Current Problems in the Treatment of Acute Myocardial Infarction: For Better Reperfusion and Long-Term Benefits

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Summary

Coronary reperfusion for an occluded vessel with ruptured vulnerable plaque and clot burden in patients with acute myocardial infarction is now more easily performed due to the development of devices and techniques for percutaneous coronary intervention. However, even after successful coronary intervention, some patients may still have complications such as heart failure, stent thrombosis, or restenosis, which require revascularization in the long-term follow-up period and may affect their survival. Here, outstanding issues concerning primary percutaneous coronary intervention and patient medical care after reperfusion therapy are discussed.

Keywords: Acute myocardial infarction; Reperfusion therapy; Stent, Clot aspiration; Cell therapy

Abbreviations

AMI: acute myocardial infarction; BMS: bare metal stent; BVS: biodegradable vessel scaffolding; DES: drug-eluting stent; FFR: fractional flow reserve; HCN: hyperpolarized and cyclic nucleotide; IRA: infarct-related artery; IVUS: intravascular ultrasonography; LAD: left anterior descending artery; LV: left ventricular or left ventricle; MACE: major adverse cardiac events; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; ST: stent thrombosis; TLR: target lesion revascularization; TVR: target vessel revascularization

With the marked development of catheterization techniques and medical instruments as well as the supportive metallurgical engineering and biological, physiological, and pharmacological research, percutaneous coronary intervention (PCI) is able to treat patients not only by simple dilatation with ballooning, but also by easy scaffolding of stenotic lesions with metal stents [1]. Imaging devices provide more accurate assessment of lesion characteristics and severity than an angiogram, and often help interventionists decide how and how much they should dilate lesions.

Vulnerable plaque is considered to be an underlying pathological cause of acute myocardial infarction (AMI), characterized by a rapid progression to plaque rupture and high likelihood of thrombotic complications. This rupture-prone plaque, known as a thin-cap fibroatheroma, contains a large lipid core and a thin outer fibrous cap, which is infiltrated by macrophages [2]. The cap thickness is only <65 μm and visualization is possible using intravascular diagnostic techniques such as optical coherence tomography (OCT) with high-resolution images [3,4], or virtual-histology intravascular ultrasonography (IVUS); the latter which is able to visualize an abundant necrotic core (>10% of the cross-sectional area) in contact with the lumen, and a plaque-volume of greater than 40% through radiofrequency data analysis [5]. Non-invasive methods have also been developed to diagnose vulnerable plaque. One useful diagnostic modality is coronary computed tomographic angiography. A lipid core appearing as a “low-attenuation” plaque, positive vessel remodeling, and spotty calcification are the three typical features of vulnerability [6]. Magnetic resonance imaging using low molecular weight gadolinium is another method; the fibrous cap in the luminal surface can be visualized with good contrast to the inner necrotic lipid core, which has low signal intensity [7]. Vulnerable blood, prone to clot formation, is also believed to play an important role in the development of coronary blockage. Imaging rupture-prone vulnerable plaque will be of great help for both the presymptomatic detection of patients at risk for coronary events and the conclusive diagnosis of acute coronary syndrome in those with atypical chest symptoms.

Stents have enabled a much higher procedural success rate by compression and scaffolding of such culprit lesions, and excellent long-term patency has been achieved by using drug-eluting stents (DES). However, there still remain issues to be solved for better management of these patients, particularly those with very tight or calcified lesions, seriously depressed left ventricular (LV) function, or renal insufficiency. Primary PCI may be harmful due to complication with contrast-induced nephropathy, which is more frequent in AMI patients than in non-AMI patients (5.6% vs. 3.0%) [8]. AMI is reported to be a multivariate independent predictor of acute renal failure following PCI.

