

Plasma catecholamines in the acute phase of the response to myocardial infarction

R. A. LITTLE, K. N. FRAYN, P. E. RANDALL,
†H. B. STONER, *C. MORTON, D. W. YATES AND
*G. S. LAING

*MRC Trauma Unit and * Accident and Emergency Department, Hope Hospital, Eccles Old Road, Salford, Manchester, England*

SUMMARY

Plasma catecholamine (adrenaline, noradrenaline and dopamine) concentrations have been measured in 48 patients within 6 hours of the onset of symptoms of an acute myocardial infarction. The concentrations of all three catecholamines were elevated, and there were positive correlations between plasma noradrenaline concentrations and the severity of infarct as assessed by the coronary prognostic index and serum LDH levels. Plasma glucose, free fatty acid, lactate and cortisol levels were elevated while insulin levels were reduced. The site of infarction did not influence the pattern of hormonal and metabolic responses although heart rate was significantly lower in the inferior than in the anterior infarct group. Seven patients went into ventricular fibrillation shortly (< 1.8 h) after blood sampling. Plasma catecholamine concentrations were markedly elevated in these patients with levels similar to those previously reported after cardiac arrest.

INTRODUCTION

It is well recognized that sympatho-adrenal activity is increased after myocardial infarction (e.g. Siggers *et al.*, 1971; Januszewicz *et al.*, 1971; Vetter *et al.*, 1974; Little *et al.*, 1985a). The response, as assessed by plasma catecholamine concentrations, is very variable and the explanation for this is not clear. The extent of myocardial ischaemia may, of course, be important (Karlsberg *et al.*, 1981), but the site of infarction may also be relevant. Pantridge (1978) and his colleagues have suggested that an anterior

Correspondence: Dr R. A. Little, MRC Trauma Unit, Stopford Building, Manchester University, Oxford Road, Manchester M13 9PT, England.

†*Present address: Department of Surgery, Hope Hospital, Eccles Old Road, Salford, Manchester M6 8HD.*

infarction leads to a pattern of response characterized by an increase in sympathetic activity whereas after an inferior infarction, an increase in cardiac parasympathetic activity is dominant (Webb *et al.*, 1972; Pantridge, 1978). The relationships between plasma catecholamine concentrations and site of infarction, together with other metabolic and hormonal responses, have now been studied in patients shortly after admission to the accident and emergency department. A small number of these patients suffered a cardiac arrest shortly (<1.8 h) after blood sampling and this allowed us to address, albeit indirectly, the contentious issue of whether high plasma catecholamine concentrations are involved in the pathogenesis of fatal arrhythmias.

Preliminary reports of some of the data included in this paper have already been published (Little *et al.*, 1985b; Little *et al.*, 1985).

METHODS

The study was confined to those patients presenting at the accident and emergency department within 6 h of the onset of symptoms of an acute myocardial infarction, subsequently confirmed by electrocardiographic changes. The site of the infarction was classified as anterior or inferior from the electrocardiogram. Diabetic patients, or those taking steroids or beta-adrenergic blockers, were excluded as were those with an elevated plasma ethanol concentration.

Venous blood samples were taken from an antecubital vein in 48 patients fulfilling these criteria. Heart rate and blood pressure were measured immediately before venepuncture. The blood samples were centrifuged at 4°C immediately and the plasma stored at -20°C until analysis. Glucose, lactate, free fatty acids, ethanol, insulin and cortisol were measured by methods described previously (Stoner *et al.*, 1979). Catecholamine (noradrenaline, adrenaline and dopamine) concentrations were assayed by high-performance liquid chromatography after extraction on ion-exchange resin and alumina (Frayn & Maycock, 1983). Concentrations are indicated in the text by the use of square brackets. Lactate dehydrogenase (LDH), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured by the hospital routine laboratory. Two scoring systems were used in an attempt to assess the severity of infarction (Peel *et al.*, 1962; Wagner *et al.*, 1982).

