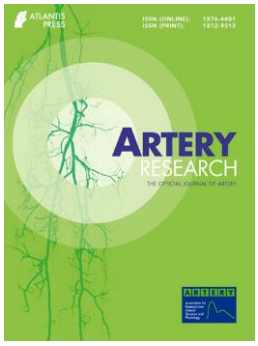

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Relationship between 24 h ambulatory central blood pressure and left ventricular mass — Rationale and design of a prospective multicenter study

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Abstract The prognostic superiority of ambulatory over clinic blood pressure has been repeatedly proven. However, due to the mechanical properties of the arterial system, systolic and pulse pressures are higher in the brachial artery than in the ascending aorta. It seems logical that central pressures are more relevant to cardiovascular disease than peripheral (brachial) pressures, and indeed, using clinic blood pressures, it has been shown that central systolic and pulse pressures are more closely associated with hypertensive end-organ damage than their brachial counterparts. Moreover, antihypertensive drugs can have differential effects on central versus brachial blood pressures. All these effects have been described on the basis of clinic blood pressure measurements. Recent advances in technology allow the estimation of central systolic blood pressure from brachial pulse waves recorded with a regular brachial oscillometric blood-pressure cuff, using a transfer-function like algorithm (ARCSolver). This method has been invasively validated and allows the recording of 24 h ambulatory central blood pressure profiles. Our multicenter study now aims for the first time to investigate

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the relationship between central ambulatory blood pressure monitoring and hypertensive end-organ damage (left ventricular mass) in untreated adults.

Introduction

Central blood pressure

Although mean and diastolic blood pressures are relatively constant in the conduit arteries, systolic and pulse pressures are higher in the peripheral than central arteries.[1] This so-called pressure amplification is the consequence of the progressive reduction of diameter and increase in stiffness from the proximal to the distal arterial vessels and modification in the transit of wave reflections.[2] It seems obvious that central pressures are pathophysiologically more relevant than peripheral pressures for the pathogenesis of cardiovascular disease: it is central systolic pressure (cSBP) against which the heart ejects (afterload), and it is central pulse pressure (cPP) to which the large elastic arteries are exposed.[3] Indeed, cSBP and cPP have been associated more closely with left ventricular hypertrophy and carotid atherosclerosis as markers of hypertensive end-organ damage than brachial pressures in various populations.[4–6] Moreover, it has been documented in a series of studies[5,7–9] and confirmed by a recent meta-analysis[10] that central blood pressures are better predictors of cardiovascular outcomes than brachial blood pressures. Finally, antihypertensive drugs can have differential effects on central and peripheral blood pressures,[11] and this may be a major determinant of outcomes with different antihypertensive drug classes.[12]

For these reasons, the estimation of cSBP (and cPP) in the clinic may be advantageous. However, the relationship between central and peripheral pressures depends on a number of variables, including age, gender, height, heart rate, and cardiovascular risk factors, together with differences in vessel stiffness and wave reflections. Thus, although highly correlated, central pressures cannot be reliably inferred from peripheral pressures by mathematical formulas.[13] For obvious reasons, invasive measurement of cSBP is not feasible during routine care and in recent years, non-invasive methods for the estimation of cSBP have been introduced.[14,15] However, these methods tend to necessitate sophisticated equipment and trained operators, which may hinder their implementation into routine clinical practice or large-scale clinical trials.[16] Recently, a novel method (the ARCSolver method — AIT Austrian Institute of Technology, Vienna, Austria) was introduced for estimating central aortic pressures based on brachial pulse waves recorded with a regular brachial oscillometric blood-pressure cuff. The method considers the influence of arterial impedance using a generalized transfer function as well as aortic hemodynamics by the means of a mathematical model[17] and has been successfully validated against a common tonometric method.[18] In addition, the ARCSolver algorithm has been implemented within a commercially available, high-quality, oscillometric brachial-cuff based sphygmomanometer (Mobil-O-Graph NG, I.E.M., Stolberg, Germany), that has been validated extensively for brachial ABPM according to the British Hypertension Society (BHS) and the European Society of Hypertension (ESH) recommendations.[19–21] The cSBP provided by the ARCSolver/Mobil-O-Graph NG device has also been prospectively validated against invasive recordings using gold-standard solid state pressure sensor-tipped catheters (Millar Instruments, Houston, USA) and against a validated, FDA-approved non-invasive system (SphygmoCor®, AtCor Medical, West Ryde, Australia).[22]

