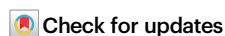


A fully degradable triboelectric vagus nerve stimulator for attenuating cardiac remodeling and heart failure at different stages

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Heart failure affects approximately 56 million people worldwide with a 5-year mortality rate exceeding 50%, necessitating new therapeutic strategies. Although low-level vagus nerve stimulation shows promise for treating heart failure, existing devices are limited by short battery life, lack of degradability, and insufficient adaptability to disease progression. Here we develop a fully biodegradable triboelectric nanogenerator for self-powered vagus nerve stimulation that prevents and reverses myocardial remodeling through acetylcholine release modulation. In a murine heart failure model, the device generates 9.07 ± 0.43 V open-circuit voltage and 4.19 ± 0.14 μ A short-circuit current, enabling stable stimulation for 4 weeks with rapid ultrasound-triggered degradation. We show that device-based vagus nerve stimulation significantly improves cardiac function, attenuates pathological remodeling, and favorably modulates heart failure-related gene expression across multiple disease stages. This technology eliminates battery replacement surgeries and device removal procedures, establishing a paradigm for personalized, stage-specific heart failure therapy.

Heart failure (HF) affects approximately 56 million people worldwide, with a 5-year mortality rate exceeding 50% and annual healthcare costs reaching \$108 billion globally^{1,2}. In pressure overload conditions such as aortic stenosis and hypertensive heart disease, cardiac remodeling represents an initially adaptive response to chronic stress that becomes maladaptive, leading to ventricular dilation, hypertrophy, and increased fibrosis^{3–5}. Current treatments including pharmacological interventions

(angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers) and mechanical devices (cardiac resynchronization therapy and implantable cardioverter-defibrillators) have improved outcomes but remain limited by variable patient response, side effects, and procedural risks, highlighting the need for therapeutic strategies^{6,7}.

The autonomic nervous system plays a crucial role in HF progression, with excessive sympathetic activation and diminished

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parasympathetic tone creating a pathological imbalance that accelerates cardiac dysfunction^{8,9}. To address this imbalance, vagus nerve stimulation (VNS) has emerged as a promising neurotherapeutic approach. Preclinical studies demonstrate that VNS improves cardiac autonomic control, reduces ventricular volumes, and increases LVEF through anti-inflammatory mechanisms^{10,11}. Clinical trials (INOVATE-HF, NECTAR-HF, ANTHEM-HF) have shown that VNS improves quality of life and functional capacity in HF patients, though effects on mortality and cardiac remodeling require further investigation^{11–13}.

Building upon these findings, low-level VNS (LL-VNS) has emerged as a safer alternative to conventional high-level stimulation. LL-VNS provides subliminal stimulation that effectively modulates cardiac ganglion plexuses without disrupting normal heart rhythms or affecting atrioventricular conduction^{14–16}. However, significant knowledge gaps remain regarding the optimal timing of LL-VNS intervention across different stages of HF progression and the mechanisms underlying stage-specific therapeutic responses¹⁷.

Current VNS devices face substantial technological limitations, including reliance on battery-powered pulse generators with finite lifespans, necessitating repeated surgical replacements and creating long-term foreign body risks. These constraints have driven interest in biodegradable alternatives, with triboelectric nanogenerators (TENGs) emerging as promising solutions due to their ability to harvest

mechanical energy from body movements and potential for complete biodegradation^{18,19}. Ultrasound can power implantable TENG systems, enabling battery-free wireless operation for biomedical applications²⁰. Biodegradable VNS devices could provide targeted therapeutic intervention during critical disease stages and then safely degrade in vivo, eliminating surgical removal and enabling stage-specific treatment approaches.

Here, we develop and evaluate a fully biodegradable triboelectric nanogenerator (BTENG) system for self-powered LL-VNS that could effectively prevent and reverse pressure overload-induced myocardial remodeling and HF across multiple disease stages by modulating acetylcholine release pathways. We sought to establish optimal LL-VNS parameters, develop a BTENG system with appropriate output characteristics (an open-circuit voltage of 9.07 ± 0.43 V and a peak-to-peak short-circuit current of 4.19 ± 0.14 μ A), demonstrate controlled biodegradation with ultrasound acceleration (Fig. 1a), and evaluate therapeutic efficacy in a murine aortic banding model across three intervention timepoints: prevention before remodeling, early intervention during initial remodeling, and treatment of established HF (Fig. 1b).

This technology provides a clinically translatable solution that eliminates battery replacement surgeries, enables stage-specific treatment withdrawal, and provides a paradigm for personalized

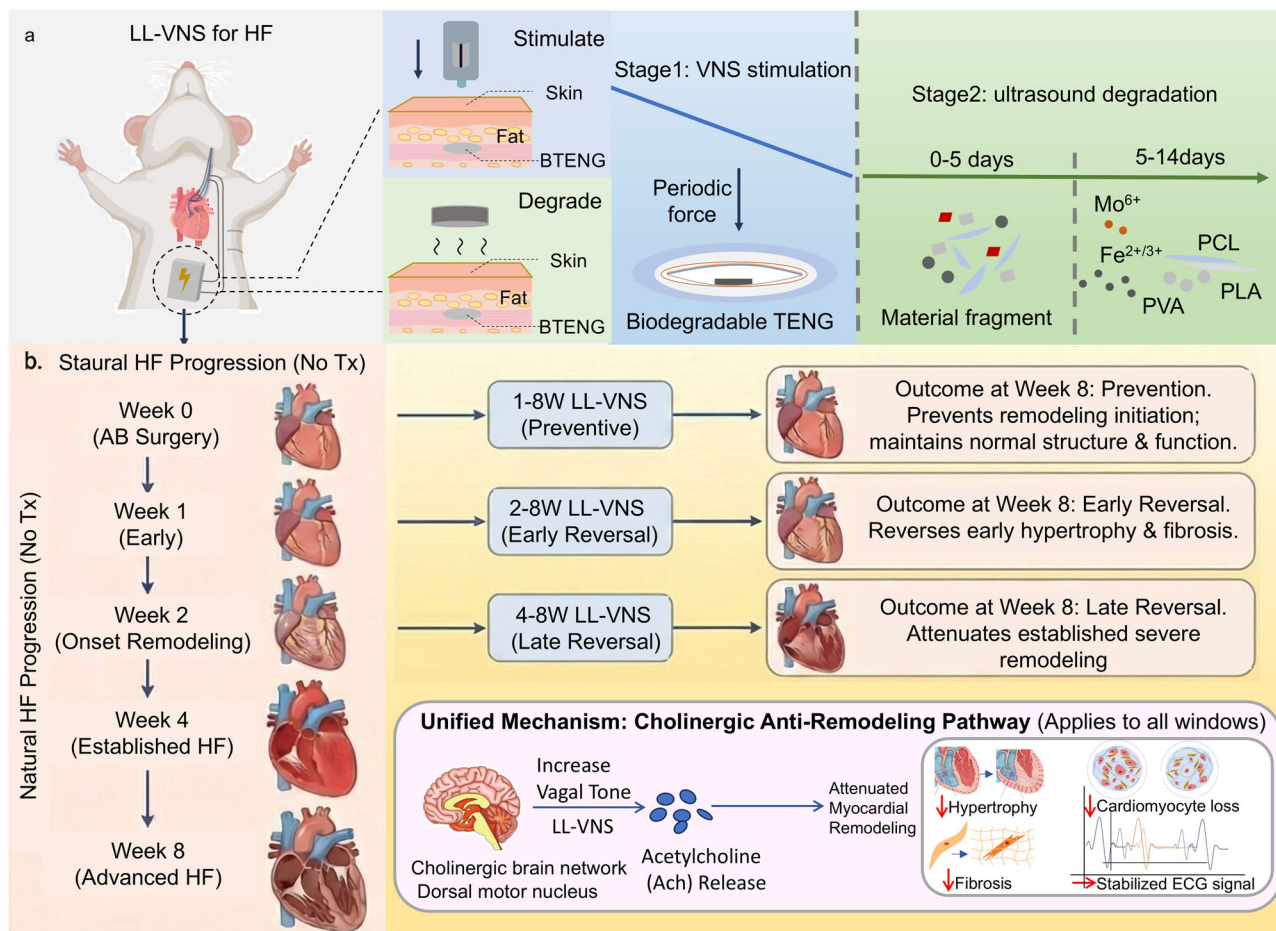


Fig. 1 | Diagram of the fully degradable triboelectric vagus nerve stimulator for heart failure patients. Schematic overview of the biodegradable triboelectric nanogenerator (BTENG) system for vagus nerve stimulation therapy. **a** Two-stage approach: (stage 1) device implantation and low-level vagus nerve stimulation (LL-VNS) therapy powered by body movement, and (stage 2) ultrasound-triggered device degradation (0–5 days) followed by material fragmentation and metabolic clearance (5–14 days). Degradation products include molybdenum ions (Mo^{6+}), iron

ions ($\text{Fe}^{2+/3+}$), polyvinyl alcohol (PVA), polycaprolactone (PCL), and polylactic acid (PLA). **b** Treatment timeline for three intervention strategies in the aortic banding (AB) mouse model with unified 8-week endpoint: preventive intervention (LL-VNS weeks 1–8, 7 weeks total), early intervention (LL-VNS weeks 2–8, 6 weeks total), and late intervention (LL-VNS weeks 4–8, 4 weeks total). Right panel: proposed cholinergic mechanism whereby LL-VNS activates the dorsal motor nucleus, leading to acetylcholine (ACh) release that acts on macrophages and cardiomyocytes.

cardiac neuromodulation therapy with significant potential to reduce healthcare costs while improving patient outcomes.

Results

Physiological and neuro-electrophysiological characterization of the effects of LL-VNS

To develop a clinically applicable LL-VNS system, we first established optimal stimulation parameters that could modulate cardiac function while maintaining safety margins. During the measurement process, gold electrodes were used to connect the nerve stimulation receiver and stimulator to the cervical vagus nerve, enabling it to receive and transmit electrical signals (Supplementary Fig. 1).

The threshold of LL-VNS was defined by Li's research team in 2009 as the maximum intensity for maintaining sinus rhythm. Half of the stimulation threshold is typically used by researchers as a safety parameter for long-term LL-VNS. Therefore, we designed a neural stimulation protocol to explore the LL-VNS threshold in experimental mice to determine the final stimulation intensity. We adopted a frequency of 2 Hz on the basis of heart rate and FDA-approved VNS applications. Moreover, we set up a current source nerve stimulator with low current and high resistance to ensure the accuracy of the VNS intensity (Supplementary Fig. 2a).

Heart rate variability (HRV), changes in electrocardiogram waveforms (which are closely related to cardiovascular status), and high-frequency power can reflect the physiological state of mice and the excitation state of the vagus nerve and were used as criteria for exploring the LL-VNS threshold. As shown in Fig. 2a, during 60-sec LL-VNS, the heart rates of the mice decreased. The heart rate decreased slowly at 0–8 μA (pp.) and decreased rapidly at 10 μA (pp.), indicating that 8 μA (pp.) was still within the stimulation threshold range. Figure 2b shows the heart rate and HRV data. With increasing stimulation intensity, the HRV increased within the range of 0–15 μA (pp.), which was not obvious after 8 μA (pp.). Within the range of 0–15 μA (pp.), the rate of change in heart rate decreased significantly and then increased slowly afterward. As mentioned earlier, LL-VNS with an absolute heart rate change rate of 15% and an HRV value within 0.5 should be within the safe range, which indirectly proves that 8 μA (pp.) is the LL-VNS threshold. The calculated ΔHRV and vagus nerve signal power density values indicate that the HF power reaches the maximum value at 8 μA (pp.), and the ΔHRV value is close to the 0 point, which also proves that 8 μA (pp.) is the LL-VNS threshold (Fig. 2c). Overall, a stimulation intensity of 8 μA (pp.) was proven to be the LL-VNS threshold, and half of the threshold (4 μA) is typically regarded as a safe parameter for long-term neural stimulation, which was also demonstrated in our experiment (Supplementary Fig. 3).