Statistical methods were based on those described by Snedecor & Cochran (1967). The distributions of the plasma concentrations of noradrenaline, adrenaline, dopamine, glucose, lactate, free fatty acids and insulin were skewed, but this was reduced by conversion to logarithms. The concentrations of cortisol were normally distributed. Relationships between pairs of variables were assessed by both distribution-free (Kendall rank correlation) and parametric (least squares regression) methods; the results were always similar. To investigate the interrelationships between three variables, parametric partial correlation methods had to be used as discussed by Frayn *et al.* (1985).

RESULTS

Some details of the patients are shown in Table 1. Most of the patients were male and the ages of the two groups were very similar. The average delay between the onset of symptoms and initial investigation was approximately 2 hours in both groups. All but four (see below) of the patients were admitted to the coronary care unit or other medical wards after assessment in the accident and emergency department. Seven patients (all male) went into ventricular fibrillation shortly (median 30 min; range 15–105 min) after blood sampling and three of these were successfully resuscitated. Overall, there were eight deaths during the fortnight following admission to hospital. Heart rate, measured just before blood sampling, was significantly lower in those with an inferior than with an anterior infarct (Table 1). This difference is emphasized by the fact that although only 1 (5%) of the 'anterior' group had a heart rate below 70 beats min^{-1} the number rose to 13 (45%) in the inferior group.

Plasma catecholamine concentrations were elevated in both groups of patients compared with control values measured in the same laboratory (noradrenaline, 2.1 nmol/l; adrenaline 0.39 nmol/l; dopamine 0.1 nmol/l—Little *et al.*, 1985a; Frayne *et al.*, 1985) and there were no significant differences between the groups (Table 2). There

Table 1 Clinical features of patients

Area of infarction	No. of patients (♀)	Age (years) Median (range)	Time (hours)* Median (range)	Heart rate	Deaths
				(beats/min) Mean \pm SEM (range)	
Anterior	19 (3)	60 (24–82)	2.0 (0.5–6.0)	92 \pm 5 (60–138)	5
Inferior	29 (10)	63 (26–83)	1.75 (0.5–6.0)	72 \pm 3 (48–110)	3

* Interval between onset of symptoms and taking of blood sample.

** Significantly different from 'anterior' value at $P < 0.01$.

Table 2 Plasma concentrations of metabolites and hormones in patients shortly after myocardial infarction (anterior or inferior). The concentrations are shown as arithmetic means or geometric means for log-normally distributed variables (shown by *) with SD ranges

Variable	Unit	Anterior		Inferior	
		Mean	SD range (n)	Mean	SD range (n)
Glucose*	mmol/l	6.57	4.59– 9.42 (19)	6.31	4.64– 8.56 (29)
Free fatty acids*	mmol/l	0.82	0.52– 1.30 (19)	0.68	0.44– 1.03 (29)
Lactate*	mmol/l	2.48	2.18– 2.81 (19)	2.06	1.28– 3.34 (29)
Noradrenaline*	nmol/l	7.42	3.17–17.4 (19)	5.39	2.44– 9.88 (29)
Adrenaline*	nmol/l	1.14	0.30– 4.40 (19)	1.21	0.53– 2.77 (29)
Dopamine*	nmol/l	0.29	0.04– 2.48 (19)	0.13	0.03– 0.60 (28)
Insulin*	munit/l	12.9	7.1 –21.2 (18)	10.8	4.0 –29.5 (29)
Cortisol	$\mu\text{mol/l}$	1.18	0.55– 1.81 (19)	1.08	0.74– 1.42 (29)

was no relationship between plasma catecholamine concentration and the time interval between onset of symptoms and sampling. It is, perhaps, of interest that the four patients with the highest plasma noradrenaline concentrations (17.7–118.0 nmol/l; median 47.6) were in the 'early-arrest' group (see above).

The plasma concentrations of glucose, lactate, free fatty acids and cortisol were all elevated compared with control values in people of similar ages (Little *et al.*, 1985a; Foster *et al.*, 1978) but again the values in the two groups were similar (Table 2). However, plasma glucose, lactate and cortisol, but not free fatty acid, concentrations were significantly higher ($P < 0.05$, in all cases) in the 'early arrest' than in the non-arrest infarction patients.