Automated ambulatory blood pressure monitoring (ABPM)

ABPM readings correlate more closely with hypertensive end-organ damage and its treatment-induced changes than clinic brachial blood pressure readings.[23] Moreover, the relationship with cardiovascular events is steeper for ambulatory than for clinic blood pressure, and ABPM provides prognostic value additional to clinic blood pressures.[24] Furthermore, ABPM provides a more accurate indication of the extent of blood pressure reduction induced by treatment than office blood pressure. For these reasons, recent guidelines have suggested that ABPM may be useful at the time of diagnosis of arterial hypertension and at varying intervals during antihypertensive treatment. However, these studies and recommendations are all based on brachial ABPM and, as yet, there are no data describing the clinical value of 24 h central blood pressure readings. Data representing arterial stiffness by means of ambulatory blood pressure monitoring are only available for the AASI (ambulatory arterial stiffness index), which represents a calculated regression of pulse pressure values und which has shown a better predictability of events compared to mean blood pressure levels,[25] although its ability to represent arterial stiffness has been questioned.[26]

Left ventricular mass (LVM)

The 2007 ESH/ESC guidelines for the management of arterial hypertension[23] recommend total cardiovascular risk to be evaluated in each patient to decide about important aspects of treatment, among them the blood pressure (BP) threshold at which to commence drug administration and the target BP to be reached by treatment.[23] In hypertensive patients, echocardiographic left ventricular hypertrophy (LVH) is associated with a high incidence of cardiovascular events.[27] Moreover, it has been shown in the LIFE study[28] that hypertensive patients in whom treatment was accompanied by regression of echocardiographic LVH or a delayed increase in LVM had less incident cardiovascular events, including sudden death, than those in whom no regression from or earlier progression to LVH occurred.

Therefore, LVM represents a useful surrogate endpoint for hypertensive patients.

Relationship between left ventricular mass, office blood pressure, 24 h blood pressure, and central blood pressure

LVM correlates better with brachial ABPM than with office measurements.[29] Regarding central pressures, in a Taiwanese study, the ranks of correlation coefficients between LVM and blood pressures (as measured in the office) in descending order were central SBP, brachial SBP, central PP, and brachial PP. Correlation coefficients were significantly higher for central SBP than for brachial SBP, brachial SBP than central PP, and central PP than brachial PP (all $p < 0.05$).[30] These results have been recently confirmed by data from American Indians.[31] However, the relationship between central blood pressures, as measured over 24 h, and LVM is currently unknown. If the relationship between central systolic pressure, as measured over 24 h, were stronger than all other correlations (as suggested by the data so far available), its introduction into clinical practice would be of value.

Furthermore, it has been suggested, that other variables linked to arterial properties, such as the Augmentation Index (AIx), Pulse wave velocity (PWV) and others, are associated with LVM and their changes with treatment.[32,33] A strong link between cardiac function, namely diastolic function, and arterial wave reflections as well as arterial stiffness has been suggested as well.[34,35] All these issues will be investigated within the framework of the proposed study as well.

Methods

Participants

Participants will be included, following written informed consent, in study centers listed above prospectively based on inclusion and exclusion criteria, as listed in Table 1. Briefly, participants must be >18 years of age and must not take antihypertensive medication. There should be a clinical indication for ABPM (suspected hypertension).

The protocol has been approved by ethics committees in the participating centers, and the study has been registered at ClinicalTrials.gov (NCT01278732).

Study procedures

All study procedures are in accordance with recent guidelines.[23]

A brief history and physical examination will be performed, including family history of cardiovascular disease, personal history of diabetes, cardiovascular disease, renal disease, physical activity, smoking habits, anthropometric characteristics, drug history, and a brief physical examination. Routine laboratory investigations as recommended in recent guidelines[23] will be undertaken, particularly fasting glucose, lipids, serum creatinine (for calculation of GFR by MDRD formula), serum potassium, urine albumin/urine creatinine ratio (mg/mg/1.73 m), and NT-pro brain natriuretic peptide levels if available.

Table 1 Inclusion and exclusion criteria.

