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A prospective study of C-reactive protein as a state marker in Cardiac Syndrome X

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ABSTRACT

Cardiac Syndrome X (CSX), the presence of angina pectoris despite normal epicardial coronary arteries seen on invasive angiography, is known to be associated with an elevation of several inflammatory biomarkers, suggesting a possible role for inflammation in its pathogenesis. We sought to establish if C-reactive protein (CRP) levels varied with disease severity and so whether it is a state or trait marker. We studied 16 CSX patients with typical angina pectoris, normal coronary arteries and an electrically positive exercise stress test (EST) and 13 age- and sex-matched healthy controls (HC). CSX patients were followed up at a subsequent visit with repeated exercise stress testing and CRP measurement. We found that CRP levels were significantly higher in the CSX group compared to the HC (1.5 [0.8–4.5] v 0.8 [0.4–1.4] mg/L, $p = 0.02$). This elevation in CRP persisted throughout the study length. CRP correlated with time to symptoms on EST at enrolment and at the second visit ($r = -0.690$, $df = 10$, $p = 0.013$ and $r = -0.899$, $df = 4$, $p = 0.015$, respectively). At the follow-up visit, 50% of CSX patients developed electrically and symptomatically negative ESTs. The mean CRP of this group was significantly lower than that of the CSX patients with ongoing symptoms and positive ESTs (1.2 ± 0.2 v 2.8 ± 0.6 mg/L, $p = 0.018$) and did not differ significantly from that of healthy controls. CRP levels also dropped in patients whose symptoms improved while they increased in patients who became more symptomatic ($p = 0.027$). We conclude that the results of this small study support the concept of CSX being an inflammatory-mediated condition with CRP levels prospectively varying with functional measures of disease severity. This indicates that CRP is a state marker in CSX.

1. Introduction

1.1. Defining Cardiac Syndrome X

Angina pectoris is a particularly emotive symptom as it is one of the few that can invoke fear of immediate death in patients. Thus, patients and physicians both correctly consider angina to be an extremely important complaint requiring urgent evaluation. Exercise stress testing is the usual non-invasive first step with exercise-induced symptoms and ST-depression being indicators of possible coronary artery disease. If positive, this is followed by an invasive coronary angiogram to assess the epicardial coronary arteries. Between 20% and 30% of angiograms performed to investigate chest pain are normal, forming the diagnosis termed "chest pain with normal coronary arteries" or CPNCA. This term encompasses a heterogeneous group of patients who may have non-cardiac sources of chest pain (e.g. gastro-oesophageal disease) or cardiac causes other than epicardial coronary artery disease (such as valvular heart disease, myocardial disease, dysrhythmias and microvascular disorders). CSX patients represent a subset of CPNCA.

CSX is defined as the presence of typical angina pectoris and exercise-induced ST-depression on EST, but with normal coronary arteries on angiography and without contributory heart disease (Lanza, 2007). It is the presence of an objective test indicating probable myocardial ischaemia that mainly separates CSX patients from other patients with CPNCA. It has proven to be difficult to characterise and to treat but remains an important condition as CSX patients, despite having a favourable cardiovascular prognosis, have a significantly impaired quality of life and can remain markedly symptomatic even years after diagnosis (Lamendola et al.,

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2010). Moreover they have been shown to have greater psychological morbidity than both healthy controls and patients with established coronary artery disease (Asbury et al., 2004). The main obstacle facing the management of CSX is that there is a lack of certainty as to its exact pathogenesis.

1.2. Inflammation and microvascular dysfunction in CSX

There is general agreement, however, that the main pathological feature in the majority of CSX patients is microvascular dysfunction (Maseri et al., 1991). This implies that the coronary arteries are dysfunctional at the level of the resistance vessels, such as small arteries and arterioles <500 μm in diameter. These vessels are too small to be visualised by conventional angiography. In CSX these vessels are believed to have a reduced capacity to dilate in response to increased cardiac workload resulting in a relative hypoperfusion of the subtended myocardium during exercise, which then results in the symptom of angina (see Fig. 1A). In fact, it is possible to demonstrate this using invasive coronary reactivity testing, where the effects of the infusion of vasoactive substances on both symptoms and coronary vasomotion are examined. It has been recently proposed that patients with CSX should be reclassified as having microvascular angina if the results of these tests are positive (Lanza and Crea, 2010; Radico et al., 2014).

