



Title	Noninvasive myocardial endothelial intervention in the persistence of coronary stenosis: a concept of myocardial endothelial nitric oxide activator through heart failure research on clinical demand
Author(s)	Yaoita, Hiroyuki; Watanabe, Kenichi; Ogawa, Kazuei; Maruyama, Yukio
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**NONINVASIVE MYOCARDIAL ENDOTHELIAL INTERVENTION
IN THE PERSISTENCE OF CORONARY STENOSIS :
A CONCEPT OF MYOCARDIAL ENDOTHELIAL NITRIC OXIDE
ACTIVATOR THROUGH HEART FAILURE RESEARCH
ON CLINICAL DEMAND**

HIROYUKI YAOITA, KENICHI WATANABE, KAZUEI OGAWA
and YUKIO MARUYAMA

*Department of Internal Medicine I, Fukushima Medical University School of Medicine,
Fukushima, 960-1295, Japan*

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Abstract : Protection of ischemic myocardium has been attempted by a variety of pharmaceutical and non-pharmaceutical methods. When the coronary intervention is not indicated by some reasons in patients with ischemic heart failure, medical treatments are expected to offer cardioprotection against the persistence of stenotic/occlusive lesions of the epicardial coronary artery. The pharmaceuticals such as the angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta blocker, Ca antagonist, ATP-sensitive K channel opener and statin, or non-pharmaceutical approaches such as physical exercise, cardiac resynchronization, ventricular assist devices, and preconditioning upon ischemic insults appear to improve myocardial endothelial nitric oxide (NO) synthase (eNOS) function. Such eNOS activation contributes to amelioration of the cardiac dysfunction and remodeling induced by myocardial ischemia. Therefore, based on clinical evidence and basic research on clinical demand, we postulate a concept of 'myocardial endothelial NO activator' from the standpoint of mechanistic insights beyond the class-effects of each pharmaceutical category and each non-pharmaceutical intervention. In addition to such continuous eNOS activation for treating chronic ischemic heart failure, rapid eNOS activation in the setting of acute ischemic events upon chronic myocardial ischemia by new strategies such as postconditioning seems to be also essential for developing further effective anti-heart-failure therapies.

Key words : nitric oxide, heart failure, endothelium, ischemia

矢尾板裕幸, 渡部研一, 小川一英, 丸山幸夫

Correspondence to: Yukio Maruyama, Department of Internal Medicine I, Fukushima Medical University, School of Medicine, Fukushima City 960-1295, Japan.

E-mail: maruyama@fmu.ac.jp

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INTRODUCTION

Patients with chronic heart failure are increasing in number, and ischemic heart disease is one of the major causes. There are several therapies for chronic ischemic heart failure, that is, pharmacotherapies [with such as angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), beta blocker, nitrates, long-acting calcium (Ca) antagonist, and ATP-sensitive potassium (K) channel (KATP) opener], lifestyle corrections, physical exercise, and percutaneous or surgical coronary interventions. These therapies have different pathways upstream to mitochondria on their effects although their downstream mechanism(s) may be shared for the ultimate objective, the amelioration of ischemic heart failure.

In ischemic heart failure, coronary interventions to coronary stenotic/occlusive lesions are essential ways to attenuate cardiac dysfunction and to improve the prognosis if a significant amount of viable myocardium is rendered ischemic, and cardiac function is deteriorated. However, such coronary interventions may not be always possible due to anatomical and/or physical difficulties, medical costs, or patient reluctance. Therefore, in the presence of epicardial coronary stenotic/occlusive lesions, non-invasive therapies such as pharmaceuticals or physical exercise may be alternatives. One of the targets, in such situations, may be the coronary microvascular endothelial function in the persistence of epicardial coronary lesions. Coronary microvascular tone less than 300 μm in diameter predominantly regulates coronary blood supply. There are myocardial flow-regulating mechanisms, such as autonomic innervation, myogenic tone, metabolic vasodilation, and endothelial function, the coronary endothelial function. Among them, especially endothelial nitric oxide (NO) synthase (eNOS), has been extensively investigated in relation to successful medical therapies^{1,2)}. However, the framework for clinical applications of eNOS activation and/or improvement of the endothelial function has not been