Inclusion criteria:
• ≥18 years of age,
• No intake of antihypertensive medications
• Indication for ABPM (e.g. suspected hypertension)
Exclusion criteria:
• No written informed consent
• Left ventricular hypertrophy due to other reasons than hypertension (hypertrophic cardiomyopathy, infiltrative cardiomyopathy, valvular heart disease, congenital heart disease)
• Inability to provide adequate echocardiographic readings
• Segmental contraction abnormalities of the left ventricle
• Contraindications for ABPM (lymphedema both arms)
• Other rhythm than stable sinus rhythm
• Unstable clinical condition, including recent severe infections

Ambulatory blood pressure measurements (ABPM) (Table 2)

24 h ABPM will be taken in all patients during regular daily life, using a validated, commercially available oscillometric brachial-cuff based sphygmomanometer (Mobil-O-Graph NG, I.E.M., Stolberg, Germany). Patients should engage in normal activities but refrain from strenuous exercise, and keep the arm extended and still at the time of cuff inflations. We will provide an adequate explanation to the patient concerning the measurement procedure.

Cuffs of appropriate sizes will be provided. Prior to ABPM, conventional BP measurements will be taken, using validated semi-automatic oscillometric devices and

Table 2 ABPM protocol according to.[36]

• Take bilateral conventional blood pressure readings. If differences less than 20/10 mmHg systolic/diastolic are present, choose the nondominant arm for ambulatory blood pressure measurement.
• Measurement period should last 24 h at least
• Program 15 min intervals of measurement between 6:00 am and 10:00 pm
• Program 30 min intervals of measurement between 10:00 pm and 6:00 am
• Edit mean systolic and diastolic blood pressure and heart rate for 24-h period
• Edit mean systolic and diastolic blood pressure and heart rate for daytime period (09:00 am—09:00 pm)
• Edit mean systolic and diastolic blood pressure and heart rate for nighttime period (01:00 am—06:00 am)
• Edit results of systolic and diastolic conventional blood pressure readings (left and right arm)
• Patients should use a diary to monitor 1)awaking hours, 2)sleeping hours, 3)activities

fulfilling criteria for BP measurement as stated in recent guidelines,[23] and values compared with first ABPM readings. If less than 70% of the expected number of valid values are available by the first ABPM measurement due to frequent artefacts, a second attempt will be undertaken.

Echocardiography

Echocardiography will be performed by experienced cardiologists according to the recommendations of the American Society of Echocardiography and the European Association of Echocardiography.[35] Dedicated recommendations regarding standard-operating-procedures are distributed across study centers. All measurements will be performed at the echocardiographic core-lab, located at Basel university, using a computerized review station. In addition to the verification of exclusion criteria (performed locally), echocardiography will include determination of ejection fraction (2D, Simpson's rule); E-wave, A-wave, deceleration time from PW-Doppler; E′, A′, S′ velocities from Tissue Doppler (PW) at medial and lateral mitral annulus; left atrial diameter (m-mode, parasternal long axis view); and left ventricular mass.

Left ventricular mass determination

Measurement of left ventricular mass will be performed according to the recommendations of the American Society of Echocardiography and the European Association of Echocardiography.[37] Briefly, chamber dimensions and wall thicknesses will be acquired from the parasternal long and short-axis view using targeted m-mode echocardiography at the level of the mitral valve leaflet tips at enddiastole, with the m-mode cursor positioned perpendicular to the septum and the left ventricular posterior wall. 10 or more consecutive beats of 2-dimensional and M-mode recordings of left ventricular internal diameter and wall thicknesses will be measured. End-diastolic left ventricular septal and posterior wall thicknesses and internal dimensions will be used to calculate left ventricular mass by a validated formula: left ventricular mass $= 0.8 \times \{1.04\ [(\text{left ventricular wall thicknesses} + \text{internal dimension})^3 - (\text{internal dimension})^3]\} + 0.6$ g. This formula correlates closely with left ventricular mass at autopsy ($r = 0.90$, $p < 0.001$).[38] The resultant left ventricular mass values also showed excellent reproducibility (intraclass $r = 0.93$; mean difference, 1.7 g; $p < 0.001$) without significant regression to the mean between 2 echocardiograms in a previous group of 183 patients with hypertension.[39]

Measurements of arterial wave reflections and arterial stiffness

Carotid-femoral pulse wave velocity will be measured using the SphygmoCor (AtCor medical, Sydney, Australia) system. Measurements will be taken according to recent recommendations[39]: rest in supine position for 15 min before, quiet environment, no large meals or smoking the hour before measurement; travel distance estimation as femoral − suprasternal notch minus carotid −suprasternal notch.