We further verified the changes in the ECG (Fig. 2e) and downstream vagus nerve signals (Fig. 2f) of the mice before, during and after stimulation at a nerve stimulation intensity of 4 μA (pp.) (Fig. 2d), and the results indicated that the frequencies of the ECG and downstream vagus nerve signals remained basically unchanged before and after stimulation at this intensity. Short-term Fourier transform was used to analyze the MSA of downstream vagus nerve signals in the low-frequency region (0–50 Hz) and the high-frequency region (500 Hz), and the results indicated that this stimulation intensity caused excitation of the vagus nerve in the low-frequency region (Fig. 2g, h, and Supplementary Fig. 2b–d). Moreover, an analysis of neural signals before and after stimulation revealed that vagus nerve function was still not affected. These findings establish 4 μA peak-to-peak current at 2 Hz as optimal LL-VNS parameters for chronic cardiac therapy, representing 50% of the identified threshold with demonstrated safety margins and effective vagal modulation. This intensity achieved therapeutic vagal activation while preserving normal cardiac conduction and autonomic function, providing the foundation for subsequent device design and therapeutic evaluation.

Design and working principle of the BTENG

The BTENG developed in this study adopts a material system and structural design to meet the requirements of long-term electrical stimulation therapy. On the basis of the LL-VNS test results, a biodegradable triboelectric nanogenerator whose output can provide a neural stimulation output of 4 μA (pp.) was designed. The BTENG is composed of multiple functional components: the positive triboelectric layer comprises a composite system of polyvinyl alcohol (PVA) and microiron powder, and the negative triboelectric layer is a pure PVA film. Metal Mo was sputtered on the reverse side of the PVA film to form an electrical circuit. These two triboelectric layers achieve electrical output through low-frequency contact separation. The spacer layer is made of a fully freeze-dried hydrogel material to ensure the effective operation of the dynamic contact separation mechanism (Fig. 3a).

The encapsulation layer comprises a polycaprolactone-poly(lactic acid) (PCL-PLA) composite system, and controllable degradation was achieved through ultrasonic responsive design. The PCL coating provides waterproof performance and anti-degradation performance, whereas the PLA substrate is used to ensure the mechanical properties of the device. Under the special design of the modulus, the PCL layer and the PLA layer are more prone to stress concentration and damage in a high-frequency ultrasonic environment, which has also been proven in COMSOL physical field simulations (Supplementary Fig. 4a–d). This protection mechanism can not only maintain the functional stability of the device in the humoral environment but also accelerate the degradation process through ultrasonic triggering.

The working process of the TENG is shown in Fig. 3b. In the design, the contact-separation mode is employed, which minimizes the stress on the triboelectric layer actuator. In the initial state, the top layer is separated from the bottom layer, with no triboelectric potential existing between the electrodes. When force is applied to the device, the upper end deforms, causing the upper and lower triboelectric layers to come into contact. As the force increases, the contact area between the two triboelectric layers gradually increases. When full contact is achieved, the triboelectric potential reaches its peak. If an external circuit is used, an electric current flows during deformation of the TENG. When the force is removed, the upper and lower triboelectric layers revert to their original positions due to the action of the middle layer, causing the electrons to be driven back to their original positions by the triboelectric potential, thereby completing an electrical cycle.

As an implantable electrical stimulation output device, output efficiency and stability are the most important parameters. Thus, the output performance and operational stability of the device were characterized experimentally. As shown in Fig. 3c, d, the open-circuit voltage of the device was approximately 9.07 ± 0.43 V, and the short-circuit current (peak-to-peak, pp.) was 4.19 ± 0.14 μA (pp.). Notably, owing to the characteristics of the BTENG, the device output is an AC output, and the positive value and amplitude of the short-circuit current output differ significantly. To better calibrate the output current intensity of the device, we use the peak-to-peak value of the current for characterization in the following text.

The impedance range of the BTENG was subsequently characterized in detail. According to the results of the *in vitro* impedance test, the instantaneous power of the device can reach half of the maximum value within the external impedance range of $50\text{k}\Omega$ – $1\text{M}\Omega$. An LCR instrument was used to evaluate the electrical stimulation impedance and capacitive reactance of the vagus nerve in mice at 100 Hz. As shown in Supplementary Fig. 5a, b, the impedance range in mice was approximately 55 – $62\text{k}\Omega$, which can effectively match the performance state of the device (Fig. 3d, e, S6a). Finally, we conducted stability tests to evaluate the device's working

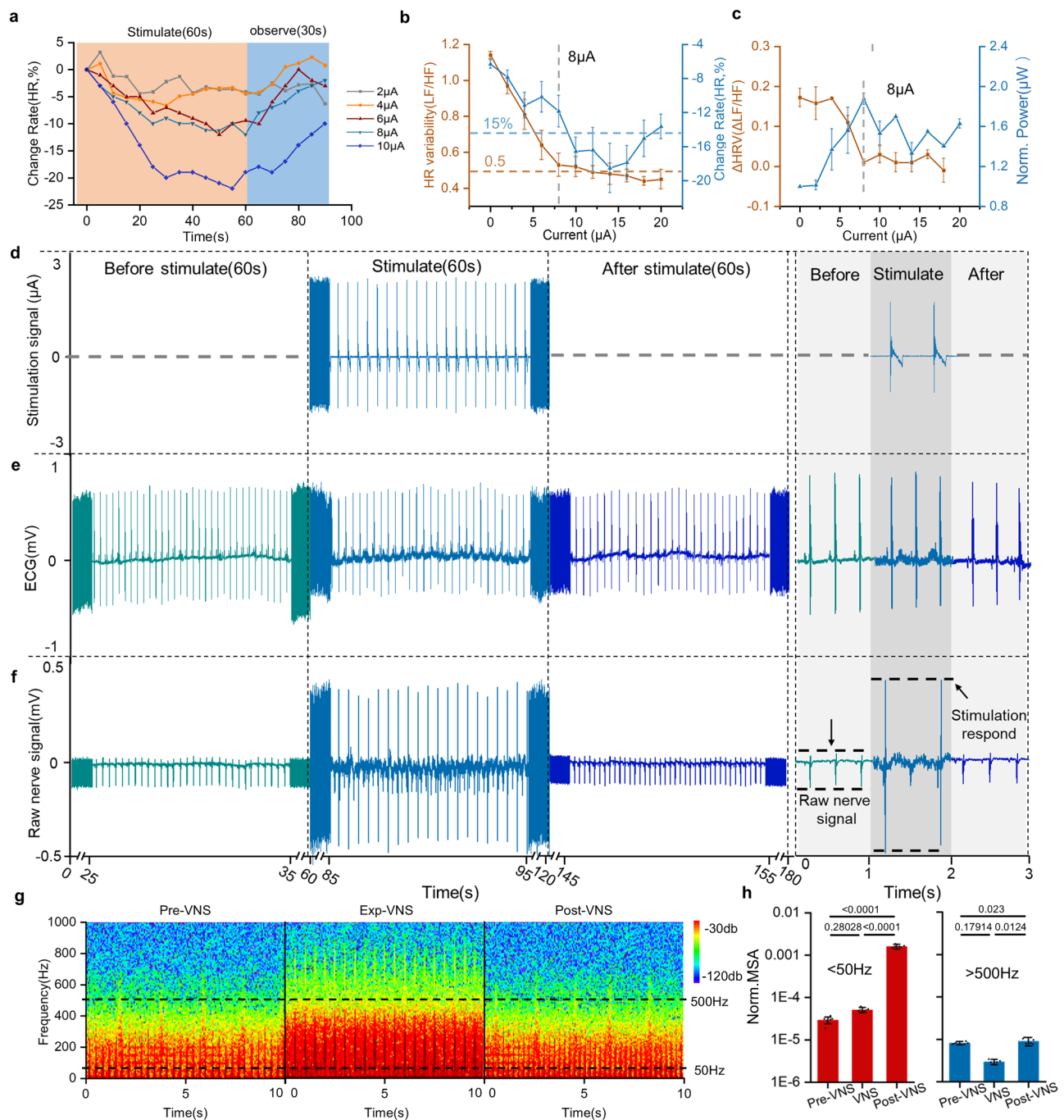


Fig. 2 | Neuroelectrophysiological and physiological characterization of low-level vagus nerve stimulation in mice. **a** Heart rate (HR) change rates at different stimulus intensities from 2 to 10 μA peak-to-peak (pp.) during 60-sec stimulation period. **b** HR variability (LF/HF ratio, left y-axis) and HR change rates (right y-axis) at stimulus intensities from 2 to 10 μA (pp.). Dashed lines indicate thresholds at 15% HR change and 0.5 HR variability. **c** ΔHRV (left y-axis) and standardized instantaneous power on ECG (right y-axis) at stimulus intensities from 2 to 20 μA (pp.). Dashed vertical line indicates threshold at 8 μA . **d–f**, Representative traces after standard stimulation (BTENG stimulator, 4 μA pp., 2 Hz): stimulation signal (**d**, top trace), ECG signals (**e**, middle trace), and raw vagus nerve signal (**f**, bottom trace) recorded before (0–40 s), during (40–100 s), and after (100–160 s) stimulation.

Right panels show magnified views of individual waveforms. **g** Time-frequency spectrograms of vagus nerve signals across 0–1000 Hz showing three phases: Pre-VNS (0–10 s), Exp-VNS (10–20 s, during stimulation), and Post-VNS (20–30 s). **h** Quantification of normalized mean squared amplitude (Norm MSA) in low-frequency band (< 50 Hz, left panel) and high-frequency band (> 500 Hz, right panel) for Pre-VNS, VNS (Exp-VNS), and Post-VNS conditions. Data in **a–c** **h** represent $n = 6$ biologically independent animals; error bars show mean $\pm$ SD. Statistical significance assessed by one-way ANOVA two-sided) with Tukey's HSD post hoc test; exact P values are shown in the figure. Source data are provided as a Source Data file 1.

performance over 8000 cycles and observed that the output remained relatively constant (Fig. 3f). This proves the reliability of the BTENG in long-term operation. During the frequency test, a linear motor was used to drive the TENG, resulting in a slight

increase in the short-circuit current as the frequency increased (Supplementary Fig. 6b). This proves that even if the output frequency is not stable enough, the device can still achieve a stable output.

