Mini Review

Post-Infarct Cardiomyopathy: Why it is the Last Challenge in ST Elevation Myocardial Infarction?

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Abstract

ST-elevation acute myocardial infarction is due to coronary artery acute occlusion. The corresponding area suffers from ischemia and stops to contract: “Area at Risk”. Early reperfusion by primary angioplasty (pPCI) does not save every cardiomyocyte. A severe late left ventricular dysfunction has been observed in up to 20 to 30 % of large AAR. Myocardial cells die by Oncosis which evolves to scar (necrosis), apoptosis and autophagy. Severe and long lasting ischemia but Reperfusion Injury (RI) too is responsible for myocardial cell deaths. pPCI must stop ischemia, prevent No-Reflow and cardiomyocyte deleterious reaction. Different tools are available: low pressure reperfusion, manual thrombus aspiration (if large thrombus), postconditioning driven by online ST monitoring have been proven to be effective. Remote conditioning seems to give hopes. Abciximab, Adenosine, Verapamil may counteract NR if needed. Modified reperfusion can therefore decreased cell death and increase myocardial salvage index (MSI) measured by Magnetic Resonance Imaging (IRM). The interventional cardiologist might better prevent late heart failure and post infarct cardiomyopathy.

INTRODUCTION

The development of early reperfusion therapy with primary percutaneous angioplasty (pPCI) and stenting (in preference, if feasible, to thrombolytic therapy) [1-4], has dramatically improved the early and late prognosis of acute ST Elevation Myocardial Infarction (STEMI).

Even though mean and long term event free survival was significantly increased the problem is not yet completely solved and much remains to be done. Many patients recover quickly and nearly completely but in the same time others still suffer from acute and delayed heart failure due to poor myocardial reperfusion result. Ischemia causes cell death but Reperfusion Injury (RI) [5-7] does it too. Both mechanisms dictate the final infarct size.

The aim of this short review is [1] to show that ventricular dysfunction incidence remains as high as 30 %, [2] to remind its mechanisms in which [3] RI takes a large place. It’s the reason why [4] modifying angioplasty technique and pharmacologic environment must be considered.

MYOCARDIAL INFARCTION AND ISCHEMIC CARDIOMYOPATHY

Patients match with the classical definition of ischemic cardiomyopathy [8] if they have systolic and/or diastolic dysfunction with or without clinical heart failure due to previous myocardial infarction or silent chronic ischemia. Here we will focus on the post-STEMI consequences. Besides ischemia, myocardial dysfunction may account for co morbidities like hypertension, diabetes, ischemic or functional mitral regurgitation, aging, aortic stenosis (Table 1).

INFARCT SIZE AND HEART FAILURE

In the recent CIRCUS trial [9] the patients were included with acute LAD occlusion and revascularized by primary percutaneous angioplasty (pPCI). At one year follow up around 25 % of the whole population sustain heart failure leading to hospitalizations. In other studies the authors show that 60 % of deaths are due to heart failure [10]. At least, in 30% of all acutely reperfused patients and alive at 6 months mean follow up late EF is less than 45% [1,12] and even less than 35% in 4% [12] with
Table 1: Reminds the most often accepted definition of ischemic cardiomyopathy:

<table>
<thead>
<tr>
<th>Low Ejection Fraction and/or Heart Failure with ...</th>
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<tbody>
<tr>
<td>History of Myocardial Infarction.</td>
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<tr>
<td>History of Myocardial Revascularization (CABG or PCI)</td>
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<tr>
<td>&gt;= 75% stenosis of left main or proximal LAD</td>
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<tr>
<td>&gt;= 75% stenosis of two or more epicardial vessels</td>
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or without clinical heart failure.

The following section will try to explain and to predict incomplete results of pPCI looking [1] on the acute and late development of ventricular dysfunction, [2] on the predictive factors. A next part will deal with the problem of RI before, as a final topic, showing how to optimize the angioplasty strategy with the aim of improving myocardial results.

In the first minutes after a sudden thrombotic coronary artery occlusion ("culprit artery"), the ischemic myocardium depending on the vessel stops to contract defining an akinetic area, called Area at Risk (AAR). Early reperfusion is able to save a variable part of AAR as shown by MRI (Resonance Magnetic Imaging): mean AAR/LV: 31+/15% leading to mean Infarct Size (IS): 1B+/−13% [13]. After reperfusion AAR includes [1] viable but stunned myocardium which will recover after days or weeks, [2] dead cells resulting in scar necrosis or disappearing from "the Battlefield" by phagocytosis (after apoptosis or autophagy). Acute heart failure depends on AAR and consequently on the extent of a kinesia and on (not frequently) mechanical complications (acute mitral valve dysfunction, septal defect, wall fissure and pericardial effusion). Thanks to an adrenergic hyperactivity [14] hyperkinesia of remote myocardium may , at least in part, compensate the loss of contraction of the AAR (but have at the same time deleterious effects including arrhythmias) [15]. Diastolic function impairment, takes a part to acute heart failure whatever is early EF [16].

