T, Smith RA, Berninger GT, Kirby RR.* Cardiovascular and pulmonary responses following etomidate induction of anesthesia in patients with demonstrated cardiac disease. Anesth Analg 1979; 58: 40–1.

34 *Ledingham IMcA, Watt I.* Influence of sedation on mortality in critically ill multiple trauma patients. (Letter). Lancet 1983; 1: 1270.

35 *Wagner RL, White PF, Kan PB, Rosenthal MH, Feldman D.* Inhibition of adrenal steroidogenesis by the anesthetic etomidate. N Engl J Med 1984; 310: 1415–21.

36 *Merin RG.* Propofol causes cardiovascular depression. I. (Letter). Anesthesiology 1990; 72: 393–4.

37 *Van Aken H, Brüssel T.* Propofol causes cardiovascular depression. II. (Letter). Anesthesiology 1990; 72: 394–5.

38 *Monk CR, Coates DP, Prys-Roberts C, Turtle MJ, Speling K.* Haemodynamic effects of a prolonged infusion of propofol as a supplement to nitrous oxide anaesthesia. Br J Anaesth 1987; 59: 954–60.

39 *Lepage J-YM, Pinaud ML, Hélias JH, et al.* Left ventricular function during propofol and fentanyl anesthesia in patients with coronary artery disease: assessment with a radionuclide approach. Anesth Analg 1988; 67: 949–55.

40 *Lepage J-YM, Pinaud ML, Hélias JH, Cozian AY, Le Normand Y, Souron RJ.* Left ventricular performance during propofol or methohexital anesthesia: isotopic and invasive cardiac monitoring. Anesth Analg 1991; 73: 3–9.

41 *Samain E, Marty HJ, Gauzit R, et al.* Effects of propofol on baroreflex control of heart rate and on plasma noradrenaline levels. Eur J Anaesthesiol 1989; 6: 321–6.

42 *Cullen PM, Turtle M, Prys-Roberts C, Way WL, Dye J.* Effect of propofol anesthesia on baroreflex activity in humans. Anesth Analg 1987; 66: 1115–20.

43 *Ebert TJ, Muzi M, Berens R, Goff D, Kampine JP.* Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. Anesthesiology 1992; 76: 725–33.

44 *Hall RI, Murphy JT, Moffitt EA, Landymore R, Pollak PT, Poole L.* A comparison of the myocardial metabolic and haemodynamic changes produced by propofol-sufentanil and enflurane-sufentanil anaesthesia for patients having coronary artery bypass graft surgery. Can J Anaesth 1991; 38: 996–1004.

45 *Patrick MR, Blair IJ, Feneck RO, Sebel PS.* A comparison of the haemodynamic effects of propofol ('Diprivan') and thiopentone in patients with coronary artery disease. Postgrad Med J 1985; 61 (Suppl 3): 23–7.

46 *Stephan H, Sonntag H, Schenk HD, Kettler D, Khambatta HJ.* Effects of propofol on cardiovascular dynamics, myocardial blood flow and myocardial metabolism in patients with coronary artery disease. Br J Anaesth 1986; 58: 969–75.

47 *Kaplan JA, Guffin AV, Mikula S, Dolman J, Profeta J.* Comparative hemodynamic effects of propofol and thiamylal sodium during anesthetic induction for myocardial revascularization. Journal of Cardiothoracic Anesthesia 1988; 2: 297–302.

48 *Russell GN, Wright EL, Fox MA, Douglas EJ, Cockshott JD.* Propofol-fentanyl anaesthesia for coronary artery surgery and cardiopulmonary bypass. Anaesthesia 1989; 44: 205–8.

49 *Mora CT, Dudek C, Epstein RH, Torjman MC, White PF.* Cardiac anesthesia techniques: fentanyl alone or in combination with enflurane or propofol. Anesth Analg 1989; 68: S202.

50 *Vermeyen KM, Erpels FA, Janssen LA, Beckman CP, Hanegreefs GH.* Propofol-fentanyl anaesthesia for coronary bypass surgery in patients with good left ventricular function. Br J Anaesth 1987; 59: 1115–20.

51 *Hall RI, Murphy JT, Landymore R, et al.* A randomized study of myocardial metabolic and hemodynamic changes during propofol anesthesia for cardiac surgery in patients with reduced ventricular function. Anesth Analg 1993 (in press).

