Br. J. Anaesth. (1986), 58, 969–975

EFFECTS OF PROPOFOL ON CARDIOVASCULAR DYNAMICS, MYOCARDIAL BLOOD FLOW AND MYOCARDIAL METABOLISM IN PATIENTS WITH CORONARY ARTERY DISEASE

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Propofol (ICI 35 868) is a rapidly acting i.v. anaesthetic, the clinical use of which was first described by Kay and Rolly (1977). Once it became evident that, in its original Cremophor EL-formulation, the drug was associated with the risk of hypersensitivity reactions (Briggs, Clark and Watkins, 1982), it was reformulated in a soya bean emulsion.

Studies with this new emulsion formulation indicated that the haemodynamic effects were similar to those observed in association with the original Cremophor formulation (Glen and Hunter, 1984). In patients without heart disease, propofol has been shown to produce significant decreases in systolic, diastolic and mean arterial pressures which were associated with decreases in cardiac output (Prys-Roberts et al., 1983; Coates et al., 1985). Similar degrees of cardiovascular depression were seen in patients with valvular and ischaemic heart disease (Al-Khudairi et al., 1982; Aun and Major, 1984; Patrick et al., 1985). Since these changes could lead to myocardial ischaemia, they could be deleterious in patients with coronary heart disease.

This study investigated the effects of propofol as a sole anaesthetic, and in combination with fentanyl, on myocardial blood flow and myocardial metabolism in patients about to undergo coronary artery bypass surgery.

SUMMARY

The effects of propofol (emulsion formulation) on cardiovascular dynamics, myocardial blood flow and myocardial metabolism were studied in 12 patients scheduled for elective coronary artery bypass surgery. Measurements were performed with the patient awake, during steady-state maintenance anaesthesia with propofol 200 μg kg^{-1} min^{-1} at rest, and during sternotomy when the propofol was supplemented with fentanyl 10 μg kg^{-1}. Propofol alone decreased mean arterial pressure and cardiac index; heart rate was increased. Myocardial blood flow and myocardial oxygen consumption were decreased by 26% and 31%, respectively. Myocardial lactate production was seen in one patient during this period. Surgical stimulation, under propofol–fentanyl anaesthesia, led to the return of arterial pressure and heart rate towards baseline; cardiac index decreased further. Myocardial blood flow and oxygen consumption increased such that they almost achieved their baseline values. Myocardial lactate production was seen in one patient. These results suggest that propofol may on occasions, lead to myocardial ischaemia in patients with coronary artery disease, but that it is able to block the sympathetic responses to surgical stimulation when combined with a suitable analgesic.

PATIENTS AND METHODS

One female and 11 male patients scheduled for two- to three-vessel coronary artery bypass surgery were studied. They ranged in age from 42 to 56 yr and in weight from 71 to 88 kg.

The study was approved by the Göttingen

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University Human Subjects Review Committee and written informed consent was given by all patients at the time of the preoperative visit. Eight patients had a history of one previous myocardial infarction. No patient gave a history of congestive heart failure or valvular heart disease, and none demonstrated angiographic evidence of pathological left ventricular wall motion. Ejection fraction was greater than 51% and the pre-angiogram left ventricular end-diastolic pressure was less than 12 mm Hg in all patients. All patients were on maintenance doses of either calcium-channel blocking drugs (verapamil 120 mg or nifidepine 30 mg per day) or β-receptor antagonists (pindolol 15 mg per day) and nitrates (isosorbide 120 mg per day), the last doses of which were given on the morning of operation.

