Vascular Dysfunction: A Key Player in Chronic Cardio-renal Syndrome

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Abstract

This review summarizes the current methods for the functional assessment of vascular damage (e.g., assessment of endothelial function, measurement of pulse wave velocity, and pressure wave analysis) and describes the association between vascular dysfunction and chronic cardio-renal syndrome. Vascular dysfunction may contribute to the development and progression of heart failure. Additionally, vascular dysfunction, especially increased arterial stiffness and abnormal pressure wave reflection and central hemodynamics, has been reported to accelerate renal function decline. Furthermore, renal dysfunction worsens vascular pathophysiological abnormalities. Therefore, the functional assessment of vascular damage may be useful in the management of cardio-renal syndrome.

Key words: cardio-renal syndrome, endothelial function, arterial stiffness, pressure wave reflection, heart failure, chronic kidney disease


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Introduction

Conventionally, heart failure and renal dysfunction have been recognized as commonly occurring comorbidities. Recently, both have drawn much attention in relation to cardio-renal syndrome, as each of the pathophysiological abnormalities tends to worsen the severity of the other (1, 2).

The risk factors for cardiovascular (CV) disease increase the risk of occurrence of CV events via accelerating atherosclerotic vascular damage, and the same risk factors also affect the initiation and progression of renal dysfunction (3). Conversely, renal dysfunction, such as that associated with chronic kidney disease (CKD), is a risk factor for CV disease and contributes to the progression of atherosclerotic vascular damage (4, 5). While vascular damage is thought to play pivotal roles in the development and progression of cardio-renal syndrome, its precise roles have not yet been fully clarified.

Recently, methods have been introduced in clinical settings for both the morphological and functional assessments of vascular damage (6). Vascular ultrasound examination, computed tomography and magnetic resonance imaging are commonly used tools for the morphological assessment of vascular damage, while the assessment of endothelial function, measurement of the pulse wave velocity (PWV), and the pressure wave analysis and analysis of the central hemodynamics are common tools for the functional assessment of vascular damage (6). The functional assessment parameters are recognized to be independent predictors of future CV events (6).

This review summarizes the current methods for the functional assessment of vascular damage and describes the association between abnormal vascular function and cardio-renal syndrome.

Functions of the Arteries

The arterial wall is composed of three layers (i.e., intima (including the endothelium), media, and adventitia); each of these three layers plays individual roles in systemic circulation.

Functions of the endothelium

The endothelium regulates the vascular tone, hemostasis and vascular permeability (7) which contributes to organ...
blood perfusion. To exert these functions, the endothelial cells biosynthesize several vasoactive substances (8). Of these, nitric oxide (NO) in particular is known to play a pivotal role in protecting against atherosclerotic vascular damage; NO has been shown to exert its effects via several mechanisms, such as the inhibition of vascular smooth muscle cell growth, nuclear transcription of cell adhesion molecules, platelet aggregation, and leukocyte adhesion to endothelial cells (7, 8).

**Functions related to the vascular medial layer (stiffness)**

The arterial tree can be simply classified as being composed of 3 compartments: elastic arteries, muscular arteries, and arterioles. Among the most important functions of the arterial tree are its function as a blood conduit (the delivery of blood to organs) and its cushioning effect (to generate continuous blood flow and reduce the exposure of the arterial tree to cardiac pulsatile energy). The elastic arteries have a high content of elastic fibers in their medial layer, and this elasticity plays pivotal roles in both of the aforementioned functions (9). The elastic arteries play a dominant role in cushioning against and dampening the pressure oscillations that result from intermittent ventricular ejection (i.e., the Windkessel effect) and transforming the pulsatile flow into a steady flow for supplying oxygen to the tissues (9). This elasticity has beneficial effects on the cardiovascular system, such as facilitating organ blood supply during diastole (especially in the heart), reducing the cardiac afterload, and protecting the arterial wall and microvasculature from the mechanical stresses generated by the cardiac contractions (9).