52 *Spiess BD, Sathoff RH, El-Ganzouri ARS, Ivankovich AD.* High-dose sufentanil: four cases of sudden hypotension on induction. Anesth Analg 1986; 65: 703–5.

53 *Claeys MA, Gepts E, Camu F.* Haemodynamic changes during anaesthesia induced and maintained with propofol. Br J Anaesth 1988; 60: 3–9.

54 *Helman JD, Leung JM, Bellows WH, et al.* The risk of myocardial ischemia in patients receiving desflurane versus sufentanil anesthesia for coronary artery bypass graft surgery. Anesthesiology 1992; 77: 47–62.

55 *Kaplan JA, Wells PH.* Early diagnosis of myocardial ischemia using the pulmonary arterial catheter. Anesth Analg 1981; 60: 789–93.

56 *Pollak PT, Hall RI, Poole LA.* Hemodynamic monitoring in anaesthetic clinical trials: need for pulmonary artery vs right atrial catheters. Clin Invest Med 1991; 14: A103.

57 *Kotter GS, Kotrly KJ, Kalbfleisch JH, Vucins EJ, Kampine JP.* Myocardial ischemia during cardiovascular surgery as detected by an ST segment trend monitoring system. Journal of Cardiothoracic Anesthesia. 1987; 1: 190–9.

58 *Kotter GS, Bernstein JS, Kotrly KJ.* ECG changes detect coronary artery bypass graft occlusion without hemodynamic instability. Anesth Analg 1984; 63: 1133–5.

59 *Slogoff S, Keats AS, David Y, Igo SR.* Incidence of perioperative myocardial ischemia detected by different electrocardiographic systems. Anesthesiology 1990; 73: 1074–81.

60 *London MJ, Hollenberg M, Wong MG, et al.* Intraoperative myocardial ischemia: localization by continuous 12-lead electrocardiography. Anesthesiology 1988; 69: 232–41.

61 *Hall RI, Moffitt EA.* Monitoring the coronary circulation. Anesth Clin N Amer 1988; 6: 839–50.

62 *Kugler G.* Myocardial release of lactate, inosine and hypoxanthine during atrial pacing and exercise-induced angina. Circulation 1979; 59: 43–9.

63 *Opie LH, Owen P, Thomas M, Samson R.* Coronary sinus lactate measurements in assessment of myocardial ischemia. Am J Cardiol 1973; 32: 295–305.

64 *Ferrari R, Bolognesi O, Raddino R.* Reproducibility of metabolic parameters during successive coronary sinus pacing in patients known to have coronary artery disease. Int J Cardiol 1985; 9: 231–4.

65 *Knight AA, Hollenberg M, London MJ, et al.* Perioperative myocardial ischemia: importance of the preoperative ischemic pattern. Anesthesiology 1988; 68: 681–8.

66 *Gottlieb SO.* Detection of myocardial ischemia using continuous electrocardiography. Int Anesthesiol Clin 1992; 30: 19–30.

67 *Leung JM, O'Kelly B, Browner WS, Tubau J, Hollenberg M, Mangano DT.* Prognostic importance of postbypass regional wall-motion abnormalities in patients undergoing coronary artery bypass graft surgery. Anesthesiology 1989; 71: 16–25.

68 *Leung JM, Goehner P, O'Kelley BF, et al.* Isoflurane anesthesia and myocardial ischemia: comparative risk versus sufentanil anesthesia in patients undergoing coronary artery bypass graft surgery. Anesthesiology 1991; 74: 838–47.

69 *Ellis JE, Shah MN, Briller JE, Roizen MF, Aronson S, Feinstein SB.* A comparison of methods for the detection of myocardial ischemia during noncardiac surgery: automated ST-segment analysis systems, electrocardiography, and transesophageal echocardiography. Anesth Analg 1992; 75: 764–72.

70 *Clements FM, de Bruijn NP.* Perioperative evaluation of regional wall motion by transesophageal two-dimensional echocardiography. Anesth Analg 1987; 66: 249–61.

71 *Häggmark S, Hohner P, Östman M, et al.* Comparison of hemodynamic, electrocardiographic, mechanical, and metabolic indicators of intraoperative myocardial ischemia in vascular surgical patients with coronary artery disease. Anesthesiology 1989; 70: 19–25.

72 *Leung JM, O'Kelly BF, Mangano DT, SPI Research Group.* Relationship of regional wall motion abnormalities to hemodynamic indices of myocardial oxygen supply and demand in patients undergoing CABG surgery. Anesthesiology 1990; 73: 802–14.

