Aortic Stiffness Determines Diastolic Blood Flow Reversal in the Descending Thoracic Aorta
Potential Implication for Retrograde Embolic Stroke in Hypertension

Junichiro Hashimoto, Sadayoshi Ito

Abstract—Aortic stiffening often precedes cardiovascular diseases, including stroke, but the underlying pathophysiological mechanisms remain obscure. We hypothesized that such abnormalities could be attributable to altered central blood flow dynamics. In 296 patients with uncomplicated hypertension, Doppler velocity pulse waveforms were recorded at the proximal descending aorta and carotid artery to calculate the reverse/forward flow ratio and diastolic/systolic flow index, respectively. Tonometric waveforms were recorded on the radial artery to estimate aortic pressure and characteristic impedance (Zc) and to determine carotid–femoral (aortic) and carotid–radial (peripheral) pulse wave velocities. In all subjects, the aortic flow waveform was bidirectional, comprising systolic forward and diastolic reverse flows. The aortic reverse/forward flow ratio (35±10%) was positively associated with parameters of aortic stiffness (including pulse wave velocity, Zc, and aortic/peripheral pulse wave velocity ratio), independent of age, body mass index, aortic diameter, and aortic pressure. The carotid flow waveform was unidirectional and bimodal with systolic and diastolic maximal peaks. There was a positive relationship between the carotid diastolic/systolic flow index (28±9%) and aortic reverse/forward flow ratio, which remained significant after adjustment for aortic stiffness and other related parameters. The Bland–Altman plots showed a close time correspondence between aortic reverse and carotid diastolic flow peaks. In conclusion, aortic stiffness determines the extent of flow reversal from the descending aorta to the aortic arch, which contributes to the diastolic antegrade flow into the carotid artery. This hemodynamic relationship constitutes a potential mechanism linking increased aortic stiffness, altered flow dynamics, and increased stroke risk in hypertension.

Key Words: aorta ■ atherosclerosis ■ blood flow velocity ■ carotid arteries ■ physiopathology ■ stroke ■ vascular stiffness

Stiffening of the aorta often precedes cardiovascular diseases. There is substantial evidence demonstrating that aortic stiffness predicts all-cause mortality and total cardiovascular events in various study populations, including patients with hypertension.1–7 Some clinical studies have specifically associated preceding aortic stiffening with the subsequent incidence of major stroke events.2,6,7 However, little is known about the underlying pathophysiological mechanisms that link these abnormalities of the aorta and brain, which are spatially distant from each other in the body.

Recent research indicates that central hemodynamics plays a mediating role between the central aorta and peripheral target organs. The central pressure dynamics, which depends on aortic stiffness through the pressure wave transmission and reflection phenomena, can determine the local tensile stress on the target organ vasculature.8–10 In fact, several cross-sectional studies have shown that aortic stiffening and the resulting increased aortic pulsatile pressure may have causal associations with microvascular (asymptomatic) brain damage.11–15 In contrast to the pressure dynamics, however, the flow dynamics of the central aorta has rarely been investigated for its potential clinical significance, despite constituting the other main component of the central hemodynamics.

The descending thoracic aorta serves fundamentally as a conduit to deliver blood downstream toward the lower body. Of interest, it is nevertheless recognized that the pulsatile blood flow pattern of the descending aorta can be bidirectional, comprising systolic forward (downward) and diastolic reverse (upward) flows.16,17 This diastolic flow reversal was conventionally attributed exclusively to aortic regurgitation,18,19 whereas some recent studies have revealed that it was seen even without aortic valve disease.20–22 In addition, aortic reverse flow has been postulated to be a potential cause of latent (retrograde) plaque embolism from the thoracic aorta in patients with cryptogenic brain infarction.20,22 So far, however, essential details of the aortic

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flow reversal about its precise pathogenesis, relationship to cerebral circulation, and prevalence in nonstroke subjects remain totally obscure.

Therefore, we sought to comprehensively assess the descending aortic and cerebral (carotid) flow waveform forms in patients with hypertension, using a noninvasive and quantitative method. Our primary objectives were as follows: (1) to clarify the physiological determinants of the aortic flow reversal (with a particular focus on aortic stiffness and pressure), and (2) to investigate the potential association between aortic reverse flow and carotid antegrade flow. We hypothesized that aortic flow reversal would increase with aortic stiffening and consequently strengthen the pathological (hemodynamic) link between thoracic aorta and cerebral macrovasculature.

