



# Fear of dying and inflammation following acute coronary syndrome

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## Aims

Many patients are afraid of dying during acute coronary syndrome (ACS), but the origins and biological correlates of these emotional responses are poorly understood. This study evaluated the prevalence of fear of dying, associations with inflammatory responses during ACS, and later heart rate variability (HRV) and cortisol secretion.

## Methods and results

Two hundred and eight patients admitted with clinically verified ACS rated their fear of dying on interview in hospital. Plasma tumour necrosis factor (TNF) $\alpha$  was recorded on admission, and HRV and salivary cortisol were assessed 3 weeks later. Intense distress and fear of dying was experienced by 21.7%, with moderate levels in 66.1% patients. Fear of dying was more common in younger, lower socioeconomic status, and unmarried patients. It was positively associated with plasma TNF $\alpha$  on admission after controlling for sociodemographic factors, clinical risk, and pain intensity (adjusted odds = 4.67, 95% C.I. 1.66–12.65). TNF $\alpha$  was associated with reduced HRV 3 weeks later, adjusting for clinical and sociodemographic factors and medication ( $P = 0.019$ ), while fear of dying was associated with reduced cortisol output ( $P = 0.004$ ).

## Conclusions

Intense distress and fear of dying and heightened inflammation may be related manifestations of an acute biobehavioural response to severe cardiac injury, and have implications for prognostically significant biological risk processes.

## Keywords

Acute coronary syndrome • Fear of dying • Inflammation • Heart rate variability • Cortisol

## Introduction

Acute cardiac events can be very frightening experiences, and a significant proportion of patients describe intense distress and fear of dying during an acute coronary syndrome (ACS).<sup>1,2</sup> Acute distress and fear of dying are more common among physically sedentary lower socioeconomic status (SES) patients who report strong chest pain during their ACS, and predicts elevated symptoms of depression in the weeks following ACS.<sup>2</sup> Since depression following ACS is associated with recurrent cardiac events and impaired quality of life,<sup>3,4</sup> investigation of the biological correlates of fear of dying is warranted. One possibility is that fear of dying is coupled with heightened inflammatory responses during ACS. Acute coronary syndrome is accompanied by a profound inflammatory response, and the magnitude of elevations in C-reactive

protein, tumour necrosis factor (TNF)  $\alpha$  and interleukin (IL) 6 levels during ACS predict both short- and long-term risk of recurrent cardiac events and adverse outcomes.<sup>5–8</sup> Acute psychological stress also stimulates increases in the concentration of TNF $\alpha$ , IL-6, and IL-1 receptor antagonist (IL-1Ra) within 1 to 2 h,<sup>9</sup> while peripheral inflammation can in turn induce acute negative mood states.<sup>10</sup> Intense acute distress and heightened inflammation may be manifestations of an integrated biobehavioural reaction to acute cardiac events.

Fear of dying and acute inflammatory responses may have implications for prognostically significant biological risk processes, two of which were investigated in this study. Inflammatory responses have a reciprocal relationship with cardiac autonomic regulation. An inverse association between TNF $\alpha$ , C-reactive protein, or IL-6 and heart rate variability (HRV) has been observed both in

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cardiac patients and healthy samples,<sup>11</sup> and the extent of inflammation on admission with ACS is negatively correlated with HRV.<sup>12</sup> Investigations of the inflammatory reflex indicate that stimulation of the vagus nerve inhibits TNF $\alpha$  responses to endotoxins,<sup>13</sup> probably through the inhibition of acetylcholine receptors on macrophages.<sup>14</sup> Additionally, endotoxin administration depresses HRV in experimental models, and these effects are mimicked by administration of recombinant TNF $\alpha$ .<sup>15</sup> Reduced HRV is also commonly observed in response to psychological stress.<sup>16</sup> Cortisol secretion is also sensitive to stress, and may be relevant following ACS since low cortisol output may lead to failure to contain inflammatory responses.<sup>17</sup> Reynolds et al.<sup>18</sup> recently showed that low cortisol on admission predicted early death after acute myocardial infarction. The first aim of this study was therefore to evaluate the association between acute distress and fear of dying and TNF $\alpha$  during ACS. The second aim was to discover whether TNF $\alpha$  and fear of dying during ACS correlated with reduced HRV and cortisol output 3 weeks later.

