British Heart Journal, 1971, 33, 290–295.

Haemodynamic effects of glucagon during acute myocardial infarction with left ventricular failure in man[1]

George Diamond,[2] James Forrester, Ronald Danzig, William W. Parmley, and H. J. C. Swan

From the Department of Cardiology, Cedars-Sinai Medical Center, and the Department of Medicine, University of California at Los Angeles, U.S.A.

Ten subjects with acute myocardial infarction, nine with associated left ventricular failure, received constant glucagon infusion, 70 μg./kg., over a two-minute period. Haemodynamic measurements were made at 5, 10, 15, and 30 minutes after infusion. Onset of action was within 5 minutes, peak effect was between 10 and 15 minutes, and duration of action was 15 to 30 minutes. Left ventricular filling pressure (pulmonary capillary wedge or pulmonary artery end-diastolic) was unchanged, but cardiac output, mean systolic ejection rate, stroke volume, and stroke work increased 25 per cent. Pulmonary vascular resistance increased 135 per cent, while systemic vascular resistance decreased 13 per cent. During the study two subjects developed transient nausea and one subject vomited. No arrhythmias were observed. Glucagon, therefore, appears to be an effective inotropic agent in selected patients with acute myocardial infarction complicated by left ventricular failure.

Clinical studies have shown the positive inotropic effects of glucagon in normal subjects (Mahon, Morch, and Klein, 1968) and in patients with variable degrees of cardiac disease, including cardiogenic shock (Mahon *et al.*, 1968; Vander Ark and Reynolds, 1969) and the postcardiac surgical state (Parmley, Matloff, and Sonnenblick, 1969) as well as during diagnostic catheterization (Klein, Morch, and Mahon, 1968; Parmley, Glick, and Sonnenblick, 1968; Linhart *et al.*, 1968; Williams *et al.*, 1969). These studies have led to variable results regarding the effects of glucagon on such haemodynamic parameters as stroke work, systemic vascular resistance, and systemic arterial pressure. It seems likely that these differences may be due to the nature and severity of cardiac disease present in different study subjects. Several recent investigations (Gold *et al.*, 1969; Williams, 1969) support this view, in that glucagon has been shown to be less effective in the presence of chronic congestive failure than in acute congestive failure. Acute left ventricular failure occurs commonly during acute myocardial infarction and may develop in the presence of pre-existing chronic compensated failure. Recent studies (Eddy, O'Brien, and Singh, 1969; Murtagh *et al.*, 1970) have shown a positive but somewhat variable response to glucagon in patients with uncomplicated acute myocardial infarction and in association with left ventricular failure and cardiogenic shock. The present study was designed to evaluate further the effectiveness of glucagon in acute myocardial infarction with left ventricular failure and to clarify its haemodynamic and metabolic effects in this selected group of patients.

Received 20 July 1970.

[1] Supported in part by a grant from the Myocardial Infarction Research Unit, NIH grant (Training Grant), and USPHS grant.

[2] Fellow under NIH Grant.

Methods

Ten subjects ranging in age from 46 to 80 (mean age 66) were studied after the diagnosis of acute myocardial infarction by historical, electrocardiographic, and laboratory criteria. Two were on a digitalis preparation. All subjects were in normal sinus rhythm. None was receiving any cardiac depressant medication at the time of the study. The clinical status of the subjects is presented in Table 1. Subjects were studied in a coronary care unit between 22 and 149 hours (mean 62 hours) after the historical event that indicated the onset of myocardial infarction – for example, unrelenting chest pain. Left ventricular failure was

TABLE I *Clinical status of subjects studied*

Patient	*Age*	*Sex*	*Class**	*Left ventricular failure*	*Location of infarct*	*Previous infarct*	*PI†*	*Time‡*	*Digitalis*
D.G.	67	F	I	+	Inferolateral	−	12	30	−
S.M.	80	M	III	+	Subendocardial	+	25	30	−
J.M.	46	M	I	−	Inferior	−	3	75	−
J.B.	74	M	II	+	Anterior	−	8	56	−
A.S.	64	M	I	+	Anteroseptal	−	7	115	−
J.K.	56	M	I	+	Inferior	−	13	74	−
E.C.	76	M	II	+	Anterolateral	+	14	44	−
M.M.	64	M	I	+	Anterior	−	10	28	+
M.R.	55	M	I	+	Anterior	−	8	22	−
B.G.	80	M	I	+	Inferior	+	21	149	+

