Aortic Blood Flow Reversal Determines Renal Function
Potential Explanation for Renal Dysfunction Caused by Aortic Stiffening in Hypertension

Junichiro Hashimoto, Sadayoshi Ito

Abstract—Aortic stiffness determines the glomerular filtration rate (GFR) and predicts the progressive decline of the GFR. However, the underlying pathophysiological mechanism remains obscure. Recent evidence has shown a close link between aortic stiffness and the bidirectional (systolic forward and early diastolic reverse) flow characteristics. We hypothesized that the aortic stiffening–induced renal dysfunction is attributable to altered central flow dynamics. In 222 patients with hypertension, Doppler velocity waveforms were recorded at the proximal descending aorta to calculate the reverse/forward flow ratio. Tonometric waveforms were recorded to measure the carotid-femoral (aortic) and carotid-radial (peripheral) pulse wave velocities, to estimate the aortic pressure from the radial waveforms, and to compute the aortic characteristic impedance. In addition, renal hemodynamics was evaluated by duplex ultrasound. The estimated GFR was inversely correlated with the aortic pulse wave velocity, reverse/forward flow ratio, pulse pressure, and characteristic impedance, whereas it was not correlated with the peripheral pulse wave velocity or mean arterial pressure. The association between aortic pulse wave velocity and estimated GFR was independent of age, diabetes mellitus, hypercholesterolemia, and antihypertensive medication. However, further adjustment for the aortic reverse/forward flow ratio and pulse pressure substantially weakened this association, and instead, the reverse/forward flow ratio emerged as the strongest determinant of estimated GFR (P=0.001). A higher aortic reverse/forward flow ratio was also associated with lower intrarenal forward flow velocities. These results suggest that an increase in aortic flow reversal (ie, retrograde flow from the descending thoracic aorta toward the aortic arch), caused by aortic stiffening and impedance mismatch, reduces antegrade flow into the kidney and thereby deteriorates renal function. (Hypertension. 2015;66:00-00. DOI: 10.1161/HYPERTENSIONAHA.115.05236.)

Key Words: aorta ▪ blood flow velocity ▪ hemodynamics ▪ kidney ▪ pathophysiology ▪ vascular stiffness

Chronic kidney disease (CKD) is a growing public health problem worldwide. Renal dysfunction, generally defined as decreased glomerular filtration rate (GFR), is known as a strong risk factor for cardiovascular disease and end-stage renal failure. Hypertensive patients with concomitant renal dysfunction are reported to have a more than twice as high mortality risk as those without.

Increased aortic stiffness is closely involved in the pathogenesis of renal dysfunction. Numerous studies have demonstrated that the aortic pulse wave velocity (PWV) is a determinant of GFR in hypertensive patients with or without CKD. In addition, in a recent prospective study, the aortic PWV was identified as a potent predictor of progressive GFR decline, suggesting that aortic stiffening causes renal dysfunction. Also, the PWV can predict cardiovascular events in patients with normal renal function and in patients with CKD. To date, however, the causal mechanisms linking aortic stiffness with renal function and cardiovascular outcome have been poorly understood.

Central hemodynamics is composed of both the aortic blood pressure and aortic blood flow, the latter of which has a close association with aortic stiffness. Through its Windkessel function, the descending thoracic aorta as a whole serves principally to deliver blood downstream (toward the abdominal aorta) when it recoils in diastole. Nevertheless, there is evidence that the flow pulse waveform in the proximal portion of the descending aorta indicates bidirectional flow; the systolic forward (downstream) flow is followed by an early diastolic reverse (upstream) flow. The aortic reverse flow normally generates the carotid forward flow in diastole, but aortic stiffening abnormally exaggerates this aortic flow reversal, potentially causing retrograde plaque embolism leading to cryptogenic cerebral infarction. This influence of the aortic flow reversal on the suprathoracic (carotid and subclavian)
flow is well established, but little is known about its potential influence on the infrathoracic (including renal) flow.

Because the aortic flow reversal increases the blood spill-over from the proximal descending aorta to the supra-aortic arteries,\(^{14}\) it can be theoretically thought to reduce the antegrade flow (ie, diastolic runoff) toward the abdominal aorta.\(^{12}\) Therefore, we hypothesized that the aortic flow reversal as exaggerated by aortosclerosis would thus reduce the renal artery flow and accordingly lead to renal dysfunction. To test this hypothesis, we performed a comprehensive, noninvasive evaluation of the central hemodynamics including the aortic pulsatile flow, as well as pressure and PWV, and their relationships with renal function in patients with hypertension. In addition, we assessed the intrarenal artery pulsatile flow to clarify whether the association between the exaggerated aortic flow reversal and renal dysfunction is mediated through alterations in the renal hemodynamics.