Therefore, the guidelines for non-invasive vascular function testing (Japanese Circulation Society 2013) summarized the function of the arterial tree as follows: “Arteries have the function of efficiently delivering blood to the peripheral organs efficiently and maintain this delivery function” (10).

**Methodologies for the Assessment of Vascular Functions**

**Assessment of endothelial function**

The assessment of endothelium-dependent vasodilatation is widely used to evaluate endothelial functions (11). Among these, the measurement of the brachial arterial diameter before and after inducing reactive hyperemia [flow mediated dilation (FMD)] to increase the shear stress on the arterial wall is the most frequently used method in clinical settings (11). The increased shear stress produced by reactive hyperemia induces activation of endothelial NO synthase (eNOS), increasing NO production in the endothelium. Thus, FMD is a non-invasive marker of the local NO bioavailability in the endothelium. The FMD measurement requires appropriate training for technical validation and good reproducibility (11), and semi-automated devices to measure FMD have been introduced to resolve such technical limitations (12) (Fig. 1A). Recently, another technique to measure the endothelial function, namely, the reactive hyperemia index measured by peripheral arterial tonometry (RH-PAT), has become available in clinical settings. The measurement of RH-PAT is based on the non-invasive measurement of pulsatile volume changes at the fingertip (before and after reactive hyperemia) by peripheral arterial tonometry (Fig. 1B) (13). The procedure for inducing reactive hyperemia is the same as that used in the measurement of FMD. PAT probes are placed on the index finger of each arm, and the post-occlusion to pre-occlusion ratio is calculated. The RH-PAT signals are corrected for measurements in the contralateral arm. The measurement of RH-PAT is less operator-dependent as compared to that of FMD.

Although FMD reflects the endothelial function in the conduit arteries and RH-PAT reflects the endothelial function in the peripheral resistance arteries, the two are not known to be closely associated with one other (6, 10, 13). However, while the two may not be interchangeable mark-
ers, several prospective studies have demonstrated that they are both independent predictors of future CV events (6, 10, 13) and both methods have an acceptable reproducibility. However, there are methodological differences in the measurement of FMD among institutions (e.g., in the placement of the pressure cuff, the duration of cuff occlusion, the method of determining the vascular diameter, and the definition of maximal dilatation of the brachial artery), and no reference values have been established. RH-PAT is measured by a uniform method; however, no reference values have been established for this parameter either.

Assessment of the arterial stiffness and pressure wave reflection

1. Pulse wave velocity

PWV reflects segmental arterial elasticity. Contraction of the left ventricle generates a pulse wave which is propagated throughout the arterial tree. The Moens-Korteweg equation states that the PWV is proportional to the square root of the incremental elastic modulus of the vessel wall, given a constant ratio of the wall thickness to the vessel radius and blood density. Therefore, increases in the arterial rigidity and arterial wall thickness act to increase the PWV (14). PWV can be measured in any arterial segment between two pulse-wave palpable regions. In clinical settings, two methods to measure PWV are available (Fig. 2).

The assessment of central arterial stiffness, rather than that of peripheral arterial stiffness, is more relevant to CV risk stratification (9, 14, 15). Carotid-femoral pulse wave velocity (cfPWV) is the most commonly used non-invasive method for the assessment of the central arterial stiffness and is considered to be the “gold standard” method (9, 14, 15). Conventionally, methodological differences existed among institutions in the measurement of the cfPWV (e.g., in the method used to determine the foot of the pressure wave or calculation of the path length); however, a standardized method is now available to measure the cfPWV (15, 16). Brachial-ankle PWV (baPWV) is measured using a volume-plethysmographic apparatus. Because the measurement of the baPWV only involves wrapping of a pressure cuff around the four extremities, it is easier than the measurement of the cfPWV; furthermore, its measurement is well standardized.

Meta-analyses have confirmed that cfPWV, and also baPWV, is an independent risk factor for CV events, and a significant positive correlation has been reported between the two (r=0.73) (17). The standard value of the cfPWV is 10 m/sec and that of the baPWV is 18 m/sec (6, 15).