In PCI, DES have been reported to reduce the restenosis rate and target lesion or vessel revascularization (TLR or TVR) rate, and thereby major adverse cardiac events (MACE), compared to uncoated bare metal stents (BMS) [9-12]. However, it has also been reported that neotatherosclerosis, which may slowly develop in the stented segment with new lipid-laden atherogenic change over the stent struts, may limit blood flow, and hence diminish the advantage over BMS years after the procedure [13-15]. Whether this phenomenon holds true of second-generation DES, which is believed to have its polymers, antiproliferative agents, and stent platform improved, and have shown comparable or even better long-term outcomes with less frequent stent thrombosis (ST) [16-22], remains to be demonstrated. Whether these slow-developing stenotic changes may simply be delayed and develop over a longer interval of time with newer DES as “very late catch-up” remains unknown. Collection of 5-year follow-up data has just started [23].

In patients with AMI, emergency primary angioplasty to recanalize the occluded infarct-related artery (IRA) is currently regarded as the standard therapy for reducing cardiac mortality. In the balloon-only era, rapid closure of the infarct lesion often took place after balloon dilatation [24]. Stent implantation, by blocking lesion recoil, proved to be quite beneficial to overcome this phenomenon, avoiding time-
compared with stenting in other coronary segments [25,26]. Currently, DES is used with more satisfactory TLR or TVR results during a 1- to 3-year follow-up period, although no significant difference in incidence of death or recurrent AMI has been observed between these two stent types [27-31]. Accumulated data, however, have instead shown a higher risk of ST in those treated with DES over a 1-year follow-up period [30-33]. Kalesan et al. [34] demonstrated in a meta-analysis that a year after AMI treatment, very late ST is significantly more likely to occur in patients receiving DES than in those with BMS placement. The large amount of intracoronary thrombus in patients with AMI may predispose them to stent malapposition due to stent undersizing or thrombus resolution. Stent malapposition at ruptured plaques has been confirmed on OCT images [35]; this may elevate the incidence of late ST, unless appropriate intimal coverage of the stent adluminal surface is achieved. This means that longer and more attentive management with steady antiplatelet treatment may be needed once patients with AMI are treated with DES. Recent studies showed that the frequencies of 5-year all-cause mortality, MACE, and overall ST were similar between those treated by DES and BMS, although DES significantly reduced TLR and TVR rates [36,37]. Surprisingly, DES was reported to increase cardiac mortality compared to BMS in one of those studies [37]. Even longer follow-up reports of DES placement, particularly for second-generation DES in AMI, are awaited. Self-expandable stents may be able to solve this problem by reducing malapposition and underexpansion, decreasing the risk of ST and restenosis [38]. The results are awaited from clinical trials using self-expandable stents in AMI [39].

Thrombus aspiration in primary PCI at the infarct lesion prior to coronary dilatation or stenting has been reported to reduce infarct size and 1-year mortality by improvement of myocardial perfusion [40-46]. However, the benefits of clot aspiration have been disputed by recent studies which demonstrated no reduction in the MACE rate in a longer 2- to 3-year follow-up period [47,48].

Bioresorbable vessel scaffolding (BVS) may be substituted for stents and may possibly require a shorter period of antiplatelet therapy [49,50]. There is much interest in how BVS interacts with clots and ruptured vulnerable plaque, and how it acts at bifurcating lesions when positioned over a side branch. Development of this device may also change the utilization of modalities which assist in judgment of the indication, lesion characteristics, and procedural endpoint among IVUS, OCT, and a pressure guidewire to measure fractional flow reserve (FFR). FFR has become an important modality to identify culprit lesions. The FAME study demonstrated that FFR measurement in patients with multivessel coronary artery disease can reduce mortality and AMI after two years compared to standard angiography-guided PCI, by deferring stent implantation in lesions showing FFR>0.80 in patients with stable angina and acute coronary syndrome [51,52].

The question of whether beta-blockers are able to additionally improve long-term clinical course remains to be further elucidated [53,54]. Beta-blockers are known to inhibit adverse arrhythmia [55] and are also known to improve LV contractility [56-58]. However, there are concerns regarding coronary vasoconstriction induction due to the beta-blocking effect on coronary vascular smooth muscle cells [59,60]. Coronary vasoconstriction is reported to be commonly induced early after AMI onset. Racial differences in its frequency were demonstrated by Pristipino et al. (2000) [61], in which Japanese patients showed more coronary vasospasm (80%) than Caucasians (still as high as 37% within 14 days of AMI onset) in spasm provocation test. A study with a small number of Japanese subjects reported that atenolol tended to increase provocative coronary vasospasm in both the IRA and non-IRA, although it did not reach statistical significance (Figure 1) [62].

