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EDITORIAL
Miscellaneous

Therapeutic potentials of sound waves in cardiovascular medicine: further important evidence

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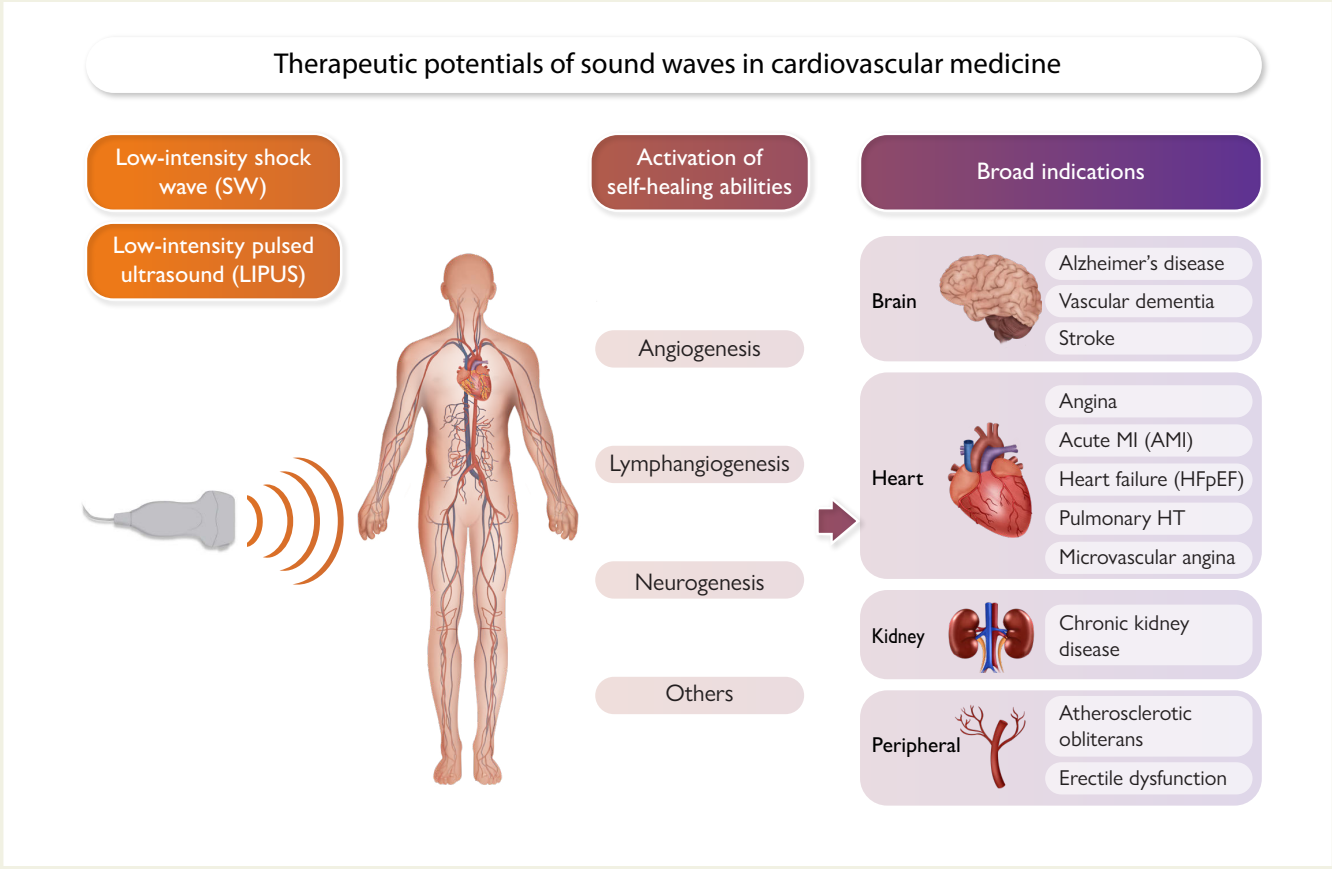
This editorial refers to 'Cardiac shockwave therapy in addition to coronary bypass surgery improves myocardial function in ischaemic heart failure: the CAST-HF trial', by J. Holfeld et al., https://doi.org/10.1093/eurheartj/ehae341.

Graphical Abstract



Therapeutic potentials of sound wave therapies with shock wave (SW) and low-intensity pulsed ultrasound (LIPUS). The SW and LIPUS therapies could activate self-healing abilities depending on disease-specific conditions, including angiogenesis in ischaemic tissue, lymph-angiogenesis in oedematous tissue, neurogenesis in damaged nervous tissue, and others. These sound therapies appear to have broad indications for the brain, heart, kidney and peripheral arteries in cardiovascular medicine. AMI, acute myocardial infarction; HFpEF, heart failure with preserved LV ejection fraction.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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In our body, many potential self-healing abilities remain and could be activated in response to exercise and other adequate physical stimuli. Sound waves, such as low-intensity shock wave (SW) and low-intensity pulsed ultrasound (LIPUS), provide such adequate mechanical stimuli to promote various self-healing responses through the so-called 'mechanotransduction' mechanism.[1–3] Indeed, it is interesting to note that sound-wave therapies with SW or LIPUS induce disease-specific regenerative responses, including angiogenesis in ischaemic tissue, lymph-angiogenesis in oedematous tissue, neurogenesis in damaged nervous tissues, and others through improvement of microvascular dysfunction (*Graphical Abstract*).[1] This therapeutic approach to stimulate endogenous self-healing abilities with sound waves appears to be feasible and promising in terms of efficacy, safety and medical cost as compared with the molecular biological approach with exogenous materials, such as genes or cells.[1] Interestingly, SW and LIPUS share the same intracellular molecular mechanisms for mechanotransduction, involving the β1-integrin/caveolin-1 complex in the endothelial caveolae followed by up-regulation of endothelial nitric oxide synthase (eNOS).[4,5] Angiogenic and thus anti-ischaemic effects of low-energy SW were first described in a porcine model of chronic myocardial ischaemia[6] and then in patients with severe coronary artery disease.[7,8]