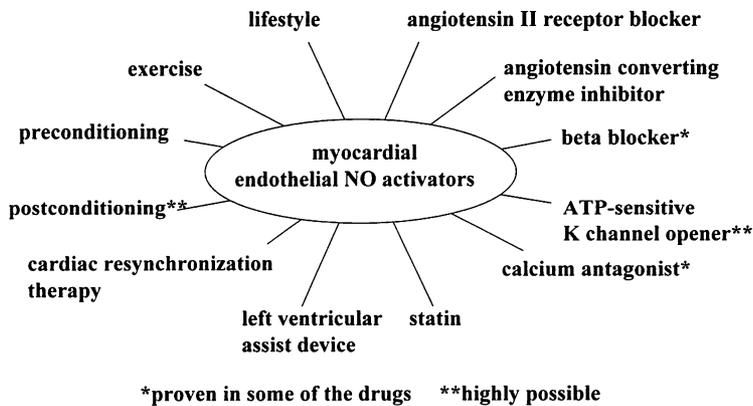


Fig. 1. Concept of 'myocardial endothelial nitric oxide (NO) activator.'

fully established. It may be possible to assume that medical therapies of the different categories mentioned above may constitute a concept of 'myocardial endothelial NO activator' (Fig. 1). The emerging and awaited issue is the answer to the question whether and how myocardial endothelial NO activation contributes to ameliorating ischemic heart failure. The clinical evidence and the basic research on clinical demand to seek for its mechanistic insights would lend a clue for it. Thus, this paper aims to introduce a concept of myocardial endothelial NO activator in the treatment of heart failure, especially of ischemic origin, to seek out the future directions for the therapies.

CASCADES OF CARDIOMYOCYTE DEATH

The cascade of cardiomyocyte injury by toxic impulses and the targets of anti-heart-failure interventions are shown in Fig. 2. Myocardial ischemia and the associated cardiotoxicity (inflammation, Ca overload, free radical generation, acidosis, etc.) given at the premitochondrial stage cause mitochondrial respiratory dysfunction. This results in an increase in the number of mitochondria as a compensative mechanism, and augmented protein production for the cellular stresses. The production of imperfect proteins, which occurs at a certain rate during the augmented protein synthesis, threatens the homeostasis of the living cells, and leads to the

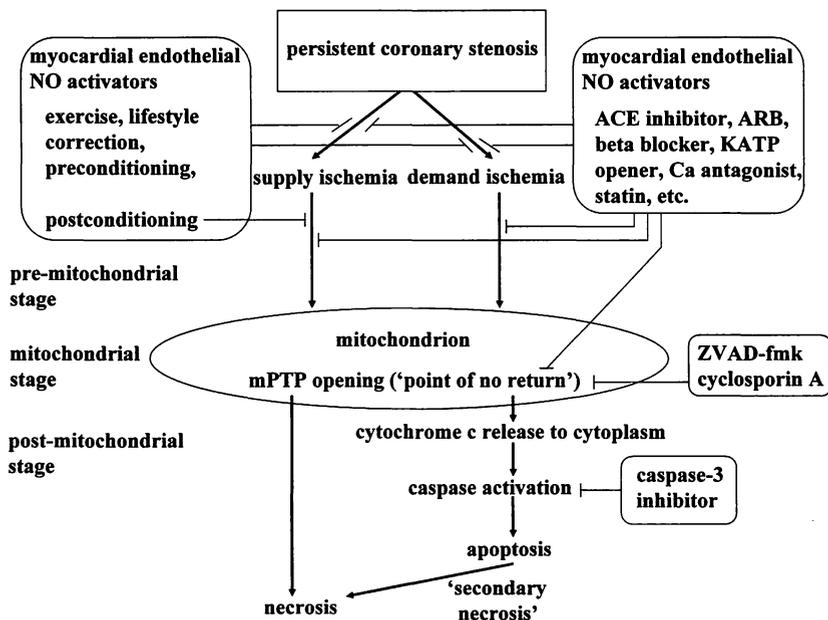


Fig. 2. Targeted stages of therapeutic interventions in cascade of cardiomyocyte injury caused by persistent coronary stenosis. mPTP, mitochondrial permeability transition pore; ARB, angiotensin II receptor blocker; KATP opener, ATP-sensitive K channel opener.

enhanced phagocytosis of such protein gavages (autophagy). Some of the autophagic cells die of exhaustion in this process (autophagic cell death)³⁾.

If a mitochondrial permeability transition pore opens by exceeding the threshold of Ca storage in damaged mitochondria, the mitochondrial trans-membrane voltage difference is lost, resulting in direct irreversible changes (necrosis) or goes transition into the energy-requiring suicide process triggered by the cytochrome *c* release into cytoplasm (apoptosis) and often subsequent structural changes mimicking necrosis (secondary necrosis). 'A point of no return' for cell death exists around the position of these processes of mitochondrial permeability transition pore opening and cytochrome *c* release (Fig. 2)⁴⁾.

