33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Evaluation of a Novel Cardiac Output Index on Healthy Elderly, Cardiovascular and Heart Failure Patients during Dynamic Exercise

L. Wang, C. C. Y. Poon, Gabriel Yip, Cheuk Man Yu and Y. T. Zhang

Abstract—**We have recently proposed a novel CO index, namely pulse time reflection ratio (PTRR), which is extracted from photoplethysmogram and electrocardiogram and measurable from wearable devices, and proved that this index is potentially useful for dynamic CO monitoring in a preliminary study carried out on young, healthy subjects. In this study, we presented an evaluation of this technique against impedance cardiography on 64 subjects undergoing incremental maximal exercise testing, including 15 healthy elderly, 19 cardiovascular patients and 30 heart failure patients. Results showed significant intra-subject correlations (r) between PTRR and reference CO in all subjects (mean r: 0.93, p<0.05) and no significant differences on mean r among subject populations (one-way ANOVA, p=0.48). With further development and testing on mobile subjects, this technique can be applied for long-term CO monitoring at home or in other dynamic situations.**

I. Introduction

Heart failure progressively occurs when the heart muscle becomes weakened and loses its ability to pump enough blood to supply the body needs. Different from other cardiovascular diseases, heart failure is not a single disease, but the end stage of many cardiovascular diseases, e.g. hypertension, diabetes mellitus, etc. [1]. Around 5.8 million people in the United States have heart failure and this disease was a contributing cause of 282,754 deaths in 2006 [2].

An effective way to reduce the mortality of heart failure is to identify patients with the highest risks, ideally with objective indicators of cardiac dysfunction, in order that appropriate and effective treatment can be instituted. Recently, several studies have showed that parameters related to cardiac output (CO) are useful indicators of risk stratification for cardiac patients [3, 4]. For instance, CO response to exercise has shown to be the strongest independent predictor of survival on chronic heart failure patients who were referred for cardiac transplantation [3]. In that study, CO was measured by thermodilution. Although highly accurate, thermodilution is usually only applied on critically ill patients due to the highly invasive operating procedures [5]. In a recent study, CO was measured during exercise using the gas re-breathing method and CO at peak exercise (peak CO) has been shown as an independent prognostic marker of modality for the chronic heart failure outpatients [4]. Gas re-breathing method is noninvasive and hence reduces the risk of the patients; however, it requires long response time to complete one measurement and this reduces its ability to track rapid hemodynamic changes [6].

For CO monitoring during dynamic exercise, we are expecting a technique not only accurate, noninvasive, but convenient to use, unobtrusive to movements in a mobile environment. In addition to the gas-rebreathing approach, the noninvasive and established CO methods include the ultrasound Doppler, bio-impedance and blood pressure (BP) contour analysis. Ultrasound Doppler needs professional operator to conduct the measurement and thus is inconvenient to be used in dynamic situations [7]. The bio-impedance is mainly limited by its signal stability and robustness to noises during dynamic exercise [8]. For BP contour analysis, a continuous BP waveform should be obtained in advance of the CO measurement, which requires a sophisticated BP measuring device [9]. The measuring devices for the above methods are also expensive. Therefore, there is urgent need to develop a wearable, low cost and noninvasive technique to measure CO during dynamic exercise.

In a previous study [10], we developed a novel CO index, namely pulse time reflection ratio (PTRR). PTRR is deduced from the tube model of the systematic arterial system, which will be introduced in detail in the Methodology section, and can be implemented using two wearable measurable signals, photoplethysmogram (PPG) and electrocardiogram (ECG). In that study, PTRR showed significantly high and direct correlation (mean r = 0.88, n = 245 trials) with reference CO measured on 18 out of 19 young, healthy subjects. This preliminary result showed the effectiveness of PTRR technique to trace CO changes.

In this paper, we further evaluated this technique on three subject groups: the elderly healthy subjects, cardiovascular patients and heart failure patients. The purposes for enrolling such a subject pool are two: 1) to validate the effectiveness of the novel CO index on these populations, especially on heart failure patients who are potentially the major target users of this technique in the future; and 2) to investigate the effect of

Manuscript received April 17, 2011. This work was supported in part by the Hong Kong Innovation and Technology Fund (ITF), the 973 Project Fund (2010CB732606) and the Guangdong LCHT Innovation Research Team Fund in China. The authors are grateful to Standard Telecommunication Ltd., Jetfly Technology Ltd., Golden Meditech Company Ltd., Bird International Ltd., Bright Steps Corporation and PCCW for their supports to the ITF projects.

