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The interaction between systemic inflammation and psychosocial stress in the association with cardiac troponin elevation: A new approach to risk assessment and disease prevention

Antonio Ivan Lazzarino, MD PhD [a,b,*], Mark Hamer, PhD [e], David Gaze, PhD [c], Paul Collinson, MD [c], Ann Rumley, PhD [d], Gordon Lowe, DSc [d], Andrew Steptoe, DSc [b]

[a] London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom
[b] Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London WC1E 6BT, United Kingdom
[c] Chemical Pathology, Clinical Blood Sciences, St George's Healthcare NHS Trust, Blackshaw Road, Tooting, London SW17 0QT, United Kingdom
[d] Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow G12 8TA, United Kingdom
[e] School of Sport, Exercise, and Health Sciences, National Centre for Sport & Exercise Medicine, Loughborough University, LE11 3TU, United Kingdom

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ABSTRACT

We have previously shown that there is a complex and dynamic biological interaction between acute mental stress and acute release of inflammatory factors into the blood stream in relation to heart disease. We now hypothesize that the presence of chronic psychosocial stress may modify the weight of single test results for inflammation as a predictor of heart disease. Using a cross-sectional design, 500 participants free from heart disease drawn from the Whitehall II study in UK in 2006–2008 were tested for plasma fibrinogen as an inflammatory factor, financial strain as a marker of chronic psychosocial stress, coronary calcification measured using computed tomography, and for plasma high-sensitivity cardiac troponin T (HS-CTnT) as a marker of cardiac risk. Fibrinogen concentration levels above the average were associated with a 5-fold increase in the odds of HS-CTnT positivity only among individuals with financial strain (N = 208, OR = 4.73, 95%CI = 1.67 to 13.40, P = 0.003). Fibrinogen was in fact not associated with HS-CTnT positivity in people without financial strain despite the larger size of that subsample (n = 292, OR = 0.84, 95%CI = 0.42 to 1.67, P = 0.622). A test for interaction on the full sample (N = 500) showed a P value of 0.010 after adjusting for a range of demographics, health behaviours, traditional cardiovascular risk factors, psychosocial stressors, inflammatory cytokines, and coronary calcification. In conclusion, elevated fibrinogen seems to be cardio-toxic only when is combined with financial strain. Chronic psychosocial stress may modify the meaning that we should give to single test results for inflammation. Further research is needed to confirm our results.

1. Introduction

Inflammation is recognised as a fundamental determinant of atherosclerosis and cardiovascular disease (CVD), which are now indeed labelled as inflammatory conditions (Epstein and Ross, 1999; Libby and Theroux, 2005; Libby, 2013).

Chronic psychosocial stressors such as anxiety and depression are associated with inflammation (Dimsdale, 2008; Lazzarino et al., 2013a, 2013b, 2013c; Steptoe and Vögele, 1991) and with heart disease with an effect size that is comparable to that of the traditional risk factors such as high blood pressure, cholesterol, smoking, etc. (Brotman et al., 2007; Dimsdale, 2008; Steptoe and Kivimäki, 2012; Kivimäki et al., 2012).

Although the mechanisms involved in these complex pathways of causation have yet to be clarified genetically and phenotypically, there have been attempts to add markers of stress and inflammation when performing cardiovascular risk assessments (Macleod et al., 2007; Schnohr et al., 2015; Fiscella et al., 2009; Pearson et al., 2003; Ioannidis and Tzoulaki, 2012). As yet, the novel biomarkers failed to add substantial predictive accuracy to the equations based on the traditional risk factors for cardiovascular disease (Boon et al., 2014; Emerging Risk Factors Collaboration et al., 2012; Goff et al., 2014). It has been argued that the linear, monophasic approaches used to explain these mechanisms are not appropriate, and that "until a paradigm shift is adopted, cardiovascular biomarker research may remain fascinating but probably unhelpful to medical practice and public health" (Ioannidis and Tzoulaki, 2012).

In clinical and research settings, chronic systemic inflammation is flagged using single blood tests for inflammatory biomarkers such as fibrinogen, C-reactive protein, and others. We hypothesize that single

* Corresponding author at: Room 142b, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom.
E-mail address: antonio.lazzarino@lshtm.ac.uk (A.I. Lazzarino).

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tests for inflammation may have failed to add accuracy to predictive models because the results from those tests may vary due to an individual's exposure to psychosocial stress (either an unhealthy chronic exposure or a healthy acute exposure). In fact, in a laboratory-based experiment we found that the plasma concentration of inflammatory biomarkers can change very rapidly (<1 min) after one brief episode of mild mental stress (Lazzarino et al., 2015). The kind of artificial stress that we have induced to our study participants was similar to the frequent, mild, stressful events of everyday life. It is therefore arguable that the concentration of inflammatory biomarkers in the blood has a physiological continuous oscillation during anyone's everyday life. Such instability affects the appropriateness of using single blood tests to flag chronic systemic inflammation. Furthermore, we found a counterintuitive association between baseline inflammation and the extent of inflammatory reaction to acute stress: people with low baseline inflammation had sharp and high inflammatory responses to acute stress, and this phenotype was associated with low cardiac risk. Conversely, people with higher baseline inflammation had blunted and lower inflammatory responses and presented higher cardiac risk (Lazzarino et al., 2015). Therefore, a finding of elevated inflammation might be an indicator of chronic elevation due to chronic psychosocial stress but also an indicator of a healthy acute response to a recent acute stressful event. In other words, a finding of elevated inflammation would be clinically unfavourable only if it is coupled with chronic psychosocial stress, and favourable if it is due to a healthy stress response in an individual with good psychosocial adaptation. These dynamics make single tests for inflammation further difficult to interpret when not impossible.