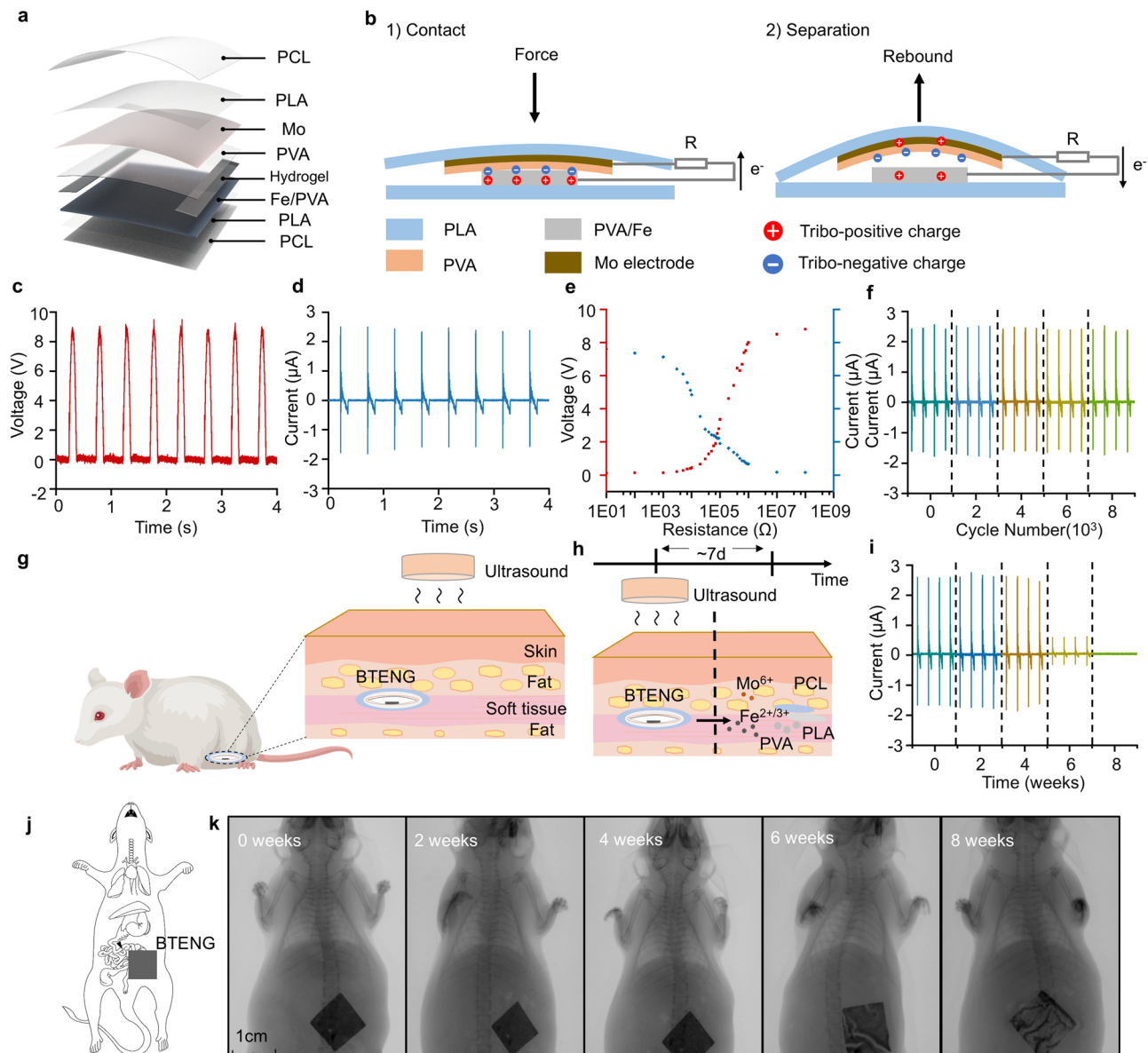


Fig. 3 | Design and characterization of the biodegradable triboelectric nano-generator. **a** Exploded view of layered structure: polycaprolactone (PCL) encapsulation, polylactic acid (PLA) substrate, molybdenum (Mo) electrode, polyvinyl alcohol (PVA) triboelectric layer, hydrogel spacer, iron/PVA (Fe/PVA) composite layer, PLA substrate, and PCL encapsulation. **b** Contact-separation working mechanism: (1) Contact state with applied force generating charge separation; (2) Separation state with rebound driving electron flow through external circuit (resistance R , capacitance C). **c** Open-circuit voltage output (~ 9 V peak) during cyclic compression over 4 sec. **d** Short-circuit current output (~ 4 μ A peak-to-peak) over 4 sec. **e** Voltage (red dots) and current (blue dots) versus external resistance ($1E01$ to $1E09$ Ω). **f** Short-circuit current stability over 8000 cycles with dashed lines

marking 2000-cycle intervals. **g** In vivo implantation schematic: left panel shows device beneath skin in fat layer; right panel shows ultrasound exposure (wave symbols) for accelerated degradation. **h** Degradation timeline showing device breakdown over ~ 7 days with ultrasound, releasing metal ions (Mo^{6+} , $Fe^{2+/3+}$) and polymer fragments (PCL, PLA, PVA). **i** Current output in phosphate-buffered saline at 37 $^{\circ}C$ measured at 0, 2, 4, 6, and 8 weeks; output stable through week 4 then declining. Dashed lines mark 2-week intervals. **j** Schematic of micro-computed tomography (micro-CT) imaging setup. **k** Representative micro-CT images at 0, 2, 4, 6, and 8 weeks post-implantation showing progressive degradation; scale bar, 1 cm. Data represent $n = 6$ devices (**c,d**), $n = 3$ devices (**f**), $n = 4$ devices (**i**). Source data are provided as a Source Data file 2.

Overall, the BTENG demonstrated good stability in durability tests, frequency tests, and output tests, and its impedance range also matched the results of in vivo experiments.

Evaluation of the biocompatibility and degradation performance of the BTENG

Following successful demonstration of therapeutic output capability, we evaluated the biodegradation and biocompatibility profiles essential for clinical translation of temporary cardiac stimulation devices. Controlled degradation eliminates the need for surgical device removal while ensuring complete biocompatible clearance, addressing

a critical limitation of permanent implantable stimulators and reducing long-term patient risks. The packaging layer plays a key role in maintaining the normal operation of the implantable vagus nerve stimulation device. In an environment containing body fluids, PCL slowly peels off due to contact with the body fluids, is hydrolyzed into monomers, and eventually dissolves. According to reports in the literature and in vivo implantation results, without external interference, the PCL packaging layer can ensure normal operation of the device for 4–6 weeks. During this process, the packaging layer will degrade and eventually rupture. After the packaging layer breaks, body fluids penetrate the device, and the BTENG quickly loses its function. Before

the PLA substrate and the Fe/PVA positive triboelectric layer become moist and softened due to the entry of body fluids, the device can maintain its structure briefly. After degradation begins, the gel material as the spacer layer and the PVA film in the negative triboelectric layer of the electrode rapidly dissolve in the body fluids and are metabolized within a few hours. In the positive triboelectric layer, Fe and PVA are mixed relatively uniformly. As PVA dissolves, the positive triboelectric layer also cracks. The degradation of metal materials is relatively complex. During the degradation process, the sputtered metal Mo fragments are oxidized to form $\text{H}_2\text{Mo}(\text{OH})_4$ and participate in metabolism in the 6-valent form. The Fe particles separated from the positive triboelectric layer are also oxidized to $\text{Fe}(\text{OH})_2$, $\text{Fe}(\text{OH})_3$, and Fe_2O_4 in a humoral environment and participate in metabolism in the 2-valent and 3-valent forms (Fig. 3g–h).

Device degradation is facilitated by the use of ultrasound as a driving source, potentially impacting device performance. To mitigate the influence of ultrasound on the triboelectric layer, we designed the thicknesses of both the packaging layer and the upper triboelectric layer of the device. Physical field simulations were used to simulate the wave behavior of the device under ultrasonic conditions. The simulation employed an experimental ultrasonic intensity of 3 W/cm^2 as a parameter and investigated two commonly used ultrasonic frequencies, 1 MHz and 0.1 MHz, as degradation parameters (Supplementary Fig. 4a–d). According to the physical field simulation, the 1 MHz ultrasonic stress was more concentrated on the lower surface of the packaging layer material. In contrast, at 0.1 MHz, sound pressure and other related factors were more concentrated in other areas than in the packaging layer. These results indicate that the unique material design used in this experiment is more efficient in degrading the device at 1 MHz. Similarly, in an ultrasonic degradation environment, the device ruptured and started degrading within 7 days (Supplementary Fig. 7). To assess systemic handling of degradation products, serum iron and molybdenum concentrations were measured at multiple timepoints throughout the degradation period. Both elements remained within normal physiological ranges with no significant accumulation detected (Supplementary Fig. 8), confirming safe metabolic clearance of degradation products. To validate the safety of ultrasound-triggered degradation, we performed comprehensive tissue analyses on mice receiving ultrasound exposure (1 MHz, 3 W/cm^2) for 7 days post-implantation compared to sham controls. Cardiac H&E staining revealed preserved myocardial architecture with no evidence of thermal injury or necrosis (Supplementary Fig. 9a). TUNEL staining showed no significant increase in apoptotic cells in ultrasound-exposed hearts (Supplementary Fig. 9b). qPCR analysis of cardiac inflammatory markers (IL-1 β , IL-6, TNF- α) demonstrated no elevation in inflammatory gene expression following ultrasound treatment (Supplementary Fig. 9c). Additionally, H&E staining of skin at the implantation site showed preserved normal histological architecture with no evidence of thermal damage. H&E staining of major organs, including liver, spleen, lungs, and kidneys, revealed no pathological changes following ultrasound exposure (Supplementary Fig. 9d). These findings confirm the safety of ultrasound-triggered device degradation across multiple tissue types.

To further demonstrate the output effect of the device's operation within the body, we conducted tests on the working and degrading situation after the device was implanted. In our experiments, the device output was monitored continuously over a 56-day period. For the ultrasonic degradation groups, ultrasound exposure was initiated on day 14 and day 28, respectively. Results showed that in both groups, the device output dropped to nearly undetectable levels within one week after the start of ultrasonic treatment (Supplementary Fig. 10a). The corresponding output waveforms after degradation are detailed in Fig. 3i. To better characterize the temporal dynamics of device output during the first week following ultrasound intervention,

we performed additional time-course measurements immediately after ultrasound initiation. Furthermore, to identify the turning point in output variation, we conducted a dedicated 7-day ultrasonic degradation study. It was observed that the device output exhibited significant fluctuations by the third day after ultrasound application. These experimental results further demonstrate the stability of the device's output both before and after degradation, as well as the reliability of the ultrasonic degradation process (Supplementary Fig. 10b).

To demonstrate the performance and degradation of the device in a liquid environment, we conducted experiments by placing the fully encapsulated device in a 37°C PBS solution *in vitro* and performing *in vivo* implantation into 6–8-week-old mice. We conducted batch tests with treatment periods of 2, 4, 6, and 8 weeks. The CT scan results revealed that the shape of the device remained unchanged at 2 and 4 weeks. Moreover, obvious fractures occurred in the devices at 4, 6 and 8 weeks. This finding proves that under normal implantation conditions, the device can maintain stability within 4 weeks (Fig. 3j, k). To evaluate long-term biocompatibility under natural degradation conditions, comprehensive tissue analyses were performed at 2-, 4-, 6-, and 8-weeks post-implantation. Cardiac TUNEL staining revealed no increase in apoptotic cells at any timepoint (Supplementary Fig. 11a). Cardiac H&E staining showed preserved myocardial architecture throughout the observation period (Supplementary Fig. 11b). qPCR analysis confirmed stable expression of cardiac inflammatory markers (IL-1 β , IL-6, and TNF- α) over time (Supplementary Fig. 11c). Additionally, H&E staining of skin at the implantation site demonstrated preserved normal histological architecture, including intact hair follicles, with no evidence of inflammatory response or tissue damage (Supplementary Fig. 12a). H&E staining of major organs, including liver, spleen, lungs, and kidneys, presented no signs of pathological changes throughout the observation period (Supplementary Fig. 12b). These comprehensive evaluations, together with the use of FDA-approved ultrasound parameters (3 W/cm^2 is well below the 7.2 W/cm^2 safety threshold), establish the biocompatibility of the BTENG system under both ultrasound-accelerated and natural degradation conditions.

These comprehensive evaluations establish that the BTENG achieves dual objectives of sustained therapeutic function during the critical 4-week treatment window followed by complete biocompatible degradation, with optional ultrasonic acceleration enabling personalized treatment duration control without requiring surgical intervention for device removal.

LL-VNS prevents cardiac remodeling and HF

To evaluate the prophylactic efficacy of LL-VNS, treatment was initiated one week after AB surgery, prior to cardiac structural and functional alterations. Transthoracic echocardiography was performed at 2-, 4-, and 8-weeks post-surgery, with cardiac tissue collection conducted in week 8 for endpoint analyses (Fig. 4a).

