Letters to the Editor

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Impact of the elevation of biochemical markers of myocardial damage on long-term mortality after percutaneous coronary intervention: results of the CK-MB and PCI study

We read with great interest the paper ‘Impact of the elevation of biochemical markers of myocardial damage on long-term mortality after percutaneous coronary intervention: results of the CK-MB and PCI study’ by Cavallini et al.1

This large cohort follow-up study is of particular relevance for the interventional cardiologist, as it gives further data about the impact of procedure-induced myocardial necrosis on long-term outcome following PCI.

However, we would like to comment on the dissociation between creatine-kinase MB and troponin I elevation, with the former exhibiting an almost linear correlation with mortality (in Figure 1 of their paper), which is not apparent for the latter (Figure 2 of their paper). According to the authors, troponin I is an extremely sensitive marker that detects even reversible myocardial injury caused by procedure-induced ischaemia or very minor myocardial necrosis, which does not influence the long-term prognosis.

Although we agree with authors about the sensitivity of the troponin assay, we believe that a methodological problem might have played a role in determining their result. In a recent paper, we were able to demonstrate a strong linear correlation between the mass of new myocardial necrosis (as measured by delayed-enhancement MRI) and post-procedural (24 h) troponin I absolute elevation ($r = 0.84, P < 0.001$).2

In their study, Cavallini et al. chose to grade troponin I elevation by the peak ratio, calculated by dividing the maximum post-procedural level of the marker by its upper reference limit or by its baseline value if the baseline value was above the upper reference limit. For troponin I, the upper reference limit for cTnI was 0.15 μg/L. Thus, in a stable patient with no pre-procedural cTnI elevation, a peak ratio of 10 (at the extreme right end in Figure 2) would mean an absolute cTnI elevation of only 1.5 μg/L, whereas in a patient with a baseline cTnI of 1, the same peak ratio would mean an absolute cTnI elevation of 10 μg/L. If these two values were interpolated in the regression curve obtained from our data, they would translate to about 2 vs. 13 g of new myocardial necrosis.

Moreover, in our paper, few (four out of 50) patients, all with normal pre-procedural cTnI, showed an absolute troponin I elevation of between 0.2 and 1 μg/L (the latter being the upper limit of normal in our laboratory), and no new areas of hyperenhancement were seen by MRI, probably because troponin I is even more sensitive than MRI in detecting small, patchy necrosis. In these patients, it is very unlikely that trivial myocardial damage will alter prognosis. This lack of relationship would be an important finding, challenging the current European Society of Cardiology/American College of Cardiology guidelines that recognize elevation of cardiac troponins within 24 h of a PCI procedure in the definition of myocardial infarction.3

We appreciated the comments by Porto et al. concerning the different prognostic impact of the increases in creatine kinase MB (CK-MB) and troponin I (cTnI) emerging from our study. They suspect that a methodological problem associated with the calculation of the cTnI ratio may have conditioned our results. In line with the Joint Ad Hoc Committee of the European Society of Cardiology and American College of Cardiology for the Redefinition of Myocardial Infarction,1 we defined CK-MB and cTnI elevations as any post-procedural level above the upper reference limit or an increase of >50% over baseline when the baseline level was already high3, a definition that does not mention the CK-MB or cTnI ratio. However, we did use the CK-MB and cTnI ratios to explore the relationship between the degree of marker elevation and the risk of death. In accordance with the available literature, we graded peak CK-MB or cTnI elevation on the basis of the ratio between the observed post-procedural peak value of the marker and its upper reference limit (or the baseline value, when high). Although we agree that calculating the peak ratio in the case of high baseline levels is arbitrary and may lead to an underestimate of the degree of elevation, we consider it a reasonable attempt to separate the amount of myocardial damage due to the interventional procedure per se from that attributed to pre-procedural myocardial necrosis. How to make a qualitative and quantitative biochemical assessment of an ongoing ischaemic insult superimposed on a recently damaged myocardium is still a matter of debate,1,3 and all of the proposed methodologies have some limitations. In this regard, even the absolute increase in marker values suggested by Porto et al. is susceptible to criticism as it does not take into account the potential spontaneous post-procedural increase in the marker during the

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Italo Porto
Universita' Cattolica del Sacro Cuore
Roma
Italy
John Radcliffe Hospital
Headley Way
OX3 3DU
UK
Tel: +44 1865 228934
E-mail address: i.porto@doctors.org.uk