There are many inter-connected indicators of chronic psychosocial stress used in the medical literature (Steptoe, 2007). Factors such as financial strain, job strain, and social network, can be measured objectively and represent someone's objective exposure to stress. On the other hand, factors such as depression and anxiety, although have more clinical meaning, are subjective mental representations. Nevertheless, there is evidence that low socioeconomic status is associated with depression and anxiety (Lazzarino et al., 2013a, 2013b) and thus the option of using financial strain as a marker of chronic psychosocial stress has the advantage of being both an objective measure and that of being highly correlated with more clinical conditions such as anxiety and depression. We have preferred financial strain over employment grade because the latter may not necessarily imply psychosocial stress.

Fibrinogen is a plasma protein produced by the liver and is a major coagulation factor. It is a positive acute-phase reactant protein (i.e. its concentration increases with inflammation), it is traditionally considered as a risk factor for cardiac disease because it promotes formation of thrombus, and it is considered as an inflammatory cytokine (Lowe et al., 2004; Stulnig, 2013).

Cardiac Troponin T is a marker of myocardial cell damage that is routinely measured in the peripheral blood plasma for the diagnosis of acute myocardial infarction in clinical settings. A high-sensitivity assay (HS-CTnT) has recently been developed and in healthy people it is associated with greater incidence of heart disease, cardiovascular mortality, and all-cause mortality, and is therefore considered the most proximal sentinel marker of heart disease (de Lemos et al., 2010; deFilippi et al., 2010).

For those reasons the aim of this study was to determine if financial strain (marker of chronic psychosocial stress) modifies the association between single test results for fibrinogen (marker of inflammation) and positivity for plasma HS-CTnT (marker of cardiac risk), so that high financial strain would increase the effect size of that association.

2. Methods

2.1. Study design

This cross-sectional study involved participants drawn from the Whitehall II epidemiological cohort (Marmot et al., 1991) between 2006 and 2008 in the United Kingdom (Hamer et al., 2010). The criteria for entry into the study included no history or objective signs of clinical or subclinical cardiovascular disease, no previous diagnosis or treatment of hypertension, inflammatory diseases, allergies, or kidney disease. Cardiovascular disease was defined as prior myocardial infarction, stable or unstable angina, revascularization procedure, heart failure, transient ischaemic attack, stroke, or electrocardiographic abnormalities (resting 12-lead electrocardiograms were taken). Volunteers were of white European origin, aged 53–76 years, and 56.5% were in full-time employment. Selection was stratified by grade of employment (current or most recent) to include both higher and lower socioeconomic status participants. From the initially invited participants (n = 1169), 27.6% were not eligible (mainly due to use of prescribed medications) and 25.9% declined to take part. There was no evidence of selection bias due to those exclusions with respect to the known characteristics of the sample (demographics, health behaviours, and traditional cardiovascular risk factors). Participants were prohibited from using any anti-histamine or anti-inflammatory medication 7 days prior to testing and were rescheduled if they reported colds or other infections on the day of testing. Participants gave full informed consent to participate in the study and ethical approval was obtained from the University College London Hospital committee on the Ethics of Human Research.

2.2. Data collection

We carried out clinical examinations in a light- and temperature-controlled laboratory. Participants were instructed to refrain from drinking caffeinated beverages or smoking for at least 2 h before the study and not to have performed vigorous physical activity or consumed alcohol since the previous evening. Venipuncture was performed using a butterfly needle. Blood pressure was taken 30 min after needle insertion (using an automated UA-779 digital monitor), as well as saliva and fasting blood samples.

Financial strain was assessed with an adaptation of the economic strain measure of Pearlin et al. (1981). This assesses difficulty paying one's bills, being able to replace items such as furniture or a car when needed, and being able to provide for one's family in terms of food, clothing, and medical care. Eight items were presented, with response options ranging from 1 = no difficulty to 3 = very great difficulty (Cronbach's alpha = 0.86). Therefore possible values range from 8 (lowest financial strain) to 24 (highest financial strain) (Steptoe et al., 2005). Other psychosocial stressors were assessed, including depression symptoms as measured using the Centre for Epidemiologic Studies Depression Scale (CES-D) (Eaton et al., 2004), and mental quality of life as measured using the 36-item Short Form Health Survey (SF-36) (Ware and Sherbourne, 1992). We derived two scores from the SF-36: mental health (items 9b–d and 9f–h) and mental component (items 5, 6, 9, and 10). We also used the PANAS scale to measure positive and negative affect (Watson et al., 1988).

We determined plasma fibrinogen concentration by an automated Clauss assay in a MDA-180 coagulometer (Organon Teknika, Cambridge, UK) using the manufacturer's reagents and the International fibrinogen standard (Gaffney and Wong, 1992).

We measured cardiac troponin T plasma concentration using a highly sensitive assay on an automated platform (Elecsys 2010 Troponin T hs STAT, Roche Diagnostics) (Collinson, 2011; Giannitsis et al., 2010).

We assessed coronary artery calcification (CAC Agatston score) in separate sessions using electron beam computed tomography (GE Imatron C-150, San Francisco, CA, USA) as previously described (Anand et al., 2007).

2.3. Data analysis

We recoded fibrinogen as a Z-score or as a binary variable. We set two different cut-off points for the binary categorisation so that we could evaluate whether the interaction between fibrinogen and