Arterial hypertension following coronary artery surgery: Influence of the narcotic agent used for anaesthesia

J.F. Hardy MD, M. Boulanger MD, J.G. MAILLÉ MD, B. Paiement MD, J. Taillefer MD, P. Sahab MD, M. Delorme MD

McIlvaine et al. reported that morphine anaesthesia ($1.5 \text{ mg} \cdot \text{kg}^{-1}$) was associated with a lower incidence of postoperative hypertension (3.8 per cent) following coronary artery bypass graft surgery (CABG), compared to 28 per cent when low dose fentanyl ($7.5\text{--}10 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$) and halogenated agents were used for anaesthesia. Since in this earlier study the relative dosage of the narcotics used could not be considered as equivalent we compared the incidence of postoperative hypertension in two groups of 24 patients operated for CABG: one group received morphine $1.5 \text{ mg} \cdot \text{kg}^{-1}$ and the other fentanyl $50 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$; these doses are considered clinically equivalent. In both groups, patients breathed a mixture of nitrous oxide oxygen (3/2). All patients had normal ventricular function. There was not a single case of postoperative hypertension in the morphine group whereas seven cases occurred in the fentanyl group (29 per cent). The incidence of preoperative hypertension was similar in both groups. During the operation, before the extracorporeal circulation, supplementation of anaesthesia to

maintain cardiovascular stability was necessary twice as often in the morphine group as in the fentanyl group (40 vs 19). These results show that morphine anaesthesia prevents postoperative hypertension in CABG; clinically equivalent doses of fentanyl do not. However, during surgery, for the period preceding the extracorporeal circulation, fentanyl seems to be preferable to morphine for the coronary patients. This work suggests that a technique combining both narcotics might be advantageous: fentanyl being used before the extracorporeal circulation and morphine during and after, to prevent the postoperative hypertension. It remains to be determined if such a combination would be effective and would not present untoward effects such as delaying recovery, prolonging intubation period and ICU stay.

Key words

ANAESTHESIA: cardiovascular, ANALGESICS: morphine, fentanyl, COMPLICATIONS: hypertension.

From the Department of Anaesthesia, Montreal Heart Institute and the Department of Anaesthesiology, University of Montreal, Faculty of Medicine, Montreal, Quebec.

Address correspondence to: Marcel Boulanger MD, Anaesthesiology Department, Montreal Heart Institute, 5000 Belanger Street East, Montreal, Quebec, Canada HIT 1C8.

The incidence of postoperative hypertension in coronary surgery has been variably reported since 1972 as between 30 and 75 per cent.¹⁻⁴ In 1977 a vigilance program set up at the Montreal Heart Institute to detect the incidence of hypertension disclosed a 3.5 per cent incidence in 200 cases of coronary surgery.

Three years later, in 1980, the same vigilance programme showed a 23.7 per cent incidence. On closer examination, it was realized that the surgical technique, the cardioplegic solution, the extracorporeal circulation time (ECC), and level of hypothermia had not changed. However, the anaesthetic technique had been modified: in 1977 all patients were anaesthetized with morphine sulfate (1.5 to $2 \text{ mg} \cdot \text{kg}^{-1}$) supplemented as needed with halogenated agents and occasionally with vasodilators.

In 1980, only one anaesthetist was still using this

technique, the others having replaced morphine with low dose fentanyl (7 to $10 \mu\text{g}\cdot\text{kg}^{-1}$) supplemented as needed by halogenated agents.

Observation of the relative incidence of hypertension according to the anaesthetic technique used showed that the anaesthetist still using morphine had one single case of hypertension in 40 patients while all the other cases were shared by the four other anaesthetists.

These findings previously reported by our group⁵ introduced the question whether the incidence of hypertension would be the same in two groups of coronary artery bypass graft patients (CABG) anaesthetized with morphine and fentanyl at clinically equivalent dosage.

The present work addresses this question and compares the incidence of postoperative hypertension in a group of 24 CABG patients receiving morphine $1.5 \text{ mg}\cdot\text{kg}^{-1}$ to a similar group receiving fentanyl $50 \mu\text{g}\cdot\text{kg}^{-1}$. These doses are considered to be clinically, but not pharmacologically equivalent (see discussion).

