MINI-SYMPOSIUM

The pathophysiology of myocardial reperfusion: a pathologist's perspective

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Coronary artery thrombosis, caused either by fissuring or erosion of atherosclerotic plaques, is the usual cause of acute myocardial infarction.¹ If a coronary occlusion persists for more than 30 minutes, irreversible damage to the myocardium occurs. Persistent coronary occlusion results in a progressive increase of the infarct size with a wave-front transmural extension from the endocardium towards the epicardium.^{2,3} Although reperfusion can occur spontaneously, thrombotic coronary artery occlusion persists in the majority of patients suffering an acute myocardial infarction. Thus, timely coronary artery recanalisation and myocardial reperfusion, either by thrombolytic therapy or primary angioplasty and/or stenting, represents the most effective way of restoring the balance between myocardial oxygen supply and demand. Prevention of myocardial cell necrosis by the restoration of blood flow depends on the severity and duration of pre-existing myocardial ischaemia. Experimental and clinical data indicate that the recovery of systolic and diastolic function and the reduction in overall mortality are more favourably influenced by early coronary blood flow restoration. Collateral coronary vessels also appear to play an additional role, providing sufficient blood flow to the myocardium as to reduce the extent of myocyte irreversible injury.³

REPERFUSION INJURY

However, although beneficial in terms of myocardial salvage, the process of reperfusion may itself elicit pathologic consequences and the term “reperfusion injury” has been introduced.^{4–6} With this term, we normally refer to causal events associated with reperfusion that had not occurred during the preceding ischaemic period. Although ischaemia–reperfusion injury is now a well accepted phenomenon in the research experimental setting, its clinical relevance remains to be proven.⁷ The main difficulty is in differentiating between the pre-existing ischaemic damage and any subsequent damage occurring during the reperfusion phase.

As summarised by Kloner,⁵ four types of reperfusion injury have been observed in experimental animals (table 1) and consist of: (1) the myocyte lethal reperfusion injury—a reperfusion-induced death of myocytes that are still viable at the time of restoration of coronary blood flow; (2) the vascular reperfusion injury—a progressive microvasculature damage leading to the phenomenon of no-reflow and loss of coronary vasodilatory reserve; (3) the stunned myocardium—myocytes display a prolonged period of contractile dysfunction following coronary blood flow restoration due to abnormal intracellular metabolism leading to reduced energy production; (4) reperfusion arrhythmias—ventricular tachycardia or fibrillation that occurs within seconds of reperfusion.

Unlike the others, the concept of “lethal” reperfusion injury of potentially salvageable myocytes is still controversial.⁶ According to this theory, ischaemia is a necessary prerequisite for lethal reperfusion injury, but not in itself

Table 1 Experimental reperfusion injury

1.	Myocyte death (“lethal reperfusion injury”)
2.	Microvascular damage (“no-reflow”)
3.	Stunned myocardium
4.	Reperfusion arrhythmias

sufficient to cause cell death. Potential causes of injury that develop during reperfusion have been difficult to analyse as these must be clearly differentiated from ischaemic causes. From a practical point of view, it is obviously impossible to evaluate, in the same sample of myocardium, changes occurring both during ischaemia and during reperfusion. Moreover, in the reperfused myocardium it is difficult to establish whether cell death is caused by the period of ischaemia or by reperfusion. Thus, the only valid criterion to attribute cell damage to the reperfusion process, and not to ischaemia, is by demonstrating that modifications of reperfusion conditions are able to prevent cell death or dysfunction.^{6,7}

Among the effects of reperfusion, several have been proved only at the experimental level but not in the clinical setting. These include oxygen free radical generation, membrane lipid peroxidation, release of oxidised glutathione, neutrophil activation, intracellular calcium overload, contractile impairment, electrical instability, myocyte death (either necrosis or apoptosis), microcirculatory alterations, endothelial dysfunction, osmotic overload, and others.

As pathologists, in this brief review we would like to analyse in more detail the morphologic features which are typical of reperfusion—that is, contraction band necrosis, the no-reflow phenomenon, and intramyocardial haemorrhage (fig 1).

