Cardiac Function Monitoring for Patients Undergoing Cancer Treatments Using Wearable Seismocardiography: A Proof-of-Concept Study

Md Mobashir Hasan Shandhi, *Student Member, IEEE,* Mandar Aras, Sarra Wynn, Joanna Fan, J. Alex Heller, Mozziyar Etemadi, Liviu Klein, and Omer T. Inan, *Senior Member, IEEE*

***Abstract*— Advances in cancer therapeutics have dramatically improved the survival rate and quality of life in patients affected by various cancers, but have been accompanied by treatment-related cardiotoxicity, e.g. left ventricular (LV) dysfunction and/or overt heart failure (HF). Cardiologists thus need to assess cancer treatment-related cardiotoxic risks and have close follow-ups for cancer survivors and patients undergoing cancer treatments using serial echocardiography exams and cardiovascular biomarkers testing. Unfortunately, the cost-prohibitive nature of echocardiography has made these routine follow-ups difficult and not accessible to the growing number of cancer survivors and patients undergoing cancer treatments. There is thus a need to develop a wearable system that can yield similar information at a minimal cost and can be used for remote monitoring of these patients. In this proof-of-concept study, we have investigated the use of wearable seismocardiography (SCG) to monitor LV function non-invasively for patients undergoing cancer treatment. A total of 12 subjects (six with normal LV relaxation, five with impaired relaxation and one with pseudo-normal relaxation) underwent routine echocardiography followed by a standard six-minute walk test. Wearable SCG and electrocardiogram signals were collected during the six-minute walk test and, later, the signal features were compared between subjects with normal and impaired LV relaxation. Pre-ejection period (PEP) from SCG decreased significantly ($p < 0.05$) during exercise for the subjects with impaired relaxation compared to the subjects with normal relaxation, and changes in PEP/LV ejection time (LVET) were also significantly different between these two groups ($p < 0.05$). These results suggest that wearable SCG may enable monitoring of patients undergoing cancer treatments by assessing cardiotoxicity.**

I. Introduction

Advances in early detection and cancer therapy have led to a sharp decrease (23%) in the cancer-related mortality rate from 1991 to 2012, with a corresponding rapid increase in cancer survivorship [1]. Unfortunately, patients undergoing cancer treatment and long-term cancer survivors remain at an elevated risk for a variety of cardiovascular toxicities, and cardiovascular disease (CVD) represents the main competing cause of death in cancer survivors across many primary malignancies [2, 3]. Previously, it was thought that only systemic chemotherapy and radiation therapy pose significant risks of cardiotoxicity. However, modern targeted cancer therapies, including human epidermal growth factor receptor 2 (HER2) inhibitors, tyrosine kinase inhibitors (TKIs), proteasome inhibitors, and immune checkpoint inhibitors, have all been associated with adverse cardiovascular events [4]. Cancer treatment-related cardiac toxicities include, but are not limited to, left ventricular (LV) dysfunction, heart failure (HF), coronary artery disease, myocardial infarction, hypertension, arterial and venous thromboembolism, and arrhythmias [5].

LV dysfunction and/or overt HF are the most common cardiovascular complications with chemotherapy, occurring in approximately 10% of patients [6]. LV dysfunction generally remains asymptomatic for a prolonged period of time, but once symptomatic, the prognosis is one of the worst in the HF population [7]. The challenge thus remains to detect subclinical myocardial toxicity before it turns into symptomatic HF. LV dysfunction induced by cardiotoxic chemotherapies is defined by a greater than 10% decrease in LV ejection fraction (LVEF) to an LVEF value of less than 53% [8]. Comprehensive assessments and follow-ups using echocardiography are, in general, carried out to monitor LV dysfunction in cancer survivors and patients undergoing cancer treatments [4].

However, the high cost of echocardiography precludes its frequent and recurrent use for this large patient population. Therefore, it is necessary to develop a low-cost alternative that can yield similar information to clinicians for longitudinal monitoring of these cancer patients and survivors. Seismocardiography (SCG) [9] is one example of such non-invasive cardiogenic signals that have proven merits for their ability to monitor LV function via estimation of health parameters such as the pre-ejection period (PEP) and LV ejection time (LVET) [10-12]. Researchers have used SCG to assess the clinical status of patients with HF doing standard exercise tests, e.g., a six-minute walk test [13-15]. For this reason, we are exploring the potential of using SCG signals to monitor LV function for patients undergoing cancer treatment, in which the pathophysiology of LV dysfunction may differ significantly from HF. To the best of our knowledge, no work has been reported to date regarding monitoring cardio-oncologic patients using SCG. Fig. 1. Illustrates a conceptual diagram of a wearable system enabling longitudinal

Research reported in this publication was supported, in part, by the National Heart, Lung, and Blood Institute under R01HL130619. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Health.

