

Heart sounds

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Chapter 6

General discussion and impact



General discussion and impact

The overarching goal of this thesis is to provide insights into the relations between heart sound characteristics and hemodynamics in heart failure, and test feasibility of measuring heart sounds on a large scale using mobile phones.

We investigated the use of heart sounds for estimation of interventricular (VV) delay in **Chapter 2**, and for optimization of atrioventricular (AV) delay in **Chapter 3**. In **Chapter 2**, a novel algorithm was proposed for automatic calculation of VV delay from second heart sounds (S2) measured in open-chest porcine experiments. A close relation was observed between algorithm-estimated S2 splitting and invasively measured VV dyssynchrony. In **Chapter 3**, we investigated optimization of AV delay in a combined experimental-clinical study. In the experimental study, heart sounds were collected from pigs under baseline and myocardial depression. In the clinical study, heart sounds were collected from the patients using a microphone incorporated in a pulse generator of a cardiac resynchronization therapy (CRT) device. Both studies indicated close relations between heart sound-derived systolic time intervals (STIs) and left ventricular (LV) contractility indicators during varying paced AV delays. Loss of hemodynamics at optimal AV delays determined by heart sounds was minor. Thus, heart sound-derived STIs can probably serve as useful indicators for optimization of AV delay in CRT.

While CRT is indicated for patients with severely reduced ejection fraction, heart failure with preserved ejection fraction (HFpEF) is faced with a scarcity of treatments. Close monitoring of these patients is nonetheless important to identify symptoms at an early stage so that drugs can be utilized to relieve the patients' symptoms. In **Chapter 4**, we conducted a pilot study with a handheld digital stethoscope to explore associations between phonocardiography (PCG) and echocardiography in patients suspected of HFpEF. The study showed that heart sound frequency, STIs and occurrence of fourth heart sound were linked to the ratio of early diastolic mitral inflow to mitral annulus velocity (E/e'), a common echocardiographic indicator of elevated LV filling pressure and diastolic dysfunction. Furthermore, we proposed a combined score based on heart sound features to differentiate E/e' below and above 9, which showed good performance in both matched patients and all enrolled patients. The study may provide novel non-invasive markers for evaluation of HFpEF patients.

One major bottleneck in the widespread application of heart sounds for home monitoring is the lack of an affordable device to measure heart sounds. In **Chapter 5**, we tested the feasibility of using the microphone of smartphones as an electronic stethoscope. Nearly 80% of the users were able to record heart sounds by themselves, and around 3 out of 4 recordings were visually labelled as good quality. The quality of recorded heart sounds did not significantly differ by sex or phone version but tended to be lower in patients with an advanced age and a high body mass index. The study was the first in investigating factors affecting heart sound quality among general users. It provided evidence and confidence to further develop smartphone for daily remote monitoring of the patients, as one of basic components of mobile health (mHealth).

In this chapter, we will discuss our findings from a broader perspective. To do so, we first present a brief review of history of heart sound research, together with evolution of device for measurement of heart sounds. Then alterations of heart sounds in heart failure are analyzed, and the novelty of our research results is evaluated. The past two decades have seen emergence of novel tools for measurement and algorithms for analysis of heart sounds. These advancements will be discussed in the broad context of mHealth. This chapter is wrapped up with discussion on scientific and social impacts of the findings of this thesis.

1. Three waves of heart sound research

Literature search for publications on heart sounds has clearly shown three waves of research enthusiasm (**Figure 1**). The first wave started from early 19th century and spanned across the whole 20th and beginning of the 21th century. Early days of heart sound research were centered on how to develop a simple tool for auscultation. History of auscultation is generally thought to start from an accidental finding by René Laennec who was able to listen to sounds of the heart by rolling a square of paper to a cylinder and applying it to the patient's precordial area in 1816 [1]. Since then, the instruments for auscultation have greatly evolved. An important landmark is the invention of the binaural stethoscope by Arthur Leared in 1851, which has been the prototype for all stethoscopes used nowadays [2]. However, human ears may not serve as the best detector of low-frequency vibrations like heart sounds. Boosted by progresses in electronic engineering, PCG machines were developed that used electronic modules for sensing vibrations and an

oscillograph for displaying signals [3]. Indeed, the first wave of heart sound research was initiated by the popularity of the PCG machine in 1950s, contributing to most (88%) of all publications on heart sounds. During this first wave, two major research topics were origin of heart sounds and applications of heart sounds to diagnosis of diseases.