In this short review we will focus on the late occurrence of left ventricular dysfunction and heart failure.

What are the predictive factors?

Magnetic Resonance Imaging (MRI—hours and days in acute phase -) is now a gold standard technique to measure these parameters [12,13,17-19]: AAR, ejection fraction (EF), infarct size (IS), myocardial salvage index (MSI=AAR-IS/AAR) and microvascular obstruction (MVO). At the same time morphological aspects (ventricular geometry, mitral valve regurgitation) can be described.

Surprisingly, acute EF does not accurately predict its 6 months value. Three different profiles have been described [20]: (1) Worsening (20%), (2) No change (20%), (3) Improvement (60%). Using MRI, extreme changes varied widely between a relative decrease of 83% and an increase of 44% [12]. Deterioration was observed in 28% of the cohort. 33% of the patients without significant LV dysfunction at the time of STEMI (acutely compensated) developed late systolic heart failure. Starting from a same AAR, the final EF depends on the myocardial salvage index and then final infarct size. Larger is AAR, greater is IS whatever is MSI. Greater is Salvage Index, more is EF increase.

Clinician cardiologist must know that early low EF can improve later and on the opposite a normal acute EF may decrease. The reason is that stunning is reversible and LV remodelling and healing is heterogeneous. Thus the feasible MRI is a better test to predict late ventricular global performance. It’s probably the reason why authors have studied more accurate indexes: (1) Left Ventricular Global Index (LVGI) [11,12], (2) early Late Gadolinium Enhancement Volume (LGEV) (Larose).

Recently, to take into account all the factors acting on cardiac performance including diastolic parameters and morphologic changes and not only EF, Newton [21] described the Left Ventricular Global Index (MRI): LVSV/LVGV*100 where LVSV means left ventricular stroke volume and LVG, left ventricular global volume. LVSV is calculated by LVEDV-LVESV and LGEV as the sum of the left VG cavity volume (LVEDV-LVESV/2) and myocardium volume. In a healthy population he found 42+/−6% as a mean normal value. Less than 37% predicted a long term poor outcome (non post-infarct group). Eitel [11,22] used it after STEMI revascularization. Low LVGFI (less than 31% - median value) predicted larger infarcts, less myocardial salvage, larger extent of Myocardial Vascular Obstruction (MVO), higher incidence of myocardial haemorrhage, more severe LV dysfunction. Patients who died or suffering from MACE’s (12 months) had a LVGFI less than 23% (median value).

LGE volume [12] measured during the first 12 hours after pPCI identifies late size of destroyed myocardium and ventricular power in the chronic phase. Despite some physiopathological concerns (combination of stunning, edema, dead cells) the authors [12] studied whether infarct characteristics evaluated in the early hours of STEMI improve the prediction of late systolic recovery and clinical outcome. LGE was presented as an absolute value (ml/m²) and related to left ventricular volume (LGE / LVV, %). Transmurality was measured too (%/ventricular wall thickness). LGE percentage is the only significant predictor of EF change in multivariate analysis. >= 23% of early LGE was the limit to consider that EF will be less than 50% at 6 months and moreover 2,3 +/− years clinical follow-up (heart failure: 10%).

Taking into account the great variability of late EF after STEMI it seems important to understand what are the mechanisms underlying such changes.

POST-INFARCT LEFT VENTRICULAR DYSFUNCTION: MECHANISMS

Starting as soon as during the first minutes after revascularization the myocardial muscle course is complex and depends on several factors whose interplay will result in the final mechanical power of the left ventricle and dictates a large part of the prognosis (together with severe ventricular arrhythmias). It is the result of (1) Duration of remote hyperkinesia, (2) Stunning recovery. (3) Extend of remodelling. Compensatory Hyperkinesia lasts a few days or weeks [14] and while having an hemodynamically positive role can induce adverse events as well (arrhythmias). Post-reperfusion non-contracting but viable cells recover (more or less completely) in several days
and even weeks. When the acutely not active area is large, left ventricle remodels [13, 23, 24]. In brief, ventricular remodeling involves (1) thinning, elongation and dilatation of the akinetic segments, (2) hypertrophy of the remote myocardium. Adverse remodeling is defined as a dilatation more than 15% of the left ventricular cavity. Its intensity is closely linked to the extent of AAR (proximal occlusions – long culprit vessels) and MSI depending on the myocardial result of pPCI [13]. It is possible to predict adverse remodelling: a recently studied inflammatory glycoprotein, Fetuin-A, when early elevated (day 2) is related to predict adverse remodelling due to dead cells. Adaptive LA remodelling occurs as well and takes place in parallel with ventricular changes [27]. MRI can assess the final atrial volume which depends on IS. Adverse LA remodelling and diastolic ventricular dysfunction can predict a poor prognosis and favour heart failure.