* NYHA classification before acute infarction.
† Peel prognostic index (Peel *et. al.*, 1962) on admission.
‡ Hours elapsed between onset of infarction and study.

diagnosed, according to criteria of the combined Myocardial Infarction Research Units (Recommendations of the Committee on Definitions, Combined Myocardial Infarction Research Units Meetings, 11–12 November 1969), if at least three of the following were present: râles, a ventricular gallop or both, radiographic evidence of pulmonary congestion, a cardiac index less than 2·20 l./min./m.^{2}, a pulmonary artery diastolic or wedge pressure greater than 14 mm. Hg, and an AV oxygen difference greater than 5·5 volumes per cent (Table 2).

A 5-French polyethylene catheter was inserted through the left median basilic vein into the pulmonary artery and its position was documented radiographically and by pressure monitoring. In four subjects the catheter was left in the right atrium. A 5-French Teflon catheter was inserted through the left brachial artery by Seldinger technique and positioned in the proximal subclavian artery. Samples of arterial and mixed venous blood were obtained for gas analysis.[1] Pressures and lead II of the electrocardiogram were recorded on a multichannel photographic recorder. Serial duplicate cardiac output determinations were obtained in eight subjects by the dye dilution technique with injection of indocyanine green into the pulmonary artery or right atrium and sampling of blood from the subclavian artery. In one subject only baseline cardiac outputs were obtained. Glucagon (Lilly) was infused through the venous catheter by a Harvard constant infusion pump such that a dose of 70 μg./kg. was delivered in a volume of 18·8 ml. normal saline over a two-minute period. Total dosage ranged from 4·6 to 5·9 mg. Phasic and mean blood pressures, electrocardiogram, and cardiac outputs were obtained before and 5, 10, 15, and 30 minutes after the midpoint of infusion of glucagon. Blood glucose and potassium were determined before and 30 minutes after drug administration. Significant changes were evaluated by the paired 't' test. If not apparent during the study, subjects were subsequently questioned for such side effects as palpitations, chest pain, nausea, weakness, dizziness, and headache.

[1] Radiometer modular microsystem PHM 27GM/35021/D616/E5046/D616/VTS-13.

Results

Haemodynamic results Table 3 shows the effects of intravenously administered glucagon upon various haemodynamic parameters in 10 subjects with acute myocardial infarction. Significant increases in the range of 20 to 30 per cent were observed in cardiac index, stroke index, stroke work index, and mean systolic ejection rate. Total systemic vascular resistance decreased 10 to 20 per cent. Mean arterial pressure, heart rate, and time-tension index increased significantly but variably from 0 to 30 per cent. There was no significant change in systolic ejection period or central venous pressure. Haemodynamic effects were unrelated to the degree of left ventricular

TABLE 2 *Criteria for diagnosis of left ventricular failure in ten subjects with acute myocardial infarction*

Patient	*Râles/ gallop*	*Radiograph*	*AV diff. > 5·5*	*Cardiac index < 2·20*	*Left ventricular filling pressure > 14*
D.G.	+	−	+	+	
S.M.	+	+	+	−	
J.M.	+	−	+	−	
J.B.	+	−	+	+	−
A.S.	−	+	+	+	−
J.K.	+	+	+	+	
E.C.	+	+	−	−	+
M.M.	+	+	+	−	+
M.R.	+	+	−		+
B.G.	+	+	−	+	+

\+ Positive finding. − Negative finding.
Blank space indicates parameter was not determined.

