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Haemodynamic Effect of a New Vasodilator, Nicergoline,* During Sternotomy in Open Heart Surgery. *F. Prigent, C. Hubscher, G. Oksenlhendler, R. Soyer and C. Winkler.*

Avoidance of increasing afterload is important during anaesthesia for cardiac surgery. We studied the haemodynamic consequence of deliberate vasodilation during sternotomy in nine patients (mean age 57 ± 12 years, mean left ventricular ejection fraction 0.51 ± 0.09) undergoing valvular replacement. Nicergoline, a new ergol derivative, produces vasodilation (alpha blocking effect), bradycardia (central effect) and has no effect on myocardial metabolism.[1] It was given as a continuous infusion, started after induction, at a rate of 0.8 $mg \cdot kg^{-1}$/hour.

This group was compared to a control group of 12 patients (mean age 60 ± 13 years; mean left ventricular ejection fraction 0.51 ± 0.1) undergoing valvular replacement (seven patients) coronary artery bypass graft (four patients) or aneurysmectomy (one patient). Premedication was pentobarbitone sodium 60–120 mg PR., with intramuscular promethazine 1 $mg \cdot kg^{-1}$ and meperidine 1 $mg \cdot kg^{-1}$. Anaesthesia was neurolepanalgesia with droperidol 100 mg and fentanyl 2 mg in 500 ml D5W infused during 15 minutes of induction at 5 $mg \cdot kg^{-1}$/hr and then maintained at 2 $mg \cdot kg^{-1}$/hr during sternotomy. Flunitrazepam 0.25 to 0.5 mg and pancuronium bromide 0.08 $mg \cdot kg^{-1}$ were given at induction. Measurements were made before and after sternotomy in the two groups of patients.

In the control group, sternotomy did result in an increased rate-pressure product ($p < 0.01$), while cardiac index and systemic vascular resistance remained unchanged. In the nicergoline group, increase in rate pressure product was not significant. Cardiac index increased significantly ($p < 0.05$) as systemic vascular resistance decreased; volume needed to maintain adequate filling pressure was higher in this group ($p < 0.05$) as was the weight gain during operation ($p < 0.05$) and postoperative bleeding. This may be related to nicergoline platelet anti-aggregation properties.

Our study suggests that deliberate vasodilation such as produced with nicergoline may yield to increased vasoplegia, bleeding and weight gain during operation despite decrease in MVO_2 and afterload.

	HR		MAP	
	C	N	C	N
BS	62 ± 11	67 ± 8	72 ± 21	69 ± 17
AS	83 ± 23*	84 ± 20*	86 ± 17	73 ± 15
	CI		SVI	
	C	N	C	N
BS	2.8 ± 0.08	2.5 ± 0.06	46 ± 10	38 ± 11
AS	3.1 ± 0.06	3.7 ± 1.5*	39 ± 11	43 ± 10

*Sernion. Laboratories Specia.

	SVR		PCV	
	C	N	C	N
BS	24 ± 8	27 ± 7	18 ± 8	15 ± 3
AS	26 ± 7	21 ± 5	19 ± 12	15 ± 4
	RPP			
	C	N		
BS	6560 ± 2480	6480 ± 1070		
AS	10400 ± 2660**	9380 ± 3870		
Volume: ml	966 ± 160	*1180 ± 200		
Weight gain: kg	5.4 ± 0.09	*7.6 ± 2.1	*P < 0.051	
Bleeding: ml	383 ± 397	703 ± 547	**P < 0.01	

Abbreviations: C – control; N – Nicergoline; BS – before sternotomy; AS – after sternotomy; HR – heart rate; MAP – mean arterial pressure; CI – cardiac index; SVI – stroke volume index; SVR – systemic vascular resistance; PCW – pilmonary capillary wedge pressure; RPP – rate pressure product.

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Myocardial and Systemic Effects of Nitroglycerin, Given Awake and During Anaesthesia. *E. Moffitt, D. Sethna, R. Gray, J. Bussell, M. Raymond and J. Matloff.*

Intravenous nitroglycerin (NG) is used in coronary patients during anaesthesia to reduce blood pressure (BP) and rate-pressure-product (RPP). It is given orally or intravenously to awake patients for angina. Does the awake patient with cerebration and an active autonomic system react to NG differently than an anaesthetized patient?

We studied seven patients having coronary grafts, both awake, sedated and, later, after sternotomy with hypertension. With a radial needle and two thermodilution catheters (pulmonary artery and coronary sinus) we determined total coronary sinus flow (CSF), cardiac index (CI), vascular resistance (SVR), total coronary sinus flow (CSF), myocardian oxygen consumption (MVO_2) and lactate extraction. Studies were done before and after NG 100 ug/min with mean doses of 1.04 mg given in 10.6 minutes awake and 1.2 mg given in 8.2 minutes after sternotomy.

These male patients had a mean age of 57.4 years and mean surface area of 1.95 m^2. Mean ejection fraction was 70 ± 10 per cent. They were sedated with secobarbitone (214 mg) and morphine 0.25 $mg \cdot kg^{-1}$.

Five were anaesthetized with halothane and two with morphine 1.0 $mg \cdot kg^{-1}$, with oxygen.

Table I gives mean and standard errors for 12

circulatory and metabolic variables determined both awake and after sternotomy. The changes after NG given awake were compared statistically to those when NG was given during anaesthesia.

NG in awake patients increased heart rate, decreased CI and wedge pressure but not BP. SVR, RPP, CSF. Coronary sinus oxygen content and MVO_2 were unchanged. During anaesthesia, decreases were seen in BP, wedge pressure, SVR, work index, RPP and MVO_2. Coronary sinus oxygen content increased as less oxygen was taken up. Lactate extraction remained normal in both situations, so myocardial oxygen supply was not grossly deficient. Stroke work index decreased in both situations but the changes were similar. Stroke volume index decreased in the awake state but not under anaesthesia.

We conclude that the same dose of nitroglycerin is more effective in treating a hyperdynamic circulation in patients with coronary artery disease when given during anaesthesia than when awake. In both instances we found that myocardial oxygenation is well maintained.

TABLE I

COMPARISON – EFFECTS OF NITROGLYCERIN

	Awake	
Variable	PreNG	PostNG
MAP mm Hg	108 ± 3*	100 ± 6
H.R.	67 ± 7	75 ± 5
C.I.	2.80 ± 0.14	2.45 ± 0.15
SWI	76.5 ± 2.5	54.7 ± 4.5
SVI	43.2 ± 2.4	33 ± 2.3
Wedge mm Hg	14 ± 0.7	10 ± 1.1
SVR	1451 ± 112	1613 ± 147
RPP	10983 ± 920	11236 ± 1163
CSF ml/min.	92.9 ± 15.1	82.1 ± 13.2
CSO_2 Cont.	6.7 ± 0.3	6.4 ± 0.4
MVO_2 ml/min.	10.3 ± 1.2	8.8 ± 0.8
Lact.Ext.%	24.9 ± 6.2	24.9 ± 4.2

	Poststernotomy		
Variable	PreNG	PostNG	p**
MAP mm Hg	106 ± 6	72 ± 5.3	0.03
H.R.	65 ± 4.9	64 ± 5	0.04
C.I.	2.2 ± 0.21	2.4 ± 0.18	N.S.
SWI	56.6 ± 5.9	41.2 ± 2.3	N.S.
SVI	35.7 ± 5.0	38.6 ± 3.8	0.02
Wedge mm Hg	21 ± 2.2	12 ± 1.4	0.03
SVR	1947 ± 280	1168 ± 161	0.02
RPP	10238 ± 1010	6585 ± 724	0.02
CSF ml/min.	89.6 ± 10.2	69.3 ± 18.3	N.S.
CSO_2 Cont.	6.3 ± 0.6	7.4 ± 0.9	0.04
MVO_2 ml/min.	8.7 ± 1.0	5.7 ± 1.2	N.S.
Lact.Ext.%	26.5 ± 4.5	28 ± 5.4	N.S.

*Mean ± S.E.M. n – 7.

**Comparing changes when awake to after sternotomy.

Haemodynamic Responses and Serum Fentanyl Levels During Fentanyl Infusion Anaesthesia. *J.M. Sprigge, J.E. Wynands, D.G. Whalley, D. Bevan, H. Nathan, G.E. Townsend and Y. Patel.*

Introduction: It has been shown that high dose fentanyl (100 $\mu g \cdot kg^{-1}$) and oxygen produce stable haemodynamics during induction and early surgical stimulation in patients with good ventricular function undergoing aortocoronary bypass surgery (ACBP). However in the period between sternotomy and the initiation of cardiopulmonary bypass (CBP), many patients develop undesirable systemic hypertension which requires treatment. We wished to determine whether fentanyl 100 $\mu g \cdot kg^{-1}$ divided into various loading doses and infusion rates could produce more stable haemodynamics and be associated with stable serum fentanyl levels.

Methods: Thirty patients scheduled for ACBP were divided into three groups of 10, each with similar demographic data. All patients were premedicated with diazepam, morphine and scopolamine. Group 1 received fentanyl 30 $\mu g \cdot kg^{-1}$ intravenously as a loading dose followed by an infusion of 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Group 2 received 40 $\mu g \cdot kg^{-1}$ as a loading dose and an infusion of 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and Group 3 received 50 $\mu g \cdot kg^{-1}$ as a loading dose and an infusion of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. A control haemodynamic profile was obtained before induction. Haemodynamic profiles were done following the loading dose of fentanyl, which was given at the rate of 1 $mg \cdot min^{-1}$, and after tracheal intubation, skin incision, sternotomy and aortic root dissection. Blood samples for radioimmunoassay determinations of fentanyl were taken at 5, 10, 20, and 30 minutes and then half-hourly from the beginning of the induction of anaesthesia. The infusion of fentanyl was continued until the patient had received a total of 100 $\mu g \cdot kg^{-1}$ or rewarming was begun on CPB.

Results: The serum fentanyl concentrations were significantly different between Groups 1 and 3 in the 5 to 30 minute time interval. Thereafter there were no significant differences in serum concentrations of fentanyl between the groups. However, it was seen that for the first 90 minutes there appeared to be a trend for the patients who received the highest infusion rate to have the highest serum levels. Serum fentanyl levels decreased by an average of 30 per cent when CPB was instituted but returned to their approximate pre-bypass levels with 30 minutes.

No significant differences between the groups were demonstrated in the haemodynamic measurements and derived indices. In addition each event was compared to control and to the previous event within each group regardless of the addition of supplemental anaesthesia. No changes from control were noted in central venous pressure, pulmonary capillary wedge pressure or left ventricular stroke work index within any group. Significant changes in heart rate, cardiac index and systemic vascular resistance occurred in Group 1. In Group 2 significant changes were seen in heart rate, systolic blood pressure and systemic vascular resistance, while in Group 3 such changes were seen only in heart rate. Thus patients who received the highest dose of fentanyl had fewer significant haemodynamic changes.

Nine patients in Group 1, seven in Group 2, and five in Group 3 required treatment of hypertension or tachycardia.

Conclusions: We conclude that a loading dose of fentanyl 50 $\mu g \cdot kg^{-1}$ followed by an infusion of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to a total dose of 100 $\mu g \cdot kg^{-1}$ will produce a serum fentanyl level of approximately 15 $ng \cdot ml^{-1}$ before CPB. This provides haemodynamic stability in about 50 per cent of patients and produces baseline anaesthesia enabling easy control of any undesirable haemodynamic changes.