TARGETS OF ANTI-HEART-FAILURE AGENTS

In the cascades of cardiomyocyte injury, therapeutic interventions focused on the post-mitochondrial stage⁴⁾ (after 'a point of no return') fail to rescue the myocardium (e.g., caspase-3 inhibition using its inhibitors, reperfusion therapy after completion of cell death in myocardial infarction) (Fig. 2). Most of the successful therapeutic interventions with different action mechanisms target the premitochondrial stage of this cell death pathway. Although not all of the interventions which affect the mitochondrial stage have been clarified, a broad caspase inhibitor (ZVAD-fmk)^{5,6)} and cyclosporin A⁷⁾ prevent the ROS-induced collapse of mitochondrial membrane potentials. Actually, both agents can reduce experimental myocardial infarct size due to acute coronary occlusion and reperfusion^{5,7)}. Mitochondrial KATP channel opener (diazoxide) also reduces Ca concentration in the mitochondrial matrix resulting in the resistance to the opening of the permeability transition pore⁸⁾. These interventions have not been in clinical use since their sites of actions are not heart-specific and may have several pharmacological effects not intended for this purpose (e.g., possible carcinogenesis by caspase inhibition although it is not proven, and hyperglycemia due to KATP channel-mediated inhibition of insulin secretion by the pancreas). In regard to this mitochondrial stage, mitochondrial NOS, a constitutive form of NOS in the mitochondrial inner membrane, exists in the heart as well as in the liver, brain and kidney. The functions of mitochondrial NOS, its regulatory mechanisms and relations to pharmacotherapies are mostly unknown⁹⁾.

In the premitochondrial stage of the cell death pathway, myocardial endothelial NO activators protect myocardium via pleiotropic mechanisms such as: 1) the reduction of Ca influx in cardiomyocytes leading to attenuation of Ca overload and suppression of apoptosis; 2) endothelium-dependent vasodilatation resulting in the improvement of myocardial perfusion and a reduction of cardiac afterload; and 3) an anti-inflammatory effect by inhibition of adhesion molecules to the endothelium, as well as a superoxide-scavenging effect.

PHARMACEUTICAL INTERVENTIONS

Nitric Oxide Precursor

L-arginine is a precursor of NO produced via eNOS. The baseline plasma concentration of L-arginine is about 25-fold higher than the Michaelis-Menten constant K_m of the isolated, purified eNOS *in vitro*. Even in such a situation, supplementation with exogenous L-arginine can improve eNOS-mediated vascular functions *in vivo* (the so-called 'L-arginine paradox'). This may be because L-arginine counteracts asymmetrical dimethylarginine (ADMA), an endogenous inhibitor of eNOS, regarding substrate availability for eNOS¹⁰. Since the plasma ADMA level increases in hypercholesterolemia, atherosclerosis, chronic renal failure, and chronic heart failure, supplementation with L-arginine may improve the eNOS function in these situations¹¹.

Beta Blocker

The beta blockers of the first (nonspecific), second (beta-1 selective) and third (vasodilating) generation are effective for the primary and secondary prevention of ischemic heart disease and heart failure. Their classic effects are mainly the reduction of the myocardial work resulting in reduced myocardial oxygen consumption. Recent large-scale clinical trials on the use of the second and third generation revealed that bisoprolol¹², metoprolol¹³ and carvedilol^{14,15} reduced the mortality rate in heart failure cases in which an ischemic origin accounts for 50–60%^{12–14} to 100%¹⁵ of the subjects. Different effects of beta blockers may be in part explained by its anti-oxidant property as a non-class-effect. Such an anti-oxidant effect helps store the eNOS function resulting in improvement of coronary microcirculation, increase in coronary flow reserve and restoration of NO-mediated suppression of myocardial respiration¹⁶.

Angiotensin-Converting Enzyme Inhibitor and Angiotensin II Receptor Blocker

Since angiotensin II is produced via both of ACE and chymase, the ACE inhibitor does not necessarily reduce tissue angiotensin II levels but activates endothelial NOS via suppression of bradykinin degradation. Although bradykinin once produced causes tachyphylaxis resulting in the attenuation of vasodilatation, ACE inhibitor prevents such attenuation by activating the endothelium-derived hyperpolarizing factor (EDHF) as a back-up system of endothelium-derived relaxing factor (EDRF), that is, NO¹⁷. On the other hand, ARB blocks the angiotensin II receptor-mediated signals including aldosterone production. Thus, aldosterone as well as angiotensin II is involved in the effects by ARB.