When all the patients were considered together it was found that the plasma concentrations of noradrenaline, adrenaline and dopamine were all correlated one with another ($P < 0.001$ in all cases). Analysis of partial correlation coefficients showed that although both the log adrenaline and log dopamine concentrations were significantly related to log noradrenaline concentration independently of each other (partial correlation coefficients 0.45, $P < 0.01$ and 0.68, $P < 0.01$ respectively) they were not significantly related to each other at a constant noradrenaline concentration, thus suggesting that dopamine was released together with noradrenaline rather than with adrenaline. There was a significant positive correlation between heart rate and plasma noradrenaline concentration ($r = 0.42$; $P < 0.01$). Blood pressure (systolic or diastolic) was not related to either plasma noradrenaline or adrenaline concentration.

Both plasma glucose and lactate concentrations were positively related to those of noradrenaline and adrenaline ($P < 0.001$ in all cases). There were no significant relationships between plasma free fatty acid concentrations and any of the catecholamines.

Plasma cortisol concentrations were positively related to both plasma noradrenaline ($r = 0.50$; $P < 0.001$) and plasma adrenaline ($r = 0.46$; $P < 0.01$) concentrations. Analysis of partial correlation coefficients showed that the relationship between cortisol and log adrenaline concentration was secondary to that between the log concentrations of adrenaline and noradrenaline.

Plasma insulin concentrations were very variable (0.5–91.7 munit/l) and not directly related to plasma adrenaline or noradrenaline concentrations. However, at plasma adrenaline concentrations above 2.0 nmol/l the plasma insulin concentrations were all low (range 4.6–21 munit/l) although plasma glucose concentrations ranged from 4.3 to 17.3 mmol/l).

The only significant correlation between plasma catecholamine and serum enzyme levels was between noradrenaline and LDH measured within 24 h of the onset of symptoms ($r = 0.44$, $P < 0.05$; $n = 21$). The QRS scoring system suggested by Wagner *et al.* (1982) was found to have too many exclusions to be of value in this study. However, there was a significant correlation between plasma noradrenaline concentrations and the coronary prognostic index (Peel *et al.*, 1982) in the 19 patients in whom it was possible to ascribe an index retrospectively ($r = 0.51$; $P < 0.05$).

DISCUSSION

The present study confirms that plasma catecholamine concentrations are increased in the acute phase of the response to myocardial infarction (Ceremuzyński, 1981). Both components of the sympathetic nervous system are involved with an increase in noradrenaline released from post-ganglionic sympathetic nerve terminals (Wollenberger *et al.*, 1967) and adrenaline from the adrenal medulla (Callingham, 1967; Cryer, 1980). Our results support the view that dopamine is released together with noradrenaline rather than with adrenaline, as is the case after accidental injury (Frayn *et al.*, 1985).

The increase in sympathetic efferent activity will be due to a number of factors including changes in cardiovascular baro- and chemoreceptor activity and a reflex stimulation of adrenal medullary secretion from cardiac receptors at the site of infarction acting via vagal afferents (Staszewska-Barczak, 1971). The tissue sites of the increased release of noradrenaline and dopamine are unknown. The heart may be important as it has a dense sympathetic innervation, although at rest spillover of noradrenaline from the heart contributes only 3% of total body noradrenaline release to plasma (Esler *et al.*, 1984). The sympathetic outflow to skeletal muscle is probably more important, especially in stress states (Wallin, 1984), and it must be remembered that blood samples were taken from an antecubital vein which drains a predominantly muscular vascular bed.