Fentanyl Infusion Anaesthesia for Patients with Poor Ventricular Function Undergoing Aortocoronary Bypass Surgery. *J.E. Wynands, P. Wong, D.G. Whalley, J. Sprigge, G. Townsend, and Y. Patel.*

Introduction: High dose fentanyl and oxygen anaesthesia has been shown to produce stable haemodynamics during induction of anaesthesia and early surgical stimulus in patients with good ventricular function undergoing aortocoronary bypass surgery (ACBP). We wished to determine if patients with poor ventricular function undergoing ACBP would differ in their haemodynamic response and serum concentrations of fentanyl from patients with good ventricular function when both groups were anaesthetized with an identical fentanyl infusion technique.

Methods: Six patients (Group 1) with poor ventricular function (ejection fraction < 0.3 and LVED > 20 torr) and ten patients (Group 2) with good ventricular function (ejection fraction < 0.45 and LVEDP > 15 torr) were studied. All patients were premedicated with diazepam, morphine and scopolamine. Anaesthesia consisted of a loading dose of fentanyl 30 $\mu g \cdot kg^{-1}$ followed by a fentanyl infusion of 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The loading dose was given at the rate of 1 $mg \cdot min^{-1}$ and the infusion was continued until rewarming was commenced on cardiopulmonary bypass. Muscle paralysis was induced with pancuronium (0.1 $mg \cdot kg^{-1}$) and the patients were ventilated with 100 per cent oxygen to normocarbia. A control haemodynamic profile was obtained before the induction of anaesthesia and repeated following induction, tracheal intubation, skin incision, sternotomy and aortic root dissection. Blood samples for serum fentanyl radioimmunoassay were obtained before the induction of anaesthesia and thereafter at 5, 10, 20, and 30 minute intervals after the beginning of the administration of fentanyl. Haemodynamic responses and serum fentanyl levels were compared in both groups.

Results: Three patients in Group 1 and nine patients in Group 2 required treatment of hypertension or tachycardia.

There was no significant difference between the groups in serum fentanyl concentrations throughout the study period. Concentrations decreased from 23.6 $ng \cdot ml^{-1}$ and 26.3 $ng \cdot ml^{-1}$ for Groups 1 and 2 respectively at five minutes to 11.7 $ng \cdot ml^{-1}$ and 11.3 $ng \cdot ml^{-1}$ respectively at 20 minutes thereafter remaining unchanged.

No difference between groups was noticed in mean arterial pressure (MAP), systolic blood pressure (SBP), stroke index (SI), systemic vascular resistance (SVR) and rate pressure product (RPP). Minor differences were noted in heart rate (HR), central venous pressure (CVP), left ventricular stroke work index (LVSWI) and pulmonary vascular resistance (PVR). Major differences occurred between groups in cardiac index (CI), mean pulmonary artery pressure (MPA), pulmonary capillary wedge pressure (PCWP) and right ventricular stroke work index (RVSWI). MPA and PCWP differed between groups at all time intervals. Differences in CI were noted in all groups at time intervals with the exception of control, and RVSWI at all time intervals with the exception of induction. The patients in Group 1 demonstrated overall haemodynamic stability for the period of the study. However minor differences were noted between time intervals and control in SI; LVSWI, and CI which decreased at aortic dissection with respect to control and LVSWI which decreased at aortic dissection from sternotomy.

Group 2, however, demonstrated more changes which reflected the greater number of patients responding to anaesthesia and surgical stimulation. HR increased after induction and remained elevated throughout. The change in HR was reflected in CI which increased with respect to control upon induction, skin incision and sternotomy. SVR and LVSWI decreased on induction and aortic dissection respectively but did not differ from control or between study periods at any other time interval.

Discussion: Patients with poor ventricular function undergoing ACBP surgery who are anaesthetized with a fentanyl infusion technique require less intervention for the treatment of hypertension and tachycardia than patients with good ventricular function anaesthetized identically. The similarity in serum fentanyl levels between the two groups would indicate similar brain concentrations of fentanyl and presumably similar depths of anaesthesia. Thus, the difference in clinical response of the two groups to stimulation may be more a function of the ability of the cardiovascular system to respond rather than depth of anaesthesia.

Intravenous Anaesthetic Agents Reversibly Depress Superoxide Dependent Chemiluminescence in Human Polymorphonuclear Leucocytes. *I.W.C. White, A.W. Gelb, H.R. Wexler and P.A. Keown.*

Normal leucocyte function, characterized by chemotactic migration, phagocytosis and the ability to kill invading organisms is important in the immunological defence against infection. Halothane has been shown to reversibly inhibit phagocytosis and killing,[1] and phagocytosis is inhibited by intravenous anaesthetic agents.[2]

A major mechanism of bacterial killing by PMNL is excited oxygen radical (EOR) generation by perturbation of the cell membrane by microbial binding. A sequence of biochemical events leads to a respiratory burst and the generation of superoxide, hydroxyl radical and hydrogen peroxide. These substances cause oxidation-reduction lysis of bacteria and cell death. This reduction of the EOR, with return of the high energy electron to the ground state, is associated with the emission of photons, and the phenomenon of chemiluminescence. We have explored whether intravenous anaesthetic agents depress leucocyte function by an effect on this system.

Leucocyte activation was achieved by C_3b receptor stimulation using opsonized Zymosan, and the magnitude and kinetic characteristics of the EOR generation was quantified by measurement of light emission with a Beckman Scintillation Counter. Within this system, the effects of the thiopentone and alfathesin on basal and stimulated EOR generation were studied.

The drugs were incubated with the leucocytes for one hour, in concentrations chosen to reflect those achieved in vivo. Following stimulation of the cells, measurements of light emission were made at 10

minute intervals for one hour. Peak activity occurred 20–30 minutes following stimulation. The area under the curve was used as an index of energy output by the cell preparation.

Basal activity was unaffected by the presence of the drugs but peak activity was depressed in a dose dependent manner. The percentage change of area under the curve shows a statistically significant ($p < 0.01$) 25 per cent depression of activity by thiopentone at 5 μg/ml and 56 per cent depression of activity by alfathesin at 1.25 μg/ml. These levels were chosen to reflect the free plasma concentration at sleep levels of anaesthesia. Extensive washing of the cells with buffered saline returned activity to that of the control cells.

These results show the depression of EOR generation by thiopentone and alfathesin. The general shape of the response curves was unchanged, suggesting that the effect is probably a generalized quenching of EOR. The site of action of these agents is unclear at the present time, but clinically the depression of EOR production reflects a decreased competence of polymorphonuclear leucocytes and may be a factor contributing to impaired host resistance in the postoperative period.

Area Under Curve

Thiopentone		Alfathesin	
Dose	% Control (± SEM)	Dose	% Control (± SEM)
100 μg/ml−	9 ± 2	2.5 μg/ml−	27 ± 4
50 μg/ml−	25 ± 5	1.25 μg/ml−	43 ± 4
25 μg/ml−	38 ± 4	0.5 μg/ml−	62 ± 5
10 μg/ml−	57 ± 6	0.25 μg/ml−	67 ± 10
5 μg/ml−	74 ± 4	0.05 μg/ml−	88 ± 7

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Error in Estimating Sensible Heat Loss from the Respiratory Tract. *F.G. King, H.J. Manson, J.W. Snellen and K.S. Chang.*

Conventionally, sensible heat loss from the respiratory tract is calculated by the product of minute volume, density of air, specific heat of air and the difference between the expired and inspired air temperature (T).[1–3] This assumes that all the expired air is at the same temperature, thus describing a square wave. In practice this cannot be so, as the initial portion of the expired temperature describes a curve.[2,3] Therefore there should be an overestimation of sensible heat loss.

Air temperature was measured continuously by a 0.122 mm copper-constantan thermocouple (60 per cent response time of 40 ms) mounted in the mouthpiece of a T-piece breathing system equipped with one way valves. Using a pneumotachograph and magnetic tape recorder, changing air temperature at the mouth and expired air volume (V_T) were recorded simultaneously while the subject breathed voluntarily at different tidal volumes (2000, 1500, 1000, 500 ml) and rates (3–18, 28–48 breaths per minute). Inspired temperatures were controlled at 12.05°C, 21.80°C and 27.74°C at a constant dewpoint temperature of 4–5°C.

Temperature-volume "loops" were constructed using a X-Y plotter. The areas of each "loop" and enclosing rectangle ($T \times V_T$) were cut out and weighed on an analytical balance. The difference was divided by the weight of the rectangle to give the percentage of overestimation of sensible heat loss. This ranged from 6.4 to 15.5 per cent. It was not affected by the inspired air temperature but increased significantly ($p < 0.001$) with decreasing V_T ($y - 13.2 - 3.21x$, where y is the per cent error and x is V_T in litres). Fast breathing further increased the error systematically by an additional two per cent over the same V_T at normal or slow breathing rates ($y - 15.2 - 2.31x$).

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Local Anaesthetics Inhibit Platelet Aggregation. *Alexander W. Gotta and Colleen A. Sullivan.*

Introduction: Local anaesthetics inhibit flux of sodium and potassium in the nerve membrane, thus impeding impulse transmission. Ionic flux in red blood cells is similarly impeded. Since maintenance of platelet membrane permeability and transmembrane flux of adenosine disphosphate and calcium are essential for platelet aggregation, local anaesthetic induced inhibition of ionic and molecular flux could decrease platelet aggregation and limit the primary haemostatic mechanism.

Methods: Twenty-seven ml of whole blood was collected from fasting healthy volunteers, with no known bleeding dyscrasia or recent exposure to drugs with anti-platelet activity. The blood was mixed with 0.11M sodium citrate 3 ml and centrifuged at 20°C for 10 minutes at 150 g. Platelet rich plasma was removed and the remaining blood was centrifuged at high speed for 25 minutes. Platelet poor plasma was then decanted. Platelet aggregation was determined by Born's turbidimetric technique using a platelet Aggregation Profiler 3 (Bio Data Corp.) measuring the response to adenosine disphosphate (ADP) 2×10^{-5} M final concentration, and collagen 0.19 mg/ml final concentration. Determination was made of total aggregation (as percentage) and the time from

introduction of collagen to the beginning of secondary aggregation. This "lag period" represents the time that platelet membrane permeability increases to the point where endogenous ADP is released. After determination of normal responses to ADP and collagen, platelet rich plasma was incubated with bupivacaine lidocaine, chloroprocaine or tetracaine at varying concentrations and response to ADP and collagen was determined again. The significance of alteration in platelet aggregation and collagen lag period was determined by Student's t test with $P < 0.05$ considered significant.

Results: Local anaesthetics induce significant decreases in ADP and collagen-induced platelet aggregation, and significant increases in collagen lag period.

PLASMA CONCENTRATION OF LOCAL ANAESTHETIC (μg/ml) INHIBITING AGGREGATION OR INCREASING LAG PERIOD

Anaesthetic	ADP	Collagen	Lag Period
Bupivacaine	250	500	150
Lidocaine	750	1500	750
Chloroprocaine	500	*	250
Tetracaine	200	200	100

*No significant inhibition up to 500 μg/ml.

Discussion: Platelet aggregation in response to ADP and collagen was significantly reduced by four local anaesthetics, but only at toxic plasma concentrations. The first indication of an alteration in platelet function induced by local anaesthetics was an increase in collagen lag period which was independent of total aggregation. This probably represents a decrease in platelet membrane permeability and inhibition of trans-membrane flux of ADP and calcium. The platelet may thus serve as a useful readily-available tool for studying local anaesthetic-induced alteration in membrane permeability which is the basic mechanism of local anaesthetic action.

Nitrous Oxide Effects on Po_2 Measurements in the Operating Room: Shift of the Oxyhaemoglobin Curve. *Louis Fournier and Diane Major.*

Since 1978,[1,2] we know that oxygen electrodes are sensitive to nitrous oxide, so that our measurements of Po_2 during anaesthesia with nitrous oxide are not as accurate as we would like.