The ACC/AHA heart failure guideline¹⁸ directs the use of several kinds of therapeutic agents for stages A to D of common heart failure. In ischemic heart failure, the focus in this review, we have our own thoughts on its treatment. ACE

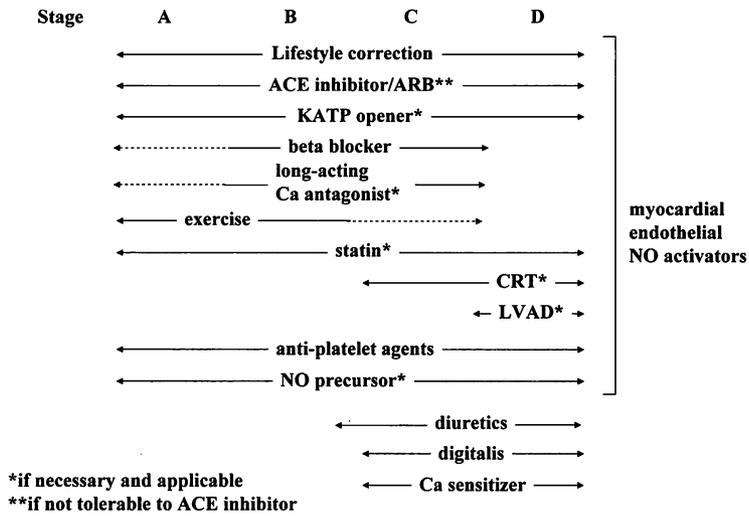


Fig. 3. Pharmaceutical therapies based on proposal for stages A to D of heart failure (ACC/AHA classification of staging, reference no.18) due to coronary artery disease. ACE inhibitor can be used even in stage A. KATP opener, beta blocker, long-acting Ca antagonist, statin, and NO precursor (L-arginine) may be used in stage A if applicable and necessary.

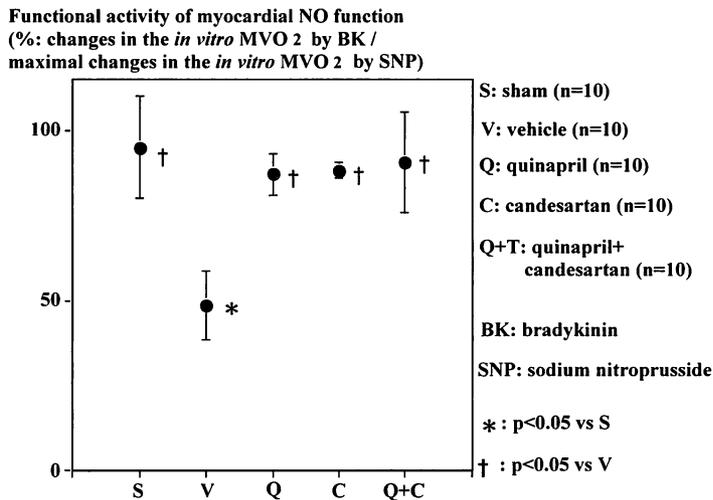


Fig. 4. Endothelial nitric oxide function assessed by *in vitro* myocardial oxygen consumption method (reproduced from reference no. 22 with permission). Coronary stenosis was created in rats. Coronary stenosis lasting for 12 weeks impaired functional activity of myocardial endothelial nitric oxide in risk area compared to sham rats. Daily treatment with ACE inhibitor (quinapril), ARB (candesartan) or their combination, in presence of coronary stenosis, ameliorated functional activity of myocardial endothelial nitric oxide.

inhibitor can be used in ischemic heart disease at the first stage (stage A) (Fig. 3). The ACE inhibitor and ARB activate the myocardial NO function¹⁾ (Fig. 4) and improve the prognosis of heart failure^{19,20)}.

Aldosterone as well as angiotensin II is involved in the effects by ARB. On the other hand, Aldosterone is known to cause myocardial hypertrophy and fibrosis although the exact mechanisms remain to be determined. Spironolactone and ephrenone can prevent such aldosterone-induced cardiotoxicity via the aldosterone receptor-mediated mechanisms. However, aldosterone also causes nongenomic vasoconstriction in tissue-resistant arteries via the angiotensin II type 1 receptor-mediated mechanism (but not via the aldosterone receptor), possibly resulting in impairment of tissue perfusion²¹⁾. Thus, the combination therapy of ACE inhibitor and ARB is sometimes performed in treating heart failure anticipating the effects of EDRF and of EDHF and in order to block the nongenomic effects of aldosterone. In fact, according to our study²²⁾, this combination therapy has been proved effective for alleviating cardiac dysfunction due to ischemic heart failure, although no additive effect on myocardial NO activity by the combination was obtained as shown in Fig. 4.