TABLE 3 *Haemodynamic effects of 70 μg./kg. glucagon in ten subjects*

	Control	*Peak effect after glucagon*	*% Change ± SEM*	*Paired 't' test*
Cardiac index* (l./min./m.^{2})	2·41	3·00	24·4 ± 1·8	< 0·005
Stroke index* (ml./beat/m.^{2})	32·5	38·5	19·8 ± 4·2	< 0·005
Heart rate* (beats/min.)	75	81	8·6 ± 4·4	< 0·05
Mean blood pressure* (mm. Hg)	98	111	13·2 ± 3·8	< 0·005
Systemic vascular resistance* (dyne sec. cm.$^{-5}$)	1856	1608	−13·3 ± 1·8	< 0·0005
Stroke work index* (g.m./beat/m.^{2})	45·1	58·1	28·9 ± 3·4	< 0·0005
Mean systolic ejection rate* (ml. sec. m.^{2})	116	141	22·2 ± 5·2	< 0·005
Time-tension index* (mm. Hg sec./min.)	2046	2407	19·2 ± 7·0	< 0·025
Pulmonary vascular resistance† (dyne sec. cm.$^{-5}$)	157	237	134 ± 64	< 0·05
Mean pulmonary artery pressure† (mm. Hg)	20	24	23·2 ± 4·8	< 0·005
Systolic ejection period* (msec./beat)	283	280		NS
Central venous pressure‡ (mm. Hg)	7	8		NS
Pulmonary artery diastolic pressure† (mm. Hg)	15	16		NS
Wedge pressure‡ (mm. Hg)	18	17		NS

* Eight patients only. † Six patients only. ‡ Four patients only.

failure. Results in the three subjects with a history of mild chronic congestive failure were indistinguishable from those in the remainder of the group, therefore these data are not presented separately. In the six subjects in whom pulmonary artery pressures were measured mean pulmonary artery pressure increased 23 per cent and pulmonary vascular resistance increased 134 per cent. There was no significant change in pulmonary artery end-diastolic or wedge pressure. It is assumed that ventricular compliance, and therefore left ventricular diastolic pressure and volume, remained essentially unchanged. Individual control and peak responses are graphed in Fig. 1 and 2. Peak response was defined in relation to the maximal increase in cardiac output.

Onset, duration, and peak effect Conspicuous changes in arterial pressure or heart rate were not usually observed. The first consistently observed effect of glucagon was an increase in cardiac output. Since all subjects were found to have an increased cardiac output on the first post-infusion determination, the onset of action occurred within 5 minutes. The peak action of glucagon occurred between 5 and 15 minutes after administration (mean 10 minutes), and the duration of action was between 15 and 30 minutes. Heart rate peaked before 5 minutes and returned to control levels between 5 and 10 minutes in every subject. Fig. 3 shows a typical time course of the changes in cardiac output after administration of glucagon.

Metabolic effects Blood glucose rises, which we have noted to peak 30 minutes after glucagon infusion, were out of phase with the haemodynamic effects observed. In most subjects a 25 per cent increase from control glucose levels occurred. Mean control blood glucose was 143 mg./100 ml., since all patients had a slow infusion of heparinized dextrose and water running to keep the intravascular lines open. One subject showed no change in blood glucose and another sustained an increase from 137 mg./100 ml. to 1040 mg./100 ml. This subject also developed a profound drop in serum potassium from 3·8 mEq/l. to 2·5 mEq/l. He remained asymptomatic and serum chemistries returned to normal within 2 hours. No arrhythmias were noted during this interval. In 7 other subjects serum potassium decreased slightly from a mean of 4·4 mEq/l. to 3·9 mEq/l. Individual responses are graphed in Fig. 4. There was no correlation between the degree of haemodynamic response and the degree of metabolic response in any subject.

Side effects During the study two subjects complained of nausea and one vomited. Haemodynamic observations during emesis did not differ from those of other subjects in the study. The onset of these side effects occurred within 2 to 3 minutes after infusion and abated within 5 minutes. One subject complained of dizziness for approximately 20 minutes after glucagon administration. In all cases the side effects were transient and well tolerated. No arrhythmias or ventricular irritability occurred during the study period and all subjects remained in normal sinus rhythm. No observable change in clinical status occurred during the study.

