# Comparison of Hemodynamic Effects of Glucagon and Ketamine in Patients with Chronic Renal Failure

G. H. Hobika, M.D.,* J. L. Evers, Ph.D.,* J. W. Mostert, M.D.,†
R. J. Trudnowski, M.D.,* R. H. Moore, M.S.,‡
G. P. Murphy, M.D., D.Sc.§

Many patients in the end stage of chronic renal disease are candidates for renal transplantation. Because of the uremic syndrome, anesthesia for such patients may present difficult problems to the anesthesiologist. These include anemia, severe hypertension, high cardiac output, fluid and electrolyte imbalance, congestive heart failure, hypertensive encephalopathy with convulsions, retinal hemorrhage, pulmonary edema, and pericarditis.[1,2] Considerable attention has been focused on the anesthetic management of uremic patients.[3-5]

* Department of Anesthesiology.
† Department of Anesthesiology. Present address: Department of Anesthesiology, The University of Chicago, 950 East 59th Street, Chicago, Illinois 60637.
‡ Department of Biostatistics.
§ Director, Roswell Park Memorial Institute, and New York State Department of Health, Buffalo, New York 14203.
Accepted for publication May 22, 1972.

Table 1. Mean Hemodynamic and Arterial Blood-Gas Values before and 5, 10, and 30 Minutes after Glucagon, 5 mg, in Five Patients with Chronic Renal Failure

| | Mean ± SEM | Change from Control, $P$ | | Mean ± SEM | Change from Control, $P$ |
|---|---|---|---|---|---|
| Cardiac output (l/min) | | | Right ventricular systolic pressure (mm Hg) | | |
| Control | 7.7 ± 0.9 | — | Control | 36 ± 6 | — |
| 5 min | 10.9 ± 0.9 | <0.05 | 5 min | 45 ± 5 | <0.01 |
| 10 min | 10.3 ± 0.8 | <0.05 | 10 min | 47 ± 3 | <0.05 |
| 30 min | 9.2 ± 0.6 | NS* | 30 min | 41 ± 6 | NS |
| Mean arterial pressure (mm Hg) | | | Right ventricular end-diastolic pressure (mm Hg) | | |
| Control | 106 ± 9 | — | Control | 7 ± 2 | — |
| 5 min | 124 ± 14 | NS | 5 min | 10 ± 2 | <0.01 |
| 10 min | 123 ± 11 | <0.05 | 10 min | 10 ± 2 | <0.05 |
| 30 min | 118 ± 6 | <0.05 | 30 min | 8 ± 2 | NS |
| Total peripheral resistance (dynes/sec/cm$^{-5}$) | | | $Pa_{O_2}$ (mm Hg) | | |
| Control | 1120 ± 77 | — | Control | 91.4 + 8.7 | — |
| 5 min | 945 ± 106 | NS | 5 min | 96.0 ± 7.5 | NS |
| 10 min | 1010 ± 140 | NS | 10 min | 92.4 ± 10.0 | NS |
| 30 min | 1042 ± 78 | NS | 30 min | 93.8 ± 8.8 | NS |
| Heart rate (beats/min) | | | $Paco_2$ (mm Hg) | | |
| Control | 75 ± 2 | — | Control | 37.4 ± 2.1 | — |
| 5 min | 93 ± 9 | NS | 5 min | 36.6 ± 1.4 | NS |
| 10 min | 106 ± 18 | NS | 10 min | 34.6 ± 1.7 | NS |
| 30 min | 84 ± 5 | <0.05 | 30 min | 34.8 ± 1.5 | NS |
| | | | $pH$ (arterial) | | |
| | | | Control | 7.310 ± 0.025 | — |
| | | | 5 min | 7.302 ± 0.033 | NS |
| | | | 10 min | 7.321 ± 0.041 | NS |
| | | | 30 min | 7.318 ± 0.025 | NS |

* NS = no significant change from control.