**Methods**

An expanded Methods section is available in the online-only Data Supplement.

**Subjects**

The study population consisted of 222 consecutive adult patients referred to our unit at Tohoku University Hospital. Patients were excluded if they had end-stage renal disease under hemodialysis therapy, kidney transplantation, aortitis syndrome or aortic coarctation, aortic aneurysm, atrial fibrillation, aortic regurgitation, chronic heart failure, or acute cardiovascular events within 6 months.

**Measurements of Central Hemodynamics**

A series of noninvasive hemodynamic assessments were made in a quiet, temperature-controlled room while the subjects were resting in a supine position, as described previously.\(^{16}\) After measuring the brachial pressure with cuff oscillometry, pressure waveforms were recorded with application tonometry on the radial, carotid, and femoral arteries. These pulse waveforms were then used to estimate the aortic systolic and pulse pressures, incident wave height, augmented pressure, augmentation index, and carotid-femoral (aortic) and carotid-radial (peripheral) PWVs.

The blood flow velocity was recorded at the proximal descending aorta through the suprasternal window using duplex ultrasonography.\(^{14}\) The systolic (maximum) forward velocity and diastolic (minimum) reverse velocity were measured to calculate the reverse/forward flow ratio. The aortic characteristic impedance and compliance were also computed, as detailed in the online-only Data Supplement.

In addition, all subjects underwent transthoracic echocardiography to measure the left ventricular internal dimensions, stroke volume, cardiac output, and total vascular resistance.

**Measurements of Renal Function and Hemodynamics**

The estimated GFR (eGFR) was determined from the age, sex, and serum creatinine. The presence of kidney dysfunction was defined as an eGFR of <60 mL/min per 1.73 m\(^2\). Intrarenal artery duplex ultrasound was performed in a subset of subjects (n=180) to measure the maximal (peak) systolic and minimum end-diastolic velocities. The mean velocity and resistive index (RI) were then derived from these values.\(^{16}\)

**Biochemical Measurements**

Venous samples were drawn to measure the creatinine, total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, fasting blood glucose, and hemoglobin A\(_1c\).

**Statistical Analysis**

Data are shown as mean±SD or percentage, unless stated otherwise. The aortic PWV, pulse pressure, and characteristic impedance were log-transformed and standardized to a normal distribution. Student t test, \(\chi^2\) test, and Pearson correlation coefficient were used, as appropriate. Linear and logistic regression analyses were performed to assess independent factors associated with eGFR or renal dysfunction. Indirect effects were evaluated by mediation analysis. A \(P\) value of <0.05 was considered statistically significant.

**Results**

**Characteristics of Patients**

The clinical characteristics of the 222 patients are summarized in Table S1 in the online-only Data Supplement. The mean age was 53±13 years. The brachial systolic/diastolic pressures as a whole were well controlled (129/73 mmHg) because most individuals (93%) were under antihypertensive medication. The mean eGFR was 66±27 mL/min per 1.73 m\(^2\), and 72 (32%) of the total patients had kidney dysfunction (eGFR<60 mL/min per 1.73 m\(^2\)). Hypercholesterolemia and diabetes mellitus were seen in 39% and 24%, respectively.

Table 1 shows the hemodynamic characteristics. The ascending aortic flow parameters were similar to those previously published,\(^{14}\) and the mean aortic reverse/forward flow ratio was 34±10%. The mean aortic characteristic impedance was computed at 3.4×10\(^2\) dyn·s·cm\(^{-5}\) and 10.8×10\(^2\) dyn·s·cm\(^{-5}\) in volumetric and velocimetric terms, respectively. The cardiac output, measured by echocardiography, was estimated as 4.8±1.2 L/min and the total peripheral resistance as 16±4.2×10\(^2\) dyn·s·cm\(^{-5}\).

