Letters to the Editor

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What is 'reperfusion injury'?

I read with great interest the article by Turschner et al., describing the echocardiographic observation of experimentally induced myocardial infarction and subsequent reperfusion in the pig model. They have demonstrated an increase in regional wall thickness in the reperfused infarct zone due to 'oedema associated with reperfusion injury'.

The phenomenon of 'reperfusion injury' (first described by Tennant and Wiggers') comes entirely from experimental laboratories; there are a number of experimental observations showing the deleterious effects of reperfusion leading to further progression of already existing ischaemic damage. Data from human studies are, however, in discrepancy with experimental models. Large clinical trials concerned with reperfusion therapy and acute myocardial infarction have shown a clearly positive effect of early reperfusion in thousands of patients. Based on these observations, early reperfusion therapy became the first-choice therapeutic option to reduce mortality, limit infarct size, and improve functional parameters in patients suffering from acute myocardial infarction. What is the reason for this discrepancy?

At least a partial explanation offers the different timing of experimental and clinical studies: the deleterious effect of experimental 'reperfusion injury' is shown in minutes or at most hours after restoration of perfusion; clinical trials showing a protective effect of reperfusion were designed as a long-term follow-up of patients after myocardial infarction in days, months, and even years. Short-term experimental settings are unable, however, to distinguish whether observed changes represent newly developed injury or just an acceleration of healing, associated with destroying the already severely damaged, non-viable cells (even if these cells have some signs of viability at the time of reperfusion). Until now, there has been no clear evidence that reperfusion may be harmful for the fully viable cardiomyocyte.4

Another fact requires our attention: 'reperfusion injury' does not occur without preceding ischaemic injury. After a short period of ischaemia, restoration of coronary flow does not induce any signs of 'reperfusion injury' and therefore ischaemic injury is a conditio sine qua non for the development of subsequent 'reperfusion injury'. This observation is clear evidence that 'reperfusion injury' is at least tightly connected with preceding ischaemia but very probably a part of 'ischaemia-reperfusion injury'.3,5

With some exaggeration, I would provide one indubitable example of deleterious effect of 'reperfusion injury': 3 years ago, there was admitted to the CCU with acute myocardial infarction a general practitioner, who was refusing reperfusion therapy because of being afraid of 'reperfusion injury'. It took at least 10 min to convince him about the beneficial effect of reperfusion; in these 10 min he could have already profited from reperfusion.

To conclude, I would emphasize that until now, there has been no clear evidence that reperfusion causes an additional injury to the ischaemic myocardium. Based on the literature data I would fully support the suggestion presented by Bolli6 that the term 'reperfusion injury' is actually a misnomer and that the appropriate term should be 'ischaemia-reperfusion injury'.

References


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What is 'reperfusion injury'? reply

We agree with Dr Ostadal that the current terminology used to describe the range of changes induced by the reperfusion of myocardium which has undergone prolonged ischaemia can be both confusing and inadequate. While the spectrum of changes could be described under the umbrella term of ischaemia-reperfusion injury, this term itself is too broad as the pathophysiology of the resultant ischaemia/reperfusion substrate will depend on the severity, transmural extent, and duration of the pre-existing ischaemia, as well as on the type of reperfusion therapy used, the characteristics of the reconstituted flow (driving pressure), and the degree of microvascular injury. However, we would disagree with Dr Ostadal that experimental animal data do not mirror the findings in clinical practice. It is perhaps more the case that the appropriate experimental studies relevant to the substrates encountered in clinical practice are only currently being carried out or are yet to be performed. While much research in this field is examining changes at the molecular and cell membrane level, remarkably few studies are being performed in closed-chest experimental models, or in clinical practice, to examine the potential differences between thrombolytic and primary angioplasty revascularization. Such studies require the appropriate use of quantitatively imaging techniques.