Y. T. Zhang (phone: 852-2609-8459; e-mail: ytzhang@ee.cuhk.edu.hk), C. C. Y. Poon and L. Wang are with the Joint Research Centre for Biomedical Engineering, Department of Electronic Engineering, The Chinese University of Hong Kong, Hong Kong SAR.

G. Yip and C. M. Yu are with the Division of Cardiology, Dept. of Medicine & Therapeutics, The Chinese Univ. of Hong Kong, Hong Kong.

L. Wang is also with the School of Biological Science and Medical Engineering, Beihang University, Beijing, China and Key Laboratory of Biomechanics and Mechanobiology of Ministry of Education, Beihang University, Beijing, China.

Y. T. Zhang is also with the Institute of Biomedical and Health Engineering, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, China, and Key Laboratory for Health Informatics, Chinese Academy of Sciences, China.

cardiovascular diseases, especially heart failure, on the performance of this index by comparing the correlation between PTRR and CO among subject groups.

II. Methodology

The PTRR index was introduced in [10] and described in detail therein. Here, we only stress the most important concepts and deducing procedures of this index.

As shown in Fig. 1, the systematic arterial system is represented by an elastic tube (aorta) terminated by a complex load (peripheral arterial system) in the tube model. In the frequency domain, the blood pressure ($P_{ao}(\omega)$), blood flow ($Q_{ao}(\omega)$) and the global reflection coefficient ($\Gamma(\omega)$) at the aortic root can be decomposed into the forward and reflected waves. And the input impedance ($Z_{in}(\omega)$) can be expressed as:

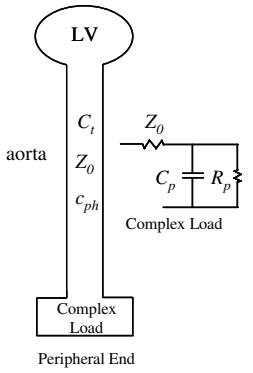

Fig. 1. The tube model. LV: left ventricle; C_t: tube compliance; Z_0: characteristic impedance of aorta; c_{ph}: pulse wave velocity; C_p: peripheral compliance; R_p: peripheral resistance.

$$Z_{in}(\omega) = \frac{P_{ao,z=0}(\omega)}{Q_{ao,z=0}(\omega)} = Z_c \frac{1+\Gamma(w)}{1-\Gamma(w)}, \quad (1)$$

where 'z' indicates the distance from the measuring site to the entrance of aorta and Z_c is the aortic characteristic impedance, a real constant for a frictionless tube (aorta). We then consider $Z_{in}(\omega)$ when ω approaches zero:

$$Z_{in}(0) = \frac{P_{ao,z=0}(0)}{Q_{ao,z=0}(0)} = \frac{\overline{P_{ao,z=0}}}{\overline{Q_{ao,z=0}}} = Z_c \frac{1+\Gamma(0)}{1-\Gamma(0)}, \quad (2)$$

where $\overline{P_{ao,z=0}}$ and $\overline{Q_{ao,z=0}}$ are the mean blood pressure and flow at the entrance of aorta, respectively. CO is calculated from mean blood flow by $\overline{Q_{ao,z=0}} \times Time$, where $Time$ = 1 min. Therefore, CO can be expressed as:

$$CO = Time \times \overline{Q_{ao,z=0}} = \frac{\overline{P_{ao,z=0}}(1-\Gamma(0))}{Z_c(1+\Gamma(0))}, \quad (3)$$

where Z_c is constant.

According to observations and deductions in other work [11], $\overline{P_{ao,z=0}}$ can be expressed in terms of PTT as follows:

$$\overline{P_{ao,z=0}} = A - B \times \ln PTT, \quad (4)$$

where A and B are constants. $B = \frac{2}{\varsigma}$ and ζ is a constant from 0.016 to 0.018. A is calculated from the elastic and geometric properties of the aorta [11].

Then, it further yields:

$$CO = D \times PTRR, \quad (5)$$

where D is the calibration factor, calculated from $D = \frac{B}{Z_c}$, and

$$PTRR = \left(\frac{A}{B} - \ln PTT\right)(1-\Gamma(0))(1+\Gamma(0))^{-1}. \quad (6)$$

Next, we measured PTT by the time delay from the ECG R peak to the root of systolic rise on PPG signal (this time delay is also called pulse arrival time, PAT) and Γ(0) from IPA, the area ratio between the diastolic portion to the whole of PPG wave. In (4), B is known if the value of ζ is made 0.017 and A can be determined by a pair of measured mean BP and PAT.

