



Central Hemodynamics for Management of Arteriosclerotic Diseases

Junichiro Hashimoto

Medical Center, Miyagi University of Education, Sendai, Japan

Arteriosclerosis, particularly aortosclerosis, is the most critical risk factor associated with cardiovascular, cerebrovascular, and renal diseases. The pulsatile hemodynamics in the central aorta consists of blood pressure, flow, and stiffness and substantially differs from the peripheral hemodynamics in muscular arteries. Arteriosclerotic changes with age appear earlier in the elastic aorta, and age-dependent increases in central pulse pressure are more marked than those apparent from brachial pressure measurement. Central pressure can be affected by lifestyle habits, metabolic disorders, and endocrine and inflammatory diseases in a manner different from brachial pressure. Central pulse pressure widening due to aortic stiffening increases left ventricular afterload in systole and reduces coronary artery flow in diastole, predisposing aortosclerotic patients to myocardial hypertrophy and ischemia. The widened pulse pressure is also transmitted deep into low-impedance organs such as the brain and kidney, causing microvascular damage responsible for lacunar stroke and albuminuria. In addition, aortic stiffening increases aortic blood flow reversal, which can lead to retrograde embolic stroke and renal function deterioration. Central pressure has been shown to predict cardiovascular events in most previous studies and potentially serves as a surrogate marker for intervention. Quantitative and comprehensive evaluation of central hemodynamics is now available through various noninvasive pressure/flow measurement modalities. This review will focus on the clinical usefulness and mechanistic rationale of central hemodynamic measurements for cardiovascular risk management.

Key words: Arteriosclerosis, Aorta, Stiffness, Blood pressure, Blood flow

Copyright©2017 Japan Atherosclerosis Society

This article is distributed under the terms of the latest version of CC BY-NC-SA defined by the Creative Commons Attribution License.

Introduction: Historical View

Arterial blood pressure (BP) has long been recognized as an important biomarker of arterial function. More than 280 years ago, Stephen Hales compared the arterial system to a fire extinguisher with an air chamber (the so-called “Windkessel”), showing that the pulse waveform of BP (e.g., systolic upstroke and diastolic exponential decay) depends on aortic distensibility¹. Until the invention of the brachial cuff auscultatory method by Riva-Rocci and Korotkoff, the BP waveform had been utilized to diagnose hypertension with arterial degeneration². In the early 20th century, it was realized that the pulsatile BP wave is transmitted along the arterial tree from the central aorta to

peripheral arteries at a speed depending on arterial stiffness³. In the mid-20th century, the reflection phenomenon of BP waves was recognized by experimental studies involving frequency domain analysis of aortic impedance^{4, 5}. Human (invasive) studies involving time domain analysis of the intra-aortic BP waveform also confirmed that it is largely explicable by the transmission and reflection phenomena and closely associated with aortic wall stiffness^{6, 7}. Clinical introduction of applanation tonometry for noninvasive BP recording revealed age-dependent (i.e., arteriosclerosis-induced) changes in the radial and carotid artery waveforms, leading to the proposal of the concept of the augmentation index (AIx)⁸. A mathematical transformation method has also been devised to generate aortic waveforms from radial waveforms and to estimate aortic BP⁹.

Similar to BP measurement, blood flow measurement has progressed from invasive intra-arterial recordings (e.g., through an electromagnetic flowmeter) to noninvasive duplex ultrasound or MRI record-

Address for correspondence: Junichiro Hashimoto, Medical Center, Miyagi University of Education, 149 Aoba, Aramaki, Aoba-ku, Sendai 980-0845, Japan
E-mail: hashimoto@med.tohoku.ac.jp
Received: March 30, 2017
Accepted for publication: April 24, 2017

ings, which enable us to evaluate pulsatile hemodynamics in the central aorta more easily and comprehensively. With the increasing availability of these new pressure/flow measurement modalities, more attention has recently been paid to the clinical significance of central hemodynamics in cardiovascular diseases (CVDs). This review will summarize the current evidence on the potential for central hemodynamic indices to stratify cardiovascular risk and/or serve as a surrogate marker of clinical endpoints. This review will also focus on the pathophysiological mechanisms underlying the link between central hemodynamic abnormalities and end-organ damage/dysfunction and discuss future directions of clinical research.

What is Central BP?

Central BP is generally defined as BP in the ascending aorta. In a broader sense, it can refer to BP in the thoracic or abdominal aorta, representing BP exerted at the level of the heart, brain, and kidney¹⁰. Due to the phenomenon of pulse pressure (PP) amplification¹¹, the central (systolic and pulse) pressures essentially differ from the brachial pressures. The central-brachial BP difference considerably varies among individuals¹²; for instance, there is an approximate difference of < 5 mmHg in some people (e.g., elderly people with a very stiff aorta), whereas it occasionally exceeds 30 mmHg in others (e.g., young people with a distensible aorta¹³ or during exercise¹⁴). This difference cannot be estimated directly from conventional cuff BP measurement alone (i.e., solely from the two extremes of brachial BPs), but it can be actually estimated by adding information on the BP pulse waveform (see “How is central BP measured?” below).

The BP pulse waveform can be explained on the basis of the wave transmission and reflection phenomena along the arterial tree. In cardiac systole, the blood ejected from the left ventricle generates an incident (forward) BP wave. The incident wave then travels antegradely from the central aorta to the peripheral arteries at a speed termed “pulse wave velocity (PWV).” When the incident wave encounters high-impedance sites (e.g., high-resistance arterioles and arterial bifurcations), it is reflected and then travels retrogradely toward the central aorta at a speed similar to PWV. PWV is high (normally around 5–10 m/s) enough for the pulse to return up to the central aorta within the same cardiac cycle so that the reflected wave interferes with the incident wave to augment BP. The degree of augmentation is generally evaluated as AIx, which is the ratio of augmented pressure to PP (**Fig. 1**¹⁵).

How is Central BP Measured?

Until a quarter-century ago, aortic BP was only available in an invasive manner by inserting an intra-arterial catheter-tip manometer or a fluid-filled catheter connected to a pressure transducer. Noninvasive estimation of aortic BP has become feasible since the technological development of applanation tonometry^{16, 17} performed on arteries running near the body surface (such as the carotid and radial arteries)⁸ and mathematical transformation of tonometric BP waveforms^{9, 18}. Applanation (flattening) of arteries can be manually performed using a pencil-type probe (i.e., tonometer) or (semi)automatically performed using a hands-free tonometric system. To date, there are three major methods available for central BP estimation.

1) Estimation from Carotid BP Waveform

This method is based on the premise that the carotid waveform is deemed to be identical to the aortic waveform¹⁹. The carotid waveform is usually recorded with applanation tonometry and then calibrated by the brachial cuff pressures [i.e., by the mean arterial pressure (MAP) and diastolic BP] to derive absolute values of central BP. The rationale for calibration by brachial BPs is the observation that MAP and diastolic BP are almost constant in the elastic and conduit arteries (e.g., between the central aorta and brachial artery)²⁰. MAP is either calculated directly from the area under the curve of the brachial (or radial) pulse waveform or estimated indirectly from an equation such as $MAP = \text{diastolic BP} + 0.4 \times PP$ ²¹. This method has the advantage of not requiring any mathematical waveform transformation to estimate absolute central BP values. Nevertheless, it may be technically difficult in some cases to record (flatten) the carotid waveforms appropriately or reproducibly because of the anatomical characteristics of the carotid artery surrounded by soft tissues. The carotid pulse wave recordings can occasionally be affected by respiratory variation. Carotid AIx correlates well with invasively determined aortic AIx, although the former is reported to be half of the latter¹⁹.

2) Mathematical Conversion from Radial to Central BP Waveform with Transfer Function

In this method, the radial waveform is recorded with applanation tonometry and then converted to the corresponding aortic waveform using a frequency domain transfer function. There are two types of transfer function: generalized^{9, 18} and individualized. The former is commercially available and more widely used. Though still debated²², a generalized transfer function is considered valid for normal subjects, for

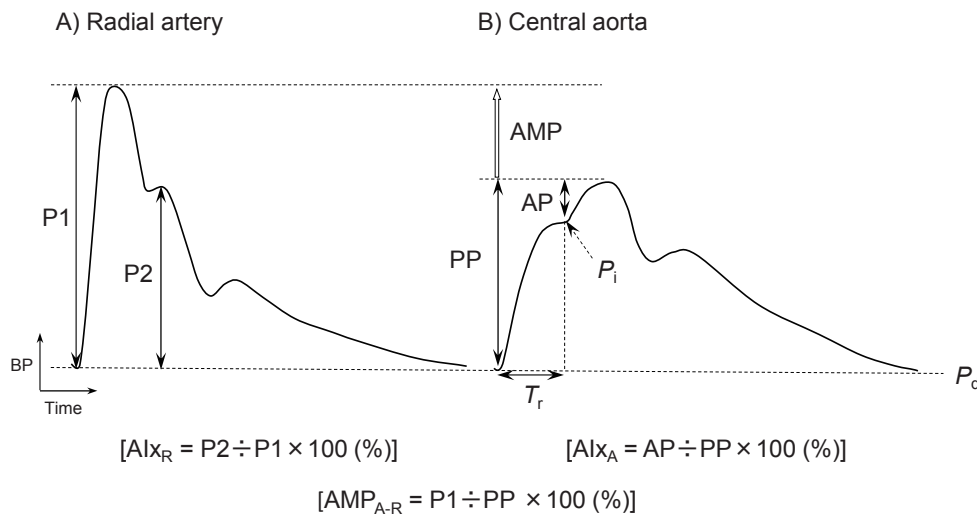


Fig. 1. Pressure pulse waveforms of radial artery (A) and central aorta (B)