73 *Smith JS, Cahalan MK, Benefiel DJ, et al.* Intraoperative detection of myocardial ischemia in high-risk patients: electrocardiography versus two-dimensional transesophageal echocardiography. Circulation 1985; 72: 1015–21.

74 *Vandenberg BF, Kerber RE.* Transesophageal echocardiography and intraoperative monitoring of left ventricular function. (Editorial). Anesthesiology 1990; 73: 799–801.

75 *Buffington CW, Coyle RJ.* Altered load dependence of postischemic myocardium. Anesthesiology 1991; 75: 464–74.

76 *Lowenstein E, Haering JM, Douglas PS.* Acute ventricular wall motion heterogeneity: a valuable but imperfect index of myocardial ischemia (Editorial). Anesthesiology 1991; 75: 385–7.

77 *Mangano DT, Browner WS, Hollenberg M, et al.* Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. N Engl J Med 1990; 323: 1781–8.

78 *Lowenstein E, McPeek B.* Capitalizing on research findings that appear to conflict (Editorial). Anesthesiology 1988; 68: 668–70.

79 *Slogoff S, Keats AS.* Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 1985; 62: 107–14.

80 *Smith RC, Leung JM, Mangano DT, SPI Research Group.* Postoperative myocardial ischemia in patients undergoing coronary artery bypass graft surgery. Anesthesiology 1991; 74: 464–73.

81 *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.

82 *Yousif H, Davies G, Westaby S, Prendiville OF, Sapsford RN, Oakley CM.* Preoperative myocardial ischaemia: its relation to perioperative infarction. Br Heart J 1987; 58: 9–14.

83 *Slogoff S, Keats AS.* Does chronic treatment with calcium

entry blocking drugs reduce perioperative myocardial ischemia? Anesthesiology 1988; 68: 676–80.

84 *Chung F, Houston PL, Cheng DCH, et al.* Calcium channel blockade does not offer adequate protection from perioperative myocardial ischemia. Anesthesiology 1988; 69: 343–7.

85 *de Lange S, Boscoe MJ, Stanley TH, Pace TH.* Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. Anesthesiology 1982; 56: 112–8.

86 *Lowenstein E.* Perianesthetic ischemic episodes cause myocardial infarction in humans – a hypothesis confirmed (Editorial). Anesthesiology 1985; 62: 103–6.

87 *Raj PP, Brannon JE.* Analgesic considerations for the median sternotomy in Pain Management. *In*: Gravlee GP, Rauck RL (Eds.). Cardiothoracic Surgery. Philadelphia: JB Lippincott Co., 1993; 101–24.

88 *Speight KL.* Perioperative stress response suppression in cardiothoracic surgery. *In*: Gravlee GP, Rauck RL (Eds.). Pain Management in Cardiothoracic Surgery. Philadelphia: JB Lippincott Co., 1993, 169–99.

89 *Slogoff S, Keats AS.* Further observations on perioperative myocardial ischemia. Anesthesiology 1986; 65: 539–42.

90 *Nademanee K, Intarachot V, Josephson MA, Rieders D, Mody FV, Singh BN.* Prognostic significance of silent myocardial ischemia in patients with unstable angina. J Am Coll Cardiol 1987; 10: 1–9.

91 *Gottlieb SO, Gottlieb SH, Achuff SC, et al.* Silent ischemia on Holter monitoring predicts mortality in high-risk postinfarction patients. JAMA 1988; 259: 1030–5.

92 *Murphy JT, Moffitt EA, Hall RI, et al.* Myocardial oxygenation and ischaemia in normotensive patients undergoing coronary revascularization. Can J Anaesth 1991; 38: A165.

93 *Mangano DT.* Anesthetics, coronary artery disease, and outcome: unresolved controversies (Editorial). Anesthesiology 1989; 70: 175–8.

94 *Reves JG, Karp RB, Buttner EE, et al.* Neuronal and adrenomedullary catecholamine release in response to cardiopulmonary bypass in man. Circulation 1982; 66: 49–55.

95 *Okutani R, Philbin DM, Rosow CE, Koski G, Schneider RC.* Effect of hypothermic hemodilutional cardiopulmonary bypass on plasma sufentanil and catecholamine concentrations in humans. Anesth Analg 1988; 67: 667–70.

96 *Bovill JG, Sebel PS, Fiolet JWT, Touber JL, Kok K, Philbin DM.* The influence of sufentanil on endocrine and metabolic responses to cardiac surgery. Anesth Analg 1983; 62: 391–7.

