Recent clinical trial of central hemodynamics

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Abstract:
Non-invasive measures of central hemodynamics, such as augmentation index (AI), and central blood pressure (BP) have emerged as a novel and more sophisticated method than brachial BP measurements. For the evaluation of cardiovascular risks and efficacy of medications, central hemodynamics have been shown to be better parameters than peripheral BP. We have introduced these measures of central hemodynamics in our clinical trials and found that 1) patients with type 2 diabetes (DM) had lower rAI but a higher central PP compared to that in the non-diabetes patients, which suggested a proximal conduit-predominant arterial stiffening causing reduced reflection coefficients at the systemic reflection sites; 2) An increased wave reflection caused by the stiffened aorta could be a key factor in the pathophysiology of hypertensive disorders of pregnancy; 3) Central BP compared to brachial clinic BP and home BP during antihypertensive treatment is better in predicting the measures of target organ damage; 4) a very aggressive antihypertensive therapy guided by home morning BP was effective for the change in the central SBP, and was correlated with the change in urinary albumin and PWV; 5) When beta-blockers were additionally used for the treatment of hypertension, bisoprolol achieved a greater reduction in pulse rate and improved baroreflex sensitivity and vascular stiffness, whereas celiprolol reduced the central BP. In conclusion, central hemodynamics might be useful for the evaluation of intra-individual changes, such as drug efficacy or that of some interventions, reflecting the pathophysiological mechanisms of cardiovascular diseases.

Key words:
Central hemodynamics, Augmentation index, Central blood pressure, Cardiovascular diseases

Introduction
Since the Conduit Artery Function Evaluation (CAFE) study, a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)\(^1\), in 2006, non-invasive measures of reflection wave, such as augmentation index (AI), and central blood pressure (BP) have been evaluated more easily in the clinical practice. These measures are expected to be used as a novel and more sophisticated method than brachial BP measurements and to gain more popularity. For the evaluation of cardiovascular risks and efficacy of medications, central hemodynamics have been shown to be better parameters than peripheral BP. However, there have been many problems pointed out\(^2\), including the excessive expectation on this new methodology. We have introduced these measures of central hemodynamics in our clinical trials, and the presentation of these data is still ongoing. In this review, I summarized the results of AI and central BP in our recent clinical studies, while considering the future perspectives on this issue.

Recent Clinical Studies
Twelve prospective cohort studies assessed the relationship between central hemodynamics and prognosis (Table \(1\)). Among them, 10 studies demonstrated a significant relationship between central BP and cardiovascular risk; however, central hemodynamics, including central systolic BP (SBP) and pulse pressure (PP) were not predictors of cardiovascular disease (CVD) in the Framingham study\(^3\). Vlachopoulos et al.\(^4\) performed a meta-analysis on central hemodynamics and prediction of cardiovascular events and all-cause mortality and showed that there was a trend for the central PP to predict CVD events better than the brachial PP. Central hemodynamic parameters are affected by many confounding factors, such as body size, heart rate, and cardiovascular medications; thus, the impact of central hemodynamics on cardiovascular diseases may vary on the basis of the characteristics of the subjects. Even in such varying populations, ranging from the general population to hemo-
dialysis patients, central hemodynamics were effective in predicting CVD events. However, in treated and/or untreated hypertensive subjects, the clinical significance of central hemodynamics has not been established because of many confounding factors. Therefore, we performed the “Antihypertensives and Blood Pressure of Central artery in Japan II (ABC-J II) Study” to evaluate the predictive values of central BP for cardiovascular events in treated Japanese hypertensive subjects. This study was a multicenter, observational study of 3,839 hypertensive patients treated with antihypertensive medications at 27 institutions in Japan; a total of 3,564 subjects were analyzed. The main results are not published yet; however, this study will provide some information on the significance of central BP in the clinical practice.

Our Own Studies

1. Why the Radial Augmentation Index (rAI) is Low in Patients with Diabetes Mellitus (DM): The Japan Morning Surge Home Blood Pressure (J-HOP) study

rAI, a marker of wave reflection, has been reported to be paradoxically lower in patients with DM than in those without DM, although the atherosclerotic change is usually progressed in DM. We sought to clarify whether rAI is truly lower in patients with DM than in those without DM who have cardiovascular risk factors.

