Plasma aldosterone levels during hospitalization are predictive of survival post-myocardial infarction

Barry R. Palmer*, Anna P. Pilbrow, Christopher M. Frampton, Tim G. Yandle, Lorraine Skelton, M. Gary Nicholls, and A. Mark Richards

Aims
Plasma aldosterone levels have been shown to be associated with adverse clinical outcomes after ST-elevation myocardial infarction (STEMI). We investigated whether aldosterone levels in patients presenting with STEMI or non-STEMI are predictive of mortality during prolonged follow-up.

Methods and results
Aldosterone levels were assayed in plasma taken from 583 patients within 24–96 h following acute myocardial infarction (MI). The median plasma aldosterone level was 108 pmol/L and all values were below the upper limit of the normal range (800 pmol/L) except for five patients (0.9%). Aldosterone tertile was significantly associated with increasing plasma levels of NTproBNP (N-terminal pro-B-type natriuretic peptide), BNP (B-type natriuretic peptide), epinephrine, and endothelin-1 (P < 0.010), but not ANP (atrial natriuretic peptide). Patients in the lowest aldosterone tertile had a significantly better survival, over 5 years’ follow-up, than those in the upper two tertiles (P = 0.0023). Multivariable analysis showed that aldosterone was a significant predictor of survival following adjustment for established predictors (tertile 1 vs. tertile 3; hazard ratio = 2.19, P = 0.018). Patients with above-median levels of both NTproBNP and aldosterone had significantly greater mortality than the remaining patients (above-median 39.8%, other patients ≥25.3% mortality, P < 0.026).

Conclusion
Plasma aldosterone levels post-MI are independent predictors of survival and hospitalization for heart failure over a 5-year-follow-up period.

Keywords
Myocardial infarction • Hormones • Mortality • Prognosis • Aldosterone

Introduction
Aldosterone has long been known as an important regulator of volume, electrolyte, and blood pressure homeostasis through actions primarily on the kidney, but also on the gastrointestinal tract and salivary glands. These effects, involving DNA-directed RNA-mediated protein synthesis, are of known pathophysiological importance in a variety of disorders including heart failure. More recently it has become clear that aldosterone also has relatively rapid onset effects on a variety of non-genomic pathways in epithelial and non-epithelial tissues.1

The central pathophysiological role of aldosterone in heart failure has been confirmed and underlined by studies showing that blockade of mineralocorticoid receptors by spironolactone or eplerenone translates into a survival benefit for patients with heart failure associated with a reduced left ventricular ejection fraction (LVEF) as shown by the Randomized Aldactone Evaluation Study and heart failure post-acute myocardial infarction (MI) in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) study.2,3 In contrast, the pathophysiological importance of aldosterone following acute MI without heart failure is less clear. A recent study by
Beguyi et al. showed that patients with plasma aldosterone levels in the highest quartile upon hospitalization with acute ST-elevation MI (STEMI) had a worse outcome over 6 months than those presenting with lower aldosterone levels. We have investigated the possibility that aldosterone levels in all patients presenting with acute MI, whether STEMI or non-STEMI, are predictive of mortality during prolonged follow-up.

Methods

Patients

Patients were admitted to Christchurch Hospital between November 1994 and June 2001 and recruited to the Post-MI (PMI) Study using criteria described previously. MI was defined by typical ischaemic symptoms, ischaemic change (including ST-elevation or depression or dynamic T-wave changes, i.e. includes ST-elevation, non-ST-elevation, Q-wave, and non-Q-wave infarcts) in two or more electrocardiogram leads and peak elevation of plasma creatine kinase (CK) to at least twice the upper limit of normal. All patients were troponin-T positive. Inclusion criteria included age <80 years, absence of immediate heart failure or cardiogenic shock, and survival for at least 24 h after the onset of symptoms associated with MI. During the study period 2963 patients with MI were admitted to the coronary care unit. Four per cent died within 24 h of onset of symptoms, 11% were excluded as peak CK did not exceed 400 U/L, and a further 45 (1.5%) were aged >80 years. Of the remaining 2473 eligible patients, 1098 consented to participate in the study. Patient follow-up was for 5 years. Clinical events over this period were determined from recruitment and follow-up questionnaires, planned follow-up clinic visits, patient notes, and the New Zealand National Health Information Service and local hospital Patient Management System database. Data on mortality/survival for the full 5 years of follow-up were available for all 583 cohort patients, but accurate information on heart failure admission was available for only 546 patients. The investigation conforms to the principles outlined in the Declaration of Helsinki and was approved by the Canterbury Ethics Committee. All participating patients provided written, informed consent.

