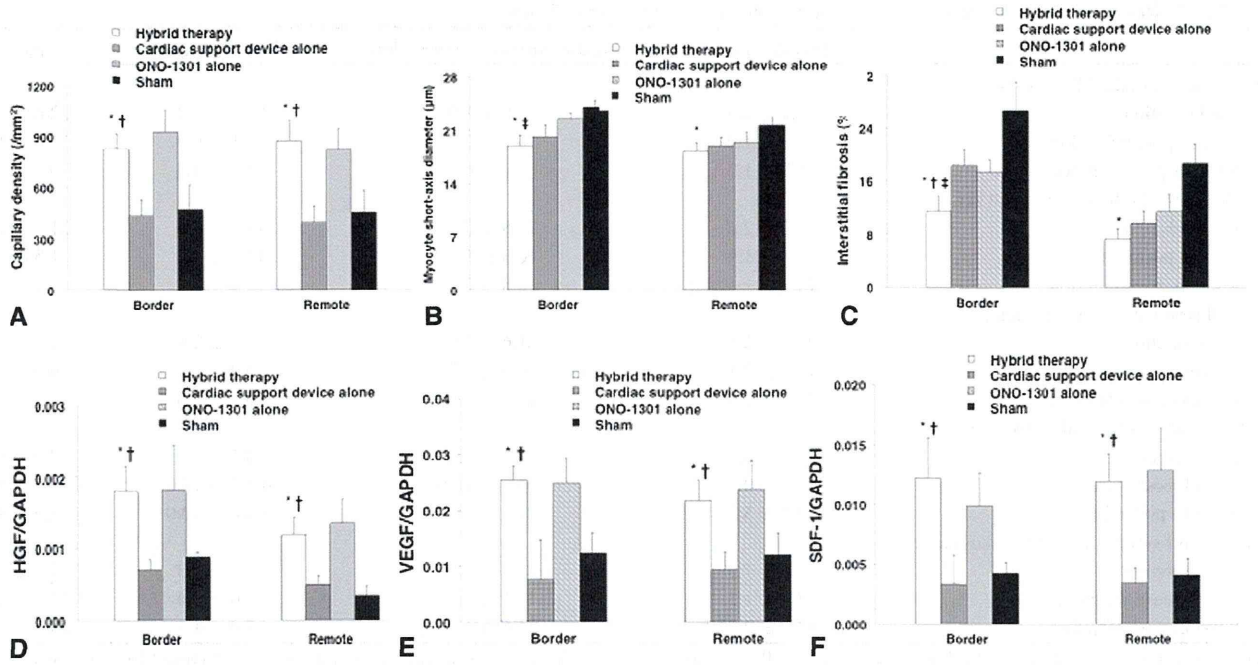

FIGURE 3. Histologic evaluation at 8 weeks postinfarction. A, Capillary density, (B) myocyte short-axis diameter, and (C) interstitial fibrosis in the border and remote areas. Expression levels of (D) HGF, (E) VEGF, and (F) SDF-1 in the border and remote areas quantified by real-time polymerase chain reaction at 8 weeks postinfarction. *$P < .05$ versus sham, †$P < .05$ versus cardiac support device alone. *GAPDH*, Glyceraldehyde 3-phosphate dehydrogenase; *HGF*, hepatocyte growth factor; *VEGF*, vascular endothelial growth factor; *SDF-1*; stromal cell–derived factor-1.

Up-Regulation of Cardiac Protective Factors

Real-time polymerase chain reaction was performed at 8 weeks postinfarction to determine the effects of the treatment on gene expression of major cardiac protective factors, such as HGF, VEGF and SDF-1 (Figure 3, *D-F*). Expression of HGF, VEGF, and SDF-1 in both the border and remote areas were similar in the hybrid therapy and ONO-1301 groups, and significantly higher in these 2 groups than in the cardiac support device alone and sham groups ($P < .05$).