Investigations on the first topic resulted in several theories on the origin of heart sounds. While early studies hypothesized that sudden tensing of ventricular muscles or cardiac valves gives rise to heart sounds, later studies tended to support the idea of vibrations of the whole cardiohemic system including valves, myocardia, blood mass and adjacent tissues as origin of heart sounds [4-7]. The recent simulation study in our group, based on the cardiohemic hypothesis, appeared quite consistent with previous observations of heart sounds in normal condition, heart failure and exercise [8]. **Chapter 4** showed a higher frequency of heart sounds in patients with elevated LV filling pressure. This was likely caused by the vibrations of a blood column encapsulated in a stiffened structure consisted of myocardia, valves and adjacent tissues.

The second distinctive feature of the first wave of heart sound research is the large number of observations on heart sounds in various diseases. The study on alterations of heart sounds in heart failure is an example and will be discussed below in **Section 2**.

The first wave of heart sound research waned at the emergence of a novel imaging technique, echocardiography. The first course dedicated to cardiac ultrasound was in 1968 and the first book on echocardiography in 1972 [9]. Virtually in parallel, researchers' interest in heart sounds has faded from the 1970s to 2000, with the number of annual publications drastically decreasing from over 400 to less than 40.

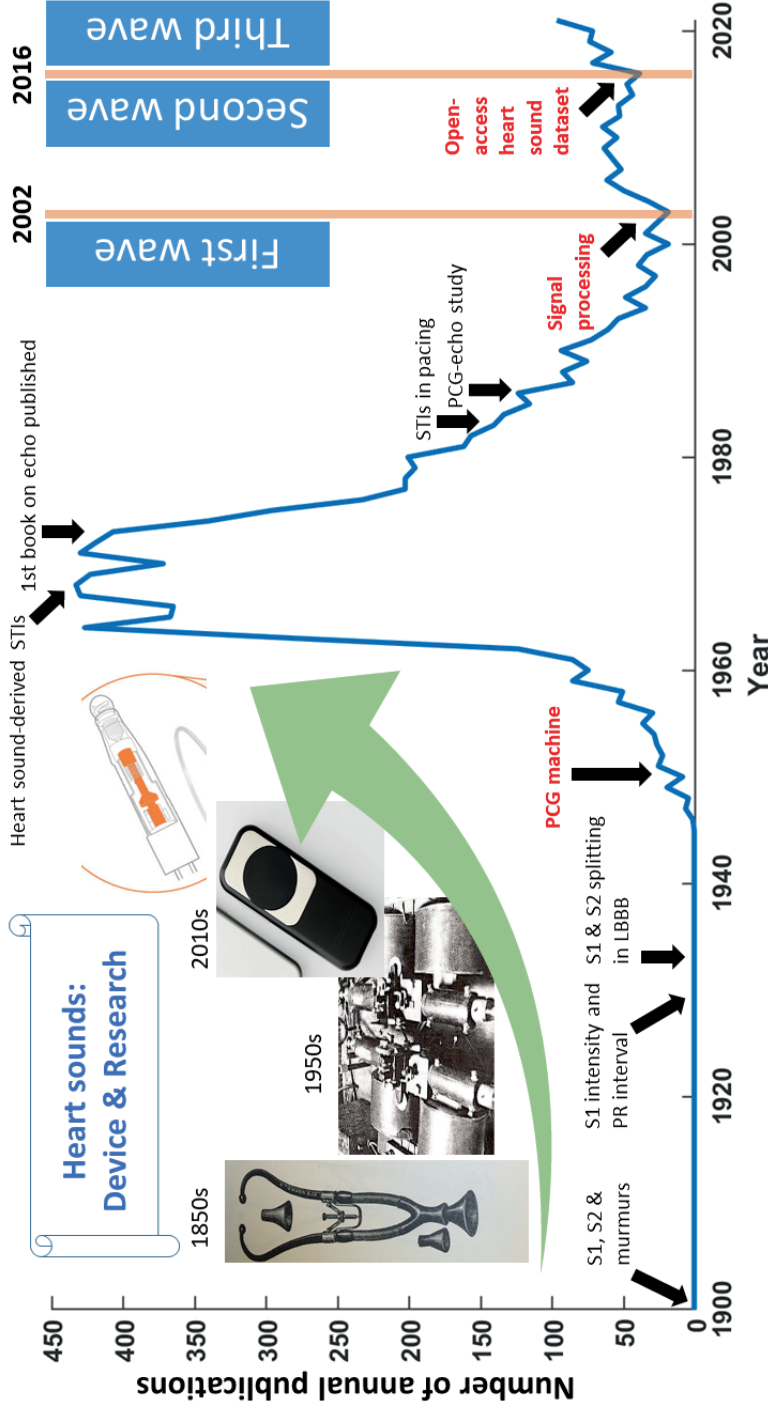


Figure 1. Trends of heart sound measurement devices and research publications Number of annual publications was retrieved from a PubMed search on 23 February 2022 using the following search query: phonocardiogr* OR "heart sound". Only data between the years 1900 and 2021 are shown. Echo, echocardiography; LBBB, left bundle branch block; PCG, phonocardiography; S1, first heart sound; S2, second heart sound; STIs, systolic time intervals.

In the first two decades of the 21st century, the second wave of heart sound research occurred because of advancements in signal processing techniques. The most important progress is the development and enhancement of multiple time-frequency representation algorithms for heart sound analysis, including short-time Fourier transform, wavelet transform, Hilbert-Huang transform and Wigner distribution, which are still widely used nowadays [10-13]. These time-frequency representation algorithms allow to project one-dimensional time-series signals such as heart sounds to a two-dimensional map for better observations of changes of frequency and energy with time. One of important applications of time-frequency projection is for estimation of heart sound splitting. In **Chapter 2**, S2 was projected to a time-frequency map using S-transform to allow automatic tracking of aortic and pulmonic components. The S2 splitting interval was calculated from the timing difference between the two components. The algorithm was validated in simulated conditions and showed a close relation to the invasively-measured "gold standard" of VV dyssynchrony. In contrast, previous studies on S2 splitting using time-frequency representation algorithms were neither validated in simulation nor shown to be related to ventricular activities in experiments [14-18].

6 The past 5 years have seen the commencement of a third wave of heart sound research, boosted by open-access heart sound datasets and machine learning algorithms. The most-cited heart sound dataset is the PhysioNet Heart Sound Database released in 2016 which contains over 2400 heart sound recordings from nearly 1300 healthy volunteers and patients [19]. The dataset has stimulated studies on algorithms for automatic segmentation, feature extraction and classification of heart sounds [20-22]. All these three tasks can be achieved using machine learning, which is discussed in **Section 3**.

The above-mentioned progress on heart sound research has benefited from continuous evolutions of heart sound measurement tools. This topic will also be covered in **Section 3**.

2. Heart sounds in heart failure

The origin of heart sounds dictates that any alterations of cardiac mechanical activities during diseased conditions may affect morphologies and timing of heart sounds. In this thesis, we focus on the alterations of heart sounds in heart failure in **Chapters 2, 3 and 4**. Heart failure may be caused by either systolic or diastolic dysfunction, or both. The former is also referred to as heart failure with reduced

ejection fraction, while the latter is called HFpEF [23]. This section will discuss the relations of various heart sound features including STIs, dominant frequency and splitting interval to heart failure. Furthermore, values of heart sounds in predicting heart failure patients' outcomes are discussed.