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

Subjects
We consecutively studied adult patients with hypertension who were seen at Tohoku University Hospital. Exclusion criteria were heart failure, valvular heart disease including aortic regurgitation (ultrasound grade >1 [trivial]), aortic stenosis, prior symptomatic stroke events, atrial fibrillation, carotid artery stenosis, prior symptomatic stroke events, and inadequate ultrasound signal quality. The final analysis included 296 patients (177 women and 119 men).

Aortic Blood Pressure and Arterial Function Measurements
A series of blood pressure measurements were made in a quiet, temperature-controlled environment, as described previously. In brief, after the brachial blood pressure measurement, pulsatile pressure signals were recorded with applanation tonometry from the radial, carotid, and femoral arteries. These pulse waveforms were used to determine various pressure and stiffness parameters, including the aortic systolic and pulse pressures, incident pressure wave height (Pia), augmented pressure, augmentation index (AIx, corrected for heart rate of 75 bpm), the aorta-to-radial and aorta-to-femoral pressure pulse amplifications, and the carotid–femoral and carotid–radial pulse wave velocities (PWVc–f and PWVc–r). The aorta-to-peripheral (ie, elastic–tissue) stiffness gradient was estimated as the ratio of PWWc–f to PWWc–r. The standardized PWVc–f was calculated with the method described by previous reports.

Aortic Blood Flow Measurements
The blood flow velocity was recorded with duplex ultrasonography from the proximal descending aorta using a suprasternal approach. The velocity pulse waveforms were ensemble averaged, and then the following parameters were determined (Figure 1): systolic forward peak velocity (Vfwd); diastolic reverse peak velocity (Vrev); time-averaged mean velocity (Vmean); forward peak flow time (Tv_fwd); and reverse peak flow time (Tv_rev). The descending aortic reverse/forward flow ratio (R/F ratio) was calculated as a percentage, which indicates the extent of aortic flow reversal:

\[ R/F \text{ ratio} = \frac{V_{\text{rev}}}{V_{\text{fwd}}} \times 100 \% \] (1)

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 characteristic impedance (Zc) was determined from aortic forward peak flow velocity, incident pressure wave height, and aortic internal radius.

Results

Subject Characteristics
The Table shows clinical and hemodynamic characteristics of the subjects. The mean age was 54±13 (range, 20–84) years. The average brachial systolic/diastolic pressure was well controlled (129/74 mmHg) because most of the subjects (90%) were under antihypertensive medication. The antihypertensive drugs (given either alone or in combination) included calcium channel blockers in 233 patients (79%), renin-angiotensin...
system inhibitors in 96 (32%), adrenergic receptor blockers in 151 (51%), diuretics in 40 (14%), and others in 5 patients (2%). Vasodilators (calcium channel blockers, renin–angiotensin system inhibitors, α-blockers, and nitrates) were being prescribed in 263 patients (89%). Hypercholesterolemia and diabetes mellitus were observed in 42% and 26% of the total subjects, respectively.

Descending Aortic Flow Waveform

The flow velocity waveform of the descending aorta was typically bidirectional with positive and negative peaks, consisting of the initial forward flow (downward into the abdominal aorta) in systole and the secondary reverse flow (upward into the aortic arch) in early diastole (Figure 1). More concretely, the flow velocity initially increased rapidly to reach a systolic peak of 41±11 cm/s with an acceleration time of 0.11±0.02 s (Table), subsequently decreased gradually during late systole, and then turned to negative in early diastole. This early-diastolic flow reversal was observed in all of the 296 subjects (100%). The reverse peak occurred 0.34±0.05 s after the start of systolic flow; the time was always longer than ejection duration (P<0.001). The absolute value of the reverse peak velocity (\(|V_{\text{Rev}}|\)) was smaller than that of the forward peak velocity (\(|V_{\text{Fwd}}|\)) for every subject (P<0.001). The reverse/forward flow ratio (\(|V_{\text{Rev}}|/|V_{\text{Fwd}}|\)) was 35% on average, and it varied considerably among the subjects (interquartile range, 27%–42%). An additional tertiary forward flow was also often seen in mid-diastole, but its peak velocity was relatively low (5±4 cm/s). There were no subjects showing a holo-diastolic reverse flow indicative of significant aortic regurgitation.