2. Augmentation index and central blood pressure

A cardiac contraction generates a pressure pulse wave, which propagates from the heart to the periphery (6, 18). Conversely, in the arterial tree, the arteries branch and taper as they reach the periphery, which is associated with an increase in the arterial resistance. A reflected pressure pulse wave (from the periphery to the heart) occurs at the sites of abrupt increase in the arterial resistance. Furthermore, an interaction between the forward and reflected pressure pulse waves may occur at some sites in the arterial tree. Under physiological conditions, this interaction is observed at a distal site of the arterial tree; therefore, the blood pressure at the level of the kidney is lower than that at the brachial level. However, in cases with increased arterial stiffness, the travelling speed of the pressure pulse waves is increased, and the interaction between the forward and reflected pressure waves occurs at a more proximal site of the arterial tree (i.e., aorta) (6, 18).

A pressure wave analysis is typically conducted at the carotid, radial or brachial artery. Because the radial bone is backboned, the radial arterial pressure wave can be easily recorded. For this reason, the radial pressure wave analysis has recently become a common approach. The AtCor device and the OMRON device are popularly used for the radial pressure wave analysis (5, 13, 16). The AtCor device estimates the central systolic blood pressure derived by the general transfer function of the radial pressure wave, and the OMRON device estimates the central systolic blood pressure derived by the regression equation from the directly measured late systolic shoulder of the radial pressure waveform. The estimation of the central systolic blood pressure (cSBP) based on the late systolic shoulder of the radial pressure wave provides comparable accuracy to that of the validated general transfer function (19). Recently, standard values of pressure wave analyses/central hemodynamics have been reported by an international project to determine the reference values of the central hemodynamic indices (20).

Vasculo-cardiac Connection

Harmful effects of vascular dysfunction on the heart

1. Endothelial dysfunction

Several prospective studies have demonstrated that endothelial dysfunction is an independent risk factor for adverse
Dysfunctions hasten the return of the pulse wave reflection.

Increased stiffness of the large arteries and microvascular both macrovascular and microvascular dysfunction (18, 28).

Increased arterial stiffness, especially of the larger arteries during heart failure, activates the sympathetic nervous system and renin-angiotensin system, increased serum levels of asymmetric dimethylarginine, inhibition of eNOS, and increased oxidative stress are thought to cause endothelial dysfunction (33). As mentioned above (25, 26), endothelial dysfunction can accelerate arterial stiffening. However, increased arterial stiffness has not been confirmed in cases of systolic heart failure because cardiac systolic function is one of the major determinants of the PWV and AI (markers from the periphery (6, 18), which augments the ventricular pressure during systole (6, 18) (Fig. 3). Recently, we demonstrated that the central pulse pressure, rather than the peripheral pulse pressure, is a significant determinant of elevation of the serum natriuretic peptide levels, a marker of cardiac afterload (29).

2-B: Impaired coronary blood flow

The cushioning effect of the elastic arteries involves their expansion during systole to store some of the blood ejected from the heart during cardiac systole and delivery of this stored blood to the tissues during cardiac diastole (6, 14, 18, 27). The coronary arteries are mostly perfused during cardiac diastole; therefore, the amount of this stored blood in the elastic arteries during systole is an important determinant of the coronary blood flow (6, 14, 18, 27). Furthermore, under healthy conditions of the arterial tree, the speeds of propagation of the pulse wave [incident (heart to periphery) and reflected pressure wave (periphery to the heart)] are not so high, causing the reflected wave to return to the aorta during diastole. This phenomenon elevates the diastolic blood pressure and contributes to the maintenance of the coronary blood flow (6, 14, 18, 27).

With increased arterial stiffness, the amount of stored blood in the large arteries during cardiac systole decreases, and the elevation of the diastolic pressure by the reflected pulse wave is reduced. The reflected pulse wave returns during cardiac systole as a result of the increased speed of pulse wave propagation (Fig. 3); together, these events cause the impairment of the coronary blood flow (6, 14, 18, 27).

