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Acute Myocardial Infarction
—— The Enduring Challenge for Cardiac Protection and Survival ——

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Although considerable advances have been made in the diagnosis and management of acute myocardial infarction (AMI), the disorder is still a major cause of morbidity and mortality worldwide and continues to pose significant therapeutic challenges. The use of biomarkers to aid the diagnosis of AMI is now increasing and has enabled better understanding of the pathophysiology of the disorder and identification of patients who require urgent reperfusion therapy. Early percutaneous coronary intervention (PCI) appears to be beneficial when performed in a timely manner with a door-to-balloon time <90 min. The goal of PCI is now shifting from simple revascularization of occluded coronary arteries to optimum reperfusion at the microvascular level. Effective strategies and pharmacological agents need to be developed for better cardiac protection during AMI. Most deaths resulting from AMI occur within 1 h of its onset, and half of them occur before hospital admission. Thus, an effective pre-hospital lifeline system should be an important priority, achieved through the chain of survival, including the immediate implementation of definitive resuscitative efforts and rapidly transporting the patients to the hospital. (*Circ J* 2009; **73:** 2000–2008)

Key Words: Adrenomudullin; Microvasculature; Myocardial infarction; Pre-hospital; Reperfusion

Acute myocardial infarction (AMI) is a major cause of morbidity and mortality worldwide. According to the World Health Organization, more than 3 million people per year are estimated to have acute ST-elevation myocardial infarction (STEMI) and more than 4 million per year have non-STEMI (NSTEMI).[1] As the population grows older and comorbidities (eg, obesity and metabolic syndrome) become more prevalent, as in recent years, the enormous public health burden caused by ischemic heart disease is likely to increase even further. In fact, in Japan, the incidence of AMI has been increasing, as recently demonstrated in the Miyagi-AMI Registry Study, where all of the AMI patients in the Miyagi prefecture (n=22,551), prospectively registered over 30 years between 1979 and 2008, demonstrated that the age-adjusted incidence of AMI (/100,000 persons/year) markedly increased by 3.6-fold, from 7.4 in 1979 to 27.0 in 2008, in the last 30 years.[2] Thus, every effort to improve both short- and long-term prognosis should be made. This review briefly covers the comprehensive approaches that are important for the optimal care of patients with AMI.

Biomarker-Guided Management and New Definition of AMI

Over many decades, the diagnosis of AMI has been based on the "two out of three" criteria, including typical chest symptoms, increase in the serum level of creatine kinase and typical ECG changes.[3] The definition of AMI was revised in 2000[4] and further refined in 2007,[5] as the European Society of Cardiology and the American College of Cardiology Consensus group recommended the diagnostic usefulness of troponins as biomarkers of myocyte necrosis. Indeed, troponins T and I are more sensitive and specific biomarkers of myocyte necrosis than creatine kinase or creatine kinase-MB.[6] However, it should be noted that it takes 2–4 h for troponins to be released after the onset of AMI, earlier blood samples are likely to be negative,[6] and moderate elevation of troponins is common in chronic renal failure patients without significant myocardial damage.[7,8]

In addition to their diagnostic usefulness, troponins have also been recognized as important prognostic factors.[9–11] In the Global Registry of Acute Coronary Syndromes (GRACE) Study of 26,267 AMI patients, cardiac troponin elevation was an important predictor of 6-month mortality independent of ECG findings or creatine kinase.[12] A recent cohort study also demonstrated that the long-term mortality of patients with AMI was significantly improved when guided by the cardiac troponin test.[13] AMI patients with higher troponin levels are at high risk and thus need appropriate management of invasive strategies.

Takotsubo cardiomyopathy resembles STEMI because the patients commonly present with chest pain or dyspnea and have ECG ST-segment elevation (**Figure 1**).[14,15] However, in takotsubo cardiomyopathy, the magnitude of increase in cardiac biomarkers is modest, less than that observed in cases with STEMI and disproportionally low when compared with extensive regional wall motion abnormalities.[16]