III. Experimental Protocol

This study was approved by the Clinical Research Ethics Committee. All subjects were unselected outpatients in the cardiology department of the Prince's Wales Hospital, Hong Kong and were asked to sign the authorization forms before they participated in the study. Finally, 64 subjects were enrolled and divided into three subject populations. 15 elderly, healthy subjects were subject to the normal control group, 19 patients with at least one cardiovascular disease belonged to the disease control group and 30 heart failure patients were included in the heart failure group. Table I lists the diagnosis and medication information related to the patients in the disease control and heart failure groups.

TABLE I
DIAGNOSIS AND MEDICATION INFORMATION RELATED TO PATIENTS.

Information on diagnosis			**Information on medications**		
Diagnosis	***D. C***	***H. F.***	***Medications***	***D. C***	***H. F.***
Systolic HF	0	9	***B-blockers***	6	26
Diastolic HF	0	14	***CCB***	7	10
CAD	2	2	***Nitrates***	1	6
Hypertension	10	16	***Diuretrics***	1	16
DM	8	9	***Lipid-Lowering***	6	14
MI	1	1	***ACEI/ARB***	7	22
IHD	1	12	***Aspirin***	4	4
Hyperlipidemia	5	8	***ASA***	6	15
			TNG	1	5

D. C.: disease control group; H. F.: heart failure group; HF: heart failure; CAD: coronary artery disease; DM: diabetes mellitus; MI: myocardial infarction; IHD: ischemic heart disease; CCB: calicium channel blockers; ACEI: non-sulfhydryl-containing inhibitors; ARB: angiotensin receptor blocker; ASA: acetylsalicylic acid; TNG: nitroglycerin.

The experiment was carried out at least one hour after meal in the morning or afternoon. Upon arrival, the subject

was asked to rest on the bicycle ergometer (Lode, Groningen, Netherland). BP was then measured on the right arm by a registered nurse using a mercury BP meter (Riester, Germany) and inputted into an impedance cardiograph (Physio Flow PF-05, Macheren, France) to calculate the baseline CO, i.e. calibration of CO. Continuous and simultaneous ECG, PPG and CO signals were recorded thereafter, until the end of the experiment. Then, subject was asked to lie on bed for another 40 seconds for rest signal recording with a simultaneous BP measurement. Then, the subject started to ride the bicycle at 25 W. The riding load was increased by 25W every two minutes until it reached the tolerant limit of the testing subject, and then the load was kept at this tolerant limit until the testing subject reached his/her target heart rate ($85\% \times (220 - Age)$). In the exercise phase, BP was first measured one minute after the start of exercise and then measured every two minutes later, until the end of exercise. After exercise, the recovery phase last until CO dropped back to the baseline level. In the recovery phase, BP was firstly measured immediately after the stop of exercise and then every two minutes later, until the end of the experiment. Signal segments each of 40s were collected simultaneously with each BP measurement and in between two sequent BP measurements.

For data acquisition, ECG and CO were measured on the chest by an impedance cardiograph, which will be described in detail in the next paragraph. PPG was acquired by an in-house designed acquisition device (MPAS, JCBME lab, CUHK, Hong Kong) on the left index finger of the subject. The PPG acquisition device was a finger clip with reflection mode LED emitter (850 nm, SFH-4250Z, Osram) and detector (850-880 nm, SFH-319 FA-3/4, Osram) embedded. It was connected to a small portable procession unit, where the PPG were filtered (band-pass filter: 0.35-16 Hz) and amplified (19× dc gain). Then, the analog output of ECG, CO and PPG were connected to an analog to digital converter (Dataq D1-719, USA), converted to digital signals, sampled at 1000 Hz, and then stored in a desktop for offline analysis.

An impedance cardiograph was utilized to measure CO in this study. PF-05 was with an improved algorithm that excludes the basal thoracic impedance Z_0 and the distance between electrodes (L) to ensure the robustness of CO readings [12]. This device calculates CO beat by beat by multiplying the body surface area with heart rate (calculated from R-R intervals of the 1st derivative of ECG) and stroke volume index (SVi). SVi is calculated from its value measured during the calibration phase (SVi_{cal}) and two shape features of the impedance signal (Z): the contractility index (CTI) and the thoracic flow inversion time (TFIT, ms). The calibration procedure lasts for 30 heart beats and is carried out under baseline condition. The PF-05 provides four analog signals: ECG, impedance (Z), SV and CO. They are internally rolling averaged to ensure signal stability. Hence, averaged CO of each trial (40 sec) was calculated for comparison.