97 *Stanley TH, Berman L, Green O, Robertson D.* Plasma catecholamine and cortisol responses to fentanyl-oxygen anesthesia for coronary-artery operations. Anesthesiology 1980; 53: 250–3.

98 *Udelsman R, Norton JA, Jelenich SE, et al.* Responses of the hypothalamic-pituitary-adrenal and renin-angiotensin axes and the sympathetic system during controlled surgical and anesthestic stress. J Clin Endocrinol Metab 1987; 64: 986–94.

99 *Halter JB, Pflug AE, Porte D Jr.* Mechanism of plasma catecholamine increases during surgical stress in man. J Clin Endocrinol Metab 1977; 45: 936–44.

100 *Mangano DT, Siliciano D, Hollenberg M, et al.* Postoperative myocardial ischemia: therapeutic trials using intensive analgesia following surgery. Anesthesiology 1992; 76: 342–53.

101 *Reier CE, George JM, Kilman JW.* Cortisol and growth hormone response to surgical stress during morphine anesthesia. Anesth Analg 1973; 52: 1003–10.

102 *Haxholdt O, Kehlet H, Dyrberg V.* Effect of fentanyl on the cortisol and hyperglycemic response to abdominal surgery. Acta Anaesthesiol Scand 1981; 25: 434–6.

103 *Philbin DM, Coggins CH.* Plasma antidiuretic hormone levels in cardiac surgical patients during morphine and halothane anesthesia. Anesthesiology 1978; 49: 95–8.

104 *George JM, Reier CE, Lanese RR, Rower JM.* Morphine anesthesia blocks cortisol and growth hormone response to surgical stress in humans. J Clin Endocrinol Metab 1974; 38: 736–41.

105 *Stanley TH, Webster LR.* Anesthetic requirements and cardiovascular effects of fentanyl-oxygen and fentanyl-diazepam-oxygen anesthesia in man. Anesth Analg 1978; 57: 411–6.

106 *Anand KJS, Hickey PR.* Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. N Engl J Med 1992; 326: 1–9.

107 *Mangano DT.* Biventricular function after myocardial revascularization in humans: deterioration and recovery patterns during the first 24 hours. Anesthesiology 1985; 62: 571–7.

108 *Mehta J, Mehta P, Ostrowski N.* Increase in human platelet α_2-adrenergic receptor affinity for agonist in unstable angina. J Lab Clin Med 1985; 106: 661–6.

109 *Zilla P, Fasol R, Groscurth D, Klepetko W, Reichenspurner, Wolner E.* Blood platelets in cardiopulmonary bypass operations. J Thorac Cardiovasc Surg 1989; 97: 379–88.

110 *Breisblatt WM, Stein KL, Wolfe CJ, et al.* Acute myocardial dysfunction and recovery: a common occurrence after coronary bypass surgery. J Am Coll Cardiol 1990; 15: 1261–9.

111 *Higgins TL.* Pro: early endotracheal extubation is preferable to late extubation in patients following coronary artery surgery. J Cardiothorac Vasc Anesth 1992; 6: 488–93.

112 *Anand KJS, Sippell WG, Aynsley-Green A.* Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. Lancet 1987; 1: 243–8.

113 *Anand KJS, Kickey PR.* Pain and its effects in the human neonate and fetus. N Engl J Med 1987; 317: 1321–9.

114 *Anand KJS, Sippell WG, Schofield NM, Aynsley-Green A.* Does halothane anaesthesia decrease the metabolic and endocrine stress responses of newborn infants undergoing operation? BMJ 1988; 296: 668–72.

115 *Anand KJS, Hansen DD, Hickey PR.* Hormonal-metabolic stress responses in neonates undergoing cardiac surgery. Anesthesiology 1990; 73: 661–70.

116 *Coles JG, Watanabe T, Wilson GJ, et al.* Age-related differences in the response to myocardial ischemic stress. J Thorac Cardiovasc Surg 1987; 94: 526–34.

117 *Wittnich C, Peniston C, Ianuzzo D, Abel JG, Salerno TA.* Relative vulnerability of neonatal and adult hearts to ischemic injury. Circulation 1987; 76 (Suppl V): 156–60.

118 *Burrows FA, Steele RW, Marmer DJ, van Devanter SH, Westerman GR.* Influence of operations with cardiopulmonary bypass on polymorphonuclear leukocyte function in infants. J Thorac Cardiovasc Surg 1987; 93: 253–60.