All patients were premedicated with flunitrazepam 2 mg by mouth, piritramide 15 mg and promethazine 50 mg i.m. 1 h before surgery. On arrival of the patient in the anaesthetic room (at 8.00 a.m.) ECG leads were attached and the following catheters were positioned percutaneously under local anaesthesia: a Goodale–Lubin catheter (7-F, USCI) into the coronary sinus via the right internal jugular vein (Seldinger technique) for measurement of myocardial blood flow and withdrawal of blood samples; a second Goodale–Lubin catheter (7-F, USCI) placed in the non-dominant radial artery for monitoring arterial pressure and for blood sampling; a thermistor-tipped, flow-directed catheter (Edwards quadruple thermodilution model no. 93A 131-7F) into the pulmonary artery via an antecubital vein for measurement of pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output; and a polyethylene catheter into the superior vena cava for administration of drugs and infusions. The position of all catheters was confirmed by fluoroscopy. Body temperature was monitored by the thermistor in the pulmonary artery catheter. Airway carbon dioxide was measured by a Normocap CO_2-Analyzer (Datex CD 102/02 Helsinki). ECG and all pressures were monitored continuously and recorded simultaneously on a 10-channel chart recorder (Hellige, Freiburg). Following baseline measurements (after 30 min of rest) anaesthesia was induced with propofol 2 mg kg^{-1}, followed by an infusion of propofol 200 μg kg^{-1} min^{-1}. Patients breathed 100% oxygen, and assisted ventilation via a face mask was used to maintain Pa_{CO_2} at 5.0–5.3 kPa as confirmed by arterial blood-gas analyses. Pancuronium 6–8 mg was administered and, following tracheal intubation, controlled ventilation with 30% oxygen and 70% air was instituted using a constant volume ventilator (Engström ER 300). After a period of 30 min a second series of measurements was performed and was followed by the administration of fentanyl 10 μg kg^{-1} to prevent the sympathetic responses to surgery. The third series of measurements was undertaken during sternotomy and sternal spread.

Measurements included: myocardial blood flow (MBF), using the argon wash-in technique (Tauchert, Kochsieck and Heiss, 1970) (coefficient of variation ±5%) with sampling of blood from the coronary sinus after inhalation of a standard concentration of argon; cardiac output (CO) by thermodilution (cardiac output computer: Fischer BN 7206); mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), and pulmonary capillary wedge pressure (PCWP) (Statham P23 IA). Before and after each measurement of myocardial blood flow samples were taken simultaneously from the coronary sinus and the radial artery and analysed for haemoglobin concentration and oxygen saturation (CO-Oximeter 282 and Lex-O_2-Con, Instrumentation Lab.), blood-gas tensions (standard electrodes, Radiometer), lactate and glucose concentrations (u.v. methods, standard test combinations, Boehringer Mannheim), free fatty acid concentrations (gas chromatography, Hewlett–Packard 5830 A), and electrolyte concentrations (absorption spectrometry, Perkin Elmer 303).

Coronary vascular resistance (CVR) was calculated as mean arterial pressure − PCWP divided by MBF. Cardiac index (CI) was calculated by dividing cardiac output by the body surface area, and stroke volume index by dividing cardiac index by heart rate. Heart rate was obtained from the electrocardiogram. Myocardial oxygen uptake ($\dot{V}m_{O_2}$) was calculated by multiplying the arterial–coronary sinus blood oxygen content difference by myocardial blood flow. Glucose, free fatty acids and lactate uptake and production, respectively, were calculated by multiplying the arterial–coronary sinus blood substrate difference by the myocardial blood flow.

Statistical analyses of the obtained data were performed using the Friedman test. $P < 0.05$ was assigned statistical significance.

TABLE I. *Haemodynamic effects of anaesthesia with propofol as the sole anaesthetic, and in combination with fentanyl. Mean values ± SD; n = 12 patients. I = Awake; II = 30 min after induction of anaesthesia with propofol 2 mg kg⁻¹ followed by an infusion of 200 μg kg⁻¹ min⁻¹; III = during sternotomy with propofol 200 μg kg⁻¹ min⁻¹ and fentanyl 10 μg kg⁻¹. Significance: P < 0.05 *I v. II **I v. III ***II v. III*

	I	II	III
Heart rate (beat min⁻¹)	65 ± 10	73 ± 12*	65 ± 12
Systolic arterial pressure (mm Hg)	139 ± 16	114 ± 22*	130 ± 15
Diastolic arterial pressure (mm Hg)	76 ± 5	73 ± 9*	80 ± 6***
Mean arterial pressure (mm Hg)	98 ± 5	83 ± 13*	93 ± 9
Mean arterial diastolic pressure (mm Hg)	84 ± 5	76 ± 11*	85 ± 11***
Mean pulmonary arterial pressure (mm Hg)	16 ± 3	14 ± 3*	14 ± 3
Pulmonary capillary wedge pressure (mm Hg)	10.9 ± 3.1	8.7 ± 2.9*	10.5 ± 2.2***
Central venous pressure (mm Hg)	5.1 ± 2.6	4.3 ± 2.2*	5.3 ± 2.5
Cardiac index (litre min⁻¹ m⁻²)	3.31 ± 0.43	2.69 ± 0.41	2.43 ± 0.54**
Stroke volume index (ml m⁻²)	51 ± 6.2	38 ± 7.5*	38 ± 8.9**
Systemic vascular resistance (mm Hg/(ml min⁻¹ kg⁻¹))	1.12 ± 0.15	1.14 ± 0.16	1.49 ± 0.38******