To obviate this problem we started to measure oxygen saturation directly in our patients receiving nitrous oxide during an operation. This did not solve the question since the results were not as expected. We then asked ourselves if nitrous oxide had a significant influence on the HbO_2 curve, contrary to what has been reported to date.[3]

We selected 20 normal patients (ASA-1) scheduled to have an operation where the maintenance of anaesthesia would be a mixture of nitrous oxide and oxygen with curare, without any other inhalation agent.

We drew a blood sample from each patient before induction of anaesthesia. On this sample we did:

(1) The HbO_2 curve on an Hem-O-Scan, tonometering from 0 to 25 per cent oxygen.

(2) An HbO_2 curve using a mixture containing a constant concentration of nitrous oxide 50 per cent, carbon dioxide 5.6 per cent, tonometering from Po_2 zero to Po_2 180 mm Hg.

Before doing this curve, we offset the nitrous oxide interference on Po_2 determination by zeroing the electrode with a mixture of nitrous oxide 50 per cent, carbon dioxide 5.6 per cent and the balance nitrogen.

After 30–60 minutes of anaesthesia with nitrous oxide and oxygen a second blood sample was drawn. The same HbO_2 curves were drawn for this blood.

(3) 2,3-DPG was measured in all cases.

Results: a) The 20 patients showed a normal preoperative HbO_2 curve. b) The HbO_2 curves with 50 per cent nitrous oxide both in vivo and in vitro, were all significantly shifted to the left for a mean of 9 torr, contrary to previous published results.[3] c) The functioning fraction of 2,3-DPG[4] had a tendency to decrease and this may contribute to shift the HbO_2 curve to the left.

In conclusion we can say that nitrous oxide not only affects the Po_2 electrode to give us false Po_2 results in the operating room but also shifts the HbO_2 curve significantly to the left.

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Change in the Tympano-Ossicular System Under General Anaesthesia With Nitrous Oxide and Oxygen. *N. Normandin, L. Perreault, L. Plamondon, P. Rousseau, R. Blain, M. Girard and G. Forget.*

Abstract: An on-going study at the Maisonneuve-Rosemont Hospital has already documented the consequences of the changes in the middle ear pressure during general anaesthesia with nitrous oxide and oxygen in patients undergoing surgical treatment for the tympano-ossicular system[1] and for other types of pathology not involving the middle ear. Patients presenting Eustachian tube dysfunction and tympanic membrane abnormalities are at risk of auditory problems following general anaesthesia.[2]

Another consequence of the diffusion of nitrous oxide and oxygen in the middle ear will be discussed here. It concerns the changes in the elasticity of the tympano-ossicular system evidenced by the changes in the shape of the tympanograms used to measure the pressure peak at maximum compliance.

The middle ear system offers an opposition to the flow of acoustic energy that passes through it. This is called acoustic impedance, the opposite of which is

acoustic admittance. The value of acoustic admittance is a composite of three factors: conductance or the reciprocal of resistance (friction), susceptance or the reciprocal of reactance (sum of mass and rigidity). The acoustic impedance on the other hand can be best described by the following equation: $Z = r^2 + (2\,fm + S/2\,f)^2$ where Z is the acoustic impedance, r is friction, m is mass, S is rigidity, f is the frequency of the probe tone.

It is evident from the previous equation that when a low frequency tone (220Hz) is used to measure acoustic impedance, pathology involving the rigidity of the tympano-ossicular system can be more precisely evidenced, whereas when a high frequency tone (660Hz) is used to measure acoustic impedance, pathology involving mass of the tympano-ossicular system is more precisely evidenced.[3]

Data were analyzed according to the two kinds of measurement with two different probe tones. Results from the data available at this time on 30 subjects show, first, that the values of the acoustic admittance are highly variable from one individual to the other during general anaesthesia and, second, that the shape of the tympanograms become highly similar to the shape of the tympanograms found in patients presenting tympanic membrane abnormalities and/or ossicular luxation. These results were compared to two control groups, a surgery group which received nitrous oxide and oxygen but did not have any impedance measurement done during the operation and a non-surgery group which did not receive nitrous oxide and oxygen but had impedance measurement done at successive intervals for 90 minutes. Discussion of the results suggests that diffusion of gases in the middle ear system influences the shape of the tympanograms by changing the elastic properties of the whole system.

Finally, diffusion of gases in the middle ear system seems to induce changes in the oto-labyrinthic function in such a way that nausea and vomiting in the recovery room are more frequent in patients who present high negative pressure in the middle ear.

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A Pharmacokinetic Study of Heparin and Protamine in Relation to Heparin Rebound. *G.S. Clark, C. Castro, S.J. Teasdale, M. Grady, and M.F.X. Glynn.*

Heparin rebound is the reappearance of the anticoagulant effect of heparin 1–18 hours after its complete neutralization with protamine sulphate. The mechanism of heparin rebound is uncertain and the fate of the heparin-protamine complex in the body is unknown. Clinically, relapse into the anticoagulant state can cause significant postoperative bleeding in patients who have been sustained with extracorporeal circulation. This has prompted the present study in which the pharmacokinetics of heparin before and after combination with protamine was investigated.

Methods: Dogs anaesthetized with pentobarbitone were given ^{35}S labelled heparin 1.0 $mg \cdot kg^{-1}$. Heparin anticoagulant levels were measured by artificial substrate (Protopath) and APTY as well as scintillation counting were carried out on blood and urine samples taken before (control) and at 15 or 30 minute intervals after heparin was given. In one group of dogs, the heparin was neutralized with an equivalent dose of protamine sulphate after an interval, usually 60 minutes but also 30 minutes and 90 minutes. Blood and urine samples were tested as before neutralization. The studies were continued for 4–7 hours and, after the dogs had been killed, specimens of organs were taken for scintillation counting.

Results: In the dogs given heparin alone, blood heparin anticoagulant activity and radioactivity were highest immediately after the drug was given and declined thereafter. The same pattern of heparin elimination was observed before neutralization in the dogs given protamine. Immediately after protamine the heparin anticoagulant activity disappeared from the blood and urine, as expected, and remained near control levels. At the same time there was a sudden unexpected drop in plasma and urine radioactivity. Thus the observed plasma radioactive count 30 minutes after neutralization had fallen to 24.8 ± 9.8 per cent (S.D.) of the value predicted by extrapolating the pre-neutralization heparin elimination curve to the same time point. This change was 90 per cent complete after five minutes. Post-neutralization values either stayed near this level for the remainder of the study or rose to a higher plateau level, so mimicking the pharmacokinetic pattern seen when a drug is given by constant infusion. As urine radioactivity fell at the same time as that of plasma, loss of the label could not be attributed to increased urinary excretion. Counts of radioactivity in the organs sampled were highest in the liver and kidney, but were not high enough to suppose that the fall in plasma radioactivity could be explained by shift of the label in these organs.

Conclusion: Our results indicate that, after its formation, the heparin-protamine complex undergoes rapid compartmental shift from the plasma. At present its fate is not clear but there is no evidence to suggest that it migrates to an organ normally associated with drug storage, such as the liver. The slow return of radioactivity to the circulation indicates the release of either free or bound heparin. Although heparin activity did not return to anticoagulant levels in our experiments, nevertheless this could be the mechanism underlying heparin rebound. Further studies to identify possible storage sites for the complex will be discussed and a hypothesis proposed to explain the results.

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Prehospital Rhythm Deterioration in a System Providing Only Basic Life Support. *W.A. Tweed and N. Donen.*

A prospective survey of prehospital patients in cardiac arrest or with "high risk" symptoms was undertaken to document cardiac rhythms in these patients before arrival in hospital. Of 21 patients in cardiac arrest a tachydysrhythmia (mainly ventricular fibrillation) was found initially in 10 and was the predominant rhythm during transport in 16, while basic life support cardiopulmonary resuscitation and ventilation with oxygen were being administered. Emergency room electrocardiographic tracings revealed, however, that deterioration of cardiac rhythms had occurred so that only five remained in a tachydysrhythmia and 15 were asystolic. Eighty high risk patients with cardiorespiratory symptoms were also monitored. In this group 129 different rhythms were observed during transport, of which 34 (occurring in 26 patients) were of ventricular origin. The incidence of complex ventricular arrhythmias was significantly greater than in a similar group of control patients.

These data demonstrate that significant rhythm deterioration occurs in cardiac arrest victims when only basic life support is provided before hospital arrival. Untreated "high risk" patients also exhibit a high incidence of threatening ventricular ectopic rhythms during ambulance transport.

Fertility and Reproduction After Male Exposure to Halothane. *W.D.B. Pope and T.V.N. Persaud.*

Epidemiological and animal studies suggest that chronic exposure to an operating room environment may adversely affect pregnant women and their unborn children, resulting in an increased risk of spontaneous abortion or a child with congenital abnormalities. Anaesthetic agents are implicated as the potential cause for this possible toxicity. However, little work has been done to examine the reproductive consequences to the female of exposing males to anaesthetic agents before mating.

Male rats were exposed to halothane 50 ppm, or 1700 ppm, or air eight hours daily for 12 days, and mated two days later. The impregnated females and their litters were carefully studied. Foetuses recovered on day 20 of gestation showed no external or visceral malformations. Litter size, foetal loss and foetal weights were unaffected. Exposure of male rats to halothane before mating did not impair fertility and did not significantly affect embryonic development and foetal viability.

Etude Clinique de Differents Opiaces par Voie Sous Arachnoidienne. *C. Devaux, M.C. Roussignol, G. Oksmendler, C. Vinckler.*

Introduction: La plupart des travaux, portant sur l'administration médullaire des opiacés ne se sont attachés qu'aux effets respiratoires ± retardés et aux effets Cv. Le but de ce travail est de réaliser un étude du profil pharmacologique de différents opiacés.

Materiel et Methodes: Six séries de 15 malades porteurs de douleurs chroniques graves (métastases secondaires de cancer digestif). SID – 5 ont été choises pour cette étude, et ont reçu par voie sous arachnoidienne à dose équipotente et en solution hyperbarre les opiacés suivants: sulfate morphine, chlorhydrate de morphine, phénopéridine, fentanyl, sulfentanyl, buprénorphine. Nous avons étudié le profil de chaque drogue et les effets secondaires.

Résultats: Sont reportés sur les tableaux I et II.

TABLEAU I

Drogues	Début activité maximum	Durée activité maximum
Morphine SO_4	33 ± 6	19.5 ± 6.5
Morphine HCL	35 ± 7	18.3 ± 3.7
Phénopéridine	18 ± 3	16.5 ± 9.1
Fentanyl	8 ± 2	5.2 ± 2.3
Sulfentanyl	6 ± 1.5	6.5 ± 1.5
Buprénorphine	13 ± 4	7.2 ± 3.5

TABLEAU II

	Effets secondaires				
Drogues	Prurit	Rétention (Urinaire)	Sommeil	Nausées	Troubles (Psychi.)
Morphine	Trés souv.	constant	vieillard	Hte dose	vieillard
Phénopéridine	fréquent	Hte dose	fréquent	souvent	0
Fentanyl	fréquent	rare	0	0	0
Sulfentanyl	fréquent	rare	0	0	0
Buprénorphine	0	0	fréquent	Hte dose	0

A Double Blind Comparison of Dezocine, Butorphanol and Placebo for Postoperative Pain Relief. *B.T. Finucane, J.B. Floyd, D.J. Petro and R. Braswell.*

Dezocine (WY-16,225) is a relatively new mixed agonist/antagonist analgesic with a bridged aminotetraline structure.