119 *Tønnesen E, Brinkløv MM, Christensen NJ, Olesen AS, Madsen T.* Natural killer cell activity and lymphocyte function during and after coronary artery bypass grafting in relation to the endocrine stress response. Anesthesiology 1987; 67: 526–33.

120 *Besedovsky HO, del Rey AE, Sorkin E.* Immune-neuroendocrine interactions. J Immunol 1985; 135: Suppl 2: 750S–4S.

121 *Lumpkin MD.* The regulation of ACTH secretion by IL-1. Science 1987; 238: 452–4.

122 *Swartz MN.* Stress and the common cold (Editorial). N Engl J Med 1991; 325: 654–6.

123 *Siliciano D.* Con: early extubation is not preferable to late extubation in patients undergoing coronary artery surgery. J Cardiothorac Vasc Anesth 1992; 6: 494–8.

124 *Russell GN.* Total intravenous anaesthesia and postoperative sedation for cardiac surgery. *In*: Kay B (Ed.). Total Intravenous Anaesthesia. New York: Elsevier Science Publishers, 1991, 225–46.

125 *Segredo V, Caldwell JE, Matthay MA, Sharma ML, Gruenke LD, Miller RD.* Persistent paralysis in critically ill patients after long-term administration of vercuronium. N Engl J Med 1992; 327: 524–8.

126 *Coyle JP, Cullen DJ.* Anesthetic pharmacology and critical care. *In*: Chernow B. (Ed.). The Pharmacologic Approach to the Critically Ill Patient. 2nd ed. Baltimore: Williams and Wilkins, 1988, 241–53.

127 *Shapiro BA, Vender JS, Peruzzi WT.* Airway pressure therapy for cardiac surgical patients: state of the art and clinical controversies. J Cardiothorac Vasc Anesth 1992; 6: 735–48.

128 *Prakash O, Jonson B, Meij S, et al.* Criteria for early extubation after intracardiac surgery in adults. Anesth Analg 1977; 56: 703–8.

129 *Gall SA Jr, Olsen CO, Reves JG, et al.* Beneficial effects of endotracheal extubation on ventricular performance. J Thorac Cardiovasc Surg 1988; 95: 819–27.

130 *Berry AJ.* Respiratory support and renal function. Anesthesiology 1981; 55: 655–67.

131 *Quasha AL, Loeber N, Feeley TW, Ullyot DJ, Roizen MF.* Postoperative respiratory care: a controlled trial of early and late extubation following coronary-artery bypass grafting. Anesthesiology 1980; 52: 135–41.

132 *Gal TJ.* Effects of endotracheal intubation on normal cough performance. Anesthesiology 1980; 52: 324–9.

133 *Chong JL, Grebenik C, Sinclair M, Fisher A, Pillai R, Westaby S.* The effect of a cardiac surgical recovery area on the timing of extubation. J Cardiothorac Vasc Anesth 1993; 7: 137–41.

134 *Shackford SR, Virgilio RW, Peters RM.* Early extubation versus prophylactic ventilation in the high-risk patient: a comparison of postoperative management in the prevention of respiratory complications. Anesth Analg 1981; 60: 76–80.

135 *Dantzker DR, Cowenhaven WM, Willoughby WJ, Kirsh MM, Bower JS.* Gas exchange alterations associated with weaning from mechanical ventilation following coronary artery bypass grafting. Chest 1982; 82: 674–7.

136 *Zurick AM, Urzua J, Ghattas M, Cosgrove DM, Estafanous FG, Greenstreet R.* Failure of positive end-expiratory pressure to decrease postoperative bleeding after cardiac surgery. Ann Thorac Surg 1982; 34: 608–11.

137 *Pepe PE, Hudson LD, Carrico CJ.* Early application of positive end-expiratory pressure in patients at risk for the adult respiratory-distress syndrome. N Engl J Med 1984; 311: 281–6.

138 *Rozanski A, Bairey CN, Krantz DS, et al.* Mental stress and the induction of silent myocardial ischemia in patients with coronary artery disease. N Eng J Med 1988; 318: 1005–12.

139 *Gray R, Maddahi J, Berman D, et al.* Scintigraphic and hemodynamic demonstration of transient left ventricular dysfunction immediately after uncomplicated coronary artery bypass grafting. J Thorac Cardiovasc Surg 1979; 77: 504–10.