AIxA indicates aortic augmentation index; AIxR, radial augmentation index; AMP, pulse pressure amplification; AMP_{A-R}, aorta-to-radial AMP ratio; AP, augmented pressure; BP, blood pressure; P1, early systolic peak pressure; P2, late systolic peak pressure; P_d, diastolic pressure; P_i, pressure at inflection point; PP, pulse pressure; and T_r, round-trip travel time. Reproduced from Hashimoto¹⁵).

patients with various diseases^{18, 23, 24}), during exercise²⁵), during pharmacological intervention²⁶), and during the Valsalva maneuver¹⁸). The synthesized aortic waveform is normally calibrated with brachial diastolic BP and MAP to obtain central BP; MAP is calculated from the area under the radial waveform on the basis that the radial and brachial waveforms are deemed to be identical⁸). Aortic BP estimated using this method somewhat underestimates systolic BP and overestimates diastolic BP as measured directly using an invasive method²⁷), but these errors almost entirely depend on the inaccurate calibration by the brachial cuff measurement²⁸). The estimated aortic BP closely correlates with invasive aortic BP²⁹). Reproducibility has been repeatedly verified in terms of aortic BP and AIx estimation³⁰⁻³²).

3) Direct Estimation from Radial BP Waveform without Using Transfer Function

It is empirically recognized that aortic systolic (maximum) BP is equal to the late systolic (second) peak (or “shoulder”) of radial BP³³). Based on this recognition, the radial waveform is calibrated with brachial systolic and diastolic BPs to determine radial late systolic BP, which corresponds to aortic systolic BP. Although this method cannot generate the aortic waveform itself, it can offer the advantage of directly estimating aortic systolic BP and PP without applying a complicated waveform transformation. Radial AIx is usually calculated as the ratio of late systolic to early

systolic BP peak amplitude (**Fig. 1**)³⁴). This method has been validated using invasive studies^{35, 36}), and the estimated radial AIx and late systolic pressure are reported to be reproducible³⁷). Though only rare (< 5%), aortic BP may be unavailable because of an undetectable radial second peak (e.g., under conditions of marked tachycardia or vasodilation).


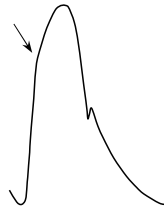
In addition, several devices have been newly developed and are currently available for noninvasive central BP recordings. Some of them adopt brachial cuff-based pulse volume plethysmography in place of applanation tonometry³⁸⁻⁴¹); therefore, they are portable and capable of measuring ambulatory 24-h central BP. The N-point moving average method has also been proposed for the estimation of the aortic BP peak from the radial BP waveform⁴²). These novel methodologies can provide more detailed information on central BP (e.g., circadian variation); further validation studies are required for general use in terms of accuracy, reproducibility, and prognostic significance.

Factors Affecting Central BP

1) Age (Arteriosclerosis)

Age is the most potent accelerating factor associated with arteriosclerosis, and it strongly influences aortic BP waveforms (**Table 1**). With advancing age, elastic fibers in the aortic medial layer gradually undergo degeneration and are replaced with stiffer collagenous fibers, and the resultant decrease in the

Table 1. Comparisons of aortic pulse waveform characteristics between subjects with and without aortosclerosis

Aortosclerosis	(-)	(+)
Aortic pressure waveform*		
Incident pressure wave	Low	High
Augmented pressure	Low	High
Pulse pressure	Narrow	Wide
Pulse wave velocity	Slow	Fast
Round-trip travel time	Long	Short
Augmentation index	Normal	High
Diastolic pressure decay	Slow	Fast
Pulse pressure amplification	Large	Small

*Arrows indicate the arrival of reflected waves.

medial elastin/collagen ratio causes progressive stiffening of the aortic wall and reduction in aortic compliance^{43, 44}. Such a pathological process is usually referred to as arteriosclerosis. Hypertension accelerates this process because of the fatiguing effects of excessive cyclic stress on elastic fibers⁴³. Aortic stiffening increases aortic PWV and shortens the return time of the reflected BP wave and thus increases the augmented pressure. Moreover, as aortic distensibility decreases with age, systolic upstroke and diastolic decay of aortic BP become steeper. All these changes are responsible for a marked widening of aortic PP with age (**Table 1**). It should be noted here that compared with central elastic arteries, peripheral muscular arteries undergo little arteriosclerotic change⁴⁵; therefore, age-dependent PP change is more remarkable in the former⁴⁶.

Epidemiological studies have shown progressive linear increases in aortic augmented pressure and reflected wave magnitude with age^{47, 48}. Aortic AIx increases until the sixth decade but reaches a plateau or even decreases thereafter^{47, 49}, probably because both the numerator (augmented pressure) and denominator (PP) increase linearly with age but with different intercepts on the pressure axis⁵⁰.

2) Gender and Height

In general, women show a higher AIx than men⁵¹. This is mainly attributed to their difference in body height⁵², which relates to the path length between the central aorta and peripheral reflecting sites and thus determines the timing of wave reflection. However, the association between gender and AIx can be observed even independently of body height, suggesting an

intrinsic gender difference in arterial function⁵³. Given a higher AIx in women, gender difference in aortic PP is less obvious than that in brachial PP⁵⁴.

3) Heart Rate and Ejection Duration

AIx increases as the heart rate decreases⁵⁵. This is because a longer ejection duration resulting from a lower heart rate causes a wider incident wave to overlap with a reflected wave, with the round-trip travel time of these two waves being little affected by the heart rate. It can also be a reason why nonvasodilating beta-blocker administration increases AIx⁵⁶.

4) Lifestyle (Smoking, Alcohol, Caffeine, and Sodium Intake)

Smoking of cigarettes or cigars increases aortic AIx and PWV acutely and chronically^{57, 58}. Chronic smokers had a higher aortic (but a similar brachial) systolic BP than nonsmokers⁵⁷. Smoking-induced AIx increase correlates with the change in the plasma cotinine level⁵⁹. Even short-term smoking cessation reduces AIx⁶⁰.

Alcohol intake has divergent effects on AIx; acute ingestion reduces aortic systolic BP and AIx, while chronic excessive consumption elevates these in men⁶¹. The effect of chronic alcohol consumption on aortic BP may differ by gender; heavier alcohol intake is associated with a higher AIx in healthy young men⁶² but not in postmenopausal women⁶³.

Caffeine affects peripheral wave reflection to elevate aortic BP to a greater extent than that apparent from brachial BP⁶⁴. Caffeinated but not decaffeinated coffee ingestion raises aortic AIx and PWV⁶⁵. Black

and green tea can also elevate AIx⁶⁶. The combination of smoking and caffeine intake produces a synergistic detrimental effect on aortic PWV and AIx⁶⁷.

Excessive sodium intake increases aortic stiffness and wave reflection, while sodium restriction improves them effectively^{68, 69}.

5) Diabetes, Hypercholesterolemia, and Obesity

Inconsistent results have been reported with regard to AIx in diabetes. Pediatric patients with type 1 diabetes are reported to have an increased aortic AIx⁷⁰, while adult patients with type 2 diabetes can have an increased⁷¹, normal⁷², or even reduced⁷³ AIx despite widened PP. The mechanism underlying these apparently conflicting observations is still debated, but some patients with type 2 diabetes may have compensatory hyperinsulinemia (in response to insulin resistance), which could induce peripheral vasodilation and diminish wave reflection, even with a stiffened aorta. It may also involve central (abdominal) obesity, which is known to reduce AIx⁷³. Aortic AIx in patients with hypercholesterolemia is reported to be higher than⁷⁴ or similar to⁷⁵ that in subjects with normocholesterolemia. Metabolic syndrome may not be associated with AIx in treated hypertension⁷⁶. Taking these reports together, metabolic disorders can have inconsistent effects on AIx and thus peripheral wave reflection, in contrast to a relatively consistent (increasing) effect on PWV and arterial stiffness⁷⁷. It should be of note, however, that aortic BP elevation can often be observed in these disorders even without any increase in wave reflection, namely through an increase in the incident wave height.

Arterial stiffness and wave reflection may be influenced not only by glucose or lipid metabolism but also by mineral metabolism abnormalities. For instance, higher serum phosphorus levels are shown to be associated with increases in PWV and AIx even among the general population with normal kidney function⁷⁸.