**Relationship Between Hemodynamic Measures and Kidney Function**

Figure 1 shows the univariate relationships between hemodynamic measures and eGFR. There was a significant inverse correlation between the eGFR and descending aortic forward/reverse flow ratio, namely, the eGFR decreased in a dose-dependent manner with an increasing aortic reverse flow ratio. The eGFR was inversely correlated with the aortic characteristic impedance and positively with the aortic compliance (\(r=−0.37\); \(P<0.001\)). The carotid-femoral, but not carotid-radial, PWV was significantly (inversely) correlated with the eGFR. The aortic pulse pressure also showed a similar inverse correlation with eGFR, whereas the mean arterial pressure did not. The aortic incident wave height had a moderate (\(r=−0.36\); \(P<0.001\)), the augmented pressure had a weak (\(r=−0.19\); \(P=0.004\)), and the augmentation index had no significant (\(r=−0.08\); \(P=0.22\)) correlation. Neither cardiac output nor total peripheral resistance was correlated with the eGFR (Figure 1). When expressed as absolute volume, the aortic reverse flow had a significant inverse correlation with eGFR (\(r=−0.27\); \(P<0.001\)), whereas the aortic forward flow had an insignificant positive correlation (\(r=0.08\); \(P=0.21\)).

When compared with the patient group without kidney dysfunction, the group with kidney dysfunction was significantly older, included more male and diabetic patients, and had a higher prevalence of antihypertensive medication (Table S2). There was no group difference in body mass index, brachial blood pressure, heart rate, or prevalence of
The patients with kidney dysfunction showed significant alterations in the aortic structure or function, namely, a higher PWV, wider pulse pressure, higher characteristic impedance, lower compliance, and greater aortic reverse/forward flow ratio.

Table 2 shows the results of multivariate analyses on the independent relationship between the central hemodynamic measures and eGFR. When adjusted for age, sex, mean arterial pressure, and other potentially related covariates, the aortic reverse flow ratio was independently correlated with eGFR ($P=0.001$); the reverse flow ratio alone was able to account for 13.7% of the total explainable variance of eGFR (partial $r^2$/model $R^2$). Similar to the reverse flow ratio, the carotid-femoral (ie, aortic) PWV and aortic pulse pressure were also capable of determining eGFR independently of the confounding factors. Even when entered simultaneously as dual measures into a subsequent model, both the aortic reverse flow ratio and PWV showed independent correlations with eGFR. In this model, these 2 measures altogether accounted for 20.4% of the total explainable eGFR variance. The interaction between these 2 measures was insignificant ($\beta=0.04$ for the interaction; $R^2$ increment=0.6%; $P=0.48$). When the triple measures (ie, aortic reverse flow ratio, PWV, and pulse pressure) were simultaneously entered into a model, only the reverse flow ratio and PWV, but not the pulse pressure, had independent relationships with the eGFR (Table 2). In this triple measure model, the reverse flow ratio was found to be the strongest determinant of the eGFR. These relationships remained unchanged after addition of the interaction term between the aortic reverse flow ratio and pulse pressure to this model ($\beta=−0.04$; $R^2$ increment=0.6%, $P=0.47$). Replacing the aortic PWV with the aortic compliance or characteristic impedance similarly made no difference. Mediation analysis showed that the relationship between the aortic PWV and eGFR was significantly mediated through the reverse flow ratio (95% confidence interval of indirect effect, $−2.72$ to $−0.43$ mL/min per 1.73 m$^2$ per 1-SD increase; $P=0.01$) but not through the aortic pulse pressure ($−4.25$ to $1.26$ mL/min per 1.73 m$^2$ per 1-SD increase; $P=0.29$).

In the univariate logistic analysis, all the 3 central hemodynamic measures significantly predicted the presence of renal dysfunction (Table S3). In the multivariate analysis, the aortic reverse flow ratio was able to predict renal dysfunction independently of the various confounders; the risk of renal dysfunction increased by 62% with each 1-SD (ie, 10%) increase in the aortic reverse flow ratio. The aortic PWV and pulse pressure, however, were not independently predictive of renal dysfunction as a categorical trait. Accordingly, the aortic reverse flow ratio was associated with a greater adjusted odds ratio for renal dysfunction than the aortic PWV and pulse pressure (Table S3).

### Relationship Between Aortic Reverse Flow and Intrarenal Flow

The mean flow velocities in the renal segmental artery were $42±9$ cm/s at peak systole and $15±4$ cm/s at end diastole. The time-averaged mean velocity and RI measured $24±6$ cm/s and $0.65±0.07$, respectively. The peak systolic (envelop) velocity in the abdominal aorta was $84±20$ cm/s, and no patient had a renal/aortic velocity ratio of $>3.5$, which is indicative of significant renal artery stenosis.

Figure 2 shows the relationship between the aortic reverse/forward flow ratio and intrarenal flow indices. The aortic reverse flow ratio was significantly and inversely correlated with the end-diastolic and peak-systolic renal flow velocities, as well as with the mean flow velocity ($r=−0.30$; $P=0.001$). Even when assessed as absolute volume, the aortic reverse (but not forward) flow showed significant correlations with these intrarenal flow indices ($r=−0.22$ to $−0.27$; $P≤0.002$). There was also a positive but weak correlation between the aortic reverse/forward flow ratio and renal RI (Figure 2).