Measurements of ***central blood pressures and wave reflections*** by pulse waveform analysis (PWA) will be performed as well, using the SphygmoCor apparatus and radial tonometry.

Table 3 shows detailed recommendations for measuring clinic BP, PWV, and wave reflections.

Table 3 Measurement of clinic blood pressure, arterial wave reflections, and pulse wave velocity throughout the study.

Measurement of clinic blood pressure (in general, follow the ESH/ESC Guidelines 2007)
- Have patient rested for 10 min in the sitting position
- Quiet environment, no large meals or smoking the hour before measurement
- Measure BP with the Mobil-O-Graph NG (I.E.M., Stolberg, Germany), using the system as an oscillometric BP monitor
- Measure on both arms, take the arm with the higher value for further measurements
- Measure three times, spaced by 1−2 min, disregard first measurement and average second and third measurement − enter this averaged value for systolic, diastolic and mean BP into the database as clinic BP
- Following measurement of clinic BP, put the patient at rest in the supine position for at least 5 min for measurement of PWA and PWV

Measurements of arterial wave reflections
- Measure BP using the Mobil-O-Graph NG (I.E.M., Stolberg, Germany) after the 5 min rest in the supine position
- Record this BP as supine SBP, MBP, DBP
- Perform radial applanation and perform PWA, using the SphygmoCor apparatus (AtCor medical, Sydney, Australia)
- Calibrate the SphygmoCor system with MBP and DBP, as derived from the Mobil-O-Graph NG
- Perform 2 measurements with built-in quality index >80%, and average
- If large difference (AIx-difference >4%) between the measurements, perform a third measurement, cancel the outlier, and average the 2 closer measurements

Measurement of carotid-femoral pulse wave velocity
- Use the SphygmoCor (AtCor medical, Sydney, Australia) apparatus
- Measurements are taken, immediately following PWA, in the supine position
- Enter the supine BP as measured into the system
- Use the "intersecting tangents" algorithm
- Travel distance is calculated as subtracted distance (suprasternal notch-femoral minus suprasternal notch-carotid)
- Perform 2 measurement and average; if large differences (>1.5 m/sec) occur, perform a third measurement; cancel the outlier and average the 2 closer PWV values

Statistics

Correlations between LVM and 24 h brachial and central systolic blood pressure will be assessed, using Pearson's correlation coefficient. Differences in the strengths of association between central and brachial blood pressures and LVM will be compared by calculation of z statistics for comparison of correlations within a single sample. Two-tailed $p < 0.05$ will be considered significant.

Sample size calculation

We have to consider that this is a pilot study, because 24 h central systolic blood pressure has never been assessed before. We only can try to estimate sample size, using single office readings that compared central versus brachial blood pressure. However, as differences between central and brachial blood pressures may be higher at night during sleep, and nighttime blood pressure is the most important from a prognostic point of view, differences in correlation coefficients may be higher as can be predicted from office readings (which would result in a smaller sample size). But taking office readings into account, sample size is calculated as follows:

Assuming a correlation coefficient of 0.40 between LV mass and 24-h brachial systolic BP, a coefficient of 0.46 between LV mass and 24-h central systolic BP and a coefficient of 0.90 between central and brachial systolic BP, a sample size of 296 subjects will have 85% power to detect a significant difference in correlation coefficients at a significance level of 0.05.

Endpoints

The primary endpoint of the study is the difference in the relationship between LVM and central versus brachial systolic blood pressure.

Secondary endpoints include the relationships between measures of arterial stiffness and wave reflections, assessed at office measurements or during ABPM, with markers of end-organ damage (LVM, renal function, urine albumine/creatinine ratio).

Perspective

If a superiority of central over brachial systolic blood pressure, as assessed during ABPM, can be shown in our study, this would be a strong argument for implementing this novel arterial biomarker into clinical routine.

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