

Bioadhesive Ultrasound for Long-term Continuous Imaging of Diverse Organs

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Abstract

Continuous imaging of internal organs over days could provide crucial information about health and diseases and enable insights into developmental biology. We report a bioadhesive ultrasound (BAUS) device, which consists of a thin and rigid ultrasound probe robustly adhered on the skin via a couplant of a soft, tough, anti-dehydrating and bioadhesive hydrogel-elastomer hybrid. The BAUS device provides 48-hour continuous imaging of diverse internal organs including blood vessels, muscle, heart, gastrointestinal tract, diaphragm, and lung. The BAUS device could enable diagnostic and monitoring tools for various diseases.

Wearable devices that can continuously monitor human physiology in a non-invasive manner represent a pivotal trend in precision and digital medicine (1). Particularly, deep-tissue physiology including internal organ signals and dynamics contains crucial information regarding health and diseases (2). While current wearable devices have successfully recorded physical and chemical signals from the skin such as electrocardiogram (3-5) and sweat metabolites and electrolytes (6-8), clinical-grade imaging of various internal organs remains a central task and a challenge in the field of wearable devices. Ultrasound imaging with zero radiation allows clinicians to evaluate tissue and organ functions and diagnose various diseases (9). If sampled frequently over days to months, ultrasound imaging of internal organs could monitor health status, observe disease progression, and assess disease risks (10-12); it could also lead to discoveries and understanding in developmental biology (13).

Wearable ultrasound devices have the potential for continuous imaging of internal organs. Conventional wearable ultrasound imaging usually relies on mounting bulky ultrasound probes on the skin by either robotic systems (14, 15) or mechanical fixtures such as straps and tapes (16-18), which hamper patients' mobility and wearing convenience and comfort. In addition, conventional wearable ultrasound imaging is only applicable to limited body parts such as muscles due to the thick ultrasound probe and the high pressure exerted by the probe (16). For example, mechanically mounting a conventional ultrasound probe on the neck to image the carotid artery, jugular vein, and vagus nerve could cause suffocation.

While the stretchable ultrasound imaging device has improved wearability (12), it still suffers from limitations including low imaging resolution, unstable imaging quality during body motions (fig. S1), short continuous imaging duration (1 hour), and susceptible to device failure (table S1). (The continuous imaging duration is defined as the longest time that a device can be adhered or worn on the skin.) These limitations mainly stem from the design of the device, which consists of piezoelectric elements over a stretchable substrate (Fig. 1A). While the stretchable substrate can deform conformally with the skin, it limits the density of elements (156 per square centimeter) and is incompatible with backing and matching layers, leading to a low imaging resolution (12). In addition, when the substrate deforms with the skin under body motions, the elements' spatial and angular positions vary unpredictably, which hampers the imaging stability of the device (fig. S1). Furthermore, existing wearable ultrasound devices, in both rigid and stretchable form factors, mostly rely on hydrogel or elastomer couplants for acoustic transmission to the skin (19-22). However, the hydrogel couplants usually get dehydrated or detached from the skin over a few hours (19, 20); the elastomer couplants are too damping to image deep organs (21, 22) (table S2, fig. S2).

We report a bioadhesive ultrasound (BAUS) device, which consists of a thin and rigid ultrasound probe robustly adhered on the skin via a couplant layer made of a soft, tough, anti-dehydrating and bioadhesive hydrogel-elastomer hybrid (Fig. 1, B to D). The BAUS probe enables a high density of elements (400 elements per square centimeter, fig. S3), stable element positions under dynamic body motions, and high reliability of the probe in long-term applications. The BAUS couplant effectively transmits acoustic waves, insulates the BAUS probe from skin deformation, and maintains robust and comfortable adhesion on the skin over 48 hours.

The BAUS probe consists of an array of high-performance piezoelectric elements with a center frequency of 3 MHz, 7 MHz or 10 MHz (Fig. 1, E and F, fig. S3, table S3). Each element is controlled by the top and bottom circuits of the BAUS probe. The circuit can be fabricated with three techniques: three-dimensional (3D) printing (Fig. 1F, fig. S4, movie S2) (23), laser etching (24), and photolithography (fig. S5) (25) which give circuit-line resolutions of 100 μm , 10 μm , and 1 μm , respectively. The bottom circuit

is covered by an optimized acoustic matching layer to enhance the acoustic transmission to the skin; the top circuit is covered by an optimized acoustic backing layer to quench the resonance effect (fig. S6, see materials and methods for details on fabrication and optimization of the matching and backing layers). The BAUS probe is sealed by a layer of epoxy for high stability and reliability in long-term applications. We further design a plug-and-play input/output (I/O) to connect with the flexible flat cable (fig. S7). The BAUS probe has a thickness of 3 mm, length and width of 1-2 cm, and weight of 10-40 g (fig. S3; table S3).