The purpose of this study was to compare the safety and efficacy of single intramuscular doses of dezocine 10 mg and 15 mg with butorphanol 2 mg and placebo in the management of moderate and severe postoperative pain. Sixty-two patients of ASA physical status I or II scheduled for routine operations participated in this study. Patients were assigned to one of the four groups, using random numbers. A number of analgesic parameters were used to test the efficacy of the analgesics and the placebo. The first of these was the *pain intensity rating*. Using a simple scoring system, patients were asked to rate the pain, before administration of the unknown medication and at several intervals afterwards. The differences in pain intensity (before and after the medication) were then plotted against time. The results clearly show that all patients in active groups achieved significant relief compared to those in the placebo group ($P < 0.05$). In the paired comparisons of *active* groups, the differences were not statistically significant; however, the highest scores were achieved by the butorphanol group during and up to the first hour. The highest scores were achieved by dezocine 15 mg between the second and fifth hours. An extension of this measurement was *the sum of the pain intensity difference* scores achieved by each group during the six hour period. The results again show that scores achieved by patients in the active groups were significantly higher than those

achieved by patients in the placebo group ($P < 0.05$). In the paired analyses of the active groups, there was no significant difference between the groups. However patients in the dezocine 15 mg group achieved the highest total scores. Finally, a simple scoring system was devised to measure *pain relief*. A plot was then made of the cumulative scores achieved in each group against time. The results showed that patients who received dezocine 15 mg achieved the highest scores and those in the placebo group, the lowest. Again the scores in the latter group were significantly lower than those in the active group ($P < 0.05$).

The most common side effects reported in those receiving active medication were nausea, vomiting, sedation and dizziness. There were no adverse effects reported in the placebo group.

In conclusion, dezocine, a relatively new analgesic, was found to be at least as effective as butorphanol in the management of patients with moderate to severe postoperative pain.

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The Effectiveness of Ranitidine as a Prophylaxis Against Gastric Aspiration Syndrome. *D.H. Morison, G.L. Dunn, A.M. Fargas-Babjak, G.C. Moudgil, K.G. Smedstad and J. Woo.*

Ranitidine is a new histamine H_2 receptor blocking agent, and would appear to be more potent and longer acting than cimetidine.[1] Previous studies have shown that preoperative administration of cimetidine is partially effective in raising gastric pH to protect against aspiration syndrome. However, 10–16 per cent of patients may still have a pH of less than 2.5 at intubation.[2,3] This double-blind study compared the effectiveness of preoperative cimetidine, ranitidine, and placebo in raising gastric pH.

Methods: Institutional approval of the protocol was obtained and all patients gave written, informed consent. One hundred and ninety patients of ASA status I and II, 18 to 70 years of age and having elective operations requiring tracheal intubation were studied. They were divided into two groups. Group A – 100 patients were randomly assigned to receive either cimetidine 300 mg, ranitidine 40 mg, ranitidine 80 mg, or placebo administered intravenously one hour before operation. Group B – 90 patients were randomly assigned to receive either cimetidine 300 mg, ranitidine 150 mg, or placebo administered orally two or four hours before operation.

Narcotic and anticholinergic premedicants were avoided. Following tracheal intubation a 16 French gauge Salem naso-gastric tube was inserted. The gastric contents were aspired after tracheal intubation and also before extubation, by an observer unaware of the medication used. Volumes were recorded and pH was measured using a Fisher Accumet 320 pH meter.

Results: The groups were similar with respect to age, weight, height, and duration of fasting. The volume and pH of aspirate at the time of tracheal intubation are shown in the tables. The extubation results were similar to those at intubation. In both groups, cimetidine and ranitidine raised the gastric pH significantly compared to placebo. In Group A, ranitidine did not raise the gastric pH significantly compared to cimetidine, but in group B the gastric pH following ranitidine was significantly higher than following cimetidine ($p < 0.009$ at two hours and $p < 0.01$ at four hours). There were also fewer patients with a pH < 2.5 following ranitidine compared to cimetidine.

GROUP A

INTRAVENOUS (MEAN ± S.E.)

	Cimetidine (300 mg)	Ranitidine (40 mg)	Ranitidine (80 mg)	Placebo
Time (min)	77.0 ± 9.83	76.3 ± 5.10	64.0 ± 4.18	75.2 ± 5.50
Vol (ml)	12.1 ± 1.88	15.1 ± 3.58	15.6 ± 3.72	19.5 ± 4.07
pH	5.0 ± 0.53	5.1 ± 0.44	5.8 ± 0.41	2.2 ± 0.23
pH < 2.5	7 (35%)	4 (19%)	1 (5%)	20 (83%)

GROUP B

ORAL (MEAN ± 1 S.E.)

	Two Hour		
	Cimetidine	Ranitidine	Placebo
Time (min)	137.0 ± 2.19	136.3 ± 9.10	138.3 ± 8.33
Vol (ml)	15.9 ± 2.88	6.8 ± 1.07	20.0 ± 0.34
pH	4.0 ± 0.53	6.1 ± 0.53	2.3 ± 0.34
pH < 2.5	4 (29%)	2 (15%)	13 (87%)
	Four Hour		
	Cimetidine	Ranitidine	Placebo
Time (min)	220.7 ± 17.52	216.8 ± 23.54	203.5 ± 14.56
Vol (ml)	11.8 ± 2.99	9.8 ± 2.22	15.2 ± 3.10
pH	3.9 ± 0.54	5.8 ± 0.46	1.9 ± 0.08
pH < 2.5	4 (33%)	1 (7%)	14 (100%)

Conclusions: Preoperative ranitidine would appear to be better than cimetidine for prophylaxis against gastric aspiration syndrome.

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Oral Diazepam Premedication: Effect on Anxiety Levels and Succinylcholine-Induced Muscle Pains. *A.O. Davies.*

Introduction: Diazepam is now commonly used as an oral preoperative sedative. Small doses of intrave-

nous diazepam (0.05 mg · kg^{-1}) have been shown to reduce the muscle pains following succinylcholine (SCH) injection. Therefore, we were interested in studying the influence of oral diazepam premedication on SCH myalgias. Previous studies have been criticized for lacking standardization of the many factors believed to influence the incidence of SCH-induced muscle pains. Therefore we undertook a double-blind randomized trial of patients undergoing a single operative procedure, with a standardized anaesthetic regimen, and who were all ambulatory in the immediate postoperative period.

Method: Written informed consent was obtained from forty patients scheduled to undergo septoplasty operations. Their preoperative anxiety was scored on a scale of 0 to 3+ by the patient (subjective assessment) and by the anaesthetist (objective assessment). Ninety minutes before operation the patients received either diazepam 10 mg orally or placebo, with a sip of water.

The patient's anxiety level was assessed again in the operating room. Anaesthesia was induced with thiopentone 5 mg · kg^{-1} and succinylcholine 1 mg · kg^{-1}. The level of fasciculations and ease of tracheal intubation were noted. The trachea was sprayed with lignocaine aerosol 1 mg · kg^{-1}. After tracheal intubation anaesthesia was maintained with halothane one per cent in 66 per cent nitrous oxide. Ventilation was by IPPB with a Bain circuit (fresh gas flow of 70 ml · kg^{-1}).

Thirty to forty hours later the patients were interviewed using a fixed questionnaire to assess levels of amnesia, nausea, surgical pain and sore throat. The second last of eight questions concerned muscle pain or stiffness. If it was present, the location and intensity (scale 1 to 3+) were noted.

Results: There were no significant differences between the control and the diazepam groups in regard to age, sex distribution, presedation anxiety or ease of tracheal intubation. Only one of 20 patients treated with diazepam had increased subjective anxiety immediately before induction compared to nine placebo patients. (Chi-square $-$ 8.6, $p < 0.01$)

In the postoperative period, only three of 20 diazepam patients (15 per cent) had myalgias compared to 10 of 20 placebo patients (50 per cent), a significant difference (Chi square $-$ 5.8, $p < 0.02$). There were no significant differences in postoperative surgical pain, nausea, vomiting or recall after premedication.

Summary: In this randomized, placebo-controlled, double-blind trial of patients undergoing septoplasty operations, diazepam 10 mg taken orally as premedication had significant effects. It prevented anxiety from increasing in the preinduction period and reduced the incidence of postoperative myalgias after succinylcholine injection.

Zomepirac and Meperidine as Analgesic Premedications. *G.L. Dunn, D.H. Morison and A.M. Fargas-Babjak.*

Zomepirac sodium has been studied in the postoperative and chronic pain models and has been shown to be an effective non-narcotic analgesic. It has been shown that 100 mg of oral zomepirac is superior to parenteral morphine 8 mg in the control of postoperative pain.[1]

The objective of the present study was to compare oral zomepirac 100 mg and parenteral meperidine 75 mg as analgesic premedicants in patients undergoing surgical removal of impacted molar teeth on an outpatient basis.

Methods: Institutional approval of the protocol was obtained and all patients gave their informed, written consent. Sixty A.S.A. I patients presenting for surgical removal of impacted molars were studied and were randomly assigned to one of two premedication regimens: Group I (30 patients) received zomepirac sodium 100 mg orally and saline with atropine 0.4 mg given intramuscularly; Group II (30 patients) received oral placebo and meperidine 75 mg with atropine 0.4 mg given intramuscularly. All premedications were administered approximately 60 minutes before the operation. A double-blind design was achieved by the use of capsules and injections which were of identical appearance and labelled by number alone. A standardized anaesthetic technique was used which avoided the use of analgesic or local anaesthetic supplements.

Measurements included pain intervals using visual analogue and ordinal pain scales, both administered by one nurse-observer. Assessments were made at 2, 2.5, 3, 4, 5 and 6 hours from the time of premedication, and all side effects were noted. In the postoperative period patients were allowed additional analgesia, but a standardized regimen was employed and the time of remedication was noted. Recovery and street fitness times were assessed.

Statistical Analysis: Remedication rates were analyzed using a survival model and pain scores were compared by analysis of variance. Binary data were analyzed using the Chi-square or Fisher Exact test.

Results: Patients in each group were similar with respect to age, weight and height and there were no significant differences between the interval from premedication to induction of anaesthesia and total anaesthetic time. Postoperative remedication rates were significantly lower in the zomepirac group ($p = 0.01$). During the first three hours following termination of anaesthesia, 27 (90 per cent) patients receiving meperidine had been remedicated compared to 17 (57 per cent) of the zomepirac group ($X^2 - 8.52$, $p < 0.01$). Pain intensity scores were similar for each group during early recovery but were lower in the zomepirac patients during the later recovery period. Recovery and street fitness times tended to be longer in the meperidine group, but this difference was not statistically significant. Postoperative nausea and vomiting occurred in 11 (36 per cent) of meperidine patients and 7 (23 per cent) of zomepirac patients ($p = 0.40$), and the incidence of postoperative drowsiness was 13 and 3 per cent respectively ($p < 0.35$).

Conclusions: On the basis of remedication rates and postoperative pain levels, zomepirac appeared to be significantly more effective than meperidine in preventing postoperative pain, and would seem to have a longer duration of analgesic action. There was a tendency for the incidence of side effects to be lower with zomepirac than with meperidine. It is therefore concluded that zomepirac is preferable to meperidine for prevention of postoperative pain in dental short stay patients.

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Succinylcholine Fasciculations: Failure of Suppression by Small Doses of Dantrolene. *Henry K. Gyasi, Sylvain Delisle and David R. Bevan.*

Introduction: The depolarizing action of succinylcholine is associated with many side effects, including muscle fasciculations and postoperative myalgia. Pretreatment with small doses of non-depolarizing muscle relaxants has been used to attenuate these side effects. This is not always effective and alters the response to a given dose of succinylcholine.

Dantrolene sodium is a muscle relaxant which acts directly on skeletal muscle. When given orally in a dose of 100–150 mg preoperatively, it reduced the severity of muscle fasciculations and the incidence of muscle pains following succinylcholine.[1]

This study was undertaken to observe the effect of small intravenous doses of dantrolene on succinylcholine fasciculations and postoperative muscle pains. Dantrolene was administered in doses that would produce depression of muscle twitch response similar to the commonly used doses of non-depolarizing muscle relaxants.