Methods

Forty-eight patients (24 in each group) scheduled for CABG surgery were studied between October and December 1981. Patients with poor ventricular function (ejection fraction lower than 0.5 and/or abnormal ventriculography) and those scheduled for mixed surgery, aneurysmectomy or valvular surgery were excluded. To minimize the influence of personal preferences of collaborators, the cases were distributed as equally as possible among them. The assignment of patients to either group was randomized by drawing lots.

The following protocol was followed.

(1) Preoperative visit and premedication

The preoperative visit was carried out along the usual practice of the Montreal Heart Institute.⁶ As the anaesthetic techniques proposed were common practice in our centre as in many others, the Ethics Committee of our institution was satisfied with the usual consent to surgery and anaesthesia.

On awakening, 50 mg of hydroxyzine was administered orally. At 0700 hours, morphine $0.1 \text{ mg}\cdot\text{kg}^{-1}$ (maximum 10 mg) and scopolamine 0.4 mg were administered by intramuscular injection.

On the night before operation, patients received diazepam or secobarbital and their usual nitrate and

beta-blocking therapy (most patients were receiving isosorbide dinitrate and propranolol).

(2) Operating room monitoring

Monitoring devices placed under local anaesthesia before induction included a radial artery cannula, internal jugular vein Swan-Ganz catheter and a CS5 EKG lead. Slow speed continuous recordings of the EKG, arterial pressure, pulmonary artery pressure and heart rate were made for all patients during the operation.

(3) Induction of anaesthesia

Patients received diazepam $0.3 \text{ mg}\cdot\text{kg}^{-1}$ followed by the opiate drug. Morphine was injected in increments to a maximum of $1.5 \text{ mg}\cdot\text{kg}^{-1}$ and fentanyl in drip infusion to a maximum of $50 \mu\text{g}\cdot\text{kg}^{-1}$. The infusion rate was adjusted according to the response of the patient, as assessed by blood pressure changes. For both drugs, the entire dose was administered before sternotomy. The patients were ventilated with 100 per cent oxygen and paralyzed with pancuronium $0.1 \text{ mg}\cdot\text{kg}^{-1}$. In some cases, the anaesthetist injected $1.5 \text{ mg}\cdot\text{kg}^{-1}$ of lidocaine intravenously before intubation to prevent hypertension. All supplemental medications given during the operation were recorded. After intubation, the bladder was catheterized, external jugular vein cannulated, a naso-gastric tube passed and oesophageal and rectal temperature probes inserted.

(4) Maintenance

Patients were ventilated with 40 per cent oxygen and nitrous oxide to maintain a normal PCO_2 (35 to 40 mmHg).

During the operation, no further opiate drug was administered and anaesthetic supplementation for maintenance consisted of halogenated agents and/or sodium nitroprusside and/or nitroglycerin. The priming solution of the pump and the composition of the cardioplegic solution are shown in Appendix A.

Following adequate heparinization ($300 \text{ units}\cdot\text{kg}^{-1}$ for an ACT* $> 400 \text{ sec}$), extracorporeal circulation (ECC) with non-pulsatile flow was started using a bubble oxygenator. The PCO_2 and PO_2 , corrected for temperature, were maintained within normal limits; the haematocrit was adjusted to about 22 per

*Activated Coagulation Time.

TABLE I Summary information

	<i>Fentanyl</i> (N: 24)	<i>Morphine</i> (N: 24)	<i>P</i>
<i>Population characteristics</i>			
Sex	Male 23 Female 1	Male 19 Female 5	
Weight	74.3 $\pm$ 10.5	71.6 $\pm$ 13.10	NS
Surface area	1.82 $\pm$ 0.16	1.81 $\pm$ 0.23	NS
Age	52.3 $\pm$ 23.5	43.6 $\pm$ 17.5	NS
<i>Preoperative medication</i>			
Coronary Vasodilators	21	16	NS
Beta-blockers	23	21	NS
<i>Intraoperative period</i>			
Dosage of narcotic (Mean)	46.8 μ g·kg ⁻¹	1.6 mg·kg ⁻¹	
Operation: no. of grafts	2.66 $\pm$ 1.16	3.04 $\pm$ 0.84	NS
Cardioplegic solution ml/min/clamping	23.5	22.2	NS
Minimal temperature °C	24.0	24.0	
Clamping (minutes)	59 $\pm$ 22.21	67 $\pm$ 20.35	NS
Extracorporeal circulation (minutes)	105 $\pm$ 34.83	125 $\pm$ 26.54	p < 0.05
Hematocrit %	24 $\pm$ 4.5	22.7 $\pm$ 2.8	NS

Mean $\pm$ SD.

cent and the body temperature lowered to 25° C. The myocardial temperature was reduced to about 10° C by injecting the cold cardioplegic solution at the root of the aorta and by keeping the heart bathed in iced solutions in the pericardium.