Discussion

Since the studies of Farah and Tuttle demonstrating a cardiovascular effect of glucagon

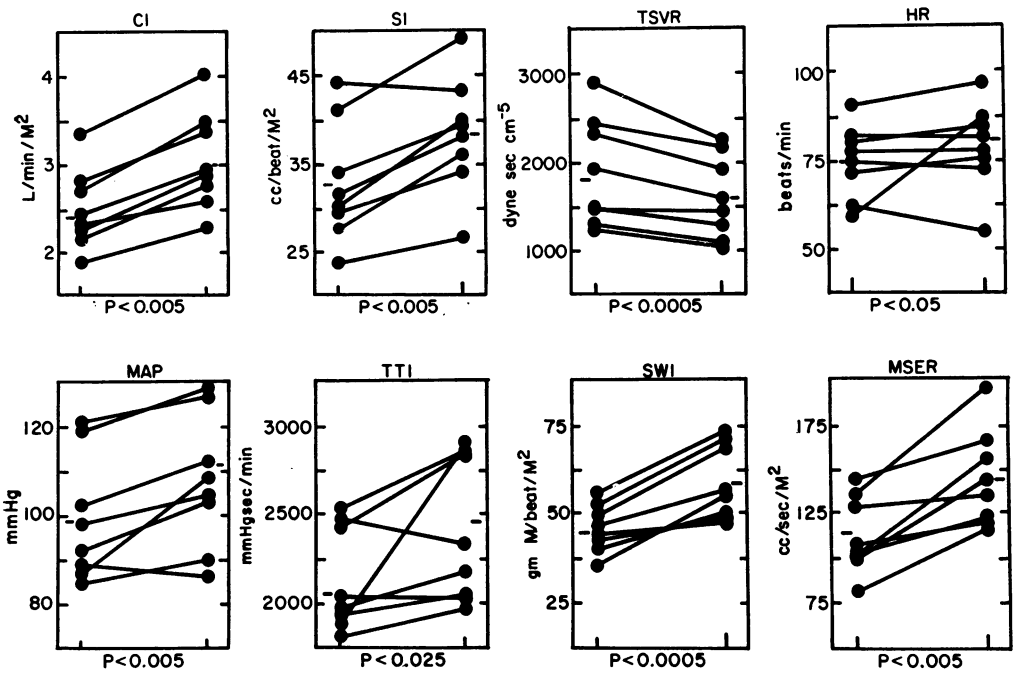
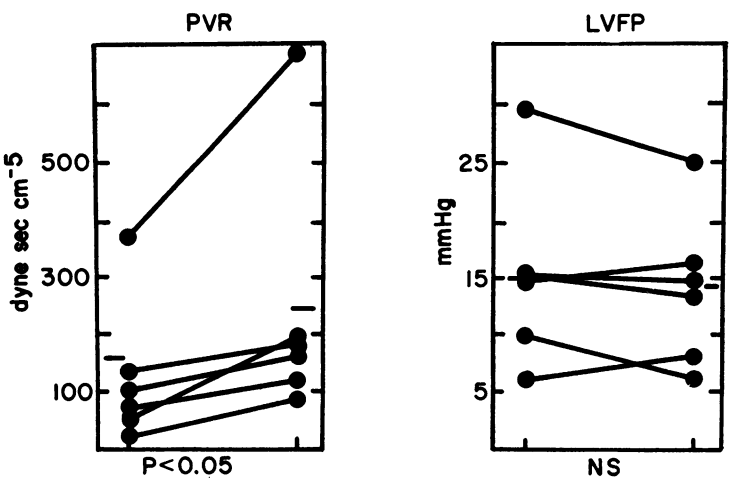


FIG. 1 *Individual control and peak responses of various haemodynamic parameters in eight subjects with acute myocardial infarction after administration of glucagon, 70 μg./kg. intravenously. Mean values are represented by small horizontal bars. CI, cardiac index; SI, stroke index; TSVR, total systemic vascular resistance; HR, heart rate; MAP, mean arterial pressure; TTI, time-tension index; SWI, stroke work index; MSER, mean systolic ejection rate.*