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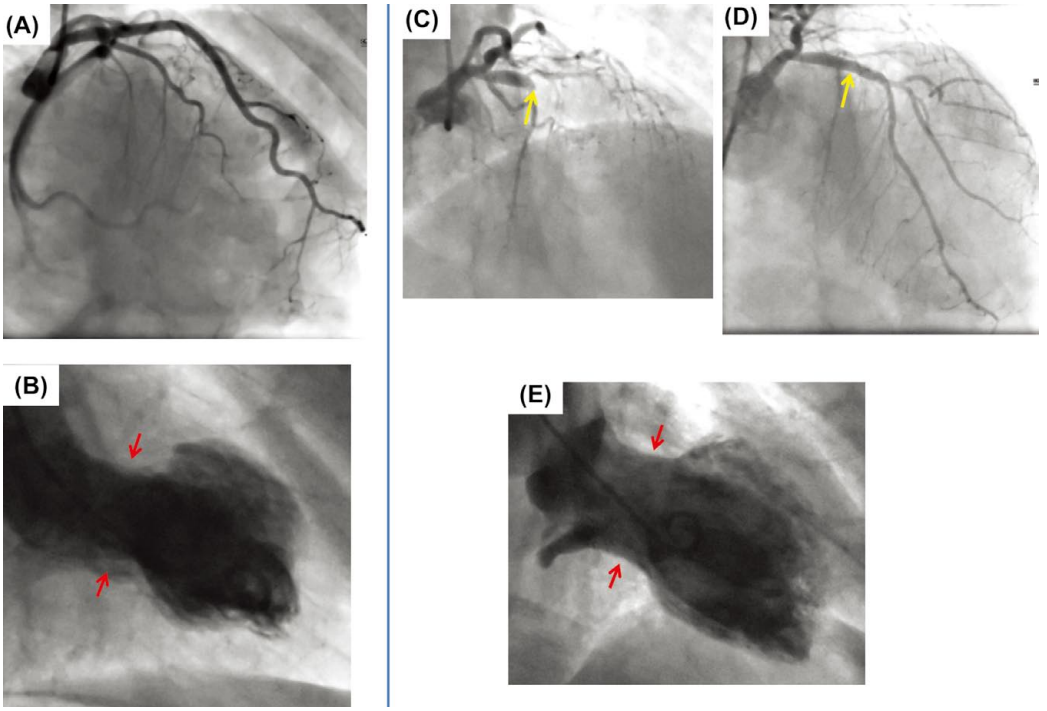

Figure 1. Takotsubo cardiomyopathy (**Left**) and acute myocardial infarction (AMI) (**Right**). In a patient with takotsubo cardiomyopathy, despite no significant coronary artery stenosis (**A**), systolic dysfunction involving the left ventricular (LV) apex and mid-ventricle, and hyperkinesis of the basal LV segments was noted (**B**). In a patient with AMI in whom the proximal site of the left anterior descending artery was occluded (**C**) and reperfused by stenting (**D**), left ventriculography showed the similar feature with takotsubo cardiomyopathy of apical ballooning (**E**). Yellow arrows indicate the occluded and reperfused site and red arrows indicate the basal hyperkinetic segments of the LV.