After weaning from ECC, anaesthesia was supplemented as needed with nitrous oxide, halogenated agents and/or vasodilators. The perfusate remaining in the oxygenator was reinfused to the patient in the operating room or in the intensive care unit during the following hours.

(5) Postoperative care

Ventilation was adjusted to maintain normal blood gases. Sedation and analgesia were achieved with alternating doses of diazepam 5 mg IV and morphine 5 mg IV. When the blood pressure remained above 160 mmHg systolic and/or 100 mmHg diastolic despite clinically adequate sedation and analgesia (quiet or asleep, tolerating respirator and non-shivering), sodium nitroprusside was administered to control hypertension. Postoperative hypertension was defined as a systolic blood pressure greater than 160 mmHg and/or a diastolic pressure greater than 100 mmHg. These criteria were adopted to allow comparison with other publications on the subject.^{1,5}

The measurement of the arterial blood pressure was performed as described previously.⁵

Several patients received intravenous nitroglycerin in the intensive care unit for problems related to myocardial ischaemia and not for hypertensive episodes.

Results

Table I describes the population studied: there were more females (21 per cent) in the morphine group than in the fentanyl group (four per cent). Patients in the morphine group were somewhat younger.

Surgery was uneventful in all cases; the morphine group received more grafts during a longer ECC period than the fentanyl group.

No patients in the morphine group developed postoperative hypertension whereas nine in the fentanyl group (37 per cent) experienced hypertension necessitating nitroprusside therapy, p = 0.0008 (Table II). Note that the same incidence of preoperative hypertension is observed in both groups (25 per cent).

When preoperative hypertensives are excluded from both groups, the incidence of postoperative hypertension in the fentanyl group is 33 per cent (6/18 patients; p = 0.0095 when compared with the morphine group). No preoperative hypertensive

TABLE II Incidence of postoperative hypertension

	<i>Fentanyl</i>	<i>Morphine</i>	
(1) Total population	9/24 (37%)	0/24	p = 0.0008
(2) Excluding preoperative hypertensives	6/18 (33%)	0/18	p = 0.0095
(3) Excluding patients who received IV propranolol	6/19 (32%)	0/13	p = 0.03

became hypertensive in the postoperative period in the morphine group whereas 50 per cent did so in the fentanyl group, $p = 0.09$.

Furthermore, if all patients who received IV propranolol during the operation are excluded, the incidence of postoperative hypertension is 46 per cent in the fentanyl group, $p = 0.03$ when compared to the morphine group.

The anaesthetic supplements necessary during maintenance of anaesthesia are presented in Table III. The pharmacological interventions deemed necessary were twice as numerous before ECC in the morphine group.

Table IV presents the postoperative use of vasodilators. As mentioned previously in our institution nitroglycerin is mainly used for treating or preventing myocardial ischaemia whereas sodium nitroprusside is used to treat hypertensive episodes. The doses presented for nitroglycerin are the maximum dose used at one time or another in the course of its administration. The number of patients receiving nitroglycerin and the maximal doses used did not differ significantly in both groups.

Discussion

The pathophysiology of the postoperative hypertension is unknown; different mechanisms are postulated regarding the protective action of morphine: prolonged analgesia and/or sedation, persisting venodilation in the postoperative period, action on myocardial receptors.

The results of this prospective study confirm the hypothesis previously presented by McIlvaine *et al.*⁵ that morphine anaesthesia at doses of $1.5 \text{ mg} \cdot \text{kg}^{-1}$ reduces the incidence of postoperative hypertension in CABG patients, and presents evidence that fentanyl in moderately high dose ($50 \mu\text{g} \cdot \text{kg}^{-1}$) does not offer such protection against post CABG hypertension.