The final issue after pPCI is linked to the number of saved cardiomyocytes which recover after stunning and on the opposite to the severity of adverse remodelling due to dead cells.

**HOW CARDIOMYOCYTES DIE?**

For a long time myocardial infarction has been synonymous with Necrosis. That is clearly a misnomer term. Table (2) summarizes the different definitions of every cause of cardiomyocytes deaths occurring during acute Ischemia/Reperfusion.

Necrosis is the final scar after death by Oncosis (cell oedema resulting in sarcolemma rupture).

Apoptosis first described by Kerr [28] is a genetically programmed cell auto-destruction which is now considered as taking a large part in I/R injury.

Autophagy can be defined as a cell autolysis. Its importance during the I/R pathology remains controversial.

The current review can’t give more details on this very interesting aspect of the topic [28-37] (Table 2).

**WHEN AND WHY CARDIOMYOCYOTES DIE?**

The question asked by Elizabeth Murphy and her answer summarized many years of controversial experimental works: “why ischemic cells die? Because they are reperfused” [6]

We now know that ischemia and reperfusion injury share the cell death responsibility.

Such an assertion has a practical issue: reducing ischemic damage needs a more rapid intervention (decreasing "pain to balloon" time). Facing RI means to modify the current pPCI technique and pharmacological environment.

During the last ten years many works have demonstrated that the classical paradigm linking ischemia time and cell death mechanisms do not fit with the modern data. It can’t be forgotten that longer is the ischemic time larger is Infarct Size. But at the same time it has become evident that reperfusion in itself takes part in myocardial destruction [6]. The death of myocardial cells during the course of STEMI depends on both stresses. One can hypothesize that the final fate of cells course is the biological sum of ischemia and reperfusion and does not depend only on ischemia. The death threshold (Figure 1) can be reached after a variable ischemic time and/or a variable RI severity [6, 38-40].

Taking into account that the immediate reperfusion cell result dictates MSI and IS, it might be important to remind the reasons why risky cells die despite reperfusion. When starting pPCI interventional cardiologists try (1) to stop ischemia, (2) to prevent the “no-reflow” phenomenon first condition to achieve a metabolically effective flow to every ischemic cardiomyocyte and (3) to counteract deleterious effects of sudden return of oxygen.

NR [41-43] depends on several mechanisms: macro or microembolizations, platelet and leucocytes aggregation, endothelial dysfunction and even destruction, vasospasm. It may impact the whole area at risk or involves only one part of the vessel bed. The consequence is the extension of ischemia. It prevents cardiomyocytes salvage but can progressively regress or stay for a long time (endothelial stunning).

Cardiomyocytes reperfusion injury is complex. Briefly it is due (as early as during the first minutes after reoxygenation) (1) to myofibrillar hypercontracture [38, 44, 45] (calcium overload and sarcoplasmic reticulum dysfunction) (2) to the opening of the mitochondrial Permeability Transition Pore (mPTP) [46-49]. The first exerts a severe mechanical stress on the sarcolemma

<table>
<thead>
<tr>
<th>Table 2: Cells Deaths Mechanisms during STEMI (summary).</th>
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<tr>
<td><strong>Mechanisms</strong></td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Oncosis</td>
</tr>
<tr>
<td>Intrinsic Apoptosis</td>
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<tr>
<td>Extrinsic Apoptosis</td>
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<tr>
<td>Autophagy</td>
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**Figure 1 Post-Ischemia/reperfusion Cardiomyocyte Fate.**

1: Ischemia - 2: Reperfusion Injury - 3: Sum I + RI
Cell Death: A: Ischemia - B: I+ RI - C: Cell Worsening but Still Viable

which results in its rupture and as a consequence in cell death. The second process suppresses the membrane barrier between the mitochondrial matrix and the cytoplasm resulting in a major oedema (oncrosis) and finally (if many mitochondria are included) in the sarcolemma rupture. Apart of oncrosis acute mitochondrial aggression increases intrinsic apoptosis.

In a second step starting early but continuing later, an autoimmune reaction will initiate extrinsic apoptosis. Why? The dead and suffering cardiomyocytes send “Danger Messages” [50-54]. These are considered as stranger and are rejected like infectious micro-organisms or a graft organ.

The no-reflow phenomenon is detected angiographically by TIMI flow score (Grade 0–2) [42,43] and Myocardial Blush Grade 0 and 1 [55,56]. The reflow success needs TIMI 3 score (complete opacification of the culprit artery without delay) and Blush 2 or 3 ones (quick myocardial opacification by the dye).