2.1 STIs

STIs are time intervals within the cardiac systole that can be derived from simultaneous heart sound and electrocardiogram (ECG) measurements, including time interval from onset of QRS to onset of S1 (QS1) and time interval between onsets of S1 and S2 (S1S2). Several studies reported a longer QS1 in heart failure patients compared with normal subjects [24-28]. Findings regarding S1S2 in heart failure were inconsistent [26, 28]. This was likely caused by differences in confounding factors between the studies, such as heart rate, gender and body mass index of the patients. **Chapter 3** circumvented these factors by using animals as their own controls while varying paced AV delays with a fixed heart rate. The study found close relations between STIs (QS1 and S1S2) and myocardial contractility evaluated using invasive pressure indicators including the maximal rate of rise of LV pressure.

In addition to myocardial contractility, atrial pressure also seems to play a crucial role in determining QS1. **Chapter 4** shows that patients with an enlarged left atrial volume and elevated LV filling pressure tend to have a longer QS1. It is likely that elevated atrial pressure at a given rate of rise of LV pressure delays the timing of atrio-ventricular pressure cross-over and thus the onset of S1 [29]. Overall, QS1 and S1S2 may serve as useful timing indicators of ventricular systolic and diastolic (dys)function.

2.2 Frequency of heart sounds

Little is known about changes of heart sound frequency in heart failure. This may have been caused by complexity of frequency calculation during the first wave of heart sound research when computers were either unavailable or primitive. From a physics perspective, frequency of a harmonic oscillator is equal to the square root of material elasticity divided by the mass of the system. An early observational study reported S1 energies shifted toward low-frequency range in patients with cardiomyopathy [30]. The authors hypothesized that decreased myocardial elasticity and volume overload together may have resulted

in reduced S1 frequency. However, myocardial elasticity is also likely increased in these patients due to more stretched myocardium by enlarged LV end-diastolic volume. This idea is supported by data from a recent porcine study showing that the dominant frequency of S1 increases with end-diastolic volume [31]. In patients suspected of HFpEF, S1 frequency tends to increase with elevated LV filling pressure (**Chapter 4**). The structural cause may come from LV hypertrophy, as evidenced by a heavier LV mass in patients with a higher E/e' ratio.

Our study is the first to demonstrate relationship between heart sound frequencies and echocardiographic parameters. In addition to S1 frequency, S2 and S4 frequencies have also been found higher in patients with elevated LV filling pressure, suggesting a stiffened cardiohemic system in these patients. However, these findings still need to be confirmed in more extensive studies.

2.3 Splitting of heart sounds

Heart sounds are initiated by valve closure, with S1 containing mitral and tricuspid components, while S2 containing aortic and pulmonic components. Measuring this heart sound splitting may be of value for evaluation of VV dyssynchrony which is not uncommon in heart failure patients. A pulsed-wave Doppler imaging study in patients with reduced LV ejection fraction (< 35%) showed that up to 72% of patients with left bundle branch block and QRS duration over 150 ms have a mechanical VV delay greater than 40 ms, which remained above 50% in patients with a QRS duration between 120 – 150 ms [32]. The benefits of correcting for VV dyssynchrony in these patients have been widely validated in large clinical trials, but the selection of eligible candidates for CRT is mainly based on electrical dyssynchrony assessed using ECG criteria such as QRS duration and LBBB morphology [23]. Addition of heart sounds to current criteria may provide an extra layer of information on mechanical dyssynchrony. In the Markers and Response to CRT (MARC) study, mechanical VV delay was shown to contribute to patient selection [33]. Following CRT implantation, splitting of heart sounds may also be useful for regular evaluation of VV contraction. The Cardiac Resynchronisation in Heart Failure (CARE-HF) study showed that CRT significantly reduced VV mechanical delay by 21 ms during 3 months follow-up, which persisted up to 18 months [34]. While the study had to rely on echocardiography for follow-up of the patients, heart sounds can be regularly recorded by the patients at

home, or using a microphone in the implanted device in combination with automated adjustment, as is the case in the SonR system.