CONTRACTION BAND NECROSIS

During the earliest phase (within minutes) of reperfusion, development of myocyte hypercontraction seems to precipitate cardiomyocyte necrosis and arrhythmias and this phenomenon (“contraction band necrosis”) has been ascribed to a rapid re-energisation of myocytes with calcium overload.⁸ Although ischaemic myocytes following reperfusion suddenly develop ultrastructural changes indicative of cell death, they are still apparently normal from a histological point of view; it is likely that most of the myocytes are already irreversibly injured by the time reperfusion occurs, due to loss of plasma membrane continuity, and reperfusion simply accelerates the phenomenon.⁹ The contraction band necrosis is a frequent finding at postmortem examination in sudden death victims caused by atherosclerotic coronary artery disease. In a series of young sudden death victims with sub-obstructive atherosclerotic plaques not complicated by thrombosis, in which ischaemia was likely precipitated by a transient vasospasm as a spontaneous model of coronary

Figure 1 Histopathologic features in the myocardium following reperfusion. (A) Contraction band necrosis (trichrome Heidenhain stain). (B) Interstitial haemorrhage (haematoxylin and eosin stain). (C) Neutrophilic plugging (haematoxylin and eosin stain). (D) Distal platelets-fibrin microembolisation (trichrome Heidenhain stain).

occlusion and reperfusion, we found evidence of extensive contraction band necrosis in the tributary myocardium, in the absence of other markers of cell death which normally develop later on if the patient survives longer.¹⁰

NO-REFLOW PHENOMONON

The “no-reflow phenomenon” refers to the absent distal myocardial reperfusion after a prolonged period of ischaemia, despite the culprit coronary artery’s successful recanalisation, and it appears to result from ischaemia-induced microvasculature damage.¹¹ Several functional and mechanical factors have been claimed to account for microvasculature obstruction following coronary artery recanalisation, either pharmacological or mechanical, including a luminal obstruction (that is, neutrophil plugging, viscosity, platelets, atherothrombotic emboli, vasospasm, endothelial swelling, etc) or an external compression (oedema, haemorrhage, myocyte swelling).¹² From the morphologic point of view, a lot of attention has been recently focused on the possible role of thrombotic-atherosclerotic plaque debris. Unlike most animal models of mechanical coronary occlusion, the clinical setting probably involves microembolic events in a substantial number of cases. However, a prospective randomised controlled multicentre trial on distal microcirculatory protection during percutaneous coronary intervention in ST segment elevation acute myocardial infarction demonstrated that, although a distal balloon occlusion and aspiration

system effectively retrieves embolic debris in most of the patients, this approach did not result in improved microvascular flow and in a better prognosis overall.¹³ These negative findings are not surprising, considering that the no-reflow phenomenon does not appear to augment myocyte death and the myocardium of the no-reflow area is usually already necrotic at the time of reperfusion onset. The relevance of the microvascular obstruction caused by thromboembolic material in determining the no-reflow phenomenon should probably be re-evaluated in view of its therapeutic implications. In a recent postmortem investigation in patients who died in the acute phase of myocardial infarction, we found that, despite a higher occurrence in treated versus untreated patients, distal microembolisation was always confined to the necrotic myocardium and its spatial distribution was not widespread.¹⁴ In other words, while distal microcirculatory embolisation occurs during coronary recanalisation procedures and is preventable, such intervention may be “too little, too late” to achieve meaningful myocardial salvage in acute myocardial infarction, which is also characterised by systemic and local mediators of inflammation and endothelial dysfunction, capillary leakage, and interstitial oedema.

MYOCARDIAL HAEMORRHAGE

Finally, reperfused myocardial infarcts frequently appear reddish because of “intramyocardial haemorrhage”¹⁵ (fig 2).

Figure 2 Non-reperfused versus reperfused acute myocardial infarction. (A) Anaemic, white anteroseptal transmural acute myocardial infarction. (B) Section of the left anterior descending coronary artery of the same patient in (A), showing occlusive thrombosis. (C) Haemorrhagic, red anteroseptal transmural acute myocardial infarction. (D) Section of the left anterior descending coronary artery of the same patient in (C) showing recanalisation with residual mural thrombosis following thrombolysis.

