THE CARDIOVASCULAR EFFECTS OF KETAMINE USED FOR INDUCTION OF ANAESTHESIA IN PATIENTS WITH VALVULAR HEART DISEASE

H. SPOTOFT, J.D. KORSHIN, M. BREDGAARD SØRENSEN AND P. SKOVSTED

KETAMINE has been shown to cause cardiovascular stimulation, which has been attributed to both sympathetic stimulation,[1,2] and a vagolytic action.[3,4] Because of its cardiovascular stimulation, ketamine has been recommended for induction of anaesthesia in poor-risk patients,[5] as well as in patients with cardiac disease and/or circulatory insufficiency.[6] Recent reports have shown that ketamine increases pulmonary vascular resistance in both patients with coronary artery disease[7,8] and in non-cardiac patients.[9] Although ketamine increases cardiac work,[9] no study has shown that cardiac work exceeds that found during only moderate exercise in patients with known arteriosclerotic heart disease.[10] The rise in pulmonary artery pressure caused by ketamine in patients with coronary artery disease appears to be inversely related to the initial pulmonary pressure.[8] Since patients with valvular heart disease, especially mitral disease, often have a high normal or even an elevated pulmonary artery pressure, we decided to study the cardiovascular changes caused by ketamine when used for induction in patients with cardiac valvular disease scheduled for valve replacement in order to evaluate its effect on the systematic and pulmonary circulations. We hoped to confirm an inverse relationship between the initial pulmonary pressure and the rise caused by ketamine.[8] The confirmation of such an action would add an important piece of information regarding the place of ketamine as an anaesthetic agent for patients with heart disease where coronary perfusion is not impaired.

MATERIALS AND METHODS

Six patients (3 women and 3 men) with valvular heart disease who were scheduled for mitral or aortic valve replacements were studied.

The experimental protocol was approved by the chairmen of the Department of Anaesthesia and the Department of Cardiothoracic Surgery. Informed consent for the study was obtained from all patients participating in the study. Detailed information about the risk of both anaesthesia and surgery was given to all patients, as is the usual practice of the cardiac surgical team. The mean age of the patients was 63 years (range 58–66 years). Three patients suffered from mitral valvular disease and underwent mitral valve replacement; three patients suffered from aortic valvular disease and underwent aortic valve replacement. Four patients were in functional group II, and two patients in functional group III according to the New York Heart Association classification. The mean preoperative cardiac index determined at cardiac catheterization was 2.5 l/min·m^2 (range 1.8–3.4). Premedication consisted of diazepam 0.1 mg·kg^{-1} and scopolamine 0.005 mg·kg^{-1} given intramuscularly two hours before induction of anaesthesia. Under local anaesthesia a radial artery was cannulated, a Swan-Ganz flow-directed thermodilution catheter was inserted through the right internal jugular vein by a percutaneous technique,[11] and a central venous catheter was inserted from a cubital vein for drug injection, as done routinely for all adult patients undergoing open heart surgery. Ketamine was injected over a period of 20 to 30 seconds. During the control period the patients breathed 100 per cent oxygen delivered by face mask for five minutes. If respiration appeared depressed after induction with ketamine, as judged clinically and by an in-circle flowmeter, ventilation was assisted manually, using a semi-open circle system with a flow of 10 litres of oxygen per minute. Five minutes after the administration of ketamine, morphine 1.0 mg·kg^{-1} was given for maintenance of anaesthesia. Three to five minutes after morphine administration, when stable cardiovascular parameters were achieved, the trachea was intubated.

The following parameters were recorded before induction of anaesthesia with ketamine 2 mg·kg^{-1} intravenously and in the period from three to five minutes after loss of consciousness: mean systemic arterial pressure (MAP), central venous pressure (CVP), pulmonary arterial mean

H. Spotoft, M.D., J.D. Korshin, M.D., M. Bredgaard Sørensen, M.D., and P. Skovsted, M.D. The Department of Anaesthesia and the Department of Cardiac Surgery, Rigshospitalet (University Hospital), Blegdamsvej 9, 2100 Copenhagen Ø, Denmark.