[a]M. M. H Shandhi and O. T. Inan are with School of Electrical and Computer Engineering, Georgia Institute of Technology, Atlanta, GA, USA. Corresponding author e-mail: mobashir.shandhi@gatech.edu.

M. Aras, S. Wynn, J. Fan, and L. Klein are with School of Medicine, University of California, San Francisco, CA, USA.

J. A. Heller and M. Etemadi are with Feinberg School of Medicine, Northwestern University, Chicago, IL, USA.

978-1-7281-1990-8/20/$31.00 ©2020 IEEE

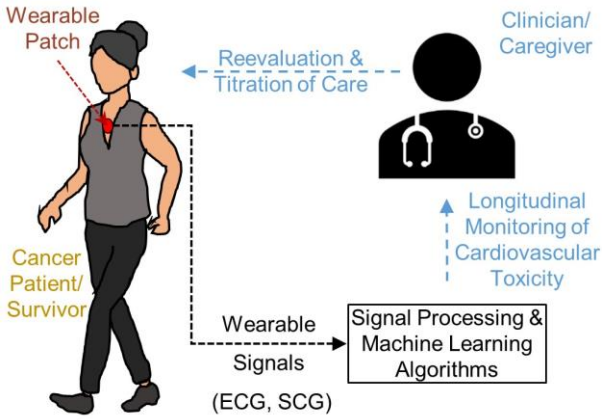

Figure 1. Concept of a wearable cardiovascular health monitoring system to enable remote longitudinal monitoring of cardiovascular toxicity related to cancer treatments by (1) recording wearable signals during daily life activities and exercise, (2) processing the signals and estimate relevant physiological variables and (3) enabling physicians/caregiver to intervene based on the longitudinal assessment of cardiovascular health (future work).

monitoring of LV function and providing the clinicians/caregivers a relevant set of physiological parameters to remotely monitor these patients. This system can potentially alert caregivers to take necessary measures to address the cardiotoxic effect of cancer treatment.

In this work, we investigate features of SCG to assess LV dysfunction, comparing patients with normal and impaired relaxation. This study thus provides a proof-of-concept validation of the ability for an SCG based wearable sensor to monitor LV function for patients undergoing cancer treatment.

II. Methods

A. Experimental Protocol

We conducted this study under a protocol approved by the University of California, San Francisco and Georgia Institute of Technology Institutional Review Boards. A total of 12 female subjects, who were undergoing cancer treatments for breast cancer, participated in this study (Age: 53±12, Weight: 65±7 kg, Height: 160±4 cm and Ejection Fraction (EF): 62±6 %). Board-certified cardiologists blindly evaluated the echocardiograms of the subjects and found that six of them had normal LV relaxation, five of them had impaired LV relaxation and one had pseudonormal LV relaxation. Out of these 12 subjects, all of them underwent chemotherapy, 10 subjects underwent targeted therapy and 6 subjects underwent radiation therapy. The time difference between the start of the cancer treatments and this echocardiogram (followed by wearable measurements) was 1248±1623 days.

Fig. 2(a) shows the placement of the wearable sensor. To record SCG, we used an improved version of our previously developed wearable patch [16], which incorporates a 3-axis accelerometer, ECG sensing circuitry and environmental sensing (atmospheric temperature, pressure, and humidity). Fig. 2(b) shows the custom-built wearable patch hardware. For each subject, the patch was placed evenly between the suprasternal notch and xiphoid process on the mid-sternal line. The data from the patch was saved into an on-board SD card and later accessed via a PC to further analyze. Fig. 2(c) shows wearable SCG and ECG signals from one subject.

