Environment and participation of adolescents with autism spectrum disorder

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Summary

中文摘要

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Heart sounds are a series of vibrations arising from impacts of blood on cardiovascular structures including valves, myocardium and blood vessels. The two most obvious heart sounds are: the first heart sound (S1) occurring at end-diastole and the second heart sound (S2) occurring at end-systole. S1 contains mitral and tricuspid components, while S2 contains aortic and pulmonic components. Splitting of heart sounds refers to a significant interval between the two components of S1 or S2. Systolic time intervals derived from combined electrocardiogram and heart sound analysis consist of QS1 (the interval between onsets of QRS on the electrocardiogram and S1) and S1S2 (the interval between onsets of S1 and S2).

Heart sounds have been used in diagnosis for over two centuries, boosted by the emergence of the stethoscope 200 years ago. Novel developments like digital stethoscopes and advanced signal analysis create new opportunities for the use of heart sounds. Heart sound-derived parameters are likely useful for evaluation of heart failure with reduced (HFrEF) and preserved ejection fraction (HFpEF).

HFrEF patients with interventricular dyssynchrony may need to be treated with cardiac resynchronization therapy. Selection of candidate and post-implant optimization of cardiac resynchronization therapy are likely improved by using splitting interval of heart sounds for adjustment of interventricular delay. In **Chapter 2**, a novel algorithm has been developed to automatically identify splitting interval between S2 components. The algorithm was tested in simulated signals and in experimental studies that showed a good relation between S2 splitting and an invasively measured indicator of interventricular mechanical dyssynchrony.

In **Chapter 3**, we analyzed data from a combined experimental-clinical study aiming to find the relationship between heart sound-derived systolic time intervals and myocardial contractility. Varying atrioventricular delays were induced using pacing and left ventricular (LV) pressure was invasively recorded. VS1, an indicator close to QS1, shortened as myocardial contractility improved during optimization of atrioventricular delay, associated with prolongation of S1S2. Using VS1 and S1S2 to predict optimal atrioventricular delay resulted in a minor loss of optimal hemodynamics judged by maximal LV pressure and maximal rate of rise of LV pressure. These findings showed that heart sound-derived systolic time intervals may be useful for optimization of

atrioventricular delay in cardiac resynchronization therapy, possibly performed using a microphone in the implanted device.

HFpEF is becoming an increasingly prevalent disease in ageing population. However, discrepancies exist in current guidelines regarding evaluation of diastolic dysfunction and elevated LV filling pressure. In **Chapter 4**, we explored the relationship between heart sounds and echocardiographic parameters in a group of outpatients suspected of HFpEF. To reduce the confounding effects of sex, body mass index and heart rate, these factors were first matched to result in two groups of patients of similar baseline characteristics. Then heart sounds and echocardiographic parameters were compared between these two groups. The results showed that patients with a higher ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e’) presented higher heart sound frequencies, a longer QS1 interval and a more frequent occurrence of S4. By assigning a score to each of these factors, we proposed a combined score for differentiation of E/e′ below and above 9. The combined score demonstrated better performance than a common serological biomarker of elevated LV filling pressure. The association between heart sounds and echocardiography makes it likely to use heart sounds for simple non-invasive screening of patients with HFpEF.

With the recent progress in sensor and communication technologies, the smartphone becomes a potential candidate to help health evaluation of the patients. Mobile health (mHealth) is increasingly recognized as part of the healthcare system, boosted by the coronavirus-19 pandemic. To enable large-scale application of heart sounds for health purposes, we explored the feasibility of turning the smartphone microphone to an electronic stethoscope in **Chapter 5**. An App named Echoes was developed for iPhone and was distributed to general users, which resulted in >1100 respondents with limited advertisement. Heart sounds and basic information of the users were collected anonymously. Visual assessment of quality of heart sound showed that about 3 out of 4 recordings had clear S1 and S2. Most users were able to make a good-quality recording of heart sounds within the first 3 attempts. Factors that tended to negatively influence heart sounds quality were age and body mass index. The findings suggest the possibility of recording heart sounds by general users using their mobile phone.

In **Chapter 6**, we summarized our findings and discussed the scientific and societal impacts. In a history of over 200 years, auscultation has undergone three waves of research enthusiasm, along with rapid development of measurement tools. Heart failure is one of central research topics in heart sound, but little is known about how splitting and frequency of heart sounds change during disease evolution. More importantly, the relationship between heart sounds and patient outcome needs to be clarified in more extensive follow-up studies. Advancements in mobile phone technology enable turning the smartphone microphone to a digital stethoscope for recording heart sounds on a large scale, which has the potential to remotely monitor the patients' status. In the 21st century, signal processing techniques, open-access heart sound datasets and machine learning algorithms are laying foundations for the third wave of heart sound research and applications.

In conclusion, this thesis explored the relationship between heart sounds and hemodynamics using animal and human studies, and preliminarily investigated the potential to use heart sound recordings for mHealth applications. These findings help facilitate the use of heart sounds as a simple, non-invasive and low-cost tool for monitoring patients remotely and in hospital.