TABLE I

HAEMODYNAMICS DURING INDUCTION OF ANAESTHESIA WITH KETAMINE IN SIX PATIENTS WITH VALVULAR HEART DISEASE. THE VALUES ARE MEANS ± 1 SE

	Control	Ketamine	Significance level
HR beats/min.	66±5.7	104±5.7	$p < 0.01$
CI l/min/m²	1.97±0.16	2.31±0.26	NS
SI ml/m²	30.0±2.6	21.7±1.7	$p < 0.05$
MAP kPa	12.5±0.5	17.1±0.7	$p < 0.01$
CVP kPa	1.0±0.2	1.8±0.2	$p < 0.01$
PCWP kPa	2.7±0.4	4.6±0.5	$p < 0.01$
PAMP kPa	3.2±0.6	5.9±0.8	$p < 0.01$
PVR kPa × sec/l	10.6±2.1	27.2±4.9	$p < 0.05$
SVR kPa × sec/l	216.4±27.2	249.0±30.3	NS
RVMWI g.m/min	471.7±113.6	1066.4±257.3	$p < 0.05$
LVMWI g.m/min	1963.5±202.6	2988.2±474.6	NS
Acid-base parametres			
Pa_{O_2} kPa	47.60±2.00	52.13±2.00	NS
Pa_{CO_2}	4.13±0.28	4.67±0.19	NS
pH	7.43±0.02	7.40±0.02	NS
St. bicarb. mmol/l	23.8±1.6	23.3±1.6	NS

pressure (PAMP), pulmonary capillary wedge pressure (PCWP), using Siemens 746 transducers positioned at the midaxillary line of the patients placed supine on the operation table. Heart rate was counted from the pulse curve. The electrocardiogram together with the parameters mentioned above were written out on a 6-channel recorder (Mingograph: Elema-Schoenander). Cardiac output was measured by the thermodilution method by a cardiac output computer (model 9510 Edwards). The mean of two cardiac output measurements was used for calculations. Cardiac index (CI) and stroke index (SI) were calculated using the height and weight nomogram of DuBois.[12] Systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), left ventricular minute work index (LVMWI), and right ventricular minute work index (RVMWI) were calculated together with mean systolic pressure and pulmonary arterial mean pressure from the formulae shown in the appendix. Blood samples were drawn from the arterial catheter and analyzed for Po_2, Pco_2 and pH, using a Radiometer ABL2 blood gas analyzer.

Statistical analyses were done by paired t-tests. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The results of induction with ketamine 2 mg·kg^{-1} are shown in Table I and on Figure 1.

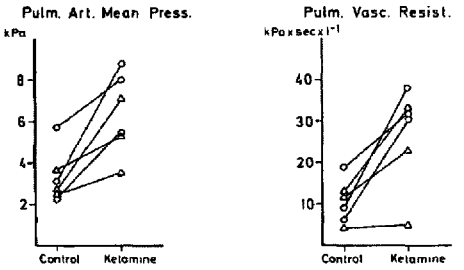

FIGURE 1 Changes in pulmonary arterial mean pressure and pulmonary vascular resistance in six patients with valvular heart disease during induction of anaesthesia with ketamine 2 mg·kg^{-1}. Δ — Δ aortic cases. O — O mitral cases.

Cardiac index was unaffected, but stroke index declined from 30.0 ± 2.6 to 21.7 ± 1.7 ml/m^2 ($p < 0.05$), which was compensated for by an increase in heart rate from 66 ± 5.7 to 104 ± 5.7 beats per minute ($p < 0.01$). Significant increases were found in mean arterial pressure, pulmonary arterial mean pressure, central venous pressure, and pulmonary capillary wedge pressure. Systemic vascular resistance increased, but the magnitude did not reach a statistically significant level, whereas pulmonary vascular resistance increased by more than 150 per cent from 10.6 ± 2.1 to 27.2 ± 4.9 kPa·sec/l ($p < 0.05$). Blood gas tensions did not change during induction. Right ventricular minute work index increased in all patients ($p < 0.05$), the mean increase being 175 per cent (range 3 to 396 per cent). Left ventricular minute work index increased in four of the six patients, but the increase was not nearly as marked as that found for right ventricular minute work index (mean 60 per cent; range −13 to 151 per cent). All pressure changes observed, were reversed by the intravenous administration of morphine 1 mg·kg^{-1}.

Discussion

Our results are in accordance with those of Gooding, *et al.*[9] who measured responses to ketamine in non-cardiac patients and found an increase in heart rate and mean systemic arterial pressure, with no significant change in cardiac output.

Kopriva,[7] studying patients scheduled for coronary artery by-pass procedures, found a significant increase in cardiac output in addition to increases in heart rate and mean systemic arterial pressure. De Master, *et al.*,[8] also investigating coronary artery by-pass patients, found dose-related increases in pulmonary arterial pressure, pulmonary arterial wedge pressure and mean arterial pressure during ketamine anaesthesia in doses up to 2 mg·kg^{-1} given intravenously, and an apparent inverse relation between initial pulmonary pressure and the magnitude of rise.

Tweed, *et al.*,[13] studying paced and unpaced patients under ketamine anaesthesia for cardiac catheterization, found ketamine to enhance myocardial contractility, which was associated with a rise in oxygen consumption. Our findings of increased minute work of the left and right ventricles and unchanged cardiac index indicate a considerable strain on the myocardium. We found no significant change in systemic vascular resistance, whereas pulmonary vascular resistance increased more than 150 per cent.