Moreover, computer simulation studies in our group showed that S2 splitting is a promising tool for evaluation of type and evolution of heart failure. S2 splitting interval is prolonged as LV function worsens at constant RV function, while shortened or even reversed as only RV function worsens [8]. Therefore, S2 splitting interval, used alone or combined with other heart sound components such as third heart sound, may be helpful for titration of drugs such as diuretics and beta-blocker, as well as optimization of pacemaker therapy in heart failure patients.

The findings in **Chapter 2** confirm that S2 splitting can be determined reliably. Several aspects of this experimental study are noteworthy. Firstly, signal-to-noise ratio of S2 in our study is much higher than previous studies because heart sounds were measured epicardially on the right ventricular outflow tract close to the pulmonic and aortic valves. In comparison, most previous studies collected heart sounds on the chest and thus might have suffered from interference by noises such as respiratory sounds. Moreover, the pulmonic component was likely poorly recorded in previous studies due to its low amplitude and damping during its transmission to the chest. Secondly, an advanced automatic signal processing technique was utilized to calculate splitting interval of S2, while previous studies had to rely on eyeballing to identify heart sound components. Each of S2 components (aortic or pulmonic) consists multiple peaks and nadirs before the signal gradually damps, creating challenges for visual inspection of heart sound components. Lastly, S2 splitting interval showed a close relation to VV mechanical dyssynchrony measured invasively with catheter, which has not been reported in any previous studies.

In **Chapter 2**, we only investigated splitting of S2 rather than S1 because the epicardial sensor on right ventricular outflow tract was assumed to optimally record S2. Nonetheless, S1 splitting may similarly provide useful information on VV dyssynchrony, as indicated in previous roentgenkymographic and echophonocardiographic studies in patients with left and right bundle branch block [35-37]. The most distinctive advantage of evaluation of S1 splitting compared to S2 splitting is the close proximity of S1 with the time to ventricular contraction, which is crucial for evaluation of cardiac function. Future studies are warranted to study in more detail the relationship between S1 splitting and VV dyssynchrony.

2.4 Relations between heart sounds and patient outcome

The close relationship between heart sounds and hemodynamics makes it reasonable to hypothesize that heart sounds can serve as useful prognosticators in heart failure. Several studies have investigated the relationship between heart sounds and patient outcome. The third heart sound (S3) detected during physical examination on hospital admission is associated with higher in-hospital all-cause mortality and cardiac death in acute heart failure [38]. During a mean follow-up of 32 months, S3 is an independent predictor of hospitalization for heart failure and death from pump failure [39]. Recently, an S3 score calculated automatically from timing, duration, intensity and frequency of S3 has been reported as prognosticator of all-cause mortality in patients with chronic heart failure [40]. In contrast, S4 is only reported in a study as an indicator of favourable outcomes in patients with hypertrophic cardiomyopathy plus sinus rhythm [41]. The finding seems contrary to most previous studies reporting S4 as a specific marker of elevated end-diastolic pressure [42-44]. Our findings in **Chapter 4** also demonstrated that S4 is more frequently observed in patients with increased LV filling pressure. The contradiction likely arises from small sample size (only 9 patients enrolled in the S4-absent group) and composite outcome (a combination of cardiac death, stroke, hospitalization for worsening heart failure, and newly developed atrial fibrillation) of the hypertrophic cardiomyopathy study [41]. Interestingly, no reports have been found on the impacts of S1 and S2 properties on patient outcomes, though they are the most distinctive parts of a heart sound recording. The results obtained on the relations between hemodynamic factors and S2 splitting (**Chapter 2**), STIs (**Chapters 3 and 4**) and dominant frequency (**Chapter 4**) indicate that studies on how S1 and S2 relate to patient outcome may be worthwhile to perform.

3. Heart sounds in the 21st century

The past two decades have seen increasing interest in research of heart sounds, as demonstrated in **Figure 1**. These studies are driven by a few key factors including emergence of new tools for recording heart sounds, advancements of digital signal processing and popularity of artificial intelligence. Furthermore, the coronavirus disease 2019 (COVID-19) pandemics in the past two years have greatly accelerated the adoption of mHealth techniques in clinical practice. The possibility

of using heart sounds for mHealth purposes in post-COVID era is also discussed in this section.