The early window of RI can be detected by continuous ECG recording. The best marker of adequate reperfusion is ST resolution. In the favourable cases ST elevation decreases immediately (50% or more). On the opposite one can observe either a paradoxical increase (ST Peak) generally associated with chest pain paroxysm [57,58] or less than 30% ST resolution.

Arrhythmias can occur including ventricular fibrillation whose late prognostic meaning is not known. Sometimes the opening of the right coronary artery can induce severe bradycardia and hypotension due to the Bezold Jarisch reflex [59]. Therefore the cell fate is decided very early and even sometimes before pPCI when initial TIMI 2/3 is noted [60,61]. In that situation prognosis is generally good [61] doesn’t need myocardial protection and the only goal of pPCI is to prevent re occlusion.

Facing TIMI 0/1, the angioplasty technique and the pharmacologic environment might be changed in order to prevent or treat RI and increase myocardial salvage. But how?

**PRIMARY ANGIOPLASTY: NEW WAYS?**

The reperfusion technique dictates the future myocardial fate and of the possibility of occurrence of post-infarct cardiomyopathy and heart failure.

When the culprit artery is occluded the interventional cardiologist starts by crossing the lesion with the guide-wire, removing large thrombus by manual aspiration and finally by implanting stent. The intervention is associated to an anti-thrombotic regimen including anti-thrombin drugs (HNF, HBPM, Bivalirudin), antiplatelet therapy (aspirin, loading dose of anti-P2Y12, sometimes inhibitors of glycoproteins Iib/IIla).

NR and Slow-Refow must be diagnosed on line (angio and ST). Distal injection of Adenosine and or Verapamil, Abciximab are the most often used molecules to provoke myocardial no-reflow.

Despite many experimental works and pilot trials, no drug has been proven to be useful to prevent or treat early wall RI. Cyclosporine A (mPTP inhibitor) has given hopes in an early small trial [62] but the large CIRCUS trial did not confirm the first results [9]. Blockers of the immune reaction didn’t reach better outcome [65-67].

**MYOCARDIAL CONDITIONING IS A NEW PROTECTIVE TOOL**

In 1986 Charles Murry, a young researcher, (from the well known Jennings and Reimer group) published a surprising experimental work (rats). He demonstrated that short non lethal ischemia/reperfusion cycles could protect myocardium from a lethal IR occurring shortly thereafter [67]. It was later shown that the benefit occurred mostly during reperfusion. Moreover it was seen that the phenomenon was effective during a closely occurring ischemia but also again 24hours later [68] (late preconditioning). Therefore patients who experiment angina before STEMI may be self protected from RI. Cardiac surgeons are able to induce transitory ischemia before operation.

In 2003 Zhao (Jakob Vinten Johansen group) crossed a new step [69]. Modifying the first minutes of reperfusion (in rats), he reached the same myocardial protection. The experimental protocol included four cycles of reocclusion and reperfusion (1 minute each) before final full flow restitution. Calcium overload and mitochondrial transition pore opening were prevented.

The technique has been used in humans [70]. But the issues were often debated probably because of lack of a clear algorithm. The current results seem to be slightly positive (meta-analysis) [71,72]. Nevertheless the last large trial (700 patients) does not show any benefit [73]. We will propose below a different protocol adapted to heart rate and on line ST resolution.

Conditioning can be instated after inducing identical cycles but Sin remote organs like arms [74]. Remote conditioning can be initiated (1) before ischemia (“remote preconditioning”, 2) during ischemia and before reperfusion (“remote perconditiong”) and finally (3) at the beginning of reperfusion (“remote post conditioning”). These strategies are now ongoing and hopeful with first positive results [75-78].

Nowadays we propose to performangioplasty as following : (1) create a new small channel with the wire or a small balloon , (2) wait a few minutes during them myocardium is slowly reperfused (slow output and low pressure , (3) observe ST changes , (4) inject abcdximab in situ , Adenosine 4 mg or (optional) Verapamil 1 mg and (5) aspirate large thrombus (systematic thrombectomy is not recommended , (6) start a first four cycles postconditioning immediately and monitoring ECG during the reperfusion phases . In unfavourable evolution it is possible to reintiate a second postcondition ingession, (7) implant the stent after having assessed flow and ST level.

Recently published [40] that strategy is adapted to the online events and corresponds to the current pathophysiological knowledges and trial will be initiated. It is able to prevent RI myocardial death and post-infarct cardiomyopathy.

**CONCLUSION**

At the acute ST-elevation myocardial infarction pPCI salvages ischemic myocardium but must be optimized to decrease RI and limit post-infarct left ventricular dysfunction, heart failure incidence and global cardiomyopathy due to whole ventricle remodelling. A few drugs (in situ abcdximab, adenosine, verapamil), and tools (progressive artery reopening, selective
manual thrombectomy, postconditioning) might prevent large infarcts. Online ST monitoring is a helpful marker of cardiomyocyte salvage.

REFERENCES


