Artery Research (2014) 8, 9–15

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/artres

Patients with refractory angina have increased aortic wave reflection and wasted left ventricular pressure energy

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Received 24 October 2013; accepted 8 January 2014
Available online 31 January 2014

KEYWORDS
Left ventricular wasted energy;
Wave reflections;
Augmentation index;
Refractory angina;
Central aortic pressure;
Arterial stiffness;
SphygmoCor

Abstract *Background:* Early return of reflected blood pressure (BP) waves from the lower body augments central systolic BP and increases systolic pressure-time index (SPTI) and wasted left ventricular (LV) pressure energy, which increase afterload and myocardial oxygen (MVO_2) demand. Accordingly, we sought to determine wave reflection characteristics and diastolic timing in a group of patients with chronic stable angina resistant to anti-anginal therapy.
Methods: Radial artery BP waveforms were recorded non-invasively by applanation tonometry in 36 patients with refractory angina (RA) and a reference control (CON) group of 36 successfully treated hypertensive patients without angina matched for age, gender, height, BMI, and mean BP. Pulse wave analysis (PWA) of the ascending aortic BP waveform was used to determine central hemodynamics, diastolic timing, wave reflection characteristics and wasted LV pressure energy (LVEw).
Results: Compared to the CON group, RA patients had higher central aortic augmented BP, augmentation index (Alx) and reflected pressure wave systolic duration (SDR). These modifications in wave reflection characteristics were associated with an increase in SPTI and LVEw and a decrease in pulse BP amplification and the diastolic pressure time fraction.
Conclusions: RA patients have changes in systolic wave reflections and diastolic timing that increase LV afterload, MVO_2 demand and wasted LV energy and reduce coronary artery perfusion. These alterations in cardiovascular function contribute to an undesirable mismatch in the MVO_2 supply/demand ratio that favors ischemia and angina pectoris and may precipitate future adverse cardiovascular events.
Published by Elsevier B.V. on behalf of Association for Research into Arterial Structure and Physiology.

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1872-9312/$ – see front matter Published by Elsevier B.V. on behalf of Association for Research into Arterial Structure and Physiology.
http://dx.doi.org/10.1016/j.artres.2014.01.003

Introduction

Myocardial ischemia and angina pectoris occur when there is an imbalance between myocardial oxygen supply and demand, and the ischemia is usually entirely or predominantly subendocardial. Animal models have shown that relative subendocardial ischemia can be predicted from the ratio of two pressure-time areas: the area beneath the aortic pressure curve during left ventricular (LV) diastole (DPTI) and the area beneath the aortic pressure curve during LV systole (SPTI).[1] Increased aortic stiffness increases aortic systolic blood pressure (SBP), decreases diastolic blood pressure (DBP) and widens pulse pressure (PP). These pressure changes negatively influence myocardial perfusion and coronary blood flow reserve and reduce the myocardial oxygen supply (DPTI)/demand (SPTI) ratio, which promotes subendocardial ischemia[2–4]; these adverse alterations are exaggerated in LV hypertrophy. Furthermore, numerous reports in humans suggest that aortic stiffness and wave reflections are associated with coronary artery atherosclerosis[5–7] and predict adverse cardiovascular (CV) events and outcome.[8–11] Recent studies have shown that central aortic PP, a surrogate for arterial stiffness, more strongly relates to adverse cardiovascular events and outcome than does brachial PP,[12–14] therefore, measurement of central blood pressure and its components may improve our understanding of angina and aid in risk stratification.[15]

The central arterial BP wave is composed of a forward traveling wave generated by LV ejection and a later arriving reflected wave from the periphery.[16] Chronic increase in stiffness of elastic arteries and the resulting increase in wave reflection are the primary cause of increased PP in subjects with degeneration and hyperplasia of the arterial wall. An increase in smooth muscle tone in peripheral arteries can also increase wall stiffness directly in these vessels and increase wave reflection in the central elastic aorta. As stiffness increases, transmission velocities of both forward and reflected waves increase, which causes the reflected wave to arrive earlier in the central aorta and augment pressure in late systole. Augmentation in central SBP increases LV mass, wasted pressure energy, SPTI and myocardial oxygen demand while a decrease in diastolic pressure time (DPT)[17] and/or DPTI decreases myocardial perfusion causing a mismatch in ventricular/vascular coupling and an imbalance in the myocardial oxygen supply/demand ratio.[18,19] Also, a minor decrease in DPT plus an increase in augmented pressure may have as much negative effect on coronary blood flow and reserve as a severe coronary artery stenosis.[20] All of the above variables can be obtained from the central aortic pressure wave. Accordingly, the objective of the present study was to investigate indices of myocardial oxygen supply and demand non-invasively using central arterial pulse wave analysis (PWA)[21] in a group of patients with refractory angina and compare these findings with a group of age, height, BMI, mean arterial BP and heart rate matched patients without angina and evidence for ischemic heart disease successfully treated for hypertension.

Methods

Institutional Review Board approved the study and written informed consent was obtained from each participant. Exclusion criteria included contraindications to provocative diagnostic testing, cardiomyopathy, New York Heart Association class III-IV congestive heart failure, recent myocardial infarction, and significant valvular or congenital heart disease. Demographic data, medical history, and symptoms were collected and are presented in Table 1. Thirty-six patients with refractory angina underwent non-invasive central aortic PWA studies and results were compared to a reference group of treated hypertensive patients without angina ($N = 36$) matched for, age, gender, height, BMI, mean arterial BP and heart rate. Non-invasive data were collected at least two hours after a meal and/or intake of coffee (or smoking) with the subject supine in a quiet, temperature-controlled room after a rest period of at least ten minutes.

Peripheral cuff blood pressure measurement

Brachial systolic, diastolic and pulse BP were measured in the left arm using a validated, automatic oscillometric BP monitor (Omron R3, Omron Healthcare, Kyoto, Japan) and an appropriate size BP cuff. Three measurements were taken at least two minutes apart and the latter two averaged and used in data analysis.

Central aortic pulse waveform analysis

Assessment of arterial wall properties, wave reflection characteristics, and event timing were performed non-invasively using the SphygmoCor system (AtCor Medical, Sydney, Australia). Radial artery pressure waveforms were recorded at the left wrist, using applanation tonometry with a high-fidelity micromanometer (Millar Instruments, Houston, Texas). After 20 sequential waveforms were

Table 1 Patient characteristics.

	CON ($N = 36$)	RA ($N = 36$)	*P*
Age (years)	60 ± 12	65 ± 9.0	0.08
Male/female	27/9	27/9	
Height (cm)	174 ± 11	173 ± 8.5	0.73
Weight (Kg)	85 ± 18	90 ± 16	0.26
BMI (Kg/m^2)	28 ± 4.7	30 ± 4.7	0.07
HR (bpm)	64 ± 8.4	63 ± 7.7	0.66
Anginal episodes/week	0.0	7.1 ± 6.0	
Medications	**Number of patients**		
Aspirin	21	25	
Plavix	0	22	
Lipid lowering agent	22	32	
Diuretic	16	14	
ACE inhibitor	17	22	
Angiotensin receptor blocker	6	5	
Calcium channel antagonist	12	14	
β-blocker	17	25	
Long acting nitrate	1	29	
Digoxin	2	7	

CON = control group of treated hypertensive patients; RA = treated refractory angina patients; BMI = body mass index; HR = resting heart rate; ACE = angiotensin converting enzyme.