The increase in plasma noradrenaline concentration was directly related to the severity of infarct, as judged by the increases in LDH levels and the coronary prognostic index. In some patients the plasma catecholamines were very high, similar to those in patients with cardiac arrest (Little *et al.*, 1985a) and indeed those patients with the highest noradrenaline levels subsequently went into ventricular fibrillation. A role for endogenous catecholamines in precipitating such a potentially fatal arrhythmia cannot be discounted and it is possible to envisage a vicious cycle in which disturbances in myocardial activity produce a reflex increase in plasma catecholamines, which stimulate the myocardium but also sensitize it to further arrhythmias thereby further reducing myocardial efficiency (Bertel *et al.*, 1982). There is no doubt that in the present study a very high plasma noradrenaline concentration shortly after myocardial infarction was a harbinger of doom and a rapid method for estimating plasma noradrenaline would aid in the identification of those patients at risk. This poses the question as to whether β -blocking agents, which may be of benefit when given late (e.g. after admission to the coronary care unit—Baber & Lewis, 1982), should be administered as soon as the diagnosis of myocardial infarction is made in the accident and emergency department. Obviously in making such a decision, due attention must be paid to any possible deleterious effects of losing the positive ino- and chronotropic influences of the catecholamines.

Heart rate was positively correlated, albeit weakly, with plasma noradrenaline concentrations. Such a relationship has not previously been found after myocardial infarction (Karlsberg *et al.*, 1981), although it agrees with findings in man at rest and during exercise or a cold pressor test (Halter *et al.*, 1984; Leblanc *et al.*, 1980). Is it possible that heart rate could be used as an indicator of the very high catecholamine levels? Unfortunately heart rate is influenced not only by the severity but also, and

perhaps most importantly, by the site of infarction. Our study confirms the observations of Pantridge and his colleagues (Webb *et al.*, 1972; Pantridge, 1978) that inferior infarctions are commonly associated with a bradycardia. It has been proposed that the bradycardia is due to a reflex increase in cardiac vagal activity elicited from receptors in the left ventricle with unmyelinated C-fibre afferents travelling in the vagus (Thoren, 1979). These ventricular receptors are activated not by chemicals but by stretch, perhaps following bulging of the ischaemic myocardium during systole. The increased incidence of bradycardias following inferior infarcts has been ascribed to an especially dense innervation by vagal afferents of the posterior part of the heart (Szentivanyi & Juhasz-Nagy, 1962; Perez-Gomez & Garcia-Aguado, 1977).

Despite the marked effects the site of infarction has on heart rate it has no influence on the metabolic and hormonal responses. The pattern of these responses was similar to that described following activation of the sympathoadrenal system by accidental injury in man (Frayn *et al.*, 1985). The hyperglycaemia is due to increased production of glucose by the liver and an impairment of peripheral glucose utilization. Adrenaline is involved in these processes as well as in stimulating lactate production from muscle glycogen. The increased plasma lactate concentration probably also reflects a reduction in tissue oxygenation secondary to disturbances in peripheral blood flow. These changes in peripheral circulation may also explain the absence of a relationship between plasma catecholamine and free fatty acid concentration (Stoner *et al.*, 1979). The fatty acid levels are elevated after myocardial infarction and it has been suggested that high levels (> 1.2 mmol/l) are associated with an increased incidence of arrhythmias (Oliver *et al.*, 1968; Januszewicz *et al.*, 1971; Tansey & Opie, 1983). This view is not supported by Nelson (1970) or by the present results in which five patients had plasma free fatty acids above 1.2 mmol/l and only one of these went into ventricular fibrillation (i.e. of the seven patients who went into ventricular fibrillation shortly after sampling, only one had a plasma fatty acid concentration above the 1.2 mmol/l threshold).

Plasma cortisol concentrations were elevated, often to very high levels (> 1.5 μ mol/l), and significantly correlated with plasma noradrenaline concentration. This was surprising as no such relationship has been found in other stress states (e.g. accidental injury—Frayn *et al.*, 1985; surgery—Mannelli *et al.*, 1982). Low plasma insulin concentrations in the presence of high glucose levels have been noted previously after myocardial infarction (Vetter *et al.*, 1974) and they can be explained by the suppression of insulin secretion by adrenaline. It has been shown that plasma adrenaline levels of 400 pg/ml (2.2 nmol/l) suppress insulin secretion in man (Clutter *et al.*, 1980) and in the present study insulin concentrations were uniformly low when plasma adrenaline was at or above this level.