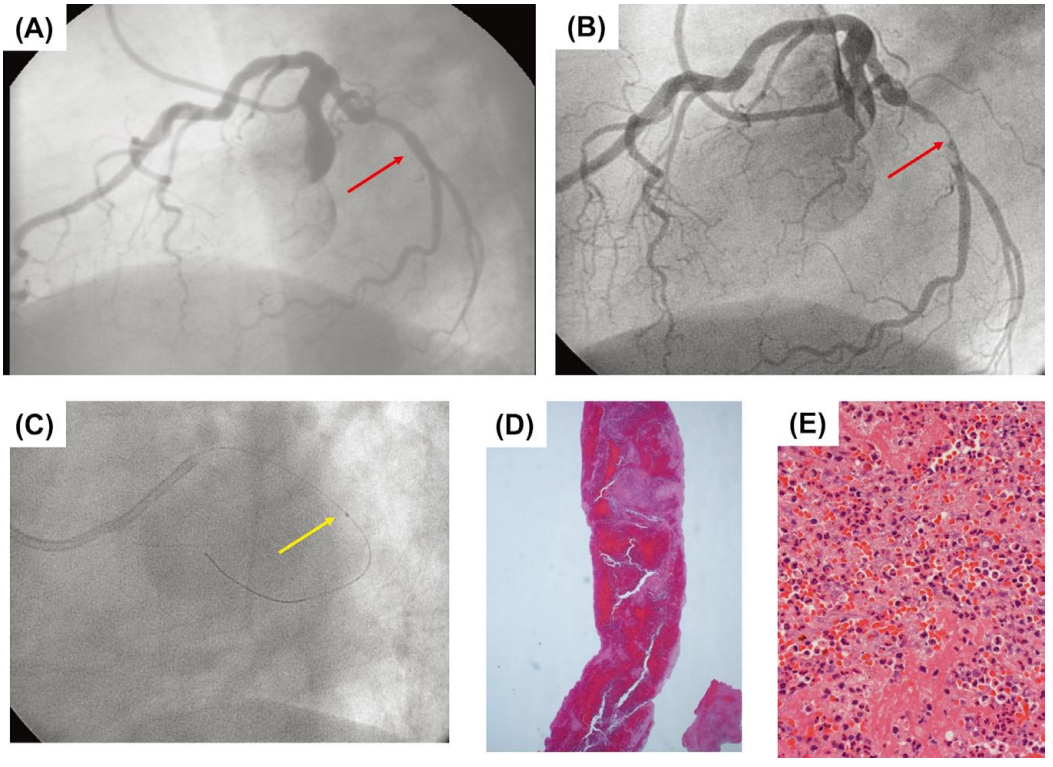

Figure 2. Thrombectomy for ST-elevation myocardial infarction (STEMI). Elective coronary angiography performed 2 weeks before (**A**) and coronary angiography urgently performed immediately after the onset of STEMI (**B**) showing rapid progression of stenosis of the left circumflex coronary artery from an insignificant stenosis to 90% severe stenosis (red arrow). Manual thrombectomy (yellow arrow) (**C**) and histological analysis (H&E) of the thrombus burden aspirated from the culprit lesion showing platelet–neutrophil aggregation (**D**, ×20; **E**, ×40).

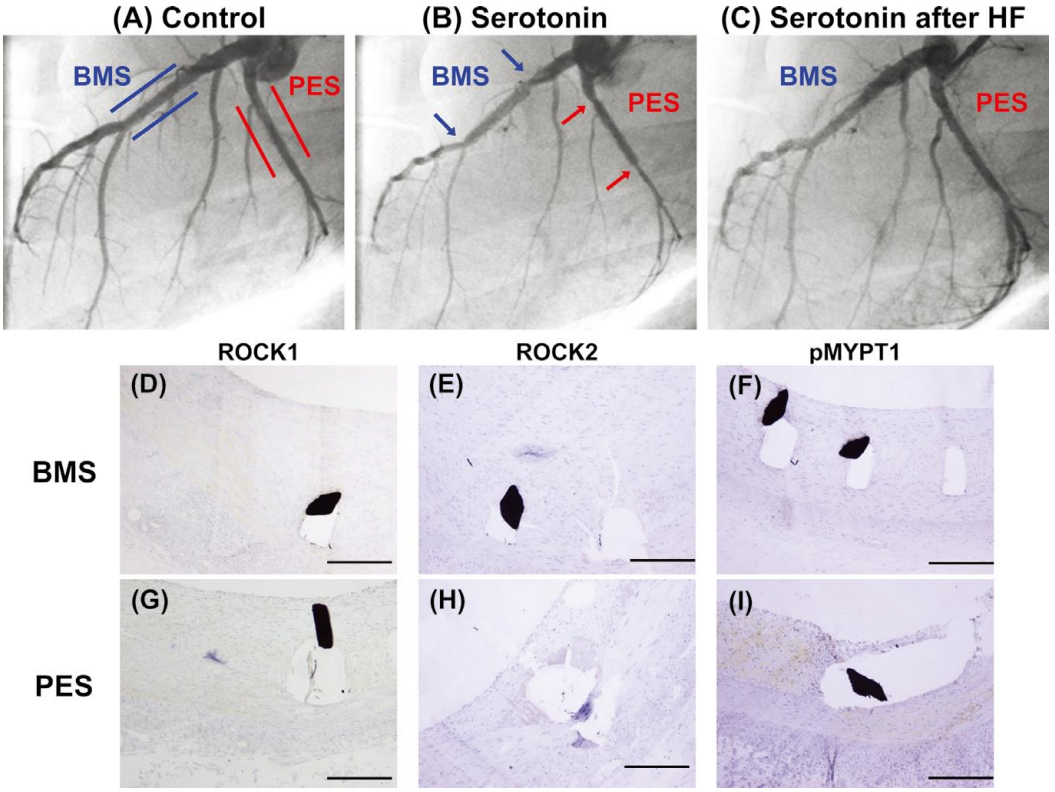

Figure 3. Involvement of Rho-kinase activation in the pathogenesis of coronary impairment induced by paclitaxel-eluting stents (PES) in pigs in vivo. Representative left coronary angiograms under control condition (**A**), after intracoronary serotonin (100 μg/kg, IC) (**B**), and after IC serotonin with hydroxyfasudil (HF, 300 μg/kg, IC), a specific Rho-kinase inhibitor (**C**). Red lines indicate the site of PES implantation and blue lines the site of bare-metal stent implantation. Representative immunostaining of bare-metal stent-treated arteries (**D**–**F**) and PES-treated arteries (**G**–**I**) for ROCK1, ROCK2 and phosphorylated myosin phosphatase target subunit 1 (phospho-MYPT1). Scale bars=200 μm. (Reprinted with permission from Shiroto et al,[55] with permission from *J Am Coll Cardiol*.)