TABLE II. *Myocardial variables during propofol and propofol–fentanyl anaesthesia in 12 patients. Mean values ± SD. I = Awake; II = 30 min after induction of anaesthesia with propofol 2 mg kg⁻¹ followed by an infusion of 200 μg kg⁻¹ min⁻¹; III = during sternotomy with propofol 200 μg kg⁻¹ min⁻¹ and fentanyl 10 μg kg⁻¹. Significance as defined in table I*

	I	II	III
Myocardial blood flow (ml min⁻¹/100 g)	91 ± 12	67 ± 14*	83 ± 12***
Coronary vascular resistance (mm Hg/(ml min⁻¹/100 g))	0.89 ± 0.14	1.06 ± 0.17	1.08 ± 0.34**
Myocardial oxygen consumption (ml min⁻¹/100 g)	10.6 ± 1.3	7.3 ± 1.6*	8.7 ± 1.2
Arterial–coronary sinus blood oxygen content difference (vol %)	11.7 ± 1.2	11.03 ± 1.5	10.5 ± 1.4**
Arterial–coronary sinus blood glucose content difference (mg dl⁻¹)	3.25 ± 1.42	1.79 ± 0.92	2.05 ± 1.09
Arterial–coronary sinus blood lactate content difference (μmol litre⁻¹)	0.12 ± 0.09	0.07 ± 0.03	0.05 ± 0.01
Arterial–coronary sinus blood free fatty acid content difference (mmol litre⁻¹)	0.19 ± 0.07	0.27 ± 0.14	0.25 ± 0.09
Glucose uptake (mg min⁻¹/100 g)	2.76 ± 1.3	1.27 ± 0.71*	1.89 ± 0.76
Lactate uptake (μmol min⁻¹/100 g)	10.74 ± 7.79	6.02 ± 3.34	4.58 ± 4.71
Free fatty acid uptake (mmol min⁻¹/100 g)	0.15 ± 0.07	0.2 ± 0.13	0.27 ± 0.15
Lactate extraction (%)	13.9 ± 9.4	9.0 ± 6.2	5.9 ± 5.5

RESULTS

Following the induction of anaesthesia with propofol, systolic and diastolic arterial pressures decreased rapidly, while heart rate remained unchanged until laryngoscopy and intubation led to significant increases in the arterial pressures. Systolic arterial pressure increased by 16% and diastolic arterial pressure by 30% above awake baseline values. Heart rate increased by 12% and did not return to baseline until the fentanyl had been administered.

Table I shows the control values and the haemodynamic responses 30 min after the induction of anaesthesia and during sternotomy. During steady-state maintenance anaesthesia with pro-