## Methods

### Participants

The participants were 208 patients admitted with ACS to St. George's Hospital in South London between June 2007 and October 2008 as part of a larger study of psychosocial aspects of ACS. Patients were included if they fulfilled the following criteria: a diagnosis of ACS based on the presence of chest pain plus verification by diagnostic electrocardiographic (EKG) changes, troponin T or troponin I  $\geq$  99th percentile of the upper reference limit and/or a creatine kinase measurement more than twice the upper range of normal for the measuring laboratory. Additional inclusion criteria were age of 18 years or older, absence of comorbid conditions that might influence either symptom presentation or mood, other conditions that might cause inflammation, and ability to complete interviews and questionnaires in English. Some of these criteria were introduced for the sake of other analyses that are not discussed here; the main comorbid conditions relevant to these analyses were cancer and severe anaemia. The study was approved by the Wandsworth Research Ethics Committee (IRB), and written consent was obtained. A total of 666 potentially eligible patients were admitted on the days of recruitment into this study. Hundred and twenty-five had been discharged or transferred on to a different hospital before the patient could be recruited into the study, 90 were too clinically fragile to take part, TNF $\alpha$  was not available for 90, 58 declined to participate, 27 could not speak English, 23 were in confusional states, 7 patients died in hospital, and a further 38 were excluded for other reasons.

### Clinical and sociodemographic measures

Information was obtained from medical notes about cardiovascular history, clinical factors during admission and management. Admission EKGs were reviewed and scrutinized for presentation as ST-elevation myocardial infarction (STEMI) or non-STEMI /unstable angina. We computed the composite risk index based on the algorithm developed in the GRACE study,<sup>19</sup> which uses nine criteria (age, congestive heart failure, history of myocardial infarction (MI), systolic blood pressure and heart rate on admission, ST segment depression, initial serum creatinine, elevated cardiac enzymes, and in-hospital percutaneous coronary intervention) to define risk of 6-month post-discharge death applicable to all types of ACS. Peak CK level and the number of

coronary vessels with significant stenosis were included as additional indicators of clinical severity, and the number of days spent in hospital as a further measure of clinical status. This variable was positively skewed so was log transformed before analysis.

Socioeconomic status was assessed using a social deprivation index based on three criteria: living in a crowded household (defined as one or more people to a room), renting as opposed to owning a home, and not having use of a motor vehicle (car or van).<sup>20</sup> Patients were classified as low deprivation (negative on all items), medium deprivation (one positive), and high deprivation (2–3 positive). The intensity of pain during the ACS was assessed on a 10-point scale, with higher values indicating greater pain.

### Assessment of acute distress and fear of dying

Acute distress and fear of dying were assessed during interviews carried out in hospital an average of within  $2.41 \pm 1.6$  days of admission. Acute distress and fear were measured with 3 items, as detailed previously: 'I was frightened when the symptoms came on', 'I thought that I might be dying when the symptoms came on', and 'I found my cardiac event stressful'.<sup>2</sup> Each was rated into 1 of 5 categories: not at all true (0), slightly true (1), somewhat true (2), very true (3), and extremely true (4). A combined score was created by averaging these ratings (Cronbach  $\alpha = 0.82$ ). Participants were divided into 3 groups: no distress and fear (average ratings of 'not at all true', 0–0.99), moderate distress and fear (average ratings of 'slightly true' and 'somewhat true', 1.0–2.99), and intense distress and fear (average ratings of 'very true' and 'extremely true', 3.0–4). Patients were also asked about whether they had attributed their symptoms to heart problems.

### Tumour necrosis factor $\alpha$ on admission

Tumour necrosis factor  $\alpha$  was measured from blood samples obtained on admission to hospital using an immunometric assay using an Immulite 1 system (Siemens Healthcare Diagnostics). Intra-assay and inter-assay coefficients of variation were 2.6–3.6% and 4.0–6.5%, respectively.

