A prostacyclin agonist and an omental flap increased myocardial blood flow in a porcine chronic ischemia model

Shin Yajima, MD,[a] Shigeru Miyagawa, MD, PhD,[a] Satsuki Fukushima, MD, PhD,[a] Yoshiki Sakai, BSc,[a] Kayako Isohashi, MD, PhD,[b] Tadashi Watabe, MD, PhD,[b] Hayato Ikeda, PhD,[b] Genki Horitsugi, BSc,[b] Akima Harada, BSc,[a] Ryoto Sakaniwa, PhD,[c] Jun Hatazawa, MD, PhD,[b] and Yoshiki Sawa, MD, PhD[a]

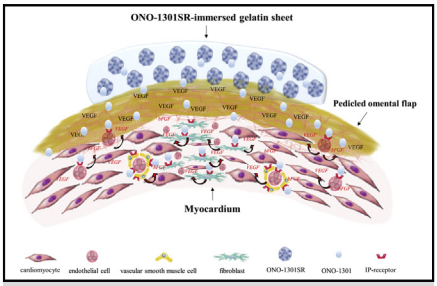
ABSTRACT

Objective: We hypothesized that therapeutic efficacy may be augmented by a combination of placing a sheet immersed in ONO-1301SR, a slow-release synthetic prostacyclin agonist-inducing multiproangiogenic cytokines, over the left ventricle and a pedicled omental flap in a chronic myocardial infarct heart.

Methods: A minipig chronic myocardial infarction was generated by placing an ameroid constrictor ring around the left anterior descending artery for 4 weeks. The minipigs were then assigned into 4 groups of 6 each: sham, omental flap only, ONO-1301SR only, and ONO-1301SR combined with an omental flap (combined). Four weeks after treatment, therapeutic efficacy was evaluated histologically and via several modalities used in the clinical setting.

Results: In an angiogram and pressure wire study, the combined group induced development of collateral arteries to decrease the resistance and increase the flow reserve of microvasculature in the left circumflex territory. In a ^{13}N-ammonia positron emission tomography study, the combined group displayed a prominent increase in myocardial blood flow and myocardial flow reserve in the left circumflex territory, particularly at the infarct-border region. Consequently, the combined group showed greater regional cardiac function in the left circumflex territory particularly at the infarct-border region, contributing to a greater global ejection fraction with a smaller left ventricular endosystolic volume. Pathologically, attenuated fibrosis, nonswollen myocytes, and upgraded capillary density and proangiogenic cytokines were prominent in the combined group.

Conclusions: ONO-1301SR combined with a pedicled omental flap synergistically promoted myocardial angiogenesis, leading to function recovery in a porcine chronic myocardial infarction model. (J Thorac Cardiovasc Surg 2018;■:1-13)



The concept of ONO-1301SR with a pedicled omental flap therapy.

Central Message

Combined treatment with ONO-1301SR and pedicle omentum produced the greatest functional recovery associated with the greatest myocardial blood flow and flow reserve in a porcine chronic MI model.

Perspective

ONO-1301SR combined with a pedicle omental flap therapy synergistically promoted myocardial angiogenesis, leading to decrease in the resistance of the microvasculature, increase in regional MBF and MFR and improvement in regional and global cardiac function in a porcine chronic MI model. This cell-free combination therapy would be useful in enhancing myocardial angiogenesis in a chronic MI heart.

See Editorial Commentary page XXX.

BS

Ischemic insults result in necrosis or apoptosis of cardiac myocytes, modulation of extracellular matrices, or failure of microvascular networks, consequently leading to left ventricle (LV) remodeling, including progressive deterioration of cardiac function.[1] Microvascular dysfunction, which induces persistent regional myocardial ischemia, is suggested as among the major pathologies causing LV remodeling. It is irreversible even with the latest medical or interventional approaches.[2] It has recently been suggested that a regenerative approach using cell transplantation therapy upregulates myocardial expression of a variety of

Scanning this QR code will take you to a supplemental video, appendix, tables, and figures for the article.

From the Departments of [a]Cardiovascular Surgery, [b]Nuclear Medicine and Tracer Kinetics, and [c]Public Health, Osaka University Graduate School of Medicine, Osaka, Japan.

Supported by Grants-in-Aid for Scientific Research (KAKENHI, grant No. 15K10214).

ONO-1301SR was supplied by Ono Pharmaceutical Co. Ltd, Osaka, Japan.

Received for publication Sept 8, 2017; revisions received Jan 29, 2018; accepted for publication Feb 7, 2018.

Address for reprints: Yoshiki Sawa, MD, PhD, Department of Cardiovascular Surgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan (E-mail: s-yajima@surg1.med.osaka-u.ac.jp).