Calcium Antagonist

The concept of the use of Ca antagonists in heart failure is that the long-acting agents, which are devoid of the secondary sympathetic stimulation, may contribute to lowering blood pressure (afterload reduction), an increase in diastolic compliance (improvement of diastolic function) and prevention of coronary vasospasm (improvement of myocardial perfusion).

The effects of Ca antagonists on endothelial protection are not simple. An experimental study revealed that nifedipine, a dihydropyridine species, generates superoxide via activation of NADPH oxidase resulting in generation of EDHF²³⁾. In contrast, amlodipine, another dihydropyridine species, releases NO from the myocardium, although the exact mechanism(s) remain(s) to be determined. The Ca antagonist may be neutral in its effects on heart failure²⁴⁾, whereas in coronary artery disease it may reduce adverse cardiovascular events²⁵⁾ (e.g., hospital admissions for angina, coronary revascularizations) with a trend towards reduced death, myocardial infarction and stroke²⁶⁾.

ATP-SENSITIVE POTASSIUM CHANNEL OPENER

Nicorandil is a KATP opener which is clinically available currently. It opens sarcolemmal KATP, and its effect on mitochondrial KATP is quite weak. Therefore, it is not known whether a KATP opener has a cardioprotective effect through the mechanism of ischemic preconditioning in which the mitochondrial KATP opening is involved. Instead, the outward K current by KATP opening causes suppression of inward Ca current in association with a shortening of the action

potential duration, leading to relaxation of vascular smooth muscle.

The above mentioned effects of nicorandil are impressed clearly in a situation of no reflow phenomenon in acute myocardial ischemia²⁷⁾. In contrast, although its effects on chronic myocardial ischemia remained to be determined, the IONA study²⁸⁾ for the first time revealed that daily nicorandil treatment reduces cardiac events and improve prognosis in chronic ischemic heart failure. A part of the pharmaceutical effects by nicorandil appears to involve myocardial eNOS activation²⁹⁾.

Statin

The statins activate eNOS, independent of the cholesterol lowering effect. There is a report that cardiac function in patients with dilated cardiomyopathy was improved by statin therapy, possibly via reduction of oxidative stresses derived from vascular endothelial NADPH-oxidase³⁰⁾. In the ischemic heart disease, statins are effective on the second prevention of cardiac events in chronic coronary artery disease³¹⁾.

NONPHARMACEUTICAL INTERVENTIONS

Lifestyle

The common accelerators of atherosclerosis, such as smoking, high blood pressure, hypercholesterolemia, hypertriglycemia, and diabetes mellitus, also cause eNOS dysfunction. There is no doubt that the restoration of a healthy lifestyle contributes to amelioration of such eNOS dysfunction. Among them, hypercholesterolemia, as with the other accelerators, is known to have a relation to heart failure. The 4S study, a large-scale clinical trial on treatment of hypercholesterolemia, documented that lowering cholesterol suppresses the occurrence of congestive heart failure³²⁾. The reasons for this epidemiological evidence may be multiple, including the reduction of obesity and its metabolic syndrome, the pleiotropic effects of statins, and secondary suppression of developing coronary artery disease. Since hypercholesterolemia is an established coronary risk factor, it is commonly believed that hypercholesterolemia accelerates coronary artery plaque formation, and that cholesterol lowering contributes to an improvement in ischemic heart disease via regression/prevention of coronary stenotic/occlusive lesions. However, cardiologists sometimes have unexpected experiences in which findings of cardiac dysfunction mimic previous myocardial infarction, although there is no such clinical history and no coronary occlusion but only coronary stenotic lesions detected by coronary angiogram. The underlying mechanisms of such clinical phenomena have been vastly not known.

We challenged the above mentioned clinical question in a basic study. Namely, in the presence of chronic coronary stenosis, the cholesterol burden aggravated heart failure without augmenting the coronary stenosis severity in rats³³⁾. Chronic

inflammation associated with eNOS dysfunction and MCP-1 expression and resultant monocyte infiltration in coronary microcirculation of the risk area appeared to be involved in this morbidity. Thus, a high cholesterol diet induces adhesion of monocytes via chemokine expression in coronary microcirculation. If myocardial ischemia is present, chemotactic factors such as complements³⁴⁾ and inflammatory cytokines attract monocytes into the myocardium at risk, resulting in myocardial inflammation and injury. These experimental results suggest that a high cholesterol diet may be a risk factor for heart failure in the presence of fixed coronary artery stenosis in addition to being a risk factor for coronary artery disease. Our result, naming that supplementation of a cofactor of eNOS ameliorated a series of such morbidity³³⁾, suggests the inevitable role of the eNOS integrity in this situation.