### Heart rate variability

Heart rate variability was analysed from EKG recordings obtained at the patients' homes an average of  $21.9 \pm 8.4$  days following ACS with Actiheart monitors (Cambridge Neurotechnology Ltd, Papworth, UK).<sup>21</sup> The N–N intervals were processed using Kubios HRV analysis software (University of Kuopio, Finland) in 5 min epochs in both the time and frequency domain (using fast Fourier transform). Heart rate variability was indexed in these analyses by the root mean square of successive differences (RMSSD), and by high frequency (0.15–0.4 Hz) HRV (HF-HRV) and low frequency (0.04–0.15 Hz) HRV (LF-HRV). Up to three 5 min epochs obtained during the home interview were averaged to generate an aggregate value. Both indicators were negatively skewed, and were log transformed before analysis.

### Cortisol secretion

Cortisol output was assessed by measuring the profile of salivary cortisol over a day. Salivary sampling with salivettes (Sarstedt, Leicester, UK) was explained and practiced during the test session in the patient's home. Patients were asked to hold the cotton dental roll in their mouths until saturated (for 2 min) at six times: immediately after waking, 30 min later, 10:00–10:30, 14:00–14:30, 19:00–19:30 h, and then just before bedtime. They also recorded the exact time of sample collection and the time of waking. Patients were instructed to avoid caffeine and acidic drinks, smoking, tooth brushing, eating,

and drinking for 15 min before collecting saliva. Salivettes were stored in domestic refrigerators before posting them back to the laboratory. Patients who did not return their samples within 2 weeks were sent reminders and replacement salivettes if necessary. Saliva samples were sent to the Technical University Dresden for the analysis of cortisol using a commercial immunoassay with chemiluminescence detection (CLIA; IBL-Hamburg, Germany). Inter- and intra-assay coefficients of variation were <8%.

## Statistical analysis

The demographic and clinical characteristics of patients reporting low, moderate, and intense distress and fear were compared using analysis of covariance for continuous and  $\chi^2$  tests for categorical variables. Associations between fear of dying and TNF $\alpha$  during ACS were tested with logistic regression, assessing the odds of a TNF $\alpha$  value in the upper tertile ( $\geq 12$  pg/pl) in relation to fear of dying, with age, gender, marital status, ethnicity, social deprivation (SES), statin, and aspirin use prior to admission, pain during the ACS, GRACE score, and days spent in hospital as covariates. Additional analyses included individual components of GRACE scores (e.g. heart failure and history of MI), but did not alter the results and so are not described here. The relationship between TNF $\alpha$  and fear of dying and HRV was analysed by means of multiple regression on RMSSD and HF-HRV; in addition to the covariates detailed above, medication at the time of HRV assessment with beta-blockers, statins, renin-angiotensin medications (including angiotensin-converting enzyme and receptor blockers) and platelet medications were included in the models. Cortisol output was analysed by computing the area under the curve (AUC) for the day.<sup>22</sup> The distributions of both HRV and cortisol AUC were skewed and so log transformed before analysis. Data were analysed using SPSS v18.0, and all analyses involved two-tailed tests.

## Attrition analysis

Of the 208 patients in this study, 161 were interviewed at home 3 weeks after their ACS, and satisfactory HRV data were obtained from 106 and cortisol from 110. Reasons for not participating in the home interview included refusal (55%), further health problems (readmission, cognitive impairment, 16%) or failure to establish contact despite repeated attempts (29%). Comparison of patients who were included and excluded from the analysis showed no differences in age, gender, ethnicity, type of ACS, clinical measures, fear of dying, or TNF $\alpha$  on admission. However, individuals who failed to provide data at the 3-week assessment point were more likely to be unmarried ( $P = 0.005$ ) and of lower SES ( $P = 0.019$ ).

## Results

Intense distress and fear of dying was reported by 45 (21.6%) patients, moderate distress by 116 (55.8%), and low distress and fear of dying by 47 (22.6%). *Table 1* details the characteristics of patients in the three categories. There were no gender or ethnicity differences, or differences related to place of birth. But patients who experienced intense distress and fear of dying were younger ( $P = 0.017$ ), more likely to be unmarried ( $P = 0.018$ ), and of lower SES ( $P = 0.006$ ). The majority of patients suffered a STEMI, but intense distress and fear of dying was not related to clinical cardiological factors. GRACE scores tended to be lower in patients with intense distress and fear ( $P = 0.056$ ), but this was no longer significant after age had been taken into account

( $P = 0.62$ ). There were no differences in peak CK or in the number of coronary vessels with significant stenosis. However, patients who reported intense distress and fear of dying experienced greater acute pain during the ACS ( $P = 0.019$ ). The majority (72%) of patients underwent percutaneous coronary interventions, 21.7% were managed medically, and 6.3% were referred for coronary artery bypass graft. Patient management was not related to distress and fear of dying.

