SCIENTIFIC LETTER

C reactive protein is associated with malignant ventricular arrhythmias in patients with ischaemia with implantable cardioverter-defibrillator

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Patients with ischaemic heart disease and low ejection fraction (EF) are at increased risk of sudden death. MADIT (Multicenter Automated Defibrillator Implantation Trial) II has shown that implantable cardioverter-defibrillators (ICDs) reduce the risk of death by 31% at two years in patients with previous myocardial infarction and EF < 30%.¹ The absolute risk reduction over an average follow up of 20 months, however, was only 5.6%. In addition, the high prevalence of patients who have had a myocardial infarction with EF ≤ 30% makes the cost of this strategy high. This has led to an ongoing search for reliable markers of future episodes of life-threatening ventricular tachycardia (VT) or ventricular fibrillation (VF) to identify a higher-risk subgroup in which ICD therapy can be more beneficial and cost effective.

The difficulty in predicting major ventricular arrhythmias probably reflects a limited understanding of their complex mechanisms. This is particularly true for patients who have had a myocardial infarction and with LV dysfunction, in whom myocardial ischaemia may trigger major ventricular arrhythmias. C reactive protein (CRP) concentration has been shown to be raised both in subjects studied at autopsy after sudden coronary death in association with plaque rupture and in healthy patients at risk of future sudden death.^{2–4} Moreover, CRP is a predictor of cardiovascular death in apparently healthy people and in patients with ischaemic heart disease. Therefore, we sought to study whether CRP concentration is associated with the risk of malignant arrhythmias in a population of patients who received an ICD according to the inclusion criteria of the MADIT II study.

METHODS

Sixty five patients (51 men, mean age 70 ± 10) with the required characteristics were studied. Patients were enrolled and blood samples were taken for CRP assessment during a routine scheduled follow-up visit at our outpatient clinic for arrhythmias. All patients with recent (≤ 1 month) infection, trauma, cardiovascular ischaemic episodes or chronic inflammatory diseases were excluded (five patients). At the time of the follow-up visit, ICDs were controlled by telemetry according to the American Heart Association/American College of Cardiology/North American Society of Pacing and Electrophysiology guidelines. The primary end point of the study was the rate of appropriate ICD shocks for sustained VT or VF. Sustained VT was defined as any VT whose ventricular rate ranged from 160 beats/min to 210 beats/min lasting ≥ 30 s determining appropriate ICD shock. VF was defined as a rapid, incessant, irregular ventricular rhythm > 210 beats/min determining appropriate ICD shock.

CRP was measured in a single batch by a high sensitivity method (DADE Behring, Marburg, Germany). The lower limit of detection was 0.05 mg/l.

Table 1 Demographic characteristics of patients according to CRP concentration (total n = 65)

	CRP concentration >3 mg/l	<3 mg/l
Number	29 (44%)	36 (56%)
Age (years)	71 (7)	69 (10)
LVEF (%)	25 (3)	26 (1)
Risk factors		
Type II diabetes	36%(10)	41%(15)
Smoking	95%(28)	82%(30)
Hypertension	86%(25)	65%(23)
Hypercholesterolaemia	36%(10)	47%(17)
Drug treatment		
ACE/AT II inhibitors	13 (44%)	24 (68%)
Statins	23 (81%)	22 (61%)
Aspirin	29 (100%)	36 (100%)
β blockers	24 (82%)	29 (80%)

All differences are not significant.

ACE, angiotensin converting enzyme; AT II, angiotensin II; CRP, C reactive protein; LVEF, left ventricular ejection fraction.

As high sensitivity CRP is not normally distributed, non-parametric tests were chosen, specifically χ^2 and Mann-Whitney tests when appropriate. CRP concentration is expressed as the median and range, and a cut off of 3 mg/l was specified pre hoc as the normal CRP concentration in our study population. A value of $p < 0.05$ was considered significant.

