

Total Arterial Compliance is a Major Determinant of Peak Oxygen Uptake

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Abstract

Total arterial compliance (TAC, defined as dV/dP) is a major component of the arterial system. A decreased TAC increases left ventricular load and has a detrimental effect on coronary perfusion. We sought to assess the influence of TAC on the functional reserve (VO_{2max}).

Fourteen patients (mean age $64 \pm 14y$) with known or suspected coronary artery disease and eleven controls ($34 \pm 5y$) underwent supine bicycle exercise echocardiography. Audio Doppler signal output of the echocardiographic machine was digitized with a customized hardware and software interface simultaneously with carotid tonometry and ECG. TAC at rest was calculated by the pulse pressure method (PPM).

By step-wise forward multivariate analysis, independent predictors of VO_{2max} were patient versus control status, peak exercise cardiac output and TAC.

The described PC-based acquisition system for tonometry and Doppler signals permits the assessment of ventricular function and arterial biomechanics.

1. Introduction

Total arterial compliance (C) is a major determinant of aortic pulse pressure (PP) and of cardiac afterload. Total arterial compliance defined as dV/dP (ml/mmHg) is a major component of the arterial system. Being considered as a hydraulic filter its role is to dampen pressure and flow waves to minimize left ventricular load and to optimize diastolic flow in the coronary arteries.

Aortic compliance is decreased in patients with atherosclerosis, arterial hypertension and in elderly.

A decreased arterial compliance increases left ventricular load and has a detrimental effect on coronary perfusion, which can lead to ischemia. Decreased aortic compliance also plays a role in the development of heart failure, especially in elderly and in association with arterial hypertension.

Peak oxygen uptake (VO_{2max} , ml/kg/min) is the maximum oxygen consumption at peak exercise and measures aerobic exercise capacity. It is considered an

important discriminator of survival in patients with systolic heart failure. In older patients with diastolic heart failure, reduced cardiac cycle-dependent changes in thoracic aorta area and distensibility has been shown, which correlate with a diminished peak VO_{2max} . [1]

Severe exertion is the most physiological stress for evaluation of the functional reserve of the left ventricle. We present in this paper the effect of aortic compliance evaluated with the pulse pressure method [2, 3] on the functional reserve evaluated by the rate of maximum oxygen uptake (VO_{2max}).

2. Material and methods

2.1 Participants. Fourteen patients (mean age $64 \pm 14y$) with known or suspected coronary artery disease and free from valvular diseases and atrial fibrillation who were referred for further evaluation of ischemic heart disease were included in the protocol. Eleven healthy subjects (mean age $34 \pm 5y$) served as controls. The study conformed to the principles of the declaration of Helsinki

2.2 Exercise testing. All subjects performed symptom-limited supine bicycle exercise testing on a tiltable ergometer using 2-minute stages with 25 Watt workload increments. Symptom status, hemodynamic response and 12-lead electrocardiogram were continuously monitored. Arterial pressure at the brachial level was measured at the end of each stage with a mercury sphygmomanometer. Maximal exercise was defined as the attainment of $> 85\%$ of maximum age-predicted heart rate response.

2.3 Measurement of ventilatory response: Continuous expired gas analysis was performed with the use of a disposable mouthpiece (pneumotach) connected to a MedGraphics CardiO₂ system (Minneapolis, MN). Nose clips were used to prevent air leak from the nostrils. Breath-by-breath analysis of the expired gas was performed, and results were reported as 30-second averages. Oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured at rest for ≥ 2 minutes before start of exercise and then continuously during exercise. Maximum oxygen uptake (VO_{2max}) was defined as the oxygen consumption at peak exercise or

when VO_2 remained constant for two 30-second periods, despite further increase in workload. The respiratory exchange ratio (RER) was calculated as the ratio of VCO_2 relative to VO_2 .

2.4 Exercise echocardiography. Transthoracic echocardiography was performed using ATL HDI 3000 or HP Sonos 5500 to obtain standard views at rest, at maximal exercise and immediately after stress. Images were stored on a 0.5-inch VHS videotape and digitized on-line into a quad-screen, cine loop format, gated to the R-wave of the electrocardiogram. Two observers independently interpreted the images using the standard 16-segments left ventricle model. Each study was scored overall as normal, scar (at least 1/16 scar segments), ischemic (at least 1/16 ischemic segments).