(Farah and Tuttle, 1960) a number of isolated papillary muscle and animal studies have appeared (Glick *et al.*, 1968; Lucchesi, 1968; Mayer, Namm, and Rice, 1970). These studies have shown that glucagon produces an increase in the contractile state of the myofibril, which results in an increase in cardiac output with a decrease in left ventricular end-diastolic pressure. The mechanism by which glucagon exerts its cardiotonic effect is related to its activation of the adenyl cyclase system with a resultant increase in 3′, 5′ cyclic adenosine monophosphate (cyclic AMP). In this respect glucagon is similar to the catecholamines.

Clinical trials of glucagon have centred on several different patient groups, including normal subjects and patients with heart disease. Normal subjects studied during cardiac catheterization have shown significant increases in cardiac output and left ventricular peak pressure (Mahon *et al.*, 1968). Patients undergoing cardiac surgery have also been studied during the first postoperative day and show similar cardiovascular responses (Parmley *et al.*, 1969). The haemodynamic effects of glucagon in cardiogenic shock have been less systematically studied, but clinical benefits

FIG. 2 *Individual control and peak responses in pulmonary vascular resistance (PVR) and left ventricular filling pressure (LVFP) (pulmonary capillary wedge or pulmonary artery end-diastolic pressure) in six patients with acute myocardial infarction after intravenous administration of 70 μg./kg. glucagon. Mean values are represented by small horizontal bars.*



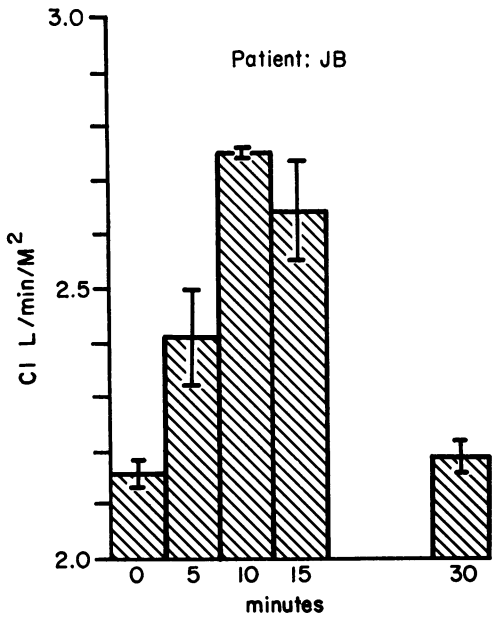


FIG. 3 *Time course of the change in cardiac index (CI) after a dose of 70 μg./kg. glucagon administered intravenously over two minutes in a patient with acute myocardial infarction and left ventricular failure. Each bar represents the average of two determinations. The individual determinations are represented by brackets.*

from glucagon administration have been observed in a small series of cases (Mahon *et al.*, 1968; Vander Ark and Reynolds, 1969; Eddy *et al.*, 1969).

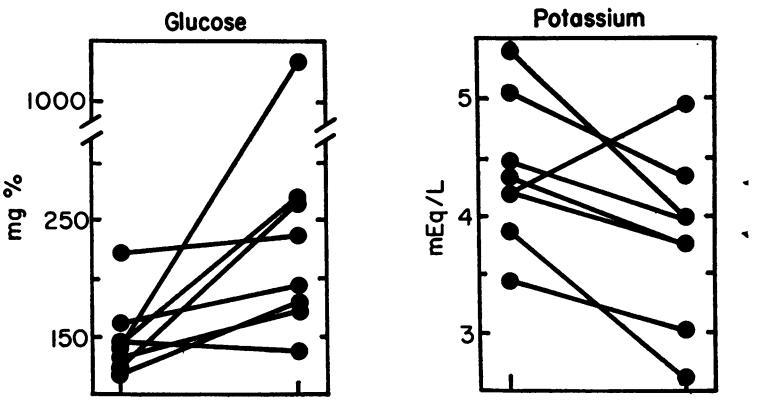
In contrast, the effectiveness of glucagon in patients with chronic congestive heart failure has been variable. Williams (1969) reported the effects of glucagon on 18 patients treated with a constant intravenous infusion of glucagon (1–4 mg./hr.) for up to 96 hours. Seven patients improved, 8 were unaffected, and 3 deteriorated during treatment. This diminished effectiveness of glucagon in chronic congestive heart failure is supported by the recent animal studies of Gold *et al.* (1969), in which an absence of any haemodynamic effects of glucagon was observed after the production of acute right ventricular hypertrophy and failure by pulmonary artery banding in cats. Further investigation by particulate fraction studies showed that glucagon failed to activate the adenyl cyclase system of these hearts.