140 *Roberts AJ, Spies SM, Sanders JH, et al.* Serial assessment of left ventricular performance following coronary artery bypass grafting. J Thorac Cardiovasc Surg 1981; 81: 69–84.

141 *Levine FH, Phillips HR, Carter JE, et al.* The effect of pulsatile perfusion on preservation of left ventricular function after aortocoronary bypass grafting. Circulation 1981; 64 (Suppl II): 40–4.

142 *Stein KL, Breisblatt W, Wolfe C, Gasior T, Hardesty R.* Depression and recovery of right ventricular function after

cardiopulmonary bypass. Crit Care Med 1990; 18: 1197–200.

143 *Svedjeholm R, Ekroth R, Joachimsson PO, Ronquist G, Svensson S, Tydén H.* Myocardial uptake of amino acids and other substrates in relation to myocardial oxygen consumption four hours after cardiac operations. J Thorac Cardiovasc Surg 1991; 101: 688–94.

144 *Mansfield AO.* Alteration in fibrinolysis associated with surgery and venous thrombosis. Br J Surg 1972; 59:754–7.

145 *Britton BJ, Hawkey C, Wood WG, Peele M.* Stress – a significant factor in venous thrombosis? Br J Surg 1974; 61: 814–20.

146 *Hoffman BB, Michel T, Brenneman TB, Lefkowitz RJ.* Interactions of agonists with platelet α_2-adrenergic receptors. Endocrinology 1982; 110: 926–32.

147 *Conti CR, Mehta JL.* Acute myocardial ischemia: role of atherosclerosis, thrombosis, platelet activation, coronary vasospasm, and altered arachidonic acid metabolism. Circulation 1987; 75: (Suppl V): V84–95.

148 *Chiara O, Giomarelli PP, Biagioli B, Rosi R, Gattinoni L.* Hypermetabolic response after hypothermic cardiopulmonary bypass. Crit Care Med 1987; 15: 995–1000.

149 *Thung N, Herzog P, Christlieb II, Thompson WM Jr, Dammann JF Jr.* The cost of respiratory effort in postoperative cardiac patients. Circulation 1963; 28: 552–9.

150 *Macrae WR, Masson AHB.* Assisted ventilation in the post-bypass period. Br J Anaesth 1964; 36: 711–7.

151 *Jaffe RS, Moldenhauer CC, Hug CC Jr, Finlayson DC, Tobia V, Kopel ME.* Nalbuphine antagonism of fentanyl-induced ventilatory depression: a randomized trial. Anesthesiology 1988; 68: 254–60.

152 *Ramsay JG, Higgs BD, Wynands JE, Robbins R, Townsend GE.* Early extubation after high-dose fentanyl anaesthesia for aortocoronary bypass surgery: reversal of respiratory depression with low-dose nalbuphine. Can Anaesth Soc J 1985; 32: 597–606.

153 *Midell AI, Skinner DB, DeBoer A, Bermudez G.* A review of pulmonary problems following valve replacement in 100 consecutive patients. The case against routine use of assisted ventilation. Ann Thorac Surg 1974; 18: 219–27.

154 *Klineberg PL, Geer RT, Hirsch RA, Aukburg SJ.* Early extubation after coronary artery bypass graft surgery. Crit Care Med 1977; 5: 272–4.

155 *Lell WA, Samuelson PN, Reves JG, Strong SD.* Duration of intubation and ICU stay after open heart surgery. South Med J 1979; 72: 773–8.

156 *Lichtenthal PR, Wade LD, Niemyski PR, Shapiro BA.* Respiratory management after cardiac surgery with inhalation anaesthesia. Crit Care Med 1983; 11: 603–5.

157 *Foster GH, Conway WA, Pamulkov N, Lester JL, Magilligan DJ JR.* Early extubation after coronary artery bypass: brief report. Crit Care Med 1984; 12: 994–6.

158 *Mathru M, Rao TLK, El-Etr AA, Pifarre R.* Hemodynamic response to changes in ventilatory patterns in patients with normal and poor left ventricular reserve. Crit Care Med 1982; 10: 423–6.

159 *Hutter JA, Aps C, Hemsi D, Williams BT.* The management of cardiac surgical patients in a general surgical recovery ward. J Cardiovasc Surg 1989; 30: 273–6.

160 *Joachimsson P-O, Nyström S-O, Tydén H.* Early extubation after coronary artery surgery in efficiently rewarmed patients: a postoperative comparison of opioid anesthesia versus inhalational anesthesia and thoracic epidural analgesia. Journal of Cardiothoracic Anesthesia 1989; 3: 444–54.