The BAUS couplant consists of a soft yet tough hydrogel composed of chitosan-polyacrylamide (PAAm) interpenetrating polymer networks (10 wt%) and water (90 wt%) (see materials and methods for details on fabrication of the BAUS couplant). The hydrogel is encapsulated by a thin elastomer membrane (thickness, $< 40 \mu\text{m}$) of polyurethane to prevent dehydration of the hydrogel and to make the skin comfortably contact with a dry couplant surface (fig. S8 and S9). The polyurethane membrane is grafted with poly(acrylic acid) coupled with *N*-hydroxysuccinimide ester (NHS ester) to form robust bonding with the hydrogel (26). The hydrogel-elastomer hybrid is further coated by a thin bioadhesive layer (thickness, $< 10 \mu\text{m}$) synthesized by copolymerizing poly(ethylene glycol) diacrylate, 2-ethylhexyl acrylate, acrylic acid, and acrylic acid *N*-hydroxysuccinimide ester (AAc-NHS ester) (fig. S10). The carboxylic acid, ethyl, and hexyl groups in the bioadhesive can form physical bonds such as hydrogen bonds and electrostatic interactions with the skin; the NHS ester groups in the bioadhesive can form covalent amide bonds with the skin (26). The total thickness of the elastomer membrane and the bioadhesive layer is less than $\frac{1}{4}$ of the acoustic wavelength to minimize the acoustic attenuation of the BAUS couplant (Fig. 2D).

To quantitatively validate that the BAUS device can robustly adhere to the skin under dynamic body motions, we develop a model of a rigid device adhered to the skin via a soft couplant layer (Fig. 2A; see fig. S11 and materials and methods for details on the model). When the skin is stretched under an applied strain ϵ_{app} , a crack may initiate at the edge of the couplant-skin interface and propagate. Crack propagation is driven by the energy release rate G (defined as the reduction of stored elastic energy in the couplant-skin system when the crack propagates by a unit area) and resisted by the interfacial toughness Γ (defined as the energy required to propagate the crack by a unit area). In Fig. 2B, we calculate the energy release rate G of a couplant-skin system under the plane-strain condition with a typical device length L of 2 cm and a typical applied strain on the skin ϵ_{app} of 20%. For simplicity of calculation, the skin and the couplant layer are taken as incompressible linear elastic materials with the same Young's modulus of 100 kPa. If the energy release rate is higher than the interfacial toughness $G > \Gamma$ (unshaded zone in Fig. 2B), the crack propagates on the interface and the device debonds from the skin. When the rigid device is physically attached on the skin without any couplant ($H=0$), the interfacial toughness is around 1 Jm^{-2} and the rigid device detaches from the skin. In contrast, when the rigid device is adhered to the skin via the BAUS couplant, the interfacial toughness exceeds 500 Jm^{-2} both in air and under water (Fig. 2C), robustly bonding the device on the skin for any couplant thickness. In fig. S11, we calculate the energy release rate of the couplant-skin system with various parameters for future design of bioadhesive devices.

To evaluate the adhesion performance of the BAUS couplant on the skin, we conduct the standard 90°-peeling test (ASTM D2861) to measure the interfacial toughness of the elastomer membrane adhered on a porcine skin via the bioadhesive layer (see materials and methods for details on the test). We choose the porcine skin as the model tissue for evaluating adhesion performance because of its resemblance to the human skin (26). The elastomer membrane can establish tough adhesion on the porcine skin upon contact, giving interfacial toughness of 853 Jm^{-2} . When the adhered sample is stored in air (relative humidity, 30-