Cardiac function was assessed via echocardiographic measurements of the left ventricular ejection fraction (LVEF) and fractional shortening (LVFS) in weeks 1, 2, 4, and 8 post-surgery (Figs. 4b, 4c). No significant intergroup differences in cardiac function were observed in week 1. In week 2, AB surgery induced significant cardiac dysfunction, with the mean EF decreasing to 51% compared with that of the sham group (80.9%; $p < 0.0001$). Device implantation alone had no therapeutic effect (EF: 52%). LL-VNS treatment resulted in a minimal EF reduction with 20-min and 10-min stimulation protocols (decreasing from 74.6% to 71% and 73.25% to 73.5%, respectively). While the implantation-only and untreated groups showed progressive EF decline, the LL-VNS groups exhibited attenuated deterioration, with modest improvement in later stages (Figs. 4b, 4c). Notably, an extended stimulation duration did not confer additional benefits for cardiac function. Endpoint M-mode echocardiography (Fig. 4d) confirmed that LL-VNS mitigated pressure overload-induced cardiac dysfunction.

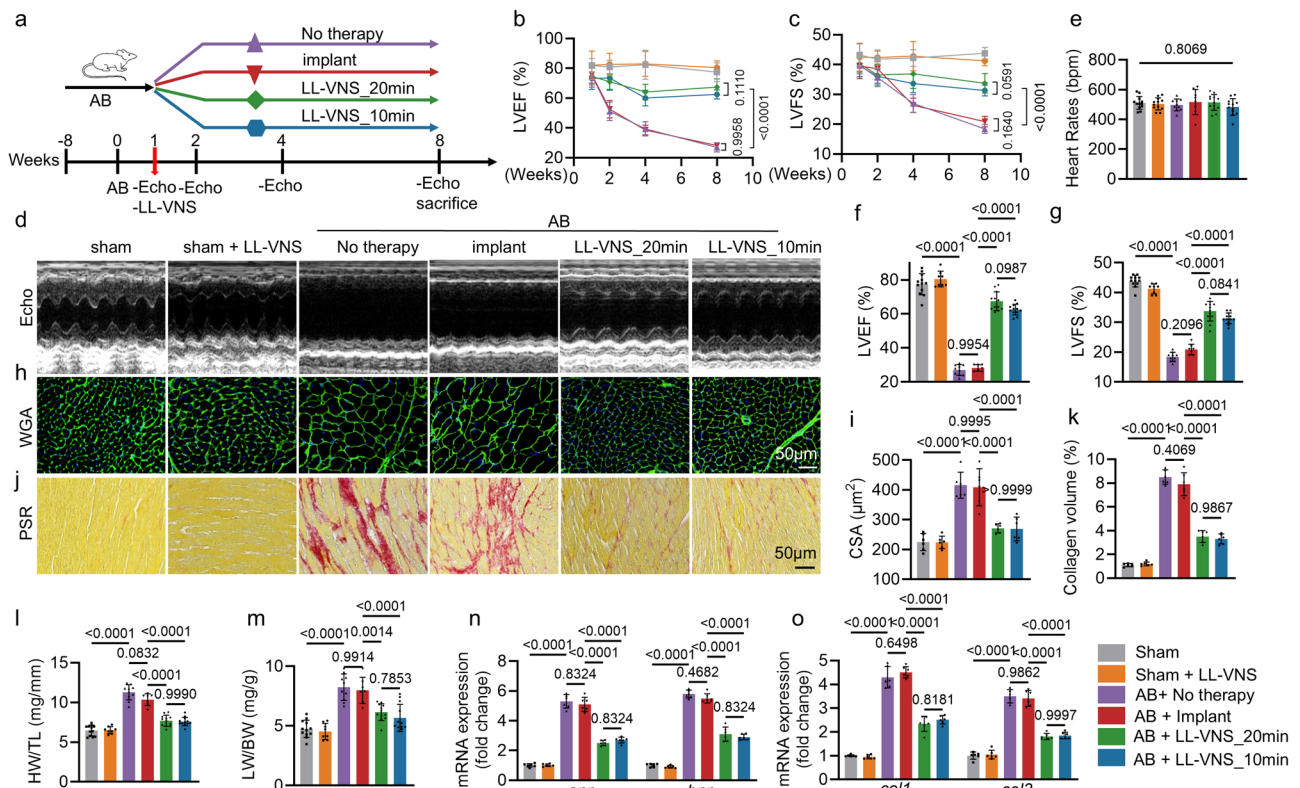


Fig. 4 | LL-VNS prevents cardiac remodeling and heart failure. **a** Experimental timeline: AB surgery at week 0, device implantation and LL-VNS initiation at week 1, echocardiography at weeks 1, 2, 4, and 8, tissue collection at week 8.

b, c Longitudinal left ventricular ejection fraction (LVEF, b) and fractional shortening (LVFS, c) at weeks 1, 2, 4, and 8 post-AB. Sample sizes: sham ($n = 12$ all timepoints), sham+LL-VNS ($n = 8$ all timepoints), AB+no therapy ($n = 12, 12, 12, 10$), AB+implant ($n = 8, 8, 8, 7$), AB+LL-VNS_20min ($n = 12$ all timepoints), AB+LL-VNS_10min ($n = 12$ all timepoints). **d** Representative M-mode echocardiograms at week 8. **e** Heart rate at week 8 endpoint. **f, g** Endpoint LVEF (**f**) and LVFS (**g**). Sample sizes for e-g: sham ($n = 12$), sham+LL-VNS ($n = 8$), AB+no therapy ($n = 10$), AB+implant ($n = 7$), AB+LL-VNS_20min ($n = 12$), AB+LL-VNS_10min ($n = 12$)

biologically independent mice. **h, i** Wheat germ agglutinin (WGA) staining (**h**; scale bar, 50 μm) and cardiomyocyte cross-sectional area quantification (**i**; $n = 6$ per group). **j, k** Picrosirius red (PSR) staining (**j**; scale bar, 50 μm) and fibrotic area quantification (**k**; $n = 6$ per group). **l, m** Heart weight to tibia length ratio (HW/TL, **l**) and lung weight to body weight ratio (LW/BW, **m**) at week 8 (same sample sizes as e). **n, o** Gene expression of hypertrophy markers (*anp*, *bnp*; **n**) and fibrosis markers (*col1*, *col3*; **o**) normalized to *gapdh* ($n = 6$ per group). Data represent mean $\pm$ SD. Statistical analysis for panels **b, c, e-g, i, k-o**: one-way ANOVA (two-sided) with Tukey's HSD post hoc test for multiple comparisons; exact P values shown in the figure. Individual data points overlaid on bar graphs. Source data are provided as a Source Data 3.

Notably, heart rate remained stable across all groups at the 8-week endpoint (Fig. 4e), and this therapeutic effect was quantitatively confirmed by preserved LVEF and LVFS (Figs. 4f, g), indicating the improvements were independent of heart rate changes.

Histological analyses using wheat germ agglutinin (WGA) staining and Sirius Red (PSR) staining were performed to examine cardiac hypertrophy and fibrosis. AB surgery induced significant cardiomyocyte hypertrophy and myocardial fibrosis, characterized by increased cell surface area (Fig. 4h, i) and increased collagen fiber deposition (Fig. 4j, k). Device implantation without stimulation had no protective effects, whereas LL-VNS treatment (with 20-min and 10-min protocols) attenuated both of these pathological changes. In addition to ameliorating cardiac functional impairments, LL-VNS significantly reduced pressure overload-induced increases in the heart weight/tibia length ratio (HW/TL) (Fig. 4l) and pulmonary edema (lung weight/body weight ratio) (Fig. 4m). Molecular analyses revealed significant upregulation of hypertrophy (*anp*, *bnp*) and fibrosis (*col1*, *col3*) markers in the pressure overload-induced HF model (Figs. 4n, o). While implantation-only therapy was ineffective, LL-VNS protocols significantly reduced the expression of these molecular markers. These findings demonstrate that LL-VNS therapy protects against pressure overload-induced pathological cardiac remodeling and HF.

LL-VNS reverses established cardiac remodeling and prevents HF in a murine model

To investigate the therapeutic potential of LL-VNS for reversing established pathological cardiac remodeling, treatment was initiated in mice two weeks after AB surgery (Fig. 5a). Serial echocardiographic analyses demonstrated that LL-VNS significantly improved cardiac function in subsequent weeks. LVEF and LVFS were evaluated at 2-, 4-, and 8-weeks post-surgery. Compared with that in the AB+ no therapy cohort, cardiac function in the LL-VNS-treated groups was significantly better at all time points (Figs. 5b, c). Endpoint M-mode echocardiography (Fig. 5d) demonstrated the LL-VNS-mediated restoration of cardiac contractile function. These therapeutic effects occurred independently of heart rate, which showed no significant differences across experimental groups (Fig. 5e). Furthermore, quantitative assessment confirmed this restoration via significant improvements in both LVEF and LVFS indices in the LL-VNS group (Figs. 5f, g).

Histological analyses using WGA staining demonstrated LL-VNS-mediated attenuation of cardiomyocyte hypertrophy, as evidenced by a reduced cardiomyocyte cross-sectional area (CSA) compared with that of untreated AB controls (Fig. 5h, i). PSR staining revealed diminished myocardial fibrosis and collagen deposition in LL-VNS-treated samples (Fig. 5j, k). Morphometric analyses, including HW/TL and LW/BW, revealed significant improvements in the LL-VNS-treated

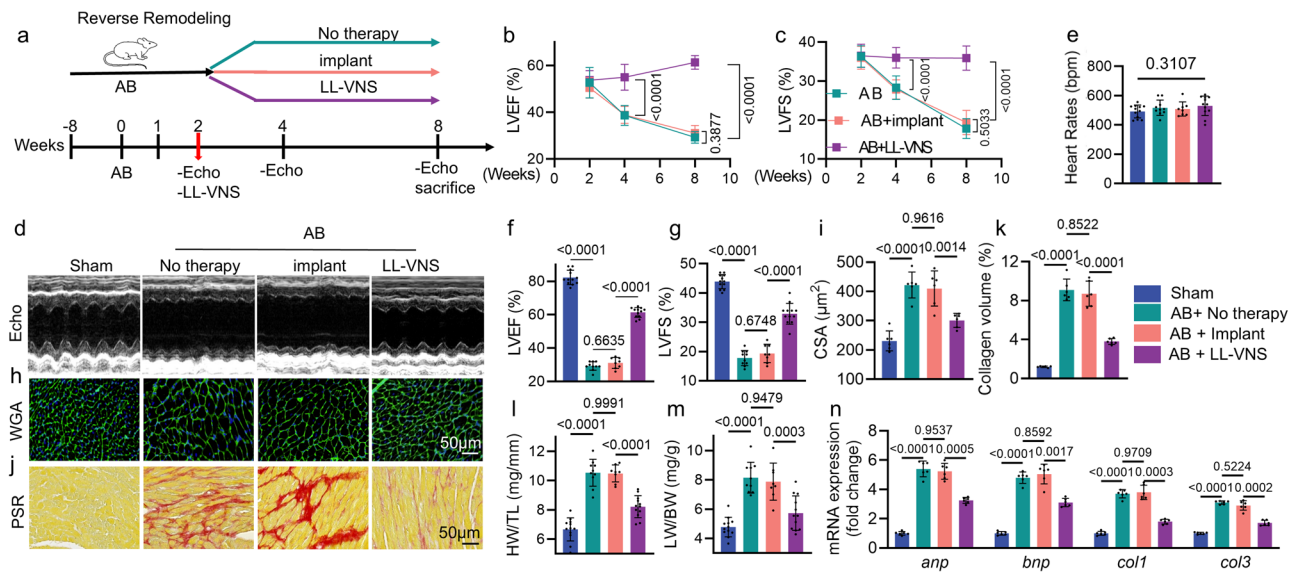


Fig. 5 | LL-VNS reverses established cardiac hypertrophy and fibrosis.