The presence of preoperative hypertension does not appear to be a predisposing factor for the

TABLE III Frequency of supplementation of anaesthesia*

	<i>Fentanyl group</i>	<i>Morphine group</i>	
Before pump: Halogenated	7	15	} 40
NTG	10	17	
Inderal	2	8	
During pump: NTG	21	21	} 21
NTP	2	1	
After pump: NTG	11	5	} 11
NTP	0	1	
HAL	3	5	

*NOTE: The figures indicate the number of pharmacological interventions; some patients having more than one.

development of postoperative hypertension (Table II). The incidence of preoperative hypertension was similar in both groups, yet there is a statistically significant difference in the postoperative incidence. Excluding preoperative hypertensives from both groups preserves the significant postoperative difference.

The same remark applies to the patients who received IV propranolol. If these patients are excluded, the difference of incidence remains significant at a level of $p = 0.03$.

Several patients in both groups received IV nitroglycerin in the postoperative period, which could have prevented hypertension from developing. However, the doses used were below the level at which nitroglycerin has any arterial dilating effect.²⁶ Moreover, it was administered through polyvinyl tubing which was likely to further reduce the amount of drug reaching the patient.

It is important to note that we have used doses of narcotics which we consider clinically equivalent. Basically, we have used nitrous oxide/relaxant anaesthesia supplemented with high dose narcotics. As for the actual analgesic potency of these two

TABLE IV Use of vasodilators in postoperative period

			Maximal systolic pressure observed before treatment
Morphine group	7/14	Nitroglycerin ($0.416 \pm 0.388 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ *)	147 mmHg
	17/24	No vasodilator	
Fentanyl group	9/24	Sodium nitroprusside	216 mmHg
	9/24	Nitroglycerin ($0.39 \pm 0.33 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ *)	155 mmHg
	6/24	No vasodilator	

*Maximum dose used at any time in the course of administration.

anaesthetic managements, we could not find any published material that could allow us to make valuable comparison. To our knowledge, there is no comparable MAC BAR value for morphine and fentanyl.¹⁰ On the other hand, the analgesic potency of both drugs is reported to have such a wide range that anyone could have this choice.^{7,9-18} Because of these shortcomings, we have not tried to achieve equianalgesic management (which is impossible to prove with the available information) but rather, we have elected to compare doses that are commonly used in the clinical setting in North America. Thus we decided to use doses that appeared to us *clinically* equivalent in the light of published reports.

The use of morphine in cardiac surgery goes back to the late 1960s when Lowenstein *et al.* reported its use in patients with severe aortic valvular diseases.¹³⁻²⁵ The cardiovascular stability obtained with morphine $1 \text{ mg} \cdot \text{kg}^{-1}$ has popularized this technique. The other advantages recognized with morphine as the main anaesthetic agent were: absence of catecholamine sensitization of the myocardium as compared to halothane, easy transition to postoperative ventilatory support and prolonged postoperative sedation and analgesia.^{14,15}

This prolonged sedation and analgesia is, in our mind, desirable: early extubation has not been shown to have advantages,¹⁵ and the pain of the early postoperative period is intense and justifies heavy analgesia. This point is supported by the personal experience of an anaesthesiologist.¹⁶ However, morphine is not without undesirable features which include: hypotension,¹²⁻¹⁴ hypertension,¹⁷ cardiovascular depression when combined with nitrous oxide,²⁴ increase in circulatory catecholamines,²⁵ increase in fluid requirements,²¹

risk of awareness during anaesthesia,¹² postoperative psychosis and medullary stimulation with doses of 7 to $8 \text{ mg} \cdot \text{kg}^{-1}$.¹⁴

In the morphine group tachycardia and increased arterial pressure following intubation and sternal spreading were commonly observed in this study as indicated by the more frequent supplementation of anaesthesia with halogenated agents, nitroglycerin and/or beta-blockers. This increased number of pharmacological interventions in the pre-bypass period in patients anaesthetized with morphine as opposed to fentanyl could lead one to conclude that in this period the drugs are not equally analgesic but it also could be related to the personal biases of the participating anaesthesiologists, which were left unopposed for lack of rigid standardization of the anaesthetic technique. However, it is unlikely that these interventions would have any influence on postoperative hypertension because only short acting or volatile agents were used; as for the propranolol administered in the pre-bypass period, the doses used were so small and were administered so many hours before the postoperative observation period, that it is unlikely to have any effect on the incidence of postoperative hypertension. Indeed, when patients who received IV propranolol were excluded, the incidence of hypertension remained significant at the 0.03 level.

