C-reactive protein: not only a marker but also a mediator of myocardial damage following acute myocardial infarction

I have greatly enjoyed reading the recently published article by Ørn et al.1 assessing the relationship between inflammatory mediators, including C-reactive protein, and indices of infarct size and left ventricular remodelling following successful primary percutaneous coronary intervention (PCI) in patients with first-time ST elevation myocardial infarction (MI).

With improved understanding of the critical role of inflammation in atherothrombosis, attention has focused on the inflammatory biomarker C-reactive protein as a risk marker.2 C-reactive protein, an acute-phase reactant, plays an important role in innate immune response, and it is now recognized to be a mediator of atherothrombotic disease.3 As in other types of tissue injury, acute MI (AMI) also generates an acute-phase reaction. The deposition of C-reactive protein in the infarcted region, co-localizing with activated fragments of complement system, indicates that complement activation enhances local inflammation during AMI.3 C-reactive protein has been reported to co-localize with activated complement fragments in infarcted myocardium in patients who died due to AMI.3 Moreover, C-reactive protein is not only a marker of the amount and activity of circulating pro-inflammatory cytokines but may also contribute to inflammation in ischaemic myocardium by activating complement system. Magadle et al.4 showed that pre-procedural serum high-sensitive (hs)-C-reactive protein levels in patients with AMI undergoing primary PCI might be considered a powerful predictor of early complications. Several studies have demonstrated that hs-C-reactive protein measured at either presentation or hospital discharge may have prognostic value in patients with acute coronary syndromes.5 Another clinical study demonstrated that hs-C-reactive protein levels on admission may predict the efficacy of reperfusion in patients with AMI.6

In the recently published article, our group demonstrated that hs-C-reactive protein levels on admission in patients with AMI undergoing primary PCI are likely to be in the causal pathway leading to the development of poor myocardial perfusion, especially when combined with prolonged pain to balloon time.7 In that study, the study population consisted of 75 patients admitted with acute anterior MI and underwent primary PCI in the left anterior descending coronary artery. Myocardial perfusion was evaluated by using TIMI myocardial perfusion grade. In multivariate logistic regression analysis, hs-C-reactive protein levels and pain to balloon time were detected to have statistically significant independent association with poor myocardial perfusion. Adjusted odds ratio was calculated as 1.85 for hs-C-reactive protein (P = 0.003; CI = 1.23–2.80).

In conclusion, when considering the clinical significance of admission high C-reactive protein levels in patients with AMI, it can be concluded that the development of poor myocardial perfusion may partially explain the relation between high C-reactive protein levels and poor clinical outcomes. I considered that poor myocardial perfusion after primary PCI is not only related to procedural factors and clinical characteristics of the patients but may also be related with microvascular damage starting before PCI.

References

5 Morrow DA, Rifai N, Antman EM, Weiner DL, McCabe CH, Cannon CP, Braunwald E. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes; a TIMI 11A substudy.

Abnormal left ventricular relaxation in patients with long QT syndrome

We read with great interest the recent report by Haugaa et al.1 and the accompanying editorial by De Ferrari and Schwartz2 on the association between abnormal ventricular repolarization and mechanical dysfunction (prolonged contraction and/or impaired diastolic function) in patients with long QT syndrome (LQTS). We were particularly interested by the statement of Haugaa et al.1 that ‘these findings imply an impairment of diastolic function in a number of symptomatic LQTS mutation carriers’. In keeping with this view, Moss et al.3 also linked the prolonged ventricular repolarization in LQT3 patients (SCN5A-ΔPKQ mutation) with slowed left ventricular (LV) relaxation.4 In these patients, the mean QTc was 578 ± 55 ms, LV isovolumic relaxation time (IVRT) was 125 ± 27 ms, mitral E-wave deceleration time was 289 ± 80 ms, and mitral E-wave velocity was 57 ± 8 ms, suggesting minor diastolic dysfunction.5 Shortening of the QTc interval by ≥ 3 ms with ranolazine, a drug that inhibits the late Na current, resulted in significant...
shortening (13%) of the IVRT, a 22% decrease in the mitral E-wave deceleration time, and a 25% increase in the mitral E-wave velocity. In the patients with LQT3, bradycardia may protect their hearts from developing overt diastolic dysfunction.

