Aortic Stiffening, Aortic Blood Flow Reversal, and Renal Blood Flow

Stéphane Laurent, Pierre Boutouyrie, Elie Mousseaux

See related article, pp 61–67

Normal arterial aging is characterized by arterial enlargement, wall thickening, and stiffening, which predominates at large arteries. Patients with chronic kidney disease (CKD) have an early vascular aging, characterized by an accelerated arterial enlargement and stiffening, which occurs in parallel with the decline in glomerular filtration rate (GFR). The relationships between central hemodynamics (either arterial stiffness or central blood pressure) and GFR decline are complex and depend mainly on both the stage of the disease—early CKD, advanced CKD or end-stage renal disease—and the level of blood pressure—optimal blood pressure, high normal, and grade 1 to 2 hypertension.

O'Rourke and Safar suggested that the torrential flow and low resistance to flow in the kidney expose small arterial vessels of the glomerulus to the high-pressure fluctuations that exist in the renal arteries. Such fluctuations, measurable as central pulse pressure, increase 3- to 4-fold with age. For instance, the loss of renal blood flow autoregulation, because of altered myogenic tone in hypertension, can expose small glomerular vessels to higher pulsatile pressure and flow and favor higher dissipation in the microcirculation, leading to hyperfiltration and glomerulosclerosis. Indeed, central pulse pressure was reported independently associated with the decline in GFR and wall thickening (lack of wall thickening) possibly related to nonhemodynamic changes, was significantly and independently associated with the progressive decline in GFR and incident end-stage renal disease, whereas aortic stiffness and central pulse pressure were not.

The influence of aortic stiffness on GFR is also not straightforward. Although several cross-sectional studies showed a significant and independent association between GFR and aortic stiffness measured through carotid-femoral pulse wave velocity, longitudinal studies in patients with CKD, such as the Nephrotest study, showed that aortic stiffness remained relatively stable during CKD progression and was elevated only during end-stage renal disease. These findings suggest that CKD and aortic stiffening have different interactions during progression, with a lower role of the aortic stiffening in the early phase of CKD but with higher consequences on GFR in end-stage renal disease. The lower influence of the aorta at early stage of CKD could be explained by drug treatment, including antihypertensive drugs.

However, nonhaemodynamic factors could explain both the GFR decline and the arterial stiffening and remodeling, and there may be no direct influence of arterial function on the progression of kidney damage. For instance, in the Nephrotest longitudinal study, carotid circumferential wall stress, which integrated maladaptive changes in diameter (enlargement) and wall thickness (lack of wall thickening) possibly related to nonhemodynamic changes, was significantly and independently associated with the progressive decline in GFR and incident end-stage renal disease, whereas aortic stiffness and central pulse pressure were not.

The article by Hashimoto and Ito published in the present issue of Hypertension provides an important contribution with regard to the mechanisms through which an increase in aortic stiffness can reduce renal function and GFR, for at least 4 reasons. First, the authors reported that aortic blood flow reversal, measured at the proximal descending aorta through the suprasternal window using duplex ultrasonography in a population of 222 hypertensive patients, 32% of whom had kidney dysfunction, was a primarily independent determinant of estimated GFR (eGFR). This relationship was significant independently of classical confounders, such as age, sex, and mean blood pressure. Thus, a novel noninvasively determined hemodynamic parameter was significantly associated with GFR. Second, although they observed that aortic (ie, carotid-femoral) pulse wave velocity was also an independent determinant of eGFR, both the aortic reverse flow ratio and carotid-femoral pulse wave velocity remained independently correlated with eGFR when both parameters were entered into a multivariate model. Aortic reverse flow ratio and carotid-femoral pulse wave velocity explained ≤12.6% and 7.8% of the total explainable eGFR variance, respectively. Third, other central hemodynamic variables were not significantly and independently correlated with GFR: carotid-radial pulse wave velocity, aortic pulse pressure, augmented pressure, augmentation index, cardiac output, mean blood pressure, characteristic impedance, and total peripheral resistance. Finally, the authors used intrarenal artery duplex ultrasound to measure renal hemodynamics in a subset of 180 subjects and found an independent, inverse correlation between the reverse/forward flow ratio in the proximal thoracic aorta and the forward flow in the distal intrarenal arteries. Combining the above
observations, the authors suggested the following mechanism, linking aortic stiffening and renal function: the diastolic run-off going downward to the abdominal aorta is reduced by the aortic flow reversal, that is, the blood spillover going upward from the proximal thoracic aorta to the supra-aortic arteries; aortic flow reversal is exaggerated by aortic stiffening and impedance mismatch (ie, the stiffness gradient between the thoracic and abdominal aorta); the reduction in diastolic run-off going downward can reduce the renal blood flow, which in turn leads to a reduction in GFR.