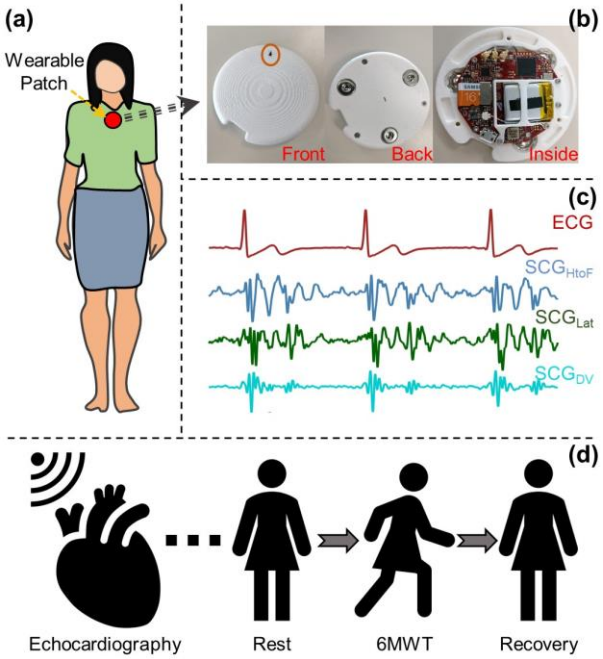

Figure 2. (a) Illustration of a subject wearing the patch. (b) The front, back and inside view of the patch, with the circle showing the arrow facing towards the head of the subject. (c) Representative wearable signals from the patch. (d) An outline of the study protocol. *6MWT= six-minute walk test.

Fig. 2(d) shows the outline of the protocol. First, patients were imaged using echocardiography to assess the LV function and overall cardiac assessment for the subjects, following standard guidelines [8] with trained sonographers. Then, the subjects were fitted with the wearable patch on the mid sternum and asked to stand as still as possible to record one-minute baseline wearable data. Following the baseline data collection, the subjects were asked to complete a standard six-minute walk test followed by two minutes of recovery while standing. The wearable data collection (rest baseline standing, walking, and recovery) elapsed approximately 10 minutes and the time difference between echocardiogram and wearable measurements was 50±33 minutes.

B. Sensing Hardware

Echocardiography images were obtained using an iE33 transesophageal echocardiogram (Philips, Amsterdam, Netherlands). Triaxial-SCG (axes: head-to-foot (HtoF), lateral (Lat), and dorsoventral (DV)) and the corresponding ECG were collected with an ADXL355 (Analog Devices, Norwood, MA) accelerometer, ADS1291 (Texas Instruments, Dallas, TX) for the ECG sensing and a BME280 (Bosch Sensortech GmbH, Reutlingen, Germany) for the environmental sensing. The patch has a diameter of 7 cm and a weight of 38.2 gm, and can record continuously for approximately 45 hours. ECG signals are sampled at 1 kHz, accelerometer signals at 500 Hz, and environmental signals at 20 Hz, and then saved onto a microSD card. A custom-built graphical user interface was used to access all the data on a computer and resample the accelerometer and environmental signals at 1 kHz to equate all wearable signal sampling frequencies. The wearable patch was synchronized with a computer, and the protocol's events were timestamped according to that computer. These timestamps were later used to extract relevant signal portions for analysis.

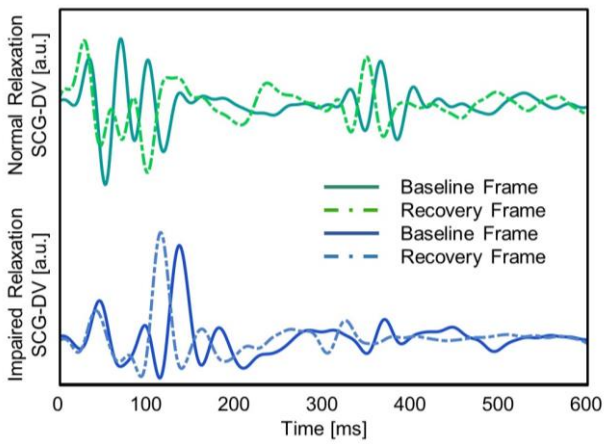

Figure 3. Ensemble averaged heartbeats of SCG_{DV} signals of two representative subjects: (top) with normal LV relaxation and (bottom) with impaired LV relaxation, during rest and recovery parts of the protocol.