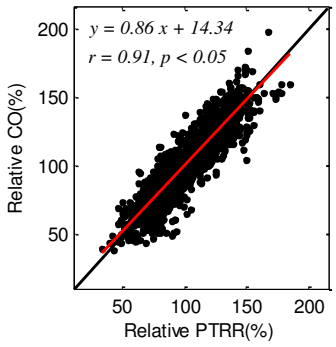

Fig. 2. Plot of linear regression analysis on relative PTRR and relative CO of all subjects. The black line is the equal line and the red line is the line drawn from the regression equation: $y = 0.86x + 14.34$, where x is relative PTRR and y is relative CO. r is the correlation coefficient between relative PTRR and relative CO.

IV. Results

In total, 1588 trials from 64 subjects were collected, including 64 trials at rest, 1006 trials during exercise and 517 trials during recovery. 70 trials cannot be analyzed due to the poor quality of the impedance signal and 52 trials were excluded due to poor PPG measurement.

There were significant, positive intra-subject correlations between reference CO and PTRR in all 64 subjects. The mean correlation coefficient (r) was 0.93 and r was above 0.9 in 85% of the subjects. Fig. 2 is the plot of linear regression analysis which shows the high correlation ($r = 0.91$) between the relative CO and PTRR changes with respect to their mean (e.g. CO relative changes of 50% and 150% in Fig. 2 would, respectively, indicate 50% decrease and 50% increase of CO with respect to its mean). Fig. 3 illustrates the values of intra-subject correlations in different subject populations separately, where mean r is 0.92 in the normal control group, 0.92 in the disease control group and 0.94 in the heart failure group. ANOVA revealed no differences in mean r among different subject populations ($p = 0.48$).

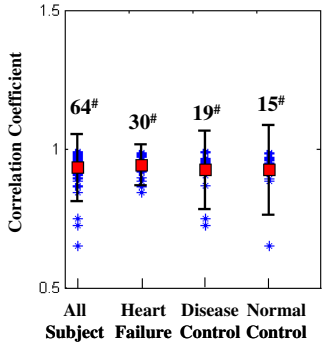

Fig. 3. Intra-subject correlation coefficients between PTRR and CO. Individual correlation coefficient is represented by '*'. In each vertical line, the solid square represents the group mean and the vertical solid line represents the range where 95% data stay. The number with superscript "#" over each vertical line indicates the no. of significant correlations.

V. Discussion and Conclusion

In summary, we have previously proposed a novel CO index PTRR and showed its ability to trace relative CO changes during exercise on young, healthy subjects. This

study is the proceeding work where the performance of the PTRR was further evaluated on three more populations, the healthy elderly, cardiovascular patients and heart failure patients. The results indicated significantly high and direct correlation between PTRR and CO in all 64 subjects. Moreover, the correlations between PTRR and CO were almost the same in different subject populations. The results are encouraging, not only because of the validity of the proposed CO technique on three more subject populations but also because of the robustness of PTRR to indicate CO changes despite of the large variations on the cardiac and arterial functions among healthy subjects and patients.

One potential limitation of this study is the choice of impedance cardiograph as the reference on chronic heart failure patients. Although this device has been proved to be accurate under exercise on several previous studies [12, 13], one study conducted on chronic heart failure patients reported that CO was overestimated by PF-05 compared with Fick's method during a constant-load exercise test and a maximal incremental exercise test [14]. In this study, the peak CO measured on heart failure patients was 12.47 ± 3.70 L min^{-1}, which is significantly lower than 15.6 ± 5.4 L min^{-1} reported in [14] but similar to 12.0 ± 3.40 L min^{-1} measured on 219 chronic heart failure patients reported in another symptom-limited exercise test using CO_2 re-breathing method [15]. The authors [14] have also reported that PF-05 was able to trace the changes of CO precisely on chronic heart failure patients and hence it can be used to evaluate the performance of a CO index to trace relative CO changes.

A constant aortic Z_c is the basic assumption of our proposed method (PTRR proportional to CO). This assumption was proposed since experimental study reported that Z_c was almost unchanged during dynamic exercise on normotensive subjects [16]. On the patients with cardiovascular disease however, this is not exactly the fact. Chirinos et al [17] measured Z_c on 40 hypertensive adults and found that Z_c increased by 12.5% from rest to exercise. Another study by Warren et al [18] showed that Z_c increased by 14% and 5%, respectively, on patients with aortic valve stenosis and normotensive subjects after supine bicycle exercise. A possible reason is that the aorta becomes stiffer due to cardiovascular diseases, resulting in more rises in pressure due to the same increase of flow. As a result, the ratio between (forward) pressure and (forward) flow, i.e. Z_c, increases during exercise, and this can bring errors to our estimation results. A possible solution is to express Z_c as a function of PTRR to eliminate this effect.