Physical Therapy

Exercise is one of the nonpharmaceutical therapies for chronic heart failure³⁵⁾. In the classic viewpoint of concept on physical therapy, endurance exercise (e.g., 60-min walking or swimming) is required to obtain optimal therapeutic effects. Recently, it was found that exercise activates eNOS via an increase in vascular shear stress. Since this shear-stress-induced focal adhesion kinase-protein kinase B (Akt) activation for eNOS activation is a rapid process³⁶⁾, it is postulated that even a short duration of exercise (short exercise) may activate eNOS. In addition, in ischemic heart failure, endurance exercise may increase the probability of unfavor-

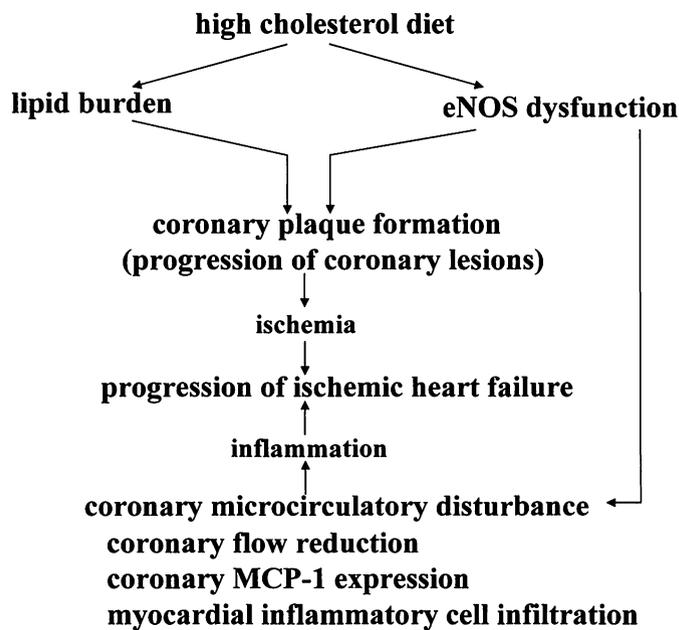


Fig. 5. Mechanisms involved in progression of coronary stenosis-induced heart failure in association with high cholesterol diet.

able events based on ischemia such as angina attacks and arrhythmias. Actually, the beneficial effect of short exercise on eNOS function in peripheral circulation has recently been reported in human³⁷⁾.

We assessed whether short exercise is able to ameliorate heart failure due to coronary artery disease through myocardial eNOS activation. In a rat model of coronary stenosis^{16,22,33)}, we performed daily short or longer exercises on a treadmill machine³⁸⁾. As a result, longer exercise caused myocardial ischemia and resultant stunning (shown by a fall in the ventricular wall-thickening fraction during exercise which is assessed by the sonomicrometric method), which failed to ameliorate myocardial endothelial NO function, and aggravated cardiac dysfunction and remodeling due to coronary stenosis. In contrast, short exercise which is completed