## Fear of dying and tumour necrosis factor $\alpha$ during acute coronary syndrome

There were marked variations in plasma TNF $\alpha$  levels during hospital admission, ranging from 2.40 to 61.80 pg/mL, with 32.4% having values  $\geq 12$  pg/mL. A positive association was observed between acute distress and fear of dying and TNF $\alpha$  during hospital admission, illustrated in *Figure 1*, with proportions having values  $\geq 12$  pg/mL of 19.8, 31.1, and 51.5% in the low-, moderate-, and high-fear-of-dying groups, respectively. Compared with the low-fear-of-dying group, the odds of TNF $\alpha$   $\geq 12$  pg/mL were 4.67 (95% confidence intervals (C.I.) 1.60–13.66,  $P = 0.005$ ) in the high- compared with lower-distress and fear-of-dying group, adjusting for age, gender, marital status, ethnicity, social deprivation, statin, and aspirin use prior to admission, pain during the ACS, GRACE score and days spent in hospital. The same association was observed when TNF $\alpha$  was analysed as a continuous variable.

## Tumour necrosis factor $\alpha$ and heart rate variability

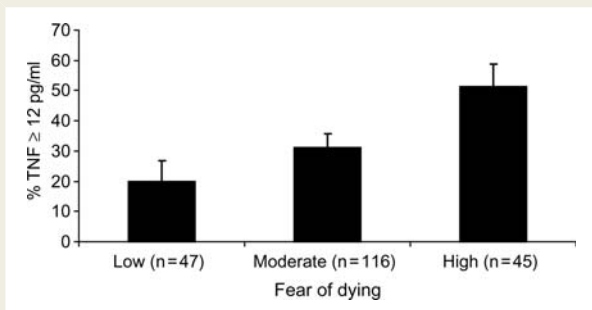
Significant associations were observed between TNF $\alpha$  during ACS and reduced HRV 3 weeks later (*Table 2*). Effects were apparent for HRV assessed in the time (RMSSD) and frequency domain (HF-HRV and LF-HRV), and were independent of age, gender, marital status, ethnicity, social deprivation, GRACE score, days spent in hospital, and medication with beta-blockers, statins, platelet, and renin-angiotensin medications (*Table 2*). The regression coefficient for TNF $\alpha$  on RMSSD was  $-0.449$  (C.I.  $-0.772$ – $-0.125$ ,  $P = 0.007$ ) and on HF-HRV was  $-0.823$  (C.I.  $-1.44$ – $-0.205$ ,  $P = 0.010$ ), while LF-HRV was positively associated with TNF $\alpha$  (0.003, C.I. 0.001–0.006,  $P = 0.002$ ). The other independent correlates of reduced HRV were being single as opposed to married, and number of days spent in hospital before discharge. There was no association between fear of dying and HRV.

## Fear of dying and cortisol output

Salivary cortisol showed a typical diurnal profile, being high on waking, increasing in the first 30 min after waking, and then falling over the remainder of the day. The cortisol AUC was inversely associated with distress and fear of dying, after controlling for age, gender, marital status, ethnicity, social deprivation, GRACE score, smoking status, statins on admission, and beta-blockers at the time of testing ( $P = 0.040$ ). This result is illustrated in *Figure 2*, contrasting individuals who reported low and high distress and fear of dying, where it is apparent that cortisol output was substantially reduced in patients who had experienced intense fear of dying. Cortisol output was not related to TNF $\alpha$  during ACS.