In contrast to traditional agents, neuroleptanesthesia or dissociative agents may have merit because of their ability to block selectively those pathways or areas in the central nervous system involved in pain conduction and perception.[6,7] For this reason, the hemodynamic effects of ketamine in uremic patients were studied. Also, because of current interest in the use of glucagon in cardiac insufficiency,[8-12] hemodynamic measurements were made in uremic patients given this drug. We were struck by the similarity between the hemodynamic effects of glucagon and ketamine.

## Materials and Methods

Twelve patients in advanced stages of chronic renal failure from several causes were studied on the day following dialysis. Patients were fasting and not premedicated. Using local anesthesia, catheters of fine bore were inserted percutaneously into the right ventricle and brachial artery. Samples of arterial and right ventricular blood were placed in an ice slush and analyzed within 20 minutes for *p*H and blood gases, using a Radiometer *p*H meter equipped with $O_2$ and $CO_2$ electrodes. Cardiac output (CO) was measured by an indicator-dilution method using indocyanine green, a Gilson densitometer, and a Lexington computer. Arterial and right ventricular pressures were measured with appropriate directly-calibrated Statham transducers. Lead II of the electrocardiogram was recorded.

After control measurements, ketamine, 2

Table 2. Mean Hemodynamic and Arterial Blood–Gas Values before and 5, 10, and 30 Minutes after 2 mg/kg Ketamine in 12 Patients with Chronic Renal Failure

| | Mean ± SEM | Change from Control, *P* |
|---|---|---|
| Cardiac output (l/min) | | |
| Control | 7.48 ± 0.6 | — |
| 5 min | 8.68 ± 0.9 | <0.05 |
| 10 min | 8.18 ± 0.7 | NS* |
| 30 min | 7.23 ± 0.8 | NS |
| Mean arterial pressure (mm Hg) | | |
| Control | 116 ± 6 | — |
| 5 min | 136 ± 7 | <0.005 |
| 10 min | 126 ± 6 | <0.01 |
| 30 min | 119 ± 7 | NS |
| Total peripheral resistance (dynes/sec/cm$^{-5}$) | | |
| Control | 1267 ± 108 | — |
| 5 min | 1222 ± 102 | NS |
| 10 min | 1211 ± 125 | NS |
| 30 min | 1366 ± 122 | NS |
| Heart rate (beats/min) | | |
| Control | 90 ± 5 | — |
| 5 min | 107 ± 5 | <0.005 |
| 10 min | 103 ± 5 | <0.01 |
| 30 min | 94 ± 5 | NS |
| Right ventricular systolic pressure (mm Hg) | | |
| Control | 36 ± 3 | — |
| 5 min | 49 ± 5 | <0.01 |
| 10 min | 46 ± 4 | <0.05 |
| 30 min | 41 ± 4 | NS |
| Right ventricular end-diastolic pressure (mm Hg) | | |
| Control | 6.3 ± 0.8 | — |
| 5 min | 7.5 ± 1.0 | NS |
| 10 min | 6.6 ± 0.9 | NS |
| 30 min | 5.9 ± 0.9 | NS |
| $Pa_{O_2}$ (mm Hg) | | |
| Control | 98 ± 3 | — |
| 5 min | 98 ± 5 | NS |
| 10 min | 91 ± 4 | NS |
| 30 min | 93 ± 3 | NS |
| $Pa_{CO_2}$ (mm Hg) | | |
| Control | 33 ± 2 | — |
| 5 min | 36 ± 1 | <0.01 |
| 10 min | 35 ± 1 | <0.01 |
| 30 min | 34 ± 1 | NS |
| *p*H (arterial) | | |
| Control | 7.32 ± 0.02 | — |
| 5 min | 7.30 ± 0.02 | NS |
| 10 min | 7.29 ± 0.02 | NS |
| 30 min | 7.30 ± 0.02 | NS |

* NS = no significant change from control.