Biochemical measurements

Blood samples were taken in hospital 24–96 h after the onset of symptoms through an intravenous cannula placed at least 30 min before sampling, with the patients resting quietly while semi-recumbent. Samples were drawn into chilled vacutainers containing ethylenediaminetetraacetic acid, placed on ice and centrifuged within 20 min at 4°C, and the plasma stored at −80°C before assay for aldosterone, the natriuretic peptides (atrial natriuretic peptide, ANP, B-type natriuretic peptide, BNP, and N-terminal proBNP, NTproBNP), catecholamines, and endothelin-1 as previously described. Levels of CK and troponin-T were measured using ELISA kits (Roche Diagnostics). Left ventricular function was assessed by radionuclide ventriculography within 24–96 h of onset of MI and within 24 h of blood sampling. Endogenous creatinine clearance was calculated by the Cockcroft–Gault formula.

Statistical analysis

Univariate analysis was performed using χ² and ANOVA tests. Skewed data (notably plasma hormones) were log-transformed. Survival and other clinical endpoints (admission for unstable angina, reinfarction, admission for acute heart failure, cardiac readmission, and other non-cardiac admissions) were assessed using Kaplan–Meier survival curves and log-rank tests. A Cox proportional hazard model was used to investigate the independent association of aldosterone and all-cause mortality. The model included established predictors of prognosis (age, NTproBNP levels, admission LVEF, ST-elevation status, β-blocker and lipid-lowering drug treatment, and creatinine clearance) and aldosterone levels. A Receiver–Operator Curve analysis of the predicted survival probabilities was employed to determine any trends in non-linearity of predictors and found no evidence of this. All analyses were performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA) and a two-sided P-value <0.05 was taken to indicate statistical significance.

Results

Baseline characteristics

Plasma aldosterone levels were available from 583 of 1098 patients admitted with acute MI over the study period. Patients were selected only by availability of stored plasma sufficient for the measurement of aldosterone and we believe this selection was essentially random. These selected patients did not differ significantly from the rest of the cohort in terms of baseline characteristics, with the exception being the prevalence of lipid-lowering drug treatment at discharge (selected 47.5%, unselected 41%, P = 0.029) (Table 1). Baseline patient characteristics are shown in Table 1. More than 80% of patients had a non-STEMI. Over a third of patients were known to have antecedent hypertension and a similar percentage had dyslipidaemia and 18% had a history of previous MI.

Hormones

The median plasma aldosterone level was 108 pmol/L and the interquartile range was 102 pmol/L. The patient population was divided into tertiles defined by aldosterone levels of: <83.2, 83.2–141, and >141 pmol/L. Only five patients (0.9%) in the highest tertile had plasma levels of aldosterone above the upper limit of normal (800 pmol/L). Aldosterone tertile was significantly associated with increasing levels of NTproBNP, BNP, epinephrine, and endothelin-1 (P ≤ 0.010), but not ANP (Table 2). Kidney function as assessed by both admission plasma creatinine and creatinine clearance was also associated with aldosterone tertile, with the highest tertile having the highest plasma creatinine and the lowest calculated creatinine clearance (P < 0.001, Table 2). Aldosterone level was also significantly correlated with NTproBNP, BNP, epinephrine, endothelin-1, creatinine, and creatinine clearance (Table 2). Ethnic profile was not significantly different between aldosterone tertiles (tertile 1: 87.2% European; tertile 2: 82.7% European; tertile 3: 79.6% European; P = 0.457).

Medications and revascularization

Drug treatment at admission and discharge was associated significantly with aldosterone level (Table 3). In particular diuretic treatment at both admission and discharge was significantly associated with higher levels of aldosterone than that observed in the untreated patient groups. Patients medicated with angiotensin converting enzyme (ACE) inhibitors at admission had significantly lower levels of aldosterone, while patients discharged on lipid-lowering drugs had significantly lower aldosterone levels during hospitalization. Thrombolytic treatment was administered...
to 61.6% of patients. Patients in tertile 1 were more likely to have received thrombolysis, but this did not reach significance (tertile 1: 65.8%, tertile 2: 60.1%, tertile 3: 58.9%; \( P = 0.355 \)). However, patients from tertile 1 were less likely to have received the thrombolytic streptokinase and more likely to have received tissue plasminogen activator (\( P < 0.001 \), Table 3). Revascularization by percutaneous transluminal coronary angioplasty (PTCA) was attempted in 110 (18.9%) patients and rates of PTCA did not differ between tertile groups (\( P = 0.183 \)).