50%; temperature, 24°C), the interfacial toughness decreases to 756 J m⁻² over 48 hours. When the adhered sample is stored in water to simulate wet environments, the interfacial toughness decreases to 518 J m⁻² over 48 hours. These results (Fig. 2C, Fig 2E) show that the bioadhesive layer can robustly adhere the BAUS device on the skin over 48 hours in dry and wet environments. The BAUS device can be detached from the skin by peeling from one edge of the BAUS couplant without leaving any residue (fig. S12). In comparison, the interfacial toughness of typical liquid (Aquasonic Clear, Parker Labs) and solid (Aquaflex, Parker Labs) hydrogel couplants and elastomer couplants including silicone (Ecoflex, Smooth-On), polyurethane (Sigma-Aldrich), and Aqualene (Olympus) are all below 10 J m⁻², which cannot give stable adhesion of ultrasound probes on the skin. While the 3M VHB acrylic tape can maintain relatively high interfacial toughness (>456 J m⁻²) in air over 48 hours, the interfacial toughness reduces to 27 J m⁻² in water, possibly leading to unstable adhesion in wet environments.

To evaluate the wearing comfort of the BAUS couplant on the skin, we adhere a set of BAUS couplants on various body locations including arm, neck, chest, and waist of 15 subjects for 48 hours (fig. S9). Most of the subjects report no positive reaction (i.e., itchiness, irritation, dryness, or redness) at any location; only 1 subject reports minor itchiness after 48 hours of continuous wearing (fig. S13). As control samples, the abovementioned typical couplants are adhered (3M VHB acrylic tape) or mechanically wrapped (others) on the arm of the 15 subjects. The liquid and solid hydrogel couplants give the highest positive reactions, and the positive reactions of the elastomer couplants are also higher than that of the BAUS couplant. These results are consistent with the comfort feelings of the subjects evaluated by the visual analogue scale (VAS): the BAUS couplant gives the most comfortable feelings; the liquid and solid hydrogel couplants give the most uncomfortable feelings (fig. S13).

To evaluate the acoustic performances of the BAUS couplant, we use the transmission-through method to measure the attenuation coefficients of the BAUS couplant. At frequencies from 1MHz to 10MHz, the attenuation coefficients of the BAUS couplant are measured to be from 0.036 dB/mm to 0.131 dB/mm (Fig. 2D, fig. S14). We further measure the acoustic impedance of the BAUS couplant to be 1.59 MRayl, which matches the acoustic impedance of the skin. In comparison, the typical liquid and solid hydrogel couplants have similar attenuation coefficients as those of the BAUS couplant at frequencies from 1MHz to 10MHz: 0.070-0.120 dB/mm and 0.117-0.174 dB/mm, respectively. However, the attenuation coefficients of all abovementioned elastomer couplants are multiple times higher than that of the BAUS couplant at the same frequency. This is consistent with the result that these elastomer couplants are too damping to allow wearable ultrasound imaging of internal organs (fig. S2).

To evaluate the performances of the BAUS probes, we first perform electrical impedance measurements on all elements in the probes (fig. S15; table S4). The measured center frequency of the elements on each BAUS probe is indeed 3 MHz, 7 MHz, or 10 MHz (with minor deviation, <5%) as prescribed; the electrical impedances of the probes at their center frequencies are 49 Ω, 36 Ω, or 43 Ω, respectively (fig. S16; table S4). We then measure the crosstalk in each BAUS probe to be below -40 dB which is sufficiently low for high-quality imaging applications (fig. S17; table S4) (27). We next perform the pulse-echo tests on all BAUS probes to measure their bandwidths. The measured bandwidths of 3 MHz, 7 MHz, and 10 MHz BAUS probes are 68%, 75%, and 78%, respectively (fig. S18, table S4).

To evaluate the imaging resolutions of the BAUS probes, we first perform the pulse-echo tests on the BAUS probes to characterize their axial resolutions (fig. S19). The axial resolutions of the 3 MHz, 7 MHz, and 10 MHz BAUS probes are 0.77 mm, 0.225 mm, and 0.1924 mm, respectively (fig. S19; table

S4). We then measure the point spread functions of the BAUS probes to characterize their lateral resolutions. The lateral resolutions of 3 MHz, 7 MHz, and 10 MHz BAUS probes are 1.79 mm, 0.38 mm, and 0.38 mm at their imaging focal depths of 6 cm, 3 cm, and 2 cm, respectively (fig. S20 to S22; table S4). These measured values are also confirmed by the acoustic simulations (fig. S20 to S22). In comparison, the axial resolution of the stretchable ultrasound imaging probe (2 MHz) is reported to be 5.775 mm (12).