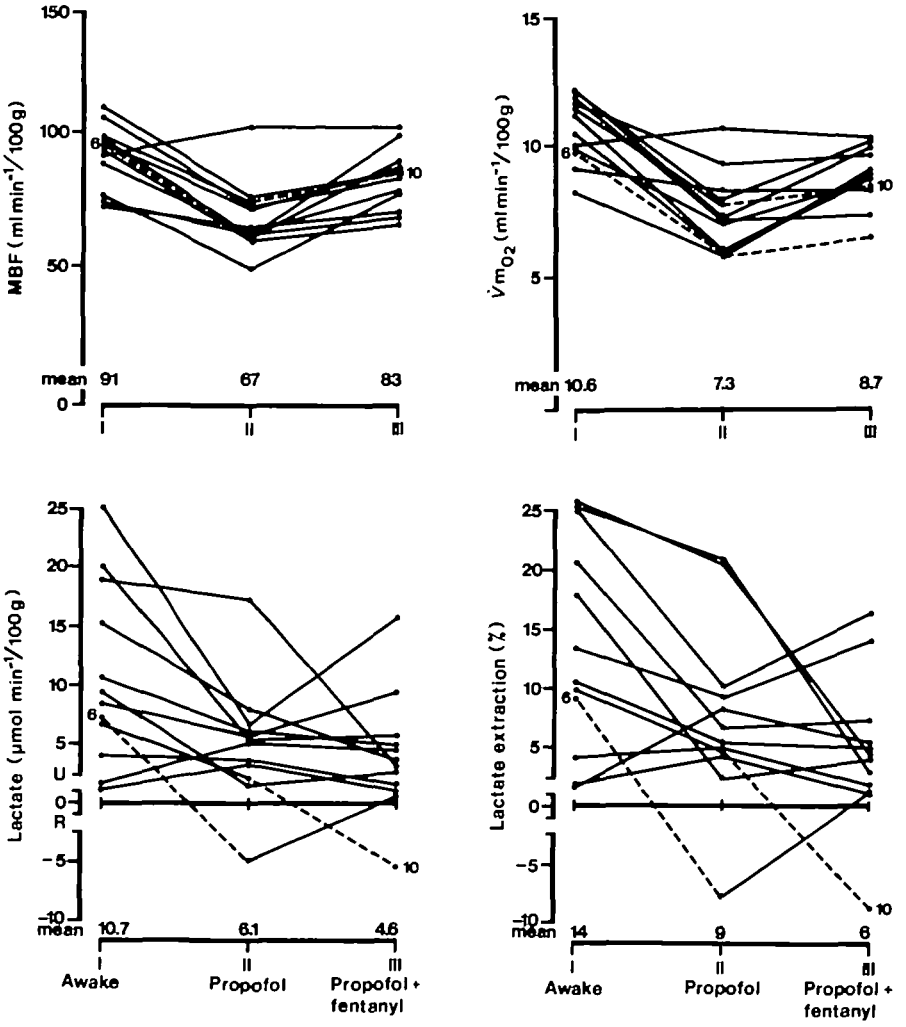

FIG. 1. Myocardial variables under propofol and propofol–fentanyl anaesthesia in 12 patients. Mean values are represented above the abscissa. I = awake; II = 30 min after induction of anaesthesia with propofol 2 mg kg^{-1} followed by an infusion of 200 μg kg^{-1} min^{-1}; III = during sternotomy with propofol 200 μg kg^{-1} min^{-1} and fentanyl 10 μg kg^{-1}. The dotted lines indicate the period of myocardial lactate release in patients 6 and 10. U = Uptake; R = release. $\dot{V}m_{O_2}$ = myocardial oxygen consumption; MBF = myocardial blood flow.

pofol, systolic arterial pressure decreased significantly by 18%, while diastolic arterial pressure decreased by only 4%. These changes resulted in a significant decrease in mean arterial pressure of 15%. Following the addition of fentanyl, surgical stimulation was associated with increases in all pressures such that they approached baseline values. Mean arterial diastolic pressure, as an indirect index of coronary perfusion pressure, decreased significantly (10%) under propofol anaesthesia, but returned to its control value during sternotomy (under propofol–fentanyl anaesthesia). Pulmonary capillary wedge pressure changed similarly. Cardiac index and stroke volume index decreased following the administration of propofol (by 19% and 25%, respectively). Stroke volume index remained unchanged during sternotomy, whereas cardiac index decreased further.

Systemic vascular resistance did not change initially, but increased significantly later (by 33%) as a result of surgical stimulation.

Although the arterial–coronary sinus blood oxygen content difference remained essentially unchanged, maintenance anaesthesia with propofol without surgical stimulation led to a significant decrease in myocardial blood flow and in myocardial oxygen consumption (by 26% and 31%, respectively) (table II). Both values increased during sternotomy under propofol–fentanyl anaesthesia, but did not achieve their baseline values. Individual values for both indices for each patient are presented in figure 1.

Coronary vascular resistance increased by 19% following the administration of propofol and did not change much thereafter in the course of the investigation.

The uptake of free fatty acids by the myocardium was increased slightly during both procedures, while glucose uptake decreased significantly under propofol and increased again during sternotomy. However, it still remained below its control value. Individual values of lactate uptake and extraction by the myocardium for all patients are shown in figure 1. Although the mean values for lactate uptake and extraction decreased progressively during the period of the study as a result of the decrease in myocardial blood flow, lactate production was observed in two patients. Lactate release from the myocardium into the coronary venous blood was seen in patient 6 30 min after induction (propofol alone) and was accompanied by a 20% decrease in mean arterial pressure. Lactate production was noted also in patient 10 during sternotomy (propofol plus fentanyl), but there was no significant change in mean arterial pressure.