This study was a subanalysis of the J-HOP study, a prospective observational study, which evaluated the predictive values of home BP for cardiovascular events in Japanese subjects with any of the cardiovascular risk factors, such as hypertension, impaired glucose tolerance or DM, dyslipidemia, smoking (including those with chronic obstructive pulmonary disease), chronic renal disease, atrial fibrillation, metabolic syndrome, or sleep apnea syndrome. Among the 4,000 subjects in the J-HOP study, radial applanation tonometry was performed in 1,787 subjects, consisting of 449 patients with DM and 1,338 without DM. rAI was determined as follows: [late systolic shoulder pressure amplitude (PP2)/[radial PP (rPP)]. The late systolic shoulder BP (SBP2) and PP2 of a radial pressure wave were used as estimates of the central SBP and central PP, respectively. Although the age (65.8±9.8 vs. 65.8±12.1 yrs) and mean brachial SBP (141±16 vs. 141±17 mmHg) were similar between the DM and non-DM groups, the rAI was significantly lower in the DM group than in the non-DM group (83.3±14.1 vs. 87.3±15.7%, p <0.001), but clinic SBP and PP were similar (51±15 vs. 49±15 mmHg, p=0.019) in the DM group than in the non-DM group. cSBP were similar (Figure 1). In the multivariable analyses adjusted for covariates, the significant determinants of rAI were the estimated glomerular filtration rate (eGFR) (β=−0.15, P<0.001) in the non-DM group and the log-transformed homeostatic model assessment of insulin resistance (HOMA-IR) (β=−0.15, P<0.001) in the non-DM group. Similar trends were also observed for central SBP and cPP. It was concluded that the lower rAI in the DM group was associated with a higher cPP compared to that in the non-DM group, which suggests a proximal conduit-predominant arterial stiffening caused by reduced reflection coefficients at the systemic reflection sites. Even when the renal dysfunction is only moderate, the related increase in cPP may overcome the increase in augmentation pressure in the DM group. Therefore, in DM, cPP may be more important than central SBP.

2. Changes in Central Hemodynamics in Hypertensive Pregnancy from before to after Delivery

Hypertensive disorders of pregnancy (HDPs) can cause pregnancy-associated complications, such as preterm birth, a small-for-gestational-age (SGA) infant, intrauterine growth restriction, and placental abruption. Although various causal factors of HDP have been examined over many years, the factor that best predicts HDP is still undetermined. Augmen-
A total of 137 pregnant women were studied: 72 with HDP, 42 with chronic hypertension (CH), and 23 with white-coat hypertension (WCH; control group). The mean age was 33.5±5.5 y. At a gestational age of ~37 wk, we measured the indices of hemodynamics using both applanation tonometry and impedance cardiography. We repeated the same tests within 6 mo after delivery. Applanation tonometry (SphygmoCor; AtCor Medical, Sydney, New South Wales, Australia) and impedance cardiography (Task Force Monitor; CNSystems Medizintechnik, Graz, Austria) were used to record the radial pulse waves, CO, and TPR. Aortic AI adjusted by a heart rate of 75 beats per minute (\(\text{AIx@75}\)), central PP, TPR, and CO before and after delivery were recorded.

\(\text{AIx@75}\) and central PP were higher in the HDP group than in the control group; however, both parameters decreased after delivery until the levels became similar to those of the control group (Figure 2). \(\text{AIx@75}\) and central PP, but not TPR or CO, significantly decreased after delivery in the HDP group; no such effects were observed in the other groups. These findings suggest that an increased wave
reflection caused by the stiffened aorta could be a key factor in the pathophysiology of HDP.

The central hemodynamic parameters were elevated in the patients with HDP but returned to normal after delivery. Opposite findings were observed in the control group. Because the CO and TPR did not significantly change before and after delivery, increased body fluid or vasoconstriction might not be the main factor. Other factors that increased the functional stiffness of the mid to large arteries, such as angiogenic factors, sex hormones, or nitric oxide sensitivity, could have also influenced the central hemodynamics in the patients with HDP. In addition to endothelial dysfunction, which plays a central role in the pathogenesis of HDP, the changes in the characteristics of central hemodynamics were clarified in this study.

3. Correlation of Central Blood Pressure to Hypertensive Target Organ Damage (TOD) During Antihypertensive Treatment: The Japan Morning Surge-Target Organ Protection (J-TOP) Study

This study aimed to determine whether central BP compared to brachial clinic BP and home BP during antihypertensive treatment is better in predicting the measures of TOD, such as urinary albumin/creatinine ratio (UACR) and left ventricular mass index (LVMI). This study was a subanalysis of the J-TOP study, an open-label randomized multicenter trial investigating the effects of the time of administration of candesartan, an angiotensin II receptor blocker (ARB)

In 180 hypertensive patients (aged 68.7±12.1 y) during the 6-mo treatment with either bedtime or awakening dosing of candesartan (plus diuretics as needed), significant reductions were found in the central SBP, UACR, and LVMI (all P<0.001). In the multivariable analyses, the decrease in the central SBP was associated with those of the log-transformed UACR (β=0.24, P<0.01) and LVMI (β=0.23, P=0.04), independent of the decrease in both clinic and home SBP. The goodness-of-fit of the association between the reduction in the SBP and UACR (P<0.01) or LVMI (P=0.04) improved by adding the central SBP to the SBP measurement. Therefore, the change in the central BP could be an important therapeutic target during antihypertensive treatment, in addition to peripheral clinic and home BP. In the treatment of hypertension, therapies that lower central BP, in addition to clinic and home BP, may be effective in protecting against TOD.

