BRIEF REPORT

LOW SERUM CORTISOL PREDICTS EARLY DEATH FOLLOWING ACUTE MYOCARDIAL INFARCTION

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Abbreviated title Low cortisol predicts death after myocardial infarction

Key (MeSH) terms
Acute Myocardial Infarction; Adrenal Insufficiency; Mortality; Nested Case-Control Study; Prognosis

Word count (main text) 1,130

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Funding NHS Health Scotland project grant and British Heart Foundation programme grant

Disclosure statement All authors declare no conflicts of interest

Abstract

Objective

Low serum cortisol concentrations have been associated with adverse prognosis in critical illness of diverse aetiology. We aimed to determine whether low serum cortisol concentrations are associated with adverse prognosis in patients with acute myocardial infarction.

Design

Nested case-control study.

Setting

Prospective cohort study of consecutive patients admitted with acute myocardial infarction to 9 Scottish hospitals.

Patients

100 patients who survived 30 days (controls) and 100 patients who died within 30 days (cases).

Measurements and Main Results

Admission cortisol concentrations were lower in patients who died than those who survived (median 1,189 versus 1,355 nmol/L, $p<0.001$). A cortisol concentration in the bottom quartile (<1,136 nmol/L) was a strong predictor of death within 30 days, and remained so after adjustment for age and cardiac troponin concentration (adjusted OR 8.78, 95% CI 3.09-24.96, $p<0.001$).

Conclusions

Patients who mount a lesser cortisol stress response to acute myocardial infarction have a poorer early prognosis.

Introduction

Serum cortisol concentrations rise dramatically and rapidly in the early phase of acute critical illness (1). Such a response is necessary, for example to mobilize energy stores and protect against excessive inflammation. Higher random cortisol concentrations have been associated with increased case-fatality from critical illness (2;3), consistent with a greater stress response during more severe underlying illness. However, in some patients, low random cortisol is associated with increased risk of death (2); this group may overlap with those considered to have 'relative adrenal insufficiency' on the basis of an impaired incremental response to exogenous ACTH (3). Most studies have included patients with diverse underlying diseases, who may have been receiving drug treatment that could interfere with the hypothalamic-pituitary-adrenal axis, such as etomidate (1). In small case series of myocardial infarction, relatively low cortisol concentrations have been associated with both increased (4) and decreased (5-7) case-fatality. Relative adrenal insufficiency has also been postulated as contributing to morbidity and case-fatality among patients suffering shock following cardiopulmonary arrest (8). We have explored the association between admission serum cortisol concentrations and 30-day case-fatality in a cohort of patients presenting with acute myocardial infarction.

Materials and methods

We previously undertook a prospective cohort study in which we recruited 2,806 patients admitted with acute myocardial infarction to nine hospitals over ten months,

from June 2005 to March 2006 inclusive (9). Acute myocardial infarction was defined according to the Universal Definition of Myocardial Infarction (10). We used probabilistic record linkage methods to link our baseline data to death certificate data in order to determine which patients died following admission and their date of death. We randomly selected 100 patients who died within 30 days of admission (cases) and 100 who were still alive at 30 days follow-up (controls). Socioeconomic status was measured using population quintiles of the Scottish Index of Multiple Deprivation (SIMD) index for the participant's usual place of residence (http://www.scotland.gov.uk/Topics/Statistics/SIMD/). Residual sera from clinical samples taken on admission to hospital were stored at -80^{o}C and used to measure cortisol concentrations by radio-immunoassay (MP Biomedicals, UK) (intra-assay CV 5.1-7.0%, inter-assay CV 6.0-7.9%). Admission cortisol concentration was categorized using quartiles and logistic regression analysis was used to determine whether cortisol quartile was associated with the risk of death within 30 days. All statistical analyses were performed using SPSS software for Windows, version 13.0 (SPSS). The study was approved by the West Glasgow Research Ethics Committee.

Results

Among the 200 patients selected at random, sufficient residual serum was available for 177. Of these, 80 had died within 30 days of admission and 97 were still alive. Those patients who had died had significantly lower admission serum cortisol concentrations (median 1,189 nmol/L, IQR 957-1,373) than those who survived (median 1,355 nmol/L, IQR 1,240-1,561) (Mann Whitney U test, $p<0.001$) and were significantly

older (Table 1). On univariate logistic regression analysis, there was a negative association between cortisol concentration and risk of death, with evidence of a threshold effect (Figure). Compared with patients whose cortisol concentration was in the top quartile (>1,437 nmol/L), those in the lowest quartile (<1,136 mmol/L) had a greater risk of death (OR 10.39, 95% CI 3.87-27.91, p<0.001) (Figure).