To test the imaging stability of the BAUS device, we adhere the BAUS device on a phantom of a blood vessel in soft tissues under various frequencies of vibration (0 Hz to 3.5 Hz with an amplitude of 2 cm) to evaluate its acoustic performance under dynamic body motions. Due to stable adhesion of the BAUS device to the phantom and the relatively high imaging frame rate (40 Hz), the motion artifact on imaging is minimal (fig. S23).

To test the thermal properties of the BAUS device, we measure the temperature of the BAUS device continuously actuated by various levels of working voltages (0V-90V) over 48 hours. Owing to its low working power and thin form factor for heat dissipation, the BAUS device can maintain a constant level of temperature (24°C) while continuously imaging for 48 hours (fig. S24 and S25), validating its thermal stability in long-term applications.

We demonstrate the BAUS imaging platform's capability of 48-hour continuous imaging of human organs including blood vessels and heart, muscle and diaphragm, stomach, and lung. These organs represent the cardiovascular, muscular, digestive, and respiratory systems, respectively. To image organs with depths less than 6 cm beneath the skin (i.e., jugular vein, carotid artery, and bicep muscle), we choose an ultrasound probe with a center frequency of 7 MHz or 10 MHz and adopt the plane wave compounding method (fig. S26). To image organs deeper than 6 cm beneath the skin (i.e., heart, stomach, diaphragm, and lung), we choose an ultrasound probe with a center frequency of 3 MHz and adopt the phased array imaging method (fig. S27 to S29, movie S3 and S4, see materials and methods for details on acoustic simulation). The probes are adhered to various locations on the skin of a healthy subject via the BAUS couplants for continuous imaging of the corresponding organs over 48 hours (see materials and methods for details on data acquisition and image processing).

Figure 3 and fig. S30 demonstrate the imaging results of the jugular vein and carotid artery obtained by the 10 MHz BAUS device adhered on the right-hand side of the neck (Fig. 3A). Dynamic body motions such as neck rotation can cause blood vessel shifting and skin deformation, which deteriorate the imaging quality and stability of existing wearable ultrasound devices (11). In contrast, the BAUS device can provide 48-hour continuous imaging of the jugular vein and carotid artery under dynamic body motions such as neck rotation with angles up to ± 30 degrees (Fig. 3B, movie S5). This is because of the robust adhesion of the BAUS device on the neck, the high imaging resolution of the BAUS probe, and the large acoustic window given by the BAUS probe aperture (2 cm $\times$ 1 cm). The BAUS imaging results show that the diameter of the jugular vein in the subject increases from the sitting/standing position to the supine position (Fig. 3C and fig. S30). The change of the jugular vein diameter strongly correlates with the right atrium pressure (28), and thus can be used to diagnose cardiac diseases such as heart failure and pulmonary hypertension (29). The BAUS imaging results further give 48-hour continuous blood flow rate and blood pressure waveform of the carotid artery (Fig. 3D to F, fig. S30). For example, we observe dramatic increases of blood flow rate (from 65 cm/s to 117 cm/s, Fig. 3D), and systolic blood pressure (from 115 mmHg to 168 mmHg, Fig. 3E) of the carotid artery in the subject before and after 0.5 hours of physical exercise (see materials and method for details on data acquisition and calculation of the blood pressure). Moreover, from

the blood pressure waveform measured after the 0.5-hour jogging (right panel, Fig. 3E), we can see a steeper drop of the blood pressure from the systolic peak in each cardiac cycle than that before the exercise, possibly due to the exercise-induced vasodilation of the carotid artery.

Fig. S31 demonstrates the imaging results of the bicep muscle obtained by the 7 MHz BAUS device adhered to the upper arm of the subject (fig. S31). The BAUS system can give 48-hour continuous imaging of the bicipital muscle. For example, we observe increased blood perfusion and echogenicity on the muscle and tendon interface 2 hours after a 1-hour weightlifting training and increased vascularity 10 hours after the training (fig. S32).