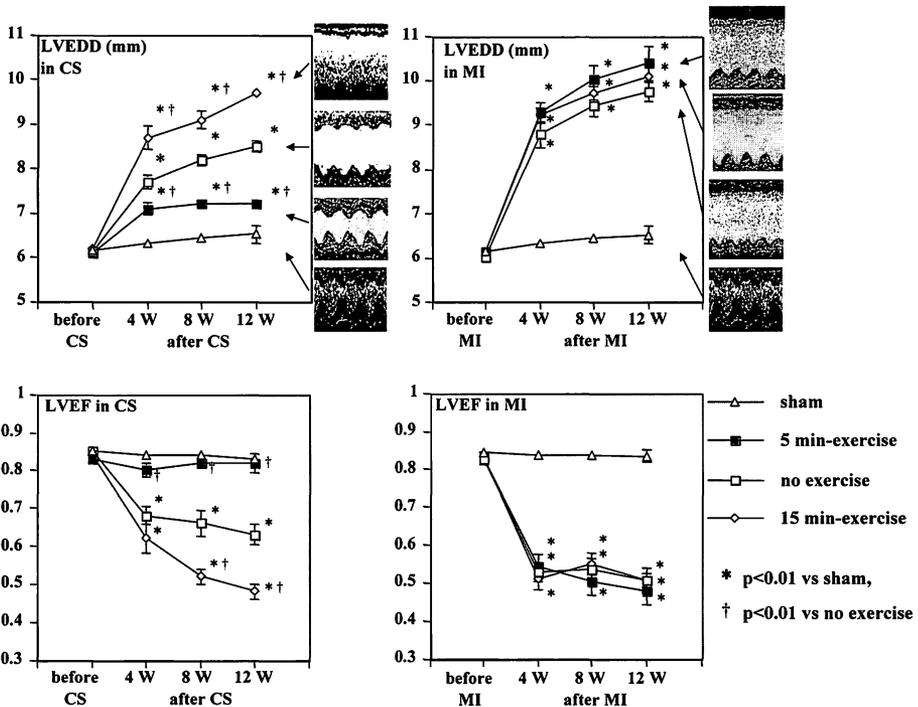


Fig. 6. Effect of exercises on ischemic left ventricular dysfunction and remodeling assessed by serial echocardiography (reproduced from reference no. 38 with permission). In rats with coronary stenosis (CS, left panels) or with myocardial infarction (MI, right panels), daily short (5 min) or longer (15 min) treadmill exercise was performed for 12 weeks after creation of coronary stenosis or infarction. Both exercises did not affect left ventricular dysfunction and remodeling induced by myocardial infarction (right panels). In contrast, longer exercise augmented and short exercise ameliorated heart failure induced by coronary stenosis (left panels). Sonomicrometric analysis of wall thickening fraction of ischemic area during exercise (data not shown; see reference no. 38) revealed occurrence of myocardial stunning not by short exercise but by longer exercise. LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter.

before induction of myocardial stunning ameliorated myocardial endothelial NO function and perfusion without modifying the coronary stenosis severity but possibly via an increase in the coronary vascular shear stress. Finally, the short exercise prevented myocardial fibrosis in the risk area and attenuated global cardiac dysfunction and remodeling (Fig. 6). However, even short exercise was ineffective for the amelioration of heart failure due to myocardial infarction which has no viability in the risk area³⁸). These results imply that eNOS activation with exercise ameliorates ischemic heart failure by protecting ischemic but viable myocardium in the risk area from ongoing cell death and fibrosis. Thus, the exercise protocols need to be customized according to the disease state (ischemic or infarcted) to obtain optimal therapeutic effects, and that the main target for the protection of ischemic but viable myocardium is eNOS activation through short exercise.

Mechanical Interventions

Cardiac resynchronization therapy is a newly-introduced electrical support for inefficient cardiac contraction due to ventricular asynchrony in moderate to severe heart failure. In the improvement of LV systolic dysfunction by this therapy, NO production may be partly involved. In patients with dilated cardiomyopathy and with the indication of cardiac resynchronization therapy, the end-tidal NO concentration in the inhaled air increased in accordance with an increase in LV ejection fraction after this therapy³⁹). Although it remains to be determined whether NO production by this therapy derives from eNOS activation, the authors assumed that restoration of asynchrony increased cardiac output so that eNOS may have been activated, and, as a result, contributing to the further amelioration of heart failure.

The left ventricular assist device has been used as a bridge to cardiac transplantation in patients with the most severe heart failure. The mechanical assistance of the pump function causes a variety of changes (upregulation or downregulation) in cardiac gene expressions. Several of the upregulated genes were related to NOS, especially eNOS and dimethylarginine dimethylaminohydrolase isoform 1, an enzyme which hydrolyzes ADMA⁴⁰). Since ADMA is an inhibitor of NOS, it is expected that upregulation of dimethylarginine dimethylaminohydrolase isoform 1 can cause eNOS activation.

Acute Ischemic Events in Chronic Heart Failure

One of the reasons for poor prognosis in patients with chronic ischemic heart failure is the overlapping new ischemic attacks based on severe coronary artery disease. Sometimes the cardiac damage by new acute ischemic events upon chronic cardiac dysfunction is life-threatening. The so-called 'ischemic preconditioning' effect may lower cardiac damage if brief ischemic insults precede the acute myocardial infarction attack⁴¹). However, clinical application of the ischemic preconditioning at the time following the onset of acute infarction is difficult. In addition, downregulation of protein kinase C occurs in chronic ischemia resulting in a reduc-