Methods: Thirty patients were studied and were randomly divided into three groups: Group A received dantrolene 5 mg/70 kg, Group B 10 mg/70 kg, and Group C a placebo of normal saline. Three minutes later, anaesthesia was induced with a sleep dose of thiopentone and succinylcholine. Muscle fasciculations and tracheal intubation conditions were observed and graded. Each patient was visited on the first postoperative day and enquiries were made for the presence or absence of muscle pains.

Results: Fasciculations were mild in five patients, moderate in thirteen, severe in nine and absent in three. Intubating conditions were good in all subjects except one.

Only six patients admitted to having muscle pains unrelated to the surgical incision and these were evenly distributed between the three groups.

Conclusion: Dantrolene given intravenously in small doses was ineffective in reducing the incidence of either fasciculations or muscle pains after succinylcholine.

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ORG-NC45 As The Sole Muscle Relaxant. *A. Williams, H.K. Gyasi and D.R. Bevan.*

ORG-NC45, a monoquaternary analogue of pancuronium, is a neuromuscular blocking drug undergoing clinical trials in North America. Previous studies have shown that it is faster in onset, of shorter duration and more easily antagonized with anticholinesterases than pancuronium[1] and it has been recommended for use as the sole muscle relaxant. However, it has not been compared directly with existing drugs in clinical practice. This study was designed to compare NC45 as the single neuromuscular blocking drug with the combination of succinylcholine for tracheal intubation and pancuronium for relaxation during maintenance.

Methods: Forty patients, ASA I or II, scheduled for elective operations, were studied. Anaesthesia was induced with thiopentone and maintained with nitrous oxide and oxygen supplemented with fentanyl. Neuromuscular transmission was monitored using train-of-four stimulation. The patients were divided randomly into four groups with 10 patients in each group for choice of neuromuscular blocking regimen. Following induction of anaesthesia they received either succinylcholine, 1 $mg \cdot kg^{-1}$ or NC45 in doses of 50, 70 or 90 $\mu g \cdot kg^{-1}$ and intubation was attempted 90 seconds later, when intubating conditions were assessed on a scale of 0–3 as described by Fahey *et al.*[1] Muscle relaxation was maintained in the NC45 group with further increments of 10 $\mu g \cdot kg^{-1}$ when the first twitch of the train-of-four recovered to 10 per cent of control, and in the succinylcholine group with pancuronium, initially as a bolus of 40 $\mu g \cdot kg^{-1}$ at full recovery from succinylcholine, followed by increments of 5 $\mu g \cdot kg^{-1}$ at 10 per cent recovery. At the end of the operation neuromuscular block was antagonized with atropine 18 $\mu g \cdot kg^{-1}$ and neostigmine 36 $\mu g \cdot kg^{-1}$ at 10 per cent recovery.

Results: All patients were intubated at 90 seconds. Succinylcholine produced 100 per cent block with uniformly excellent conditions whereas the three doses of NC45 were associated with blocks of 7.5, 18.7 and 30.7 per cent and acceptable intubating conditions in only 30 per cent of patients. The overall requirements to maintain 90 per cent block with pancuronium was 1.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ compared with 1.28 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for NC45. No cumulative effects were seen with either drug during the first hour of neuromuscular blockade. Recovery of neuromuscular activity was more rapid with NC45 than pancuronium: five minutes after neostigmine the mean train-of-four recovery was 50.6 ± 2.6 per cent after NC45 compared with 41.6 ± 2.5 per cent after pancuronium ($P < 0.05$).

Conclusion: We conclude that the lack of cumulation, easy reversibility and lack of cardiovascular effects[2] suggests that NC45 has advantage over currently available non-depolarizing muscle relaxants, but that its onset of action is too slow for rapid intubation.

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Are Present Day Oropharyngeal Airways Outdated? *R.T. Williams.*

Guedel designed his oral airway in 1933 and Berman described his in 1950; both airways have been, and are, very popular. However, believing that in present day anaesthesia and resuscitation something more should be expected from an oropharyngeal airway, an airway intubator was designed in 1979. Its proximal half is cylindrical in shape and its distal half is open on the lingual surface. In addition to its designed value as an oropharyngeal airway, it has the following four advantages over other commonly used airways:

1. Partial airway obstruction despite the presence of an oral airway can be relieved by the passage of a tracheal tube through the airway intubator.
2. Suctioning of the pharynx can be effected by insertion of even a tonsil sucker through the airway intubator.
3. Indirect oral ("blind") intubation can be done easily in the awake or unconscious patient by both experienced (anaesthetists) and inexperienced (surgeons, nurses, dentists, paramedics) intubators.
4. An excellent guide is provided for fibre-optic laryngoscopy.

The technique of use of the airway in each of these four situations will be described and case examples given.

Evaluation of The Jet Injector in Paediatric Bronchoscopes. *I.A.J. Sloan and M.E. McLeod.*

The use of a venturi system of jet ventilation has been recommended as an alternative to spontaneous ventilation during bronchoscopy in children. Although this technique has been used safely, it is important to recognize that peak flow rates and inflation pressures may vary considerably with only small changes in the diameter of the injector or its angle from the axial line. These factors vary between manufacturers and it is therefore essential to investigate the characteristics of individual systems.

We compared the Hollinger bronchoscope (Pilling) with its injector of 0.89 mm internal diameter used in the axial line of the bronchoscope to the Storz bronchoscope which is equipped with an injector of 1.5 mm internal diameter that enters the instrument through a sidearm at an angle of 20 degrees to the axial line. Bronchoscopes 3.0, 4.0 and 5.0 mm diameter were assessed in a test lung at various driving pressures.

The Storz bronchoscopes produced consistently higher inflation pressures and peak flow rates at all driving pressures. In the 3.0 mm Storz bronchoscope, dangerously high inflation pressures were reached, 7.35 kPa (75 cmH_2O) with a driving pressure of only 207 kPa (30 psi), while with the Hollinger system, a maximum inflation pressure of only 3.14 kPa (32 cmH_2O) was produced with a driving pressure of 276 kPa (40 psi). To use the Storz system safely in infants, driving pressures should be maintained below 18 kPa (20 psi) or an injector of smaller diameter should be substituted.

The introduction of new injector equipment for paediatric bronchoscopy demands careful evaluation before use in infants, as small changes in the specifications may affect the safety of the system.

Physical Characteristics of Paediatric Tracheal Tubes. *B.G. Anderton and D.J. Steward.*

Paediatric tracheal tubes should be thin-walled and should conform readily to the shape of the airway but should resist kinking or compression by external pressure. Though studies have been reported of the physical characteristics of adult tracheal tubes, little information is available concerning paediatric tubes.

Methods: We have tested a range of each of 10 different models of paediatric tracheal tubes of sizes 3.0 mm–5.5 mm inclusive. The measurements included:

1. Internal diameter (I.D.) and wall thickness, from which the external diameter (E.D.) for each tube was derived.
2. External force (gram Newtons) required to compress each tube to a point at which resistance to flow is increased by 50 per cent (gram Newtons R ÷ 50).
3. The angle at which each tube kinked to produce a 50 per cent increase in resistance to flow (° bend R + 50).

Measurements 2 and 3 were made with the tracheal tubes at a temperature of 40° ± 1°C.

Results: I.D., wall thickness, and E.D. varied significantly among tubes tested of similar labelled I.D. The true calculated E.D. frequently differed from that marked on the tube.

The compressibility (gram Newtons R + 50) decreased with increasing tube size (mm I.D.) and with increasing wall thickness in similar I.D. tubes. Differing compressibility in tubes of identical I.D. and wall thickness is a function of the plastic material of the tubes which can thus be documented.

The angle at which kinking resulted in increased flow resistance (Bend R + 50) decreased with increasing tube size. This angle increased with greater wall thickness in tube of similar I.D. size.

Discussion and Conclusions: It is important to define the physical characteristics which will result in a tracheal tube with ideal clinical performance.

1. The tendency of a tube to collapse due to external pressure is determined by physical principles (Lame's Law) and the material of the tube. The standardized test which we have used can be used to document these factors for each tube.
2. The tendency of a given size tracheal tube to kink is largely determined by wall thickness; thus tracheal tube design must involve a compromise between the adequacy of the I.D., and the wall thickness. The design of improved tracheal tubes will require standardized tests to select ideal properties for plastic materials.

Potentiation of D-Tubocurarine by Isoflurane in Infants. *D.J. Steward.*

It is recognized that isoflurane potentiates the neuromuscular blocking effect of d-tubocurarine (dTc) to a greater extent than other commonly used volatile anaesthetic agents. The extent of this potentiating effect has not been reported for the newborn human nor has the reversibility of this effect on withdrawal of the volatile agent been documented.

Neuromuscular blockade was monitored in a series of infants (aged newborn to two months) following intravenous administration of dTc in a dose of 0.1 $mg \cdot kg^{-1}$. Isometric contraction of the adductor pollicis muscle was recorded by a Grass FT103C force displacement transducer. The ulnar nerve was stimulated through surface electrodes and the response to single repeated stimuli (1 Hz and 0.2 Hz) and train-of-four stimuli was recorded on a chart recorder. Measurements were made during nitrous oxide, halothane, and isoflurane anaesthesia. End-tidal carbon dioxide was recorded using a Puritan Bennett carbon dioxide monitor and sampling from the distal tip of the tracheal tube.

Results and Conclusions:

1. In infants, as in adults, isoflurane potentiates dTc to a greater extent than halothane.
2. The potentiation of dTc is reversed when isoflurane is discontinued.
3. The extent of potentiation of neuromuscular block in infants is at least as great as that seen in adults.
4. The neuromuscular block of dTc potentiated by isoflurane anaesthesia is decreased during hypocapnia.
5. Because of the marked potentiating effect of isoflurane, the initial dose of dTc administered to infants receiving this agent should be reduced to 0.1 $mg \cdot kg^{-1}$ and repeat doses given as indicated by a "block aid" monitor or similar equipment.

Post-Anaesthetic Recovery in Young Children: Morphine Infusion Compared with Halothane and Isoflurane. *H.M. Chinyanga, H. Vandenberghe, S.J. Soldin and S. MacLeod.*

After major surgery we compared the speed and degree of recovery of 25 children under five years of age (mean 3.33 ± 1.76 years) who were anaesthetized with 70 per cent nitrous oxide and 30 per cent oxygen, supplemented with one of the following:

Group I (6 patients): Continuous intravenous morphine infusion 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to achieve serum morphine level 87.3 ± 5.8 μg.[1-3]

Group II (11 patients): halothane 0.5 per cent.

Group III (8 patients): isoflurane 1.0 per cent.

All patients were paralysed with metocurine and ventilated artificially to maintain good oxygenation and normocarbia.

Recovery of consciousness, spontaneous respiration, and limp movement were scored using a modification of the postoperative recovery scoring system by Steward.[4]

A: After the effect of the muscle relaxant was adequately reversed.

B: After nitrous oxide was discontinued for five minutes.

C: After passing a suction catheter into the trachea to stimulate the carina.

D: After suctioning the oropharynx.

E: After extubation of the trachea.

The duration of the assessment period was 13.0 ± 3.7 to 15.0 ± 2.8 minutes. For Group II and III assessment of recovery began five minutes after the inhalation anaesthetic was discontinued.

Results and Comments: Recovery of spontaneous respiration occurred early in GROUPS II and III. When nitrous oxide was discontinued the three groups recovered to almost the same degree. There was no statistically significant difference between the three groups. Thereafter GROUP I and III recovered with the same speed and to about the same degree, though the latter group scored slightly better after extubation. GROUP II scored poorly in the last three assessment periods.

Conclusion: The speed and degree of postanaesthetic recovery after morphine infusion at 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and isoflurane one per cent was excellent and almost identical. The morphine group had the added advantage of not requiring immediate administration of postoperative analgesia and sedation.