In this issue of the Journal,[9] Holfeld *et al*. added important evidence to the literature of therapeutic potentials of sound waves in cardiovascular medicine. In their single-blind, parallel-group, sham-controlled trial (CAST-HF), patients with left ventricular ejection fraction (LVEF) < 40% requiring surgical revascularization were enrolled. The patients were randomly assigned to undergo direct cardiac SW therapy ($n = 30$) or sham treatment ($n = 28$) in addition to coronary artery bypass grafting (CABG) surgery and were followed up for one year. The results showed that improvement in LVEF measured by cardiac MRI (primary endpoint) was greater in the SW group than in the sham treatment group (△ from baseline to 360 days: SW 11.3% vs. Sham 6.3%, $P = .0146$), which was also the case for improvement in 6-min walk distance (△ from baseline to 360 days: SW 127.5 m vs. Sham 43.6 m, $P = .028$), whereas no difference was noted between the two groups for Minnesota Living with Heart Failure Questionnaire (SW 11.0 point vs. Sham 17.3 point, $P = .15$). In contrast to the previous studies with extracorporeal cardiac SW therapy,[7,8] the authors employed direct SW therapy during CABG surgery after complete revascularization, while still on cardiopulmonary bypass.[9] The SW irradiation conditions were also different; in this study by Holfeld *et al*., 300 impulses for coronary supply territory for all three coronary territories due to three vessel disease, intensity of 0.38 mJ/mm^2 and a frequency of 3 Hz,[9] whereas in the previous studies, 200 shots/spot for 20∼40 spots (depending on the extent of ischaemic myocardium), intensity of 0.09 mJ/mm^2 and in a manner of heart rate synchronization.[7,8] Nonetheless, the impact of the SW therapy on cardiac function in the study by Holfeld *et al*. is meaningful in daily practice, suggesting the usefulness of the routine use of the SW therapy during CABG surgery for patients with ischaemic heart failure. It is also interesting to note that the authors demonstrated the involvement of innate immune receptor Toll-like receptor 3 (TLR3) pathway in the effects of the SW therapy.[10] This suggests the cross-talk between the TLR3 and the eNOS pathways in the effects of the SW therapy. In addition to the discussion by the authors on the study limitations,[9] several points remain to be examined. First, the potential usefulness of additional extracorporeal cardiac SW therapy after this intraoperative SW therapy remains to be examined in future studies. Second, it remains to be elucidated whether the intraoperative therapy improves cardiac diastolic function in addition to systolic function, as demonstrated with the LIPUS therapy.[11] Third, it remains to be examined whether this intraoperative SW therapy actually improves long-term prognosis of patients with ischaemic heart failure.

Some comments should be made on the LIPUS therapy.[1] Specific irradiation conditions of LIPUS (32 cycles, 0.25 W/cm^2, 1.875 MHz for the heart and 0.5 MHz for the brain) have been demonstrated to induce similar biological effects as SW.[1] LIPUS therapy may have some advantages over SW therapy in terms of efficacy and safety, including shorter treatment time (as compared with extracorporeal SW therapy) and no harmful effects on the lung, etc. LIPUS therapy has been suggested to be effective and safe for severe angina[12,13] and also Alzheimer's disease.[14,15] For Alzheimer's disease, it has been demonstrated that multiple neuroprotective responses are up-regulated in the whole brain in response to the LIPUS stimulation.[14] This is in contrast to the fact that drug therapies need a certain therapeutic target for drug development, which may cause polypharmacy issue, and cell therapies, where the fate of exogenously administered cells may not be completely controlled. Currently, new therapies remain to be developed for major organ diseases, including dementia in the brain, heart failure in the heart and chronic kidney disease in the kidney, where microvascular dysfunction plays a major pathogenetic role.[1] Sound-wave therapies appear to be promising modalities to treat these diseases through improvement of microvascular dysfunction (*Graphical Abstract*).[1]

In conclusion, sound-wave therapies with SW or LIPUS are a new emerging class of therapy to activate self-healing abilities depending on disease-specific conditions with reasonable efficacy and safety and appear to have broad indications as compared with current drug therapies and cell therapies (*Graphical Abstract*).

Declarations

Disclosure of Interest

HS is the founder and executive chairman of the Sound Wave Innovation, Ltd. (https://sw-innovation.com/).

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