The present study reports our experience in the administration of glucagon to individuals with acute myocardial infarction and a variable degree of left ventricular failure. In these individuals cardiovascular responsiveness to glucagon administration was maintained whether or not mild chronic left ventricular failure was present before acute infarction. Cardiac output increased 25 per cent. This increase is felt to represent a direct inotropic effect for two reasons. Firstly, arterial pressure increased in the presence of a significant decrease in peripheral vascular resistance. Secondly, stroke index and stroke work both increased while left ventricular filling pressure remained relatively unchanged, thus showing that the increase in cardiac output is not due to a Starling effect.

Pulmonary vascular resistance significantly increased in every patient after glucagon administration. This increase in calculated pulmonary vascular resistance resulted from a widening of the mean pulmonary artery/left ventricular filling pressure gradient in excess of the measured increase in cardiac output, suggesting a primary pulmonary vasoconstriction action of glucagon. Since small changes in the mean pulmonary artery/left ventricular filling pressure gradient can produce large changes in pulmonary vascular resistance the increase may be more apparent than real. The clinical significance of this observation is unclear, however.

Other characteristics of glucagon may contribute to its usefulness in acute myocardial infarction. The effectiveness of glucagon is not attenuated by prior digitalization (Parmley *et al.*, 1968; Williams *et al.*, 1969; Glick *et al.*, 1968) nor blocked by beta-adrenergic blocking agents such as propranolol (Glick *et al.*, 1968; Lucchesi, 1968). Moreover, glucagon does not increase ventricular automaticity

FIG. 4 *Individual control and peak responses in blood glucose and serum potassium in eight patients with acute myocardial infarction after a dose of 70 μg./kg. glucagon administered intravenously.*



in man (Lucchesi, Stutz, and Winfield, 1969), decreases AV conduction time (Whitsitt and Lucchesi, 1968), and increases nodal automaticity (Lucchesi *et al.*, 1969), thereby suggesting its use in heart block. Glomerular filtration rate, filtration fraction, and sodium excretion are all increased (Pullman, Lavender, and Aho, 1967) by a direct action on the renal tubule. This effect may be augmented by the increase in cardiac output and the osmotic diuresis induced by hyperglycaemia.

We have had occasion to treat only two patients with cardiogenic shock by constant intravenous infusion of glucagon. The first patient was unresponsive to large doses of norepinephrine, isoprenaline, and dopamine. Glucagon did not produce any observable benefit in this patient. She continued to manifest irreversible hypotension and died. At necropsy only 15 to 20 per cent viable myocardium was found. The second patient was treated with glucagon after isoprenaline, norepinephrine, and dopamine in small doses all resulted in severe ventricular arrhythmias without increasing the cardiac output. Intravenous infusion of glucagon, 0·2 to 0·5 mg./min., increased the cardiac output, blood pressure, and urine volume while decreasing the central venous pressure and heart rate. No arrhythmias were observed during 18 hours of infusion, after which the patient was able to be maintained without any further inotropic intervention.

In conclusion, glucagon has been shown to be an effective inotropic agent in subjects with acute myocardial infarction and associated left ventricular failure. Potential ancillary benefits may be achieved by its effects on AV nodal conduction and renal dynamics. Side effects, furthermore, are mild in comparison with other inotropic agents and do not appear to be limiting. In selected patients with acute myocardial infarction, therefore, glucagon may be a valuable adjunct to the pharmacological armamentarium.