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Haemodynamics of Halothane Anaesthesia Plus Fentanyl. *L. Abrams, R. Griepp, A. Ergin and M. Matsuoka.*

While a pure fentanyl anaesthetic is reported to avoid cardiac depression it may not prevent hypertension or decreased MVO_2. Halothane used alone avoids hypertension but may markedly depress the myocardium leading to decreased MVO_2, low cardiac output, hypotension and cardiac failure. The haemodynamic consequences of adding fentanyl to a halothane anaesthetic were evaluated in this study.

Ten patients for coronary artery bypass were induced with thiopentone 3 $mg \cdot kg^{-1}$ and maintained with halothane 1–1.5 per cent inspired, with pancuronium as relaxant. The data were collected during a period of minimal surgical stimulation while veins were being prepared and after the halothane had been administered for at least one hour. Measured baseline data included mean arterial pressure (MAP), systolic pressure (SP), diastolic pressure (DP), pulmonary artery diastolic (PAD), heart rate (HR), and cardiac output (CO). Stroke volume (SV) and total peripheral resistance (TPR) were computed from the measured data. An index of ejection fraction (EFI) was derived by the ratio (SV/PAD). Fentanyl 1 $\mu g \cdot kg^{-1}$ was given through the right atrial line and measurements were repeated 8–10 minutes later. This procedure was repeated as additional fentanyl was given for a total dose 2, 5, and 10 $\mu g \cdot kg^{-1}$ or until MAP fell below 8 kPa (60 torr). Statistical significance was determined

using analysis of variance for each measured or derived variable.

MAP, SP, DP all fell consistently with each dose increment and significantly over the dose range. Cardiac output did not change significantly nor was there a detectable trend ($P < 0.950$). HR, PA, PAD, and TPR decreased consistently and EFI increased consistently with each dose increment. However, the changes did not reach statistical significance due to large standard deviation and small sample size. Final dosage of 5 and 10 $\mu g \cdot kg^{-1}$ were not reached in some patients due to MAP falling below 8 kPa (60 torr). Arterial pressure rose consistently as the halothane was discontinued.

The decrease in arterial pressure during low level halothane anaesthesia when fentanyl is added appears to be dose related, beginning with small dosages. The fall in arterial pressure can be dramatic, necessitating discontinuation of the halothane. A synergistic action is suggested by the stability of arterial pressure with halothane alone and then the return toward baseline when halothane is discontinued after fentanyl administration. Decreased TPR appears to explain the arterial pressure fall as CO did not change. The stability of CO was secondary to the fall in PAD and HR being offset by the increased EFI. Fentanyl should be given with great care to patients receiving halothane.

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Site of the Selective Action of Halothane on the Peripheral Chemoreflex Arc. *R.L. Knill, A.M. Lam and J.L. Clement.*

Halothane anaesthesia in man abolishes the normal ventilatory response to isocapnic hypoxaemia, as well as responses to other physiological and pharmacological stimuli sensed by peripheral chemoreceptors.[1,2] Furthermore, halothane in subanaesthetic or sedating doses markedly reduces these responses, while having little or no effect on ventilation or the ventilatory response to added carbon dioxide. This suggests a selective action of halothane on components of the peripheral chemoreflex arc that are distinct from the central carbon dioxide reflex, i.e. peripheral chemoreceptors, their central connections, or neural circuits which modulate their input. The purpose of this study was to test the hypothesis that this action is at the peripheral chemoreceptors themselves.

The subjects were seven fit volunteers. In each, isocapnic hypoxaemia (P_{ETCO_2} 6.0 kPa) was induced and maintained steady by manipulating the composition of inhaled gas. When the subject was unaware, a small dose of halothane (0.15 per cent) was introduced in the inhaled gas to induce sedation, while isocapnic hypoxaemia was maintained.

Upon exposure to halothane, hypoxaemic-driven ventilation decreased progressively over the first minute, and the relationship of end-tidal halothane concentration to ventilatory depression at 30 and 60 seconds was nearly identical to the relationship observed during steady states of halothane sedation, i.e. after 20 minutes of inhalation.

These results indicate that the site of the selective action of halothane on the peripheral chemoreflex arc is at a tissue in which the halothane level bears a nearly constant relationship to end-tidal concentration through the early period of sedation induction and in the steady state of sedation. That tissue would require to be located within a few seconds circulatory time from the lungs and to have a very high rate of perfusion to halothane capacity ratio. The only components of the peripheral chemoreflex arc which satisfy these requirements are the peripheral chemoreceptors themselves.

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Hypertension Post-Chirurgie Cardiaque: Influence de la Conduite Péri-Opératoire. *J. Bussieres, M. Heroux, H. Joncas and P. Randour.*

Dans la littérature médicale actuelle, on publie que l'incidence d'HTA post-revascularisation se situe entre 33 et 50 pour cent suite aux remplacements valvulaires elle se situe entre 10 pour cent pour les valves aortiques et 5 pour cent pour les valves mitrales.

Dans une étude retrospective de 206 cas consécutifs, non sélectionnés, opérés entre les mois de mars et juin 1981 dans notre milieu, nous avons noté une absence d'HTA post-opératoire. Cette première série comportait 148 cas de revascularisation myocardique et 58 cas de remplacements valvulaires dont 26 aortiques, 25 mitraux et 7 mitroaortiques.

Devant ces résultats discordants avec ceux de la littérature, une étude prospective fut entreprise dans le but de découvrir des éléments pouvant expliquer l'absence de cette complication dans notre pratique. Ainsi furent pris en considérations les paramètres cliniques, biologiques, pharmacologiques et hémodynamiques au cours des périodes pré et per-opératoire, ainsi que durant les 48 premières heures post-opératoires. Cette dernière série comprend 50 cas consécutifs, non sélectionnés, opérés au cours du mois de novembre 1981 et bénéficiant de la même conduite péri-opératoires que ceux de la première série.

Les résultats préliminaires de cette série permettent de confirmer l'absence d'HTA dans la période post-opératoire. Cette série incluait 42 cas de revascularisation myocardique et huit cas de remplacement valvulaire dont quatre aortiques, trois mitraux et un mitro-aortique.

Cette différence significative entre les résultats publiés antérieurement et les nôtres semblent reliés à

notre conduite péri-opératoire en regard de ce type du chirurgie. Les éléments fondamentaux de cette approche sont:

1. La préparation psychologique du patient.
2. Le maintien des médications anti-angineuse et anti-hypertensive jusqu'au soir précédent l'intervention.
3. La prémédication comprend du dropéridol 2.5 à 5 mg i.m. associé à du diphénhydramine 10 à 20 mg i.m. administrée 46 à 60 minutes avant l'arrivée à la salle d'opération. Chez les coronariens, de la nitroglycérine en pommade à la posologie de 1 à 2 pouces est appliquée au même moment.
4. La technique anesthésique consiste en l'emploi de thiopentone, de diazépam, de fentanyl (9 à 26 $\mu g \cdot kg^{-1}$; moyenne 15.7 $\mu g \cdot kg^{-1}$) et du mélange fentanyl-dropéridol (2 à 5 ml).
5. La courte durée de ventilation mécanique post-opératoire.

Nous concluons donc que l'HTA post-chirurgie cardiaque déjà rapportée à de haute incidence par de nombreux centres peut être minimisée sinon abolie par une conduite péri-opératoire se préoccupant de tous les éléments pouvant influencer la survenue de cette terrible complication.

Reversal of Succinylcholine Tachyphylaxis with Isoflurane Anaesthesia. *F. Donati and D.R. Bevan.*

Isoflurane has been shown to potentiate non-depolarizing muscle relaxants. Succinylcholine exhibits non-depolarizing features, "dual block", after prolonged administration but the possibility of its potentiation by isoflurane has not been investigated.

Methods: Twenty adult patients, ASA I or II, scheduled for elective operations, were given thiopentone and nitrous oxide in oxygen. Anaesthesia was supplemented with isoflurane (0.75 to 1.5 per cent inspired) for ten patients and fentanyl (0.10 to 0.15 mg every 30 minutes) in the other ten. Muscle relaxation was provided by a continuous infusion of succinylcholine 0.5 per cent adjusted to keep 85 to 90 per cent neuromuscular blockade. The mechanical response of the adductor pollicis muscle to train-of-four stimulation of the ulnar nerve was recorded. All infusions lasted between 120 and 240 minutes. The neuromuscular junction was allowed to recover spontaneously for 10 minutes after the infusion was stopped and neostigmine (1.25 to 2.5 mg) was given with atropine to the patients whose train-of-four ratios did not exceed 0.5.

Results: Succinylcholine requirements increased by comparable amounts in both groups of patients. Initial infusion rates were 63 ± 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the isoflurane group and 54 ± 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the fentanyl group. These increased to maximum values of 106 ± 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 94 ± 17 $\mu g \cdot kg^{-1} \cdot min^{-1}$ respectively. However, this peak was reached after only 82 ± 8 minutes in patients receiving isoflurane, after which infusion rates decreased to a mean value of 61 ± 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at the end of the infusion. This decrease in succinylcholine requirement did not occur in patients anaesthetized with nitrous oxide-fentanyl, whose infusion rate continued to increase. Non-depolarizing block was more pronounced with isoflurane. Nine of ten patients given isoflurane but only three of ten who received fentanyl had only one visible twitch (out of four) at the end of the infusion. Train-of-four ratios after 10 minutes of spontaneous recovery were much smaller with isoflurane (14 ± 6 per cent) than fentanyl (54 ± 8 per cent).

Discussion: Although tachyphylaxis was observed with isoflurane, it was followed by a period of increased sensitivity to succinylcholine. This corresponds to the establishment of profound non-depolarizing blockade. Two explanations, which are not mutually exclusive, could account for this "reversal of tachyphylaxis". It may be an intrinsic property of succinylcholine which would be observed with nitrous oxide-fentanyl anaesthesia if the infusion were sufficiently prolonged to allow full development of non-depolarizing blockade. It seems more likely, however, that during profound non-depolarizing blockade, isoflurane potentiates succinylcholine as it does tubocurarine, pancuronium and gallamine.

The Anti-Arrhythmic Effects of Verapamil and Propranolol in Aminophylline Toxic Dogs. *Robert M. Friesen and Jorge F. Bonet.*

Phosphodiesterase inhibition, stimulation of catecholamine synthesis and release, as well as altered calcium kinetics, are actions of aminophylline possibly responsible for its arrhythmogenic properties. These cardiac effects can result in potentially lethal arrhythmias. In an effort to better understand these arrhythmogenic properties and to provide a more rational approach to pharmacological management, we explored the usefulness of the calcium blocker verapamil and the beta adreno-receptor blocker propanolol in aminophylline toxic dogs. Verapamil was studied because of its effects on calcium kinetics mediated by cyclic AMP.

Method: Eighteen dogs were intubated and ventilated after induction of anaesthesia with pentobarbitone 30 $mg \cdot kg^{-1}$ and pancuronium 0.1 $mg \cdot kg^{-1}$. Electrocardiogram, arterial blood pressure and left ventricular pressure were monitored continuously. Cardiac output and systemic vascular resistance, calcium, arterial blood gases and serial aminophylline levels were measured. All animals were rendered toxic by aminophylline infusion, an initial dose of 50 $mg \cdot kg^{-1}$ over five minutes with subsequent doses of 10 $mg \cdot kg^{-1}$ over 30 seconds. Twenty minutes after each aminophylline infusion, the dog was challenged with phenylephrine 10 to 20 $\mu g \cdot kg^{-1}$. This resulted in hypertension of short duration and reproducible emergence of ventricular arrhythmias. The dogs continued to receive additional aminophylline infusion until these arrhythmias became persistent for longer than a 120 second observation period. Arrhythmias were defined as frequent PVC's, ventricular tachycardia, or ventricular fibrillation. The dogs were divided into three groups of six animals each. Group I (control) received no anti-arrhythmics whereas Group II received verapamil 0.2 $mg \cdot kg^{-1}$ and Group III received propranolol 0.1 $mg \cdot kg^{-1}$ for the treatment of persistent ventricular arrhythmias.