Eighteen of 65 (28%) patients were found to have had VT/VF triggering an appropriate ICD shock. Twenty nine of 65 patients (45%) had CRP concentrations > 3 mg/l and 36 (55%) had CRP < 3 mg/l. Clinical characteristics of patients with high compared with low CRP concentrations were similar (table 1). VT/VF had occurred in 14 of 29 patients (48%) with CRP > 3 mg/l versus only 4 of 36 (11%) of those with CRP < 3 mg/l ($p < 0.003$). After CRP concentrations were divided into tertiles, patients in the top tertile had a significantly higher occurrence of VT/VF in comparison with patients in the first two tertiles ($p = 0.01$). Receiver operating characteristic curve analysis confirmed the discriminatory capacity of CRP in distinguishing patients experiencing VT/VF (area under the curve 0.72, $p = 0.008$).

DISCUSSION

Our study shows that CRP concentration > 3 mg/l is significantly associated with the occurrence of VT/VF in a population

Abbreviations: CRP, C reactive protein; EF, ejection fraction; ICD, implantable cardioverter-defibrillator; MADIT, Multicenter Automated Defibrillator Implantation Trial; VF, ventricular fibrillation; VT, ventricular tachycardia

of patients similar to those enrolled in MADIT II, suggesting that CRP can be used as a simple tool to risk stratify these patients. This is an important finding, as no marker among those investigated to date has shown consistent advantages over assessment of LV function by EF. Our findings are in line with the results of Shehab *et al.*⁵ who found that CRP was associated with the risk of sudden death in 34 patients with chronic heart failure and low EF. Furthermore, CRP was raised in patients who died suddenly and who were found to have coronary plaque rupture in a postmortem study, suggesting that VT/VF may be triggered by sudden myocardial ischaemia.³ CRP may also be a marker of the myocardial substrate prone to develop arrhythmias. Indeed raised CRP serum concentrations have consistently been associated with recurrence of atrial fibrillation in patients who do not have ischaemic heart disease and may reflect the proarrhythmic effect of proinflammatory cytokines. Accordingly, we have recently found widespread myocardial inflammation in patients with a previous myocardial infarction. Larger prospective studies are required to consider these important issues. Some important limitations of this study must be raised, in particular its retrospective design and the small sample size. Therefore, the results can be considered only hypothesis generating, yet this study suggests, for the first time, a role for CRP in risk stratification of arrhythmic events in patients similar to those in MADIT II.

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IMAGES IN CARDIOLOGY

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Bladder compression: an unusual presentation of retroperitoneal haematoma

A 56-year-old man underwent percutaneous intervention with an unsuccessful attempt to open a chronic total occlusion of the right coronary artery and successful implantation of a 4 × 12 mm paclitaxel eluting stent in the circumflex. Before the procedure he received clopidogrel and aspirin and periprocedural anticoagulation was attained with 9000 units of unfractionated heparin (bodyweight 102 kg). The activated clotting time peaked at 330 seconds.

An 8 French sheath was inserted in the right femoral artery and a 6 French in the left femoral artery to allow contralateral injections for distal visualisation. At the end of the procedure femoral angiography was performed before access site closure using 2 Closer S devices (Perclose, Abbott Vascular, Redwood City, California, USA).

Two hours later the patient became progressively hypotensive (blood pressure 90/50 mm Hg) and complained of right iliac fossa pain. He was immediately resuscitated with intravenous colloids and catecholamines. Manual compression on the right groin was applied for 30 minutes and 30 mg of protamine sulfate was given (activated clotting time 180 seconds). A computed tomographic (CT) scan confirmed the presence of a right sided retroperitoneal haematoma. Clinical recovery was uneventful.

Later we reviewed the femoral angiography carried out at the end of the procedure. We noted a normal convex bladder outline

on the left side (panel A); on the right side, however, the bladder outline was concave suggesting some early compression from the retroperitoneal haematoma (panel B). We feel this case highlights an additional rare but important benefit of performing femoral angiography before access site closure. While this sign is subtle, early diagnosis of this potentially fatal complication could allow aggressive prompt management including fluid resuscitation and the possibility of reversing anticoagulation and performing prolonged manual compression.

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