The study by Hashimoto and Ito\(^8\) has several strengths. Aortic stiffness and central blood pressure have been measured according to gold standards\(^9\) in a large number of patients within a large range of age and eGFR. Renal and cardiac hemodynamics have been measured in parallel with bidirectional blood flow dynamics in the proximal descending aorta. Multivariate analyses showed the independent and significant influence of aortic stiffness and aortic flow reversal on eGFR, after adjustment on classical confounding factors. However, there are some limitations which should be pointed out. First, even if age was taken into account in the multivariate analysis, it is a major determinant of eGFR (with sex and creatinine) and could still play a role in the relationship between aortic flow reversal and aortic stiffness, which are both influenced by age and eGFR. Second, this is a cross-sectional and not a longitudinal study, and a cause to effect relationship cannot be established between the amount of aortic flow reversal and the level of GFR. Only a working hypothesis can be generated, which requests a longitudinal study to be demonstrated. Particularly, as discussed above, the issue of the relationship between central hemodynamics and renal function has already given significant findings in cross-sectional studies but not during longitudinal ones. Third, if aortic stiffness was the true mediator and not only a modulator of the relationship between aortic flow wave velocity and eGFR, then the influence of aortic stiffness on eGFR should not be significant any more after entering both terms (aortic stiffness and aortic flow reversal) into the multivariate analysis. Indeed, the complex relationship between age, true GFR (and not eGFR confounded by age), aortic stiffness (carotid-femoral pulse wave velocity), and reversed flow pattern is difficult to establish in a cross-sectional study. Only longitudinal studies, using directly measured renal function\(^1-5\) coupled with corresponding experimental models, can provide mechanistic explanations.

The findings of Hashimoto and Ito\(^8\) are also stimulating because of the noninvasive method that has been used to measure aortic flow reversal.\(^10\) Indeed, blood flow velocity was recorded with duplex ultrasonography from the proximal descending aorta using a suprasternal approach. Several velocity pulse waveforms were averaged, and then systolic forward peak velocity (VFwd) and diastolic reverse peak velocity (VRev) were determined. The aortic reverse flow ratio was then calculated as VRev/VFwd and expressed as a percentage ([VRev/VFwd]×100), which may indicate the extent of aortic flow reversal. The volumetric reverse and forward blood flows were calculated from the integral of the velocity curve and the cross-sectional area of the descending aorta. The authors underline the advantages of the duplex Doppler method: high temporal and spatial resolutions, on line visualization of data, low cost, and large availability in clinical settings. However, as they acknowledged, some patients could not be measured because of intervening air-filled organs or bones, which can act as barriers to ultrasound; in addition, the precise measurement of the arterial lumen area was technically impractical, thus the velocimetric rather than volumetric flow was used to assess the renal hemodynamics in this study; finally, because ultrasonography focused on the proximal descending aorta and not the ascending aorta, some age-related changes in the ascending aorta could have been missed by the duplex Doppler method.

More recently, cardiovascular magnetic resonance uniquely allowed for accurate and noninvasive estimation of both forward and reversal aortic flow, as well as central aortic stiffness parameters, such as distensibility and pulse wave velocity, in addition to indexes of aortic geometry, such as diameters or arch length. A qualitative analysis of flow patterns and a quantitative analysis of either blood flow velocity or flow volume in the ascending aorta over age is now possible with cardiovascular magnetic resonance.\(^11\) Quantitative reversal flow has been shown to be more related to aortic geometry than to aortic stiffness and pressure reflection wave.\(^11\) The ascending aorta is worth to be analyzed compared with the proximal descending aorta that has been investigated in this study by Hashimoto and Ito.\(^8\) Indeed, the thoracic aorta dilates to a greater extent than the descending aorta with age.\(^11\) It also becomes stiffer over life course with concomitant variations of blood flow patterns and with occurrence of reversal flow, suggesting that spatial pressure gradient can reverse locally and temporally (ie, the direction of flow is always driven by spatial pressure gradient with particles going from high- to low-pressure areas). The mechanism suggested here by Hashimoto and Ito\(^4\) that reversal flow can reduce antegrade flow into the kidney has to be confirmed, particularly through a 4-dimensional phase contrast cardiovascular magnetic resonance of the renal artery. Indeed, aortic blood flow reversal may rather indicate flow dispersion and loss of kinetic energy, further damaging locally the aortic wall.

In conclusion, the study by Hashimoto and Ito\(^8\) provides a valuable contribution to the ongoing research on the determinants of GFR decline in patients with hypertensive, namely the influence of aortic stiffness. This is the first time that the relationship between aortic bidirectional flow dynamics and renal function was investigated in hypertension. The major finding of this mechanistic cross-sectional study is that the extent of aortic flow reversal (reverse/forward flow ratio) is independently associated with eGFR and renal hemodynamics. Longitudinal studies, if possible using cardiovascular magnetic resonance, are required to confirm these findings and demonstrate the cause-to-effect relationship between aortic stiffening and exaggeration of aortic flow reversal and between the later and the decline in GFR.

**Sources of Funding**

INSERM (Institut National de la Santé et de la Recherché Médicale), Paris-Descartes University, and Assistance Publique-Hôpitaux de Paris

**Disclosures**

None.


Aortic Stiffening, Aortic Blood Flow Reversal, and Renal Blood Flow
Stéphane Laurent, Pierre Boutouyrie and Elie Mousseaux

Hypertension. 2015;66:10-12; originally published online April 27, 2015;
doi: 10.1161/HYPERTENSIONAHA.115.05357

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/66/1/10

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/