**Five-year-follow-up**

Patient survival was associated with aldosterone tertile. Patients in the tertile with the lowest aldosterone levels had significantly better survival than those in the other two tertiles (Figure 1). Multivariable analysis using a Cox’s proportional hazards model showed that aldosterone tertile or aldosterone as a continuous variable was significantly associated with survival following adjustment for the established predictors of age, NTproBNP levels, admission LVEF, \( \beta \)-blocker and lipid-lowering drug treatment, and creatinine clearance (Table 4). The independent association of aldosterone level with survival was observed in both STEMI and non-STEMI subgroups of the cohort, and STEMI status was not a significant independent predictor of survival in our multivariable model (Table 4).

An overall trend towards a greater incidence in heart failure admissions (\( P = 0.085 \)) was associated with aldosterone tertile, and heart failure admissions were significantly greater within 5 years in tertile 3 compared with tertile 1 (tertile 3: 5.43%, tertile 1: 2.72%, \( P = 0.033 \) (Figure 2). Other clinical outcomes such as PTCA, coronary artery bypass graft, reinfarction and time to first cardiovascular readmission were not significantly associated with aldosterone tertile during the 5-year-follow-up period (\( P > 0.144 \)). There was no association of time to first non-cardiovascular admission with aldosterone tertile (\( P = 0.676 \)).

The cohort was also stratified by above- and below-median aldosterone and above- and below-median NTproBNP levels. Kaplan–Meier analysis showed that patients with both above-median aldosterone and above-median NTproBNP levels during the index admission were significantly more likely to die within the follow-up period than the other three groups of patients (Figure 3).

**Discussion**

**Aldosterone post-myocardial infarction**

Neurohormonal activation at the time of acute MI is well documented. The emphasis, however, has been on the hypothalamic–pituitary–cortisol axis, the sympathetic nervous system as reflected by circulating levels of catecholamines, and the renin–
angiotensin system. That aldosterone levels in both urine and plasma often rise PMI, especially with large infarcts and when complicated by the development of cardiac failure, is less well known despite observations from as early as the 1950s—as summarized in 1981 by Ceremuzynski. The possibility that aldosterone may have adverse effects in the peri-infarct period was raised as early as the 1960s. In patients developing heart failure after MI, the pathophysiological importance of aldosterone is underlined by the EPHEUS study wherein blockade of mineralocorticoid receptors with eplerenone provided benefits with regard to both mortality and morbidity over the 16-month-follow-up period. What is not known is whether higher vs. lower aldosterone levels in patients, who do not develop heart failure in the immediate post-infarct period, is associated with adverse effects. The answer to this question for patients suffering from a STEMI might now be viewed in the affirmative since, as reported by Beygui et al., higher vs. lower plasma aldosterone levels were associated with early and late adverse clinical outcomes. The question, however, remains unanswered for the much larger number of patients who present with a non-STEMI.

Aldosterone levels and survival

Our study is in a large cohort of patients with acute MI from a single centre and with prolonged follow-up. Patients included those with either STEMI or non-STEMI, and immediate heart failure was an exclusion criterion. Study conditions were carefully controlled and our hormone assays are well established. The principal finding is that patients in the highest tertile for aldosterone levels on admission had a worse survival over the 5-year-follow-up compared with those in the lowest tertile. Multivariable analysis revealed that aldosterone tertile remained a significant predictor of survival following adjustment for established predictors. These data, therefore, are confirmatory of the findings of Beygui et al. for patients with STEMI. More importantly, they extend their findings by showing that higher vs. lower aldosterone levels predicted survival in the much larger group of non-STEMI patients who made up >80% of the total cohort. Figure 3 provides evidence that the addition of aldosterone measurements could be used as an adjunct to NTproBNP levels to define a subgroup of patients with very high risk of mortality after acute MI.