Thus, minute work of the right ventricle is increased to contend with a significantly increased afterload. Gooding, *et al.*[9] also found a more pronounced effect of ketamine on the pulmonary vascular system and right-sided cardiac performance than on the systemic vascular system and left ventricular function. Kopriva[7] states that no change in ventricular work occurred after induction with ketamine. However, his calculations were of ventricular *stroke* work, which does not take into account changes in heart rate. The considerable increase in the preload and afterload of the right ventricle indicates an increase in minute heart work which was as much as 400 per cent in our study and statistically significant, but with a considerable variation in magnitude.

Since we found no significant change in cardiac index, the increase in pulmonary vascular resistance indicates a vasoconstriction within the pulmonary circulation not due to changes in P_{O_2} or P_{CO_2} but caused by ketamine itself. This agrees with observations made by de Master, *et al.*,[8] although the inverse relation between initial pressure and extent of increased pulmonary pressure which they found was not confirmed in our study; indeed, not even a trend in such a direction was observed (Figure 1).

Thus ketamine causes a marked increase in pulmonary vascular resistance and minute work of the right ventricle. In patients with restricted cardiac reserve, where the right ventricle cannot increase its work in response to an increased central venous pressure, the use of ketamine for induction may prove to be deleterious or even dangerous. This may also be the case when ketamine is administered to patients with severe

pulmonary hypertension. We found no relationship, however, between the initial pressure in the pulmonary circulation and the extent of the rise in pressure after ketamine (Figure 1).

Tweed and Mymin,[14] measuring myocardial force-velocity relations during ketamine anaesthesia for cardiac catheterization in patients with coronary artery disease, found that ketamine increased ventricular preload and end-diastolic volume to such a degree that they concluded that it could be detrimental to patients already utilizing the Starling mechanism to maintain cardiac compensation.

The findings in our study definitely confirm those of Tweed and Mymin,[14] even though the patients in our study suffered from valvular heart disease rather than coronary artery disease.

Thus we conclude that ketamine used for induction in patients with valvular heart disease increases pulmonary vascular resistance and increases the minute work of the heart, especially of the right ventricle. Ketamine could be disastrous in patients with minimal right ventricular functional reserve due to the presence of fat, clots or amniotic fluid in the pulmonary circulation, or with cardiac tamponade or constrictive pericarditis; and especially where there is concomitant impairment of coronary circulation to the right ventricle.

Summary

The effects of induction of anaesthesia by ketamine 2 mg·kg^{-1} were studied in six patients with valvular heart disease before tracheal intubation and operation. Cardiac index was unaffected because a mean decrease in stroke index was compensated for by a mean increase in heart rate. A significant increase was found in mean arterial pressure, pulmonary arterial mean pressure, pulmonary capillary wedge pressure and central venous pressure. Systemic vascular resistance increased, but not significantly, whereas pulmonary vascular resistance increased significantly by more than 150 per cent. Right ventricular minute work index increased in all patients, and the increase was as much as 400 per cent. Left ventricular minute work index increased in four of the six patients, but the magnitude of the increase was not so marked. It is therefore concluded that ketamine causes pronounced pulmonary vasoconstriction and an undesirable strain on the myocardium. Such effects could prove deleterious in patients with limited functional reserve of the right ventricle.

Résumé

On a étudié les effets de la kétamine à la dose de 2 mg·kg^{-1} comme agent d'induction de l'anesthésie chez six patients porteurs de cardiopathies valvulaires. Les observations ont été effectuées après l'induction, avant l'intubation et la chirurgie. L'index cardiaque est demeuré inchangé, la diminution moyenne de l'index d'éjection étant compensée par une augmentation de la fréquence cardiaque. On a observé une élévation significative de la pression artérielle moyenne, de la pression capillaire pulmonaire moyenne, de la pression veineuse centrale et de la pression capillaire bloquée. La résistance vasculaire systémique s'est élevée de façon non significative, alors que la résistance vasculaire pulmonaire s'élevait de façon significative (plus de 150 pour cent). L'index de travail ventriculaire droit-minute s'est élevé chez tous les sujets; on a même observé des élévations de l'ordre de 400 pour cent. L'index de travail ventriculaire gauche minute s'est élevé chez quatre des six patients, mais les élévations n'étaient pas si importantes que celles observées au niveau du ventricule droit. Les auteurs concluent que la Kétamine taxe le myocarde de façon indésirable et produit une vasoconstriction pulmonaire prononcée. Ces effets pourraient s'avérer nocifs chez des malades à réserve myocardique limitée.

Acknowledgements

The authors would like to acknowledge the excellent assistance given by our staff nurses Jette Søgaard R.N. and Lotte Himmerland R.N. during conduct of the study. Similarly we thank our engineer Ole Bergsten for his able technical assistance.