3.1 Evolution of tools for measurement of heart sounds

In the past two decades, miniaturization of sensors and data processing units gives rise to portable, implantable and wearable digital stethoscopes for recording heart sounds [28, 45, 46]. Various ways of measuring heart sounds have been explored in this thesis. In **Chapter 2**, heart sounds were measured using a miniaturized accelerometer that can be further incorporated in a pacing lead like the SonR system [46]. In **Chapter 3**, heart sounds were measured by a microphone implemented in a pulse generator. In **Chapter 4**, a handheld digital stethoscope was utilized for simultaneous measurements of heart sounds and ECG on the skin. In **Chapter 5**, a smartphone was turned into an electronic stethoscope to enable a large-scale collection of heart sounds. All these measurement techniques are considerably better than the early studies with PCG machine. An important feature of all the newly developed tools is that they allow data collection both at hospital and at home, enabling continuous monitoring of patients' conditions. This may have implications for reducing healthcare costs and hospital visits in the future.

3.2 Advancements of digital signal processing

Digital signal processing aims to enhance features of a given signal using mathematical calculation. It is crucial for heart sound analysis because heart sounds are noisy (often mixed with lung sounds and baseline noise), impulsive (all heart sound components occurring within tens of millisecond) and low-frequency (most energies < 100 Hz). Human ears are not well adapted to listen to heart sounds.

In the past two decades, three central tasks of signal processing are heart sound denoising (**Chapters 2, 3, 4 and 5**), splitting identification (**Chapter 2**), and frequency analysis (**Chapters 2 and 5**). Bandpass filtering is the most commonly and earliest used technique for denoising heart sounds with a frequency range between 20 – 250 Hz [6, 47]. Recently, wavelet transform has been proposed to better suit to impulsive signals such as heart sounds. However, no consensus has been reached on selection of mother wavelet, level of decomposition or thresholding type during wavelet denoising [48, 49]. Since heart sounds are mixed with relatively stable sources of noises such as

respiratory sounds, a technique named harmonic regeneration noise reduction was applied to remove baseline noises in **Chapter 3** [50].

Splitting detection of heart sounds has been performed with eyeballing in early studies [51, 52]. The drawbacks of this approach are obvious: it is subject to human judgements and vulnerable to noise interference. To better observe heart sound splitting, the one-dimensional time-series signals must be projected to a two-dimensional time-frequency map. An example is provided in **Chapter 2** in which S2 is projected to a time-frequency spectrum using S-transform. The results showed that heart sound splitting can be automatically traced on time-frequency spectrum and the algorithm is robust to factors such as baseline noises. A recent progress on time-frequency analysis is the development of synchrosqueezing techniques which squeeze time-frequency components to their ridges, like our proposed S-transform amplitude ridge tracking algorithm [53, 54]. While time-frequency analysis provides better observations of signals, frequency analysis alone such as Fast Fourier analysis also provides valuable information including dominant frequency of signals. In **Chapter 4**, dominant frequencies of S1 and S2 are higher in patients with elevated LV filling pressure, suggesting increased myocardial stiffness. Overall, advancements of signal processing have greatly enhanced our abilities to extract useful information from heart sounds.

3.3 Machine learning for heart sound

Machine learning is a statistical method that “learns” implicit patterns of given data mostly based on prespecified features [55]. It has been reported for heart sound-based classification of cardiovascular diseases including aortic stenosis, heart failure and various congenital heart diseases [56-60]. The first step of machine learning is usually to identify heart sound features for training the classification model. Though many features including timing, frequency and amplitude may be calculated using heart sounds, some of them are heavily influenced by confounding factors (e.g., gender, body mass index and heart rate) rather than by the disease of interest. To minimize the effect of confounding factors, we obtained patients of similar baseline characteristics by “matching” these confounding factors (**Chapter 4**). Then these patients were divided by echocardiographic parameter of interest such as E/e' ratio into low and high groups. Heart sound features were compared between these two groups, and only features that significantly differed between the two groups were eligible for our