Because of the absence of obstructive epicardial coronary atherothrombosis, impairment of coronary microcirculation may be involved in takotsubo cardiomyopathy.[17,18] The precipitating mechanisms seem to be complex, including microvascular dysfunction and catecholamine cardiotoxicity.[19,20] Indeed, takotsubo cardiomyopathy might be a unique entity of acute coronary and/or myocardial syndrome.

Importance of Reperfusion at the Microvascular Level

In patients with AMI, the extent of infarct size is crucial because residual left ventricular (LV) function determines the prognosis.[21–24] In the past 2 decades, it has been well established that the most effective strategy for limiting infarct size is early restoration of coronary blood flow to the ischemic myocardium by thrombolysis, percutaneous coronary intervention (PCI) or both.[25,26] However, in a relatively large population of patients, successful recanalization of the epicardial coronary artery does not necessarily improve myocardial perfusion,[27–29] and structural disruption and/or obstruction of the microvasculature (eg, no-reflow phenomenon) may be involved.[30–32] Thus, the goal of PCI is now shifting from simple revascularization of the occluded coronary artery to optimum reperfusion at the microvascular level.[33]

Microvascular dysfunction following recanalization of the epicardial coronary artery is a complex process involving various interrupting factors.[34] Downstream microembolism of platelets could cause distal embolization by plugging coronary microvessels and activating the inflammatory cascade, leading to myocardial injury, probably through enhanced production of reactive oxygen species.[34] In the clinical setting, distal embolization can be detected in real time by using an intracoronary Doppler guidewire.[35] Thrombus aspiration devices can retrieve thrombi from culprit coronary lesions and the aspirated samples may provide intraluminal pathological information. A recent histological analysis revealed that neutrophils were numerous in the aspirated thrombus burden from patients with STEMI (**Figure 2**).[36] Importantly, high neutrophil density in aspirated thrombus is associated with impaired coronary microcirculation (assessed by myocardial blush grade and ST-segment resolution),[37,38] and consequent myocardial damage and LV dysfunction. Inflammation is related not only to the pathogenesis of atherothrombotic vascular events, but also to the outcome of PCI,[39] post-infarction ventricular remodeling[40] and adverse events.[41] In fact, pretreatment with statins that exert antiinflammatory effects appears to have a cardioprotective effect in patients undergoing PCI. The Atrovastatin for Reduction of MYocardial Damage During Angioplasty (ARMYDA-ACS) trial[42] randomly assigned 171 patients with non-ST-elevation acute coronary syndrome to pretreatment with a high dose of atrovastatin (80 mg, 12 h before PCI) or placebo. The patients in the atrovastatin arm had a significantly lower incidence

of 30-day cardiac events, driven mostly by a lower incidence of AMI within the first 24 h.[42]

Recently, in addition to intensive antiplatelet therapy,[43] adjunctive coronary devices to prevent distal embolization during primary PCI for AMI have been developed. There are 2 main strategies that are widely used: devices that aspirate the thrombus (thrombectomy devices), and devices that trap and remove dislocated thrombi (protection devices). However, the Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris (EMERALD) trial showed a lack of efficacy of the Guardwire distal protection device, raising the question of whether all anti-embolic devices are similar.[44] Subsequently, Bavry et al performed a comprehensive meta-analysis of 30 major trials, including the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS),[45,46] demonstrating that the differences in technical difficulties among the devices depending on coronary anatomy should be considered as a potential bias. However, manual thrombus aspiration (through syringe suction) prior to PCI seems to be associated with reduced mortality compared with PCI alone, whereas mechanical thrombectomy appears to increase mortality and embolic protection devices may neither increase nor decrease mortality.[45,46] Taken together with similar findings from another meta-analysis,[47] adjunctive manual thrombectomy devices with flexible and user-friendly catheter profiles should be used routinely in patients with STEMI undergoing primary PCI (**Figure 2**)[48] because it is difficult to define which patients have significant thrombus burden, especially when the vessels are totally occluded on emergency coronary angiography.[49]

Drug-eluting stents (DES) have dramatically reduced the restenosis rate after PCI, revolutionizing interventional cardiology.[50,51] A recent meta-analysis of the 8 major randomized trials comparing DES with bare-metal stents (BMS) in primary PCI for AMI demonstrated that DES significantly reduced the need for re-intervention.[52] However, a recent autopsy study has found that arterial healing is delayed and the late stent thrombosis rate is increased at the culprit site after DES implantation in AMI patients.[53] We have recently demonstrated in a pig model that Rho-kinase, a downstream effector of the small GTP-binding protein Rho,[54] plays an important role in the pathogenesis of DES-induced coronary impairment, including coronary hyperconstriction and thrombus formation (**Figure 3**).[55] Currently, the Japanese reimbursement committee of the health insurance organization recommends that DES should not be used in patients with AMI.[56] Further studies are needed to optimize the efficacy and safety of DES.