References

1. Traber, D.L. & Wilson, R.D. Involvement of the sympathetic nervous system in the pressor response to ketamine. Anesth. Analg. *48*: 248 (1969).
2. Ivankovich, A.D., Miletich, D.J., Reiman, C., Albrecht, R.F. & Zahed, B. Cardiovascular effects of centrally administered ketamine in goats. Anesth. Analg. *53*: 924 (1969).
3. McGrath, J.C., Mackenzie, J.E. & Millar, R.A. Effects of ketamine on central sympathetic discharge and the baroreceptor reflex during mechanical ventilation. Brit. J. Anaesth. *47*: 1141 (1975).
4. Traber, D.L., Wilson, R.D. & Prianol, L. A detailed study of the cardiopulmonary response to ketamine and its blockade by atropine. South. Med. J. *63*: 1077 (1970).

5. LORHAN, P.H. & LIPPMANN, M. A clinical appraisal of the use of ketamine hydrochloride in the aged. Anesth. Analg. *50*: 448 (1971).
6. CORSSEN, G., ALLARDE, R., BROCH, F. & ARBENZ, G. Ketamine as sole anesthetic in open heart surgery. A preliminary report. Anesth. Analg. *49*: 1025 (1970).
7. KOPRIVA, C.J. Hemodynamic effects of intravenous ketamine in patients with coronary artery disease. Abstracts of scientific papers. ASA Annual Meeting, p. 233 (1974).
8. DE MASTER, R.J. & FOGDALL, R.P. The effects of ketamine on the pulmonary and systemic circulations in patients with coronary heart disease. Abstracts of scientific papers. ASA Annual Meeting, p. 721 (1977).
9. GOODING, J.M., DIMICK, A.R., TAVAKOLI, M. & CORSSEN, G. A physiologic analysis of cardiopulmonary responses to ketamine anesthesia in noncardiac patients. Anesth. Analg. *56*: 913 (1977).
10. BILLE-BRAHE, N.E., SØRENSEN, M.B., MONDORF, T. & ENGELL, H.C. Central haemodynamics during induction of neurolept anaesthesia in patients with anteriosclerotic heart disease. Acta Anaesth. Scand. Suppl. *67*: 47 (1978).
11. KORSHIN, J., KLAUBER, P.V., CHRISTENSEN, V. & SKOVSTED, P. Percutaneous catheterization of the internal jugular vein. Acta Anaesth. Scand. Suppl. *67*: 27 (1978).
12. DUBOIS, E.F. Basal metabolism in health and disease. Lea and Fibiger, Philadelphia, p. 120 (1927).
13. TWEED, W.A., MINUCK, M. & MYMIN, D. Circulatory responses to ketamine anesthesia. Anesthesiology *6*: 613 (1972).
14. TWEED, W.A. & MYMIN, D. Myocardial force-velocity relations during ketamine anesthesia at constant heart rate. Anesthesiology *41*: 49 (1974).

APPENDIX

Symbols and abbreviations

HR: heart rate (beats/min)
CO: cardiac output (l/min).
CI: cardiac index (l/min· m²).
SI: stroke index (ml/m²).
CVP: central venous pressure (mm Hg ~ 0.133 kPa).
PAMP: pulmonary arterial mean pressure (mm Hg ~ 0.133 kPa).
PCWP: pulmonary capillary wedge pressure (mm Hg ~ 0.133 kPa).
MAP: systemic mean blood pressure (mm Hg ~ 0.133 kPa).
PVR: pulmonary vascular resistance (dynes· sec· cm^{-5} ~ 0.1 kPa· s/l).
SVR: systemic vascular resistance (dynes· sec· cm^{-5} ~ 0.1 kPa· s/l).
Pa_{O_2}: arterial oxygen tension (mm Hg ~ 0.133 kPa).
Pa_{CO_2}: arterial carbon dioxide tension (mm Hg ~ 0.133 kPa).
LVMWI: left ventricular minute work index.
RVMWI: right ventricular minute work index.

Formulae

MAP: diastolic pressure + 1/3 of the pulse amplitude (mm Hg ~ 0.133 kPa).
PAMP: diastolic pressure + 1/3 of the pulse amplitude (mm Hg ~ 0.133 kPa).
CI = CO/body surface area (l/m²· min).
SI = CI 1000/HR (ml/m²).
PVR = (PAMP − PCWP) × 80/CO (dynes· sec· cm^{-5} ~ 0.1 kPa· s/l).
SVR = (MAP − CVP) × 80/CO (dynes· sec· cm^{-5} ~ 0.1 kPa· s/l).
LVMWI = CI (MAP − PCWP) × 13.6 g· m/min.
RVMWI = CI (PAMP − CVP) × 13.6 g· m/min.

Conversion factor: 1 kPa = 7.5 mm Hg.