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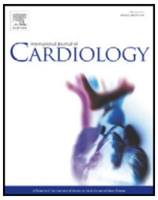

Reservoir and excess pressures predict cardiovascular events in high-risk patients ☆

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ABSTRACT

Background: Analysis of the arterial pressure curve plays an increasing role in cardiovascular risk stratification. Measures of wave reflection and aortic stiffness have been identified as independent predictors of risk. Their determination is usually based on wave propagation models of the circulation. Another modeling approach relies on modified Windkessel models, where pressure curves can be divided into reservoir and excess pressure. Little is known of their prognostic value.

Methods and results: The aim of this study is to evaluate the predictive value of parameters gained from reservoir theory applied to aortic pressure curves in a cohort of high-risk patients. Furthermore the relation of these parameters to those from wave separation analysis is investigated.

Central pressure curves from 674 patients with preserved ejection fraction, measured by radial tonometry and a validated transfer function, were analyzed. A high correlation between the amplitudes of backward traveling pressure waves and reservoir pressures was found ($R = 0.97$). Various parameters calculated from the reservoir and excess pressure waveforms predicted cardiovascular events in univariate Cox proportional hazards modeling. In a multivariate model including several other risk factors such as brachial blood pressure, the amplitude of reservoir pressure remained a significant predictor ($HR = 1.37$ per SD, $p = 0.016$).

Conclusions: Based on very different models, parameters from reservoir theory and wave separation analysis are closely related and can predict cardiovascular events to a similar extent. Although Windkessel models cannot describe all of the physiological properties of the arterial system, they can be useful to analyze its behavior and to predict cardiovascular events.

1. Introduction

Measurement and analysis of aortic pressure curves plays an increasing role in cardiovascular risk stratification. Arterial stiffness has emerged as a major independent risk factor for cardiovascular disease. Recent guidelines underline the importance of measures of arterial stiffness together with wave reflection parameters and it has been proposed that they should be incorporated into clinical practice [1,2].

Two classes of models are widely used to describe cardiovascular phenomena — propagation and Windkessel models. In propagation models, waves are envisaged as traveling through the arterial system. Wave speed as well as the relative importance of forward- and backward-going waves can be quantified [3,4]. Since waves propagate faster in stiffer arteries, pulse wave velocity (PWV) serves as a measure of arterial stiffness. Wave separation analysis (WSA) in the frequency domain [5] or alternatively in the time domain [6] provides methods to estimate the magnitude and timing of forward and backward traveling waves in the vessels.

Otto Frank introduced the first Windkessel model more than a century ago, and since then a variety of Windkessel-like models [7] have been used as simplified models to describe the relation between pressure and flow in the arterial system. The aorta and elastic arteries are modeled as a single compartment and act like a Windkessel in hydraulic

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systems [7]. Wang et al. modified this approach by combining the 2-element Windkessel and wave propagation models, terming it reservoir theory, but the validity of this approach is subject to an on-going debate [3,8–13]. The predictive strength of wave separation parameters such as the amplitude of the reflected pressure wave has already been demonstrated in different cohorts [14–17]. Although the importance of the capacitive effect of the elastic arteries has been recognized for centuries, its incorporation into clinical studies is very recent. Even though reservoir theory was applied to central pressure curves in several studies [18,19], its potential for predicting cardiovascular events has received very little attention.

The aim of this work, therefore, was to evaluate the predictive strength of parameters gained from reservoir theory by fitting a modified Windkessel model to aortic pressure curves in a cohort of high-risk patients. Furthermore the relation of these parameters to those from impedance wave separation analysis was investigated.

2. Methods

2.1. Patients

All subjects included in this study were patients undergoing coronary angiography for suspected coronary artery disease between 2004 and 2009 at the cardiology department of the university teaching hospital Klinikum Wels-Grieskirchen in Wels, Austria.

Exclusion criteria were rhythm other than stable sinus rhythm, valvular heart disease, pericardial constriction, primary pulmonary hypertension, congenital heart disease, and unstable clinical conditions. Furthermore only patients with normal or only slightly impaired systolic function (i.e. ejection fraction >45%) were included. Altogether 674 subjects participated in this study, 56.5% were male and the median age was 64 years (55–72 years interquartile range), see also Table 1. All of the patients were studied while on regular medications (drugs were not withheld before measurements) and gave written, informed consent. The study was approved by the regional ethics committee. For survival analysis the primary endpoint was a combination of death, myocardial infarction, stroke and coronary, cerebrovascular or peripheral revascularization. The study participants have been included in a previous publication on the prognostic value of reflected waves determined from wave separation analysis. Further details on study population, measuring techniques and the determination of end points for survival analysis can be found in Ref. [14].

2.2. Central pressure

Assessment of pressure waveforms was performed noninvasively by applanation tonometry of the radial artery. The SphygmoCor System (AtCor Medical, West Ryde, Australia) was used to generate central pressure curves by applying a validated general transfer function [20]. For that purpose peripheral curves were calibrated with brachial systolic and diastolic pressure readings measured with a validated, automated, oscillometric sphygmomanometer (Omron M5-I, Omron Healthcare, Kyoto, Japan) [21].