6) Other Related Diseases

An elevation in AIx is observed in hypothyroidism⁷⁹ and hyperparathyroidism⁸⁰, both of which represent the endocrine disorders considered responsible for hypertension. In obstructive sleep apnea syndrome, aortic (but not peripheral) BP and AIx can be elevated, particularly in the early morning⁸¹. Aortic BP may decrease in response to nasal continuous positive airway pressure treatment even without parallel changes in peripheral BP⁸². In patients with Kawasaki disease who develop coronary artery lesions, wave reflection indices are elevated and the aortic waveforms resemble those observed in the elderly⁸³. Primary inflammatory diseases, including rheumatoid

arthritis, may be independently associated with increased central BP and AIx⁸⁴, although it remains controversial whether systemic inflammation in primary hypertension and chronic kidney disease (CKD) is a cause or consequence of aortic stiffness⁸⁵. Systemic sclerosis, which often involves microvascular lesions, is associated with enhanced peripheral wave reflection despite normal aortic stiffness⁸⁶. Sickle cell disease with the hemoglobin SS genotype is associated with lower arterial stiffness and wave reflections owing to higher nitric oxide availability⁸⁷.

Is Central BP Useful for Risk Stratification of CVD?

1) Prospective Studies

So far, a number of prospective observational cohort studies have been conducted to investigate the predictive ability of central BP indices for CVD events. The results are summarized in **Table 2**⁸⁸⁻¹⁰⁶ and have been discussed elsewhere in our previous review¹⁰⁷. These study cohorts can be classified according to the underlying diseases, e.g., patients with renal disease, patients with coronary heart disease, and the general population. As a whole, most (but not all) of currently available data indicate that central BP indices (such as central PP, AIx, and PP amplification) can predict CVD events more precisely than and/or independently of brachial BP, particularly in high-risk populations (**Table 2**; for more details, please refer to the previous review¹⁰⁷).

2) Cut-Off Value

The definition of the cut-off values for central BP has not yet been established. While the normal upper limits of brachial (casual) BP are usually defined as 140/90 mmHg, it is difficult to set corresponding thresholds for central BP because of the PP amplification, which considerably varies among individuals according to age and BP levels¹². Based on a distribution approach from an epidemiological cross-sectional database, brachial BP values of 140/90 mmHg correspond to central BP values of ~125/90 mmHg¹⁰⁸. Based on a prognostic outcome-driven approach from a prospective database, central BP of 130/90 mmHg has been proposed as a diagnostic threshold value¹⁰⁹. Clearly, the validity of these cut-off values needs to be confirmed by further investigation.

Does Central BP Serve as a Surrogate Marker for Intervention?

Brachial BP has long been recognized as a useful marker for the management of CVD as well as hyper-

Table 2. Prospective observational studies on predictive value of central blood pressure parameters for cardiovascular events

First Author	Subjects	N	Male (%)	Age (years)*	Brachial BP (mmHg) [†]	Follow-up (years)*	Recording/ Estimation	Endpoint	Event rate [‡]	Central BP parameter	Adjusted RR	Lower 95%CI	Upper 95%CI	Central vs. brachial
London ⁸⁸⁾	ESRD	180	60	54	156/83	4.3	Carotid	All-cause mortality CV mortality	89.7 51.3	AIx (/10%) AIx (/10%)	1.51 1.48	1.23 1.16	1.86 1.90	Sup, Ind Ind
Safar ⁸⁹⁾	ESRD	180	59	54	156/83	4.3	Carotid	All-cause mortality	89.7	PP (/25 mmHg) AMP (/16%)	1.40 0.50	1.10 0.30	1.80 0.80	Sup Sup
Covic ⁹⁰⁾	ESRD	92	54	43	129/84	5.1	Radial	All-cause mortality	32.1	AIx (>24.6 vs. <12.0%)	0.64	0.13	3.15	n/a
Briet ⁹¹⁾	CKD	180	74	60	134/74	3.1	Carotid	Hemodialysis	73.5	PP (/10 mmHg)	1.24	1.03	1.49	n/a
Verbeke ⁹²⁾	Renal Tx	512	59	53	135/80	5.0	Radial	CV events	37.1	AugP (/8.6 mmHg)	1.49	1.22	1.81	Ind
Ueda ⁹³⁾	CAD	103	78	63	(139/72)	0.5	Intraaortic	Coronary restenosis	699.0	AIx (/10%) Tr (/10 ms)	1.70 1.34	1.16 1.10	2.48 1.63	n/a n/a
Weber ⁹⁴⁾	CAD	262	71	66	132/78	2.0	Radial	CV events	116.0	AIx@Hr75 (/1%)	1.04	1.01	1.07	Sup
Chirinos ⁹⁵⁾	CAD	297	100	64	136/70	3.2	Intraaortic	CV events	132.3	AugP (/10 mmHg) AIx (/10%)	1.19 1.28	1.06 1.09	1.34 1.50	Sup Sup
Jankowski ⁹⁶⁾	CAD	1109	74	58	(135/72)	4.4	Intraaortic	CV events	50.5	PP (/18.2 mmHg)	1.28	1.10	1.49	Sup
Weber ⁹⁷⁾	CAD	520	100	64	133/80	4.1	Radial	CV events	80.1	AIx (/10%) AIx@Hr75 (/10%)	1.15 1.25	1.01 1.06	1.32 1.47	Ind Ind
Roman ⁹⁸⁾	General	2403	35	63	132/75	4.8	Radial	CV events	27.7	PP (/10 mmHg)	1.15	1.07	1.24	Sup
Roman ⁹⁹⁾	General	2405	35	63	132/75	5.6	Radial	CV events	25.5	PP (≥ 50 vs. ≤ 31 mmHg)	1.69	1.20	2.39	Sup
Pini ¹⁰⁰⁾	General	398	45	73	145/84	8.0	Carotid	CV events	38.3	PP (/10 mmHg)	1.23	1.10	1.37	Sup
Leone ¹⁰¹⁾	General	3337	39	73	145/82	3.6	Nomogram	Coronary events	10.6	PP (/14.6 mmHg)	1.39	1.17	1.60	n/a
Benetos ¹⁰²⁾	General	125151	58	40	132/81	12.1	Nomogram	All-cause mortality CV mortality	2.6 0.5	PP (/7.8 mmHg) PP (/7.8 mmHg)	1.18 1.21	1.12 1.15	1.25 1.28	Sup Sup
Wang ¹⁰³⁾	General	1272	53	52	139/88	10.8	Carotid	CV mortality	2.7	PP (/10 mmHg)	1.26	1.02	1.56	Sup
Wang ¹⁰⁴⁾	General	1272	53	52	139/88	15.0	Carotid	CV mortality	3.3	Pb (/6 mmHg)	1.59	1.21	2.09	Sup, Ind
Huang ¹⁰⁵⁾	General	1014	54	52	139/89	15.0	Carotid	All-cause mortality	13.2	PP (/1 mmHg)	1.16	1.01	1.32	Sup
Mitchell ¹⁰⁶⁾	General	2232	42	63	127/74	7.8	Carotid	CV events	8.7	PP (/1 mmHg) AIx (/1%)	1.00 0.91	0.99 0.77	1.01 1.07	n/a n/a

AIx: augmentation index; AIx@Hr75: AIx adjusted for heart rate of 75 bpm; AMP: pulse amplification; AugP: augmented pressure; BP: blood pressure; CAD: coronary artery disease (or suspect); CI: confidence interval; CKD: chronic kidney disease; CV: cardiovascular; ESRD: end-stage renal disease; Ind: predictive independency of central BP parameters from brachial BP; n/a: data not available; Pb: reflected wave amplitude; PP: pulse pressure; RR: relative risk; Sup: predictive superiority of central BP parameters over brachial BP; Tr: travel time; Tx: transplantation. *Mean or median. [†]Except for aortic BP in parentheses. [‡]Per 1000 person-year (by estimate). Reproduced from Hashimoto *et al.*¹⁰⁷⁾

tension. For introducing central BP measurement into routine clinical practice, the most critical issue is to determine whether central BP is superior to brachial BP in evaluating therapeutic effects and predicting their consequences.

It is known that nitroglycerine has a stronger hypotensive effect on central BP than that apparent from brachial BP measurement¹¹⁰⁾. This is attributable to a reduction in wave reflection resulting from the peripheral vasodilating action of nitroglycerine. The opposite effects are observed for nonvasodilating β -blockers, which lower central BP to a lesser extent than brachial BP¹¹¹⁾. So far, different effects of various

antihypertensive drug classes on central BP have been demonstrated by several randomized multicenter clinical trials. For instance, the CAFÉ substudy⁵⁶⁾ of the ASCOT trial¹¹²⁾ showed that individuals assigned to the amlodipine/perindopril group had a 4.3 mmHg lower central systolic BP than those assigned to the atenolol/thiazide group, despite a similar brachial BP. The EXPLOR study¹¹³⁾ demonstrated that an amlodipine/valsartan combination decreases central BP and AIx more effectively than an amlodipine/atenolol combination. In addition, the PARAMETER study has recently shown that sacubitril/valsartan (LCZ696), an angiotensin receptor neprilysin inhibitor, is more

potent than olmesartan in reducing central BP¹¹⁴).

Central BP can serve as a therapeutic surrogate marker for the prevention of major CVD events. Data from the abovementioned CAFÉ study indicate that the modest intergroup difference in central BP, which is undetectable by conventional brachial BP measurement, contributed to the better cardiovascular outcome in the amlodipine group observed in the ASCOT study¹¹²). In addition, compared with brachial BP, central BP can better predict the regression of target organ damage (e.g., left ventricular hypertrophy¹¹⁵) and carotid artery wall hypertrophy¹¹⁶) during antihypertensive treatment. Such regression, which likely results from vasodilator-induced reduction in peripheral wave reflection^{117, 118}), could be closely linked to a reduction in CVD events. These lines of evidence suggest a potential benefit of central BP-guided antihypertensive therapy for CVD management.