Results: All dogs in Group I died of ventricular arrhythmias when the serum aminophylline level reached 152 ± 23.3 mg per cent (mean ± SD). There was no statistically significant difference between the serum aminophylline level at the time of persistent ventricular arrhythmias in all three groups. In Group

II, these arrhythmias were promptly terminated by verapamil. Apart from its anti-arrhythmic effect, verapamil produced a fall in blood pressure (−33 per cent) and systemic vascular resistance. In Group III, propranolol resulted in rapid but partial arrhythmia control. Three dogs required additional doses of propranolol. No significant haemodynamic changes other than heart rate were seen in this group. Subsequent challenge with phenylephrine could not re-institute these arrhythmias in Group II while transient ventricular ectopics were seen in four dogs in Group III.

Discussion: Verapamil and propranolol exerted an anti-arrhythmic effect in aminophylline-induced ventricular arrhythmias. The efficacy of verapamil was independent of a reduction in blood pressure and systemic vascular resistance as subsequent phenylephrine-induced hypertension could not re-institute these arrhythmias. Propranolol appeared less effective since it did not completely suppress the arrhythmias in three dogs and could not prevent emergence of PVC's in four after repeat phenylephrine challenge. Although mechanisms of anti-arrhythmic action remain speculative, these observations suggest that verapamil, and perhaps propranolol, hold promise in pharmacological management of aminophylline-induced cardiac arrhythmias.

Hypertension Post-Opératoire en Chirurgie de Pontage Coronarien: Incidence en Fonction du Morphinique Employé. *J.F. Hardy, M. Boulanger, J.G. Maille, J. Taillefer, P. Sahab and M. Delorme.*

Les travaux de McIlvaine et collaborateurs ont montré que l'anesthésie à base de morphinique 1.5 $mg \cdot kg^{-1}$ semble prévenir l'hypertension paroxystique post-opératoire dans la chirurgie du pontage 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 halogènes.[1]

Ce travail compare l'incidence de l'hypertension post-opératoire chez un groupe de 24 malades recevant morphine 1.5 $mg \cdot kg^{-1}$ à un autre groupe de 24 malades recevant fentanyl 50 $\mu g \cdot kg^{-1}$ (ces doses étant considérées comme équipotentes). 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: Hypertension post-opératoire: On n'a observé aucun cas d'hypertension chez les malades recevant de la morphine contre sept cas sur 24 dans les malades du groupe fentanyl (29.1 pour cent).

Produit fréquence × pression: A la suite de l'intubation, le produit fréquence × pression a augmenté au delà de 13000 dans six cas sur 23 (26 pour cent) dans le groupe morphine et en aucun cas sur 24 dans le groupe fentanyl.

Durant l'intervention avant la CEC, on a dû employer la nitroglycérine dans 17 cas sur 24 (70 pour cent) dans le groupe morphine et dans 10 cas sur 24 (41 pour cent) dans le groupe fentanyl.

De même on a jugé bon d'employer l'inderal dans sept cas sur 24 (29.1 pour cent) dans le groupe morphine et deux sur 24 (8.3 pour cent) dans le groupe fentanyl.

Conclusion: Ces résultats montrent que l'anesthésie à la morphine posséde un effet préventif de l'hypertension paroxystique post-opératoire par rapport à des doses équipotentes de fentanyl.

Que durant la chirurgie pour la période précédent la circulation extra-corporelle, le fentanyl apparaît supérieur à la morphine pour l'anesthésie du malade coronarien.

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The Effect of Metocurine and Metocurine-Pancuronium Combination on Intraocular Pressure. *A.J. Cunningham, C. Patrick Kelly, James Farmer and A.G. Watson.*

The patient undergoing ocular surgery presents special problems. Satisfactory surgical conditions require a stationary eye; intraoperative coughing, bucking and vomiting must be avoided; intraocular pressure rises, which can cause extrusion of globe contents, must be avoided. Choice of muscle relaxant is of paramount importance. The ideal relaxant should be potent, with a rapid onset and appropriate duration of action, and be readily reversible. In addition autonomic and cardiovascular side effects should be minimal.

Metocurine, a non-depolarizing neuromuscular blocking agent, has been recently reintroduced into clinical practice. In doses of 0.3 $mg \cdot kg^{-1}$ metocurine produced 96.1 mean twitch height depression within 4.8 ± 0.6 (SEM) minutes[1] allowing easy tracheal intubation. Metocurine offers the clinically advantageous cardiovascular effects of stable heart rate and mean blood pressure. Combination of metocurine and pancuronium produces potentiation of neuromuscular blocking effect so that administration of small doses of both drugs, pancuronium 0.18 $mg \cdot kg^{-1}$ and metocurine 0.072 $mg \cdot kg^{-1}$, produces clinically effective neuromuscular blockade with stable haemodynamic parameters and rapid reversal of neuromuscular blockade.[2]

This study was designed to examine the effects of metocurine 0.3 $mg \cdot kg^{-1}$ and metocurine 0.08 $mg \cdot kg^{-1}$ plus pancuronium 0.02 $mg \cdot kg^{-1}$ combination on intraocular pressure and to assess their suitability for patients undergoing ocular surgery. Thirty-nine male and female subjects aged 16–50 years undergoing elective minor surgical procedures were studied. The patients were allocated to two treatment groups.

Treatment Group 1: (N-20) Each patient was induced with sodium thiopentone 3–5 $mg \cdot kg^{-1}$ and metocurine 0.3 $mg \cdot kg^{-1}$.

Treatment Group 2: (N-19) Each patient was induced with sodium thiopentone 3–5 $mg \cdot kg^{-1}$ and metocurine 0.08 $mg \cdot kg^{-1}$ plus pancuronium 0.02 $mg \cdot kg^{-1}$.

The time interval between relaxant administration and complete peripheral nerve twitch suppression was recorded and the degree of vocal cord relaxation was evaluated at the time of intubation using the criteria of Lund and Stovner.[3]

Intraocular pressure was recorded, using a portable

Perkins applanation tonometer, on arrival in the operating room (control) and every two minutes for a total of 10 minutes following relaxant administration.

The results of the study showed that metocurine 0.3 $mg \cdot kg^{-1}$ produced satisfactory to excellent intubating conditions in 4.5 (±.83 S.E.) minutes. Intraocular pressure was reduced to 70 per cent of control level at two and four minutes after induction. A slight rise occurred at six minutes which returned to 70 per cent of control level at eight and ten minutes. The metocurine-pancuronium combination group produced satisfactory to excellent intubating conditions in 4.37 ± .71 minutes. Intraocular pressure was reduced to 75 per cent of control values two minutes after relaxant administration and, despite a rise between the 4th and 8th minutes, intraocular pressure remained below control values. This study demonstrates that metocurine and metocurine-pancuronium combination, given as a relaxant with sodium thiopentone produces a pattern of intraocular stability which is highly desirable for elective intraocular surgery. The delayed onset of sufficient paralysis for tracheal intubation, 4.5 ± .83 minutes for metocurine and 4.37 ± .71 minutes for the combination would make these techniques unsuitable for emergency ocular surgery because of the long time interval when the airway is unprotected.

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Ventilatory Compensation for Continuous Loads During Halothane Anaesthesia in Man. *C.A. Moote, R.L. Knill and J.L. Clement.*

Ventilatory impedance or "loaded breathing" has been widely studied only in awake subjects. Surgical patients may experience a variety of loads created by preoperative disease states, anaesthetic equipment and surgical positioning. We have studied ventilatory compensation for continuous loads during anaesthesia.

Elastic loads were constructed from rigid drums of various sizes, linearized flow resistive loads from layers of wire mesh and sponge. Eighteen subjects were studied during steady state halothane 1.1 MAC anaesthesia. In each subject we tested the responses to both an elastic and a flow resistive load of small, medium or large size, i.e. loads which reduced initial tidal volume approximately 10, 30 or 50 per cent respectively. Loads were applied to the airway during inspiration only and continued for five minutes while halothane levels were maintained constant and $F_{I_{O_2}}$ greater than 0.05. Ventilation was measured with a pneumotachograph and with chest wall magnetometers.

With the addition of each load we observed an initial reduction of ventilation followed by progressive compensation to a new steady state of ventilation over two or three minutes. After five minutes of loading, $\dot{V}_{CO_2}$ and arterial halothane levels were unchanged from control. There were no consistent changes in the relative contributions of the rib cage and diaphragm to ventilation at any time during addition of loads. Steady state values of $\dot{V}_I$ and P_{aco_2}, control and after five minutes of continued loading are given in the table below (means ± S.E.M.). P_{ao_2} values remained greater than 135 torr.

Compensation for continuous loads was unexpectedly good; indeed for small and medium loads it was complete. This is difficult to explain on the basis of altered chemical drive alone, since there were no detectable change of P_{aco_2} values in the steady loaded state with small and medium loads. Furthermore, upon removal of the loads ventilation increased transiently above control values, a response which was also inexplicable on the basis of chemical drive. This suggests that other factors, reflex or neuromuscular in nature, played a role in stabilizing ventilation during loads.

ELASTIC LOADS

Load Size	Small	Medium	Large
(cm H_2O/l)	(4.0 ± 0)	(17.0 ± 2.0)	(57.0 ± 14.0)
$\dot{V}_I$ (l/min · m^2)			
Control	3.8 ± 0.2	3.5 ± 0.2	3.3 ± 0.1
Loaded	3.6 ± 0.2	3.4 ± 0.3	2.6 ± 0.1*
P_{aco_2} (torr)			
Control	48.2 ± 1.5	44.5 ± 1.6	45.5 ± 2.2
Loaded	48.3 ± 1.9	45.4 ± 1.5	51.1 ± 2.3*

RESISTIVE LOADS

Load Size	Small	Medium	Large
(cm H_2O/l · s^{-1})	(7.0 ± 0.1)	(20.0 ± 3.0)	(100.0 ± 25.0)
$\dot{V}_I$ (l/min · m^2)			
Control	3.8 ± 0.2	4.0 ± 0.4	3.5 ± 0.2
Loaded	3.8 ± 0.2	3.6 ± 0.2	3.0 ± 0.1*
P_{aco_2} (torr)			
Control	48.1 ± 1.4	44.4 ± 1.6	45.0 ± 1.7
Loaded	48.3 ± 1.3	44.8 ± 1.5	49.3 ± 1.8*

*Significantly different from control values. $P < 0.01$

Haemodynamic Effects of Intravenous Nitroglycerin in Patients with Coronary Artery Disease. *W.A.C. Mutch, J.D. Culligan and I.R. Thomson.*

Introduction: Previous reports of the haemodynamic effects of intravenous nitroglycerin infusion may be invalid because the investigators infused nitroglycerin by delivery systems containing polyvinyl chloride (PVC) plastic. Adsorption of nitroglycerin (NTG) to PVC results in reduced delivery of nitroglycerin.[1] We employed a delivery system free of PVC to assess the haemodynamic effects of intravenous nitroglycerin 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in awake premedicated patients with coronary artery disease.