The eGFR had moderate, positive correlations with the renal Doppler flow velocities (end-diastolic: $r=0.42$; peak-systolic: $r=0.28$; mean: $r=0.37$; $P<0.001$ for all) and an inverse correlation with the renal RI ($r=−0.41$; $P<0.001$). The relationships between the intrarenal flow velocities and eGFR remained highly significant after controlling for the renal RI (partial $r=0.22–0.29$; $P≤0.003$). After adjustment of the aortic...
PWV and pulse pressure, the aortic reverse flow ratio was still significantly (P<0.001) associated with the intrarenal diastolic (partial \( r=-0.23 \)), mean (partial \( r=-0.25 \)), and systolic (partial \( r=-0.24 \)) flow velocities, indicating that increased aortic flow reversal contributes to reduced intrarenal flow even independently of increased aortic stiffness and pulsatile pressure.

**Discussion**

Previous studies have shown that aortic stiffness predicts renal function, whereas the (patho)physiological mechanism underlying this aortorenal association remained unknown. The present investigation revealed that the aortic reverse/forward flow ratio, known as a close correlate of aortic stiffness, is a primarily independent determinant of eGFR in patients with hypertension (Figure 1; Table 2). Furthermore, the aortic reverse/forward flow ratio was found to correlate inversely with the intrarenal blood flow, which correlates positively with the eGFR (Figure 2). These findings indicate that the central and renal flow dynamics are primary mediators between aortic stiffness and renal function. To the best of our knowledge, this study is the first to demonstrate that the exaggerated aortic flow reversal mediates the well-established associations of aortic stiffening and widened aortic pulse pressure with deteriorated renal function in hypertension.

We 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 (Figure 2). This finding indicates that the flow reversal in the thoracic aorta affects not only the upstream or supra-aortic (eg, carotid) flow but also the downstream flow toward the abdominal aorta (Figure S1). It is known that there is a difference in the flow pattern between the proximal thoracic aorta and the suprarenal abdominal aorta; the latter is basically unidirectional with no or only minimal reverse flow. The diastolic forward flow in the abdominal aorta is mainly generated by the recoil (Windkessel) function of the elastic thoracic aorta, and it positively contributes to delivering blood into the renal arteries.

Taken together with these facts, our data suggest the following (Figure S1): (1) the blood spillover going upward from the proximal thoracic aorta to the supra-aortic arteries (caused by the flow reversal) reduces the diastolic runoff going downward to the abdominal aorta; (2) this reduction accordingly decreases the inflow from the suprarenal aorta to the renal...
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arteries; and (3) the decreased renal inflow eventually leads to a reduction in the GFR.

These assumptions are in fact supported by the present additional observations that renal dysfunction is characterized by increased aortic characteristic impedance (which exaggerates the aortic flow reversal) and decreased aortic compliance (which reduces the diastolic runoff; Table S2). The persistence of the association between the intrarenal flow and eGFR even after adjustment for the renal RI also indicates that eGFR can be determined by the aorta-to-renal inflow independently of renal peripheral resistance. Interestingly, we also observed that, in addition to the diastolic and mean intrarenal flow, the systolic intrarenal flow was also inversely proportional to the aortic reverse/forward flow ratio (Figure 2). A potential explanation for this systolic intrarenal flow relationship is that the aorta-to-supra-aorta blood spillover reduces the amount of blood pooled within the aortic reservoir; this logically should reduce the renal inflow in the subsequent systole. Moreover, the impedance mismatch (ie, stiffness gradient between the thoracic and abdominal aortas21 or between the thoracic aorta and supra-aortic arteries14) can also affect the extent of aortic flow reversal and hence the renal flow.

It may be of value here to discuss our previous studies on the femoral artery flow waveform,17,18 which demonstrated that the reverse flow from the lower body increases (rather than reduces) the renal blood flow. Initially, it might seem as if the previous results17,18 contradicted the results of our present study showing an inverse (rather than positive) relationship between the aortic reverse flow and renal forward flow. However, the apparent contradiction is readily explicable based on the proposition of Bogren and Buonocore24 that the renal blood flow in diastole is supplied from both the upstream and downstream aortas (ie, the kidney is supplied by forward flow from the suprarenal aorta and reverse flow from the infrarenal aorta). In fact, there is evidence of a distinct difference in flow waveforms between the suprarenal and infrarenal abdominal aortas; the former typically has no reverse of flow component, whereas the latter has a definite flow reversal in early diastole.22,25 This may indicate that the kidney exerts suction force on blood from the supra- and infrarenal aortas, a phenomenon observed similarly in the coronary arteries.26