Aldosterone levels

There are a number of potential mechanisms that could contribute to elevation of plasma aldosterone levels after acute MI. Stimulation of the renin–angiotensin system after MI and hence high circulating levels of angiotensin II, is a likely contributor to enhanced aldosterone secretion. In this regard, medications used by our patients may have had modulatory actions with diuretics tending to stimulate angiotensin II (and hence aldosterone) production, whilst contrary changes occur with β-blocker and ACE inhibitor therapy. Activation of the hypothalamic–pituitary–adrenal axis may also contribute, since this axis is stimulated soon after MI and adrenocorticotrophic hormone is a potent secretagogue of aldosterone in the short term. Other stimuli to the adrenal glomerulosa may also contribute, such as rise in plasma potassium or a fall in plasma sodium concentration. Finally, it is possible that a decrease in the plasma clearance of

<table>
<thead>
<tr>
<th>Table 2: Hormones and renal function in post-myocardial infarction cohort stratified by tertiles of aldosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma concentration</strong></td>
</tr>
<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td>BNP (pmol/L)</td>
</tr>
<tr>
<td>NTproBNP (pmol/L)</td>
</tr>
<tr>
<td>ANP (pmol/L)</td>
</tr>
<tr>
<td>Endothelin-1 (pmol/L)</td>
</tr>
<tr>
<td>Creatinine (mmol/L)</td>
</tr>
<tr>
<td>Creatinine clearance (mL/s)</td>
</tr>
</tbody>
</table>

aGeometric mean (95% confidence interval).
bCreatinine clearance was calculated using the Cockcroft–Gault equation.
aldosterone, particularly through a reduction in hepatic blood flow and hence clearance of aldosterone by the liver, contributed to the levels of aldosterone we observed.

In fact, plasma aldosterone levels in our study were elevated in only a small minority of patients. This is perhaps not surprising given that blood sampling was undertaken up to 96 h after the onset of symptoms and the percentage of patients with a STEMI (in whom activation of neurohormonal systems is likely to be most vigorous) was small. If indeed higher vs. lower aldosterone levels have deleterious effects after acute MI, one may question what the underlying mechanisms might be. In this regard, the well-known action of aldosterone to retain urinary sodium may lead to expansion of circulating volume and increased cardiac preload at a time of major insult to the left ventricular myocardium. Aldosterone-induced loss of potassium and magnesium into the urine could contribute to arrhythmogenesis. Finally, the more recently described direct, adverse pro-fibrotic actions of aldosterone on the heart, blood vessels, including the endothelium, and baroreflexes might also contribute.

### Table 3

<table>
<thead>
<tr>
<th>In-hospital aldosterone levels of post-myocardial infarction cohort patients stratified by drug treatment status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treated</strong></td>
</tr>
<tr>
<td><strong>Admission medication</strong></td>
</tr>
<tr>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>β-Blocker</td>
</tr>
<tr>
<td>Diuretic</td>
</tr>
<tr>
<td>Lipid-lowering drug</td>
</tr>
<tr>
<td><strong>Discharge medication</strong></td>
</tr>
<tr>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>β-Blocker</td>
</tr>
<tr>
<td>Diuretic</td>
</tr>
<tr>
<td>Lipid-lowering drug</td>
</tr>
<tr>
<td><strong>Thrombolytic drug</strong></td>
</tr>
<tr>
<td>Streptokinase</td>
</tr>
<tr>
<td>TPA</td>
</tr>
</tbody>
</table>

*aGeometric mean (95% confidence interval).

*bACE, angiotensin converting enzyme; TPA, tissue plasminogen activator.

### Figure 1

Survival in the post-myocardial infarction cohort stratified by tertiles of baseline aldosterone level.
**Study limitations**

This was a study not specifically designed to determine the pathophysiological role of aldosterone. Ideally we should like to have measured aldosterone in plasma from all 1098 patients included in the original acute MI cohort but adequate samples were available from only 583 subjects. However those included in the present study appeared representative of the total cohort regarding indices known to alter aldosterone levels including age and vasoactive medications. The cohort was predominantly composed of patients of European ethnicity and these findings should not be extrapolated to other ethnic groups.

**Implications**

Although it is conceivable that the linkage we observed between aldosterone levels on admission and subsequent outcome was not related in a cause and effect manner, we believe it is more likely that higher vs. lower aldosterone levels around the time of acute MI contributed to the differences in mortality we observed. Support for this premise comes from studies in experimental animals which have demonstrated that blockade of mineralocorticoid receptors inhibits the development of cardiac arrhythmias, reduces myocardial necrosis, impairs reactive cardiac fibrosis and limits ventricular remodelling after MI or infusion of.