At present, only limited data are available regarding the therapeutic impact of medication other than antihypertensive drugs (e.g., statin and antidiabetic drugs). In the CAFÉ-LLA substudy¹¹⁹), atorvastatin therapy sufficient to reduce CVD events in the ASCOT trial¹¹²) had no influence on central BP or AIx. In contrast, in a placebo-controlled study¹²⁰), atorvastatin but not the placebo induced significant reductions in central BP, AIx and PWV. Linagliptin (a dipeptidyl peptidase-4 inhibitor) did not affect central BP and AIx in a placebo-controlled study of patients with diabetes¹²¹). Metformin (but not the placebo) reduces central BP and AIx in patients with nonalcoholic fatty liver disease¹²²) and in young women with polycystic ovary syndrome¹²³). Tetrahydrobiopterin, a nitric oxide synthase cofactor, can lower central AIx but not PWV in patients with CKD¹²⁴). Anti-inflammatory treatment may reduce PWV and/or AIx in some patients with primary inflammatory disorders¹²⁵). Obviously, further investigation is required.

Pathophysiological Relations of Central Hemodynamics to Arteriosclerotic Diseases: Hypothetical View and Future Directions

As the central aorta stiffens, peripheral end-organs undergo progressive degeneration in the vascular structure and gradual deterioration in the physiological function, which can lead eventually to the sudden occurrence of symptomatic CVD. There is substantial evidence showing that aortic PWV predicts major cardiovascular events, including myocardial infarction, heart failure, stroke, and renal failure^{126, 127}). Until quite recently, however, relatively little was known about the underlying mechanisms by which

aortic stiffening causes target organ damage or dysfunction. Results of the latest studies indicate that the central hemodynamics, including aortic BP and flow, plays a pivotal role in the causal mechanisms.

Aortic pulsatile flow is an important constituent of central hemodynamics. The flow waveform differs from the pressure waveform and greatly varies among different aortic sites¹²⁸). According to previous studies based on Doppler ultrasound, the flow waveform in the proximal descending aorta is biphasic (to-and-fro) comprising systolic forward and diastolic reverse components, and the reverse/forward flow ratio linearly increases with aortic stiffening¹²⁹). Such an increase in aortic flow reversal could alter the blood flow distribution to various organs and thus directly relate to the pathophysiological mechanisms of arteriosclerotic CVD (see below). The bidirectional (i.e., antegrade and retrograde) nature of aortic flow seems quite intriguing from a physiological view, given its potential relevance to aortic BP composed of the two waves going in opposite directions (i.e., forward and reflected waves). The PP amplification (i.e., pressure gradient) and aortic/peripheral PWV ratio (i.e., stiffness gradient) also seem to be significant determinants of pulsatile flow production¹³⁰⁻¹³²).

1) Stroke

Cerebrovascular disease can be broadly divided into two categories: microvascular and macrovascular stroke (**Table 3**). Cerebral microvascular diseases include lacunar infarction, white matter hyper-intensity lesions, and intracerebral hemorrhage (including microbleeds), which are often observed in the regions perfused by deep perforating arteries. Several previous studies have associated these microvascular lesions with elevations in aortic PWV and BP¹³³⁻¹³⁷). The underlying mechanisms are likely that 1) the small perforating arteries are directly branched from the large cerebral arteries and 2) BP and flow pulsations are prone to deeply transmitting into the cerebral microvasculature on account of its low impedance properties^{132, 138}). It is thought that with aortic stiffening, BP pulsation in large arteries becomes greater; thus, higher pulsatile stress is imposed on the fragile microvascular walls, which results in microvascular injury and eventually causes ischemic or hemorrhagic stroke.

In contrast to microvascular stroke, macrovascular stroke usually occurs in the regions perfused by large cortical arteries and could be fatal in some cases. Studies have demonstrated that aortic PWV is an independent predictor of fatal stroke¹³⁹). The underlying hemodynamic mechanisms linking aortic stiffness to macrovascular stroke may include 1) cerebral

Table 3. Different characteristics of micro- and macrovascular stroke

Stroke types	Microvascular	Macrovascular
Designations	· Lacunar infarction · Hemorrhagic stroke (including microbleeds)	· Cortical infarction
Main causes	Lipohyalinosis	· Atherosclerosis · Thromboembolism
Vascular territories	Small deep perforating arteries	Cerebral/carotid/vertebral arteries
Association with aortic stiffness	+	+
Suggested central hemodynamic mechanisms	· High aortic pressure	· High aortic pressure · Aortic flow reversal

thromboembolism due to plaque rupture in the carotid/cerebral arteries and 2) cardiogenic embolism due to atrial fibrillation, both of which are triggered by widened central PP and/or enhanced peripheral wave reflection^{140, 141}. In addition, another mechanism has recently been proposed: 3) retrograde plaque embolism due to the abovementioned aortic flow reversal¹²⁹. In particular, the term “retrograde embolism” means that atherosclerotic mobile plaques are detached from the aortic arch or descending aortic walls and then retrogradely delivered through the supra-aortic (i.e., carotid and subclavian) arteries up to cerebral arteries to cause “cryptogenic” stroke. This type of stroke can indeed occur¹⁴² because diastolic reverse flow in the descending aorta directly contributes to forward flow into the supra-aortic arteries. In addition, the risk of the retrograde embolism may be heightened by aortic stiffening because the stiffer the aorta is, the greater the aortic flow reversal becomes¹²⁹. The rationale for this retrograde embolism also includes the facts that 1) cryptogenic stroke can occur without any embolic sources in the heart or ascending aorta and 2) mobile plaques are more often seen in the descending aorta than in the ascending aorta¹⁴³.

2) CKD

CKD is defined as the presence of (micro)albuminuria and/or a reduced glomerular filtration rate (GFR). Both albuminuria and GFR reduction are often preceded by aortic stiffening, but they can predict future CVD events independently of each other¹⁴⁴. This indicates the existence of at least partially different etiologies underlying these distinct entities. Recent investigation does suggest different mediating influences of central hemodynamic (i.e., BP and flow) abnormalities on these aorto-renal associations.

The kidney has a unique structure and function. The renal arteries branch off from the abdominal

aorta into intrarenal smaller arteries, leading to tiny afferent arterioles and fragile glomerular capillaries. Intraglomerular pressure is as high as 60/40 mmHg even under normal conditions, reflecting the low impedance properties of the renal vasculature. In case of aortosclerosis, the central PP widens, and then, the high BP pulsation is transmitted down to the glomerular capillaries. This most likely results in intraglomerular hypertension and endothelial injury, leading to albuminuria¹³². In fact, central PP and PWV have been shown to be independent predictors of the urinary albumin/creatinine ratio^{131, 145}.

Aortic stiffness is also known to be associated with GFR decline^{146, 147}. The GFR decline may result from such glomerular injury, as mentioned above, but another possibility has recently been raised that aortic flow abnormality is a primary cause of renal dysfunction accompanying aortosclerosis. As mentioned earlier, aortic stiffening increases flow reversal in the thoracic descending aorta and thus reduces forward flow toward the suprarenal abdominal aorta¹²⁹. This reduction in suprarenal aortic flow (also caused by an impaired Windkessel function) could reduce blood inflow into the renal arteries (i.e., renal blood flow) and thereby deteriorate GFR¹⁴⁸. This flow mechanism could also explain why renal function decreases with age in the general population (i.e., even in the absence of albuminuria).

3) Heart Disease

For over a half century, numerous studies have shown an important etiological role of central hemodynamics in cardiac diseases. The details have been extensively reviewed previously^{43, 149}. In brief, an elevation in central BP, which directly reflects left ventricular afterload, is primarily responsible for left ventricular hypertrophy^{150, 151}, causing various cardiac dysfunctions (e.g., heart failure and arrhythmia). Hastening of exponential decay of central BP during diastole, which is accelerated by aortic stiffening, reduces

the diastolic inflow from the ascending aorta to the coronary arteries and thereby predisposes hypertensive patients to myocardial ischemia¹⁵². The risk of myocardial ischemia could be further heightened by the presence of atherosclerotic coronary artery stenosis¹⁵³ and/or left ventricular hypertrophy with increased oxygen demand¹⁵⁴. Obviously, more studies are needed to investigate the crucial link between aortic and coronary pulsatile flow.

Conclusions

The quantitative assessment of central pulsatile hemodynamics has now been enabled by noninvasive tonometry/ultrasound and pulse waveform analysis. Central hemodynamic indices have some advantages in terms of 1) the technical facility for repeated measurements, 2) the immediate response to antihypertensive treatment, and 3) the predictive ability of therapeutic consequences (e.g., preventive effects on CVD). Recent international guidelines or recommendations for vascular biomarkers have also endorsed their usefulness^{155, 156}. In the future, for wider application to clinical practice, further investigation is needed to determine the normal reference values, develop handy apparatuses with high precision and dedicated analytical programs, and verify the epidemiological evidence and mechanistic rationale for general use in CVD risk management.

Conflict of Interest

The author belonged to an endowment department supported with unrestricted grants from Omron Healthcare and MSD.