Fig. 4A, Fig. 4B, and fig. S33 demonstrate the imaging results of the lung obtained by the 3 MHz BAUS phased array device adhered on the right chest (longitudinal direction) of the subject (Fig. 4A). The BAUS system can give 48-hour continuous imaging of key characteristics of the lung including the pleural line and A-lines. The BAUS device is also able to continuously and stably image the lung under body motions such as jogging and cycling (fig. S34). The BAUS imaging shows a smooth pleural line and repetitive A-lines of the subject over 48 hours, indicating a healthy, normally-aerated lung. While lung ultrasonography has proven to be an effective tool for diagnosing COVID-19 patients (30), it is mostly available in hospitals for infrequent and non-continuous imaging of the lung. In contrast, the wearable BAUS system could continuously monitor the symptoms of possibly infected COVID-19 patients at home.

Fig. 4C and Fig. 4D demonstrate the imaging results of the diaphragm motility obtained by the 3 MHz BAUS phased array device adhered on the right anterior subcostal region of the subject before and after 0.5 hours of physical exercise. The BAUS imaging shows that the diaphragm motility after training is more dramatic in amplitude and frequency compared with quiet breathing before training.

Fig. 4E and fig. S35 demonstrate the imaging results of the heart obtained by the 3 MHz BAUS phased array device adhered on the left chest of the subject (imaging through the apical 4-chamber view). The BAUS system can give 48-hour continuous imaging of the dynamics of four cardiac chambers including the right ventricle, right atrium, left ventricle, and left atrium. The BAUS device is also able to continuously and stably image the heart under body motions such as jogging and cycling (fig. S34). For example, we observe the size of the left ventricle significantly increases after 0.5 hours of physical exercise. The continuous images of the cardiac chambers (fig. S35) can be further processed to calculate the dynamics of cardiac strain – an important parameter that could indicate cardiomyopathy.

Fig. 4F and fig. S36 demonstrate the imaging results of the stomach obtained by the 3 MHz BAUS phased array device adhered on the upper abdomen skin of the subject. The BAUS imaging system gives 48-hour continuous imaging of the gastric antral cross-section. For example, we can observe an extended gastric antrum once the subject drinks 450 ml of juice (Fig. 4F). Over the next 2 hours, the gastric antral cross-sectional area gradually decreases due to the gastric emptying (Fig. 4F and fig. S36).

While the imaging resolutions of the BAUS probes are superior to those of existing wearable ultrasound devices (Fig. 1G and table S1), the BAUS probes can be further improved for better imaging quality in the future. The pitch of the current BAUS probes is relatively large (0.5 mm, table S3) and can cause grating lobes especially in the 7 MHz and 10 MHz BAUS probes. While the grating-lobe artifacts can be alleviated by using the plane wave compounding method (fig. S26) (31), the pitches of future BAUS probes will be reduced to eliminate the artifacts. While the current BAUS probes do not have elevation focusing, thin-profile (<1 mm) elevation lenses (32) can be added to future BAUS probes for elevation focusing to achieve better imaging quality especially for deep organs.

Since the current work is focused on designing and fabricating the BAUS devices, we use an external system (Verasonics Vantage system) for data acquisition. Despite the large size of the data acquisition system, the BAUS devices may find immediate applications in non-mobile imaging in clinical settings such as long-term imaging of patients in intensive care units. In addition, since the data acquisition systems of point-of-care ultrasound devices (e.g., GE VScan, Butterfly IQ, and Phillips Lumify) have been miniaturized to the size of a cell phone, the data acquisition system of BAUS can be miniaturized in the future. Beyond clinical applications, the BAUS imaging platform could provide long-term continuous imaging of the developments of tissues and organs including embryo, tumors, and brain in a non-invasive manner (33, 34).

The current paradigm for bio-integration of devices is to make the devices thin and stretchable for conformal attachment on the body. In this paper, we propose a different paradigm for bio-integration: to robustly adhere thin and rigid devices on the body via a soft, tough and bioadhesive couplant (Fig. 1 and 2). Developing bioadhesive couplants that enable electrical, optical, thermal, chemical, and/or biological interfacing with the body could open new avenues to future bio-integrated devices.