0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2018.02.086

Abbreviations and Acronyms

CFR = coronary flow reserve
CS = circumferential strains
CSR = circumferential strain rates
FGF = fibroblast growth factor
HGF = hepatocyte growth factor
IMR = index of microvascular resistance
LAD = left anterior descending artery
LCX = left circumflex artery
LV = left ventricle
MBF = myocardial blood flow
MFR = myocardial flow reserve
MI = myocardial infarction
MRI = magnetic resonance imaging
PET = positron emission tomography
RCA = right coronary artery
SDF-1 = stromal cell derived factor-1
VEGF = vascular endothelial growth factor

proangiogenic factors. This leads to reorganization of microvascular networks and regional myocardial blood flow (MBF) increases, consequently inducing functional recovery in chronic myocardial infarct (MI) hearts,[3,4] although cell transplantation therapy is limited by the cell preparation process in clinical scenarios.

Prostacyclin is an endogenous factor that protects and regenerates damaged tissues and/or organs[5-7]; therefore, it may enhance regeneration in chronic pathologies. However, the use of clinically available prostacyclin analogues for treating chronic pathologic conditions is limited due to their short half-lives. A new reagent, ONO-1301SR, is a slow-release form of ONO-1301, a unique synthetic prostacyclin agonist conjugated with lactic and glycolic acid polymer. Reports suggest that ONO-1301SR constitutively releases prostacyclin analogues to adjacent tissues for 4 weeks, indicating its therapeutic potential via slow-release delivery into a specific organ.[8-10] Our laboratory demonstrated that administration of ONO-1301SR into several acute MI and dilated cardiomyopathy animal models yielded proangiogenic cytokines, such as vascular endothelial growth factor (VEGF) or hepatocyte growth factor (HGF), and stromal cell derived factor-1 (SDF-1), recruiting damaged ischemic myocardium and inducing functional recovery.[11-13]

Furthermore, we have been developing treatments that enhance therapeutic angiogenesis in the myocardium, such as ONO-1301SR,[12-15] pedicle omentum,[16-18] and cell sheet.[19-21] Of them, clinical availability would be prominent in ONO-1301SR only, which in contrast is therapeutically limited by the nature of the myocardium. In the myocardium, in which endothelial cells, fibroblasts, or vascular smooth muscle cells are severely damaged, therapeutic effects of ONO-1301SR would be severely limited.

Pedicle omentum is a proangiogenic tissue that enhances therapeutic angiogenesis in the myocardium.[22-24] However, the omentum alone is insufficient to produce clinically identifiable therapeutic benefits, because the positive effects of the omentum are counterbalanced by surgical damage in retrieval of the omentum from the abdomen. We recently reported that a skeletal myoblast sheet[16,18] or induced pluripotent stem cell-derived cardiomyocyte sheet[17] covered with a pedicled omental flap yielded further cardiac functional recovery, including increased angiogenesis and attenuated fibrosis in ischemic cardiomyopathy models. We believe that a combination of ONO-1301SR and pedicle omentum would compensate for each option's drawbacks to achieve clinically identifiable therapeutic benefits, and hypothesized that ONO-1301SR covered with a pedicled omental flap over the LV surface could be synergic to augment proangiogenic effects on a chronic MI heart.

METHODS

The institutional ethics committee approved all experimental procedures. Animal care was conducted humanely in compliance with the principles of laboratory animal care.[25] We took care of the animals in a controlled nonstressed environment for at least a week before the study to avoid possible confounding problems related to constructive myocardial preconditioning.

Preparation of ONO-1301SR

ONO-1301SR (Ono Pharmaceutical Co, Ltd, Osaka, Japan) is a polylactic acid to glycolic acid ratio of 50:50-polymerized form of ONO-1301 designed to achieve a sustained-release system.[26] It is a synthetic prostacyclin receptor agonist lacking typical prostanoid structures, including a 5-membered ring and allylic alcohol, which is rapidly metabolized by 15-hydroxyprostaglandin dehydrogenase in vivo.[27] In addition, ONO-1301 has a 3-pyridine radical to exert thromboxane A2 synthase inhibitory activity that induces an intrinsic prostaglandin I2 synthesis-promoting effect to augment prostacyclin receptor agonistic activity.[27] ONO-1301 and polylactic co-glycolic acid were dissolved in dichloromethane. The dissolved polymer was added to polyvinyl alcohol aqueous solution to form an oil-in-water emulsion. Then, dichloromethane was evaporated by stirring. After centrifugation and washing, YS-1402 was isolated using lyophilization.[28]

Study Protocol

The study protocol is shown in Figure E1, *A*. Göttingen minipigs weighing 20 to 25 kg (Ellegaard, Dalmose, Denmark) were anesthetized, endotracheally intubated, and mechanically ventilated. A minipig chronic MI model was generated by placing an ameroid constrictor ring (MRI-2.50-TI; Research Instruments NW Inc, Lebanon, Ore) with an internal diameter of 4.0 mm around the proximal portion of the left anterior descending artery (LAD) through the left fourth intercostal space. Four weeks after ameroid placement, cardiac magnetic resonance imaging (MRI) was performed followed by random assignment of the minipigs into 4 treatment groups (all $n = 6$): saline alone (sham group), saline combined with pedicled omental flap (OM group), saline-dissolved ONO-1301SR (ONO group), and saline-dissolved ONO-1301SR combined with a pedicled omental flap (combined group).