References

- 1) Hales S: Statistical Esseys: Haemastatics. History of Medical Series, Hafner Publishing (reproduced 1964), New York, 1733
- 2) Mahomed FA: The etiology of Bright's disease and the prealbuminuric stage. *Med Chir Trans*, 1874; 57: 197-228
- 3) Bramwell JC, Hill AV: Velocity of transmission of the pulse wave. *Lancet*, 1922; 891-892
- 4) O'Rourke MF, Taylor MG: Input impedance of the systemic circulation. *Circ Res*, 1967; 20: 365-380
- 5) O'Rourke MF: The arterial pulse in health and disease. *Am Heart J*, 1971; 82: 687-702
- 6) O'Rourke MF, Avolio AP: Pulsatile flow and pressure in human systemic arteries. Studies in man and in a multi-branched model of the human systemic arterial tree. *Circ Res*, 1980; 46: 363-372
- 7) Murgo JP, Westerhof N, Giolma JP, Altobelli SA: Aortic

input impedance in normal man: relationship to pressure wave forms. *Circulation*, 1980; 62: 105-116

- 8) Kelly R, Hayward C, Avolio A, O'Rourke M: Noninvasive determination of age-related changes in the human arterial pulse. *Circulation*, 1989; 80: 1652-1659
- 9) Karamanoglu M, O'Rourke MF, Avolio AP, Kelly RP: An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. *Eur Heart J*, 1993; 14: 160-167
- 10) Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Struijker Boudier HA, et al.: 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*, 2007; 28: 1462-1536
- 11) Avolio AP, Van Bortel LM, Boutouyrie P, Cockcroft JR, McEniery CM, Protogerou AD, Roman MJ, Safar ME, Segers P, Smulyan H: Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. *Hypertension*, 2009; 54: 375-383
- 12) Herbert A, Cruickshank JK, Laurent S, Boutouyrie P, Reference Values for Arterial Measurements C: Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk factors. *Eur Heart J*, 2014; 35: 3122-3133
- 13) Mahmud A, Feely J: Spurious systolic hypertension of youth: fit young men with elastic arteries. *Am J Hypertens*, 2003; 16: 229-232
- 14) Rowell LB, Brengelmann GL, Blackmon JR, Bruce RA, Murray JA: Disparities between aortic and peripheral pulse pressures induced by upright exercise and vasomotor changes in man. *Circulation*, 1968; 37: 954-964
- 15) Hashimoto J: Pulse wave velocity and pulse wave analysis. *Curr Rev Clin Pathol*, 2013; 151: 27-37 (Japanese)
- 16) Pressman GL, Newgard PM: A Transducer for the continuous external measurement of arterial blood pressure. *IEEE Trans Biomed Eng*, 1963; 10: 73-81
- 17) Drzewiecki GM, Melbin J, Noordergraaf A: Arterial tonometry: review and analysis. *J Biomech*, 1983; 16: 141-152
- 18) Chen CH, Nevo E, Fetics B, Pak PH, Yin FC, Maughan WL, Kass DA: Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. *Circulation*, 1997; 95: 1827-1836
- 19) Chen CH, Ting CT, Nussbacher A, Nevo E, Kass DA, Pak P, Wang SP, Chang MS, Yin FC: Validation of carotid artery tonometry as a means of estimating augmentation index of ascending aortic pressure. *Hypertension*, 1996; 27: 168-175
- 20) Pauca AL, Wallenhaupt SL, Kon ND, Tucker WY: Does radial artery pressure accurately reflect aortic pressure? *Chest*, 1992; 102: 1193-1198
- 21) Mahieu D, Kips J, Rietzschel ER, De Buyzere ML, Verbeke F, Gillebert TC, De Backer GG, De Bacquer D, Verdonck P, Van Bortel LM, Segers P: Noninvasive assessment of central and peripheral arterial pressure

- (waveforms): implications of calibration methods. *J Hypertens*, 2010; 28: 300-305
- 22) Hope SA, Meredith IT, Cameron JD: Arterial transfer functions and the reconstruction of central aortic waveforms: myths, controversies and misconceptions. *J Hypertens*, 2008; 26: 4-7
 - 23) Westerhof BE, Guelen I, Stok WJ, Lasance HA, Ascoop CA, Wesseling KH, Westerhof N, Bos WJ, Stergiopoulos N, Spaan JA: Individualization of transfer function in estimation of central aortic pressure from the peripheral pulse is not required in patients at rest. *J Appl Physiol*, 2008; 105: 1858-1863
 - 24) Payne RA, Lilitkarntakul P, Dhaun N, Melville V, Asai T, Goddard J, Webb DJ: Renal dysfunction does not affect the peripheral-to-central arterial pressure transfer function. *Hypertension*, 2010; 56: 1083-1088
 - 25) Sharman JE, Lim R, Qasem AM, Coombes JS, Burgess MI, Franco J, Garrahy P, Wilkinson IB, Marwick TH: Validation of a generalized transfer function to noninvasively derive central blood pressure during exercise. *Hypertension*, 2006; 47: 1203-1208
 - 26) Pauca AL, O'Rourke MF, Kon ND: Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. *Hypertension*, 2001; 38: 932-937
 - 27) Cloud GC, Rajkumar C, Kooner J, Cooke J, Bulpitt CJ: Estimation of central aortic pressure by SphygmoCor requires intra-arterial peripheral pressures. *Clin Sci*, 2003; 105: 219-225
 - 28) Smulyan H, Siddiqui DS, Carlson RJ, London GM, Safar ME: Clinical utility of aortic pulses and pressures calculated from applanated radial-artery pulses. *Hypertension*, 2003; 42: 150-155
 - 29) Ding FH, Fan WX, Zhang RY, Zhang Q, Li Y, Wang JG: Validation of the noninvasive assessment of central blood pressure by the SphygmoCor and Omron devices against the invasive catheter measurement. *Am J Hypertens*, 2011; 24: 1306-1311
 - 30) Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, Cockcroft JR, Webb DJ: Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. *J Hypertens*, 1998; 16: 2079-2084
 - 31) Siebenhofer A, Kemp C, Sutton A, Williams B: The reproducibility of central aortic blood pressure measurements in healthy subjects using applanation tonometry and sphygmocardiography. *J Hum Hypertens*, 1999; 13: 625-629
 - 32) Filipovsky J, Svobodova V, Pecan L: Reproducibility of radial pulse wave analysis in healthy subjects. *J Hypertens*, 2000; 18: 1033-1040
 - 33) Pauca AL, Kon ND, O'Rourke MF: The second peak of the radial artery pressure wave represents aortic systolic pressure in hypertensive and elderly patients. *Br J Anaesth*, 2004; 92: 651-657
 - 34) Hashimoto J, Watabe D, Hatanaka R, Hanasawa T, Metoki H, Asayama K, Ohkubo T, Totsune K, Imai Y: Enhanced radial late systolic pressure augmentation in hypertensive patients with left ventricular hypertrophy. *Am J Hypertens*, 2006; 19: 27-32
 - 35) Hickson SS, Butlin M, Mir FA, Graggaber J, Cheriyan J, Khan F, Grace AA, Yasmin, Cockcroft JR, Wilkinson IB, McEniery CM: The accuracy of central SBP determined from the second systolic peak of the peripheral pressure waveform. *J Hypertens*, 2009; 27: 1784-1788
 - 36) Takazawa K, Kobayashi H, Kojima I, Aizawa A, Kinoh M, Sugo Y, Shimizu M, Miyawaki Y, Tanaka N, Yamashina A, Avolio A: Estimation of central aortic systolic pressure using late systolic inflection of radial artery pulse and its application to vasodilator therapy. *J Hypertens*, 2012; 30: 908-916
 - 37) Funada J, Takata Y, Hashida H, Matsumoto Y, Sato S, Hiasa G, Inoue K, Higaki J, Okayama H: Dysfunctional central hemodynamic regulation after daily meal intake in metabolic syndrome. *Atherosclerosis*, 2010; 210: 268-273
 - 38) Lowe A, Harrison W, El-Aklouk E, Ruygrok P, Al-Jumaily AM: Non-invasive model-based estimation of aortic pulse pressure using suprasystolic brachial pressure waveforms. *J Biomech*, 2009; 42: 2111-2115
 - 39) Horvath IG, Nemeth A, Lenkey Z, Alessandri N, Tufano F, Kis P, Gaszner B, Cziraki A: Invasive validation of a new oscillometric device (Arteriograph) for measuring augmentation index, central blood pressure and aortic pulse wave velocity. *J Hypertens*, 2010; 28: 2068-2075
 - 40) Ageenkova OA, Purygina MA: Central aortic blood pressure, augmentation index, and reflected wave transit time: reproducibility and repeatability of data obtained by oscillometry. *Vasc Health Risk Manag*, 2011; 7: 649-656
 - 41) Weber T, Wassertheurer S, Rammer M, Maurer E, Hametner B, Mayer CC, Kropf J, Eber B: Validation of a brachial cuff-based method for estimating central systolic blood pressure. *Hypertension*, 2011; 58: 825-832
 - 42) Williams B, Lacy PS, Yan P, Hwee CN, Liang C, Ting CM: Development and validation of a novel method to derive central aortic systolic pressure from the radial pressure waveform using an N-point moving average method. *J Am Coll Cardiol*, 2011; 57: 951-961
 - 43) O'Rourke MF, Hashimoto J: Mechanical factors in arterial aging: a clinical perspective. *J Am Coll Cardiol*, 2007; 50: 1-13
 - 44) Hashimoto J, O'Rourke MF: Physical factors in arterial ageing. In: *Oxford Textbook of Geriatric Medicine*, ed by Michel JP, Beattie BL, Martin FC, and Walston J, Oxford University Press, London, 2018 (In press)
 - 45) Avolio AP, Deng FQ, Li WQ, Luo YF, Huang ZD, Xing LF, O'Rourke MF: Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. *Circulation*, 1985; 71: 202-210
 - 46) McEniery CM, Wilkinson IB, Avolio AP: Age, hypertension and arterial function. *Clin Exp Pharmacol Physiol*, 2007; 34: 665-671
 - 47) McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR: Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol*, 2005; 46: 1753-1760
 - 48) Namasivayam M, McDonnell BJ, McEniery CM, O'Rourke MF: Does wave reflection dominate age-related change in aortic blood pressure across the human life span? *Hypertension*, 2009; 53: 979-985