combined diagnostic score of E/e'. This "match-and-compare" strategy quickly shrinks the number of heart sound features to those relevant to research question of interest. Our proposed procedures may contribute to "explainability" of machine learning by fine-tuning selection of features for training the model, which is crucial for high-stakes decision-making scenarios in health care where machine learning has been criticized for its nature of "black box" [61]. In addition to heart sound features, patients' baseline characteristics such as age and sex may be directly fed into machine learning algorithm, but this has not been applied in most current heart sound classification algorithms which have solely been based on heart sound signals [56-60]. Inclusion of this information may help to further fine-tune the algorithms to assess the patients' status more precisely. Furthermore, the algorithms have the chance to become more powerful as more data become available for training during their use. The fact that automatic speech recognition is probably one of the most successful applications of machine learning indicates that similar success may also be achieved for "speech recognition" of the heart in the near future [62].

3.4 Heart sound for mHealth

Driven by rapidly expanding number of phone users in the past decades, mHealth has been proposed to take the advantage of mobile phone for health care purposes. In the past two years, a crucial driving force of mHealth is the need for remote and/or large-scale monitoring of patients during the COVID-19 pandemics. The power of even a simple mHealth approach was demonstrated by us in a study performed during the first few weeks of the COVID-19 outbreak in China. In order to assist the general population, we designed and released an online questionnaire for surveillance of COVID-19 (see **Appendix**) [63]. A total of 18161 questionnaires were returned, including 6% (1171) from Wuhan City in around 3 weeks. This first surveillance study of COVID-19 showed that the percentage of users reporting fever peaked in 2 weeks following the governmentally-enforced lockdown, consistent with official daily monitoring of COVID-19 confirmed cases. While the study only collected data via an online questionnaire, more data can be obtained by utilizing built-in sensors of mobile phone.

The applications of mHealth can be roughly divided by the type of sensor for data collection into camera-, inertial measurement unit-, and microphone-related. Camera-related applications, usually termed photoplethysmography, make use of pulsatile blood flow-caused subtle

colour changes of skin on sites such as finger and face [64, 65]. The inertial measurement unit is a built-in element of smartphone that combines accelerometer, gyroscope, and sometimes magnetometer. To measure heart rate, the user is required to lay down and put the smartphone on the chest so that any body vibrations can cause movements of the phone [66]. Drawbacks of this approach are: 1) the low-energy vibrations caused by cardiac mechanical activities might not induce visible movements of the phone, and 2) built-in inertial measurement unit generally has a low sampling rate (≤ 100 Hz) and signal resolution.

These two drawbacks are avoided by using the smartphone microphone for heart sound measurement. After nearly 150-year development, the microphone equipped in mobile phones has a high sampling rate (mostly 44100 Hz) and signal resolution (16 bit or higher). In comparison, most energies of heart sound lie in the range below 250 Hz. The ability of smartphone microphones to record heart sounds has also been confirmed in **Chapter 5** that shows nearly 3/4 of all recordings collected by participants from the general public are identifiable for S1 and S2. These findings have clinical implications for turning smartphone microphone into a digital stethoscope for daily monitoring of patients. More importantly, heart sounds provide more information than only heart rate and rhythm compared with either camera- or inertial measurement unit-based applications. As discussed above, long before the invention of the mobile phone (since 1973), heart sounds have been widely used as a simple tool for evaluation of cardiovascular diseases such as congenital heart disease, valvular abnormalities, arrhythmias and heart failure. Ongoing studies on heart sounds for mHealth will greatly benefit from these previous findings.

Impact

Scientific: revival of an old art for new applications

Auscultation is a technique with a history of over 200 years but has been overlooked in the past decades. One of the reasons is probably the unreliability of human ears to discern subtle changes of heart sounds. While this issue can be addressed by registering heart sounds on paper for visual analysis, PCG machines in early days were mostly clumsy and limited to hospital use. A key innovative feature of this thesis is the multiple ways we could measure digital recordings of heart sounds using implantable (**Chapters 2 and 3**) and portable (**Chapters 4 and 5**) devices. These studies provided preliminary experience for future researchers to work on heart sounds using new tools.

