The EMIP Project

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The publication of the results of the European Myocardial Infarction Project–Free Radicals (EMIP-FR) on the short- and long-term outcome of myocardial infarction patients treated with trimetazidine was certainly overdue, following their early report in a Late Breaking Trials Session, in 1996.

The findings of the trial, one of the largest collaborations in the field of cardiovascular research, are clear-cut, and negative with respect to the free radicals (FR, in the trial acronym) hypothesis which originated the study: despite its suggestive conceptual and experimental rationale, trimetazidine does not provide any clinical advantage over placebo in patients exposed to the risk of reperfusion injury following thrombolytic therapy. The (moderate) claim of the authors, to give trimetazidine (or better: to the biological hypothesis it represents) another chance, because of the beneficial effect found (only in the per-protocol analysis) in patients who did not receive thrombolysis, can hardly be supported: it would be necessary in fact to revise completely, re-formulate, and provide a brand new conceptual and experimental framework for trimetazidine as well as for the reperfusion injury hypothesis.

In the results of the subanalysis, it would be even less justified to find remote grounds for the use of trimetazidine (or of molecules with the same pharmacological and biological rationale) in non-thrombolysed patients, for whom the trial hypothesis was anticipating a difference (if any) exactly in the opposite direction.

The clear negative answer of the trial, to a clearly formulated and documented hypothesis, must be seen as its main strength in the understanding of the relevance of the biological events which occur in the scenario of reperfusion.

Discussion and research into the likelihood of a risk which could be worse than, or at least substantially limit, the benefits of reperfusion have for decades been in the background, and often at the forefront, of developments in the ‘thrombolytic era’. The EMIP-FR accurately summarizes, in its introduction and in the discussion, the main terms of reference of the problem. While the quotations are obviously focused on and around trimetazidine, the implications are easily generalizable: (a) physiopathological models and experimental data support the idea that the various pieces of evidence on damaging cellular mechanisms activated at the time of reperfusion are consistent with the formulation of a comprehensive paradigm of ‘reperfusion injury’; (b) weakly controlled clinical observations and experiments with ad hoc-targeted end-points confirm the plausibility of the paradigm, and advocate its relevance, further emphasized by the fact that pharmacology provides molecules able to act on one or other of the biological mechanisms or steps of the paradigm; (c) the hypothesis is fully falsified as soon as it is tested with a proper methodology under real clinical conditions, where the paradigm indicates the site of the reperfusion injury and that damage could be controlled and antagonized.

Two alternatives could explain such results: either the drug is perfectly inactive, or the hypothesis has no clinical relevance or implications. The role of real trials to discriminate between suggestive biological and pharmacological data and hard pathogenetic mechanisms is at least as important as their power to assess drug efficacy. The case of trimetazidine, and of its free radical biological background is the last of a long series, which includes, notably, the antiarrhythmics, the Ca++-channel blockers, and the inotropes.

The relevance of clinical and research (positive as well as negative) population trials, as tools for the verification of the degree of correctness of pathophysiological paradigms, is rarely appreciated and used in educational exercises. The almost exclusive focus on positive results tends to reinforce the idea that there is a continuum of rationality and linearity between the different domains of research. The non-scientific (psychological, as well as market) reasons for such a preference are clear: it should be emphasized, however, that a greater risk is a systematic bias in favour of a forced coherence between experimental and clinical research.

The EMIP-FR investigators must be congratulated for confronting a question which has been around for so many years, despite the fact that the by now historical trials on thrombolysis, and more directly the papers produced from the databases of the GISSI group, have clearly documented the clinical non-relevance (if not the existence or the plausibility) of reperfusion injury. The fascination of the biological–biochemical–experimental world was, however, left almost untouched. Thanks to the publication of these results, could it be said that a chapter is officially closed?
To underline and stress the highly positive nature of this and other ‘negative’ trials, their ever-growing anthology should be used intensively and recommended as part of any training curriculum. It could be seen as a uniquely effective tool for the promotion of more realistic and dialectic attitudes in the appreciation of the interplay between clinical needs and strategies on the one side, and the promises and expectations of biology, on the other.

G. TOGNONI  
Department of Cardiovascular Research,  
Istituto ‘Mario Negri’,  
Milan, Italy

References


Growth hormone and insulin-like growth factor — friends of the infarcted heart?

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Acute myocardial infarction is the single leading cause of death in developed countries. In patients who survive the acute event, the loss of contractile mass triggers hypertrophy of the surviving myocardium and profound alteration in the ventricular architecture that may eventually result in ischaemic cardiomyopathy and heart failure. It has been suggested that detrimental activation of neurohormonal and cytokine cascades may play a critical role in acute myocardial infarction and remodelling of the heart.

In this issue, Friberg et al. report on the changes in serum levels of growth hormone and insulin-like growth factor-1 in 52 consecutive patients presenting with acute myocardial infarction[1]. None of the patients required inotropic support, indicating that a relatively stable patient population was studied. This is the first study to investigate the growth hormone—insulin-like growth factor-1 axis in the clinical setting of acute myocardial infarction. The most salient findings can be summarized as follows. Serum growth hormone levels were increased two- to threefold during the early hours after myocardial infarction and returned to baseline within 24–48 h. Growth hormone levels correlated with infarct size, as assessed by serum markers, and were inversely correlated with left ventricular ejection fraction as determined by echocardiography. By contrast, changes in serum insulin-like growth factor-1 levels during acute myocardial infarction were subtle and remained within the normal range throughout the study period. Interestingly, however, patients who died from cardiovascular causes over 2 years of follow-up had higher initial levels of growth hormone and lower levels of insulin-like growth factor-1 as compared to survivors, suggesting that decreased growth hormone sensitivity during the acute phase of myocardial infarction indicates a poor long-term prognosis. Although the observational design of this study does not allow firm conclusions about the potential role of growth hormone and insulin-like growth factor-1 in the pathophysiology of acute myocardial infarction to be drawn, the data raise an important question, i.e. whether the surge of growth hormone during the early hours of acute myocardial infarction promotes salutary or detrimental effects. In this regard, experimental data indicate that growth hormone and insulin-like growth factor-1 can influence the susceptibility of myocytes to ischaemic cell death and modify the early remodelling process after acute myocardial infarction.