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The Role of Reperfusion in the Prevention and Treatment of Heart Failure

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Heart failure (HF) is a clinical syndrome that is characterised by the presence of structural and functional disturbances of the heart, in combination with the symptoms and signs of HF, such as dyspnoea on effort or at rest, oedemas, moist rales, etc. Its overall prevalence is estimated to be 2-3% of the population, but is significantly greater in the elderly (10-20% of individuals aged over 70 years). As an indication of the burden HF entails for health services and the resultant cost, it is responsible for 5% of all admissions to hospital and 2% of national spending on health.

The human cost is just as heavy, given that clinically manifest HF, despite the introduction of new, quite effective drugs to treat it – angiotensin-converting enzyme inhibitors, beta-blockers, angiotensin receptor blockers, aldosterone antagonists – has a five-year mortality around 50%, which means that about half the patients who are admitted for HF will not live more than five years.

Far and away the major cause of HF (70%) in the developed world is coronary artery disease. Myocardial necrosis, the unfavourable remodelling of ventricular myocardium, and systolic dysfunction of the ischaemic (stunned or hibernating) myocardium is the main mechanism by which coronary artery disease leads to HF. If the first condition becomes established and cannot be treated effectively (despite modern attempts at myocardial regeneration, such as stem cell therapy), the second is susceptible to preventive medication regimens, while the third is probably the most easily reversible through reperfusion interventions.

In the setting of chronic coronary artery disease, the main mass of the ischaemic, but viable myocardium is represented by so-called "hibernating" myocardium, which may be treated effectively mainly through reperfusion. Hibernation of the myocardium is a protective mechanism for preserving viability via a reduction in oxygen and energy requirements; however, it has a time limit, beyond which the cellular destruction leads inevitably to permanent functional compromise and probably to HF with all its consequences.

Stunned myocardium, on the other hand, expresses a transient disturbance of contractility as the result of ischaemia, probably related to the production of free radicals and a transient calcium overload in the cells.

The view has often been expressed that these two conditions (hibernation and stunning) are two sides of the same coin and simply occur at different degrees and durations of ischaemic insult. Given the above, in a patient with coronary artery disease there are at the same time four categories of myocardium: normal myocardium, which may suffer dysfunction only in conditions of increased oxygen and energy requirements; stunned myocardium; hibernating myocardium; and myocardial scar.

At present, the only established way of managing myocardial scar is through prevention. This means rescue of the myocardium, mainly using emergency reperfusion techniques for the treatment of acute coronary syndromes (primary angioplasty or thrombolysis). The relevant guidelines are clear and are summarised in the often quoted phrase, "time is myocardium", for patients with ST-elevation myocardial infarction. The superiority of primary angioplasty over thrombolysis is clear in almost all patients of this category, while for those with an acute coronary

syndrome without ST elevation, where thrombolysis in any case has no place, it seems that prompt reperfusion is beneficial in the long term when compared to conservative therapy, especially in patients with high risk characteristics, such as troponin elevation, dynamic ST-segment changes, increasing pain, etc.

While in acute clinical coronary artery disease syndromes early reperfusion is indisputably the best strategy for preventing the future occurrence of HF, in chronic coronary artery disease with left ventricular dysfunction things are less clear. In patients of this category it appears that the benefit from a costly and possibly risky intervention is related to the percentage of viable myocardium (which consists mainly of hibernating myocardium). In contrast, reperfusion of non-viable myocardium seems to be without benefit or even harmful. There is strong evidence, from both functional studies of viability and histological studies, that around 50% of hypokinetic myocardium at rest is viable, as opposed to the akinetic or dyskinetic regions, where viability is clearly limited. It is easy to understand that the ability of modern diagnostic methods to locate and quantify hibernating/viable myocardium is of critical importance for these patients. Of the established methods, the electrocardiogram seems to be of limited diagnostic value, whereas the resting echocardiogram can provide important information, given that the maintenance of ventricular wall thickness (>6 mm end-diastolic posterior wall thickness) is associated with viability, while the presence of hypokinesis, as opposed to akinesis or dyskinesis, is also indicative, as stated above.

Greater specificity and sensitivity in the detection of viable myocardium can be achieved with thallium perfusion scintigraphy, or stress echocardiography with low-dose dobutamine. Contrast echo also appears to be useful in this context. Extremely sensitive techniques are cardiac magnetic resonance imaging with gadolinium and positron emission tomography using 18F-deoxyglucose. It should be noted that each of these techniques has its weaknesses and its advantages and often a combination of them is required, since none is perfect.

Moreover, apart from the accuracy of the technique used to detect viable myocardium, there are also questions regarding how much viable myocardium is needed before we can expect functional improvement from reperfusion. In other words, even if we had a method that was 100% effective in determining viable myocardium, do we know how much of it we need in order to proceed with reperfusion? The answer is probably in the negative, and things are made even more difficult by the fact that these decisions concern patients with a limited ejection fraction, often with multiple comorbidities, and therefore high risk, whether the reperfusion involves angioplasty or coronary artery bypass grafting. There are no randomised studies of the long-term benefit from reperfusion in patients with HF, while the relevant data come mainly from observational studies. In the ACC/AHA Guidelines on HF it is stated that coronary artery bypass is contraindicated in patients with a low ejection fraction who show no signs of having a significant quantity of viable myocardium.

To conclude, in patients with significantly impaired left ventricular systolic function as a consequence of coronary artery disease, the following questions must be answered by the clinician:

- Are the dysfunctional myocardial regions viable?
- Are the viable regions sufficient to expect a functional benefit from reperfusion?
- Are they perfused by arteries with haemodynamically significant stenoses?
- Are these stenoses susceptible to a reperfusion procedure?
- Is the periprocedural risk acceptable?

The combination of answers to the above questions will guide the clinical decision as to whether to refer the patient to the cardiac surgeon or the interventional cardiologist.