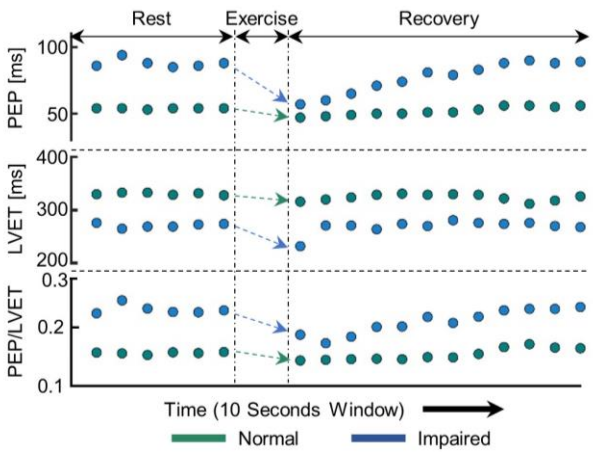

Figure 4. Trend of PEP, LVET, and PEP/LVET ratio between two representative subjects (one with normal LV relaxation and another with impaired LV relaxation), with the chronology of the study protocol. Wearable signals during rest and recovery parts of the protocol were analyzed only. Each feature point on the graph was computed from ensemble-averaged heartbeats from every ten-second non-overlapping windows in the SCG_{DV} signal. This window was chosen for visualization only, whereas feature extraction for PEP and LVET was performed on ensemble-averaged heartbeats from thirty-second non-overlapping windows in the SCG_{DV} signal. Green and blue arrows are showing the changes in respective features from the end of the rest baseline period to the initiation of the recovery period.

C. Signal Processing and Feature Extraction

All the raw wearable signals were filtered with finite impulse response (FIR) Kaiser window band-pass filters (cut-off frequencies: 0.5-40 Hz for the ECG, and 1-40 Hz for the SCG signals) to remove out-of-band noise without distorting the shape of the signals [12]. After filtering, we segmented the signals into 30-second windows for further processing. In each 30-second window, we identified R-wave peaks in the ECG signal with a simple thresholding-based peak detection method, and SCG signals were segmented into individual heartbeats by using these R-wave peaks. We then cropped each SCG heartbeat to a window of 500 ms starting from the R-peak. For all three axes of SCG, we computed ensemble-averaged heartbeats [17] from all the individual heartbeats within each 30-second window. As a result, for each 30-second window, we computed one ensemble-averaged heartbeat for each axis of wearable signals.

After the ensemble averaging steps, we extracted PEP (time difference between R-peak of ECG and aortic valve opening from SCG_{DV} signals) and LVET (time difference between aortic valve opening and aortic valve closing from SCG_{DV} signal) from averaged heartbeats during the baseline and recovery portions of the protocol only. We investigated the changes in PEP, LVET, and PEP/LVET from baseline to the first 30 seconds into recovery, between subjects with normal and impaired LV relaxation. We then analyzed the features (PEP, LVET, and PEP/LVET) to determine if we can assess clinical status (normal vs impaired LV relaxation) of the patients. We used unpaired t-tests to compare the wearable features between these two groups, assuming unequal variance. All the signal processing, feature extraction, and statistical tests were performed in Matlab 2018b®.

III. Results and Discussion

Fig. 3 shows the ensemble average heartbeats of SCG_{DV} signal for two representative subjects; one with normal and another with impaired LV relaxation during the last 30-second of baseline standing period and the first 30-second of recovery standing period. Fig. 4 shows the difference in trends of PEP, LVET and, PEP/LVET for two representative subjects; one with normal and another with impaired LV relaxation. In our analysis, subjects with impaired relaxation had a higher resting PEP (87±18 ms for subjects with impaired relaxation compared to 66±11 ms for subjects with normal relaxation, $p=0.05$) and lower resting LVET compared to subjects with normal relaxation. With impaired relaxation, LV end-diastolic volume (i.e., preload) decreases, which increases resting PEP [18]. With increased resting PEP and decreased resting LVET, subjects with impaired relaxation had higher PEP/LVET ratios compared to subjects with normal relaxation. Fig. 4 shows that PEP, LVET, and PEP/LVET ratio all decreases with exercise (with sharper changes in the case of subjects with impaired relaxation) and reverts to baseline values during recovery. Fig. 5(left) shows the changes in PEP from baseline to recovery (from SCG_{DV}) for both subjects with normal and impaired LV relaxation. Subjects with impaired relaxation have a significantly larger change in PEP ($p<0.05$) with the same sub-maximal effort task, compared to subjects with normal relaxation. PEP has been used to assess cardiac contractility outside of clinical settings [19, 20], and changes in PEP from exercise can illustrate the ability of the heart to accommodate increasing cardiac demand for blood flow to the peripheral muscles. LV stroke volume is regulated by three factors: preload (i.e., LV end diastolic volume [EDV]), afterload, and cardiac contractility [21-23]. In healthy individuals during exercise, afterload increases such that increases in stroke volume can be achieved primarily by increasing preload (increasing LVEDV) and/or by increasing contractility [24]. Subjects with impaired relaxation cannot increase LVEDV as readily [25] and hence must increase cardiac contractility to increase stroke volume with exercise. Fig. 5(left) thus demonstrates that subjects with impaired LV relaxation increase their cardiac contractility ($PEP \propto 1/(\text{contractility})$) significantly more compared to subjects with normal LV relaxation to accommodate similar exercise-driven cardiac demand.