a Experimental timeline: AB surgery at week 0, LL-VNS initiation at week 2, echo-cardiography at weeks 2, 4, and 8, tissue collection at week 8. **b**, **c** Longitudinal left ventricular ejection fraction (LVEF, **b**) and fractional shortening (LVFS, **c**) at weeks 2, 4, and 8 post-AB. Sample sizes: AB+no therapy ($n = 12, 12, 10$), AB+implant ($n = 8$ all timepoints), AB+LL-VNS ($n = 12$ all timepoints). **d** Representative M-mode echocardiograms at week 8. **e**, Heart rate at week 8 endpoint. **f**, **g** Endpoint LVEF (**f**) and LVFS (**g**). Sample sizes for **e**–**g**: sham ($n = 12$), AB+no therapy ($n = 10$), AB+implant ($n = 8$), AB+LL-VNS ($n = 12$) biologically independent mice. **h**, **i** Wheat germ agglutinin (WGA) staining (**h**; scale bar, 50 μ m) and cardiomyocyte cross-

sectional area quantification (**i**; $n = 6$ per group). **j**, **k** Picrosirius red (PSR) staining (**j**; scale bar, 50 μ m) and fibrotic area quantification (**k**; $n = 6$ per group). **l**, **m** Heart weight to tibia length ratio (HW/TL, **l**) and lung weight to body weight ratio (LW/BW, **m**) at week 8 (same sample sizes as **e**). **n** Gene expression of hypertrophy markers (*anp*, *bnp*) and fibrosis markers (*col1*, *col3*) normalized to *gapdh* ($n = 6$ per group). Data represent mean $\pm$ SD. Statistical analysis for panels (**b**, **c**, **e**–**g**, **i**, **k**–**n**): one-way ANOVA (two-sided) with Tukey's HSD post hoc test for multiple comparisons; exact P values shown in the figure. Individual data points overlaid on bar graphs. Source data are provided as a Source Data file 3.

groups (Fig. 5l, m). Molecular analyses of hypertrophy and fibrosis markers (*anp*, *bnp*, *col1*, and *col3*) revealed significant downregulation following LL-VNS treatment (Fig. 5n). These findings demonstrate that LL-VNS initiation two weeks post-AB surgery effectively reverses cardiac remodeling, as evidenced by comprehensive improvements in functional, structural, and molecular cardiac parameters in this murine model.

LL-VNS reverses established HF

To evaluate the therapeutic efficacy of LL-VNS in established HF, treatment was initiated four weeks after AB surgery and continued for 4 weeks until the study endpoint at week 8, providing 4 weeks of treatment for reversal of established disease (Fig. 6a). Cardiac function improved following LL-VNS intervention, as quantified by elevated LVEF and LVFS values at weeks 4 and 8 post-surgery (Fig. 6b, c). This was further confirmed by endpoint analysis, where M-mode echocardiography (Fig. 6d) showed enhanced cardiac contractility. Notably, heart rate remained comparable between groups (Fig. 6e), while quantification revealed significant improvements in both LVEF and LVFS (Figs. 6f, g) in the LL-VNS-treated animals. Histological assessment using WGA and PSR staining revealed that LL-VNS attenuated cardiomyocyte hypertrophy and myocardial fibrosis, as indicated by reduced cardiomyocyte CSA and decreased collagen deposition, respectively (Fig. 6h–k). The therapeutic efficacy of LL-VNS was further supported by a decrease in the HW/TL ratio and reduced LW/BW ratio, suggesting that LL-VNS alleviated cardiac hypertrophy and pulmonary congestion (Fig. 6l, m). Molecular analyses revealed significant downregulation of hypertrophy (*anp*, *bnp*) and fibrosis (*col1*, *col3*) marker expression following LL-VNS treatment, suggesting favorable modulation of cardiac gene expression profiles (Fig. 6n). These results establish that LL-VNS effectively reverses established HF progression through improvement of cardiac function and attenuation of pathological remodeling in the context of pressure overload-induced HF.

LL-VNS modulates gene expression profiles in cardiac tissue post-AB surgery

To elucidate the molecular mechanisms underlying LL-VNS cardioprotective effects, we performed comprehensive transcriptomic analysis of cardiac tissue from treated and control animals. This approach aimed to identify specific biological pathways and gene networks responsible for the observed therapeutic benefits.

Initial transcriptional profiling confirmed that device implantation alone had minimal impact on cardiac gene expression, with high concordance observed between AB+implant and AB groups (Supplementary Fig. 13a). Based on this validation, subsequent analyses focused on comparing AB+implant controls with sham, AB+LL-VNS_20 min, and AB+LL-VNS_10 min groups. Comparative analysis between the two LL-VNS treatment durations revealed remarkably similar gene expression patterns, indicating equivalent molecular responses regardless of stimulation duration (Supplementary Fig. 13b, c). Differential expression analysis identified 681 genes altered between AB+implant and sham groups, representing the disease-induced transcriptional changes, while 522 genes differed between AB+implant and AB+LL-VNS_20 min groups, reflecting LL-VNS therapeutic effects (Supplementary Fig. 13d). Gene set enrichment analysis revealed that LL-VNS-regulated genes were enriched in three critical biological processes: extracellular matrix organization, muscle structure development, and programmed cell death (Supplementary Fig. 13e, f). Similar gene expression pattern was found in group with 10-min treatment (Supplementary Fig. 14a, b). Comprehensive transcriptomic analysis of the 10-min treatment group, including pathway enrichment and hierarchical clustering, confirmed that DEGs from both durations cluster into identical biological pathways—extracellular matrix organization, programmed cell death, muscle structure development, growth regulation, cell migration, and inflammatory modulation—with comparable enrichment patterns and magnitudes (Supplementary Fig. 14c–d, Supplementary Fig. 13). These pathways

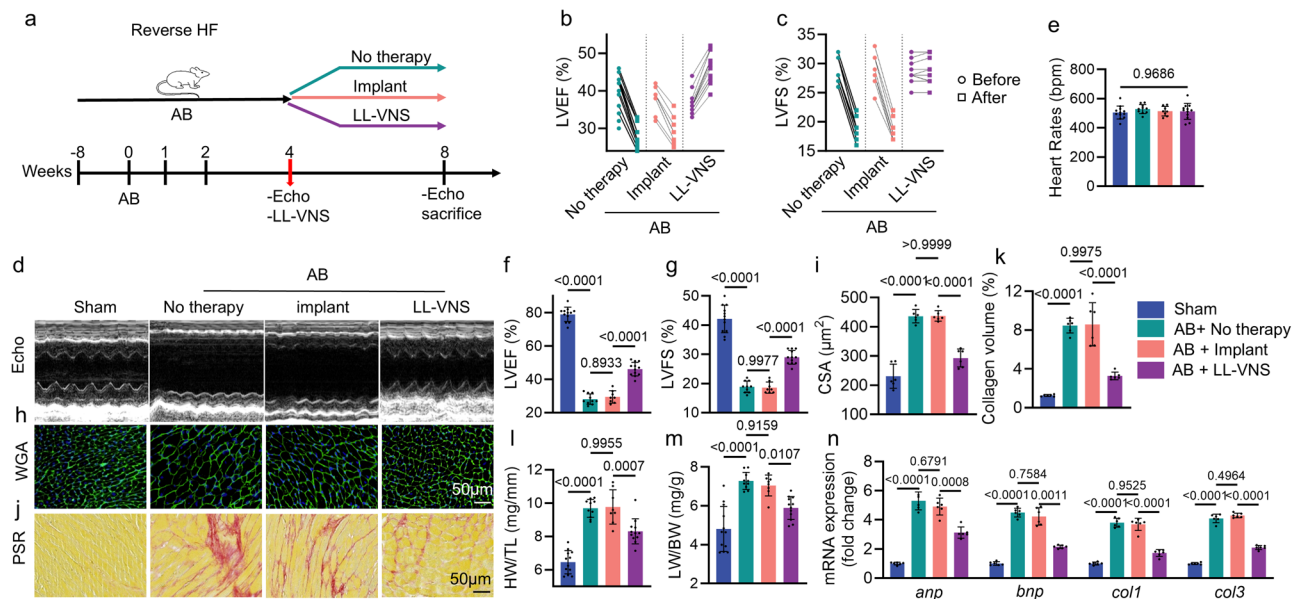


Fig. 6 | LL-VNS reverses established HF. **a** Experimental timeline: AB surgery at week 0, LL-VNS initiation at week 4, echocardiography at weeks 4 and 8, tissue collection at week 8. **b, c** Left ventricular ejection fraction (LVEF, **b**) and fractional shortening (LVFS, **c**) at weeks 4 and 8 post-AB. **d** Representative M-mode echocardiograms at week 8. **e**, Heart rate at week 8 endpoint. **f, g**, Endpoint LVEF (**f**) and LVFS (**g**). Sample sizes for e–g: sham ($n=12$), AB+no therapy ($n=10$), AB+implant ($n=8$), AB + LL-VNS ($n=12$) biologically independent mice. **h, i** Wheat germ agglutinin (WGA) staining (**h**; scale bar, 50 μm) and cardiomyocyte cross-sectional

area quantification (**i**; $n=6$ per group). **j, k** Picrosirius red (PSR) staining (**j**; scale bar, 50 μm) and fibrotic area quantification (**k**; $n=6$ per group). **l, m**, Heart weight to tibia length ratio (HW/TL, **l**) and lung weight to body weight ratio (LW/BW, **m**) at week 8 (same sample sizes as **e**). **n** Gene expression of hypertrophy markers (*anp*, *bnp*) and fibrosis markers (*col1*, *col3*) normalized to *gapdh* ($n=6$ per group). Data represent mean $\pm$ SD. Statistical analysis for (**e–g**, **i**, **k–n**): one-way ANOVA (two-sided) with Tukey's HSD post hoc test; exact P values shown in the figure. Individual data points overlaid on bar graphs. Source data are provided as a Source Data file 3.

directly correlate with the observed improvements in cardiac structure and function, providing molecular evidence for LL-VNS therapeutic mechanisms. Previous studies have demonstrated that vagal acetylcholine release during LL-VNS modulates inflammatory and neuro-humoral pathways^{21,22}, which regulate extracellular matrix dynamics and muscle function²³. Additionally, acetylcholine-mediated receptor signaling influences cell survival and apoptotic pathways, potentially contributing to enhanced cardiac resilience under stress conditions^{24,25}.

Integrated analysis combining 268 differentially expressed genes from the 20-min group with 217 additional genes from the 10-min group confirmed consistent enrichment in the same biological processes (Fig. 7a). Hierarchical clustering analysis demonstrated distinct expression patterns between LL-VNS-treated and control groups, with both treatment durations producing similar molecular signatures (Fig. 7b). Gene cluster network analysis revealed intricate connections among LL-VNS-regulated genes, highlighting coordinated modulation of cardiac remodeling pathways (Fig. 7c). Temporal analysis at 2- and 4-weeks post-treatment confirmed sustained regulatory effects on extracellular matrix-associated genes, indicating durable molecular changes (Supplementary Fig. 15a–d).

These comprehensive transcriptomic analyses, combined with functional studies, suggest that LL-VNS mediates its cardiac regulatory effects through vagus nerve-dependent acetylcholine release, establishing a mechanistic framework for the observed therapeutic benefits.