161 *Jindani A, Aps C, Neville B, Sonmez B, Tun K, Williams BT.* Postoperative cardiac surgical care: an alternative approach. Br Heart J 1993; 69: 59–64.

162 *Elia S, Liu P, Chrusciel C, Hilgenberg A, Skourtis C, Lappas D.* Effects of tracheal extubation on coronary blood flow, myocardial metabolism and systemic haemodynamic responses. Can J Anaesth 1989; 36: 2–8.

163 *Elia S, Liu P, Hilgenberg A, Skourtis C, Lappas D.* Coronary haemodynamics and myocardial metabolism during weaning from mechanical ventilation in cardiac surgical patients. Can J Anaesth 1991; 38: 564–71.

164 *Paulissian R, Salem MR, Jospeh NJ, et al.* Hemodynamic responses to endotracheal extubation after coronary artery bypass grafting. Anesth Analg 1991; 73: 10–5.

165 *Hall RI, Sullivan JA.* Does cardiopulmonary bypass alter enflurane requirements for anesthesia? Anesthesiology 1990; 73: 249–55.

166 *Holley FO, Ponganis KV, Stanski DR.* Effect of cardiopulmonary bypass on the pharmacokinetics of drugs. Clin Pharmacokinet 1982; 7: 234–51.

167 *Buylaert WA, Herregods LL, Mortier EP, Bogaert MG.* Cardiopulmonary bypass and the pharmacokinetics of drugs: an update. Clin Pharmacokinet 1989; 17: 10–26.

168 *Doak GJ, Li G, Hall RI, Sullivan JA.* Does hypothermia or hyperventilation affect enflurane MAC reduction following partial cardiopulmonary bypass in dogs? Can J Anaesth 1993; 40: 176–82.

169 *Maitre PO.* Postoperative sedation with midazolam in heart surgery patients: pharmacokinetic considerations. Acta Anaesthesiol Scand Suppl 1990; 34: 103–6.

170 *Lange H, Stephan H, Rieke H, Kellermann M, Sonntag H, Bircher J.* Hepatic and extraheptic disposition of propofol in patients undergoing coronary bypass surgery. Br J Anaesth 1990; 64: 563–70.

171 *Kumar K, Crankshaw DP, Morgan DJ, Beemer GH.* The effect of cardiopulmonary bypass on plasma protein binding of alfentanil. Eur J Clin Pharmacol 1988; 35: 47–52.

172 *Snellen F, Lauwers P, Demeyere R, Byttebier G, Van Aken H.* The use of midazolam versus propofol for short-term sedation following coronary artery bypass grafting. Intensive Care Med 1990; 16: 312–6.

173 *Shapiro BA, Lichtenthal PR.* Inhalation-based anesthetic techniques are the key to early extubation of the cardiac surgical patient (Editorial). J Cardiothorac Vasc Anesth 1993; 7: 135–6.

174 *Breheny FX, Kendall PA.* Use of isoflurane for sedation in intensive care. Crit Care Med 1992; 20: 1062–4.

175 *Millane TA, Bennett ED, Grounds RM.* Isoflurane and propofol for long-term sedation in the intensive care unit. Anaesthesia 1992; 47: 768–74.

176 *Henthorn TK.* Opiate infusions. *In*: Fragen RJ (Ed.). Drug Infusions in Anesthesiology, New York: Raven Press, 1991, 85–105.

177 *Flacke JW, Bloor BC, Flacke WE, et al.* Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. Anesthesiology 1987; 67: 11–9.

178 *Robinson RJS, Brister S, Jones E, Quigly M.* Epidural meperidine analgesia after cardiac surgery. Can Anaesth Soc J 1986 33: 550–5.

179 *Hug CC Jr.* Does opioid 'anesthesia' exist? (Editorial). Anesthesiology 1990; 73: 1–4.

180 *Schwieger IM, Hall RI, Hug CC Jr.* Less than additive antinociceptive interaction between midazolam and fentanyl in enflurane-anesthetized dogs. Anesthesiology 1991; 74: 1060–6.

181 *Gammage G.* Analgesia in the intensive care unit. Problems in Anesthesia 1988; 2: 450–6.

182 *Lumb PD.* Sedatives and muscle relaxants in the intensive care unit. Critical Care – State of the Art, The Society of Critical Care Medicine 1989; 10: 145–71.