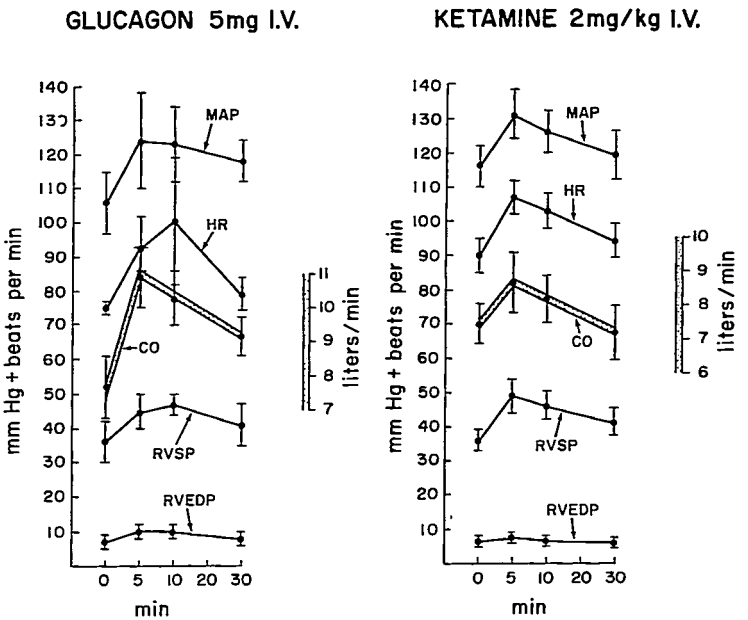


FIG. 1. Changes in mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), right ventricular systolic pressure (RVSP), and right ventricular end-diastolic pressure (RVEDP) following glucagon, 5 mg IV, and ketamine, 2 mg/kg IV, in patients with end-stage renal disease.

mg/kg, was injected into the right ventricle of each patient, and the measurements were repeated after 5, 10, and 30 minutes. Five other patients in renal failure were similarly studied after introduction of glucagon, 5 mg, into the right ventricle. Statistical treatment of the data consisted of calculation of mean values, standard errors of the means, and self-paired differences.[14]

## RESULTS

Patients in end stages of chronic renal failure characteristically have elevated cardiac output (CO), mean arterial pressure (MAP), right ventricular systolic pressure (RVSP), and right ventricular end-diastolic pressure (RVEDP). Total peripheral resistance (TPR) is within the normal range.[15, 16] Our patients had these characteristics (see control values in tables 1 and 2).

After glucagon was injected into the right ventricle, CO, MAP, and RVEDP attained peak values at 5 minutes (table 1, fig. 1). HR and RVSP increased to a peak at about 10 minutes. There was no statistically significant change in TPR. No arrhythmias were observed. Following injection of ketamine into the right ventricle, CO, RVSP, MAP, and HR increased and peaked at 5 minutes (table 2, fig. 1). There were no statistically significant changes in TPR or RVEDP. The mean values for stroke volume computed from mean HR and mean CO did not change after either drug.

In both groups $Pa_{O_2}$'s greater than 80 mm Hg were well within the normal range for healthy adults breathing air,[17] and they did not change following administration of either drug. In both groups, $Pa_{CO_2}$'s between 33 and 37 mm Hg were at the low end of the normal

range,[18] and did not change during the 30-minute period of observation. Arterial *p*H reflected the metabolic acidosis which is characteristic of severe renal disease and was unaltered by either drug. No respiratory depression was observed after either drug.

## Discussion

The hemodynamic effects of bolus injections of glucagon [9, 10, 13] and ketamine [19–21] intravenously, into pulmonary artery, or into the right heart in healthy adults are comparable and transient. Typically, MAP, CO, and HR all increase after either drug. Similar responses were observed in our patients with advanced renal disease.