ACKNOWLEDGEMENTS

We are grateful to Mrs R. Atkins, Miss J. Fairhurst, Miss S. Matthews, Miss P. Maycock, Mr B. Passingham and Mr J. Rose for their skilled technical assistance and to the senior nursing staff of the Accident and Emergency Department for their co-operation.

REFERENCES

- Baber N. S. & Lewis J. A. (1982) Confidence in results of beta-blocker postinfarction trials. *British Medical Journal* **284**, 1749–50.
- Bertel O., Bühler F. R., Baitchs G., Ritz R. & Burkart F. (1982) Plasma adrenaline and noradrenaline in patients with acute myocardial infarction. Relationship to ventricular arrhythmias of varying severity. *Chest* **82**, 64–8.
- Callingham B. A. (1967) The Catecholamines. Adrenaline, noradrenaline. In *Hormones in Blood*, vol. 2, C. H. Gray & A. L. Bacharach (eds), 519–89. New York, Academic Press.
- Ceremuzynski L. (1981) Hormonal and metabolic reactions evoked by acute myocardial infarction. *Circulation Research* **48**, 767–76.
- Clutter W. E., Bier D. M., Shah S. D. & Cryer P. E. (1980) Epinephrine plasma metabolic clearance rates and physiologic thresholds for metabolic and hemodynamic actions in man. *Journal of Clinical Investigation* **66**, 94–101.
- Cryer P. E. (1980) Physiology and pathology of the human sympathoadrenal neuroendocrine system. *New England Journal of Medicine* **303**, 436–44.
- Esler M., Jennings G., Leonard P., Sacharias N., Burke F., Johns J. & Blombery P. (1984) Contribution of individual organs to total noradrenaline release in humans. *Acta Physiologica Scandinavica Supplementum* **527**, 11–16.
- Foster K. J., Alberti K. G. M. M., Hinks L., Lloyd B., Postle A., Smythe P., Turnell D. C. & Walton R. (1978) Blood intermediary metabolite and insulin concentrations after an overnight fast: Reference values for adults, and interrelations. *Clinical Chemistry* **24**, 1568–72.
- Frayn K. N., Little R. A., Maycock P. F. & Stoner H. B. (1985) The relationship of plasma catecholamines to acute metabolic and hormonal responses to injury in man. *Circulatory Shock* **16**, 229–40.
- Frayn K. N. & Maycock P. F. (1983) Sample preparation with ion-exchange resin before liquid-chromatographic determination of plasma catecholamines. *Clinical Chemistry* **29**, 1426–8.
- Halter J. B., Stratton J. R. & Pfeifer M. A. (1984) Plasma catecholamines and hemodynamic responses to stress states in man. *Acta Physiologica Scandinavica Supplement* **527**, 31–8.
- Januszewicz W., Sznajderman M., Ciswicka-Sznajderman M., Wocial B. & Rymaszewski Z. (1971) Plasma free fatty acid and catecholamine levels in patients with acute myocardial infarction. *British Heart Journal* **33**, 716–18.
- Karlsberg R. P., Cryer P. E. & Roberts R. (1981) Serial plasma catecholamine response early in the course of clinical acute myocardial infarction: relationship to infarct extent and mortality. *American Heart Journal* **102**, 24–9.
- Leblanc J., Cote J., Jobin M. & Labrie A. (1980) Effects of physical and mental stress on plasma catecholamines and cardiovascular parameters. In *Catecholamines and Stress: Recent Advances*, E. Usdin, R. Kuetnamski & I. J. Kopin (eds), 255–8. Developments in Neuroscience, Vol. 8. Elsevier, Amsterdam.
- Little R. A., Frayn K. N., Randall P. E., Stoner H. B., Yates D. W., Laing G. S., Kumar S. & Banks J. M. (1985a) Plasma catecholamines in patients with acute myocardial infarction and in cardiac arrest. *Quarterly Journal of Medicine, New Series* **54**, 214, 133–40.
- Little R. A., Frayn K. N., Randall P. E., Stoner H. B. & Maycock P. F. (1985b) Plasma catecholamine concentrations in acute states of stress and trauma. *Archives of Emergency Medicine* **2**, 46–7.
- Little R. A., Frayn K. N., Randall P. E. & Yates D. W. (1985) Plasma catecholamines and cardiac arrest (letter). *Lancet*, 509–10.
- Mannelli M., Gheri R. G., Selli C., Turini D., Pampanini A., Giusti G. & Serio M. (1982) A study on human adrenal secretion. Measurement of epinephrine, norepinephrine, dopamine and cortisol in peripheral and adrenal venous blood under surgical stress. *Journal of Endocrinological Investigation* **5**, 91–5.
- Nelson P. G. (1970) Effect of heparin on serum free fatty acids, plasma catecholamines, and the incidence of arrhythmias following acute myocardial infarction. *British Medical Journal* **3**, 735–7.
- Oliver M. F., Kurien V. A. & Greenwood T. W. (1968) Relation between serum free fatty acids and arrhythmias and death after acute myocardial infarction. *Lancet* **1**, 710–15.
- Pantridge J. F. (1978) Autonomic disturbance at the onset of acute myocardial infarction. In *Neural Mechanisms in Cardiac Arrhythmias*, P. J. Schwartz, A. M. Brown, A. Malliani & A. Zanchetti (eds), 7–17. New York, Raven Press.
- Peel A. A. F., Semple T., Wang I., Lancaster W. M. & Dall J. L. G. (1962) A coronary prognostic index for grading the severity of infarction. *British Heart Journal* **24**, 745–60.