Haemoglobin concentration, Pa_{O_2}, Pa_{CO_2}, acid–base measurements, electrolyte concentrations and body temperature remained within their physiological ranges throughout the period of the study.

DISCUSSION

Cardiovascular dynamics

It is difficult to compare the results of our study with those of other investigators, on account of variations in anaesthetic technique, the condition of the patients, their preoperative drug therapy and premedication. All our patients suffering from coronary heart disease were receiving β-adrenoceptor blockers or calcium-channel blocking drugs, or both, and were heavily premedicated with opioids and sedatives before the induction of anaesthesia,—all of which might have affected their cardiovascular responses to propofol as shown by Briggs and colleagues (1982). The haemodynamic responses may also have been affected by the actual dose of propofol administered (Briggs et al., 1981; Major et al., 1981). To obtain a sufficient depth of anaesthesia we gave propofol 2 mg kg^{-1} (in the new emulsion formulation) as an induction dose and followed this with a maintenance infusion of 200 μg kg^{-1} min^{-1} as recommended by Major and coworkers (1982) for total i.v. anaesthesia. As the haemodynamic response to laryngoscopy and intubation was not suppressed by propofol alone, which confirms the study of Prys-Roberts and colleagues (1983), fentanyl 10 μg kg^{-1} was given as an analgesic before the start of surgery.

However, the decreases in systolic and diastolic arterial pressures (18% and 4%, respectively) were less pronounced than those found by Prys-Roberts and colleagues (1983), who infused propofol in Cremophor EL and observed a decrease in systolic arterial pressure of 31% and of 27% in diastolic arterial pressure. Coates and colleagues (1985) noted decreases of 55% (systolic) and 33% (diastolic) during maintenance anaesthesia with propofol in emulsion. This may be attributable partly to the fact that both groups administered nitrous oxide as an analgesic, thus needing only about half of the dose of propofol by infusion that we did. Pa_{CO_2} may play a further role, as both above groups described the association of higher pressures with controlled ventilation when compared with pressures obtained during spontaneous breathing. Prys-Roberts and coworkers (1983) and Coates and associates (1985) performed their measurements mainly in spontaneously breathing patients, whose ventilation was significantly impaired in the course of the investigation, while artificial ventilation was used in our patients from the beginning of the study to maintain carbon dioxide at physiological values. The decrease in mean arterial pressure (15%) found by our group after 30 min of maintenance anaesthesia with propofol was broadly comparable to that found by Al-Khudairi and colleagues (1982) (20%) and by Patrick and coworkers (1985) (22%) in patients with coronary heart disease, and with that found by Aun and Major (1984) in patients with valvular heart disease (19%), although, in the investigations by Al-Khudairi and coworkers (1982) and Aun and Major (1984), single bolus doses of propofol either 1.5 or 2 mg kg^{-1} were administered, resulting in

the described changes of mean arterial pressure after 5 and 6 min, respectively.

The fact that arterial pressures did not exceed control values during sternotomy shows that the combination of fentanyl and propofol was more able to block the autonomic sympathetic responses to surgical stimulation than either propofol or fentanyl alone. In an earlier study, Sonntag and coworkers (1982) reported marked increases in arterial pressure and heart rate even with high doses of fentanyl.

The influence of propofol on heart rate is controversial. Prys-Roberts and colleagues (1983) and Cummings and coworkers (1984) observed minimal changes in heart rate following propofol whereas, in patients with valvular heart disease Aun and Major (1984), and in patients with ischaemic heart disease Patrick and colleagues (1985), observed decreases in heart rate. In our study, and that by Al-Khudairi and coworkers (1982) in patients with coronary heart disease, heart rate increased significantly. The reason for these differences is not clear. Like other workers (Prys-Roberts et al., 1983; Coates et al., 1985; Patrick et al., 1985), we have demonstrated a decrease in cardiac index (by 19%) following the administration of propofol and a reduction in stroke volume index (by 25%)—the degree of which was different to that noted in most studies because of the differences in heart rate.