There may be a number of possible explanations for the stimulating effects of ketamine, a direct cardiovascular depressant drug,[22] on CO, MAP, and HR in the usual clinical doses. These include excitation of the vasomotor center of the medulla and depression of the baroreceptor reflexes.[22] This cardiac stimulation may be decreased by alpha-adrenergic blocking agents.[23] Pretreatment with a ganglionic blocking agent (hexamethonium) [24] produced no change in MAP and HR when ketamine was given to dogs. The pressor response to ketamine, which may be mediated by the sympathetic nervous system, is not abolished by the use of beta-adrenergic blockade (propranolol) in dogs.[25]

The mechanism of action of glucagon [9, 10, 13] may resemble that of the natural catecholamines. Recent evidence has shown activation of adenyl cyclase and an increase in cyclic AMP levels of the heart.[8] While this may be true in a non-failing heart, cyclic AMP may not be increased in the failing heart muscle preparation, and the effectiveness of glucagon is then diminished.[11, 12, 26] One group, injecting 3 to 5 mg of glucagon as a bolus, found no change in LVEDP and only a modest increase in HR.[9] We noted a significant chronotropic effect with either glucagon or ketamine, accompanied by increased CO. Some investigators consider glucagon a potent inotropic agent.[9, 27] The slight increase in RVEDP following glucagon in our patients is not expected with an inotropic drug. This change in RVEDP points to the Frank-Starling mechanism as contributing to the increased CO. There may be an associated increase in stroke work as well, because changes of RVEDP as small as 1 cm $H_2O$ can result in increases of right ventricular stroke work (RVSW).[28]

We found no significant change in TPR, while others [9, 27] have reported a decrease in TPR. In our hemodynamic results with glucagon, we did not see the disparity shown by others in the degrees of inotropic responses, which apparently is related to both the functional severity and the type of heart disease.[11, 12] No studies regarding catecholamine release following either glucagon or ketamine have been published. Our observed low values of $Pa_{CO_2}$ seem to preclude sympathoadrenal discharge due to hypercarbia.[29] Further biochemical and metabolic studies are needed to help clarify the mechanisms of action of both drugs.

## References

1. Kerr DNS: Chronic renal failure, Cecil-Loeb Textbook of Medicine. Thirteenth edition. Edited by PB Beeson, W McDermott. Philadelphia, Saunders, 1971, pp 1144–1160
2. Merrill JP, Hampers CL: Uremia—Progress in Pathophysiology and Treatment. New York, Grune and Stratton, 1971
3. LeVine DS, Virtue RW: Anaesthetic agents and techniques for renal homotransplants. Can Anaesth Soc J 11:425–428, 1964
4. Vandam LD, Harrison JH, Murray JE, et al: Anesthetic aspects of renal homotransplantation in man. Anesthesiology 23:783–791, 1962
5. Trudnowski RJ, Mostert JW, Hobika GH, et al: Neuroleptanalgesia for patients with kidney malfunction. Anesth Analg Curr Res 50:679–683, 1971
6. Zauder HL, Nichols RJ: Intravenous anesthesia, Clinical Anesthesia a Decade of Progress. Edited by LW Fabian. Philadelphia, Davis, 3/1969, pp 318–357
7. French JD, Verzeano M, Magoun HW: A neural basis of the anesthetic state. Arch Neurol Psychiatry 69:519–529, 1953
8. Williams JF: Glucagon and the cardiovascular system (editorial). Ann Intern Med 71: 419–423, 1969
9. Parmley WW, Glick G, Sonnenblick EH: Cardiovascular effects of glucagon in man. N Engl J Med 279:12–17, 1968
10. Linhart JW, Barold SS, Cohen LS, et al: Cardiovascular effects of glucagon in man. Am J Cardiol 22:706–709, 1968
11. Glick G: Glucagon (editorial). Circulation 45:513–515, 1972

