Impact of cardiac support device combined with slow-release prostacyclin agonist in a canine ischemic cardiomyopathy model

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Background: The cardiac support device supports the heart and mechanically reduces left ventricular (LV) diastolic wall stress. Although it has been shown to halt LV remodeling in dilated cardiomyopathy, its therapeutic efficacy is limited by its lack of biological effects. In contrast, the slow-release synthetic prostacyclin agonist ONO-1301 enhances reversal of LV remodeling through biological mechanisms such as angiogenesis and attenuation of fibrosis. We therefore hypothesized that ONO-1301 plus a cardiac support device might be beneficial for the treatment of ischemic cardiomyopathy.

Methods: Twenty-four dogs with induced anterior wall infarction were assigned randomly to 1 of 4 groups at 1 week postinfarction as follows: cardiac support device alone, cardiac support device plus ONO-1301 (hybrid therapy), ONO-1301 alone, or sham control.

Results: At 8 weeks post-infarction, LV wall stress was reduced significantly in the hybrid therapy group compared with the other groups. Myocardial blood flow, measured by positron emission tomography, and vascular density were significantly higher in the hybrid therapy group compared with the cardiac support device alone and sham groups. The hybrid therapy group also showed the least interstitial fibrosis, the greatest recovery of LV systolic and diastolic functions, assessed by multidetector computed tomography and cardiac catheterization, and the lowest plasma N-terminal pro-B-type natriuretic peptide levels ($P < .05$).

Conclusions: The combination of a cardiac support device and the prostacyclin agonist ONO-1301 elicited a greater reversal of LV remodeling than either treatment alone, suggesting the potential of this hybrid therapy for the clinical treatment of ischemia-induced heart failure. (J Thorac Cardiovasc Surg 2014;147:1081-7)

Left ventricular (LV) remodeling in ischemic and nonischemic dilated cardiomyopathy is characterized by progressive dilatation and dysfunction of the left ventricle, leading to severe heart failure.[1,2] The cardiac support device is a mesh net designed to reduce diastolic ventricular wall stress by mechanical means and thus prevent LV dilatation. It has been shown to halt LV remodeling in dilated cardiomyopathy in preclinical studies.[3-5] Clinical trials undertaken on the basis of these favorable results showed beneficial effects on LV remodeling, including significantly decreased LV end-systolic (LVESV) and end-diastolic volumes (LVEDV), and a significant improvement in New York Heart Association functional class.[6-8] However, despite these positive effects, the device has not been associated with reductions in mortality and has not been approved for clinical use.[9]

The synthetic prostacyclin agonist ONO-1301 acts as a myocardial regenerative biological drug to enhance reversal of LV remodeling.[10-12] The beneficial effects of ONO-1301 on the heart are mediated by up-regulation of angiogenic and antifibrotic molecules, such as hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), and stromal cell–derived factor-1 (SDF-1).[10-12] This mechanism has been shown to result in the active suppression of ischemic and fibrotic changes in the myocardium.[10-12]

We hypothesized that the biological effects of the slow-release form of the synthetic prostacyclin agonist ONO-1301 might complement the mechanical effects of the cardiac support device, thus enhancing its therapeutic effects in ischemic cardiomyopathy.

MATERIALS AND METHODS

All animals used in this study received care in compliance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health publication no. 85-23, revised 1996).

Animal Treatment

A total of 28 beagles (Oriental Yeast, Co, Ltd, Tokyo, Japan) weighing 9 to 11 kg were used. General anesthesia was administered with intramuscular ketamine (10 mg/kg) and intravenous propofol (5 mg/kg) for induction,

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Abbreviations and Acronyms

ANOVA	= analysis of variance
dp/dt	= delta pressure/delta time
Ees	= end-systolic elastance
HGF	= hepatocyte growth factor
LV	= left ventricular
LVEDV	= left ventricular end-diastolic volume
LVESV	= left ventricular end-systolic volume
MDCT	= multidetector computed tomography
MI	= myocardial infarction
NT-proBNP	= amino-terminal pro-brain natriuretic peptide
SDF-1	= stromal cell–derived factor-1
VEGF	= vascular endothelial growth factor

and inhaled sevoflurane (1%–2%) for subsequent maintenance, with endotracheal intubation and mechanical ventilator support. After completion of the experiments, the animals were killed under general anesthesia, using an overdose of intravenous sodium pentobarbital (18 mg/kg) to achieve complete sedation, followed by administration of an intravenous potassium-based solution.

Myocardial Infarction Induction

With the animals under general anesthesia, a minimal left thoracotomy was performed through the fifth intercostal space, and the heart was exposed by pericardiotomy. The left descending artery and diagonal vessels were ligated both proximally and distally using 5-0 polypropylene sutures to produce an anterior myocardial infarction (MI). Akinesis of the anterior wall was confirmed by epicardial echocardiography and the chest was closed in layers. The animals were allowed to recover.