ACKNOWLEDGMENT

Special thanks to Yinbo Liu, Wenbo Gu and Cindy Chung at JCBME for their contributions to data collection. The authors are also thankful to research staffs at the Division of Cardiology at the Princes Wales Hospital, Hong Kong.

REFERENCES

[1] K. Swedberg, et al., "Guildlines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): the task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology," *European Society of Cardiology*, 2005.

[2] D. Lloyd-Jones, R. J. Adams, T. M. Brown, et al., "Heart Disease and Stroke Statistics—2010 Update. A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee," *Circulation*, vol. 121, pp. e1-e170, 2010.

[3] D. B. Chomsky, C. C. Lang, G. H. Rayos, et al., "Hemodynamic exercise testing: a valuable tool in the selection of cardiac transplantation candidates," *Circulation*, vol. 94, pp. 3176-3183, Dec. 1996.

[4] C. C. Lang, P. Karlin, J. Haythe, et al., "Peak cardiac power output, measured noninvasively, is a powerful predictor of outcome in chronic heart failure," *Circ. Heart Fail.*, vol. 2, pp. 33-38, Jan. 2009.

[5] C. M. Gomez and M. G. Palazzo, "Pulmonary artery catheterization in anaesthesia and intensive care," *British Journal of Anaesthesia*, vol. 81, pp. 945–956, 1998.

[6] M. B. Jaffe, "Partial CO_2 rebreathing cardiac output: operating principles of the NICO system," *J. Clin. Monit. Comput.*, vol. 15, pp. 387-401, Aug. 1999.

[7] S. Meyer, D. Todd, I. Wright, et al., "Review article: non-invasive assessment of cardiac output with portable continuous-wave Doppler ultrasound," *Emerg. Med. Australas.*, vol. 20, pp. 201-208, Apr. 2008.

[8] F. Compton and J. H. Schäfer, "Noninvasive cardiac output determination: broadening the applicability of hemodynamic monitoring," Semin. Cardiothorac. Vasc. Anesth., vol. 13, pp. 44-55, 2009.

[9] S. Houtman, B. Oeseburg and M. T. Hopman, "Non-invasive cardiac output assessment during moderate exercise: pulse contour compared with CO_2 rebreathing," *Clin. Physiol*, vol. 19, pp.230-237, 1999.

[10] L. Wang, C. C. Poon and Y. T. Zhang, "The non-invasive and continuous estimation of cardiac output using a photoplethysmogram and electrocardiogram during incremental exercise," Physiol. Meas., vol. 31, pp. 715-726, 2010.

[11] W. Chen, T. Kobayashi, S. Ichikawa, Y. Takeuchi and T. Togawa, "Continuous estimation of systolic blood pressure using the pulse arrival time and intermittent calibration," *Med. Biol. Eng. Comput.*, vol. 38, pp. 569-574, Sep. 2000.

[12] R. Richard, E. Lonsdorfer-Wolf, A. Charloux, et al., "Non-invasive cardiac output evaluation during a maximal progressive exercise test, using a new impedance cardiograph device," *Eur. J. Appl. Physiol.*, vol. 85, pp. 202-207, Aug. 2001.

[13] N. Tordi, L. Mourot, B. Matusheski, et al., "Measurements of cardiac output during constant exercises: comparison of two non-invasive techniques," *Int. J. Sports Med.*, vol. 25, pp. 145-149, Feb. 2004.

[14] H. M. Kemps, E. J. Thijssen, G. Schep, et al., "Evaluation of two methods for continuous cardiac output assessment during exercise in chronic heart failure patients," *J. Appl. Physiol.*, vol. 105, pp. 1822-1829, Oct. 2008.

[15] S. G. Williams, G. A. Cooke, D. J. Wright, et al., "Peak cardiac power output: a powerful prognostic indicator in chronic heart failure," *Eur. Heart J.*, vol. 22, pp. 1496–1503, 2001.

[16] J. P. Murgo, N. Westerhof, J. P. Giolma, et al., "Effects of exercise on aortic input impedance and pressure wave forms in normal humans, " *Circ. Res.*, vol. 48, pp. 334-343, 1981.

[17] J. A. Chirinos, P. Segers, A. Raina, "Arterial pulsatile hemodynamic load induced by isometric exercise strongly predicts left ventricular mass in hypertension," *Am J Physiol Heart Circ Physiol.*, vol. 298, pp. H320-H330, 2010.

[18] W. K. Laskey, W. G. Kussmaul and A. Noordergraaf, "Systemic arterial response to exercise in patients with aortic valve stenosis," Circulation, vol. 119, pp. 996-1004, 2009.