International Journal of Cardiology 190 (2015) 308–314

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Determinants and covariates of central pressures and wave reflections in systolic heart failure

Stephanie Parragh [a,b,*], Bernhard Hametner [a], Martin Bachler [a,b], Jörg Kellermair [c], Bernd Eber [c], Siegfried Wassertheurer [a], Thomas Weber [c]

[a] AIT Austrian Institute of Technology GmbH, Health & Environment Department, Biomedical Systems, Donau-City-Str. 1, 1220 Vienna, Austria
[b] Vienna University of Technology, Institute of Analysis and Scientific Computing, Wiedner Hauptstr. 8-10, 1040 Vienna, Austria
[c] Klinikum Wels-Grieskirchen, Cardiology Department, Grieskirchnerstr. 42, 4600 Wels, Austria

ARTICLE INFO

Article history:
Received 13 November 2014
Received in revised form 23 February 2015
Accepted 21 April 2015
Available online 23 April 2015

Keywords:
Arterial wave reflections
Systolic heart failure
Reduced ejection fraction
Wave separation
Pulse wave velocity
Pulse wave analysis

ABSTRACT

Background: In general, higher blood pressure levels and increased central pulsatility are indicators for increased cardiovascular risk. However, in systolic heart failure (SHF), this relationship is reversed. Therefore, the aim of this work is to compare pulsatile hemodynamics between patients with SHF and controls and to clarify the relationships between measures of cardiac and arterial function in the two groups.
Methods: We used parameters derived from angiography, echocardiography, as well as from pulse wave analysis (PWA) and wave separation analysis (WSA) based on non-invasively assessed pressure and flow waves to quantify cardiac function, aortic stiffness and arterial wave reflection in 61 patients with highly reduced (rEF) and 122 matched control-patients with normal ejection fraction (nEF).
Results: Invasively measured pulse wave velocity was comparable between the groups (8.6/8.05 m/s rEF/nEF, $P = 0.24$), whereas all measures derived by PWA and WSA were significantly decreased (augmentation index: 18.1/24.8 rEF/nEF, $P < 0.01$; reflection magnitude: 56.3/62.1 rEF/nEF, $P < 0.01$). However, these differences could be explained by the shortened ejection duration (ED) in rEF (ED: 269/308 ms rEF/nEF, $P < 0.01$; AIx: 22.2/22.8 rEF/nEF, $P = 0.7$; RM: 59.3/60.6 rEF/nEF, $P = 0.47$ after adjustment for ED). Ventricular function was positively associated with central pulse pressures in SHF in contrast to no or even a slightly negative association in controls.
Conclusions: The results suggest that the decreased measures of pulsatile function may be caused by impaired systolic function and altered interplay of left ventricle and vascular system rather than by a real reduction of wave reflections or aortic stiffness in SHF.

1. Introduction

While arterial hypertension is the leading attributable risk factor for developing heart failure [1], and preventing heart failure is the largest benefit associated with blood pressure lowering drugs [2], this relationship reverses as soon as systolic heart failure (SHF) develops: raised blood pressure can disappear [3], and a higher systolic blood pressure has been found to be associated with better outcomes in a meta-analysis of 10 prospective observational trials [4]. In fact, the latest version of heart failure guidelines in the US states: "Little is known about the benefits of treating hypertension … in patients with established reduced LVEF [left ventricular ejection fraction] and symptoms of HF [heart failure]" [5].

The lack of evidence may be due to the shortcomings of considering only brachial blood pressure when investigating pulsatile phenomena. However, the quantification of central (aortic) blood pressure, arterial stiffness and wave reflection has become an emerging concept in cardiovascular research. The application of pulse wave analysis (PWA) improved the understanding of the mechanisms underlying cardiovascular pathophysiology and disease [6]. In general, higher arterial stiffness, higher central pressures, lower pulse pressure amplification, and a higher amount of wave reflection are associated with a worse prognosis [7–9]. With respect to the heart failure syndrome, increased aortic stiffness, increased central pressures, and increased wave reflections may be a hallmark of heart failure with preserved ejection fraction [10–12], and may have prognostic implications in that situation [13]. In contrast and somewhat resembling the situation with brachial blood pressures, similar relations could not be found in SHF. Pulse pressure and augmentation index are typically lower in these cohorts compared to control groups [14–16], thereby altering their meaning for cardiac risk stratification in such cases [17,18]. This inverse relationship between pulse pressure and prognosis has been shown only for

* Corresponding author at: AIT Austrian Institute of Technology GmbH, Health & Environment Department, Biomedical Systems, Donau-City-Strasse 1, 1220 Vienna, Austria.
E-mail address: Stephanie.Parragh.fl@ait.ac.at (S. Parragh).

http://dx.doi.org/10.1016/j.ijcard.2015.04.183
0167-5273/

brachial pressures so far [18,19]. Moreover, recent data suggest that a low pulse pressure is not always associated with a low amount of wave reflection, depending on the interplay between ventricular and vascular function [20].

We recently investigated wave reflections in patients with SHF compared to controls [16]. In this methodological study, the main focus was on the non-invasive validation of mathematical blood flow models for wave separation analysis in patients with SHF. However, we found that observed differences in hemodynamics might be explained by left ventricular function. Therefore, the aim of the present work is to compare measures of aortic stiffness, central pressures and their components (antegrade waves, reflected waves) between patients with severely impaired systolic function and controls in a clinical context and, in particular, to clarify the relationships between measures of cardiac and arterial function in the two groups.