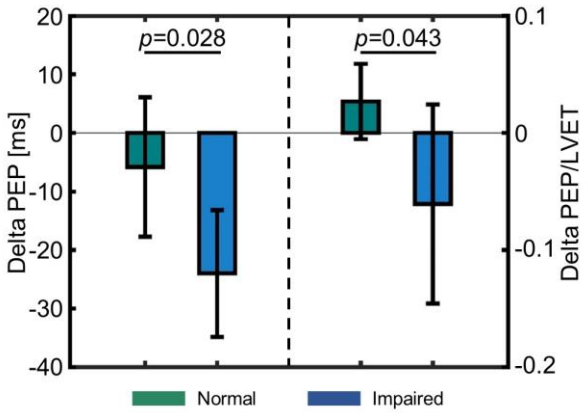

Figure 5. Bar plots of wearable features between subjects with normal (N=6) and impaired (N=5) LV relaxation: (left) changes in PEP, (right) changes in PEP/LVET from SCG_{DV} following exercise.

Fig. 5(right) shows that PEP/LVET changes significantly more ($p<0.05$) for subjects with impaired LV relaxation compared to subjects with normal LV relaxation. PEP/LVET is another measure used to assess cardiac contractility and overall LV function [10]. From this initial analysis, it can be concluded that patients with impaired LV relaxation modulate their ventricular performance significantly more compared to patients with normal LV relaxation to meet similar exercise-driven cardiac demands in a sub-maximal task. Consequently, changes in PEP and PEP/LVET following exercise may be used to assess LV relaxation dysfunction for patients undergoing cancer treatment. These preliminary findings, however, need verification in a larger patient population that includes a variety of patients with various malignancies undergoing cancer treatments.

IV. Conclusion

In this work, we have demonstrated the potential of using SCG to assess the clinical status of patients with LV relaxation dysfunction, when monitoring cancer treatment-related cardiovascular toxicity in patients undergoing cancer treatment. This analysis shows the potential of using this wearable signal in longitudinal monitoring of cancer patients outside of the clinic, in their daily environment, to identify and to stratify risks with ongoing treatment. It may, in turn, improve the quality of life and the chance of long-term survival in cancer survivors. Future work should verify these preliminary findings in a larger patient population.

Disclosure

O. T. Inan is a scientific advisor to Physiowave, Inc., a manufacturer of ballistocardiogram sensing systems.

References

[1] K. D. Miller *et al.*, "Cancer treatment and survivorship statistics, 2016," *CA: a cancer journal for clinicians,* vol. 66, no. 4, pp. 271-289, 2016.

[2] H. Abdel-Qadir *et al.*, "A population-based study of cardiovascular mortality following early-stage breast cancer," *JAMA Cardiology,* vol. 2, no. 1, pp. 88-93, 2017.

[3] F. Bray *et al.*, "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *CA: a cancer journal for clinicians,* vol. 68, no. 6, pp. 394-424, 2018.

[4] B. Kenigsberg *et al.*, "Left ventricular dysfunction in cancer treatment: Is it relevant?," *JACC: Heart Failure,* vol. 6, no. 2, pp. 87-95, 2018.

[5] E. T. Yeh *et al.*, "Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management," *J. of the Am. Coll. of Cardiol.,* vol. 53, no. 24, pp. 2231-2247, 2009.