There were no significant differences between the dead and alive groups in terms of sex (male 56% versus 58%, χ^2 test p=0.807) or in the breakdown by SIMD quintile (χ^2 test for trend, p=0.586). Those who died were significantly older (median 77 years, IQR 71-84) than survivors (median 68 years, IQR 54-79) (Mann Whitney U test, p<0.001), and increasing age was a significant predictor of risk of death (unadjusted OR for one year increase in age 1.07, 95% CI 1.04-1.10, p<0.001). After adjusting for age as a potential confounder, the lowest cortisol quartile was still significantly associated with increased risk of death (adjusted OR 9.37, 95% CI 3.32-26.40, p<0.001) (Figure). There was no significant difference between the dead and alive groups with regard to troponin concentration (Mann Whitney U test, p=0.132) and adjustment for troponin only slightly attenuated the association between cortisol and risk of death (adjusted OR 8.78, 95% CI 3.09-24.96, p<0.001).

Discussion

As previously reported (5), admission serum cortisol concentrations on admission were raised following acute myocardial infarction, by a magnitude in keeping with other severe acute illnesses. However, cortisol concentrations were significantly lower amongst

patients who subsequently died compared with those who survived. ACTH stimulation tests were not undertaken in this cohort, so the criteria for 'relative adrenal insufficiency' identified in previous studies of critical illness cannot be applied (3). Nonetheless, our results suggest that inability of the hypothalamic-pituitary-adrenal axis to mount a full stress response is associated with adverse outcomes not only in patients with multi-organ failure due to trauma or sepsis, but also in those with acute myocardial infarction.

Previous studies of the association between cortisol concentration and prognosis following acute myocardial infarction are few and results conflicting. A previous study of just 34 patients also reported a negative association between cortisol concentration and risk of death (4). By contrast, three small studies of between 22 and 70 patients with few deaths suggested increased risk of death among patients with high cortisol concentrations (5-7). It is possible that sub-groups of patients exist in whom either very high or very low cortisol confers an adverse prognosis in acute myocardial infarction, as in more heterogeneous critical illness (2). However, in our study which comprised substantially larger number of deaths than any previous study, we found no evidence of increased risk of death among patients with high serum cortisol concentrations.

In the association we demonstrated between low cortisol concentration and increased risk of case-fatality, we cannot exclude the possibility of residual confounding. We lacked data on a number of factors that vary with cortisol concentration, such as renal dysfunction and corticosteroid binding globulin. We were able to demonstrate that the association between cortisol and survival was independent of the potential confounding

effects of age and troponin concentration. Larger infarct size is positively associated with both higher cortisol concentration (5) and greater risk of death. Therefore, had we been able to adjust for infarct size, this could only have increased the association between low cortisol concentration and increased risk of death. Cortisol concentration may be causally related to blood pressure, glucose and lipid levels, all of which could therefore act as potential mediators of the association between low cortisol and risk of death. However, in the absence of data, we were unable to explore these possible mechanisms.

Conclusions

Low cortisol concentration on admission is an adverse prognostic indicator in patients with acute myocardial infarction, as it is in critically ill patients following sepsis or trauma. Further studies are required to corroborate our findings, adjust for potential residual confounders, establish the underlying mechanisms, determine the prevalence of relative adrenal insufficiency as defined by ACTH-stimulation testing, and establish the therapeutic value of glucocorticoid replacement therapy in patients with relatively impaired cortisol responses.

Acknowledgements

We are grateful to Judith Anderson, Anne Andrews, Sharon Cameron, Jackie Dougall, Carole Gibson, Joanne Kelly, John Rodgers, Karen Smith, Fiona Stevenson, Helen Waldie, Ann Wright and Jim Young for recruiting patients and collecting baseline data,

to Carolynn Cairns for performing the cortisol assays and to the Wellcome Trust Clinical Research Facility in Edinburgh for storing the samples.

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Table 1. Characteristics of acute coronary syndrome patients according to whether or not they were dead by 30 days follow-up

	Alive at 30 days N=97		**Dead at 30 days** N=80		**P value***
	N	**%**	**N**	**%**	
Sex					
Male	54	56	46	58	0.807
Female	43	44	34	43	
Scottish deprivation quintile					
1	10	13	9	13	0.586
2	10	13	7	10	
3	15	20	11	16	
4	16	21	16	24	
5	24	32	24	36	
Missing	22		13		
	median	**IQR**	**median**	**IQR**	
Age (years)	68	54-79	77	71-84	<0.001
Cortisol (nmol/L)	1,355	1,240-1,561	1,189	957-1,373	<0.001

N number, IQR inter-quartile range
*χ^2 for sex, χ^2 for trend for deprivation quintile, Mann Whitney U for age and cortisol

Figure. Univariate and multivariate logistic regression analysis of the association between cortisol quartile and death within 30 days of myocardial infarction