2. Materials and methods

2.1. Study population

The study was carried out within the scope of ongoing studies at the university teaching hospital of Wels-Grieskirchen in Wels, Austria on the relationship between cardiac disease and aortic and arterial function, which have been approved by the regional ethics committee. A total number of 183 patients with suspected coronary artery disease were included in the present analysis and all participants provided written informed consent. Of these 183, 61 were diagnosed with severely reduced ejection fraction, based on echocardiography and/or cineangiography. The control group, 122 patients with normal ejection fraction (EF), was matched for age, gender, brachial blood pressure levels and body mass index (BMI). Exclusion criteria were arrhythmias, valvular heart disease and unstable clinical conditions. According to the criteria given in [12], namely an elevation of end-diastolic pressures and amino-terminal pro-brain natriuretic peptide levels in the presence of preserved ejection fraction, 14 subjects in the control group could be categorized as having heart failure with preserved ejection fraction (HFpEF).

2.2. Measurements of cardiac function

Left sided pressures and related indices were measured automatically with our coronary angiography system (Siemens Artis Zee with AXIOM Sensis hemodynamic recording system, Siemens healthcare, Erlangen, Germany) during cardiac catheterization before contrast cineangiography, using 6 French fluid filled pigtail catheters. Aortic pulse wave velocity (PWV) was measured from ascending aorta to bifurcation during catheter pullback. Cardiac volumes and ejection fraction were quantified from monoplane cineangiograms in RAO view [21]. Right sided cardiac pressures and cardiac output were measured, using standard thermodilution catheters, in a subgroup of 36 patients. Vascular resistances were calculated using standard formulas [21]. A detailed 2-dimensional and Doppler echocardiogram according to the recommendations of the American Society of Echocardiography [22] was obtained in all patients immediately before or after measurement of arterial stiffness/wave reflections, using a Philips iE33 (Philips, Eindhoven, Netherlands) machine. For pulsed wave tissue Doppler imaging, the sample volume was located at the medial and at the lateral border of the mitral annulus in the apical 4-chamber view, where we obtained early diastolic mitral annulus velocity (E′), late diastolic velocity (A′) and peak systolic velocity (S′). Due to logistic constraints in the catheter laboratory, invasive and non-invasive measurements could not always be performed at the same day. Occasionally, the non-invasive measurements took place the day before or after catheterization.

Plasma levels of N-terminal pro-B-type natriuretic peptides (NT-proBNP) were measured with the commercially available electrochemiluminescence immunoassay "ECLIA" on the Elecsys 1020 analyzer (Roche Diagnostics, Mannheim, Germany).

2.3. Pulse wave analysis (PWA)

Aortic pressure waveforms and the corresponding pulse wave analysis (PWA) parameters were computed with the validated SphygmoCor system (AtCor Medical Pty. Ltd., West Ryde, Australia) and its inbuilt general transfer function [23], from recordings of the radial pressure curve (Millar SPT 301 tonometer). With the estimated aortic blood pressure levels, central pulse pressure (cPP) as well as pulse pressure amplification (PPAmp), the ratio of brachial pulse pressure (bPP) to cPP, were calculated. In brief, the considered PWA parameters are based on identifying the two shoulders, inflection point and maximum in either order, in the central pressure curve. The pressure at the first shoulder minus diastolic blood pressure represents the unaugmented pressure (P1) and the pressure difference between the two shoulders the augmented pressure (AP), which is positive if the inflection point occurs before the maximum and negative elsewise. In theory, P1 corresponds to the incident pressure caused directly by left ventricular ejection, whereas AP represents the pressure augmentation due to the returning of reflected waves. The augmentation index (AIx) is defined as the ratio of AP to cPP and is, as such, considered to be a relative measure of wave reflections. The SphygmoCor system also provides an estimate of the ejection duration (ED) which was used to compute the gender specific left ventricular ejection time index (LVETI) by $LVETI = 1.7 * HR + ED$ for male and $LVETI = 1.6 * HR + ED$ for female patients [24].

2.4. Wave separation analysis (WSA)

The derived central pressure waves Pm were separated into an antegrade (Pf) and retrograde wave (Pb) according to the formulas $Pf = 0.5 * (Pm + Zc * Qm)$, $Pb = 0.5 * (Pm - Zc * Qm)$, [25,26], where Qm denotes the central flow wave and Zc the characteristic impedance. Qm was acquired by manually digitizing the Doppler velocity profiles of the blood flow in the left ventricular outflow tract (acquired in the apical 5 chamber view). Zc was estimated using the moduli of the ratio of Pm to Qm in the frequency domain for the harmonics 4 to 10 [27]. Therefore, Pm and Qm were first manually aligned in time using visual indicators. To quantify wave reflections, the amplitude of Pb (|Pb|), of Pf (|Pf|) as well as their ratio, the reflection magnitude (RM), was computed. Similar to the concept of P1 and AP, Pf represents the forward component resulting from the ejection of blood and Pb the reflected, backward traveling component. All computations were realized in Matlab (The MathWorks, Inc., Natick, United States).

2.5. Statistics

Statistical analyses were performed using MedCalc 12.7.5 (MedCalc Software, Ostend, Belgium). Results are presented as mean (standard deviation) for normally distributed data and median, 95% central range for non-normally distributed data, unless indicated otherwise. Normality was tested for with the Shapiro–Wilk test. Bivariate associations were determined with Pearson's correlation coefficient and stepwise linear regression models were used for multivariable analysis. Differences between groups were assessed with Student's (equal variances) or Welch's (unequal variances) *t*-test for normally or log-normally distributed data and the Mann–Whitney-test otherwise. Adjustment for confounding factors was realized by analysis of covariance (ANCOVA). A two-tailed $P < 0.05$ was considered significant.

3. Results

Patients with severely reduced ejection fraction (rEF) did not differ from controls with normal EF (nEF) with respect to age, weight, height, BMI as well as the prevalence of hypertension, whereas diabetes was