There are several potential causes of microvascular dysfunction, including many of the conventional cardiac risk factors such as hypertension, dyslipidemia and smoking (Lanza and Crea, 2010). Significantly, inflammation is also associated with endothelial and vascular dysfunction potentially limiting the bioavailability of nitric oxide, the main endothelial-derived mediator of vasodilatation (Arroyo-Espliguero and Kaski, 2006). CRP, an acute phase protein and a crude measure of general inflammatory status, has been consistently shown to be elevated in CSX. Furthermore, studies have shown that CRP concentrations correlate with indicators of microvascular and endothelial function. For example, high CRP was shown to be associated with impairment of coronary flow reserve and of flow-mediated dilation (FMD) of the brachial artery, a measure of endothelial-dependent vasodilation (Recio-Mayoral et al., 2013; Ong et al., 2012). Finally, it is known that CRP levels correlate with symptom burden in patients with CPNCA (Cosin-Sales et al., 2003).

1.3. Other considerations in CSX

It has also been demonstrated that some patients with CSX have abnormalities in the cortical processing of painful stimuli (including reduced habituation) as well as an increased sensitivity to intracardiac stimuli and this may also contribute to their symptoms (Chauhan et al., 1994; Valeriani et al., 2005; Rosen et al., 2002). Furthermore, as CSX patients suffer from higher levels of psychological morbidity (such as depression and health anxiety) than healthy controls it is possible that some patients with CSX are experiencing a pain or somatic symptom disorder. CRP is also known to be elevated in many stress-related conditions.

To our knowledge no previous study has prospectively examined CRP in patients with CSX. The objective of this prospective, longitudinal observational study is to determine if CRP levels correlate with symptoms in CSX patients over time in order to further the case of a causal link between inflammation and CSX.

2. Materials and methods

2.1. Participants

CSX patients were consecutively recruited from the coronary catheterisation laboratory of Cork University Hospital, a tertiary referral centre, from November 2011 to March 2013. Inclusion criteria for CSX patients included (a) the presence of typical angina pectoris (viz. substernal chest discomfort of characteristic quality and duration that is exacerbated by exertion or stress and relieved by rest and/or nitrates); (b) an angiographically normal coronary angiogram; and (c) an electrically positive EST (defined by the presence of $\geqslant$1 mm horizontal or downsloping ST-depression 80 ms after the J-point in two contiguous leads). Patients were excluded if they had (a) other cardiac disease (such as significant dysrhythmia, myocardial or valvular heart disease) (b) moderate or greater hypertension (c) diabetes mellitus or (d) other pro-inflammatory conditions (such as active infection, chronic kidney disease, etc.). Healthy controls were matched for age, gender and statin use. They were recruited from a primary care centre, had never suffered any cardiac-related symptoms and were bound by the same exclusion criteria as CSX patients. We enroled a total of 16 patients with CSX and 13 controls. Almost 1850 patients undergoing coronary angiography for chest pain were screened to obtain this sample cohort of CSX patients. Every suitable patient was approached and all agreed to be enroled in the study. The study protocol was approved by the local research ethics committee.

2.2. Investigations

At enrolment all subjects gave full-informed written consent and filled out a cardiac risk factor questionnaire. Venous blood samples were taken between 0900 and 1200 and were drawn into dipotassium EDTA tubes and immediately centrifuged at 112 RCF for 15 min. Plasma was then aliquoted into 2 ml microtubes and frozen at −80 °C for later analysis. CSX patients also completed the Seattle Angina Questionnaire (SAQ), the list of threatening experiences questionnaire (LTE-Q) and the Perceived Stress Scale (PSS) questionnaire. No symptomatic treatment was undertaken in CSX patients at diagnosis. The CSX patients were followed at a further visit, planned to occur between 6 and 12 months after the angiogram, when the exercise stress test, blood sampling and questionnaires were repeated.

2.2.1. Questionnaires

The SAQ is a validated questionnaire that examines the impact of angina on the life of symptomatic patients (Spertus et al., 1995). When completed it provides results in the form of five scales each of which is numbered from 0 to 100, with higher numbers being associated with improved health status. These scales include estimates of physical limitation, angina frequency, treatment satisfaction and disease-related quality of life. The LTE-Q is a list of 12 actual recent life events that have been shown to have an effect on psychological health (Brugha and Cragg, 1990). The PSS is widely used in research to evaluate the subject's perception of their own recent life stress. Higher scores in these scales indicate higher actual and perceived life stress (Cohen et al., 1983).

2.2.2. Exercise stress testing

All ESTs were performed between 0900 and 1130. CSX patients performed a treadmill-based BRUCE protocol stress test at baseline and at the second visit. The time taken to symptoms and ST-depression (if present) was recorded as was the overall exercise time and rate-pressure product at peak exercise. An EST was considered symptomatically positive if the patient experienced typical angina pectoris and electrically positive (a requirement for a diagnosis of CSX) and suggestive of ischaemia when horizontal or down-sloping ST –depression of $\geqslant$1 mm was noted 80 ms after the j-point in two contiguous leads.