Contrary to the findings of all these authors, who reported decreases in systemic vascular resistance, propofol did not influence systemic vascular resistance before surgery in our study. The onset of surgery was accompanied by an increase in systemic vascular resistance of 33%, while cardiac index decreased slightly—results similar to those of Coates and coworkers (1985) and Prys-Roberts and colleagues (1983), although we had used fentanyl as the analgesic instead of nitrous oxide.

Myocardial blood flow and metabolism

As yet there has been no clinical report of the effects of propofol on coronary blood flow and myocardial oxygen consumption in patients with coronary heart disease. Patrick and coworkers (1985) and Al-Khudairi and associates (1982) used the rate–pressure product (RPP) as an indirect index of myocardial oxygen consumption and noted decreases in RPP of 40% and 15%, respectively. Although a good correlation between RPP and $\dot{V}m_{O_2}$ has been demonstrated during exercise in patients with coronary heart disease (Gobel et al., 1978), the correlation is poor during anaesthesia (Reiz et al., 1981; Sonntag et al., 1982) indicating that the RPP is of limited practical value in the calculation of myocardial oxygen demand.

In our study propofol anaesthesia was associated with a significant decrease (31%) in the oxygen consumption of the left ventricle, with a corresponding decrease in myocardial blood flow (by 26%), both changes being the result of a decreased haemodynamic load on the myocardium. The arterial–coronary sinus blood oxygen content difference remained almost unchanged, while coronary vascular resistance increased by 19%. During sternotomy, myocardial blood flow and myocardial oxygen consumption increased in proportion to the increase in arterial pressure.

Although mean diastolic arterial pressure, a major influence on coronary blood flow, decreased by only 10% under the influence of propofol alone, myocardial lactate production was seen in one patient (patient 6 in figure 1), thus giving evidence of myocardial ischaemia during this period. In this patient propofol produced a decrease in mean arterial pressure of 20% and a decrease in coronary perfusion pressure of 9%, and these changes may have led to local myocardial ischaemia coincident with an impairment of coronary blood flow in areas supplied by a stenotic artery, despite the fact that there was a net increase in oxygen supply to the myocardium as a whole—as indicated by an increase in coronary venous oxygen saturation. This supports the opinion of Francis and coworkers (1982), that diastolic arterial pressure can only be a crude indicator of the adequacy of coronary blood flow during anaesthesia in patients with coronary artery disease. In contrast, in patient 10 there was evidence of lactate production by the myocardium (during sternotomy) at a time when, under propofol–fentanyl anaesthesia, all vascular pressures, and heart rate, were similar to control values. In this patient the development of myocardial ischaemia cannot be explained by changes in the haemodynamic determinants of oxygen supply. Surgical stimulation may obviously lead to a redistribution of coronary blood flow from the subendocardium to epicardial zones, resulting in regional subendocardial ischaemia in patients with coronary artery disease. The increase in coronary vascular resistance and the actual morphology of the coronary artery stenosis may

have played a role. However, the reason for the redistribution of coronary blood flow is still unknown. The myocardial oxygen and substrate supply-and-demand relationships were maintained in the other 10 patients during the entire study. Myocardial glucose uptake appeared to follow the haemodynamic changes produced by propofol at rest and by the combination of propofol and fentanyl during sternotomy, whereas the uptake of free fatty acids increased progressively. Lactate uptake decreased in all patients in line with the propofol-induced depression of cardiovascular function, but responded differently in all patients during sternotomy (fig. 1). The increase in the uptake of free fatty acids might be related to the increases in blood concentration of propofol—since it was solubilized in an emulsion. More detailed studies would be necessary to clarify this point.

In conclusion, our findings demonstrate that propofol, administered to patients with coronary artery disease, may result in some imbalance of regional myocardial oxygen demand and supply, and that the combination of propofol and fentanyl is more capable of blocking autonomic sympathetic responses to noxious stimuli than fentanyl alone. Thus propofol, if combined with a suitable analgesic and carefully adjusted to provide an appropriate depth of anaesthesia, might be useful in patients undergoing coronary artery bypass surgery. However, these conclusions are applicable only to patients not in cardiac failure.

ACKNOWLEDGEMENTS

This study was supported by the German Research Foundation, SFB 89 Cardiology Göttingen.

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