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Differential effects of brachial and central blood pressures on circulating levels of high-sensitivity cardiac troponin I in the general population

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ABSTRACT

Background and aims: Severe cardiac load increases circulating concentrations of high-sensitivity cardiac troponin I (hs-cTnI) through non-ischemic mechanisms. The present study was designed to investigate the effect of central blood pressure (BP), which reflects cardiac load rather than peripheral BP, on serum concentrations of hs-cTnI in subjects with or without increased arterial stiffness.
Methods: We enrolled 1210 participants taking part in a yearly health checkup program. Laboratory measurements included serum concentrations of hs-cTnI and derivative reactive oxygen metabolites (d-ROM), as well as plasma concentrations of B-type natriuretic peptide (BNP). Central BP and the radial augmentation index (rAI) were evaluated non-invasively using an automated device.
Results: Univariate and multivariable regression analysis showed that both brachial and central BP were significantly associated with hs-cTnI. When subjects were divided into two groups according to the mean rAI value, those with higher rAI had higher hs-cTnI concentrations than those with lower rAI. In subgroup analyses, in those with lower rAI, brachial but not central systolic BP was independently associated with hs-cTnI, whereas in those with higher rAI, central but not brachial systolic BP was independently associated with hs-cTnI. These associations remained significant after further adjustment for BNP and/or d-ROM concentrations.
Conclusions: Circulating levels of hs-cTnI increase with increasing brachial and central BP, but the effect of central BP was greater in subjects with higher rAI. This indicates that central BP may have a strong effect on silent myocardial damage, assessed as increased circulating hs-cTnI, particularly in subjects with increased arterial stiffness.

1. Introduction

Cardiac troponins are myocardial constitutive proteins, and cardiac troponin I (cTnI) and cardiac troponin T (cTnT) are often used for the diagnosis of myocardial damage, especially in ischemic myocardial disease [1,2]. Increased circulating concentrations of high-sensitivity (hs)-cTnI and hs-cTnT support the diagnosis of small as well as large myocardial damage in the early phase of acute myocardial infarction [3,4]. However, hs-cardiac troponins are not only specific markers of ischemic myocardial damage; severe cardiac load also increases hs-cardiac troponins through non-ischemic mechanisms [5–7]. Indeed, relatively small increases in cardiac troponin levels have been reported in subjects with non-ischemic cardiac damage and have been shown to predict an increased incidence of heart failure and cardiovascular death [6–10].

Arterial pressure and the pressure waveform are not homogeneous at different sites of the arterial tree, such as the central aorta and peripheral arteries [11]. Central blood pressure (BP) comprises the forward ejection wave and the reflected wave from peripheral

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arteries [12–14]. Conversely, arterial stiffness is primarily dependent on arterial wall properties related to the elastic fiber content and increases with age, hypertension, and arteriosclerosis [11,15]. Augmentation index (AI) is a ratio of pressure augmentation to local pulse pressure, and depends on the relative amplitude and timing of the both direct and reflected pressure waves that sum to produce the overall waveform [16]. Central aortic AI and radial AI (rAI) were reported to have a strong association and to be markers of arterial stiffness and future cardiovascular events [11,16–19]. The advantages of using radial waveform to assess rAI are a simple technique, time-saving, and high reliability. Whereas, the disadvantage of using rAI for assessment of arterial stiffness is characterized by the concept that decreased arterial elasticity following the loss of elastic fiber content in the vascular smooth muscle layer shows different features from vascular endothelial dysfunction which is a common initial pathway of atherosclerosis. It is already known that central BP is lower than peripheral BP in the same individual and increases gradually with increasing arterial stiffness [11,15]. In subjects with increased arterial stiffness, pulse wave velocity and reflection wave velocity are increased. Moreover, in subjects with increased arterial stiffness, central BP is amplified with the addition of the reflected wave pressure to the forward ejection wave peak [11,15]. Thus, central BP and arterial stiffness are closely associated and may become indicators of future cardiovascular events.

Central BP is measured directly using a catheter technique, but an automated apparatus has recently been developed that can estimate central BP non-invasively [13,14]. Recent studies emphasize the importance of central BP in the management of hypertension [20], because central BP reflects cardiac load and is closely related to hypertensive organ damage [12] and cardiovascular events [21]. Previously, we reported the close association between central BP estimated by an automated device and left ventricular load [22,23]. Although brachial BP is widely used to routinely assess vascular damage, central BP rather than brachial BP is suitable for the assessment of cardiac load.