References

Eddy, J. D., O'Brien, E. T., and Singh, S. P. (1969). Glucagon and haemodynamics of acute myocardial infarction. *British Medical Journal*, **4**, 663.

Farah, A., and Tuttle, R. (1960). Studies on the pharmacology of glucagon. *Journal of Pharmacology and Experimental Therapeutics*, **129**, 49.

Glick, G., Parmley, W. W., Wechsler, A. S., and Sonnenblick, E. H. (1968). Glucagon, its enhancement of cardiac performance in the cat and dog and persistence of its inotropic action despite beta-receptor blockade with propranolol. *Circulation Research*, **22**, 789.

Gold, H. K., Prindle, K. H., Levey, G. S., and Epstein, S. E. (1969). Effects of glucagon on the failing myocardium. *Circulation*, **40**, Suppl. III, 91.

Klein, S. W., Morch, J. E., and Mahon, W. A. (1968). Cardiovascular effects of glucagon in man. *Canadian Medical Association Journal*, **98**, 1161.

Linhart, J. W., Barold, S. S., Cohen, L. S., Hildner, F. J., and Samet, P. (1968). Cardiovascular effects of glucagon in man. *American Journal of Cardiology*, **22**, 706.

Lucchesi, B. R. (1968). Cardiac actions of glucagon. *Circulation Research*, **22**, 777.

——, Stutz, D. R., and Winfield, R. A. (1969). Glucagon: its enhancement of atrioventricular nodal pacemaker activity and failure to increase ventricular automaticity in dogs. *Circulation Research*, **25**, 183.

Mahon, W. A., Morch, J. E., and Klein, S. W. (1968). Cardiovascular effects of intravenous glucagon in man. *Circulation*, **38**, Suppl. VI, 132.

Mayer, S. E., Namm, D. H., and Rice, L. (1970). Effect of glucagon on cyclic 3′, 5′ -AMP, phosphorylase activity and contractility of heart muscle of the rat. *Circulation Research*, **26**, 225.

Murtagh, J. G., Binnion, P. F., Lal, S., Hutchison, K. J., and Fletcher, E. (1970). Haemodynamic effects of glucagon. *British Heart Journal*, **32**, 307.

Parmley, W. W., Glick, G., and Sonnenblick, E. H. (1968). Cardiovascular effects of glucagon in man. *New England Journal of Medicine*, **279**, 12.

——, Matloff, J. M., and Sonnenblick, E. H. (1969). Hemodynamic effects of glucagon in patients following prosthetic valve replacement. *Circulation*, **39**, Suppl. I, 163.

Peel, A. A. F., Semple, T., Wang, I., Lancaster, W. M., and Dall, J. L. G. (1962). A coronary prognostic index for grading the severity of infarction. *British Heart Journal*, **24**, 745.

Pullman, T. N., Lavender, A. R., and Aho, I. (1967). Direct effects of glucagon on renal hemodynamics and excretion of inorganic ions. *Metabolism*, **16**, 358.

Recommendations of the Committee on Definitions, Combined Myocardial Infarction Research Units Meetings, November 11–12, 1969, Dallas, Texas. (Unpublished syposium).

Vander Ark, C. R., and Reynolds, E. W., Jr. (1969). Continuous infusion of glucagon in cardiogenic shock. *Circulation*, **40**, Suppl. III, 206.

Whitsitt, L. S., and Lucchesi, B. R. (1968). Effects of beta-receptor blockade and glucagon on the atrioventricular transmission system in the dog. *Circulation Research*, **23**, 585.

Williams, J. F. (1969). Glucagon and the cardiovascular system. *Annals of Internal Medicine*, **71**, 419.

Williams, J. F., Jr., Childress, R. H., Chip, J. N., and Border, J. F. (1969). Hemodynamic effects of glucagon in patients with heart disease. *Circulation*, **39**, 38.