Determinants of Aortic Flow Reversal

Figure 2 shows the relationships between the descending aortic reverse/forward flow ratio and arterial stiffness parameters. There was a significant positive association between the aortic reverse flow ratio and aortic PWV; namely, the aortic reverse flow ratio increased in a dose-dependent manner, with increasing quartiles of carotid–femoral PWV. A similar association was also observed with the characteristic impedance (\(Z_0\)) of the descending aorta. In contrast, no association was found with carotid–radial (peripheral) PWV; this was linked to a proportional increase in the reverse flow ratio, with increasing quartiles of the aortic/peripheral PWV ratio. In addition, a higher aortic reverse flow ratio was associated with a higher aortic pulse pressure, despite the lack of association with the aortic mean pressure. When adjusted for age, sex, and heart rate, the reverse flow ratio was significantly correlated with aortic characteristic impedance and aortic/peripheral PWV ratio. In addition, a higher aortic reverse flow ratio was associated with a higher aortic pulse pressure, despite the lack of association with the aortic mean pressure. When adjusted for age, sex, and heart rate, the reverse flow ratio was significantly correlated with aortic characteristic impedance and aortic/peripheral PWV ratio (Figure 2). The reverse flow ratio showed a weak but significant correlation with the aortic augmentation index (\(r=0.12; P=0.03\)). There was no difference in the reverse/forward flow ratio between the subjects with trivial (I°; n=44) and no (0°; n=252) aortic valve regurgitation (37.1±10.7% and 34.3±10.3%; \(P=\text{NS}\)), and the overall results were similar even when I° subjects were excluded from analysis.

When expressed as absolute volume, the aortic reverse flow tended to increase with increases in the aortic PWV and aortic/peripheral PWV ratio (\(P=0.1\) for both), whereas the forward flow decreased significantly (\(P=0.03\) and \(P=0.002\), respectively). Furthermore, the differences in these trends showed a statistical significance (\(P=0.009\) and \(P=0.001\)), indicating that aortic stiffness had opposite effects on the reverse versus forward flows. The aortic incident pressure wave height (\(P_{\text{ih}}\)) was positively correlated with absolute reverse flow (\(P=0.01\),
The highest reverse flow tertile tended to have a greater aortic mean pressure, heart rate, or prevalence of antihypertensive medication. There was no difference in brachial pressure volume. There was also a significant correlation between the aortic reverse and carotid diastolic maximum flow velocities (r=0.35 s), indicating a direct relationship between the 2 time measures.

Subject characteristics were compared among the tertile groups classified by the aortic reverse/forward flow ratio (Table S1). The highest (versus the lowest) tertile of the reverse flow ratio was older, tended to be more overweight, included more patients with hypercholesterolemia and diabetes mellitus, and showed higher reverse and lower forward aortic flow volume. There was no difference in brachial pressure, heart rate, or prevalence of antihypertensive medication. The highest reverse flow tertile tended to have a greater aortic augmentation index and a smaller aorta-to-radial (but not aorta-to-femoral) pulse amplification. Aortic diameter was similar among the tertiles. The carotid–femoral PWV showed a highly significant tertile difference, whether evaluated with raw or standardized data.

Table S2 shows the results of multivariate analyses. When entered into a model, together with other potentially relevant covariates, the descending aortic characteristic impedance was found to be a major independent determinant of the reverse/forward flow ratio (model 1). The other independent determinants in this model included age, body mass index, and aortic diameter, all of which showed positive relationships to the reverse flow ratio. Hypercholesterolemia, diabetes mellitus, and use of vasodilators did not have independent relationships. When substituted for aortic impedance, the aortic PWV (model 2) and the aortic/peripheral PWV ratio (model 3) were also identified as independent positive determinants. In each model, descending aortic impedance, aortic PWV, and aortic/peripheral PWV ratio alone were able to explain 25.5%, 13.2% and 17.0% (partial r²/model R²), respectively, of the total explainable variance of the aortic reverse flow ratio. However, aortic pulse pressure, aortic augmentation index, and pulse pressure amplifications had no independent associations with the aortic reverse flow ratio, when entered in replacement of the aortic stiffness parameters (ie, Z₀ and PWVCₐ₋ₙ).