In this study, no correlation was observed between the eGFR and cardiac output (Figure 1). Previous relevant studies have also reported inconsistent (ie, no to moderate) correlations between cardiac output and renal blood flow,27–30 despite a consistently close correlation between renal blood flow and GFR.30–33 Considered collectively, these data imply that renal blood flow (and thereby GFR) is not necessarily determined as a fixed fraction of the cardiac output, but it rather depends directly on the aortic flow, which is strongly influenced by the degree of flow reversal. Such an interpretation agrees well with a previous finding of the age-dependent decrease in the renal fraction of cardiac output (ie, the ratio of renal blood flow/cardiac output) in hypertensive patients,30 suggesting

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model $R^2$ $\dagger$</th>
<th>$B\pm SE$</th>
<th>$\beta$</th>
<th>Increment, $%\ddagger$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic reverse flow ratio</td>
<td>0.272</td>
<td>$-5.66\pm1.72$</td>
<td>$-0.21$</td>
<td>13.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Carotid-femoral PWV*</td>
<td>0.258</td>
<td>$-6.03\pm2.36$</td>
<td>$-0.22$</td>
<td>8.9</td>
<td>0.011</td>
</tr>
<tr>
<td>Aortic pulse pressure*</td>
<td>0.249</td>
<td>$-5.52\pm2.77$</td>
<td>$-0.20$</td>
<td>5.6</td>
<td>0.048</td>
</tr>
<tr>
<td>Dual measures</td>
<td>0.295</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic reverse flow ratio</td>
<td></td>
<td>$-5.66\pm1.70$</td>
<td>$-0.21$</td>
<td>12.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Carotid-femoral PWV*</td>
<td></td>
<td>$-6.03\pm2.30$</td>
<td>$-0.22$</td>
<td>7.8</td>
<td>0.009</td>
</tr>
<tr>
<td>Triple measures</td>
<td>0.301</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic reverse flow ratio</td>
<td></td>
<td>$-5.66\pm1.69$</td>
<td>$-0.21$</td>
<td>12.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Carotid-femoral PWV*</td>
<td></td>
<td>$-5.06\pm2.41$</td>
<td>$-0.19$</td>
<td>7.6</td>
<td>0.037</td>
</tr>
<tr>
<td>Aortic pulse pressure*</td>
<td></td>
<td>$-3.72\pm2.82$</td>
<td>$-0.14$</td>
<td>1.9</td>
<td>0.189</td>
</tr>
</tbody>
</table>

All models adjusted for age, sex, body mass index, mean arterial pressure, heart rate, hypercholesterolemia, diabetes mellitus, and antihypertensive medication. $\beta$ indicates standardized regression coefficient; $B$, eGFR change per 1-SD increase in hemodynamic measure; eGFR, estimated glomerular filtration rate; and PWV, pulse wave velocity.

$\dagger$Log-transformed.

$\ddagger$Data are presented as percentage of total explainable variance.

Figure 2. Relationships between aortic reverse/forward flow ratio and intrarenal (segmental) artery flow indices. Closed circles indicate intrarenal end-diastolic velocity; open circles, intrarenal peak systolic velocity; and open triangles, renal resistive index.
that renal hyperperfusion and dysfunction because of aging can occur without accompanying cardiac dysfunction, and they are likely attributable to aortic stiffening and the resulting exaggerated aortic flow reversal.

There are several strengths and limitations to this study. The aortic flow parameters were determined in a noninvasive, quantitative, and bias-free manner by suprasternal Doppler ultrasound, requiring no angle correction, and by the automatic generation of an ensemble-averaged waveform during as long as 10 consecutive beats. Extensive assessment with cardiac and renal artery ultrasound enabled us to exclude heart failure and renal artery stenosis, both of which can have a confounding influence on the aortorenal hemodynamic relationship. The duplex Doppler method also has several advantages compared with MRI in terms of high temporal and spatial resolutions, real-time data visualization, relative inexpensiveness, and widespread availability in clinical settings. However, some patients could not be measured because of intervening air-filled organs or bones, which can act as barriers to ultrasound. The MRI method is becoming available in laboratory settings to analyze arterial flow in such areas inaccessible by ultrasound. Another limitation is that we measured the volumetric rather than volumetric flow for assessment of the renal hemodynamics because precise measurement of the arterial lumen area was technically impractical. However, previous studies have demonstrated a close correlation between intrarenal Doppler velocity and renal blood flow volume.