- 49) Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D: Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension*, 2004; 43: 1239-1245
- 50) Namasivayam M, Adji A, O'Rourke MF: Aortic augmentation index and aging: mathematical resolution of a physiological dilemma? *Hypertension*, 2010; 56: e9-10
- 51) Hayward CS, Kelly RP: Gender-related differences in the central arterial pressure waveform. *J Am Coll Cardiol*, 1997; 30: 1863-1871
- 52) Smulyan H, Marchais SJ, Pannier B, Guerin AP, Safar ME, London GM: Influence of body height on pulsatile arterial hemodynamic data. *J Am Coll Cardiol*, 1998; 31: 1103-1109
- 53) Gatzka CD, Kingwell BA, Cameron JD, Berry KL, Liang YL, Dewar EM, Reid CM, Jennings GL, Dart AM: Gender differences in the timing of arterial wave reflection beyond differences in body height. *J Hypertens*, 2001; 19: 2197-2203
- 54) Stoner L, Faulkner J, Westrupp N, Lambrick D: Sexual differences in central arterial wave reflection are evident in prepubescent children. *J Hypertens*, 2015; 33: 304-307
- 55) Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ: The influence of heart rate on augmentation index and central arterial pressure in humans. *J Physiol*, 2000; 525 Pt 1: 263-270
- 56) Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H, O'Rourke M: Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation*, 2006; 113: 1213-1225
- 57) Mahmud A, Feely J: Effect of smoking on arterial stiffness and pulse pressure amplification. *Hypertension*, 2003; 41: 183-187
- 58) Vlachopoulos C, Alexopoulos N, Panagiotakos D, O'Rourke MF, Stefanadis C: Cigar smoking has an acute detrimental effect on arterial stiffness. *Am J Hypertens*, 2004; 17: 299-303
- 59) Lemogoum D, Van Bortel L, Leeman M, Degaute JP, van de Borne P: Ethnic differences in arterial stiffness and wave reflections after cigarette smoking. *J Hypertens*, 2006; 24: 683-689
- 60) Rehill N, Beck CR, Yeo KR, Yeo WW: The effect of chronic tobacco smoking on arterial stiffness. *Br J Clin Pharmacol*, 2006; 61: 767-773
- 61) Mahmud A, Feely J: Divergent effect of acute and chronic alcohol on arterial stiffness. *Am J Hypertens*, 2002; 15: 240-243
- 62) van Trijp MJ, Beulens JW, Bos WJ, Uiterwaal CS, Grobbee DE, Hendriks HF, Bots ML: Alcohol consumption and augmentation index in healthy young men: the ARYA study. *Am J Hypertens*, 2005; 18: 792-796
- 63) Sierksma A, Lebrun CE, van der Schouw YT, Grobbee DE, Lamberts SW, Hendriks HF, Bots ML: Alcohol consumption in relation to aortic stiffness and aortic wave reflections: a cross-sectional study in healthy postmenopausal women. *Arterioscler Thromb Vac Biol*, 2004; 24: 342-348
- 64) Vlachopoulos C, Hirata K, O'Rourke MF: Pressure-altering agents affect central aortic pressures more than is apparent from upper limb measurements in hypertensive patients: the role of arterial wave reflections. *Hypertension*, 2001; 38: 1456-1460
- 65) Mahmud A, Feely J: Acute effect of caffeine on arterial stiffness and aortic pressure waveform. *Hypertension*, 2001; 38: 227-231
- 66) Vlachopoulos C, Alexopoulos N, Dima I, Aznaouridis K, Andreadou I, Stefanadis C: Acute effect of black and green tea on aortic stiffness and wave reflections. *J Am Coll Nutr*, 2006; 25: 216-223
- 67) Vlachopoulos C, Kosmopoulou F, Panagiotakos D, Ioakeimidis N, Alexopoulos N, Pitsavos C, Stefanadis C: Smoking and caffeine have a synergistic detrimental effect on aortic stiffness and wave reflections. *J Am Coll Cardiol*, 2004; 44: 1911-1917
- 68) Seals DR, Tanaka H, Clevenger CM, Monahan KD, Reiling MJ, Hiatt WR, Davy KP, DeSouza CA: Blood pressure reductions with exercise and sodium restriction in postmenopausal women with elevated systolic pressure: role of arterial stiffness. *J Am Coll Cardiol*, 2001; 38: 506-513
- 69) Gates PE, Tanaka H, Hiatt WR, Seals DR: Dietary sodium restriction rapidly improves large elastic artery compliance in older adults with systolic hypertension. *Hypertension*, 2004; 44: 35-41
- 70) Haller MJ, Samyn M, Nichols WW, Brusko T, Wasserfall C, Schwartz RE, Atkinson M, Shuster JJ, Pierce GL, Silverstein JH: Radial artery tonometry demonstrates arterial stiffness in children with type 1 diabetes. *Diabetes Care*, 2004; 27: 2911-2917
- 71) Schram MT, Henry RM, van Dijk RA, Kostense PJ, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Westenhof N, Stehouwer CD: Increased central artery stiffness in impaired glucose metabolism and type 2 diabetes: the Hoorn Study. *Hypertension*, 2004; 43: 176-181
- 72) Lacy PS, O'Brien DG, Stanley AG, Dewar MM, Swales PP, Williams B: Increased pulse wave velocity is not associated with elevated augmentation index in patients with diabetes. *J Hypertens*, 2004; 22: 1937-1944
- 73) Maple-Brown LJ, Piers LS, O'Rourke MF, Celermajor DS, O'Dea K: Central obesity is associated with reduced peripheral wave reflection in Indigenous Australians irrespective of diabetes status. *J Hypertens*, 2005; 23: 1403-1407
- 74) Wilkinson IB, Prasad K, Hall IR, Thomas A, MacCallum H, Webb DJ, Frenneaux MP, Cockcroft JR: Increased central pulse pressure and augmentation index in subjects with hypercholesterolemia. *J Am Coll Cardiol*, 2002; 39: 1005-1011
- 75) Saba PS, Roman MJ, Longhini C, Scorzoni D, Pini R, Devereux RB, Ganau A: Carotid intimal-medial thickness and stiffness are not affected by hypercholesterolemia in uncomplicated essential hypertension. *Arterioscler Thromb Vac Biol*, 1999; 19: 2788-2794
- 76) Protogerou AD, Blacher J, Aslangul E, Le Jeune C, Lekakis J, Mavrikakis M, Safar ME: Gender influence on metabolic syndrome's effects on arterial stiffness and pressure wave reflections in treated hypertensive subjects. *Atherosclerosis*, 2007; 193: 151-158
- 77) Morigami H, Morioka T, Yamazaki Y, Imamura S,