Protecting the Heart Against Ischemia–Reperfusion Injury

To further advance the effects of interventional reperfusion strategies, pharmacological approaches directed at the myocardium, injured either by an ischemic event or by reperfusion, are being investigated.[57] Various studies aimed at reducing the myocardial infarct size using adjunctive medical therapies have been conducted. Beta-blockers, when intravenously administered in the early hours of infarction, were shown to be beneficial for reducing cardiac arrhythmias and mortality, although they are contraindicated for cardiogenic shock, severe congestive heart failure, atrioventricular block or severe bradycardia.[58] Just as nicorandil is an ATP-dependent mitochondrial potassium channel opener,[59] adenosine has unique pharmacological effects, including microvascular dilatation, platelet and neutrophil inhibition, and a substrate for replenishment of ATP, and is an important mediator of preconditioning.[60] In the Acute Myocardial Infarction Study of Adenosine (AMISTAD)-II, 2,118 patients with STEMI undergoing reperfusion therapy within 6 h of the onset of symptoms were randomized to a 3-h infusion of either 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ adenosine, 70 $\mu g \cdot kg^{-1} \cdot min^{-1}$ adenosine, or a placebo. A dose–response relationship with infarct size (assessed by technetium-99 m sestamibi tomography) was found (11% at high dose, 23% at low dose vs 27% with placebo). A significant correlation between infarct size and clinical outcome was seen, accompanying a weak trend towards fewer occurrences of heart failure or death.[61] However, an infusion of glucose–insulin–potassium had no benefit on survival or heart failure in the Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS)-6 trial, or in a combined analysis of these data with the Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation-Estudios Clinicos Latino America (CREATE-ECLA).[62,63] Eicosapentaenoic acid (EPA), a major component of the ω-3 fatty acid contained in fish oil, possesses several beneficial effects against acute myocardial ischemia, including inhibition of thrombotic responses, suppression of inflammation and stimulation of endothelial release of nitric oxide.[64,65] A meta-analysis of interventional studies showed that ω-3 fatty acids decrease sudden cardiac death in patients with coronary artery disease.[66] This finding suggests potential electrophysiologically stabilizing effects of EPA. Indeed, we have recently demonstrated in a pig model that long-term treatment with EPA attenuates ischemia-induced electrical instability of the LV, for which modulation of K_{ATP} channels may be involved (**Figure 4**).[67]

Recently, the RISK (signaling pathway compromising the reperfusion–injury salvage kinase) pathway, including phosphatidylinositol 3-kinase (PI3K)-Akt and extracellular signal-regulated kinase (ERK) 1 and 2, was shown to be a potential pharmacological target for cardioprotection.[68,69] In isolated rabbit hearts, Yang et al showed that atrial natriuretic peptide (ANP), when administered at reperfusion, limited the infarct size by activating PI3K-Akt and ERK 1/2.[70] In the clinical setting, the prospective, randomized, placebo-controlled Japan-Working Groups of Acute Myocardial Infarction for the Reduction of Necrotic Damage (J-WIND) study was carried out on AMI patients undergoing reperfusion therapy with or without ANP.[71] In that study, ANP reduced the plasma level of creatine kinase by 15% compared with the placebo, increased the LV ejection fraction by 5% and reduced reperfusion injury by 26%.[71]

Adrenomedullin is a 52-amino-acid vasodilator peptide that was originally isolated from human pheochromocytoma.[72] In a previous experimental study using a rat myocardial ischemia–reperfusion model, adrenomedullin was shown to reduce infarct size,[73] inhibit cardiomyocyte apoptosis through the PI3K-Akt pathway[73] and suppress the production of oxygen-derived free radicals.[74] In patients with their first AMI who were hospitalized within 12 h of the onset of symptoms, adrenomedullin treatment ameliorated oxidative stress, as evaluated by urinary levels of 8-iso-prostaglandine $F_{2\alpha}$.[75,76] Furthermore, in patients with AMI undergoing primary PCI, adjunctive treatment with adrenomedullin significantly limited the infarct size, as evaluated by magnetic resonance imaging and brain natriuretic peptide