2-C: Arterial-ventricular stiffening

Age, hypertension, and diabetes not only cause stiffening of the arteries, but also cause stiffening of the heart. This coupling of stiffness between the arteries and the heart (arterial-ventricular coupling) causes the impairment of the cardiac functional reserve and an increase in the fluctuation of blood pressure (30).

Recently, Chirinos et al. reported that an increased traveling velocity of the reflected arterial wave represents a novel strong risk factor for the development of heart failure in the Multiethnic Study of Atherosclerosis (MESA) population (31). Furthermore, Meguro et al. reported that increased arterial stiffness (as assessed by the baPWV) is an independent poor prognostic factor in patients with heart failure (32).

Heart failure as a causal factor for vascular dysfunction

During heart failure, activations of the sympathetic nervous system and renin-angiotensin system, increased serum levels of asymmetric dimethylarginine, inhibition of eNOS, and increased oxidative stress are thought to cause endothelial dysfunction (33). As mentioned above (25, 26), endothelial dysfunction can accelerate arterial stiffening. However, increased arterial stiffness has not been confirmed in cases of systolic heart failure because cardiac systolic function is one of the major determinants of the PWV and AI (markers...
of arterial stiffness and wave reflection) (6, 18). Conversely, increased arterial stiffness is observed in cases of heart failure with preserved systolic function (34). In this case, the risk factors for CV disease may be common causal factors of diastolic heart failure and increased arterial stiffness.

Summary of the vasculo-cardiac connection

Abnormal vascular functions (i.e., endothelial dysfunction, increased arterial stiffness, or abnormal pressure wave reflection) have harmful effects on the heart, and such effects may contribute to the development and the progression of heart failure. Conversely, heart failure causes endothelial dysfunction, but it has not yet been fully clarified whether this endothelial dysfunction is a causal factor for the progression of heart failure or a comorbidity of heart failure.

Vasculo-renal Connection

Harmful effects of vascular dysfunction on the kidney

1. Endothelial dysfunction

Based on several experimental data, endothelial dysfunction is thought to be an important factor in the development and progression of CKD (35). Perticone et al. reported that endothelial dysfunction assessed by strain-gauge plethysmography during intra-arterial infusion of acetylcholine, which reflects the endothelial NO bioavailability in the peripheral resistance arteries, was a risk factor for accelerated renal function decline during a minimum 2-year follow-up period in subjects with treated hypertension (36). Nakamura et al. reported that FMD, which reflects the NO bioavailability in the conduit arteries, is useful for assessing the future risk of renal dysfunction in patients with coronary artery disease (37). Conversely, Peralta et al. reported that FMD was not identified as a risk factor for accelerated renal function decline during the 4.8-year follow-up period in the MESA cohort (38). Because of the contradictory results, there is no definitive conclusion on whether endothelial dysfunction may be a risk factor for the development and progression of CKD.

2. Increased arterial stiffness and abnormal pressure wave reflection and central hemodynamics

Differing from other parameters of vascular damage, arterial stiffness is thought to serve as a risk factor for accelerated renal function decline, independent of the conventional risk factors for CV disease, via abnormal central hemodynamics and pulsatile nephropathy (6, 18).

Elevated blood pressure is a risk factor for accelerated renal function decline, and conventionally, blood pressure is determined at the brachial artery. As mentioned above, the arterial tree has a blood pressure gradient, and under physiological conditions, the blood pressure at more central sites is lower than that at distal sites (5, 13, 16). When the arterial stiffness increases, the travelling speeds of both the forward pressure wave and the reflected pressure wave in the arterial tree are increased, and interaction between the two pressure waves is observed at a more proximal site in the arterial tree. This results in a decrease of the pressure gradient in the arterial tree. For the same blood pressure measured at the brachial artery, the blood pressure at the level of the kidney is higher in cases with increased arterial stiffness than in those without increased arterial stiffness, and the renal function may decline more rapidly in the former...
Conventionally, blood pressure is measured in the unit of mm of mercury, and the specific gravity of mercury is 13. Therefore, a blood pressure of 140 mm Hg would correspond to the energy that can push up water up to a height of 180 cm. Thus, the heart generates a large amount of energy during in every cardiac contraction, which is mostly absorbed in the aorta by the shock absorber effect of the aorta. However, increase of the aortic stiffness attenuates this cushioning effect and increases the transmission of the pulsatile energy generated in the heart to the peripheral microcirculation. These phenomena cause the condition referred to as pulsatile nephropathy that results in accelerated renal function decline (6, 18, 39) (Fig. 4).