Methods: Twenty patients about to undergo myocardial revascularization entered a randomized double-blind study comparing the haemodynamic

effects of intravenous nitroglycerin (n9) vs placebo (P) (n11). All patients had angina unresponsive to medical management. Patients were fasted and had nitrates withheld from midnight of the day of the operation. Following premedication with diazepam 0.15 $mg \cdot kg^{-1}$ by mouth and intramuscular morphine 0.1 $mg \cdot kg^{-1}$ and atropine 0.007 $mg \cdot kg^{-1}$, nasal oxygen (3 l/min) was administered. Intravenous, radial artery and thermodilution pulmonary artery catheters were inserted under local anaesthesia. Electrocardiograph leads V5 and II were monitored continuously. Haemodynamic variables were measured before and after 20 minutes of intravenous NTG/P infusion. Infusions were administered by a Sage pump from a polypropylene syringe with polyethylene tubing connected to a Teflon catheter in a peripheral vein. Haemodynamic effects of NTG and P were compared by Student's t test.

Results: (See Table). The P and NTG groups did not differ before infusion for any haemodynamic variable. After 20 minutes of NTG/P infusion significant differences were noted between groups. Nitroglycerin caused significant decreases in MAP, MPAP, PCWP, CVP, and CI compared to P. DPTI/SPTI was improved by NTG.

Discussion: Intravenous NTG 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ produced significant haemodynamic effects, including myocardial oxygen supply/demand ratio at a dose below that previously reported to cause minimal haemodynamic changes.[1,2] The apparent potency of NTG in our study is a direct result of the exclusion of PVC plastic from our intravenous delivery system. Used in this way, intravenous NTG is a potent vasodilator which must be administered cautiously. Reports of haemodynamic effects of intravenous NTG should not be accepted unless details of administration techniques are provided.

	Pre-Infusion	
	P	NTG
HR beats/min	64.6 ± 2.3	60.9 ± 4.2
MAP (torr)	101.5 ± 3.6	106.1 ± 4.8
MPAP (torr)	22.8 ± 2.5	20.8 ± 1.9
PCWP (torr)	13.2 ± 1.9	13.6 ± 1.3
CVP (torr)	6.8 ± 1.3	7.9 ± 1.5
CI ($l \cdot min^{-1}/m^2$)	2.8 ± 0.16	2.42 ± 0.10
SI (ml/m^2)	43.6 ± 2.2	40.3 ± 1.3
SVRI ($dynes \cdot sec \cdot m^2/cm^5$)	2757 ± 185	3276 ± 189
PVRI ($dynes \cdot sec \cdot m^2/cm^5$)	275.4 ± 30.9	234.9 ± 15.7
RPP	9699 ± 572	9672 ± 797
DPTI/SPTI	0.99 ± 0.07	1.16 ± 0.11
	20 Minutes	
	P	NTG
HR beats/min	7.04 ± 2.2	65.3 ± 4.3
MAP (torr)	105.7 ± 3.1	93.0 ± 4.7*
MPAP (torr)	23.1 ± 2.7	13.6 ± 1.7*
PCWP (torr)	14.7 ± 2.7	7.7 ± 1.2*
CVP (torr)	6.8 ± 1.0	3.6 ± 1.0*
CI ($l \cdot min^{-1}/m^2$)	2.90 ± 0.16	2.38 ± 0.14*
SI (ml/m^2)	41.3 ± 2.4	36.9 ± 2.1
SVRI ($dynes \cdot sec \cdot m^2/cm^5$)	2841 ± 229	3025 ± 132
PVRI ($dynes \cdot sec \cdot m^2/cm^5$)	244.4 ± 24.6	200.5 ± 26.4
RPP	10760 ± 519	9449 ± 804
DPTI/SPTI	0.91 ± 0.07	1.34 ± 0.11*

*$p \leq 0.05$ vs. placebo.

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Haemodynamic Effects of Intra-Aortic Versus Intravenous Protamine for Reversal of Heparin in Swine. *Kent H. Rogers, Brian Milne and Tomas A. Salerno.*

A recent report[1] and our own clinical experience have shown that hypotension caused by intravenous (IV) protamine sulphate for neutralization of heparin may be prevented by intra-aortic (IA) administration of the drug. To investigate this difference we studied the haemodynamic effects of IA versus IV protamine in the pig model. Two groups of five pigs (one IV and one IA) were anaesthetized with thiopentone, nitrous oxide, oxygen and halothane. Twenty minutes after heparinization (3 $mg \cdot kg^{-1}$) the following haemodynamic parameters were measured: heart rate (HR), arterial pressure (AP), pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure, left ventricular end-diastolic pressure (LVEDP) and cardiac output (CO). Protamine 3 $mg \cdot kg^{-1}$ was injected over 30 seconds either intravenously (IV) or into the ascending aorta (IA) as in our clinical practice. Following injection the above measurements were repeated at 60 seconds, 2.5, 5 and 15 minutes.

Results: In both groups statistically significant decreases in cardiac output and marked increases in

		HR (beats/min)	Systolic AP (mm Hg)	Systolic PAP (mm Hg) ‡
pre-protamine				
	IV	148 ± 16*	146 ± 9	35.2 ± 4.1
	IA	137 ± 9	160 ± 6	34.0 ± 1.9
post-protamine				
60 sec.	IV	156 ± 19	160 ± 22	62.8 ± 2.9
	IA	148 ± 11	135 ± 18	60.8 ± 4.8
2.5 min.	IV	162 ± 20	158 ± 6	60.5 ± 5.0
	IA	150 ± 11	174 ± 10	48.7 ± 6.6
50. min.	IV	167 ± 17	166 ± 9†	49.8 ± 5.9
	IA	158 ± 16	132 ± 11†	46.2 ± 1.7
15 min.	IV	158 ± 15	167 ± 9†	37.8 ± 4.6
	IA	143 ± 16	134 ± 9†	35.2 ± 2.3

		LVEDP (mm Hg)	CO l/min. ‡	SVR dynes/sec. cm^{-5}	PVR dynes/sec. cm^{-5}
promatamine					
	IV	15.6 ± 1.9	3.20 ± 0.24	3328 ± 227	371 ± 113
	IA	20.0 ± 5.1	20.0 ± 5.1	2882 ± 213	187 ± 54
post-protamine					
60 sec.	IV	16.7 ± 2.4	2.74 ± 0.31	3941 ± 1030	1018 ± 228
	IA	18.0 ± 1.9	2.11 ± 0.17	3685 ± 459	1234 ± 134
2.5 min.	IV	20.3 ± 3.2	3.15 ± 0.13	3903 ± 649	885 ± 218
	IA	20.7 ± 0.9	2.40 ± 0.4	4060 ± 887	730 ± 117
5.0 min.	IV	17.2 ± 0.9	2.63 ± 0.12	3819 ± 568	673 ± 176
	IA	19.4 ± 1.8	3.03 ± 0.39	2913 ± 172	563 ± 74
15 min.	IV	15.4 ± 1.0	3.36 ± 0.41	3465 ± 567	391 ± 123
	IA	17.0 ± 2.0	3.17 ± 0.16	2358 ± 82	181 ± 13

* = mean ± standard error of mean.
† = significant difference between IA and IV ($p < 0.05$ Student's t-test).
‡ = significant difference between baseline and post-protamine (analysis of variance).

PAP (IV 78 per cent, IA 79 per cent) and PVR occurred at 60 seconds. The intra-aortic group showed a statistically significant drop in systolic blood pressure at five and 15 minutes compared to the intravenous group.

Conclusion: We conclude that, in contrast to the apparent effect in humans, intra-aortic injection of protamine does not prevent the haemodynamic changes associated with the intravenous route. The mechanism for the marked elevation of PAP and PVR is unknown but may indicate either the release of a vasoactive substance or a direct vascular effect. In addition, the marked increase in PAP seen in pigs has not been observed in humans (research in progress).

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High Dose Fentanyl Infusion and Renin Response in Open Heart Surgery. *G. Townsend, J.E. Wynands, D.G. Whalley, D. Bevan, Y. Patel.*

Introduction: Despite the advent of high dose narcotic techniques undesirable hypertensive episodes continue to occur in patients undergoing coronary artery bypass graft surgery. The renin-angiotensin system has been implicated as a mediator of hypertension during this surgery. We wished to determine whether a continuous fentanyl infusion would attenuate adverse haemodynamic responses and if the renin-angiotensin system was associated with hypertensive episodes.

Methods: Twelve patients with comparable preoperative demographic data undergoing elective cardiac revascularization operations were studied. Premedication consisted of diazepam, morphine, and hyoscine. Supplemental oxygen was given en route to the operating room. Beta blockers and nitrates were continued to the time of operation. A haemodynamic profile and blood for plasma renin determination were obtained before induction of anaesthesia and after tracheal intubation, skin incision, sternotomy, and aortic dissection. Blood for plasma renin determination was subsequently obtained at regular intervals or before therapeutic intervention for the treatment of hypertensive episodes. Plasma for fentanyl assay was taken at intervals of 5, 10, 20, 30, 45, 60, 90 and 120 minutes. All patients were pre-oxygenated and then anaesthesia was induced with fentanyl 75 $\mu g \cdot kg^{-1}$ at a rate of 1 $mg \cdot min^{-1}$ and paralysis was produced with pancuronium 0.15 $mg \cdot kg^{-1}$. Six of twelve patients received no additional fentanyl (Bolus Group). The remaining six patients received additional fentanyl 0.75 $\mu g \cdot kg^{-1} \cdot min^{-1}$ by infusion until either time of rewarming on cardiopulmonary bypass (CPB) or a cumulative dose of 200 $\mu g \cdot kg^{-1}$ had been given (Infusion Group). Normocarbia was maintained throughout.

Results: In the period before CPB an increase of systolic blood pressure greater than 20 per cent of preinduction levels was considered an adverse response necessitating therapeutic intervention. Five

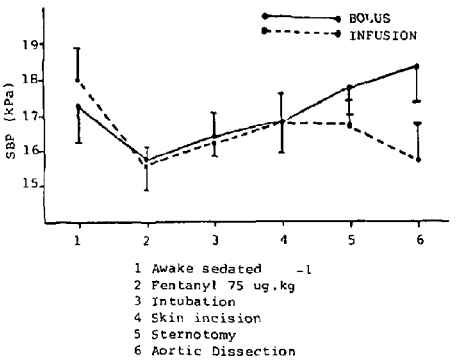

FIGURE 1

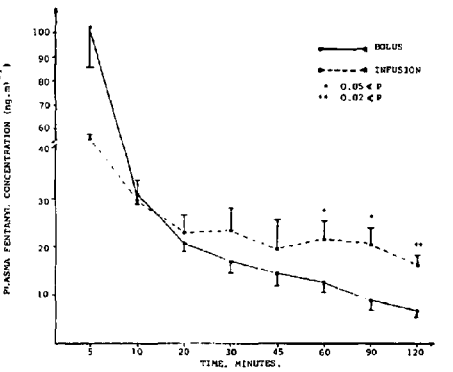

FIGURE 2

of six patients in the bolus group versus one of the six in the infusion group required such intervention. Comparison of mean systolic blood pressures revealed a tendency to lower levels in the infusion group (Figure 1).

A mean arterial pressure on CPB greater than 13.3 kPa (100 mm Hg) at a flow rate of 1.8 $l \cdot m^2$ was considered unacceptable hypertension and was treated. All of the bolus group required treatment and one of the infusion group. Mean plasma fentanyl concentrations were greater in the infusion group from 20 minutes on, reaching statistical significance at 60 minutes. (Figure 2). Mean plasma renin values, although within normal limits, were greater in the bolus group than in the infusion group. There was no correlation of peak plasma renin values with hypertension in any patient.

Conclusions: A loading dose of fentanyl 75 $\mu g \cdot kg^{-1}$ followed by an infusion of 0.75 $\mu g \cdot kg^{-1} \cdot min^{-1}$ provided a more haemodynamically stable anaesthetic with fewer additional pharmacological interventions when compared to a loading dose alone. Higher mean plasma fentanyl concentrations resulted in lower mean renin values. This study strongly suggests that hypertension encountered during aorto-coronary bypass surgery in patients under fentanyl anaesthesia is not due to the renin-angiotensin system.