Cardiac Support Device

The cardiac support device (0.9–1.0 g), made from polyglycolic acid (Nipro Corporation, Osaka, Japan), was designed on the basis of data obtained from multidetector computed tomography (MDCT) and a heart excised at 1 week postinfarction.

Treatments

The animals were assigned randomly to 1 of 4 groups at 1 week after infarct induction as follows: cardiac support device alone, cardiac support device plus ONO-1301 (hybrid therapy), ONO-1301 alone, or sham control group. In the cardiac support device alone group, 2 sheets of atelocollagen (50 × 50 mm) (Integran; Nippon Zoki Pharmaceutical Co, Ltd, Osaka, Japan) immersed in suspended polylactic and glycolic acid (10 mg/kg) were fixed on the whole surface of the ventricles and the cardiac support device was placed as described previously.[3-5] The same procedure was used in the hybrid therapy group, with the addition of ONO-1301[10-12] (10 mg/kg) (ONO Pharmaceutical Co, Ltd, Osaka, Japan) instead of the polylactic and glycolic acid. In the ONO-1301 alone group, 2 sheets of atelocollagen (50 × 50 mm) immersed in suspended ONO-1301 (10 mg/kg) were fixed on the whole surface of the ventricles. The sham group was subjected to the same procedures as the ONO-1301 alone group, except for the use of polylactic and glycolic acid instead of ONO-1301.

Transthoracic Echocardiography

Transthoracic echocardiography was performed using a 5.0-MHz transducer (Altida; Toshiba Medical Systems Corporation, Tochigi, Japan) for 2-dimensional speckle-tracking echocardiography under general anesthesia. The data were analyzed using 2-dimensional Wall Motion Tracking software (Toshiba Medical Systems Corporation) as previously described.[13]

MDCT

Electrocardiography-gated MDCT was performed using a 16-row MDCT scanner (SOMATOM Emotion 16-Slice Configuration; Siemens, Munich, Germany) during an end-expiratory breath-hold under general anesthesia. MDCT was performed after intravenous injection of 30 mL of nonionic contrast medium (Iomeron; Bracco, Milan, Italy). All images were analyzed on a workstation (AZE VirtualPlace Lexus64; AZE, Tokyo, Japan). LVEDV and LVESV, LV ejection fraction, LV end-diastolic and end-systolic sphericity indices, and LV/right ventricular end-diastolic and end-systolic diameter values were obtained from the workstation.

Cardiac Catheterization

Under general anesthesia, a 3F micromanometer-tipped catheter (SPR-249; Millar Instruments, Houston, Tex) was inserted through the ventricular apex via a left thoracotomy to measure hemodynamic parameters and cardiac functions, including end-systolic pressure and end-diastolic pressure, delta pressure/delta time (dp/dt) maximum, dp/dt minimum, end-systolic elastance (Ees), and the time constant of relaxation in the left and right ventricles. LV volume was altered by occluding the inferior vena cava with tape via a left thoracotomy.

Wall Stress Calculation

LV wall stress was evaluated using specifically developed software (YD, Ltd, Tokyo, Japan) on an off-line personal computer. Global end-systolic and end-diastolic wall stresses were calculated on the basis of the data obtained from MDCT and cardiac catheterization.[14]

Cardiac Positron Emission Tomography

^{13}N-ammonia (200–300 MBq) positron emission tomography (PET) was performed using a HeadtomeV/SET2400W (Shimadzu, Co, Kyoto, Japan) under general anesthesia. Myocardial blood flow was quantitated using PMOD software (version 3.2) (PMOD Technologies, Ltd, Zurich, Switzerland) and divided into 17 segments as recommended by the American Heart Association.

Histologic Analysis

Paraffin-embedded transverse sections of the excised hearts were stained with periodic acid-Schiff to measure the short-axis diameter of the myocytes, and with Masson trichrome to assess the extent of fibrosis. The sections were immunostained with anti-CD31 antibody in LSAB kits (DakoCytomation, Glostrup, Denmark). Myocyte diameters and vascular density were measured in 10 different randomly selected fields using a Biorevo BZ-9000 fluorescence microscope (Keyence, Osaka, Japan), and percentage fibrosis was calculated using MetaMorph software (Molecular Devices, Tokyo, Japan).

Real-Time Polymerase Chain Reaction

Total RNA extracted from cardiac tissue was reverse-transcribed using TaqMan reverse transcription reagents (Applied Biosystems, Foster City, Calif), and assayed using the ABI PRISM 7700 (Applied Biosystems). The average copy number of gene transcripts was normalized to that of glyceraldehyde 3-phosphate dehydrogenase for each sample.

Statistical Analysis

All statistical analyses were performed using JMP software (JMP9; SAS institute, Inc, Cary, NC). Results are presented as the mean ± standard deviation. Cardiac catheterization and histologic data were compared by 1-way analysis of variance (ANOVA). MDCT, echocardiography, wall stress, and amino-terminal pro-brain natriuretic peptide (NT-proBNP)

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