

A novel therapeutic approach for coronary inflammation and lymphatic vessels using non-invasive low-intensity pulsed ultrasound in a porcine model with DES-induced coronary hyperconstricting responses

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Background: The coronary adventitia harbors lymphatic vessels (LVs). We previously demonstrated that coronary adventitial inflammation and LV dysfunction play important roles in the pathogenesis of coronary artery spasm, including drug-eluting stent (DES)-induced coronary hyperconstricting responses, in pigs and humans. However, a direct therapeutic approach to the coronary adventitia remains to be developed.

Purpose: In this study, we aimed to examine whether our novel and non-invasive therapy with low-intensity pulsed ultrasound (LIPUS) ameliorates DES-induced coronary hyperconstricting responses, and if so, what mechanisms are involved.

Methods: An everolimus-eluting stent (EES) was implanted into the left anterior descending (LAD) coronary artery in normal male pigs. They were randomly assigned to the LIPUS or the sham therapy groups. After EES implantation, in the LIPUS group, LIPUS (32 cycles, 193 mW/cm²) was applied to the heart at 3 different levels (proximal and distal stent edges and middle portion of the stent) through X-ray fluoroscopy for 20 min at each level for every other day for 2 weeks (6 days in total) (Fig. 1A, B). The sham therapy group was treated in the same manner but without LIPUS. At 4 weeks after the procedure, we performed coronary angiography to examine coronary vasoconstricting responses to intracoronary serotonin in vivo. Finally, stented coronary vessels were harvested for immunohistochemistry of vasa vasorum (vWF), LVs (LYVE-1), vascular inflammation

(CD68-positive macrophages and IL-1 β expression), vascular endothelial growth factor A (VEGF-A, angiogenesis marker), VEGF-C and VEGF receptor 3 (VEGFR3, lymphangiogenesis markers).

Results: Coronary vasoconstricting responses to intracoronary serotonin at the DES edges in the LAD were significantly enhanced in the sham group but were significantly suppressed in the LIPUS group, while those responses were comparable at the non-DES implanted left circumflex (LCx) coronary artery between the 2 groups (Fig. 1C, D). In addition, in vivo lymph transport speed was significantly faster in the LIPUS group than in the sham group (Fig. 1E–G). In histological analysis, the number of LVs was significantly increased in the LIPUS group compared with the sham group, whereas those of CD68 and IL-1 β expressions were significantly reduced in the LIPUS group compared with the sham group. In contrast, the density of vasa vasorum was comparable between the 2 groups. Mechanistically, the extents of VEGF-C and VEGFR3 expressions were increased in the LIPUS group, whereas that of VEGF-A was comparable between the 2 groups (Fig. 1G–K). Importantly, there were significant correlations among the LV-related changes and enhanced coronary vasoconstricting responses.

Conclusion: These results provide the first evidence that the LIPUS therapy ameliorates DES-induced coronary hyperconstricting responses in pigs in vivo through structural and functional alterations of LVs (Fig. 1L).

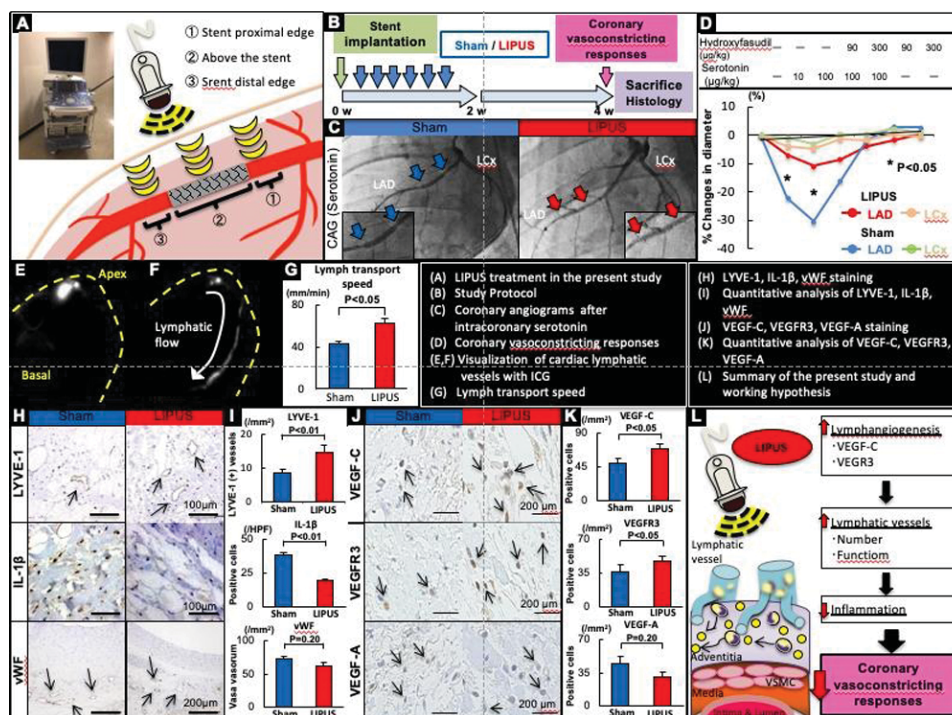


Figure 1