Table 1

Baseline characteristics; values are given as total numbers (n) and percentage (%) or as median value and interquartile range (bSBP — brachial systolic blood pressure, bDBP — brachial diastolic blood pressure, bPP — brachial pulse pressure).

n	674	
Men, n (%)	381	56.5
Age, y	64	55–72
Hypertension, n (%)	492	73.0
Diabetes mellitus, n (%)	126	18.7
Smokers, n (%)	98	14.5
Body mass index, kg/m^2	28.1	25.3–31.2
Coronary artery disease, n (%)	271	40.2
Angioscore	0	0–3
Systolic function: normal/slightly reduced, n (%)	637/37	94.5/5.5
Previous myocardial infarction, n (%)	35	5.2
ACE inhibitors or angiotensin receptor blockers, n (%)	347	51.5
Beta-blockers, n (%)	342	50.7
Calcium channel blockers, n (%)	111	16.5
Nitrates, n (%)	103	15.3
Statins, n (%)	258	38.3
bSBP, mmHg	134	123–148
bDBP, mmHg	80	72–86
bPP, mmHg	54	47–64
Heart rate/min	61	55–69

The SphygmoCor system provides a number of parameters derived from the calculated central pressure waveform and several of these are used for further analysis: central diastolic pressure (cDBP), central systolic pressure (cSBP), central pulse pressure (cPP), augmentation index (AIx) and a supposed augmentation index for a heart rate of 75 beats per minute (AIx75).

For a subgroup of 30 patients, invasive aortic pressure measurements using 5F Millar SPC-454D catheters (Millar Instruments, Houston, TX, USA) were available, see [22] for further details. The same algorithms as for the calculated central pressure curves were applied to evaluate the influence of the non-invasive measurement technique and the transfer function.

2.3. Wave separation analysis

To perform wave separation, central pressure curves were exported from the SphygmoCor software and further processed in Matlab (Mathworks, Natick, MA, USA). All algorithms applied are part of the ARCSolver software package and have been described in detail previously [14,23,24]. Briefly, for each aortic pressure curve an individual flow curve is calculated via a recently developed blood flow model [23]. This model is based on an optimization of left ventricular work [25]. Combining information of central pressure (P) and flow (Q), characteristic impedance (Z_c) can be calculated [26]. Then wave separation into a forward (P_f) and a backward traveling wave (P_b) following the method of Westerhof et al. [5] can be performed.

$$P_f = \frac{P + Z_c Q}{2} \tag{1}$$

$$P_b = \frac{P - Z_c Q}{2} \tag{2}$$

As measures for these waves, their amplitudes are used, see Fig. 1A. Furthermore the ratio of the amplitude of the backward wave to the amplitude of the forward wave can be calculated, which is denoted as the reflection magnitude (RM).

2.4. Arterial reservoir

While wave travel through the arterial system is the basic idea for wave separation, in this alternative approach the aorta and elastic arterial system are modeled as one

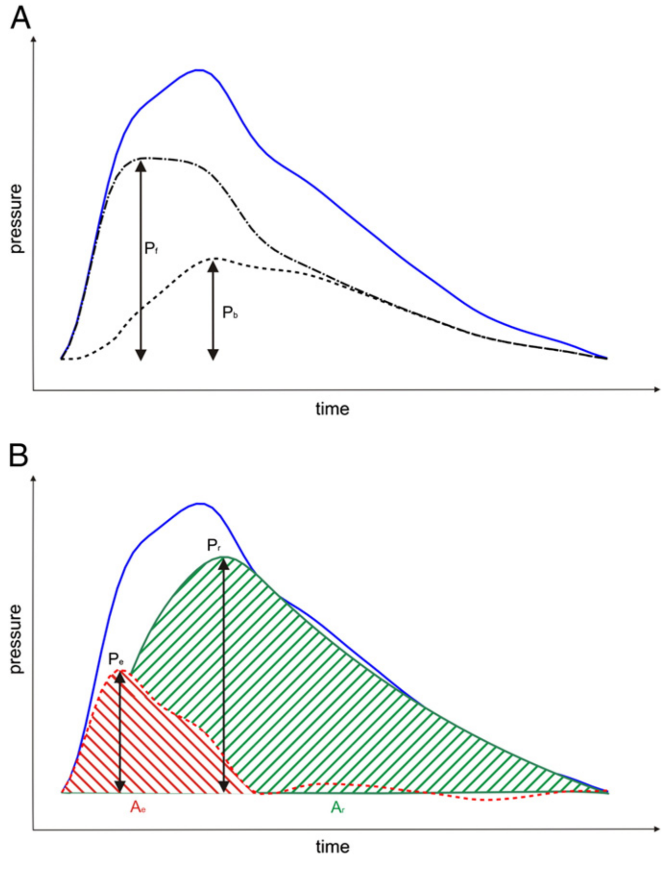

Fig. 1. Separation of the aortic pressure waveform obtained in a typical patient into: A) forward (P_f) and backward (P_b) traveling pressure waveforms; B) reservoir and excess pressure; area of reservoir pressure (A_r) and excess pressure (A_e); amplitudes of reservoir pressure (P_r) and excess pressure (P_e).