### Carotid Artery Flow Waveform
The flow velocity pulse waveform of the carotid artery was basically unidirectional and bimodal, consisting of the 2 maximal peaks in early systole and early diastole (Figure S1). In most subjects, an additional peak (or shoulder) was also detectable in late systole. The mean values of the peak systolic, peak diastolic, end-diastolic, and time-averaged mean flow velocity were 46±14, 22±6, 13±4, and 22±6 cm/s, respectively, and the diastolic/systolic flow index was computed at 27.9±9.0%. The mean systolic peak flow time was 0.08±0.04 s, and the diastolic peak time was 0.36±0.03 s. The carotid artery lumen measured 6.4±0.8 mm in diameter.

### Relationship Between Aortic Reverse Flow and Carotid Diastolic Flow
Figure 3 depicts the relationship between aortic reverse/forward flow ratio and carotid diastolic/systolic flow index. There was a highly significant association between them, which was manifest by a sequential increase in the carotid diastolic/systolic flow index across increasing tertiles of the aortic reverse flow ratio. There was also a significant correlation between the aortic reverse and carotid diastolic maximum flow velocities (r=0.21; P<0.001). In addition, the Bland–Altman histogram showed a close correspondence between the carotid diastolic peak flow time (T₉₀₋₄₀, 0.36±0.03 s) and the aortic reverse peak flow time (T₉₀₋₄₀, 0.34±0.05 s), with only a slight difference of 0.02±0.04 s for each subject (Figure S2). Furthermore, the 2SD of the difference (0.08 s) was far smaller than the mean (0.35 s), indicating a direct relationship between the 2 time measures.

In a multivariate model including various potential covariates, the aortic reverse/forward flow ratio was found to be an independent correlate of the carotid diastolic/systolic flow index (Table S3). To be more specific, the aortic reverse flow ratio, as well as age and mean arterial pressure, had a positive relationship, whereas the heart rate had an inverse relationship with the carotid diastolic flow index. The aortic reverse flow ratio alone explained 22.0% of the total explainable variance of the carotid diastolic flow index. Additional inclusion of the aortic pulse pressure as a covariate in this model did not substantively alter the results. The aortic AIx, when added to this model, constituted an independent correlate, together with the...
Figure 3. Carotid diastolic/systolic flow index in tertile groups classified according to aortic reverse/forward flow ratio. P values for trend are evaluated by ANOVA. *P<0.05, vs the lowest tertile (Bonferroni test).

Aortic reverse/forward flow ratio (%)

![Bar chart showing the aortic reverse/forward flow ratio in different tertile groups with P = 0.001.](chart.png)

The existence of diastolic blood flow reversal in the thoracic aorta has been recognized in some selected populations, such as patients with stroke, whereas little has been clarified about its prevalence in uncomplicated hypertension and the etiologic mechanism responsible for this reversal phenomenon. To our knowledge, this study is the first to systematically investigate this phenomenon by applying a novel, quantitative flow pulse waveform analysis, and it was conducted on the largest population so far. Our investigation revealed that the flow reversal in the descending aorta is (1) commonly seen in patients with uncomplicated hypertension; (2) closely associated with aortic stiffness (as measured by the aortic PWV and characteristic impedance); and (3) directly linked to the carotid early-diastolic antegrade flow, none of which was proven in humans before this study. The present results serve to improve the general understanding of the (patho)physiological features of the aortic flow reversal, which may provide further insights into the interplay between the central and cerebral hemodynamics.

It was generally believed until recently that the flow reversal in the thoracic aorta is a sign of aortic regurgitation. However, later studies using transesophageal echocardiography or MRF have shown that aortic flow reversal can be seen even without aortic regurgitation. Our present study corroborates these previous observations, because patients were excluded from analysis if they showed a significant (mild-to-severe) regurgitant flow across the aortic valve. Furthermore, none of the included subjects had holo-diastolic reversal, with an extremely high reverse flow in end diastole (Table), which is strongly suggestive of aortic regurgitation. Despite the established absence of aortic regurgitation, the presence of aortic flow reversal was confirmed in 100% of our subjects, suggesting that other mechanisms rather than aortic valve disorder are primarily involved in the generation of aortic reverse flow.