- Numaguchi R, Asada M, Motoyama K, Mori K, Fukumoto S, Shoji T, Emoto M, Inaba M: Visceral adiposity is preferentially associated with vascular stiffness rather than thickness in men with type 2 diabetes. *J Atheroscler Thromb*, 2016; 23: 1067-1079
- 78) Wang J, Wang F, Dong S, Zeng Q, Zhang L: Levels of serum phosphorus and cardiovascular surrogate markers. *J Atheroscler Thromb*, 2016; 23: 95-104
- 79) Owen PJ, Rajiv C, Vinereanu D, Mathew T, Fraser AG, Lazarus JH: Subclinical hypothyroidism, arterial stiffness, and myocardial reserve. *J Clin Endocrinol Metab*, 2006; 91: 2126-2132
- 80) Smith JC, Page MD, John R, Wheeler MH, Cockcroft JR, Scanlon MF, Davies JS: Augmentation of central arterial pressure in mild primary hyperparathyroidism. *J Clin Endocrinol Metab*, 2000; 85: 3515-3519
- 81) Phillips C, Hedner J, Berend N, Grunstein R: Diurnal and obstructive sleep apnea influences on arterial stiffness and central blood pressure in men. *Sleep*, 2005; 28: 604-609
- 82) Phillips CL, Yee B, Yang Q, Villaneuva AT, Hedner J, Berend N, Grunstein R: Effects of continuous positive airway pressure treatment and withdrawal in patients with obstructive sleep apnea on arterial stiffness and central BP. *Chest*, 2008; 134: 94-100
- 83) Senzaki H, Chen CH, Ishido H, Masutani S, Matsunaga T, Taketazu M, Kobayashi T, Sasaki N, Kyo S, Yokote Y: Arterial hemodynamics in patients after Kawasaki disease. *Circulation*, 2005; 111: 2119-2125
- 84) Klocke R, Cockcroft JR, Taylor GJ, Hall IR, Blake DR: Arterial stiffness and central blood pressure, as determined by pulse wave analysis, in rheumatoid arthritis. *Ann Rheum Dis*, 2003; 62: 414-418
- 85) Hashimoto J, O'Rourke MF: Inflammation and arterial stiffness in chronic kidney disease: cause or consequence? *Am J Hypertens*, 2017; 30: 350-352
- 86) Bartoloni E, Pucci G, Cannarile F, Battista F, Alunno A, Giuliani M, Cafaro G, Gerli R, Schillaci G: Central hemodynamics and arterial stiffness in systemic sclerosis. *Hypertension*, 2016; 68: 1504-1511
- 87) Lemogoum D, Van Bortel L, Najem B, Dzudie A, Teutcha C, Madu E, Leeman M, Degaute JP, van de Borne P: Arterial stiffness and wave reflections in patients with sickle cell disease. *Hypertension*, 2004; 44: 924-929
- 88) London GM, Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME: Arterial wave reflections and survival in end-stage renal failure. *Hypertension*, 2001; 38: 434-438
- 89) Safar ME, Blacher J, Pannier B, Guerin AP, Marchais SJ, Guyonvarc'h PM, London GM: Central pulse pressure and mortality in end-stage renal disease. *Hypertension*, 2002; 39: 735-738
- 90) Covic A, Mardare N, Gusbeth-Tatomir P, Prisada O, Scau R, Goldsmith DJ: Arterial wave reflections and mortality in haemodialysis patients—only relevant in elderly, cardiovascularly compromised? *Nephrol Dial Transplant*, 2006; 21: 2859-2866
- 91) Briet M, Collin C, Karras A, Laurent S, Bozec E, Jacques C, Stengel B, Houillier P, Froissart M, Boutouyrie P: Arterial remodeling associates with CKD progression. *J Am Soc Nephrol*, 2011; 22: 967-974
- 92) Verbeke F, Marechal C, Van Laecke S, Van Biesen W, Devuyst O, Van Bortel LM, Jadoul M, Vanholder R: Aortic stiffness and central wave reflections predict outcome in renal transplant recipients. *Hypertension*, 2011; 58: 833-838
- 93) Ueda H, Hayashi T, Tsumura K, Yoshimaru K, Nakayama Y, Yoshikawa J: The timing of the reflected wave in the ascending aortic pressure predicts restenosis after coronary stent placement. *Hypertens Res*, 2004; 27: 535-540
- 94) Weber T, Auer J, O'Rourke M F, Kvas E, Lassnig E, Lamm G, Stark N, Rammer M, Eber B: Increased arterial wave reflections predict severe cardiovascular events in patients undergoing percutaneous coronary interventions. *Eur Heart J*, 2005; 26: 2657-2663
- 95) Chirinos JA, Zambrano JP, Chakko S, Veerani A, Schob A, Willens HJ, Perez G, Mendez AJ: Aortic pressure augmentation predicts adverse cardiovascular events in patients with established coronary artery disease. *Hypertension*, 2005; 45: 980-985
- 96) Jankowski P, Kawecka-Jaszcz K, Czarnecka D, Brzozowska-Kiszka M, Styczkiewicz K, Loster M, Kloch-Badelek M, Wilinski J, Curylo AM, Dudek D: Pulsatile but not steady component of blood pressure predicts cardiovascular events in coronary patients. *Hypertension*, 2008; 51: 848-855
- 97) Weber T, O'Rourke MF, Lassnig E, Porodko M, Ammer M, Rammer M, Eber B: Pulse waveform characteristics predict cardiovascular events and mortality in patients undergoing coronary angiography. *J Hypertens*, 2010; 28: 797-805
- 98) Roman MJ, Devereux RB, Kizer JR, Lee ET, Galloway JM, Ali T, Umans JG, Howard BV: Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. *Hypertension*, 2007; 50: 197-203
- 99) Roman MJ, Devereux RB, Kizer JR, Okin PM, Lee ET, Wang W, Umans JG, Calhoun D, Howard BV: High central pulse pressure is independently associated with adverse cardiovascular outcome the strong heart study. *J Am Coll Cardiol*, 2009; 54: 1730-1734
- 100) Pini R, Cavallini MC, Palmieri V, Marchionni N, Di Bari M, Devereux RB, Masotti G, Roman MJ: Central but not brachial blood pressure predicts cardiovascular events in an unselected geriatric population: the ICARE Dicomano Study. *J Am Coll Cardiol*, 2008; 51: 2432-2439
- 101) Leone N, Ducimetiere P, Garipey J, Courbon D, Tzourio C, Dartigues JF, Ritchie K, Alperovitch A, Amouyel P, Safar ME, Zureik M: Distension of the carotid artery and risk of coronary events: the three-city study. *Arterioscler Thromb Vac Biol*, 2008; 28: 1392-1397
- 102) Benetos A, Thomas F, Joly L, Blacher J, Pannier B, Labat C, Salvi P, Smulyan H, Safar ME: Pulse pressure amplification a mechanical biomarker of cardiovascular risk. *J Am Coll Cardiol*, 2010; 55: 1032-1037
- 103) Wang KL, Cheng HM, Chuang SY, Spurgeon HA, Ting CT, Lakatta EG, Yin FC, Chou P, Chen CH: Central or peripheral systolic or pulse pressure: which best relates to target organs and future mortality? *J Hypertens*, 2009; 27: 461-467
- 104) Wang KL, Cheng HM, Sung SH, Chuang SY, Li CH, Spurgeon HA, Ting CT, Najjar SS, Lakatta EG, Yin FC,

- Chou P, Chen CH: Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular mortalities: a community-based study. *Hypertension*, 2010; 55: 799-805
- 105) Huang CM, Wang KL, Cheng HM, Chuang SY, Sung SH, Yu WC, Ting CT, Lakatta EG, Yin FC, Chou P, Chen CH: Central versus ambulatory blood pressure in the prediction of all-cause and cardiovascular mortalities. *J Hypertens*, 2011; 29: 454-459
- 106) Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ: Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation*, 2010; 121: 505-511
- 107) Hashimoto J, Ito S: Central blood pressure and prediction of cardiovascular events. *Curr Hypertens Rev*, 2012; 8: 108-113
- 108) McEniery CM, Yasmin, McDonnell B, Munnerly M, Wallace SM, Rowe CV, Cockcroft JR, Wilkinson IB: Central pressure: variability and impact of cardiovascular risk factors: the Anglo-Cardiff Collaborative Trial II. *Hypertension*, 2008; 51: 1476-1482
- 109) Cheng HM, Chuang SY, Sung SH, Yu WC, Pearson A, Lakatta EG, Pan WH, Chen CH: Derivation and validation of diagnostic thresholds for central blood pressure measurements based on long-term cardiovascular risks. *J Am Coll Cardiol*, 2013; 62: 1780-1787
- 110) Kelly RP, Gibbs HH, O'Rourke MF, Daley JE, Mang K, Morgan JJ, Avolio AP: Nitroglycerin has more favourable effects on left ventricular afterload than apparent from measurement of pressure in a peripheral artery. *Eur Heart J*, 1990; 11: 138-144
- 111) Morgan T, Lauri J, Bertram D, Anderson A: Effect of different antihypertensive drug classes on central aortic pressure. *Am J Hypertens*, 2004; 17: 118-123
- 112) Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J: Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*, 2005; 366: 895-906
- 113) Boutouyrie P, Achouba A, Trunet P, Laurent S: Amlodipine-valsartan combination decreases central systolic blood pressure more effectively than the amlodipine-atenolol combination: the EXPLOR study. *Hypertension*, 2010; 55: 1314-1322
- 114) Williams B, Cockcroft JR, Kario K, Zappe DH, Brunel PC, Wang Q, Guo W: Effects of sacubitril/valsartan versus olmesartan on central hemodynamics in the elderly with systolic hypertension: the PARAMETER study. *Hypertension*, 2017; 69: 411-420
- 115) Hashimoto J, Imai Y, O'Rourke MF: Indices of pulse wave analysis are better predictors of left ventricular mass reduction than cuff pressure. *Am J Hypertens*, 2007; 20: 378-384
- 116) Boutouyrie P, Bussy C, Hayoz D, Hengstler J, Dartois N, Laloux B, Brunner H, Laurent S: Local pulse pressure and regression of arterial wall hypertrophy during long-term antihypertensive treatment. *Circulation*, 2000; 101: 2601-2606
- 117) Hashimoto J, Westerhof BE, Westerhof N, Imai Y, O'Rourke MF: Different role of wave reflection magnitude and timing on left ventricular mass reduction during antihypertensive treatment. *J Hypertens*, 2008; 26: 1017-1024
- 118) Hashimoto J, Ito S: Some mechanical aspects of arterial aging: physiological overview based on pulse wave analysis. *Ther Adv Cardiovasc Dis*, 2009; 3: 367-378
- 119) Williams B, Lacy PS, Cruickshank JK, Collier D, Hughes AD, Stanton A, Thom S, Thurston H: Impact of statin therapy on central aortic pressures and hemodynamics: principal results of the Conduit Artery Function Evaluation-Lipid-Lowering Arm (CAFE-LLA) Study. *Circulation*, 2009; 119: 53-61
- 120) Kanaki AI, Sarafidis PA, Georgianos PI, Kanavos K, Tziolas IM, Zebekakis PE, Lasaridis AN: Effects of low-dose atorvastatin on arterial stiffness and central aortic pressure augmentation in patients with hypertension and hypercholesterolemia. *Am J Hypertens*, 2013; 26: 608-616
- 121) de Boer SA, Heerspink HJ, Juarez Orozco LE, van Roon AM, Kamphuisen PW, Smit AJ, Slart RH, Lefrandt JD, Mulder DJ: Effect of linagliptin on pulse wave velocity in early type 2 diabetes (RELEASE): a randomized, double-blind, controlled 26-week trial. *Diabetes Obes Metab*, 2017;
- 122) Sofer E, Boaz M, Matas Z, Mashavi M, Shargorodsky M: Treatment with insulin sensitizer metformin improves arterial properties, metabolic parameters, and liver function in patients with nonalcoholic fatty liver disease: a randomized, placebo-controlled trial. *Metabolism*, 2011; 60: 1278-1284
- 123) Agarwal N, Rice SP, Bolusani H, Luzio SD, Dunseath G, Ludgate M, Rees DA: Metformin reduces arterial stiffness and improves endothelial function in young women with polycystic ovary syndrome: a randomized, placebo-controlled, crossover trial. *J Clin Endocrinol Metab*, 2010; 95: 722-730
- 124) Park J, Liao P, Sher S, Lyles RH, Deveaux DD, Quyyumi AA: Tetrahydrobiopterin lowers muscle sympathetic nerve activity and improves augmentation index in patients with chronic kidney disease. *Am J Physiol Regul Integr Comp Physiol*, 2015; 308: R208-218
- 125) Jain S, Khera R, Corrales-Medina VF, Townsend RR, Chirinos JA: Inflammation and arterial stiffness in humans. *Atherosclerosis*, 2014; 237: 381-390
- 126) Vlachopoulos C, Aznaouridis K, Stefanadis C: Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*, 2010; 55: 1318-1327
- 127) Hashimoto J, O'Rourke MF: Is arterial stiffness better than blood pressure in predicting cardiovascular risk? *Curr Cardiovasc Risk Rep*, 2008; 2: 133-140
- 128) Mills CJ, Gabe IT, Gault JH, Mason DT, Ross J, Jr., Braunwald E, Shillingford JP: Pressure-flow relationships and vascular impedance in man. *Cardiovasc Res*, 1970; 4: 405-417
- 129) Hashimoto J, Ito S: Aortic stiffness determines diastolic blood flow reversal in the descending thoracic aorta: potential implication for retrograde embolic stroke in