Several prospective studies have demonstrated that parameters related to arterial stiffness and the pressure wave reflection and central hemodynamics may be useful for predicting the progression of renal function decline (3, 18).

Renal dysfunction as a causal factor for vascular dysfunction

1. Endothelial dysfunction

CKD is frequently accompanied by the conventional risk factors for CV disease. Additionally, anemia, sympathetic nerve activation, oxidative stress and inflammation, endothelial dysfunction, coagulation disorders, abnormal mineral metabolisms, and uremic toxins are thought to be additional risk factors for atherosclerotic vascular damage in cases of CKD (3). Yilmaz et al. reported that endothelial dysfunction was observed even in the early stages of CKD (41); however, Lilikutkar and et al. reported that endothelial dysfunction was significant only in subjects with stage 5 CKD (42). Hypertension and diabetes mellitus, both of which can cause endothelial dysfunction, are common disorders in CKD and may be confounding factors in the evaluation of the association of CKD with endothelial dysfunction (43). Therefore, it has not been concluded whether endothelial dysfunction occurs in the early stages of CKD.

2. Increased arterial stiffness and abnormal pressure wave reflection and central hemodynamics

Previously, we reported from a 5.6-year follow-up study which demonstrated that early CKD was not a risk factor for the progression of arterial stiffening, as assessed by measurement of the baPWV (40). Conversely, a high serum creatinine level (>1.0 mg/dL) was associated with accelerated worsening of the cfPWV over a 6-year observation period in subjects with treated hypertension (44). Furthermore, in subjects under maintenance hemodialysis, CKD-related risk factors, such as advanced glycation end products, have been reported to contribute to the accelerated worsening of the cfPWV (45). Thus, renal dysfunction may affect the rate of progression of vascular dysfunction, particularly arterial stiffening, in patients with moderate or severe CKD.

Summary of the vasculo-renal connection

Vascular dysfunction, especially increased arterial stiffness and abnormal pressure wave reflection and central hemodynamics, may accelerate renal function decline; conversely, renal dysfunction may worsen vascular damage and dysfunction.

Perspective: Why are Functional Assessments of Vascular Damage Necessary for the Management of Chronic Cardio-renal Syndrome?

The morphological assessment of vascular damage reflects the extent of subclinical vascular damage in the arterial tree, which is related to future CV events. Apart from the morphological vascular damage in the coronary or renal arteries, cardio-renal syndrome represents the connection between cardiac dysfunction (heart failure) and renal dysfunction. As aforementioned, abnormal vascular function plays a role in the development and progression of cardio-renal syndrome independent of the conventional CV risk factors. Thus, the functional assessment of vascular damage may be useful in predicting the development and progression of cardio-renal syndrome. The risk factors for CV disease are also major risk factors for the development and progression of cardio-renal syndrome. For example, the effect of pharmacological/non-pharmacological treatments of hypertension on the regression of the carotid intima-media thickness, a representative marker of morphological assessment of vascular damage, is small (46), but such effect on arterial de-stiffening is significant (47, 48). Thus, for evaluating the effect of the management of risk factors for CV disease on vascular damage, the functional assessments of vascular damage may be more suitable than the morphological assessment. Therefore, the parameters of the functional assessment of vascular damage may have the potential of being developed as markers to assess the effect of the management of cardio-renal syndrome. The next logical step would be to clarify whether the management of vascular dysfunction may be a useful therapeutic strategy for cardio-renal syndrome.

The authors state that they have no Conflict of Interest (COI).

References

5. Mahmoodi BK, Matsushita K, Woodward M, et al; Chronic Kid-


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http://www.naika.or.jp/imonline/index.html