Similarly, in an animal model that mimics LQT2, we observed that the prolongation of the LV monophasic action potential duration (APD) and QTc interval caused by the IKr blocker clofilium was associated with a delay in LV relaxation (unpublished data). This finding is consistent with those reported in LV myocytes isolated from failing canine and human hearts where prolongation of APD is accompanied by abnormal intracellular Ca2+ transients and twitch contractions that are characterized by a phasic (spike) and tonic (dolomlike) component. Similar to the results of Moss study, shortening of the APD of these failing myocytes suppresses EADs and abrogates the tonic component of the intracellular Ca2+ transients and twitch contraction without affecting the phasic component.

Prolonged contraction/systole and delayed relaxation may also affect myocardial blood flow. Coronary blood flow is minimal during systole and reaches a maximum during the initial relaxation phase coincident with the IVRT period. Directly relevant to this issue is the work of Mayet’s group using wave intensity analysis of coronary blood flow. They showed that during ventricular relaxation the relief of myocardial compression of the coronary microcirculation generates a ‘backward travelling suction wave’ that becomes the dominant driver of the increase in coronary blood flow in diastole. This wave generated by the rapid ventricular relaxation pulls blood into the microcirculation. Therefore, it is conceivable that patients with prolonged ventricular repolarization have a reduced ‘suction wave’ and thereby reduced diastolic coronary flow. This condition may also apply to acquired diseases wherein ventricular repolarization is slowed (e.g. heart failure and left ventricular hypertrophy).

In summary, we agree with De Ferrari and Schwartz that evidence is accumulating that abnormal ventricular repolarization due to ion channelopathies may not only cause a ‘pure electrical disease’ but also affects contractile function and possibly impairs myocardial perfusion. Whether a compromised myocardial perfusion contributes to the symptoms or the risk for cardiac events in patients with LQTS remains to be established.

References

Abnormal left ventricular relaxation in patients with long QT syndrome: reply

We appreciate the interest and comments from Dr Belardinelli et al. regarding the accumulating evidence of cardiac contraction abnormalities in long QT syndrome (LQTS) patients. The study referred to from Moss et al. showed slowed ventricular relaxation in LQT3 patients which was, to some extent, reversed by ranolazine-induced shortening of action potential duration (APD). The patients with LQT3 differ genetically and clinically from LQT1 and LQT2 patients who constituted the majority of our patients, but nevertheless the study by Moss et al. represents an important and valuable link between electrical and mechanical dysfunction in LQTS patients.

In our study, contraction abnormalities were most evident in LQT1 and LQT2 patients with arrhythmic events compared with silent mutation carriers. This implies that the degree of the electrical defects may be translated into mechanical dysfunction. We note with interest that ‘dysynchrony score’ used by Moss et al. was reduced by ranolazine infusion, which is well compatible with our findings of pronounced mechanical dispersion in LQTS patients. Our study focused on prolongation of contraction duration and systole in LQTS patients. Given a fixed heart rate, prolonged duration of systole necessarily results in reduced duration of diastole.

The length of diastole is indeed important for coronary blood flow as commented by Belardinelli and in the work of Mayet’s group. Importantly, duration of diastole shortens relatively more at higher heart rates than duration of systole. This fact may be of particular importance in LQT1 patients. At higher heart rates, defect Ica channels in LQT1 patients lead to a reduced shortening of the QT interval, i.e. systole, and as a consequence diastole duration may be significantly reduced. As discussed by Dr Belardinelli et al., bradycardia was considered to protect LQT3 patients from developing overt diastolic dysfunction. However, considering that bradycardia can be a trigger of arrhythmias in LQT3 patients, preventing diastolic dysfunction by inducing bradycardia may be ambiguous. In LQT1 and LQT2 patients, β-blocker therapy is the treatment of choice and is shown to be protective against arrhythmic events, mainly due to inhibition of catecholaminergic stimuli. In the context of diastolic duration, β-blocker treatment lowers heart rate and prolongs diastole. The favourable effect of β-blockers in LQT1 and LQT2 patients may therefore consist of both protection from arrhythmias in addition to prolongation of diastole that facilitates diastolic filling.

Finally, we totally agree with Belardinelli et al. and De Ferrari and Schwartz that traditional cardiac electrical disorders should be studied beyond electricity, since electrical and mechanical function are closely related.

References