[6] D. Cardinale *et al.*, "Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy," *Circ.,* vol. 131, no. 22, pp. 1981-1988, 2015.

[7] G. M. Felker *et al.*, "Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy," *New England Journal of Medicine,* vol. 342, no. 15, pp. 1077-1084, 2000.

[8] J. C. Plana *et al.*, "Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging," *European Heart Journal–Cardiovascular Imaging,* vol. 15, no. 10, pp. 1063-1093, 2014.

[9] O. T. Inan *et al.*, "Ballistocardiography and seismocardiography: A review of recent advances," *IEEE journal of biomedical and health informatics,* vol. 19, no. 4, pp. 1414-1427, 2015.

[10] M. Di Rienzo *et al.*, "Wearable seismocardiography: Towards a beat-by-beat assessment of cardiac mechanics in ambulant subjects," *Autonomic Neuroscience,* vol. 178, no. 1, pp. 50-59, 2013.

[11] P. Kh Dehkordi *et al.*, "Comparison of Different Methods for Estimating Cardiac Timings: A Comprehensive Multimodal Echocardiography Investigation," *Frontiers in physiology,* vol. 10, p. 1057, 2019.

[12] M. M. H. Shandhi *et al.*, "Performance Analysis of Gyroscope and Accelerometer Sensors for Seismocardiography-Based Wearable Pre-Ejection Period Estimation," *IEEE journal of biomedical and health informatics,* 2019.

[13] O. T. Inan *et al.*, "Activity-contextualized wearable ballistocardiogram measurements can classify decompensated versus compensated heart failure patients," ed: Am Heart Assoc, 2016.

[14] O. T. Inan *et al.*, "Using ballistocardiography to monitor left ventricular function in heart failure patients," *J. Car. Fail.,* v. 22, no. 8, p. S45, 2016.

[15] O. T. Inan *et al.*, "Novel Wearable Seismocardiography and Machine Learning Algorithms Can Assess Clinical Status of Heart Failure Patients," *Circulation: Heart Failure,* v. 11, no. 1, 2018.

[16] M. Etemadi *et al.*, "A wearable patch to enable long-term monitoring of environmental, activity and hemodynamics variables," *IEEE TBioCAS,* v. 10, no. 2, pp. 280-288, 2016.

[17] L. Sörnmo *et al.*, *Bioelectrical signal processing in cardiac and neurological applications*. Academic Press, 2005.

[18] S. Hassan *et al.*, "Systolic time intervals: a review of the method in the non-invasive investigation of cardiac function in health, disease and clinical pharmacology," *Postgraduate medical journal,* vol. 59, no. 693, pp. 423-434, 1983.

[19] D. B. Newlin *et al.*, "Pre-ejection period: Measuring beta-adrenergic influences upon the heart," *Psychophysiology,* vol. 16, no. 6, pp. 546-552, 1979.

[20] R. C. Talley *et al.*, "Evaluation of the pre-ejection period as an estimate of myocardial contractility in dogs," *The American journal of cardiology,* vol. 27, no. 4, pp. 384-391, 1971.

[21] D. L. Brutsaert *et al.*, "Cardiac muscle mechanics in the evaluation of myocardial contractility and pump function: problems, concepts, and directions," *Progress in cardiovascular diseases,* vol. 16, no. 3, pp. 337-361, 1973.

[22] S. J. Sarnoff *et al.*, "The regulation of the performance of the heart," *The Am. J. of Med.,* vol. 30, no. 5, pp. 747-771, 1961.

[23] C. Tan *et al.*, "Left ventricular outflow tract velocity time integral outperforms ejection fraction and Doppler-derived cardiac output for predicting outcomes in a select advanced heart failure cohort," *Cardiovascular ultrasound,* vol. 15, no. 1, p. 18, 2017.

[24] M. B. Higginbotham *et al.*, "Regulation of stroke volume during submaximal and maximal upright exercise in normal man," *Circulation research,* vol. 58, no. 2, pp. 281-291, 1986.

[25] M. R. Zile *et al.*, "Effects of exercise on left ventricular systolic and diastolic properties in patients with heart failure and a preserved ejection fraction versus heart failure and a reduced ejection fraction," *Circulation: Heart Failure,* vol. 6, no. 3, pp. 508-516, 2013.