**Table 1** Factors associated with distress and fear of dying during acute coronary syndrome

|                              | Distress and fear of dying |                    |               | P     |
|------------------------------|----------------------------|--------------------|---------------|-------|
|                              | Low (n = 47)               | Moderate (n = 116) | High (n = 45) |       |
| Men/women                    | 40/7                       | 99/17              | 36/9          | 0.51  |
| Age                          | 61.79 ± 11.9               | 60.00 ± 10.8       | 55.38 ± 11.3  | 0.017 |
| Ethnicity (white)            | 37 (78.7%)                 | 102 (87.9%)        | 35 (77.8%)    | 0.17  |
| Married                      | 34 (72.3%)                 | 85 (73.3%)         | 22 (48.9%)    | 0.018 |
| Social deprivation           |                            |                    |               |       |
| Low                          | 33 (70.2%)                 | 83 (73.5%)         | 19 (43.2%)    | 0.006 |
| Intermediate                 | 10 (21.3%)                 | 20 (17.7%)         | 15 (34.1%)    |       |
| High                         | 7 (8.5%)                   | 10 (8.8%)          | 10 (22.7%)    |       |
| Previous MI                  | 6 (12.8%)                  | 19 (16.4%)         | 4 (8.9%)      | 0.43  |
| Statins prior to admission   | 37 (78.7%)                 | 77 (66.4%)         | 35 (77.8%)    | 0.16  |
| ST elevation MI              | 41 (87.2%)                 | 105 (90.5%)        | 41 (91.1%)    | 0.54  |
| Symptoms attributed to heart | 11 (23.4%)                 | 34 (29.8%)         | 18 (40.0%)    | 0.086 |
| Pain during ACS              | 6.49 ± 2.6                 | 7.17 ± 2.1         | 7.91 ± 2.79   | 0.019 |
| GRACE score                  | 97.28 ± 26.4               | 91.61 ± 24.6       | 84.24 ± 28.3  | 0.056 |
| Mean CK (U/L)                | 1729.7 ± 1644              | 1830.0 ± 1527      | 2066.5 ± 2208 | 0.62  |
| Stenosed vessels             | 2.08 ± 0.90                | 1.83 ± 0.84        | 1.80 ± 0.89   | 0.18  |
| Days in hospital             | 5.55 ± 3.23                | 5.34 ± 4.35        | 5.13 ± 3.42   | 0.42  |



**Figure 1** Proportion of patients with tumour necrosis factor  $\alpha$  values  $\geq$  12 pg/mL reporting low, moderate, or intense distress and fear of dying. Values are adjusted for age, gender, ethnicity, marital status, social deprivation, statin use on admission, GRACE score, number of days in hospital, and pain intensity. Error bars are standard error of the mean.

## Discussion

The purpose of this study was to investigate links between acute emotional and acute inflammatory responses to ACS, and to test their associations with cardiac autonomic control and cortisol secretion. We found that intense distress and fear of dying was experienced by one in five patients, and was positively related to the levels of plasma TNF $\alpha$  recorded during ACS. This association was independent of demographic and clinical variables. TNF $\alpha$  on admission in turn correlated with reduced HRV, a potent indicator of cardiac vulnerability,<sup>23,24</sup> 3 weeks later. Fear of dying was related to reduced cortisol output at the same time point, a response that

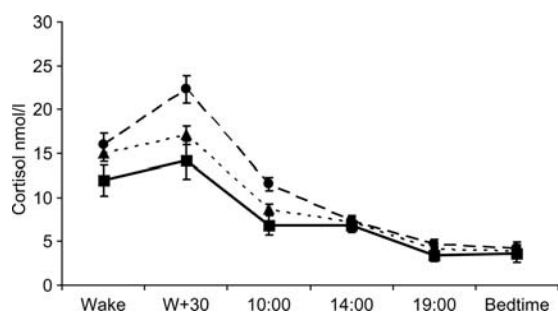
could exacerbate heightened inflammation, but was not related to HRV.

The distribution of ratings of acute distress and fear of dying were similar to those we reported in an earlier cohort of ACS patients.<sup>2</sup> In the previous study, 40/184 (21.7%) of patients reported intense distress and fear of dying, while 95 (51.6%) experienced moderate distress. This compares with 45/208 (21.6%) reporting intense distress and fear of dying in the present study, and 116 (55.8%) having moderate distress. We replicated associations between acute distress and fear of dying and lower SES and greater chest pain.<sup>2</sup> But in addition, being unmarried and relatively young were relevant (Table 1). Interestingly, acute distress and fear of dying were not related to previous experience of MI or to indicators of the clinical severity of the cardiac event. It appears that acute distress and fear of dying may be stimulated by symptomatic experience during ACS, while being accentuated in more socially isolated and economically deprived patients.