---

**Table 4** Cox proportional hazards model of predictors of 5-year mortality (n = 450 patients, 87 deaths)

<table>
<thead>
<tr>
<th></th>
<th>df</th>
<th>Significance level</th>
<th>Hazard Ratio</th>
<th>95% Confidence interval for hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>0.017</td>
<td>1.04</td>
<td>1.01</td>
</tr>
<tr>
<td>Log 10 NTproBNPa</td>
<td>1</td>
<td>0.001</td>
<td>4.09</td>
<td>1.79</td>
</tr>
<tr>
<td>LVEF</td>
<td>1</td>
<td>0.006</td>
<td>0.973</td>
<td>0.955</td>
</tr>
<tr>
<td>β-Blocker treatment</td>
<td>1</td>
<td>0.001</td>
<td>2.20</td>
<td>1.36</td>
</tr>
<tr>
<td>Lipid-lowering-drug treatment</td>
<td>1</td>
<td>0.013</td>
<td>1.84</td>
<td>1.14</td>
</tr>
<tr>
<td>ST-elevation (Y vs. N)</td>
<td>1</td>
<td>0.757</td>
<td>1.09</td>
<td>0.621</td>
</tr>
<tr>
<td>Creatinine clearance (Y vs. N)</td>
<td>1</td>
<td>0.156</td>
<td>0.568</td>
<td>0.260</td>
</tr>
<tr>
<td>Log 10 aldosterone (Y vs. N)</td>
<td>1</td>
<td>0.006</td>
<td>2.77</td>
<td>1.33</td>
</tr>
</tbody>
</table>

*a*Hazard ratio represents the change in risk for every 10-fold increase in NTproBNP or aldosterone level.

*b*Creatinine clearance was calculated using the Cockcroft-Gault formula.

---

**Figure 2** Hospitalization for heart failure in the post-myocardial infarction cohort stratified by tertiles of baseline aldosterone level.
catecholamines. With regard to studies in man, Modena et al.\textsuperscript{27} reported that a mineralocorticoid receptor inhibitor, administered at hospital discharge to patients suffering a first episode anterior transmural MI and already receiving an angiotensin-converting enzyme inhibitor, reduced left ventricular volumes and serum levels of the aminoterminal propeptide of type III procollagen at 6 and 12 months. Hayashi et al.\textsuperscript{28} studied a similar cohort of patients with first anterior acute MI and showed that acute (canrenoate) then chronic (spironolactone) mineralocorticoid receptor blockade improved LVEF, reduced left ventricular end-diastolic volume index and suppressed plasma levels of procollagen type III aminoterminal at 1 month. These data from studies in man together with the results of the aforementioned animal studies reinforce the possibility that higher vs. lower plasma levels of aldosterone can adversely affect the outcome after acute MI.

Of particular note in our study is the fact that plasma aldosterone levels were elevated outside the normal range in only a tiny percentage of patients admitted with acute MI. It appears likely, therefore, that variations in circulating aldosterone concentrations within the normal range could have important biological effects which have an impact on long-term survival. Accordingly, our study can be seen as hypothesis generating. The hypothesis is that there may be benefits regarding PMI morbidity and mortality from blocking the actions of aldosterone even in patients whose plasma levels of the hormone are not elevated.

**Clinical perspective**

We have observed that plasma aldosterone levels determined soon after acute MI are independent predictors of survival and hospitalization for heart failure over a 5-year-follow-up period. Our patients are representative of the typical cohort admitted with acute MI. These data extend the findings of Beygui et al.\textsuperscript{4} from STEMI to all types of MI and raise the possibility that blockade of mineralocorticoid receptors might provide benefit with regard to the survival and morbidity in a wide spectrum of patients presenting with acute MI.

**Funding**

Funding from the Health Research Council of NZ and the National Heart Foundation (NHF) of NZ is acknowledged. A.P.P. held a Foundation of Research, Science and Technology Postdoctoral Fellowship and A.M.R. the NHF Chair of Cardiovascular Studies.

**Acknowledgements**

The authors thank participants of the study, Endolab staff for the hormone assays, and study coordinators of the Cardioendocrine Research Group for assistance with the recruitment and follow-up of the patients.

**Conflict of interest:** none declared.

**References**


The above article uses a new reference style being piloted by the EHJ that shall soon be used for all articles.