2.5 Estimation of aortic flow: In the absence of important mitral regurgitation, aortic flow is the instantaneous rate of volume change of the left ventricle. The aortic annulus diameter was measured from the parasternal long axis view at rest, and assumed to remain constant with exercise. At rest and at peak exercise level, immediately on cessation of exercise, the aortic root was insonified from the apical five-chambers window using continuous wave (CW) Doppler, with optimal alignment of the ultrasound beam in the left ventricular outflow tract (LVOT) to measure Ao velocities (V_{ao}). The velocity-time-integral (VTI) and the RR-interval were manually measured to derive the cardiac output (CO). Concomitantly, the audio Doppler signal output of the echocardiographic machine was digitized with a customized hardware and software interface. Audio Doppler signals were acquired with an A/D board (Wavebook/512, IOTech Inc., Cleveland, OH) and a laptop computer (Dell LM/P133, Austin, TX) at twice the frequency corresponding to the maximal velocity of the CW mode selected. Fast Fourier Transform was computed on-line to display the spectrogram, along with simultaneously acquired tonometric and ECG signals. Data were archived in binary files. Off-line analysis was programmed in MatLab 4.2 (MathWorks Inc., UK). Instantaneous aortic flow (Q_{Ao}) was computed as the cross-sectional aortic annulus area times V_{Ao} . The ECG was recorded throughout the procedure. Post-processing by averaging multiple beats gave flow data (Q_{Ao}) for one representative heart cycle.

2.6 Estimation of aortic blood pressure (BP) and compliance: We performed non-invasive tonometric recording of the carotid artery. Principles of tonometry has been extensively described.[4] Close agreement at the carotid level with invasive high-fidelity BP_{Ao} recordings has been reported. Tonometry was performed with a Millar SPT-301 pen-like transducer (Millar Instruments Inc., Houston, TX). The output of the TCB-500 control unit was directly digitized with the ECG and the Doppler audio signal. The acquisition software displayed on-line consecutive calibrated tonometric BP signals (ECG-

gated), for visual assessment of the reproducibility and the quality of the successive waves recorded, along with the Doppler spectrogram. For calibration, diastolic and mean (obtained by integration over the heart period) tonometric BP were set equal to the diastolic and mean cuff pressure measurements at the brachial level, at rest and at peak exercise. Mean sphygmomanometer BP was computed as $(2 \times \text{Diastolic BP} + \text{Systolic BP})/3$.

Total arterial compliance at rest was calculated by the pulse pressure method (PPM), an iterative search of the best fit between the measured Ao PP and the PP predicted by a 2-element Windkessel (2-WK).[2]

2.7 Statistical methods: All values are expressed as mean \pm standard deviation. Comparison of hemodynamic variables between patients and normal subjects was performed by t-test. Statistical significance was defined as a two-tailed p value of <0.05 . Pearson's two-tailed correlation and linear regression were used to compare continuous variable. Analysis were obtained with SPSS release 7.5.2, 1997 (SPSS Inc., Chicago, IL).

3. Results

Patient characteristics: Of the fourteen patients (age 64 ± 14 years), five were female, one had a resting ejection fraction $<45\%$. Indications for evaluation were known (5) or suspected (9) coronary artery disease. The exercise echocardiograms included 6 negative tests and 3 non-diagnostic tests due to inadequate heart rate response. Five tests demonstrated rest or exercise-induced wall motion abnormalities. All the eleven control subjects (age 34 ± 5 years) were males, with normal resting and exercise echocardiograms.

Hemodynamic and metabolic parameters at baseline and peak exercise: Comparison of baseline and stress parameters is shown in Table.

	<i>Baseline</i>	<i>Peak</i>
HR(bpm)	70 \pm 10	143 \pm 24
SBP(mmHg)	139 \pm 15	197 \pm 18
DBP(mmHg)	88 \pm 9	104 \pm 12
CO(l/min)	5.2 \pm 1.3	11.6 \pm 4.2
EF(%)	58 \pm 10	72 \pm 10

At baseline, only the estimated Ao pulse pressure (PP_{Ao} = systolic BP - diastolic BP; 45 ± 10 vs 32 ± 5 mmHg, $p < 0.01$) was significantly higher in the patient's group ($p < 0.001$). Patients showed a significantly decreased total arterial compliance (1.2 vs 1.7 ml/mmHg, $p < 0.01$). With exercise, control subjects achieved a higher heart rate (160 ± 13 vs 129 ± 21 b/min), rate pressure product (32.3 ± 4.9 vs $25.1 \pm 4.7 \times 10^3$ mmHg/min), cardiac output (13.9 ± 3.9 vs 9.6 ± 3.4 l/min), and VO_{2max} (35 ± 8 vs 18 ± 6

ml/kg/min). RER at peak exercise was 1.2 ± 0.1 , indicating good efforts and maximal exercise. Three patients and one control failed to reach a RER of 1.1, three other patients and one control failed to reach 85 % of the maximum age-predicted heart rate response.