12. Lvoff R, Wilcken DEL: Glucagon in heart failure and in cardiogenic shock. Circulation 45:534–542, 1972
13. Klein SW, March JE, Mahon WA: Cardiovascular effects of glucagon in man. Can Med Assoc J 98:1161–1164, 1968
14. Dixon WJ, Massey FJ Jr: Introduction to Statistical Analysis. Second edition. New York, McGraw-Hill, 1957, pp 124–130
15. Mostert JW, Evers JL, Hobika GH, et al: The valsalva maneuver as a clinical test for circulatory congestion in chronic uremia. J Surg Oncology 2:207–219, 1970
16. Neff MS, Kim KE, Persoff M, et al: Hemodynamics of uremic anemia. Circulation 43: 876–883, 1971
17. Gambino SR: Water, electrolytes, acid–base and oxygen, Todd-Sanford Clinical Diagnosis. Fourteenth edition. Edited by I Davidsohn, JB Henry. Philadelphia, Saunders, 1969, p 670
18. *Ibid:* p 663 for *p*H and $P_{CO_2}$.
19. Domino EF, Chodoff P, Corssen G: Pharmacologic effects of CL-581, a new dissociative anesthetic in man. Clin Pharmacol Ther 6:279–291, 1966
20. Kreuscher H, Gaugh H: Die Wirkung des Phencyclidinderivatives Ketamine (CL-581) auf das kardiovasculaere System des Menschen. Anaethesist 16:229–233, 1967
21. Virtue RW, Alanis JM, Mori M, et al: An anesthetic agent: 2-orthochlorophenyl 2-methylamine cyclohexanone HCl (CL-581). ANESTHESIOLOGY 28:823–833, 1967
22. Dowdy EA, Kaya K: Studies of the mechanism of cardiovascular response in CL-581. ANESTHESIOLOGY 29:931–943, 1968
23. Traber DL, Wilson RD: Involvement of the sympathetic nervous system in the pressor response to ketamine. Anesth Analg (Cleve) 248–252, 1969
24. Traber DL, Wilson RD, Priano LL: Blockade of the hypertensive response to ketamine. Anesth Analg (Cleve) 49:420–426, 1970
25. Traber DL, Wilson RD, Priano LL: The effect of beta adrenergic blockade on the cardiopulmonary response to ketamine. Anesth Analg (Cleve) 49:604–613, 1970
26. Epstein SE, Levey GS, Skelton CL: Adenyl cyclase and cyclic AMP: Biochemical link in the regulation of myocardial contractility. Circulation 43:437–450, 1971
27. Westlie L, Andersen A, Jervell J, et al: Cardiovascular effects of glucagon. Acta Med Scand 189:179–184, 1971
28. Shimosato S, Etsten BE: Effect of anesthetic drugs on the heart, Clinical Anesthesia a Decade of Progress. Edited by LW Fabian. Philadelphia, Davis, 3/1969, pp 18–72
29. Seehzer PH, Egbert LD, Linde HW, et al: Effect of $CO_2$ inhalation on arterial pressure. ECG and plasma catecholamines and 17-OH corticosteroids in normal man. J Appl Physiol 15:454–458. 1960

# Anesthetic Management of Lobectomy for Massive Pulmonary Hemorrhage

HAROLD CARRON, M.D., AND SUSAN HILL, M.D.

Massive pulmonary hemorrhage may necessitate emergency thoracotomy as a life-saving measure. In such a situation, anesthetic management is of critical importance for the patient's survival.

## REPORT OF A CASE

A 61-year-old Caucasian woman was admitted for the third time for hemoptysis. On previous admissions, blood losses had been minimal and had been self-limiting with conservative treatment. Bronchoscopy and sputum and x-ray studies revealed old cavitary tuberculosis of the right upper lobe as the source of bleeding. On the current admission, hemorrhage was massive, causing acute respiratory distress. In the four hours preceding operation, 1,300 ml of blood were expectorated. Blood–gas analysis revealed $P_{O_2}$ 61 torr, $P_{CO_2}$ 55 torr, and *p*H 7.34; hematocrit was 33 per cent. Because of failure of the bleeding to abate and increasing respiratory distress, emergency pulmonary lobectomy was scheduled.

The patient, orthopneic and apprehensive, was brought to the operating room at 10:00 PM. During insertion of additional intravenous catheters and application of monitoring devices, the patient had continuous hemoptysis of more than 600 ml in a 10-minute period. Although tracheostomy

Received from the Department of Anesthesiology, University of Virginia Medical Center, Charlottesville, Virginia 22901. Accepted for publication May 22, 1972.