DISCUSSION

This study examined the therapeutic efficacy of hybrid therapy, comprising a cardiac support device and a synthetic prostacyclin agonist (ONO-1301), in a canine model of ischemic cardiomyopathy, compared with the efficacy of either treatment alone. Hybrid therapy significantly improved both systolic and diastolic functions and reduced LV wall stress compared with the other treatments, and histologic examination indicated significantly greater reversal of LV remodeling in the hybrid therapy group. These results were reflected by a significantly greater reduction of NT-proBNP by hybrid therapy.

The cardiac support device used in this study comprised a net made of polyglycolic acid, which is a hydrolytically bioabsorbable polymer. This represents a major difference from the net used in previous studies,[3-5] and was designed to remain around the heart for approximately 10 weeks by adjusting the diameter of the thread. The cardiac support device remained in place at 8 weeks postinfarction, although it had become hydrolyzed to some extent. Our net was functionally equivalent to the nets used in previous studies; it prevented dilatation of the left ventricle, improved the LV sphericity index, and reduced diastolic LV wall stress, thus avoiding the positive feedback loop of cardiac dilatation, the change from an efficient ellipsoidal to a spherical LV chamber, interstitial fibrosis, and, ultimately, heart failure that occurs in ischemic dilated cardiomyopathy.[9] However, one disadvantage of this bioabsorbable net is that it could allow LV remodeling to progress after absorption. The present study did not investigate this aspect and further studies are needed to assess the relative advantages and disadvantages of bioabsorbable and nonabsorbable cardiac support devices.

ONO-1301 is a synthetic prostacyclin agonist that is not yet used in clinical practice. However, several experimental studies have shown its therapeutic efficacy in ischemic and nonischemic cardiomyopathy.[10-12] ONO-1301 was administered to the heart differently in the current study compared with previous studies,[10-12] but its plasma concentrations and reversal of LV remodeling were similar to those seen in previous studies, suggesting that this mode of administration was appropriate. In addition, ONO-1301 administration by incorporation in the cardiac support device could decrease

adverse effects such as hypotension, which may occur with systemic administration. Finally, LV remodeling generally progresses slowly, and long-term drug efficacy therefore is necessary. ONO-1301 has a slow-release time of approximately 4 weeks, and thus may be a suitable agent for the prevention of remodeling.

The favorable results of the current study regarding use of hybrid therapy may be attributed to the angiogenic and active antifibrotic effects of ONO-1301, acting via HGF, VEGF, and SDF-1, which complemented the mechanical effects of the cardiac support device with a consequent enhancement of therapeutic efficacy. Up-regulation of these cytokines and increased capillary density were observed in the hybrid therapy group, whereas PET examination showed significantly greater myocardial blood flow in the hybrid therapy group compared with the cardiac support device alone and sham groups. The additional benefits of ONO-1301 resulted in enhanced recovery of radial wall strain and the suppression of interstitial fibrosis in the border area in the hybrid therapy group, with consequent recovery of cardiac function.

This study was limited by the use of a canine model, which may not completely reflect clinical ischemic cardiomyopathy pathologies. In this experiment, there was no atherosclerosis, and no use of drugs such as β-blockers and angiotensin-converting enzyme inhibitors, which might be used in the clinical arena. However, a similar canine ischemic cardiomyopathy model has been established previously,[2,12] and it is possible to use this model to assess cardiac function and evaluate the therapeutic effects of interventions. Our model therefore was deemed adequate to show the therapeutic effects of the hybrid therapy with various modalities used in the clinical arena. However, this model may not be suitable for further studies of the mechanisms of hybrid therapy, and rodent models may be better suited for such investigations. This study also was limited in that it was not clear whether remodeling would remain suppressed even after complete absorption of the cardiac support net because the net remained at the end of this study. Therefore, longer-term studies lasting after absorption of the biodegradable net will be necessary.

The authors thank Shigeru Matsumi, Toshika Senba, Masako Yokoyama, and Akima Harada for excellent technical assistance.

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