We found that coronary vasoconstriction varied from 11% diameter stenosis to complete occlusion, and vasoconstriction with more than 60% diameter stenosis was more severe in the IRA than in non-IRA (Figure 2).

However, one of the adjusted multivariate predictors of vasospasm in non-IRA was the presence of rich collaterals to the infarct territory on the initial angiogram [63]. In such cases, special attention should be paid to avoid vasospasm in non-IRA, which supplies areas of preserved LV function remote from the infarct region, in order to prevent hemodynamic collapse. Thus, it is important to consider the possibility of beta-blockers inducing coronary spasm even after successful reperfusion. Their various cardiac effects need to also be taken into consideration, which diverge depending upon the pharmacological characteristics (e.g. beta1-adrenoceptor selectivity, intrinsic sympathomimetic activity) of each beta-blocking agent used. Their short- and long-term influence on AMI patients should be
evaluated in large-scale randomized trials, with attention paid to the agent(s) used and the racial background of subjects.

Anterior AMI involving the LAD is often associated, starting from its onset, with cardiac pump failure due to its broad supply of the myocardial area. It has also been reported that an anterior infarct is more likely to end with incomplete revascularization complicated with a no-reflow or slow flow phenomenon [64,65], which contributes to increase in infarct size and LV dysfunction [66,67]. As a consequence, a higher rate of reinfarction [66], ST [68], and mortality [25] can be anticipated. Thus, treatment of continuing heart failure is another issue which remains to be solved.

Percutaneous direct myocardial laser revascularization has been attempted to improve myocardial ischemia and thereby LV function by production of small myocardial channels in ischemic endocardial regions guided by electromechanical LV mapping. Although this treatment was helpful for increasing exercise duration and the time to onset of angina [69], it failed to improve LV ejection fraction [70].

A new type of pharmacological approach is generating much interest. The sinus node produces cardiac impulses via activation of I_{f} (funny) ionic current running through hyperpolarization and cyclic nucleotide (HCN)-gated channels. By selectively blocking these HCN channels, the heart rate has been reported to decrease by 20-30% without affecting ventricular contractility, peripheral vascular resistance, or intracardiac electrical conductance such as the PQ, QRS, and QT intervals [71]. This is in good contrast with beta-blockers and calcium channel blockers which influence multiple cardiovascular functions and may therefore induce adverse effects in patients with heart failure. Iribradine, a selective I_{f}-pacemaker current blocker, was evaluated in heart failure patients with LV systolic dysfunction (ejection fraction <35%) in sinus rhythm with a heart rate >70rpm (SHIFT study). This placebo-controlled randomized study demonstrated that iribradine significantly reduced composite of cardiovascular death and hospital admission for worsening heart failure [72]. With its beneficial anti-anginal and anti-ischemic effects [73], this agent may provide a favorable long-term clinical scenario and improved quality of life for patients after AMI.

Cell therapy is now becoming an attractive field in the treatment of chronic heart failure and restoration of LV function after AMI. Many attempts using a variety of cell origins (e.g. autologous bone marrow cells, peripheral blood stem cells) have been reported; however, the long-term beneficial effects remain controversial, including concerns about promoting intimal hyperplasia following coronary intervention [74-84]. New technologies such as surgical coverage of the damaged LV with a myocardial sheet produced by autologous cell culture or transformation of induced pluripotent stem cells [85,86] may emerge as promising therapeutic options. Together with basic translational research, rapid but solid development in this field is awaited with great hope and expectation.

A number of issues remain to be solved in the treatment of AMI. We hope that many exciting studies will be performed to develop new diagnostic and therapeutic methods. Such advancements will surely contribute to more efficient clinical practice to improve the long-term management of patients with AMI.

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