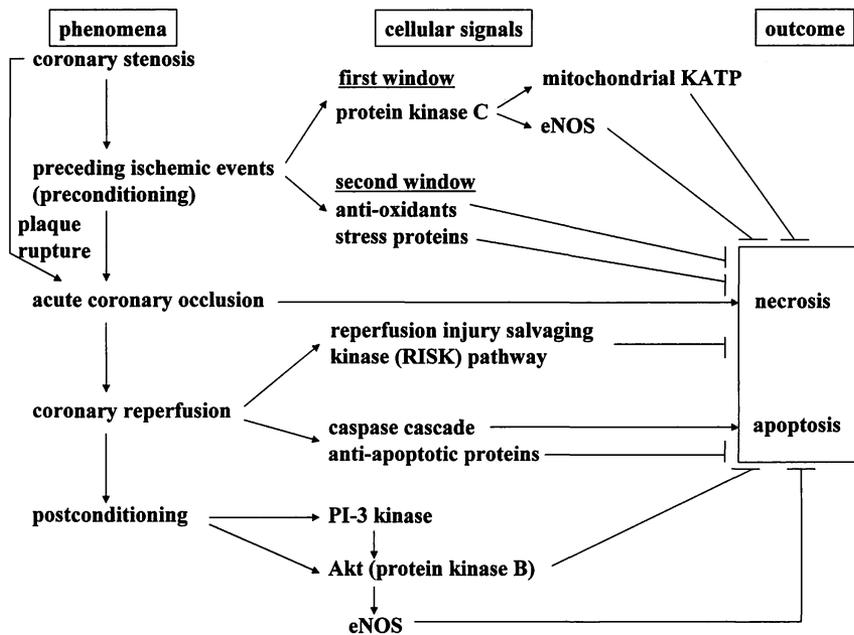


Fig. 7. Signals involved in myocardial injury and protection upon acute myocardial infarction.

tion of this cardioprotective mechanism⁴²). More recently, it was found that several cycles of brief coronary occlusion-reperfusion, added just after successful coronary reperfusion therapy, elicited cardioprotection comparable with ischemic preconditioning. This phenomenon has been termed 'postconditioning'⁴³ in contrast to preconditioning. This new intervention is quite attractive since it is applicable in the cath lab. The signals involved in cardiomyocyte death by acute ischemia (necrosis and apoptosis) are shown in Fig. 7.

Ischemic preconditioning exerts its acute (first window) cardioprotective effect via protein kinase C, mitochondrial KATP channel and eNOS. Coronary reperfusion itself causes activation of the 'RISK' pathway⁴⁴) constituted of several kinases and also upregulation of anti-apoptotic proteins such as BCL-2. In addition, if postconditioning is performed just after reperfusion, phosphatidylinositol-3 kinase, Akt, and eNOS are activated to protect the ischemic myocardium (Fig. 7)⁴⁵). Thus, since eNOS is one of the downstream mechanisms of several cardioprotective signals including those of postconditioning, in the presence of eNOS dysfunction, the welcome cardioprotective effect by interventions may be diminished. In this meaning, it is highly probable that restoration of eNOS dysfunction in chronic ischemic heart failure is requisite for preventing further worsening of cardiac dysfunction and prognosis.

FUTURE DIRECTIONS

The conventional and newly-introduced medical and mechanical interventions mentioned above will continue to improve treatment of ischemic heart failure. In addition to these therapies widely applicable for ischemic heart failure, specialized therapies for patients refractory to such treatment and coronary interventions also need to be developed. Cardiac regeneration therapy may well be one of them. The current technology for human cardiac regeneration is serving to develop angiogenetic therapies, and may advance to the next stage for cardiomyocyte regeneration. Regarding present angiogenic therapy, it is unclear whether regenerated small vessels possess the functions of normal native vessels such as endothelial vasodilation. If not, eNOS expression and activation will be an inevitable direction for research in this field.

CONCLUSIONS

When coronary intervention is not indicated due to the many reasons previously mentioned in patients with ischemic heart failure, medical treatments are expected to offer cardioprotection against the persistence of stenotic/occlusive lesions of the epicardial coronary artery. A majority of such anti-ischemic heart failure pharmaceuticals and non-pharmaceutical therapies are now found to improve myocardial endothelial NO function in relation to eNOS activation. Such eNOS activation seems to contribute to amelioration of the cardiac dysfunction and remodeling induced by myocardial ischemia. Therefore, based on clinical evidence and basic research on clinical demand to seek for its mechanistic insights, we postulate a concept of 'myocardial endothelial NO activator' beyond the class-effects of each pharmaceutical category and each non-pharmaceutical intervention. In addition to continuous eNOS activation for treating chronic ischemic heart failure, rapid eNOS activation in the setting of acute ischemic events upon chronic myocardial ischemia by new strategies will be required to develop further effective anti-heart-failure therapies.

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