A strong association between central BP and small myocardial injury has been assumed. However, the relationship between hs-cTnI and central BP, and the effects of central and brachial BP on circulating concentrations of hs-cTnI have not been sufficiently investigated. Recently, hs-cTnI and hs-cTnT assays that can detect low levels of myocardial injury have been developed and are commercially available for clinical use [8–10]. In the present study, we investigated the hypothesis that the associations of central and brachial BP with the serum concentrations of hs-cTnI differ, and that the association of central BP with hs-cTnI is greater in subjects with than without increased arterial stiffness.

2. Materials and methods

Subjects without physical deconditioning who participated in a routine health checkup at Enshu Hospital were enrolled in the study. The study protocol was approved by the ethics committees of Nagoya City University Graduate School of Medical Sciences and Enshu Hospital. The study was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant prior to the start of the study.

2.1. Subjects

Male and female subjects who visited Enshu Hospital from 2015 to 2016 for an annual physical checkup were screened for their eligibility to be included in the present study. Subjects with renal dysfunction (creatinine $\geq$1.5 mg/dL), malignant neoplasm, active inflammatory disease (acute and chronic inflammatory disease which needs medical treatment), atrial fibrillation, or a history of cardiovascular events (stroke, peripheral artery disease, and myocardial infarction) were excluded from the study. Smokers were instructed not to smoke on the day of the physical checkup. Blood samples were taken early in the morning after an overnight fasting. BP was measured in the non-dominant arm using a validated oscillometric technique (HEM-7070; Omron Corporation, Kyoto, Japan) in a seated position. Three consecutive BP measurements were taken at 2-min intervals, and the mean of the second and third measurements was recorded as the BP. Subjects with systolic BP (SBP) $\geq$140 mmHg and diastolic BP (DBP) $\geq$90 mmHg were defined as having hypertension [24]. Subjects with high-density lipoprotein cholesterol (HDL-C) <40 mg/dL, low-density lipoprotein cholesterol (LDL-C) $\geq$140 mg/dL, or triglycerides $\geq$150 mg/dL were defined as having dyslipidemia [25]. Subjects with fasting plasma glucose (FPG) $\geq$126 mg/dL were defined as having diabetes [26]. The estimated glomerular filtration rate (eGFR) was calculated using the formula reported by the Modification of Diet in Renal Disease study [27].

2.2. Biochemical analysis

Biochemical tests, including serum levels of total cholesterol, LDL-C, HDL-C, and triglycerides, and plasma BNP concentrations, were performed using standard laboratory assays. In the present study, to evaluate the degree of oxidative stress, a simple method of detecting hydroperoxide levels by measuring derivative reactive oxygen metabolites (d-ROM) was used [28]. Circulating concentrations of hs-cTnI were measured using the ARCHITECT high-sensitive Troponin I assay (Abbott, Matsudo, Japan) according to the manufacturer's instructions.

2.3. Measurement of central BP and radial augmentation index

Measurement of radial artery pressure waveforms and estimation of central BP were performed by an automated device (HEM-9000AI, Kyoto, Japan), as described previously [13,14]. Briefly, the systolic pressure corresponding to the second systolic peak of the radial artery pressure waveform (SBP2) was calculated [13,14]. Inflection points or peaks that corresponded to early and late SBP were obtained by multidimensional derivatives of the original pulse pressure waveforms. Maximal systolic and diastolic pressures in the radial artery were corrected to the brachial SBP and DBP, respectively. SBP2 was calculated using the following equation:

$$SBP2 = (P2/PP) \times (SBP - DBP) + DBP$$

where P2 and PP are the height of the late systolic shoulder/peak pressure and the pulse pressure of the radial arterial pressure contour, respectively. In the present study, the SBP2 reading was taken as central BP because this value is very close to the central BP value estimated using the SphygmoCor technique [13,14,17,18]. The rAI, one of the indicators of arterial stiffness [18,19], was determined as described previously [13,14] using the following equation:

$$rAI\ (\%) = (P2/PP) \times 100$$

The coefficients of variation for the intra- and inter-observer measurement of radial AI by the method were 3.6% and 2.4%, respectively [13].

2.4. Statistical analysis

Data were analyzed using IBM SPSS Statistics 19 (IBM Corp.,