Also, the present investigation dealt exclusively with the eGFR as a marker of renal impairment, and the influence of eGFR on renal function may be partly different for albuminuria and reduced GFR.

In addition, the antihypertensive medication given to most (93%) of our patients may have affected the observed hemodynamic relationship, although the overall results were unaltered even after controlling for drug treatment. This study was not a pure pathophysiological study but a cross-sectional investigation under clinical practice, although this feature may enhance the applicability of the results. Finally, on account of the cross-sectional nature of this study, the suggested causation between the exaggerated aortic flow reversal and deteriorated renal function needs to be verified further by prospective studies.

**Perspectives**

The coexistence of atherosclerosis and CKD worsens the renal and cardiovascular prognosis. This study demonstrates a key mediating role of the central hemodynamic factors, particularly an exaggerated aortic flow reversal, in this aortorenal syndrome. This in turn implies that pharmacological and nonpharmacological treatment aiming to minimize the aortic flow reversal (potentially through reducing aortic stiffness and pulse pressure) can prevent and, even if only partially, improve renal dysfunction in hypertension. To this end, noninvasive monitoring of the central hemodynamics with duplex ultrasound and applanation tonometry may serve as a useful guide for renal protection. Clearly, future intervention studies are necessary to test this hypothesis.

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**Disclosures**

None.

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Expanded Methods

Subjects
The study population consisted of 222 consecutive adult patients referred to our unit at Tohoku University Hospital for the assessment of hypertension and related cardiovascular risk factors. Patients were excluded from this study if they had 1) end-stage renal disease under hemodialysis therapy, 2) kidney transplantation, 3) aortitis syndrome or aortic coarctation, 4) aortic aneurysm, 5) sustained atrial fibrillation, 6) aortic regurgitation (ultrasound grade >I°), 7) chronic heart failure (New York Heart Association [NYHA] class >I° and/or ejection fraction <40%), or 8) acute cardiovascular events within 6 months. The diagnosis of hypertension was based on casual brachial blood pressure values >140/90 mmHg and/or antihypertensive treatment. All subjects gave written informed consent, and the medical ethics committee of Tohoku University approved the study protocol.

Measurements of Central Hemodynamics
A series of noninvasive hemodynamic assessments were made in a quiet, temperature-controlled room while the subjects were resting in a supine position, as described previously.1,2 Briefly, after 20 minutes of rest, the brachial blood pressure was measured twice with a cuff-oscillometric device (HEM-907, Omron Healthcare, Kyoto, Japan). Applanation tonometry was recorded on the radial, carotid and femoral arteries using a strain gauge transducer (SPT-301, Millar Instruments, Houston, TX). The radial pressure pulse waveforms were converted to the corresponding aortic waveforms using a generalized transfer function (SphygmoCor, AtCor Medical, West Ride, Australia). The radial and aortic waveforms were ensemble-averaged and then calibrated with the brachial pressures to estimate the mean arterial pressure (MAP) and the aortic systolic and pulse pressures. The aortic incident wave height (P1h), augmented pressure (AP) and augmentation index (AIx) were determined as reported previously.1,2 The pulse wave velocity (PWV) was measured between the carotid and femoral arteries and between the carotid and radial arteries, with the linear distances determined from the suprasternal notch to the pulse recording sites using a tape measure. The carotid-femoral PWV (PWVCF) and carotid-radial PWV (PWVCR) reflect aortic (elastic) and peripheral (muscular) stiffness, respectively.

The blood flow velocity was recorded at the proximal descending aorta through the suprasternal window using duplex ultrasonography (Vivid i, GE Healthcare, Tokyo, Japan), as described previously.2 The instantaneous, spatially averaged mean velocities
were interpolated every 10 ms, and the velocity pulse waveforms were
ensemble-averaged for 10 consecutive cardiac beats. From the ensemble pulse wave, the
systolic (maximum) forward velocity ($V_F$) and diastolic (minimum) reverse velocity ($V_R$) were measured to calculate the reverse/forward flow ratio (R/F ratio):

$$R/F \text{ ratio} = \frac{|V_R|}{|V_F|} \times 100 \, \%.$$

The luminal diameter ($D$) of the descending aorta was measured by B-mode imaging. The absolute volume of the reverse and forward flows were calculated, as reported previously. The aortic characteristic impedance ($Z_0$) was computed in volumetric and velocimetric terms from the maximal forward flow and incident pressure wave height:

$$Z_0 \text{ (volumetric)} = \frac{4 \times P_{th}}{V_F \times \pi D^2} \, (\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5});$$

$$Z_0 \text{ (velocimetric)} = \frac{P_{th}}{V_F} \, (\text{dyn} \cdot \text{s} \cdot \text{cm}^{-3}).$$