Atropine abrogates LL-VNS-mediated cardioprotection against myocardial remodeling and HF post-AB surgery

To elucidate the mechanism underlying vagal acetylcholine release in LL-VNS-mediated cardioprotection, we employed atropine, a selective muscarinic acetylcholine receptor antagonist. Following sham or AB surgery, the mice were randomized to receive either atropine or vehicle control for 7 weeks (Fig. 8a). To rule out potential confounding

effects of chronic atropine administration, we evaluated systemic safety parameters throughout the 7-week treatment period. Body weight monitoring showed no significant differences among all groups (Supplementary Fig. 16a). Comprehensive serum biochemistry analysis revealed that liver function markers (AST, ALT) and kidney function markers (creatinine, BUN) remained within normal ranges across all groups, with no significant differences between atropine-treated and vehicle-treated animals (Supplementary Fig. 16b–e). Heart rate measurements during echocardiography showed modest, statistically non-significant elevations in both atropine-treated groups compared to vehicle controls, consistent with expected muscarinic receptor blockade (Fig. 8c). Importantly, despite identical atropine exposure and comparable physiological parameters between AB+atropine and AB + LL-VNS+atropine groups, their cardiac function differed dramatically (Fig. 8d, e), demonstrating that the loss of LL-VNS benefits reflects specific blockade of vagal acetylcholine signaling rather than nonspecific systemic effects. These findings establish that chronic atropine administration at the dose used does not induce systemic toxicity or confounding hemodynamic alterations.

Cardiac functional analyses revealed that atropine coadministration significantly abolished LL-VNS-induced myocardial improvements post-AB surgery, as evidenced by compromised cardiac parameters in the AB + LL-VNS+atropine group compared with those in the AB + LL-VNS cohort (Fig. 8b–e). Histological assessments, including WGA and PSR staining, revealed that the presence of atropine negated the efficacy of LL-VNS in ameliorating myocardial hypertrophy and fibrosis, elucidating the cellular mechanisms underlying the disruption of LL-VNS-mediated cardioprotection by atropine (Fig. 8f–i). Morphometric analyses further supported the antagonistic effects of atropine, as evidenced by sustained increases in the HW/TL ratio and the LW/BW ratio in the atropine-treated groups despite LL-VNS intervention (Fig. 8j, k). At the mRNA level, the expression profiles of hypertrophy and fibrosis markers in cardiac tissue confirmed the detrimental effect of atropine on LL-VNS-mediated cardioprotection, with the AB + LL-

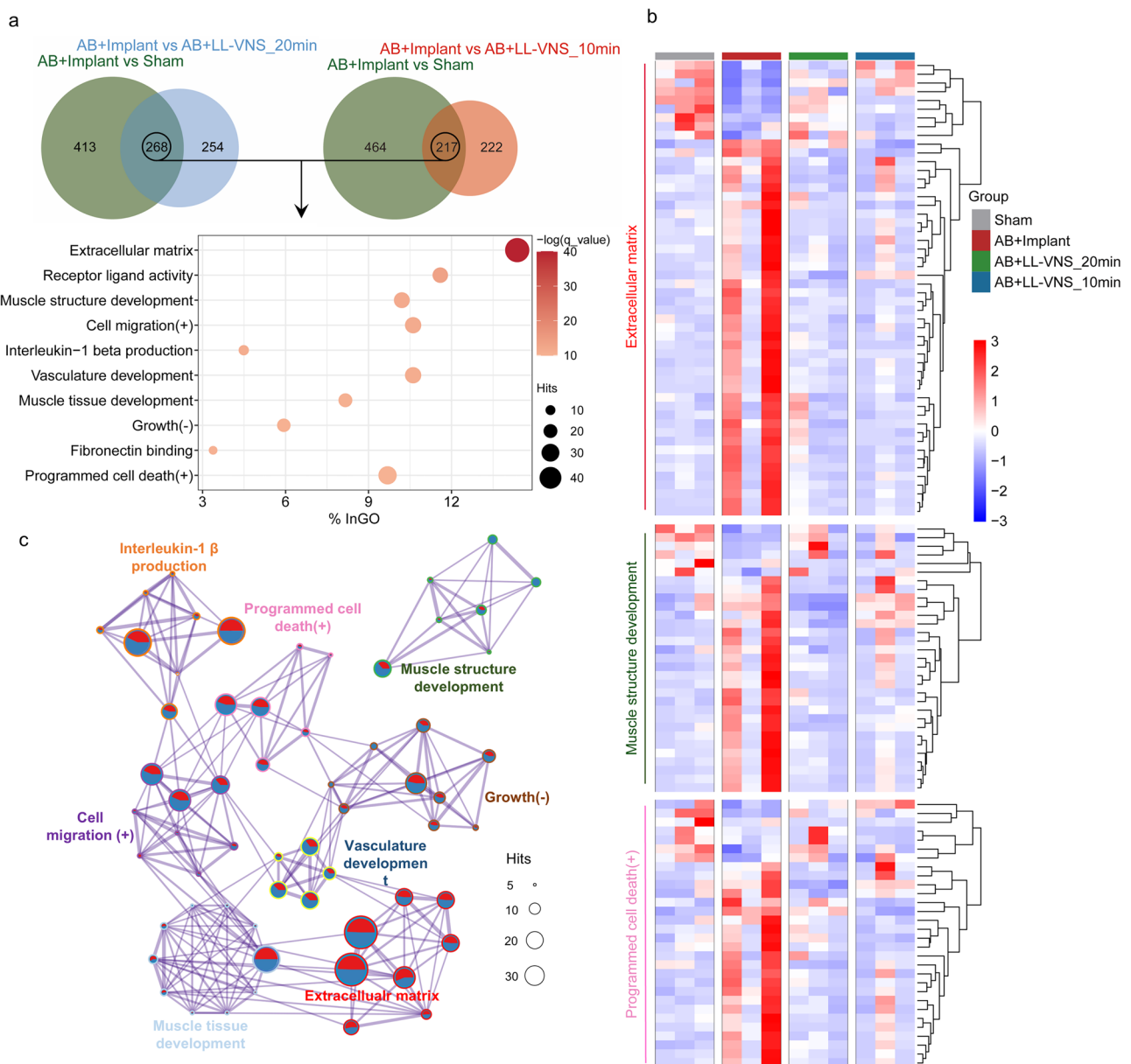


Fig. 7 | Integrated gene expression and pathway analysis of LL-VNS-treated cardiac tissue. RNA-sequencing of cardiac tissue collected at week 8 from preventive intervention cohort (LL-VNS initiated week 1 post-AB). **a** Venn diagrams and Gene Ontology (GO) enrichment analysis. Left diagram: overlap of differentially expressed genes (DEGs) between AB+implant vs sham and AB + LL-VNS_20min vs AB+implant, yielding 268 shared genes. Right diagram: overlap between AB +implant vs sham and AB + LL-VNS_10min vs AB+implant, yielding 217 shared genes. Bubble plot below shows GO enrichment of the 268 shared DEGs. Bubble size represents gene count (Hits); color intensity indicates significance ($-\log_{10} P$ value). Enriched processes include extracellular matrix organization, receptor ligand activity, muscle structure development, cell migration, interleukin-1 β production, vasculature development, muscle tissue development, fibronectin binding, and programmed cell death(+). **b** Hierarchical clustering heatmaps of shared DEGs across groups (sham, AB+implant, AB + LL-VNS_20min, AB + LL-VNS_10min). Color scale represents Z-score normalized expression. **c** Gene cluster network analysis for the shared DEGs, illustrating the interconnected pathways and key biological processes modulated by LL-VNS treatment, including extracellular matrix interactions, muscle development, and apoptosis regulation. DEGs defined by $|\log_2 \text{FoldChange}| > 1$ and $\text{FDR} < 0.05$ using edgeR. Enrichment analysis performed using ClusterProfiler with hypergeometric test ($q < 0.05$). Network generated with Metascape. $n = 3$ biologically independent samples per group. Source data are provided as a Source Data file 3.

VNS+atropine cohort failing to show the characteristic downregulation of *anp*, *bnp*, *col1*, or *col3* associated with LL-VNS (Fig. 8i). These findings demonstrate that the pharmacological blockade of muscarinic acetylcholine receptors by atropine abolishes LL-VNS-mediated cardio-protection post-AB surgery, establishing vagal acetylcholine release as the primary mechanism underlying the therapeutic efficacy of LL-VNS.

Discussion

This study demonstrates the therapeutic efficacy of a fully BTENG in HF management across multiple disease stages. The designed VNSr,

powered by the TENG, generates periodic nerve stimulation under minimal external stress, producing an open circuit voltage of 9.07 ± 0.43 V and a short-circuit current of 4.19 ± 0.14 μ A, functioning effectively for over 4 weeks after in vivo implantation. Notably, 1 MHz, 3 W/cm² ultrasound promotes rapid device degradation without affecting output performance. Early implementation of LL-VNS following aortic banding demonstrated significant attenuation of pathological cardiac remodeling and preservation of cardiac function, evidenced by reduced cardiomyocyte hypertrophy and decreased myocardial fibrosis. Mechanistic investigations revealed that LL-VNS

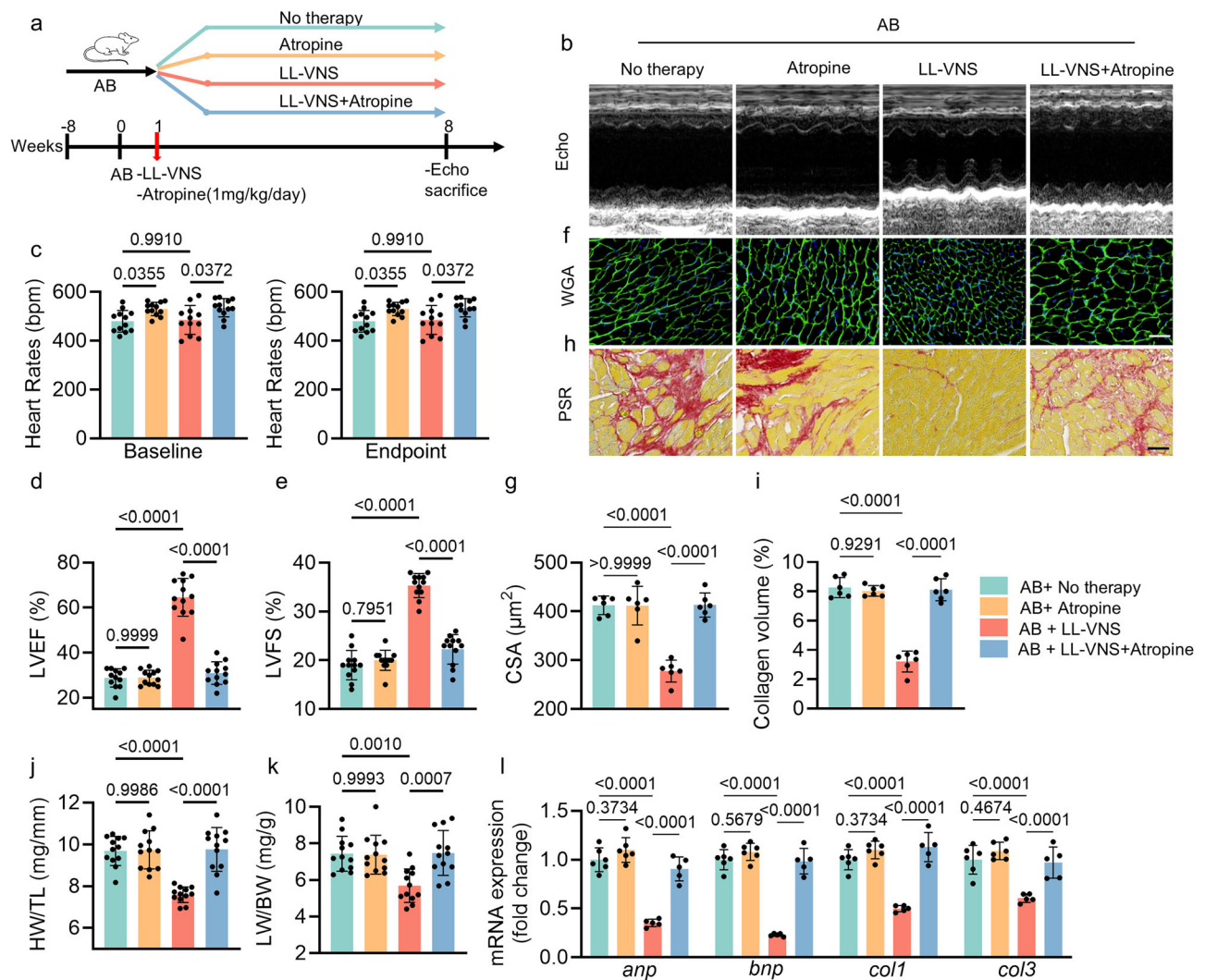


Fig. 8 | Atropine negates the cardioprotective effects of LL-VNS against myocardial remodeling and HF. **a** Experimental timeline: AB surgery at week 0, simultaneous LL-VNS and atropine administration (1 mg/kg/day intraperitoneally) at week 1, tissue collection at week 8, Echo sacrifice at week 8. **b** Representative M-mode echocardiograms at week 8 from four groups: AB+no therapy, AB+atropine, AB+LL-VNS, AB+LL-VNS+atropine. **c** Heart rate at baseline (week 1) and endpoint (week 8). **d, e** Left ventricular ejection fraction (LVEF, **d**) and fractional shortening (LVFS, **e**) at week 8. Sample sizes for **c-e**: AB+no therapy ($n=12$), AB+atropine ($n=12$), AB+LL-VNS ($n=12$), AB+LL-VNS+atropine ($n=12$) biologically independent mice. **f, g** Wheat germ agglutinin (WGA) staining (**f**; scale bar, 50 μ m) and cardiomyocyte cross-