4. Aggressive Blood Pressure-Lowering Therapy Guided by Home Blood Pressure Monitoring Improves Target Organ Damage in Hypertensive Patients With Type 2 Diabetes/Prediabetes

This study tested the hypothesis that a very aggressive antihypertensive treatment guided by home morning BP monitoring (i.e., home morning BP <125/75 mmHg) is effective in improving the measures of TOD in patients with type 2 DM/prediabetes. We enrolled 60 patients with uncontrolled hypertension (i.e., home morning SBP >135 mmHg) and DM/prediabetes and performed clinic, home, and ambulatory BP monitoring at baseline and after 6 mo. Irbesartan (ARB), amiodipine [calcium channel blocker (CCB)], and indapamide (diuretic) were used in accordance with a titration schedule from steps 1 to 5 for a target home BP level <125/75 mmHg. The flow-mediated vasodilatation (FMD), rAI, pulse wave velocity (PWV), and UACR, as a surrogate marker of TOD, were also measured at baseline and after 6 mo. The mean age of the patients was 62.6±9.4 y, and 51.7% were men.

Compared with baseline, clinic (clinic SBP: from 147±18 mm Hg to 125±15 mm Hg, P<0.001), home (home morning SBP: from 145±17 mm Hg to 128±11 mm Hg, P<0.001), and ambulatory SBP (24-hour SBP: 138±13 mm Hg to 125±11 mm Hg, P<0.001) measures, as well as DBP measures, were significantly lowered after sixth months. Central SBP (i.e. SBP2) also decreased from 132±20 to 112±13 mmHg (P<0.001) (Figure 3). FMD increased significantly, and rAI (Figure 3), PWV, and UACR significantly decreased using the treatments. Therefore, a very aggressive antihypertensive therapy guided by home morning BP was effective for the
surrogate end points in the patients with DM/prediabetes. The change in the central SBP was not correlated with the change in the FMD but was correlated with the change in urinary albumin and PWV. Because of the limited number of subjects, whether central BP measures are superior to clinic or home BP measures is unknown; however, in cases of large fluctuations in clinic or home BP measures, central BP measures would be effective in predicting the actual antihypertensive effects.

5. Effects of Celiprolol and Bisoprolol on Blood Pressure, Vascular Stiffness, and Baroreflex Sensitivity

The antihypertensive effect of beta-blockers, such as atenolol, has been shown to be insufficient, and the protection against cardiovascular events was inferior to those of other drugs. Therefore, beta-blockers were expelled from among the first choice of hypertensive medications and were even deemed harmful in patients without heart diseases. On the other hand, 3rd-generation beta-blockers, such as nebivolol, carvedilol, and celiprolol, have been reported to not influence metabolism but have significant effects on vascular functions in patients with essential hypertension. In this study, we investigated whether a vasodilating beta-blocker, celiprolol, and non-vasodilating beta-blocker, bisoprolol, would have metabolic effects and differential effects on BP and vascular functions, such as endothelial function and vascular stiffness.

We enrolled 102 hypertensive subjects (mean age: 59±14 y) treated with medications other than beta-blockers. The subjects were randomized to receive an add-on treatment with either celiprolol 100-200 mg (C group) or bisoprolol 2.5-5 mg (B group) and followed up for 3 mo. In addition to clinic, home, and ambulatory BP monitoring, the FMD, rAI, brachial-ankle PWV (baPWV), UACR, and BRS were measured at baseline and at the end of the study.

Compared to the baseline values, home and 24-h BPs significantly decreased in the third mo in both groups (all $P<0.05$). Pulse rates (PR) and baPWV decreased ($P<0.001$), and BRS increased significantly only in the B group ($P=0.02$). rAI was unchanged in the C group but significantly increased in the B group ($P<0.001$). Central BP significantly decreased in the C group ($P=0.003$) but was unchanged in the B group. FMD significantly increased in both groups (both $P<0.01$) (Figure 4).

Bisoprolol achieved a greater reduction in PR and improved BRS and vascular stiffness, whereas celiprolol reduced the central BP. Thus, in treating hypertensive patients,
an add-on use of celiprolol may be favorable in the uncomplicated stage of hypertension. On the other hand, bisoprolol may be useful in hypertensive patients with cardiac or vascular diseases who have advanced atherosclerotic changes and sympathetic nervous system activation. Recently, the decrease in PR with ivabradine was associated with an increase in central SBP in patients with coronary artery disease. However, in our study, such an effect was not observed in the hypertensive subjects, and the treatments did not cause a cardiovascular overload.

Conclusion

The clinical studies that evaluated central hemodynamics were described. There are several confounding factors that influence these measures; thus, central hemodynamics are not always suitable for cross-sectional studies. However, central hemodynamics might be useful for the evaluation of intra-individual changes, such as drug efficacy or that of some interventions. The concept of central hemodynamics is attractive when considering the pathophysiological mechanisms of cardiovascular diseases. Further studies, especially prospective outcome studies, are needed to establish the clinical significance of central hemodynamics.

Conflicts of Interest

None.

References