William Van Gaal
John Radcliffe Hospital
Oxford
UK

We appreciate the comments by Porto et al. concerning the different prognostic impact of the increases in creatine kinase MB (CK-MB) and troponin I (cTnI) emerging from our study. They suspect that a methodological problem associated with the calculation of the cTnI ratio may have conditioned our results. In line with the Joint Ad Hoc Committee of the European Society of Cardiology and American College of Cardiology for the Redefinition of Myocardial Infarction,1 we defined CK-MB and cTnI elevations as any post-procedural level above the upper reference limit (or an increase of >50% over baseline when the baseline level was already high3), a definition that does not mention the CK-MB or cTnI ratio. However, we did use the CK-MB and cTnI ratios to explore the relationship between the degree of marker elevation and the risk of death. In accordance with the available literature, we graded peak CK-MB or cTnI elevation on the basis of the ratio between the observed post-procedural peak value of the marker and its upper reference limit (or the baseline value, when high). Although we agree that calculating the peak ratio in the case of high baseline levels is arbitrary and may lead to an underestimate of the degree of elevation, we consider it a reasonable attempt to separate the amount of myocardial damage due to the interventional procedure per se from that attributed to pre-procedural myocardial necrosis. How to make a qualitative and quantitative biochemical assessment of an ongoing ischaemic insult superimposed on a recently damaged myocardium is still a matter of debate,1,3 and all of the proposed methodologies have some limitations. In this regard, even the absolute increase in marker values suggested by Porto et al. is susceptible to criticism as it does not take into account the potential spontaneous post-procedural increase in the marker during the
early post-myocardial infarction phase; this is particularly true in the case of a marker such as troponin, which has a slow wash-out and a delayed peak. To eliminate the potential effect of high pre-procedural cardiac marker levels on the results of our study, we also performed a separate analysis after excluding the patients whose baseline marker levels were above the upper reference limit and obtained similar results. We would finally like to point out that increasing the troponin cut-off value to considerably above the 99th percentile of the distribution of a reference control group would probably have shown an association between cTnI elevation and a worse outcome; in this case, however, the post-procedural increase in cTnI would have been easily associated with a simultaneous increase in CK-MB, thus leaving the issue of the prognostic significance of the minor post-procedural myocardial damage, revealed by an isolated cTnI elevation, unaddressed. Our data now suggest that isolated cTnI elevations do not influence long-term mortality.

References


Claudio Cavallini
Division of Cardiology
Ca’ Foscari Hospital
Piazza Ospedale 1
31100 Treviso
Italy
Tel: +39 0422 322767
E-mail address: clcaval@tin.it

Stefano Savonitto
Department of Cardiology
Niguarda Hospital

Diego Ardissino
Division of Cardiology
Maggiore Hospital
Via Gramsci 14
43100 Parma
Italy

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The emerging role of inflammation in atrial fibrillation and the potential of anti-inflammatory interventions

We read with considerable interest the article by Engelmann and Svendsen providing a concise overview of the current knowledge about the association of inflammation with atrial fibrillation (AF). A continuously increasing number of investigations examine the role of inflammation in AF. Interestingly, two recent studies indicated that C-reactive protein relates to the left atrial size and AF duration before cardioversion, providing evidence of an association between inflammation and atrial structural remodelling. Moreover, it has been demonstrated that baseline C-reactive protein levels prior cardiovension of persistent AF represent an independent predictor of sinus rhythm maintenance after cardioversion.6,5 Of note, in a recent small study, we examined the variation of inflammatory indexes during the first week after successful cardioversion of persistent AF. We found that fibrinogen levels increased significantly in patients who relapsed into AF, but remained stable in patients who remained in sinus rhythm.6 In the latter patients, C-reactive protein values tended to decrease post-cardioversion, but white blood cell (WBC) count was significantly lower on the seventh day when compared with baseline values.6 Thus, we concluded that the variation of inflammatory indexes post-cardioversion might have prognostic implications with regard to sinus rhythm maintenance.

There is substantial evidence that inflammation augments oxidative stress and vice versa, whereas such interrelation has also been implicated in the pathophysiology of AF.7 Carnes et al.8 were the first to show that an antioxidant intervention with vitamin C ameliorates atrial electrical remodelling in experimental animals and significantly reduces the incidence of post-operative AF in patients undergoing coronary bypass surgery. Very recently, we demonstrated that treatment with vitamin C reduces the early recurrence rates after electrical cardioversion of persistent AF and attenuates the associated low-level inflammation.9 A significant variance was found in the serial measurements of WBC counts and of fibrinogen levels in the two groups (vitamin C and control), whereas in the vitamin C group, C-reactive protein levels were lower on the seventh day post-cardioversion when compared with baseline.10 It can therefore be speculated that antioxidant interventions might have an impact against AF-associated inflammation.

As mentioned by Engelmann and Svendsen, accumulating evidence suggests that anti-inflammatory interventions might exert favourable effects on AF. It has recently been shown that administration of n-3 fatty acids in patients undergoing coronary bypass surgery substantially reduces the incidence of post-operative AF.10 Besides direct electrophysiological effects, it has been proposed that the anti-inflammatory effects of these natural compounds may favourably affect the atrial remodelling.11 Finally, we agree with the authors that angiotensin-converting enzyme-inhibitors and angiotensin receptor blockers represent a promising approach. We have further proposed that aldosterone antagonists such as spironolactone might exert beneficial effects on AF, as aldosterone induces inflammation, oxidative stress, and fibrosis.12

Undoubtedly, more studies are needed to elucidate the exact role of inflammation and to clarify the impact of anti-inflammatory interventions in the setting of AF.

Conflict of interest: none declared.

References

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