In the quest for the ideal agent, fentanyl has been used at very high doses.^{9,18} The intraoperative haemodynamic stability appears superior to that obtained with morphine, possibly due to better analgesia.¹¹ Fentanyl does not produce venodilation and the fluid requirements are not increased;⁷ unconsciousness, however, is not always guaranteed.⁸ Indeed, the plasma level of fentanyl falls rapidly below the level where unconsciousness

occurs even with doses greater than $75 \mu\text{g}\cdot\text{kg}^{-1}$.¹⁸ The use of a loading dose followed by a constant maintenance drip is more rational and possibly safer for the patient.²³

Previous work on postoperative hypertension and this study suggest that a technique combining morphine and fentanyl could possibly offer the best of two worlds: cardiovascular stability before the start of ECC and prevention of postoperative hypertension. The ideal doses have not been determined. When well tolerated, supplementation with nitrous oxide and/or halogenated agents can further reduce the narcotic doses and insure unconsciousness.

The ideal dose and timing of morphine administration to prevent postoperative hypertension remains to be determined. Previous work⁵ has shown a tendency (not statistically significant, however) to reduce the incidence of postoperative hypertension from 28 to 18.7 per cent when morphine was administered following ECC. The ideal moment for administering morphine would appear to be immediately before ECC, thus providing analgesia during ECC and hopefully preventing postoperative hypertension. However, it remains to be determined whether this combination will be effective in preventing postoperative hypertension, without delaying awakening; the risk of prolonging the intubation period and the ICU stay needs to be evaluated.

The ideal anaesthetic agent does not yet exist and we suggest a combination of both opiates in the overall perioperative management of CABG patients. This is currently being tested in our department.

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Résumé

Les travaux de McIlvaine et collaborateurs ont montré que l'anesthésie à base de Morphine $1.5 \text{ mg} \cdot \text{kg}^{-1}$ semble prévenir l'hypertension paroxystique post-opératoire dans la chirurgie du pontage aorto-coronarien. L'incidence observée a été de 3.8 pour cent versus 28 pour cent lorsque l'anesthésie était faite de Fentanyl à petites doses complétée par des agents halogénés.

Ce travail compare l'incidence de l'hypertension post-opératoire chez un groupe de 24 malades recevant Morphine $1.5 \text{ mg} \cdot \text{kg}^{-1}$ à un autre groupe de 24 malades recevant Fentanyl $50 \mu\text{g} \cdot \text{kg}^{-1}$ (ces doses étant considérées comme cliniquement comparables). Tous les patients recevaient d'autre part protoxyde d'azote-oxygène (3/2) et avaient une fonction ventriculaire

normale. La prémédication et la technique d'induction étaient identiques dans les deux groupes.

Résultats: On a observé aucun cas d'hypertension chez les malades recevant de la Morphine, contre 9/24 cas (37 pour cent) dans les malades du groupe Fentanyl. Notez que l'incidence d'hypertension pré-opératoire était la même dans les deux groupes.

Durant l'intervention avant la circulation extra-corporelle, on a dû intervenir pharmacologiquement (agents halogénés, Nitroglycérine, Nitroprussiate, bêta-bloquants) deux fois plus fréquemment dans le groupe Morphine que dans le groupe Fentanyl.

Conclusion: Ces résultats montrent que l'anesthésie à la Morphine possède un effet préventif de l'hypertension post-opératoire par rapport à des doses communément employées de Fentanyl. Cependant, durant la chirurgie, pour la période précédant la C.E.C., le Fentanyl apparaît supérieur à la Morphine pour l'anesthésie du malade coronarien.

Ces travaux suggèrent que la combinaison des deux morphiniques, Fentanyl avant la circulation extra-corporelle et Morphine administrée pendant et après la C.E.C., serait bénéfique en assurant la stabilité cardiovasculaire pendant l'intervention et la prévention d'hypertension paroxystique post-opératoire. Il reste à savoir si cette combinaison sera efficace et n'aura pas d'effets indésirables tels que prolongation du temps de réveil et de l'intubation post-opératoire, de même qu'un allongement du séjour aux soins intensifs.

Appendix A

Cardioplegic solution composition

Procaine 100 mg	}	500 ml Dextrose 5% in Ringer's Lactate
KCl 12 meq		
Manitol 12.5 g		
HCO ₃ - ad pH 7.40		

Oxygenator prime

1/3 DW 5%	}	2 l-2.5 l
2/3 Ringer's Lactate		