The aortic compliance per unit length ($C_l$) was calculated by integrating Branwell-Hill and water-hammer equations:

$$C_l = \frac{1}{Z_0 \times PWV_{CF}} \, (\text{cm}^4/\text{dyn}).$$

In addition, all subjects underwent transthoracic echocardiography to measure the left ventricular end-systolic and end-diastolic internal dimensions. The stroke volume and cardiac output (CO) were calculated according to the Teichholz method. The total vascular resistance (TPR) was then derived from the following equation on the premise that the central venous pressure approximates zero:

$$TPR = \frac{MAP}{CO} \, (\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}).$$

**Measurements of Renal Function and Hemodynamics**

The estimated GFR (eGFR) was determined from the age, gender and serum creatinine, using an equation that was originally derived from the Modification of Diet in Renal Disease (MDRD) study and modified specifically for Japanese patients. The presence of kidney dysfunction was defined as eGFR<60 ml/min per 1.73 m². Intrarenal artery duplex ultrasound was also performed in a subset of subjects ($n = 180$) to record the flow velocity profiles in the segmental arteries using the appropriate Doppler angle correction, as described previously. From the waveform envelope, the maximal (peak) systolic velocity ($V_S$) and minimum end-diastolic velocity ($V_{ED}$) were measured to derive the mean velocity ($V_M$) and resistive index (RI).
\[ V_M = \frac{V_S - V_{ED}}{3} + V_{ED} \text{ (cm/s)}; \]

\[ RI = \frac{V_S - V_{ED}}{V_S}. \]

**Biochemical measurements**
Venous samples were drawn from each patient to measure the creatinine, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, fasting blood glucose and hemoglobin A\textsubscript{1c}. The diagnosis of diabetes mellitus was based on a fasting blood glucose concentration \(\geq 126\) mg/dL and/or antihyperglycemic drug treatment, and the diagnosis of hypercholesterolemia on a LDL-cholesterol \(\geq 140\) mg/dL and/or antihypercholesterolemic drug treatment.

**Statistical analysis**
Data are shown as mean±SD or percentage, unless stated otherwise. The aortic PWV and pulse pressure were log-transformed to reduce heteroscedasticity and standardized to a normal distribution. For two-group comparisons, Student's \(t\)-test and \(\chi^2\)-test were used, as appropriate. The univariate linear relationships between continuous variables were evaluated using Pearson's correlation coefficients (\(r\)). Multivariate linear regression analyses were performed to assess which factors were independently associated with eGFR. For the initial models, each of the three central hemodynamic measures (ie, aortic PWV, pulse pressure and reverse flow ratio) was forcibly entered as an explanatory variable together with various classical risk factors known to be related to eGFR. For subsequent models, dual measures (ie, aortic PWV and reverse flow ratio) or triple measures (ie, all 3 measures) were simultaneously entered in addition to the classical factors. Mediation analysis was performed to examine whether the relationship between the aortic PWV and eGFR was mediated by the aortic reverse flow ratio or pulse pressure. Indirect effects and confidence intervals were estimated by bootstrapping with 5,000 resamples using the PROCESS program.\textsuperscript{9} Univariate and multivariate logistic regression analyses were also conducted to investigate the predictive ability for renal dysfunction.

A \(P\) value of <0.05 was considered statistically significant. All statistical analyses were performed with SPSS 19.0 (IBM, Armonk, NY).

**References**
1. Hashimoto J, Ito S. Pulse pressure amplification, arterial stiffness, and peripheral...


Table S1. Clinical Characteristics of Patients (n=222)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53 ± 13</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>134 (60)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>161 ± 10</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>64 ± 15</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.8 ± 4.3</td>
</tr>
<tr>
<td>Brachial systolic pressure, mmHg</td>
<td>129 ± 19</td>
</tr>
<tr>
<td>Brachial diastolic pressure, mmHg</td>
<td>73 ± 11</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73m²</td>
<td>66 ± 27</td>
</tr>
<tr>
<td>&gt;60, n (%)</td>
<td>150 (68)</td>
</tr>
<tr>
<td>&lt;60, n (%)</td>
<td>72 (32)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>189 ± 39</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>52 ± 15</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>112 ± 33</td>
</tr>
<tr>
<td>Fasting blood glucose, mg/dL</td>
<td>106 ± 32</td>
</tr>
<tr>
<td>Hemoglobin A₁c, %</td>
<td>5.6 ± 0.8</td>
</tr>
<tr>
<td>Antihypertensive medication, n (%)</td>
<td>206 (93)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>86 (39)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>52 (24)</td>
</tr>
</tbody>
</table>