- hypertension. *Hypertension*, 2013; 62: 542-549
- 130) Hashimoto J, Ito S: Pulse pressure amplification, arterial stiffness, and peripheral wave reflection determine pulsatile flow waveform of the femoral artery. *Hypertension*, 2010; 56: 926-933
 - 131) Hashimoto J, Ito S: Central pulse pressure and aortic stiffness determine renal hemodynamics: pathophysiological implication for microalbuminuria in hypertension. *Hypertension*, 2011; 58: 839-846
 - 132) Hashimoto J: Central hemodynamics and target organ damage in hypertension. *Tohoku J Exp Med*, 2014; 233: 1-8
 - 133) Hashimoto J, Aikawa T, Imai Y: Large artery stiffening as a link between cerebral lacunar infarction and renal albuminuria. *Am J Hypertens*, 2008; 21: 1304-1309
 - 134) Henskens LH, Kroon AA, van Oostenbrugge RJ, Groenenschild EH, Fuss-Lejeune MM, Hofman PA, Lodder J, de Leeuw PW: Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. *Hypertension*, 2008; 52: 1120-1126
 - 135) Ochi N, Kohara K, Tabara Y, Nagai T, Kido T, Uetani E, Ochi M, Igase M, Miki T: Association of central systolic blood pressure with intracerebral small vessel disease in Japanese. *Am J Hypertens*, 2010; 23: 889-894
 - 136) Shrestha I, Takahashi T, Nomura E, Ohtsuki T, Ohshita T, Ueno H, Kohriyama T, Matsumoto M: Association between central systolic blood pressure, white matter lesions in cerebral MRI and carotid atherosclerosis. *Hypertens Res*, 2009; 32: 869-874
 - 137) Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson O, Garcia M, Aspelund T, Harris TB, Gudnason V, Launer LJ: Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility – Reykjavik study. *Brain*, 2011; 134: 3398-3407
 - 138) O'Rourke MF, Safar ME: Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. *Hypertension*, 2005; 46: 200-204
 - 139) Laurent S, Katsahian S, Fassot C, Tropeano AI, Gautier I, Laloux B, Boutouyrie P: Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. *Stroke*, 2003; 34: 1203-1206
 - 140) Lovett JK, Howard SC, Rothwell PM: Pulse pressure is independently associated with carotid plaque ulceration. *J Hypertens*, 2003; 21: 1669-1676
 - 141) Shaikh AY, Wang N, Yin X, Larson MG, Vasan RS, Hamburg NM, Magnani JW, Ellinor PT, Lubitz SA, Mitchell GF, Benjamin EJ, McManus DD: Relations of arterial stiffness and brachial flow-mediated dilation with new-onset atrial fibrillation: the Framingham Heart Study. *Hypertension*, 2016; 68: 590-596
 - 142) Harloff A, Strecker C, Dudler P, Nussbaumer A, Frydrychowicz A, Olschewski M, Bock J, Stalder AF, Strohal AL, Weiller C, Hennig J, Markl M: Retrograde embolism from the descending aorta: visualization by multidirectional 3D velocity mapping in cryptogenic stroke. *Stroke*, 2009; 40: 1505-1508
 - 143) Kronzon I, Tunick PA: Aortic atherosclerotic disease and stroke. *Circulation*, 2006; 114: 63-75
 - 144) Levin A, Stevens PE: Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. *Kidney Int*, 2014; 85: 49-61
 - 145) Temmar M, Jankowski P, Peltier M, Mouquet V, Debicka-Dabrowska D, Hamida F, Kawecka-Jaszcz K, Safar ME: Intraaortic pulse pressure amplification in subjects at high coronary risk. *Hypertension*, 2010; 55: 327-332
 - 146) Ford ML, Tomlinson LA, Chapman TP, Rajkumar C, Holt SG: Aortic stiffness is independently associated with rate of renal function decline in chronic kidney disease stages 3 and 4. *Hypertension*, 2010; 55: 1110-1115
 - 147) Sedaghat S, Mattace-Raso FU, Hoorntje EJ, Uitterlinden AG, Hofman A, Ikram MA, Franco OH, Dehghan A: Arterial stiffness and decline in kidney function. *Clin J Am Soc Nephrol*, 2015; 10: 2190-2197
 - 148) Hashimoto J, Ito S: Aortic blood flow reversal determines renal function: potential explanation for renal dysfunction caused by aortic stiffening in hypertension. *Hypertension*, 2015; 66: 61-67
 - 149) Chirinos JA, Segers P: Noninvasive evaluation of left ventricular afterload: part 2: arterial pressure-flow and pressure-volume relations in humans. *Hypertension*, 2010; 56: 563-570
 - 150) Kollias A, Lagou S, Zeniodi ME, Boubouchairpoulou N, Stergiou GS: Association of central versus brachial blood pressure with target-organ damage: systematic review and meta-analysis. *Hypertension*, 2016; 67: 183-190
 - 151) Hashimoto J, Nichols WW, O'Rourke MF, Imai Y: Association between wasted pressure effort and left ventricular hypertrophy in hypertension: influence of arterial wave reflection. *Am J Hypertens*, 2008; 21: 329-333
 - 152) Hashimoto J, Ito S: Central diastolic pressure decay mediates the relationship between aortic stiffness and myocardial viability: potential implications for atherosclerosis-induced myocardial ischemia. *J Hypertens*, 2017 (In press)
 - 153) Weber T, Auer J, O'Rourke MF, Kvas E, Lassnig E, Berent R, Eber B: Arterial stiffness, wave reflections, and the risk of coronary artery disease. *Circulation*, 2004; 109: 184-189
 - 154) Hoffman JI, Buckberg GD: The myocardial oxygen supply:demand index revisited. *J Am Heart Assoc*, 2014; 3: e000285
 - 155) Vlachopoulos C, Xaplanteris P, Aboyans V, Brodmann M, Cifkova R, Cosentino F, De Carlo M, Gallino A, Landmesser U, Laurent S, Lekakis J, Mikhailidis DP, Naka KK, Protogerou AD, Rizzoni D, et al.: The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: Endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. *Atherosclerosis*, 2015; 241: 507-532
 - 156) Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, Heffernan KS, Lakatta EG, McEniery CM, Mitchell GF, Najjar SS, Nichols WW, Urbina EM, Weber T: Recommendations for improving and standardizing vascular research on arterial stiffness: a scientific statement from the American Heart Association. *Hypertension*, 2015; 66: 698-722