中文摘要

心音是血流冲击心血管相关组织包括瓣膜、心肌和血管引起的一系列振动。心音的两个主要成分是第一心音（S1）和第二心音（S2）。前者发生在心室舒张末期，后者发生在心室收缩末期。S1 由二尖瓣和三尖瓣分量构成。S2 由主动脉瓣和肺动脉瓣分量构成。S1 或 S2 的两个分量如果发生时间相距较远，则产生心音分裂。此外，心音可以联合心电图进行分析，其中最常见的指标是收缩时间参数。它包含两个指标，分别是 QS1（从心电图 QRS 波起始至心音 S1 起始的时间差）和 S1S2（心音 S1 起始至 S2 起始的时间差）。

从二百余年前起，医生即开始用心音来协助诊断疾病。随后，听诊器的出现更促进了心音在临床上的应用。新近出现的一些技术，比如电子听诊器和数字信号处理技术，使得心音的采集和分析更为便捷。本论文主要探讨心音相关参数在评估心力衰竭，包括射血分数降低的心力衰竭（HFrEF）和射血分数保留的心力衰竭（HFpEF）中的应用。

HFrEF 的患者如果被查出双心室收缩不同步，则有可能需要接受心室再同步化治疗。在这种情况下，心音分裂间期可以反映双心室收缩不同步的时间，有助于选择心室再同步化治疗的人群以及调整术后起搏器参数。在本书**第二章**中，我们提出了一种新算法自动计算 S2 的分裂时间。信号仿真实验和动物实验结果均证实了该算法得到的 S2 分裂时间和侵入性导管测得的双心室机械收缩不同步之间，存在良好的相关性。

在**第三章**中，我们联合了动物实验和临床研究，探讨心音收缩时间参数与心肌收缩力的关系。我们通过起搏的方式逐步延长心房-心室耦合时间，并同时测量左心室（LV）内压。通过联合心音和心电图，我们计算了 VS1 间期，即从心室刺激电位开始至心音 S1 产生的时间差。结果表明，该指标随着起搏过程中，心肌收缩力的改善而逐步缩短，同时伴随着 S1S2 间期逐步延长。进一步分析表明，这两个指标对心房-心室优化起搏治疗的最佳参数之估计误差较小，同时血流动力学参数的预测吻合度较高。该发现有助于促进心音收缩时间参数在起搏器治疗参数优化中的应用。

近些年，HFpEF 的流行率逐渐上升，特别是在老年群体中。但是，目前医学指南对该病的相关评估，比如心室舒张功能障碍和 LV 内压升高均未达成共识。在**第四章**中，我们初步探讨了心音和彩超在评估 HFpEF 疑似患者方面是否存在相关性。为了减少性别、体重指数和心率这些混杂因素的影响，我们首先匹配了这三个因素，从而获得两组基线数据相似的患者。通过比较这两组患者的心音和彩超数据，我们发现若患者的舒张早期跨二尖瓣血流最大速度/二尖瓣环最大速度的比值（E/e’比值）较高，则心音频率也较高，同时 QS1 间期延长，第四心音的发生率升高。通过对这些因素进行加权，我们提出了一种基于积分的方法来区分 E/e’比值是否大于 9。该方法比常规血清学检查更能反映 LV 灌注压力升高。该研究发现的心音和彩超相关性，为进一步发展心音用于无创筛查 HFpEF 奠定了基础。

随着近年传感技术和通信技术的快速发展，智能手机逐渐成为一个健康评估的工具。移动医疗（mHealth）日益受到重视，特别是在过去两年新冠疫情的阴霾下。为了将心音大规模应用于健康监测，我们初步探讨了用手机麦克风来测量心音的可能性（**第五章**）。我们基于 iPhone 平台开发了一款 App（Echoes），并将其分发给普通用户。我们让这些用户自己采集心音，并提供简单的个人数据。随后，我们分析了超过 1100 名用户的 7500 条心音数据。结果表明，大约 3/4 患者的心音数据质量较好，可以用于分析 S1 和 S2，而多数患者可以在前 3 次成功采集心音。年龄较大和体重指数较高的患者，心音质量偏差。这些结果提示，普通用户可以通过智能手机来采集心音。

在**第六章**中，我们总结了本书的发现，并分析了这些发现的科学价值和社会价值。心音听诊有着 200 多年的历史，并正在经历第三轮研究浪潮。这些发展得益于近年飞速发展的心音测量技术。心力衰竭是心音研究的中心课题之一，但目前对于心音分裂及心音频率如何随着心力衰竭变化，仍知之甚少。更重要的是，目前缺乏随访研究来证实这些心音参数与患者预后之间的关系。随着移动技术的发展，智能手机可以被用作电子听诊器，来帮助大规模采集心音数据，使远程监测患者状况成为可能。在目前的第三波心音研究浪潮中，三大基石分别是电子信号处理、开源心音数据库和人工智能算法。

总之，本书通过动物实验和人体研究，探讨了心音与血流动力学的关系，并初步研究了心音在移动医疗方面的应用。在未来，心音有可能作为一种简单、无创和廉价的工具，用于医院内和家庭患者监测。