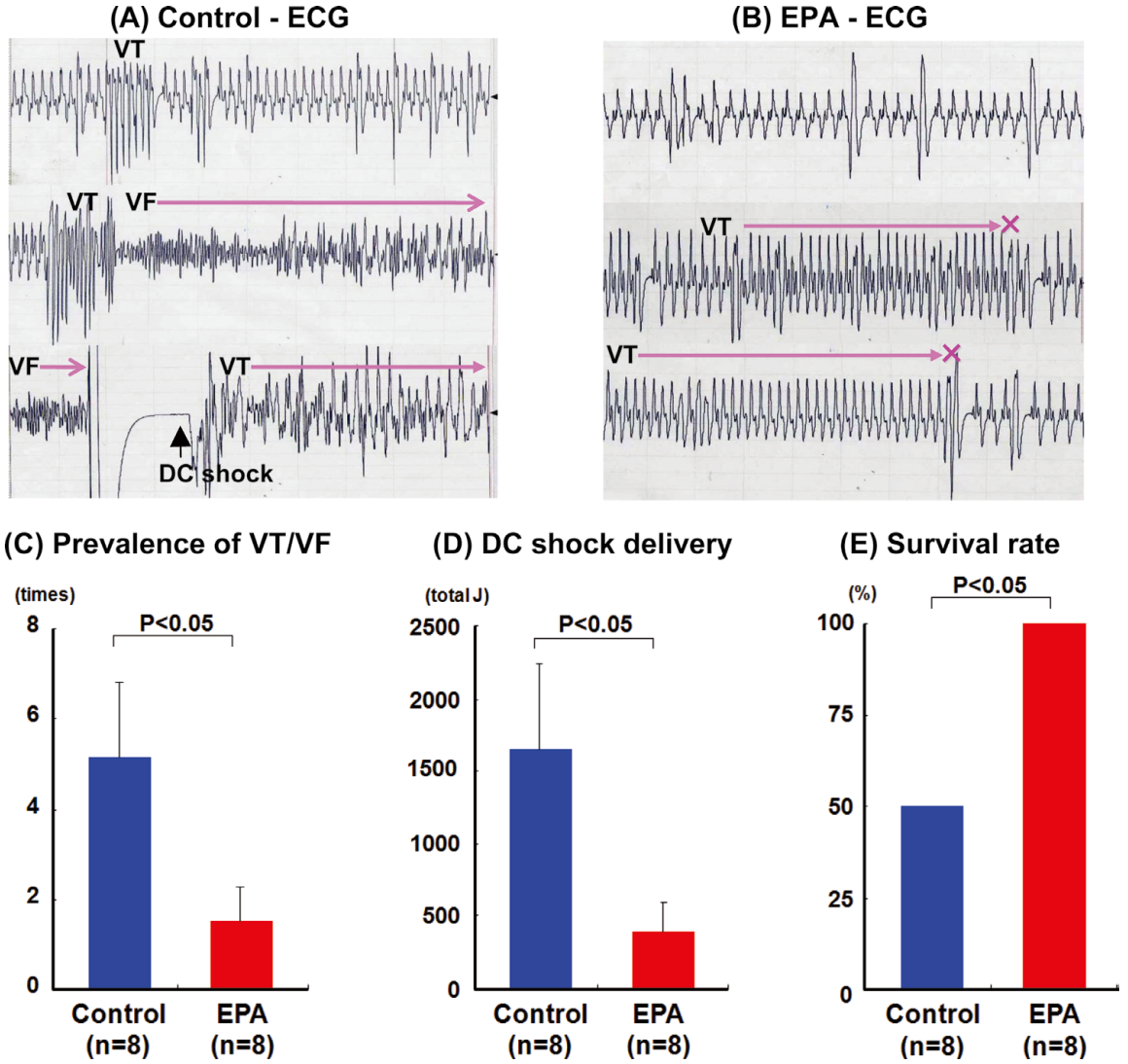

Figure 4. Electrophysiologically stabilizing effects of long-term treatment with eicosapentaenoic acid (EPA) during myocardial ischemia in pigs in vivo. During myocardial ischemia, ventricular fibrillation (VF) was frequently induced and refractory to direct counter (DC) shocks in the control pigs (**A**), whereas in EPA-treated pigs, ventricular tachycardia (VT) was spontaneously terminated and was unlikely to be sustained (**B**). Long-term treatment with EPA significantly ameliorated the prevalence of VT/VF (**C**), the total amount energy of DC shock delivery (**D**) and survival rate during myocardial ischemia (**E**). Results are expressed as mean±SEM.

levels (**Figure 5**).[75,76] Although a randomized control trial of adrenomedullin therapy is needed to translate the present preliminary findings into clinical use, pharmacological agents that activate the RISK pathway may have therapeutic potential for cardioprotection.