Turschner et al.,1 in their closed-chest experimental animal study confirmed that full-pressure reperfusion of an acute transmural infarct causes immediate massive extracellular oedema which disrupts myocardial integrity. In an extension of this work, Streb et al.,2 attempting to simulate the result of clinical thrombolysis, have shown that the degree of extracellular oedema is diminished if there is a residual stenosis in the supplying artery and thus a reduced driving pressure in the reperfused epicardial vessel. Subsequent correlative clinical studies, in patients undergoing primary angioplasty for ST-elevation myocardial infarction, by
Herbots et al. have shown that the degree of induced increase in wall thickness in the infarct zone is related to the transmurality of the infarct, as reflected in scar distribution detected by CMR late-enhancement imaging at 3–6 months post-infarction. Merli et al., in an ongoing prospective clinical study, have compared the development of intramural oedema (reflected by the immediate increase in wall thickness) following primary coronary angioplasty versus changes induced by thrombolytic therapy in ST-elevation infarcts. They have shown that changes in wall thickness differ between the two reperfusion strategies, with little or no immediate increase in wall thickness in patients undergoing thrombolysis in whom there is a residual stenosis in the epicardial vessel, compared with the marked increase in wall thickness associated with successful primary angioplasty. Both Herbots and Merli have confirmed that, in the setting of a primary angioplasty procedure, a failure to record an immediate increase in wall thickness was highly suggestive of sub-optimal reperfusion in the long term. It is interesting to note that these clinical findings were predicted from the results of a series of prior experimental animal studies which set out to simulate the clinical substrate.

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Aortic elastic properties in athletes with Marfanoid habitus: the need for early and accurate diagnostic methods

It was with great interest that I read the paper by Nollen et al. on the predictive value of aortic stiffness on the occurrence of progressive aortic dilatation in patients with Marfan syndrome. Their major finding was that aortic distensibility is an independent predictor of progressive aortic dilatation.

The early diagnosis of Marfan syndrome and the identification of patients at high risk of aortic complication are still important. Although quantification of individual aortic root growth using a newly developed formula may serve to establish the diagnosis, the discrimination formula may still need to be tested in a different Marfan population to find true sensitivity and specificity values.

Moreover, blood pressure increases during physical effort, which causes stress to aortic walls, with a possible more rapid progression of the disease. Identification of Marfan syndrome is therefore of the greatest importance in sports cardiology. Furthermore, the prevalence of aortic dilatation may be unexpectedly high among athletes, but no such data concerning the prevalence of Marfan syndrome are currently available. The prevalence of aortic dilatation among basketball and volleyball players was more than 10 times greater than among other athletes. Intensive physical activity is largely restricted for persons with Marfan syndrome because of the increases in volume and pressure load, which can be acutely deleterious to the weakened aorta.

Aortic mechanical functions in athletes show excellent adaptation (like a secondary pump) and this depends on exercise type, duration, and capacity. These changes positively affect left ventricular performance, especially diastolic functions. Increased stiffness with decreased left ventricular function in athletes may be a signal for cardiovascular risk.

Although the diagnosis of Marfan syndrome without gradual aortic dilatation remains a difficult entity using the standard diagnostic criteria, it strikes me that periodic measurements of aortic stiffness in athletes may provide a useful tool for diagnosis at an earlier stage. Also, the importance of diagnosis in athletes before major complications might justify such an additional effort.

References


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Aortic elastic properties in athletes with Marfanoid habitus: the need for early and accurate diagnostic methods: reply

We agree with Dr Kasikcioglu that early diagnosis is of utmost importance in athletes with Marfanoid habitus. The major question therefore in these athletes should be: do the athletes have Marfan...
syndrome or not? To obtain a diagnosis, the Ghent criteria should be fulfilled. Aortic stiffness is not yet accepted as a diagnostic criterion for Marfan syndrome. In the Ghent criteria, however, dural ectasia was added as a major criterion for diagnosis. Recently, quantitative criteria were established using MRI imaging. A dural sac-vertebral body ratio at L3 > 0.47 or at S1 > 0.57 could identify Marfan syndrome with 95% sensitivity and 98% specificity.

If the diagnosis of Marfan syndrome can be established, physical activity and competitive sports should be restricted because increases in blood pressure, heart rate, and peripheral vascular resistance elicited by athletic activity are believed to be acutely deleterious to the weakened aorta of patients with Marfan syndrome. In Marfan syndrome, the haemodynamic stress placed on the aorta by increased blood pressure and stroke volume during intense activity (particularly with rapid acceleration and deceleration) may promote and increase the rate of aortic dilatation.

Increased aortic stiffness has been demonstrated in patients with Marfan syndrome. In our recent study we were able to demonstrate that local distensibility is a predictive factor of progressive aortic dilatation. However, the role of aortic stiffness in athletes without Marfan syndrome has never been investigated.

So, in athletes with Marfanoid habitus, screening for Marfan syndrome should be performed according to the Ghent criteria. If the diagnosis of Marfan syndrome can be confirmed, aortic stiffness measurements are useful for the prediction of aortic growth. Although competitive and isometric sports should be avoided in patients with Marfan syndrome, the health benefits of exercise are of course applicable to patients with Marfan syndrome. Recently, the AHA has published recommendations for physical activity and recreational sports in young patients with Marfan syndrome.

References

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