The TNF $\alpha$  values recorded on admission were markedly elevated compared with levels in healthy individuals, with one-third of patients having levels  $\geq$  12 pg/mL, and only 5% showing values within two standard deviations of those measured in previous studies of healthy adults of comparable age.<sup>25</sup> The processes underlying the positive association between acute distress and fear of dying and TNF $\alpha$  observed in this study are uncertain. The relationship was independent of sociodemographic factors and the severity of the cardiac event. The association is unlikely to be causal. Although acute mental stress stimulates increases in TNF $\alpha$ ,<sup>9</sup> the levels observed during ACS are substantially greater than those recorded in any previous studies of mental stress. Conversely, even though systemic inflammation stimulates disturbances in mood as part of the sickness behaviour syndrome,<sup>10</sup> effects are

**Table 2** Regression of tumour necrosis factor  $\alpha$  and covariates on heart rate variability. Unstandardized regression coefficient B and 95% confidence intervals

|                                 | RMSSD                 |       | HF-HRV                |       | LF-HRV                |       |
|---------------------------------|-----------------------|-------|-----------------------|-------|-----------------------|-------|
|                                 | B (95% C.I.)          | P     | B (95% C.I.)          | P     | B (95% C.I.)          | P     |
| Age                             | 0.008 (−0.017–0.034)  | 0.51  | 0.027 (−0.021–0.075)  | 0.27  | −0.005 (−0.011–0.001) | 0.12  |
| Gender <sup>a</sup>             | 0.009 (−0.493–0.511)  | 0.97  | 0.202 (−0.757–1.16)   | 0.68  | −0.067 (−0.192–0.058) | 0.29  |
| Ethnicity <sup>b</sup>          | 0.063 (−0.362–0.487)  | 0.77  | 0.078 (−0.734–0.890)  | 0.85  | 0.041 (−0.147–0.064)  | 0.44  |
| Marital status <sup>c</sup>     | −0.396 (−0.767–0.024) | 0.037 | −0.967 (−1.68–0.257)  | 0.008 | 0.110 (0.017–0.203)   | 0.020 |
| Social deprivation <sup>d</sup> | −0.039 (−0.283–0.205) | 0.75  | −0.001 (−0.468–0.466) | 0.99  | −0.047 (−0.107–0.014) | 0.13  |
| GRACE score                     | −0.006 (−0.018–0.005) | 0.28  | −0.016 (−0.038–0.005) | 0.13  | 0.001 (−0.003–0.003)  | 0.86  |
| Days in hospital                | 0.360 (0.018–0.703)   | 0.039 | 0.667 (0.012–1.32)    | 0.046 | −0.007 (−0.094–0.081) | 0.88  |
| Beta-blockers                   | −0.227 (−0.609–0.154) | 0.24  | −0.351 (−1.08–0.379)  | 0.34  | 0.014 (−0.080–0.108)  | 0.77  |
| Statins                         | 0.463 (−0.203–1.13)   | 0.17  | 0.371 (−0.902–1.64)   | 0.56  | 0.039 (−0.126–0.204)  | 0.64  |
| Renin–angiotensin medications   | 0.187 (−0.328–0.702)  | 0.47  | 0.623 (−0.362–1.61)   | 0.21  | 0.104 (−0.024–0.232)  | 0.11  |
| Platelet medication             | 0.994 (−0.362–0.487)  | 0.25  | 2.131 (−1.15–5.41)    | 0.20  | −0.192 (−0.615–0.231) | 0.37  |
| TNF $\alpha$ during admission   | −0.449 (−0.772–0.125) | 0.007 | −0.823 (−1.44–0.205)  | 0.010 | 0.003 (0.001–0.006)   | 0.002 |