Emerging Importance of Pre-Hospital Management for Life Saving

Although remarkable advances have been made in the management of AMI, there is still room for improvement. For example, more than 50% of AMI patients die prior to reaching hospital because of structural and functional cardiac impairment,[77–79] indicating that strategies that improve the pre-hospital setting is crucial for the improvement of survival. Most pre-hospital deaths occur within 1 h of the onset of AMI and are usually caused by ventricular fibrillation.[80] The 2 key approaches in the chain of survival concept that have been proven to improve the chances of survival for AMI patients with out-of-hospital cardiac arrest are (1) immediate performance of basic cardiopulmonary resuscitation by bystanders and (2) immediate delivery of specialized countershock in cases of ventricular fibrillation (eg, public access to autonomic defibrillators).[81] Recent studies from the Survey of Survivors of Out-of-Hospital Cardiac Arrest in the Kanto Region of Japan (SOS-KANTO)[82] and the Utstein Osaka Project[83] have demonstrated that resuscitation with chest compression alone resulted in improved survival that is comparable or rather preferable in comparison with chest compressions plus mouth-to-mouth ventilation in patients with witnessed arrest and shockable rhythm. Continuous chest compressions may contribute to maintaining myocardial and cerebral perfusion prior to defibrillation,[84] which is essential for patient survival.

If ventricular fibrillation is refractory to countershocks, anti-arrhythmic medications such as a class Ⅲ agent (eg,

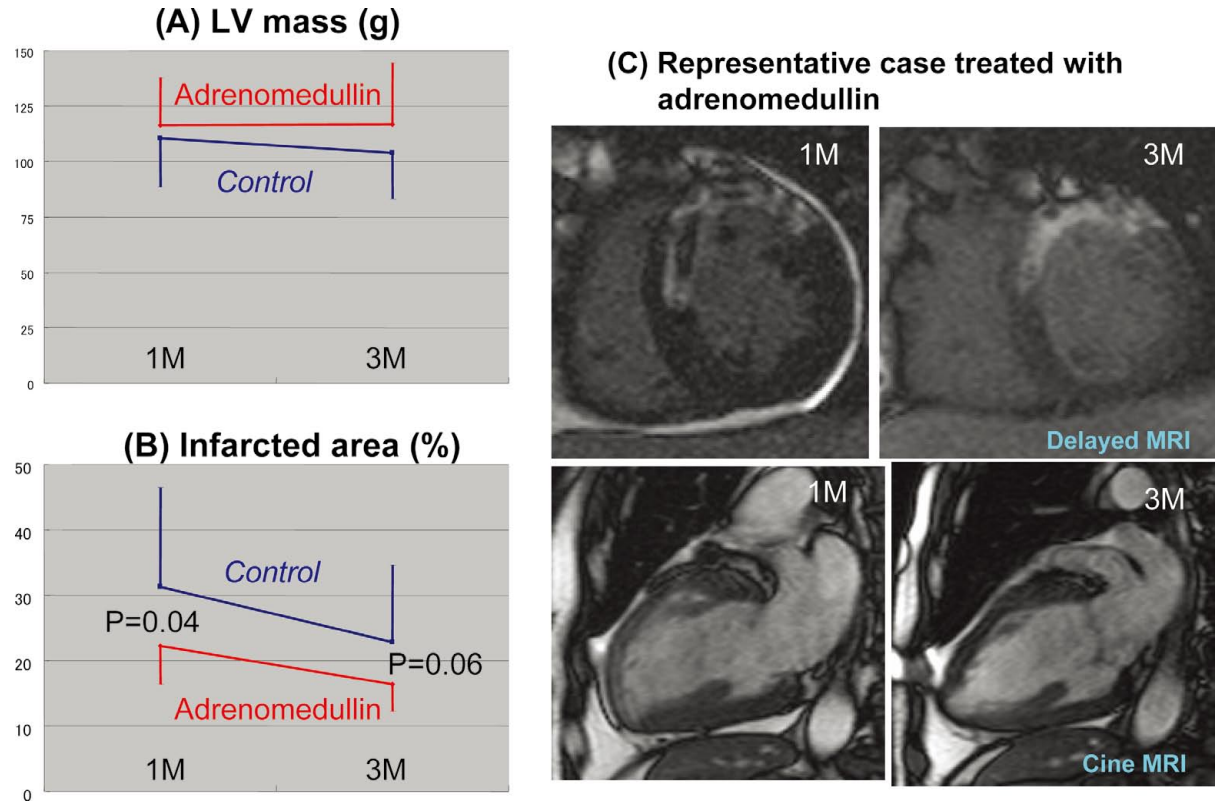

Figure 5. Cardioprotecive effect of intravenous adrenomedullin infusion in patients with acute myocardial infarction (AMI). Although the left ventricular (LV) mass index was comparable (**A**), the infarct area in patients with their first AMI was significantly different between the control (n=10) and adrenomedullin-treated groups (n=10) at 1 month after AMI (**B**). This tendency remained but did not reach a statistically significant level at 3 months after AMI (**B**). Results are expressed as mean±SD. Representative magnetic resonance imaging (MRI) in an AMI patient treated with adrenomedullin (**C**) showed that wall thinning did not develop at 3 months after AMI, although extensive anterior AMI and antero-apical expansion were found at 1 month as evaluated by delayed and cine MRI, respectively.