- Perez-Gomez F. & Garcia-Aquado A. (1977) Origin of ventricular reflexes caused by coronary arteriography. *British Heart Journal* **39**, 967–73.
- Siggers D. G., Salter C. & Fluck D. C. (1971) Serial plasma adrenaline and noradrenaline levels in myocardial infarction using a new double isotope technique. *British Heart Journal* **33**, 878–83.
- Snedecor G. W. & Cochran W. G. (1967) *Statistical Methods* (6th ed.), Ames, Iowa State University Press.
- Staszewska-Barczak J. (1971) The reflex stimulation of catecholamine secretion during the acute stages of myocardial infarction in the dog. *Clinical Science* **40**, 419–39.
- Stoner H. B., Frayn K. N., Barton R. N., Threlfall C. J. & Little R. A. (1979) The relationships between plasma substrates and hormones and the severity of injury in 277 recently injured patients. *Clinical Science* **56**, 563–73.
- Szentivanyi M. & Juhasz-Nagy A. (1962) Two types of coronary vasomotor reflexes. *Quarterly Journal of Experimental Physiology* **47**, 289–98.
- Tansey M. J. B. & Opie L. H. (1983) Relation between plasma free fatty acids and arrhythmias within the first twelve hours of acute myocardial infarction. *Lancet* **ii**, 419–22.
- Thoren P. (1979) Role of cardiac vagal c. fibres in cardiovascular control. *Reviews Physiology, Biochemistry and Pharmacology* **86**, 1–94.
- Vetter N. J., Adams W., Strange R. C. & Oliver M. F. (1974) Initial metabolic and hormonal response to acute myocardial infarction. *Lancet* **i**, 284–9.
- Wagner G. S., Freye C. J., Palmeri S. T., Roark S. F., Stack N. C., Ideker R. E., Harrell R. E. & Silvester R. H. (1982) Evaluation of a QRS scoring system for estimating myocardial infarct size: I Specificity and observer agreement. *Circulation* **65**, 342–7.
- Wallin B. G. (1984) Muscle sympathetic activity and plasma concentrations of noradrenaline. *Acta Physiologica Scandinavica Supplementum* **527**, 21–4.
- Webb S. W., Adgey A. A. J. & Pantridge J. F. (1972) Autonomic disturbance at onset of acute myocardial infarction. *British Medical Journal* **3**, 89–92.
- Wollenberger A., Krause E. G. & Shabab L. (1967) Endogenous catecholamine mobilization and the shift to anaerobic energy production in the acutely ischaemic myocardium. In *Coronary circulation and energetics of the myocardium*, G. Marchetti & B. Taccardi (eds). Basel, Karger.