sectional area (CSA) quantification (**g**; $n=6$ per group). **h, i** Picrosirius red (PSR) staining (**h**; scale bar, 50 μ m) and fibrotic area quantification (**i**; $n=6$ per group). **j, k** Heart weight to tibia length ratio (HW/TL, **j**) and lung weight to body weight ratio (LW/BW, **k**) at week 8 (same sample sizes as **c**). **l** Gene expression of hypertrophy markers (*anp*, *bnp*) and fibrosis markers (*col1*, *col3*) normalized to *gapdh* ($n=6$ per group). Data represent mean $\pm$ SD. Statistical analysis for (**c-e**, **g**, **i-l**) one-way ANOVA (two-sided) with Tukey's HSD post hoc test for multiple comparisons; exact P values shown in the figure. Individual data points overlaid on bar graphs. Source data are provided as a Source Data file 3.

mediates its cardioprotective effects through vagal acetylcholine release, confirmed by the complete abolishment of therapeutic benefits following muscarinic receptor blockade with atropine. The integration of complete biodegradability, sustained neural stimulation efficacy, and ultrasound-controlled degradation positions this BTENG-based VNSr as a promising therapeutic platform for clinical translation.

The multifaceted pathophysiology of HF necessitates therapeutic approaches beyond conventional pharmacological and mechanical interventions. While conventional pharmacotherapy remains foundational, its efficacy is frequently limited by patient-specific variables and the progressive nature of HF²⁶. Current nonpharmacological approaches face significant limitations, ranging from compliance challenges to organ donor scarcity^{27–31}. Staged therapeutic approaches enable stage-specific interventions in HF management, enabling stage-specific interventions that optimize therapeutic outcomes. This precision medicine approach addresses the heterogeneity inherent in HF

pathophysiology while providing a structured framework for incorporating emerging therapeutic modalities, establishing a foundation for more effective, personalized therapeutic strategies³².

Despite progress in implantable VNS systems, technical constraints hinder widespread adoption. Primary challenges include the absence of self-sufficient power mechanisms and post-therapeutic device management. Existing devices rely on nonrenewable batteries with finite lifespans, necessitating recurrent surgical replacements that increase infection risks, healthcare costs, and patient burden. Additionally, VNS implants not designed for permanent deployment require invasive surgical extraction. Although bioresorbable electronics offer an alternative, the currently employed materials lack precise spatiotemporal control over degradation. Our BTENG stimulation platform employs transdermal mechanical energy harvesting for continuous energy replenishment while maintaining therapeutic parameters. After treatment, ultrasound-mediated selective hydrolysis

achieves complete device resorption within 48–72 h, eliminating secondary removal procedures and ensuring biocompatible clearance.

Compared with traditional treatments, LL-VNS offers distinct advantages. Conventional interventions often employ a one-size-fits-all approach that inadequately addresses pathophysiological diversity among patients. The existing methods of electrical stimulation for treating heart failure include, for example, ANTHEM-HF, INOVATE-HF, and NECTAR-HF, etc. We compared these existing stimulation methods, and found that they far exceeded LL-VNS in terms of stimulation intensity and stimulation power (Supplementary Table 2)^{11–13}. LL-VNS results in fewer side effects and greater personalization potential, aligning treatments with specific disease trajectories. Its anti-inflammatory and antifibrotic effects can complement the hemodynamic benefits of existing drug treatments, potentially slowing or reversing HF progression more effectively than pharmacological interventions alone. However, the long-term efficacy and safety of LL-VNS, particularly its interactions with HF drugs and devices, require further investigation, as does the optimization of stimulation parameters.

The therapeutic efficacy of LL-VNS is mediated primarily by modulation of acetylcholine release. This parasympathetic neurotransmitter exhibits anti-inflammatory properties and attenuates cardiac fibrosis and hypertrophy^{33–36}. The cholinergic anti-inflammatory pathway³⁵ represents a critical mechanism whereby LL-VNS-induced acetylcholine release suppresses proinflammatory cytokine production through $\alpha 7$ nicotinic acetylcholine receptor activation on macrophages³⁷. Our GSEA and protein network analyses confirmed that LL-VNS influences several critical pathways, particularly those that modulate DEGs related to the extracellular matrix and muscle structure development. The extracellular matrix not only provides structural support but also regulates cellular signaling, influencing cardiomyocyte survival and function³⁸. By mitigating extracellular matrix dysregulation, LL-VNS promotes physiological remodeling, preserving cardiac function and interrupting HF progression. This mechanistic framework aligns with evidence supporting modulation of the neuro-cardiac axis in HF therapy, where enhanced parasympathetic tone is correlated with improved outcomes and symptom reduction^{39,40}.

In conclusion, this study addresses critical limitations of existing VNS devices by developing a fully biodegradable, self-powered vagus nerve stimulation system for pressure overload-induced HF therapy. Our BTENG system fundamentally advances the field by eliminating battery replacement surgeries, enabling complete in vivo degradation, and providing ultrasound-controlled treatment duration. The findings demonstrate effective prevention and reversal of cardiac remodeling across multiple disease stages through acetylcholine-mediated pathways. His work provides a paradigm for cardiac neuromodulation that combines vagal stimulation benefits with practical advantages of biodegradable devices, offering a clinically translatable solution that reduces healthcare costs and improves patient outcomes. Future research integrating LL-VNS with existing therapies will further expand therapeutic options for HF patients.

Methods

Ethical Statement

All animal experimental protocols were approved by the Animal Care and Use Committee of Renmin Hospital of Wuhan University (Approval No. WDRM20230901C) and conducted in strict accordance with the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (NIH Publication No. 85-23, revised 1996). All surgical procedures were performed under appropriate anesthesia to minimize animal suffering. This study follows the ARRIVE (Animals in Research: Reporting In Vivo Experiments) guidelines for reporting animal research.

Fabrication of the BTENG stimulator

PLA substrate: PLA powder and ultrapure water at a ratio of 10:1 were heated to 99 °C for one h until fully dissolved. The solution was poured into the mold and placed in a 40 °C oven for drying for 12 h to obtain the desired PLA film.

PVA/Mo film: A low-temperature dissolvable PVA film was purchased from Solebault and subjected to magnetron sputtering at 80 W for 1 h to achieve a PVA/Mo film with one side coated with metal Mo.

Freeze-dried hydrogel (spacer): Sodium alginate and gelatin were mixed at a ratio of 5:1, resulting in a gel solution with a concentration of 4 wt%. The mixture was vigorously stirred at room temperature for 4 hours until it formed a uniform gel, which was subsequently freeze-dried using a freeze-drying machine for 12 hours.

PVA/Fe thick film: PVA powder (6:1) and ultrapure water were used to prepare the solution, and the same weight of Fe powder (100 μm) was added after stability, strongly stirred in a magnetic field for 1 h, and freeze-dried in a freeze-drying machine for 2 h. Then, a part of the sample was collected, and its conductive surface resistivity <100 Ω/cm was evaluated.

Encapsulation materials: PCL powder was dissolved in dichloroethane at a mass fraction of 5 (5 wt%).

Fabrication of the BTENG: A PVA/Fe thick film of 1 cm $\times$ 1 cm was cut, and two freeze-dried hydrogels of size 1 cm $\times$ 0.1 cm were pasted on the edge with PLA glue and then dried for 1 h to ensure that the solvent in the gel had evaporated. A 1 cm $\times$ 1 cm PVA/Mo film was placed on the other side of the hydrogel, ensuring that the PVA surface was in contact with the conductive surface of the PVA/Fe thick film. Wires were drawn as electrodes on the Mo metal surface and PVA/Fe thick film conductive surface of PVA/Mo, respectively, and the components of the device were properly connected. A flexible PLA film was used to cover the whole device, PLA glue was used to seal the edge, and the mixture was allowed to dry for 1 h to ensure that the solvent in the glue evaporated. Afterward, the device was uniformly covered with the prepared 5 wt% package solution, and the homogenizer was rotated at 700 rpm for 30 s. After drying in a 37 °C oven for 1 h, the dichloromethane solvent was completely evaporated. The last step was repeated until a uniform and stable encapsulation layer was produced. All methods are shown in Supplementary Fig. 17.

Characterization of the BTENG

The mechanical properties of the BTENG were tested with a force gauge (Mark-10 ESM303, Mark-10 Corporation, USA). The signals of the BTENG stimulator were measured using an electrometer (Keithley 6517 B, Tektronix, Inc., USA) and an oscilloscope (LeCroy HDO6104, Testwall Ltd., UK). A linear motor (LinMot EI100, LinMot Inc., USA) was used to provide the periodic external force applied to the BTENG (frequency of 2 Hz, operating distance of 30 mm, acceleration of 10 m/s², deceleration of 10 m/s², and maximum speed of 10 m/s). All the in vitro device tests described in the text were completed using a linear motor drive.

Neuroelectrical signals and physiological tests

The electrocardiogram (ECG) 100 C module of a physiological signal recording system (MPI50WSW, BIOPAC, USA) was used in the physiological tests. The clockwise electrode for collecting physiological signals was connected to the skin of the mice. The positive electrode was connected to the left upper limb, the negative electrode was connected to the left lower limb, and the grounding terminal was connected to the right upper limb. Fast Fourier transform was used as a calculation algorithm for HR variability.

LFP neural signal acquisition was achieved with the BLACKROCK neural signal acquisition system. After the neural connection was tested by the LCR instrument, Spike signal extraction and collection were performed with the software of the BLACKROCK system, and the

algorithm was the principal component analysis algorithm. The stimulation electrode was obtained from the KEDOU Company. The electrode was a polar Kraft electrode with a diameter of 1 mm, the electrode material was platinum, and the coating material is PLA. C57BL/6 mice were anesthetized for nerve signal collection, and the collection electrode was directly connected to the left vagus nerve in the neck of each mouse. The stimulation electrodes were also from the KEDOU Company. For simultaneous nerve signal acquisition, a four-electrode kraft electrode was used directly, with two electrodes at the distal end for stimulation and two electrodes at the proximal end to collect the nerve signal. The electrode spacing was 2 mm. Balance capacitors and resistors are connected to the nerve stimulator to guarantee the consistency of the stimulation (Supplementary Fig. 2e).