eGFR indicates estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Table S2. Patient characteristics with and without kidney dysfunction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Kidney dysfunction</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(−) eGFR ≥ 60 mL/min/1.73m²</td>
<td>(+) eGFR &lt; 60 mL/min/1.73m²</td>
</tr>
<tr>
<td>Age, y</td>
<td>52 ± 12</td>
<td>58 ± 13</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>99 (66)</td>
<td>35 (49)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.8 ± 4.3</td>
<td>24.6 ± 4.4</td>
</tr>
<tr>
<td>Brachial systolic BP, mmHg</td>
<td>127 ± 18</td>
<td>131 ± 21</td>
</tr>
<tr>
<td>Brachial diastolic BP, mmHg</td>
<td>74 ± 11</td>
<td>72 ± 11</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>64 ± 11</td>
<td>63 ± 10</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73m²</td>
<td>80 ± 17</td>
<td>37 ± 20</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>57 (38)</td>
<td>29 (40)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>23 (15)</td>
<td>31 (43)</td>
</tr>
<tr>
<td>Antihypertensive medication, n (%)</td>
<td>134 (89)</td>
<td>72 (100)</td>
</tr>
<tr>
<td>Aortic pulse pressure, mmHg</td>
<td>43 ± 14</td>
<td>48 ± 16</td>
</tr>
<tr>
<td>Carotid-femoral PWV, m/s</td>
<td>7.5 ± 1.6</td>
<td>8.2 ± 2.0</td>
</tr>
<tr>
<td>Carotid-radial PWV, m/s</td>
<td>7.4 ± 1.0</td>
<td>7.4 ± 1.0</td>
</tr>
<tr>
<td>Aortic reverse/forward flow ratio, %</td>
<td>33 ± 10</td>
<td>38 ± 11</td>
</tr>
<tr>
<td>Aortic Z₀, 10²·dyn·s·cm⁻5</td>
<td>3.3 ± 1.5</td>
<td>3.7 ± 1.5</td>
</tr>
<tr>
<td>Aortic Z₀, 10²·dyn·s·cm⁻³</td>
<td>10.3 ± 4.4</td>
<td>12.0 ± 4.7</td>
</tr>
<tr>
<td>Aortic compliance, 10⁻⁵·cm⁴·dyn⁻¹</td>
<td>0.51 ± 0.24</td>
<td>0.43 ± 0.21</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.8 ± 1.2</td>
<td>4.7 ± 1.3</td>
</tr>
<tr>
<td>TPR, 10²·dyn·s·cm⁻5</td>
<td>16.3 ± 4.1</td>
<td>16.5 ± 4.3</td>
</tr>
</tbody>
</table>

eGFR indicates estimated glomerular filtration rate; BP, blood pressure; PWV, pulse wave velocity; Z₀, characteristic impedance; TPR, total peripheral resistance.
### Table S3. Univariate and multivariate-adjusted associations between central hemodynamic measures and renal dysfunction (eGFR<60 mL/min per 1.73m²)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th></th>
<th>Multivariate†</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>P</td>
<td>OR (95%CI)</td>
<td>P</td>
</tr>
<tr>
<td>Aortic reverse flow ratio</td>
<td>1.67 (1.23–2.24)</td>
<td>0.001</td>
<td>1.62 (1.12–2.35)</td>
<td>0.01</td>
</tr>
<tr>
<td>Carotid-femoral PWV*</td>
<td>1.49 (1.12–1.99)</td>
<td>0.006</td>
<td>1.02 (0.64–1.61)</td>
<td>0.93</td>
</tr>
<tr>
<td>Aortic pulse pressure*</td>
<td>1.43 (1.08–1.89)</td>
<td>0.01</td>
<td>1.12 (0.67–1.87)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Odds ratios for renal dysfunction are shown as per 1SD increase in hemodynamic measures. *log-transformed. †Adjusted for age, sex, body mass index, mean arterial pressure, heart rate, hypercholesterolemia, diabetes, and antihypertensive medication. OR indicates odds ratio; CI, confidence interval.
Figure S1. Suggested blood flow pattern in aorta and renal arteries during systole and early diastole. Magnitude and direction of blood flow are depicted as black arrows separately in patients with distensible aorta (left) and stiff aorta (right). Gray arrows represent Widkessel function of descending thoracic aorta. For details, refer to the text.