<sup>a</sup>Men reference group;<sup>b</sup>White European reference group;<sup>c</sup>Married reference group;<sup>d</sup>Low-deprivation reference group.**Figure 2** Salivary cortisol profiles over the day in patients experiencing low (dashed line), moderate (dotted line), or intense distress and fear of dying (solid line). Samples were obtained on waking (wake), 30 min later (w + 30), then at 10:00 h, 14:00 h, 19:00 h, and at bedtime. Values adjusted for age, gender, ethnicity, marital status, social deprivation, GRACE score, statins on admission, and smoking status. Error bars are standard error of the mean.

typically manifest as increases in fatigue and depressed mood rather than extreme fear or anxiety. Nevertheless, the acute emotional and inflammatory responses may be linked as related manifestations of an integrated biobehavioural response to severe cardiac injury.

Although ACS is associated with inflammatory responses that can be indexed by a number of markers, we focused on TNF $\alpha$  because of its known relationship with HRV through the inflammatory reflex.<sup>14</sup> There appears to be a reciprocal association between TNF $\alpha$  and HRV: stimulation of the vagus (promoting

heightened HRV) inhibits TNF $\alpha$  production through action on the nicotinic acetylcholine receptor alpha7 subunit,<sup>26</sup> while TNF $\alpha$  administration reduces HRV.<sup>15</sup> An inverse association between TNF $\alpha$  and HRV has previously been observed in cross-sectional studies of community samples<sup>27</sup> and patients with CHD and heart failure.<sup>28</sup> Provocation of inflammation using influenza vaccination has been shown to reduce HRV in people with type 2 diabetes.<sup>29</sup> The present findings extend these observations in demonstrating a prospective association between TNF $\alpha$  during ACS and HRV 3 weeks later that was independent of clinical and demographic factors including medication. The magnitude of inflammation during ACS may be an additional factor determining cardiac autonomic dysregulation in the post-ACS phase.

Cortisol secretion arises through activation of the hypothalamic–pituitary–adrenocortical axis, and is a key stress hormone. Elevated levels of cortisol are associated with a range of central nervous system, metabolic, endocrine, and cardiovascular health problems.<sup>30</sup> However, some stressful experiences such as early-life adversity are correlated with diminished cortisol responses.<sup>31</sup> Patients with inflammatory disorders show blunted cortisol responsivity,<sup>32</sup> and in healthy individuals greater cortisol stress responsivity is correlated with less inflammatory response.<sup>33</sup> The reduced cortisol output over the day among patients who experienced intense distress and fear of dying may therefore reflect dysregulation of neuroendocrine responses that limit inflammation, promoting adverse outcomes following ACS.

Interpretation of these findings must take into account the drop out from study. Attrition analyses showed that participation in the 3-week home interview was 77%, and was lower in unmarried and lower SES patients. Such individuals are frequently more likely to withdraw from medical research and population surveys, but importantly, they did not differ from the remainder on the key



aspects of the present study, namely fear of dying and inflammatory responses. The sample contained a high proportion of STEMI, possibly because of selection factors such as excluding patients who suffered from comorbidities that might affect mood or inflammation. This may have eliminated a higher proportion of individuals with other types of ACS, limiting the generalizability of results beyond STEMI presentation. Further validation is therefore required for patients who experienced non-STEMI or unstable angina. Additional limitations of this study include the small number of women and ethnic minority patients, which restricts the generalizability of the findings. We did not assess inflammation at the 3-week follow-up but only during hospitalization, and so cannot confirm that lower cortisol was associated with persistent inflammation. Additional clinical variables such as ejection fraction might have helped explain the results, but data were incomplete. Heart rate variability was not monitored under standardized clinical conditions, but in patients' own homes, and the time of day was not controlled. Finally, although serial blood samples were obtained over consecutive days of hospitalization from some patients, data were incomplete so we were not able to track the profile of inflammatory responses over time.

In conclusion, heightened inflammation during ACS and intense distress and fear of dying may be related manifestations of an acute biobehavioural response. The association between the two indicates a linkage between emotional and inflammatory responses during ACS that is independent of background characteristics and other aspects of clinical disease. They were both related to biological responses relevant to longer-term risk. These findings may help understand the reciprocal relationship between psychological and biological factors in acute heart disease, raising the possibility of new avenues for patient management.