183 *Editorial.* Sedation in the intensive care unit. Lancet 1984; 1: 1388–9.

184 *Nussmeier NA, Arlund C, Slogoff S.* Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. Anesthesiology 1986; 64: 165–70.

185 *Zaidan JR, Klochany A, Martin WM, Ziegler JS, Harless DM, Andrews RB.* Effect of thiopental on neurologic outcome following coronary artery bypass grafting. Anesthesiology 1991; 74: 406–11.

186 *Allonen H, Ziegler G, Klotz U.* Midazolam kinetics. Clin Pharmacol Ther 1981; 30: 653–61.

187 *Booker PD, Beechey A, Lloyd-Thomas AR.* Sedation of children requiring artificial ventilation using an infusion of midazolam. Br J Anaesth 1986; 58: 1104–8.

188 *Mathews HML, Carson IW, Collier PS, et al.* Midazolam sedation following open heart surgery. Br J Anaesth 1987; 59: 557–60.

189 *Maitre PO, Funk B, Crevoisier C, Ha HR.* Pharmacokinetics of midazolam in patients recovering from cardiac surgery. Eur J Clin Pharmacol 1989; 37: 161–6.

190 *Crevoisier CH, Ziegler WH, Eckert M, Heizmann P.* Relationship between plasma concentration and effect of midazolam after oral and intravenous administration. Br J Clin Pharmacol 1983; 16: 51S–61S.

191 *Persson MP, Nilsson A, Hartvig P.* Relation of sedation and amnesia to plasma concentrations of midazolam in surgical patients. Clin Pharmacol Ther 1988; 43: 324–31.

192 *Fragen RJ.* Infusions of intravenous anesthetics. *In*: Fragen RJ (Ed.). Drug Infusions in Anesthesiology, New York: Raven Press, 1991, 63–84.

193 *McMurray TJ, Collier PS, Carson IW, Lyons SM, Elliott P.* Propofol sedation after open heart surgery: a clinical and pharmacokinetic study. Anaesthesia 1990; 45: 322–6.

194 *Massey NJA, Sherry KM, Oldroyd S, Peacock JE.* Pharmacokinetics of an infusion of propofol during cardiac surgery. Br J Anaesth 1990; 65: 475–9.

195 *Grounds RM, Lalor JM, Lumley J, Royston D, Morgan M.* Propofol infusion for sedation in the intensive care unit: preliminary report. BMJ 1987; 294: 397–400.

196 *Newman LH, McDonald JC, Wallace PGM, Ledingham IMcA.* Propofol infusion for sedation in intensive care. Anaesthesia 1987; 42: 929–37.

197 *Beller JP, Pottecher T, Lugnier A, Mangin P, Otteni JC.* Prolonged sedation with propofol in ICU patients: recovery and blood concentration changes during periodic interruptions in infusion. Br J Anaesth 1988; 61: 583–8.

198 *Shafer A, Doze VA, Shafer SL, White PF.* Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. Anesthesiology 1988; 69: 348–56.

199 *Adam HK, Kay B, Douglas EJ.* Blood disoprofol levels in anaesthetized patients. Correlation of concentrations after single or repeated doses with hypnotic activity. Anaesthesia 1982; 37: 536–40.

200 *Schüttler J, Kloos S, Schwilden H, Stoeckel H.* Total intravenous anaesthesia with propofol and alfentanil by computer-assisted infusion. Anaesthesia 1988; 43 (Suppl): 2–7.

201 *Tackley RM, Lewis GTR, Prys-Roberts C, Boaden RW, Dixon J, Harvey JT.* Computer controlled infusion of propofol. Br J Anaesth 1989; 62: 46–53.

202 *Glass PSA, Markham K, Ginsberg B, Hawkins ED.* Propofol concentrations required for surgery. Anesthesiology 1989; 71: A273.

203 *Ramsay MAE, Savege TM, Simpson BRJ, Goodwin R.* Controlled sedation with alphaxalone-alphadolone. BMJ 1974; 2: 656–9.

204 *Cockshott ID, Douglas EJ, Prys-Roberts C, Turtle M, Coates DP.* Pharmacokinetics of propofol during and after i.v. infusion in man. Br J Anaesth 1987; 59: 941P–2P.

205 *Kay NH, Sear JW, Uppington J, Cockshott ID, Douglas EJ.* Disposition of propofol in patients undergoing surgery. A comparison in men and women. Br J Anaesth 1986; 58: 1075–9.