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EDITORIAL

The Future of Non-Invasive Angiogenic Therapy Using Acoustic Waves

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As the population ages, the morbidity of cardiovascular disorders such as ischemic heart disease (IHD) and peripheral arterial disease (PAD) is increasing in developed countries.[1,2] Therefore, new, non-invasive therapeutic strategies are expected. In the early 21 century, attempts at applying acoustic waves to the treatment of IHD started. Shock waves (SW), a type of acoustic wave, were clinically introduced more than 30 years ago as extracorporeal shock wave lithotripsy (ESWL), which markedly alleviated the invasiveness of treatment of urolithiasis. In the 2000s, we and others have reported that low-energy SW (≈10% of the energy density used for urolithiasis) upregulated vascular endothelial growth factor (VEGF) and nitric oxide in human cultured endothelial cells.[3,4] Based on those findings, we have developed low-energy extracorporeal cardiac SW therapy. Low-energy SW therapy enhanced the expression of VEGF, capillary growth, myocardial perfusion and contractile function in a pig model of chronic myocardial ischemia.[3] and also improved symptoms, myocardial perfusion and exercise tolerance in patients with severe angina pectoris for the first time.[5,6] In addition, low-energy SW therapy improves the walking ability of patients with PAD and intermittent claudication.[7] Ultrasound, another type of acoustic wave, is widely used for ultrasound diagnostic devices and also applied clinically at high intensity to tumor ablation, related mainly to its thermal effect. Recently, low-intensity pulsed ultrasound (LIPUS) was reported to exert angiogenic effects in a rat model of hindlimb ischemia.[8] We also demonstrated that LIPUS improved myocardial ischemia in a pig model of chronic myocardial ischemia to the same extent as low-energy SW therapy.[9]

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In this issue of the Journal, Nazer et al compare the therapeutic effects of LIPUS with those of SW in a rat model of hindlimb ischemia.[10] They report that LIPUS was more effective than SW in promoting hindlimb perfusion when their peak negative pressures were matched. This work is interesting

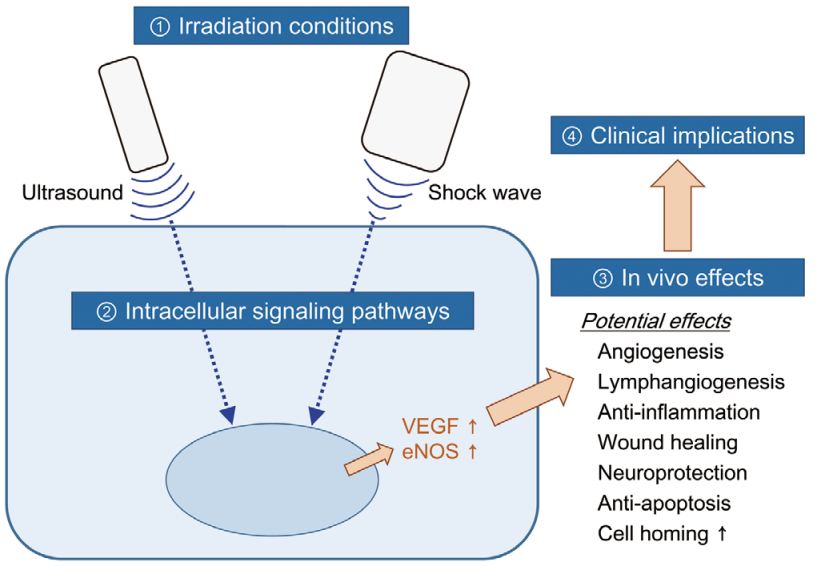

Figure. Research foci in the acoustic wave-induced regenerative therapy. (**1**) Irradiation conditions, (**2**) intracellular signaling pathways, (**3**) in vivo effects, (**4**) clinical implications. eNOS, endothelial nitric oxide synthase; VEGF, vascular endothelial growth factor.

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because the angiogenic effects of 2 types of acoustic wave are directly compared under certain conditions of irradiation. Because, however, there is a wide variety of parameters of the acoustic wave that may potentially affect the angiogenic effects of LIPUS or SW, the irradiation settings in this study may not be always optimal for each therapy. It is also possible that the optimal irradiation condition might vary by organ or by disease. In addition to angiogenic effects, other actions, such as anti-inflammatory effects and neuroprotection, by acoustic waves have been reported in animals and humans.[11–13] To find the optimal treatment conditions for LIPUS therapy and SW therapy, we may need to elucidate the intracellular signaling pathways responsible for mediating angiogenesis and other effects. Further studies are needed.

Another approach to the use of acoustic waves is the combination of cell therapy. Low-energy SW therapy was reported to facilitate stem and progenitor cell therapy by pretreating the ischemic myocardium or the cells.[14,15] Recently, Assmus et al reported that an improvement of contractile function with intracoronary administration of autologous bone marrow-derived mononuclear cells was enhanced by SW therapy in patients with ischemic cardiomyopathy.[15] These positive results need to be confirmed in larger clinical trials.

Because of their non-invasive nature, both LIPUS and SW are promising strategies for the treatment of IHD and PAD, especially in elderly patients. This research field is still under development (**Figure**). Collaborations between clinicians and engineers may facilitate and expand the future of non-invasive regenerative therapies.

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