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## CARDIOVASCULAR FLASHLIGHT

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# A monstrous aneurysm of the descending aorta as a sole manifestation of tertiary syphilis treated endovascularly

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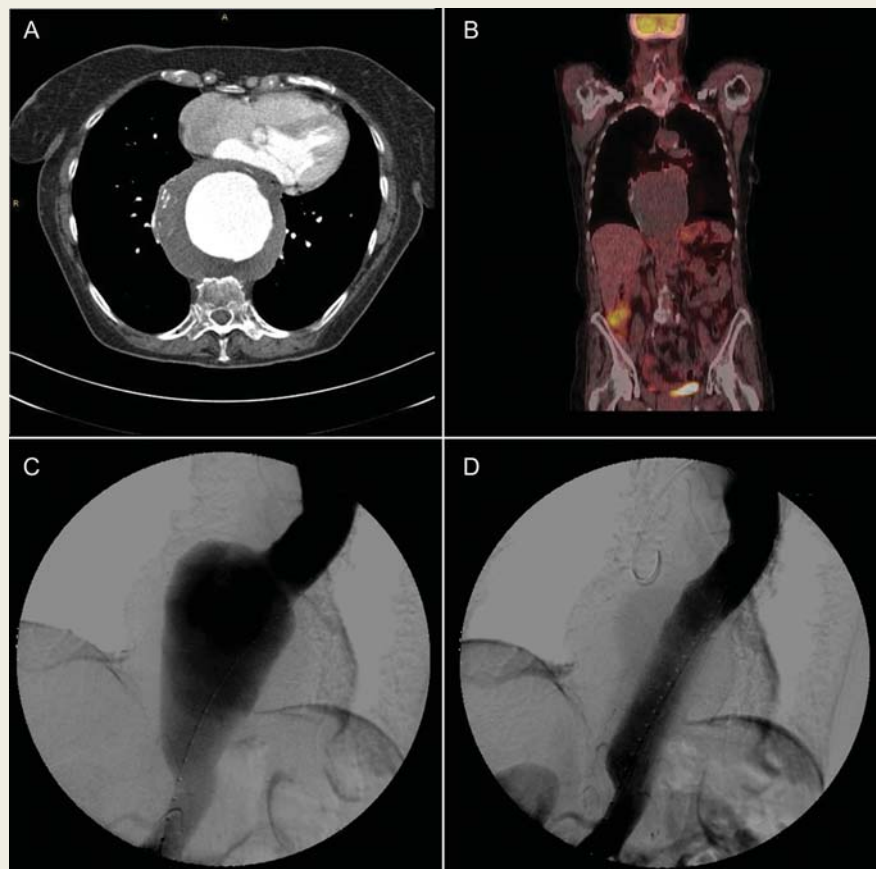
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In May 2010, a 65-year-old female went to her family doctor complaining about persistent epigastric discomfort and back pain. X-rays were done and surprisingly showed a widened mediastinum. Suspecting an aortic aneurysm as a rare cause for the patient's epigastric and back-pain symptoms, an angio-CT was performed. The CT revealed a monstrous aneurysm of the thoracic descending aorta with thickened wall and intraluminal thrombotic bedding, compressing the oesophagus and the heart (Panel A).

The patient was then referred to our university interdisciplinary clinic for aortic disease. On evaluation in our institution, the patient confirmed the earlier symptoms. She denied a family history of aortic disease and had not experienced symptoms of arteritis. To exclude active vasculitis, a PET-CT was done, which did not show any enhanced uptake denoting any inflammatory activity (Panel B). The serological tests, performed to reveal the underlying pathology, surprisingly revealed positive *Treponema pallidum* haemagglutination assay (TPHA) and Venereal

Disease Research Laboratory (VDRL) tests, as well as a positive Syphilis-Titre (IgG positive, IgM negative) which led to the diagnosis of late latent syphilis with syphilitic aortitis. After confirmation of diagnosis, the patient received intravenous penicillin therapy for 3 weeks. Based on the general condition of the patient and the high risk of an operative intervention on an aneurysmatic descending aorta of that size, the aneurysm was successfully treated by endovascular stenting of the descending aorta with excellent results (Panels C and D). The patient recovered fully, and went home symptom free with a successfully treated aneurysmatic aorta.



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