Automated assessment of aortic flow: Figure 1 demonstrates a typical recording at rest, with the average Doppler spectrogram reconstructed from 5 cardiac cycles and the automatically determined contour of maximal velocity (+). Peak V_{Ao} at rest was 1.2 ± 0.2 m/s ($n=25$) by manual tracing of the Doppler spectrograms, and VTI was 0.25 ± 0.04 m, with no difference between patients and controls. At maximal exercise, peak V_{Ao} reached 1.7 ± 0.3 m/s and 2.0 ± 0.2 m/s, respectively for the patients and the controls ($p < 0.005$), and VTI was 0.28 ± 0.05 m, with no difference between the two groups. Computerized assessment of V_{Ao} gave nearly identical results: at rest, peak V_{Ao} was 1.1 ± 0.2 m/s and VTI 0.24 ± 0.04 m, and at peak exercise, peak V_{Ao} reached 1.6 ± 0.3 m/s and 2.0 ± 0.2 m/s, respectively for the patients and the controls, and VTI was 0.28 ± 0.05 m. The analysis following Bland and Altman including baseline and peak exercise values showed a clinically non-significant bias of 0.06 m/s for peak V_{Ao} (mean difference between manual and computerized values). The agreement interval, computed as the bias ± 2 sd of the difference, was $[-0.20; 0.31]$ m/s, for an overall mean V_{Ao} of 1.5 m/s.

Estimation of central aortic blood pressure: The upper part of figure 1 illustrates, at rest, tonometric recordings at the carotid and at the radial levels. The reconstructed aortic blood pressure obtained by means of a transfer function applied to the radial recording is superimposed on the carotid recording. A gross low-frequency feature such as the pulse pressure is very well reconstructed.

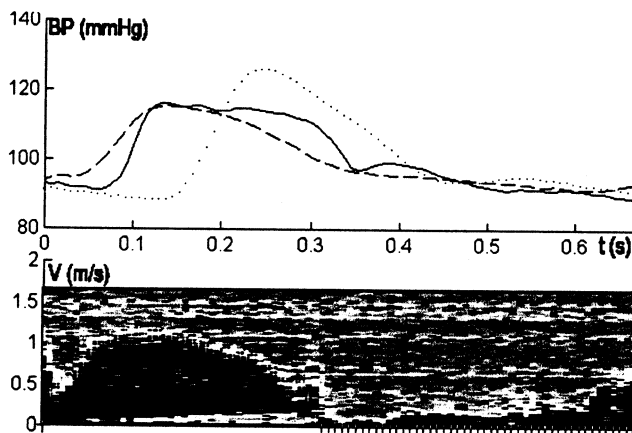


Figure 1: Upper panel: measured radial (dotted line) and carotid (solid line) calibrated tonometric pressure and the estimated aortic pressure (broken line) via a transfer function applied to the radial recording. Lower panel: simultaneously acquired and recomputed Doppler spectrogram with the automatically detected maximal velocity contour (+).

At the carotid level, at rest, systolic BP tended to be higher for the patients (133 ± 14 mmHg) than for the controls (123 ± 10 mmHg, $p=0.06$).

Correlation between hemodynamic parameters and maximal oxygen uptake: As expected, there was no correlation between rest hemodynamic parameters and VO_{2max} . At maximal exercise, VO_{2max} was highly correlated to peak heart rate, Ao pulse pressure, cardiac output, rate pressure product and total arterial compliance. With the exceptions of ejection fraction and mean arterial pressure, all the increases in the hemodynamic parameters were correlated with VO_{2max} . By step-wise forward multivariate analyses, independent predictors of VO_{2max} ($r^2=0.91$, $p < 0.001$) were patient versus control status ($B=-5.1$, $p=0.03$), peak exercise CO ($B=0.8$, $p < 0.01$) and total arterial compliance ($B=13.9$, $p < 0.001$).

4. Discussion

In our population of control volunteers and patients with known or suspected coronary artery disease, the major findings of this study were:

- (i) Total arterial compliance could be fully non-invasively assessed with the combined use of Doppler-echocardiography and arterial tonometry
- (ii) This PC based acquisition system for tonometry and Doppler signals permits precise assessment of ventricular function and the evaluation of arterial biomechanics
- (iii) A decrease in arterial compliance, which may be responsible of an impaired ventriculo-arterial coupling, appears a strong predictor of poor functional reserve.