Degradation test of the BTENG

For the degradation experiments, the conventional in vitro degradation test environment was 1×PBS at 37 °C. The ultrasonic parameters for in vitro accelerated degradation were 1 MHz and 3 W/cm². In the in vivo degradation test, the device was implanted under the skin of the abdomen in each mouse abdomen.

Animals and treatment

Male C57BL/6 mice (8 weeks old, 25–27 g) were obtained from Institute of Laboratory Animal Science, Chinese Academy of Medical Sciences and used to establish a left ventricular pressure overload model through aortic banding (AB) surgery. Male mice were selected to avoid potential hormonal variation attributed to estrogen production in female specimens, ensuring experimental consistency. Animals were housed under stringent specific pathogen-free conditions at Wuhan University's Experimental Animal Center, maintaining controlled temperature (22–24 °C), controlled humidity (40–70%), and a 12-hour light-dark cycle with unrestricted access to food and water. A minimum 7-day acclimatization period was provided before experimental procedures.

Sample sizes were determined based on power analysis using preliminary data from pilot studies. With an expected effect size of 20% difference in LVEF between treatment groups, $\alpha = 0.05$, and power = 0.80, a minimum of 8 animals per group was calculated, with group sizes of 8–12 used to account for potential attrition. Animals were randomly assigned to experimental groups using computer-generated randomization sequences, and investigators performing echocardiographic assessments and histological analyses were blinded to group allocation.

The aortic banding procedure involved precise thoracotomy under isoflurane anesthesia (2–3% in oxygen), followed by transverse ligation of the ascending aorta using 7-0 silk suture and a 26-gauge needle as a spacer, which was subsequently removed to create standardized constriction. Doppler echocardiography verified complete aortic constriction immediately post-surgery. Sham-operated controls underwent identical surgical procedures without aortic ligation. Post-operative analgesia was provided using buprenorphine (0.05 mg/kg subcutaneously) every 12 h for 48 h. Animals were monitored daily for signs of distress, and predefined humane endpoints included severe cardiac decompensation or weight loss exceeding 20% from baseline.

Cardiac functionality was assessed at baseline and at 1-, 2-, 4-, and 8-weeks post-AB through transthoracic echocardiography. Primary outcomes included left ventricular ejection fraction (LVEF) and fractional shortening (LVFS), while secondary outcomes encompassed morphometric indices (heart weight/body weight, heart weight/tibia length, lung weight/body weight ratios), histological changes, and molecular markers.

For preventive intervention studies, treatment was initiated 1-week post-AB with mice randomly assigned to sham ($n = 12$), sham + LL-VNS ($n = 8$), AB+no therapy ($n = 12$), AB+implant ($n = 8$), AB + LL-VNS_20 min ($n = 12$), and AB + LL-VNS_10 min ($n = 12$) groups. Early

intervention studies began 2 weeks post-AB with sham ($n = 12$), AB+no therapy ($n = 12$), AB+implant ($n = 8$), and AB + LL-VNS_20 min ($n = 12$) groups. Late intervention studies commenced 4 weeks post-AB using sham ($n = 12$), AB+no therapy ($n = 12$), AB+implant ($n = 8$), and AB + LL-VNS ($n = 12$) groups. For mechanistic validation, atropine (1 mg/kg/day i.p.) was administered starting 1-week post-AB in four groups: AB+no therapy ($n = 12$), AB+atropine ($n = 12$), AB + LL-VNS ($n = 12$), and AB + LL-VNS+atropine ($n = 12$).

At study termination, animals were euthanized by CO₂ asphyxiation followed by cervical dislocation, and cardiac tissue, lungs, and tibiae were collected immediately for comprehensive morphometric and histological analyses.

Low-level vagus nerve stimulation protocol

In the experiment, we used BTENG as the stimulus source. The driving method of BTENG is a linear motor (frequency of 2 Hz, operating distance of 30 mm, acceleration of 10 m/s², deceleration of 10 m/s², and maximum speed of 10 m/s). Before the stimulation, LCR was used to determine that the neural electrode has good contact (1–100 KHz scan, lasting 2 seconds). Each group's stimulation time is divided into 10 min and 20 min. The stimulation begins every day from the morning, and it lasts for seven days each week.

Echocardiography

Echocardiographic assessments of cardiac structure and function were systematically conducted at 1-, 2-, 4-, and 8-weeks post-AB surgery in alignment with established protocols from our prior research⁴¹. All evaluations were performed using the MyLab 30CV system (Biosound Esaote, Inc.) equipped with a high-resolution 15-MHz transducer under light anesthesia induced with 1.5–2% isoflurane delivered via nose cone. Animals were positioned in supine position on a heated platform to maintain body temperature, and anesthetic depth was carefully monitored to ensure adequate sedation while preserving physiological heart rate and cardiac function.

Critical echocardiographic parameters including heart rate (HR), left ventricular ejection fraction (LVEF), and left ventricular fractional shortening (LVFS) were measured using standard techniques. M-mode and two-dimensional imaging were employed to assess left ventricular dimensions and wall thickness in both systole and diastole. All measurements were performed by investigators blinded to experimental group assignments and were averaged across three to five consecutive cardiac cycles to ensure accuracy and reliability of cardiac functional analysis. Images were acquired during stable anesthetic planes to minimize variability, and measurements were performed offline using the system's integrated analysis software according to American Society of Echocardiography guidelines.

Histological analysis

Heart tissues were fixed in 4% paraformaldehyde for 24 hours, processed through graded alcohols, embedded in paraffin, and sectioned into 5 μ m thick slices for comprehensive histological analysis. To assess myocardial fibrosis and cardiac hypertrophy, tissue sections were stained with picrosirius red (PSR) and wheat germ agglutinin (WGA), respectively, using standard protocols. PSR-stained sections for collagen volume evaluation were imaged using an Aperio VERSA 8 whole slide scanner (Leica Biosystems) under bright-field illumination, while WGA-stained sections for cardiomyocyte cross-sectional area measurements were captured using an Olympus BX53 fluorescence microscope equipped with appropriate filter sets.

For WGA fluorescence staining, tissue sections were incubated with Alexa Fluor™ 488-conjugated WGA (#W11261, Invitrogen) to delineate cardiomyocyte membrane boundaries, and nuclei were counterstained with SlowFade™ Gold Antifade Mountant containing DAPI (#S36939, Invitrogen). Sections were incubated at 37 °C for 2 h to ensure optimal antibody penetration and binding. Image

quantification was conducted in a blinded manner by investigators unaware of experimental group assignments using ImageJ software (version 1.53t, National Institutes of Health, USA). For cardiomyocyte hypertrophy assessment, the average cross-sectional area was calculated from measurements of over 30 randomly selected cells per heart across multiple microscopic fields. Fibrotic volume analysis involved quantification of PSR-positive areas from more than 10 randomly selected fields per heart, with results expressed as percentage of total tissue area. This comprehensive quantitative approach provided robust assessment of pathological features indicative of cardiac remodeling and treatment responses.

RNA purification and qPCR

Total RNA was extracted from tissue using TRIzol reagent (Invitrogen) according to the manufacturer's instructions. Reverse transcription was subsequently performed on aliquots of the purified RNA using an SSTIII kit (Invitrogen) to synthesize cDNA. This cDNA served as a template for SYBR-based quantitative real-time PCR (qPCR), employing the following thermal profile: an initial hold at 50 °C for 2 min and 95 °C for 10 min to activate the Taq polymerase, followed by 40 amplification cycles (95 °C for 10 sec, 60 °C for 1 min). Relative quantification of mRNA levels was achieved through the comparative Ct method, with normalization to *gapdh* expression. The primer sequences for the targeted genes are detailed in Supplementary Table 1.

RNA-seq

In our investigation, we conducted a detailed analysis of gene expression alterations in cardiac tissue harvested from mice subjected to a sequence of interventions post-AB. All cardiac tissue samples were collected at week 8 post-AB surgery (study endpoint), with $n = 3$ biological replicates per group. The study delineated distinct intervention phases: preventive intervention (1-week post-AB), early intervention (2 weeks post-AB), and late intervention (4 weeks post-AB), categorizing the subjects into several groups, as described previously: sham, sham+LL-VNS, AB+no therapy, AB+implant, AB + LL-VNS_20 min, and AB + LL-VNS_10 min.

RNA sequencing was executed in collaboration with Wuhan IGEBNEBOOK Biotechnology Co., Ltd. Following the RNAPrep Pure Kit DP432 (TIANGEN Biotech Co., Ltd., Beijing, China) protocol, total RNA was extracted and assessed for integrity. The VAHTS mRNA-seq V3 Library Prep Kit for Illumina facilitated RNA library construction from 1 µg of total RNA, including polyA RNA isolation, fragmentation, reverse transcription primed with random hexamers, and 150 nt paired-end sequencing on the Illumina NovaSeq 6000 platform.

Adapter sequences and low-quality reads were excised using Cutadapt (version 1.11). Clean reads were aligned to the reference genome with HISAT2 (version 2.1.0), permitting up to two mismatches. Gene mapping against the NR database allowed for transcript abundance estimation and FPKM normalization using feature count (v1.6.0). Differential expression analysis via edgeR was performed with stringent thresholds of $FDR < 0.05$ and $|\log_2\text{FoldChange}| > 1$. Enrichment analysis for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways was conducted using ClusterProfiler, and a hypergeometric distribution with a q value cutoff of 0.05 was applied.

Further analytical techniques included principal component analysis (PCA), which employed the R packages dplyr for data acquisition, FactoMineR for PCA computation, and ggplot2 for visualization, to elucidate the variance within our dataset. Heatmaps were generated using the R package pheatmap and tidyverse for data manipulation and visualization, offering a comprehensive view of gene expression patterns. GO enrichment analyses, with both bar and bubble plots, were performed using ggplot2, revealing significant biological processes and pathways. Enrichment network diagrams were produced

with Metascape⁴² and visualized using Cytoscape to depict intricate relationships among significantly enriched terms. All RNA-sequencing data, including raw FASTQ files and processed gene expression matrices, have been deposited in the Gene Expression Omnibus (GEO) under accession number GSE310767.

Statistical analysis

In this study, quantitative data are reported as the mean $\pm$ standard deviation (SD). Adherence to randomization and blinding protocols was maintained throughout all animal experimental phases to mitigate bias. Blinded analysis was strictly enforced during imaging quantification to ensure objectivity. Statistical rigor was applied through the utilization of Student's t test (two-sided) for binary comparisons and one-way analysis of variance (ANOVA, two-sided) for assessments involving multiple groups, with subsequent Tukey's honest significant difference (HSD) post hoc test to adjust for multiple comparisons. Differences for which $P < 0.05$ were considered significant. The analyses employed GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA) and IBM SPSS Statistics version 22.0 (IBM Corporation, Armonk, NY, USA).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The RNA-sequencing data generated in this study have been deposited in the Gene Expression Omnibus (GEO) database under accession code GSE310767. Source data for Supplementary Fig. 3 are available in Figshare (<https://doi.org/10.6084/m9.figshare.30877082>). All other data generated in this study are provided in the Source Data file 1–3. Source data are provided with this paper.

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Author contributions

Z.G., S.Y.C., C.Y.K., L.L.X., and X.C. contributed equally to this work. Z.G. performed animal experiments, surgical procedures, echocardiography, and data analysis. S.Y.C. designed and fabricated the BTENG device and conducted device characterization. C.Y.K. performed histological and molecular analyses. L.L.X. optimized device fabrication and characterization. X.C. conducted electrical measurements. Y.X. performed RNA-sequencing and bioinformatics analyses. Y.C.Q., M.Y.W., Y.L.M., and X.J.D. assisted with experiments and data collection. Z.L. and Q.Z.T. conceived and supervised the project, designed experiments, secured funding, and wrote the manuscript. All authors discussed results and approved the final manuscript.

Competing interests

All authors declare no competing interests.

Additional information

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