Experimental models first showed myocardial haemorrhage in the setting of prolonged coronary occlusion and reperfusion. Then myocardial haemorrhage after reperfusion was also described in humans following cardiac surgery, percutaneous transluminal coronary angioplasty and fibrinolysis. Haemorrhagic infarcts are thought to be caused by vascular cell damage with leakage of blood out of the injured vessels. It is well known that cell vascular damage occurs after myocardial cell necrosis and thus it represents a relatively late event in the course of acute myocardial infarction at the time of already irreversible myocyte damage. Moreover, infarct haemorrhage occurs always within the area of necrosis and it is significantly related to the infarct size and to the period of coronary occlusion.¹⁶ As such, haemorrhage is not related to the type of recanalisation as was originally thought, when it was advanced that a lytic state associated with thrombolytic therapy could play a major role. In fact, haemorrhagic infarcts can develop after percutaneous coronary interventions without thrombolysis as well, and the major determinant is the time interval between coronary occlusion and reflow. Unfavourable mechanical consequences of intramyocardial haemorrhage could comprise increased myocardial stiffness, propensity to rupture, and a delayed healing process. However, at present the clinical implications of haemorrhagic versus white infarcts remain undetermined, because of the absence of reliable and reproducible imaging modalities to detect its presence in vivo.

CONCLUSION

While there is general agreement that reperfusion can prove detrimental by causing life-threatening arrhythmias and myocardial stunning, it still remains unclear whether haemorrhagic infarcts are at increased risk of rupture or unfavourable remodelling or whether they are just a cosmetic effect of the reperfusion era. Moreover, a clear demonstration of a lethal reperfusion injury in the clinical setting has not yet been unequivocally provided.

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IMAGES IN CARDIOLOGY

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Live three dimensional echocardiography in evaluation of left ventricular to right atrial shunt (Gerbode defect)

A 76-year-old man with a history of renal cell carcinoma was referred for evaluation of chest pain and progressive dyspnoea on exertion. Physical examination showed distended neck veins up to 10 cm above the sternal angle with large V waves and on auscultation a loud 3/6 systolic murmur was heard along the left parasternal border radiating toward the right side of the upper sternum. The patient was evaluated by spiral computed tomography (CT) to rule out the presence of pulmonary embolus. A right retrocrural metastatic adenopathy was observed but there was no evidence of pulmonary emboli. A subsequent transthoracic echocardiogram (TTE) demonstrated enlarged right sided chambers. Colour Doppler interrogation revealed a left-to-right shunt from the left ventricle (LV) to the right atrium (RA) across the ventriculo-atrial septum immediately above the tricuspid valve (panel A). The estimated gradient between LV to RA was 70.2 mm Hg (panel B). This finding was consistent with Gerbode defect, a rare defect of the ventriculo-atrial septum.

To further define the anatomy of the shunt, a live three dimensional echocardiogram (L3D, Philips 7500) was performed. Full volume images were cropped to localise the right atrial, tricuspid, and septal structures in three dimensions. Three dimensional colour Doppler interrogation of the defect demonstrated acceleration of flow on the ventricular side of the septal leaflet of the tricuspid valve. The LV to RA communication involved the base of the septal leaflet of the tricuspid valve as it extended across the ventriculo-atrial septum into the right atrium (video files 1 and 2; to view video footage visit the *Heart* website—<http://www.heartjnl.com/supplemental>).

LV to RA communications could be either congenital or acquired defects from endocarditis, myocardial infarction, aortic or mitral valve replacement and trauma. The cause of our patient's defect remains unclear. The patient did not demonstrate clinical or echocardiographic evidence of endocarditis.

(A) Transthoracic two dimensional echocardiogram with colour Doppler from apical four chamber view shows colour flow jet directed from left ventricle (LV) to right atrium (RA) across the ventriculo-atrial septum. (B) Continuous wave Doppler through the ventriculo-atrial septum demonstrates the left to right shunt with a maximum velocity of 4.19 m/s. This calculates to an LV to RA gradient of 70.2 mm Hg.

Myocardial infarction was ruled out by serial myocardial enzymes and ECGs. After aggressive diuresis the patient clinically improved. Given the advanced stage of his malignancy, he requested hospice care.

Live three dimensional echocardiography delineated the origin and the path of the left to right shunt involving the base of the septal leaflet of the tricuspid valve and the ventriculo-atrial septum. To our knowledge, this is the first reported case of a Gerbode defect demonstrating the involvement of the tricuspid valve in the shunt. These findings have clinical implications when surgical repair is planned.

To view video footage visit the *Heart* website—<http://www.heartjnl.com/supplemental>

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