Non-invasive determination of aortic compliance by tonometry and Doppler-echocardiography has been invasively validated in subjects undergoing cardiac catheterization by Kelly et al.[5] A coefficient of variation of $< 9\%$ has been reported. They were only performing off-line realignment of echocardiographic and tonometric data, sequentially recorded. Based on these results, we did not repeat an invasive validation, hardly justified in the population we investigated. To the best of our knowledge, this study is the first to report the relation between total arterial compliance using tonometry and functional reserve assessed by peak oxygen uptake. We believe that the developed software and hardware set-up for on-line assessment of the quality of the simultaneously recorded tonometric and Doppler signals facilitated the assessment of total arterial compliance with PPM. The PPM relies on the systolo-diastolic pulse of the pressure recording. In a computer model of the arterial tree Stergiopoulos et al found that the PPM proved to be the most accurate of all methods reported for the evaluation of total arterial compliance.[6]

In patients with diastolic heart failure, aortic distensibility has been assessed non-invasively using an alternative to tonometry and it was shown that in older

patients with diastolic heart failure there is reduced cardiac cycle-dependent changes in proximal thoracic aorta area and distensibility, which correlates with and may contribute to their exercise intolerance as shown by a diminished peak exercise oxygen consumption.[1]

We could perform tonometric recordings in all our patients. However, we must admit that this technique required the presence of an additional person during the stress echocardiographic test and that there is some extra time required to record carotid tonometry at rest. We could demonstrate a very good agreement between manual and automatic assessments of V_{A0} and VTI.

The rate of maximal oxygen uptake (VO_{2max}) is the best test of overall functional reserve. In untrained normal people, VO_{2max} is determined by the cardiac output at maximal exercise. There is an age-related decline in maximal oxygen uptake that may be influenced by several factors. A lower stroke volume, heart rate, and arterio-venous oxygen difference at maximal exercise all contribute to the age-related decline in VO_{2max} [7]. For patients with heart failure or pulmonary disease, VO_{2max} is influenced by changes in peripheral oxygen extraction and pulmonary gas exchange and reflects more the functional capacity of the whole organism, and may be the best objective index of aerobic work capacity. VO_{2max} was thus considered the reference measurement of physiological cardiac capacity in this study.

Echocardiographic measurements of resting cardiac function do not predict functional reserve. Our data confirmed that there is no correlation between ejection fraction and VO_{2max} . On the other hand, total arterial compliance, peak exercise CO and patient vs control status are major determinants of VO_{2max} .

A major limitation of this study is the assessment of mean BP as $(2 \times \text{Diastolic BP} + \text{Systolic BP})/3$. This relation might be no more valid in patients with heart failure or modified arterial distensibility, where reflecting waves modify peripheral pressure recordings and ventricular function.

5. Conclusion

From simultaneously acquired tonometric and Doppler echocardiographic recordings, we describe a fully non-invasive assessment of total arterial compliance during exercise echocardiography. This index reflects cardiac afterload and ventriculo-arterial coupling. A strong linear relationship with VO_{2max} was demonstrated.

The PC-based acquisition system for tonometry and Doppler signals permits precise assessment of ventricular function and the evaluation of arterial biomechanics.

References

- [1] Hundley WG, Kitzman DW, Morgan TM, Hamilton CA, Darty SN, Stewart KP, et al. Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. *J Am Coll Cardiol* 2001;38(3):796-802.
- [2] Stergiopoulos N, Segers P, Westerhof N. Use of pulse pressure method for estimating total arterial compliance in vivo. *Am J Physiol* 1999;276(2 Pt 2):H424-8.
- [3] Carlier S, Segers P, Pasquet A, Armstrong G, Greenberg N, Stergiopoulos N, et al. Non-invasive characterization of total arterial compliance by simultaneous acquisition of pressure and flow: advantages of the pulse pressure method. *Computers in Cardiology. IEEE Computer Society Press* 1998:665-668.
- [4] Chen CH, Ting CT, Nussbacher A, Nevo E, Kass DA, Pak P, et al. Validation of carotid artery tonometry as a means of estimating augmentation index of ascending aortic pressure. *Hypertension* 1996;27(2):168-175.
- [5] Kelly R, Fitchett D. Noninvasive determination of aortic input impedance and external left ventricular power output: a validation and repeatability study of a new technique. *J Am Coll Cardiol* 1992;20(4):952-963.
- [6] Stergiopoulos N, Meister JJ, Westerhof N. Evaluation of methods for estimation of total arterial compliance. *American Journal of Physiology* 1995;268(Heart Circ. Physiol. 37):H1540-H1548.
- [7] Ogawa T, Spina RJ, Martin WH, 3rd, Kohrt WM, Schechtman KB, Holloszy JO, et al. Effects of aging, sex, and physical training on cardiovascular responses to exercise. *Circulation* 1992;86(2):494-503.

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