Revival of the old auscultation technique has also benefited from advancements of digital signal processing which enables detailed analyses of heart sounds. For example, the time-frequency representation algorithm utilized in **Chapter 2** showed clearly two components of S2 with different timing, frequencies and energies when VV dyssynchrony occurs. Algorithms for analysis of heart sounds may be automated to avoid biases introduced by conventional auscultation by humans. Furthermore, these algorithms may be deployed using mHealth techniques for automatic monitoring of heart sounds in real-time.

Findings from this thesis also show that heart sounds may provide useful information for evaluation of less consistently defined diseases such as HFpEF. For the first time, we demonstrated the potential link between elevated LV filling and dominant frequency of heart sounds in HFpEF (**Chapter 4**). Moreover, a combined score was proposed to differentiate E/e' below and above 9, which may serve as a novel tool for non-invasive screening of patients suspected with HFpEF.

Societal: remote monitoring for reducing healthcare cost

Heart failure affected 33.5 million people worldwide in 1990, which nearly doubled to 64.3 million in 2017 [67]. An economic estimation showed the global cost of heart failure in 2012 to be 108 billion US dollars [68]. For hospitalizations with first-time heart failure, the estimated mean cost was 11 552 dollars per patient in 2014, totaling an estimated 11 billion dollars in the United States alone [69]. The situation is worsened by the fact that as a chronic disease, heart failure recurs frequently in patients with a poor management. Around 24% of cases are rehospitalized within 30 days of discharge, which rises to over

50% within 6 months [70]. To reduce rehospitalization, closely monitoring the patients' conditions is necessary to detect and manage early signs of disease worsening at home.

To enable remote monitoring of heart failure, the patients have to be given a simple tool so that they can collect daily data. **Chapter 5** provides a low-cost tool for measuring heart sounds on a daily basis by turning smartphone to digital stethoscope. Considering the wide use of mobile phone nowadays, this finding will generate considerable societal impacts by combining patients' self-monitoring with doctors' remote guidance. A similar example is the use of mobile phone camera for assessment of heart rhythm during teleconsultations between patients and doctors in TeleCheck-AF project, which reduced hospital visits of the patients during COVID-19 pandemics [65]. These mHealth techniques have been reported to reduce cost of healthcare in most economic studies [71]. However, whether remote monitoring using heart sounds measured from mobile phone helps reduce the cost of healthcare remains to be clarified in the future.

Heart sounds for the public

Our studies have drawn the public's interest in heart sounds and more broadly on medicine, as evidenced by the large number of users (over 1100) who used our Apps named Echoes with only a few advertisements via social media of the universities in less than 5 months (**Chapter 5**). The fact that around 4/5 of general users were able to record good-quality heart sounds justifies the use of smartphone as a tool for measuring heart sounds on a large scale. Thus, the public can not only actively gain knowledge about their health but also contribute to scientific research. The solution of using smartphone for health monitoring may be particularly valuable for underdeveloped and/or remote areas with insufficient healthcare resources.

Medical education can also benefit from turning smartphone into digital stethoscope. For example, medical students can use the App to record and replay heart sounds of typical cases to learn heart sounds of diseased conditions. Since some components of heart sounds such as S3 and S4 are low-frequency and low-amplitude and difficult to be heard by human ears in some cases, recorded heart sounds allow visualizing these components so that they are more easily identified. Similar advantages also apply to S2 splitting which generally occurs in tens of millisecond. The use of smartphones for measuring heart sounds is also a cost-effective solution for medical students.

Conclusions

This thesis contributes to the revival of heart sound measurements for evaluation of patients with cardiovascular diseases. Features like systolic time intervals, frequency and splitting of heart sounds proved to contain important information. These features can be measured by a range of techniques from implanted sensors to “ordinary” mobile phones. As also evidenced in this thesis, with the progress in measurement tools, signal processing and machine learning, heart sounds are likely to become important tool in the mHealth era.

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