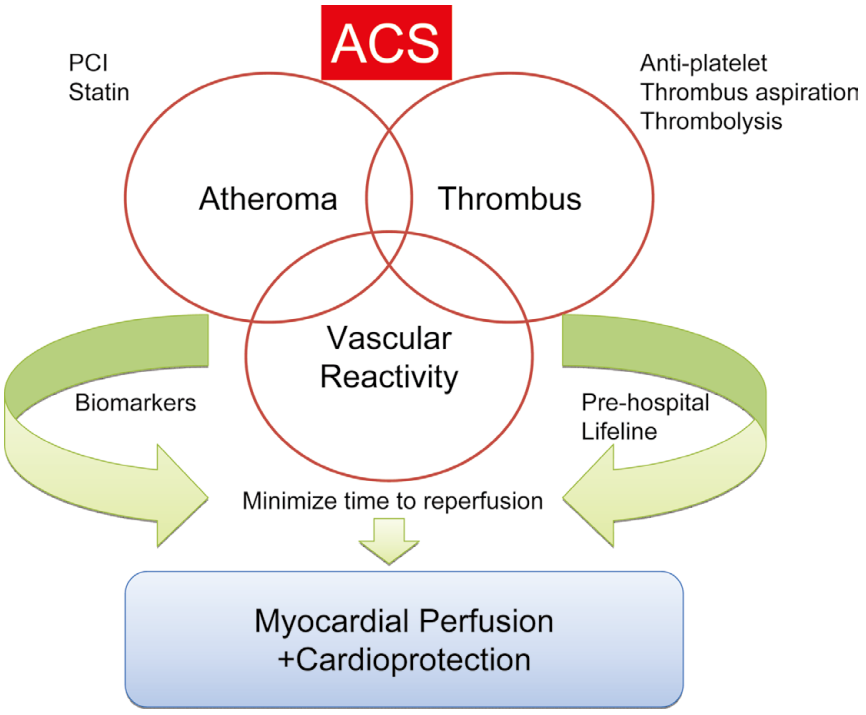

Figure 6. Current concept of the pathogenesis of acute coronary syndrome (ACS) and its therapeutic strategy.

amiodarone) may have a role in the treatment of patients with cardiac arrest.[85] Compared with amiodarone, nifekalant hydrochloride has unique pharmacokinetics for rapid action and clearance, and has several advantageous characteristics, particularly for emergency care, including the improvement of the defibrillating threshold and minimal cardiac depressant effect.[86–88] In addition to a previous single center experience,[89] the recent multicenter registry study of Japanese Population-based Utstein-style study with basic and advanced Life Support Education (J-PULSE) demonstrated that nifekalant hydrochloride improved the survival rate of hospitalized patients compared with out-of-hospital cardiac arrest to more than 70%.[90] Thus, intravenous administration of nifekalant hydrochloride seems to be feasible and can be adjunctive to advanced cardiac life support.

It should be noted again that prompt reperfusion therapy improves the survival of patients with AMI. Although primary PCI offers a better clinical outcome for AMI patients, the procedure is resource-intensive and more difficult to implement quickly than thrombolysis.[91,92] Considering the importance of early reperfusion for better cardioprotection, particularly in patients who present very early after the onset of symptoms (<2 h),[93] thrombolysis is likely to be preferred, because of the anticipated delay in performing PCI, if the patients are at low risk for intracranial hemorrhage. A meta-analysis of 6 randomized trials demonstrated that thrombolytic treatment reduced the time from onset of symptoms to treatment by an average of 58 min.[94] Several randomized trials have evaluated the potential benefits of pre-hospital vs in-hospital thrombolysis. The Comparison of Angioplasty and Prehospital Thrombolysis In acute Myocardial infarction (CAPTIM) trial reported a trend towards a lower rate of 30-day mortality in patients with AMI who received pre-hospital thrombolysis compared with those who had primary PCI alone, especially within 2 h after the onset of symptoms.[95] This trend remained stable over a 5-year follow up.[96] Including pre-hospital thrombolysis, the focus is now on improving the entire "lifeline" system for early reperfusion to shorten the total ischemic time.[97,98]

Conclusions

The most important goal in the treatment of AMI is to minimize the time from the onset of symptoms to reperfusion and to maximize the probability of achieving complete and sustained reperfusion at both the epicardial coronary artery and microcirculation levels (**Figure 6**). A system of both rapid triage of patients and strategies for optimal reperfusion using an integrated approach of catheter-based devices to retrieve embolic thrombi and pharmacologic interventions to protect myocardium ise evolving.

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