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FIGURE CAPTIONS

Figure 1. Design and imaging performances of the bioadhesive ultrasound (BAUS) device. (A) Existing epidermal wearable ultrasound imaging usually relies on thin and stretchable devices physically attached on the skin. (B) The BAUS device consists of a thin and rigid ultrasound probe robustly adhered on the skin via a couplant of a soft, tough, anti-dehydrating and bioadhesive hydrogel-elastomer hybrid. (C) The BAUS couplant consists of a tough hydrogel, containing 90 wt% water, that is encapsulated by an elastomer membrane further coated by a thin bioadhesive layer. The BAUS couplant maintains robust adhesion between the BAUS probe and the skin over 48 hours and insulates the BAUS probe from skin deformation during dynamic body motions. (D) Scanning electron microscopy (SEM) image of the cross-section of the BAUS couplant. The total thickness of the elastomer membrane and the bioadhesive layer is below $\frac{1}{4}$ of the ultrasound wavelength λ . Scale bar 10 μm . (E) Schematics of the BAUS probe structure. The BAUS probe consists of an array of high-performance piezoelectric elements, which are controlled by the top and bottom circuits. The top and bottom circuits are covered by the acoustic backing and matching layers, respectively. (F) Optical microscopic image of a BAUS probe with 3D-printed top and bottom circuits. Scale bar, 1 mm. The insert image gives a zoomed-in top view of the device showing the top circuit and piezoelectric elements. Scale bar, 0.5 mm. (G) Comparison of axial imaging resolutions and continuous imaging durations of existing wearable ultrasound imaging devices and the BAUS device.

Figure 2. Adhesion and acoustic performances of the BAUS device. (A) Schematics of the mechanical model for a rigid device adhered on the skin via a couplant layer. (B) The energy release rate G as a function of the couplant thickness H calculated by the model with typical parameters: skin and couplant Young's modulus $E_s = E = 100$ kPa, device length $L=2$ cm, applied strain on the skin $\varepsilon_{app} = 20\%$, and interfacial toughness between the couplant and the skin Γ . (C) Interfacial toughness between the BAUS couplant and a porcine skin measured over 48 hours after adhesion formation. Error bars indicating standard deviation ($\pm$ SD) of interfacial toughness ($n = 4$ independent samples). (D) Acoustic attenuation coefficients of the BAUS couplant at frequencies from 1MHz to 10MHz over 48 hours in air. (E) The BAUS device adhered on the skin can withstand high pulling forces and maintain robust adhesion on the skin over 48 hours. Scale bar, 10mm.

Figure 3. Long-term continuous BAUS imaging of blood vessels (also see fig. S30 and movie S5). (A) Schematics of the BAUS device adhered on the neck of the subject to image the carotid artery and jugular vein. (B) The BAUS device can stably image the blood vessels under dynamic body motions such as neck rotation with angles up to ± 30 degrees. Scale bar, 0.5 cm. (C) The diameter of the jugular vein increases significantly from the sitting/standing position to the supine position (D) Color flow imaging of the carotid artery by the BAUS device. The diameter of the carotid artery and the blood flow rate in the carotid artery increase significantly after 0.5 hours of physical exercise. Scale bar, 0.5 cm. (E) Blood pressure waveforms of the carotid artery before and after 0.5 hours of physical exercise. The systolic blood pressure of the carotid artery increases significantly after 0.5 hours of physical exercise. The drop of the blood pressure from the systolic peak in each cardiac cycle is much steeper after 0.5 hours of

physical exercise. (F) The systolic blood pressure of the carotid artery over 48 hours measured from the BAUS imaging. The systolic blood pressure is measured by calculating the mean and standard deviation of 15 consecutive systolic peaks every 0.5 hours. Error bars indicating standard deviation (+/- SD) of measured systolic pressure (n = 15 independent samples). The 0.5-hour training periods are labelled by the dashed lines.

Figure 4. Long-term continuous BAUS imaging of lung, diaphragm, heart, and stomach (also see fig. S33 to S36). (A) Schematics of the BAUS device adhered on the chest of the subject to image the lung. (B) The BAUS imaging shows a smooth pleural line and repetitive A-lines of the lung. (C) The BAUS imaging shows clear diaphragm morphology. (D) The diaphragm motility increases significantly in amplitude and frequency after 0.5 hours of physical exercise. (E) The BAUS imaging shows the dynamics of the four chambers of the heart. The size of the left ventricle significantly increases after 0.5 hours of physical exercise. (F) The BAUS imaging shows the dynamics of the stomach. The gastric antrum cross-sectional area gradually decreases after the subject drinks 450 ml of juice.

SUPPLEMENTARY MATERIALS

Materials and Methods

Figs. S1 to S36

Tables S1 to S4

Captions for Movies S1 to S5