We found that the aortic reverse/forward flow ratio was independently associated with aortic characteristic impedance and PWV (Figure 2; Tables S1 and S2). This finding indicates that aortic stiffening is directly related to an increased proportion of the aortic flow reversal. Furthermore, our data suggest that this flow reversal is ascribed to the reservoir and recoil (Windkessel) function of the elastic aorta, as described below.

The proximal descending aorta (ie, the flow recording site) is anatomically located between the upper aortic arch and the lower straight portion of the descending (thoracic and abdominal) aorta, and the aortic arch includes 3 branches (ie, the brachiocephalic trunk, left carotid artery, and left subclavian artery) that supply blood flow into the upper part of the body. Functionally, the descending aorta (as a whole) dilates in systole to store some of the blood delivered from the aortic arch, and then it recoils in diastole to push the stored blood principally toward the lower body. However, our present observation clearly shows that the most proximal part of the descending aorta expels blood in early diastole exclusively upward (ie, toward the upper body), and this expel is increased with aortic stiffening. This runoff may be explained by the following 2 assumptions: (1) some excess blood spills over in early diastole from the proximal end orifice of the expanded descending aorta when it recoils; and (2) as the descending aorta becomes stiffer and more resistant to expansion (ie, with impaired reservoir function), this spillover rate becomes greater and more blood flows backward into the upper body. (It should be noted here that the absolute spillover volume normally depends on the inflow into the descending aorta, because there was a close correlation between the absolute maximum reverse and forward velocities (r=0.43, P<0.001).) Furthermore, this flow reversal would become more marked when the upstream arteries are more compliant than the downstream arteries, because our data actually show a significant association between the aortic reverse/forward flow ratio and aortic/peripheral (ie, elastic/muscular) PWV ratio (Figure 2). This indicates that a lack of (or even inverted) elastic-to-muscular artery stiffness gradient, resulting from aortic stiffening, accelerates the diastolic runoff (spillover) toward the more distensible arteries in the upper body.

The aorta-to-peripheral pulse pressure amplifications, unlike the aortic stiffness parameters (ie, Zc and PWV), were not independently associated with aortic flow reversal in the multivariate analysis. Initially, it may seem that these results are in partial disagreement with our previous study, which showed that pulse pressure amplification is an independent determinant of reverse flow in the femoral artery. However, this apparent disagreement may be readily explicable by the anatomic difference in artery branching between the upper and lower body. Specifically, the aortic branches supplying the upper body (including the head, neck, and upper limbs) are more complex in comprising elastic and muscular arteries. Therefore, the aorta-to-radial or aorta-to-femoral pulse pressure amplification, as evaluated in this study, may not represent the total pressure gradient between the descending
thoracic aorta and all supra-aortic arteries. In fact, distinct hemodynamic features are noted between the carotid (elastic) artery and arm (muscular) arteries; for instance, blood flow in early diastole normally shows antegrade in the carotid artery (Figure S1) even when retrograde in the arm artery.35,36

The observed positive association between aortic augmentation index and aortic reverse/forward flow ratio on the univariate (though not multivariate) analysis suggests that the pressure wave reflection from the lower body also has some influence on the diastolic flow reversal.31 This association may be partly explained by the effect of augmented pressure (caused by the reflected wave) on reducing the aortic forward flow (or cardiac outflow)37 in late systole, as shown by the present and previous37 studies. In the case of absolute reverse flow, the influence of the pressure wave reflection was less obvious in this study. This might be the result of an underestimation caused by wave reflection being gauged only in systole (by the conventional systolic augmented pressure and augmentation index) rather than in early diastole.38 However, despite the fact that aortic stiffening causes early wave reflection leading to a reduction in diastolic pressure augmentation,31 the diastolic reverse flow rather exhibited the opposite tendency to increase with aortic stiffening. This finding, taken together with previously mentioned findings, implies that the exaggerated flow reversal resulting from aortic stiffening is more largely attributable to impaired Windkessel function than to early wave reflection.

It is of particular note that we did find a close link between aortic reverse flow and carotid diastolic antegrade flow. This link was verified in terms of both flow velocity and time, namely, (1) a linear association between the aortic reverse flow ratio and carotid diastolic flow index (Figure 3 and Table S3) and (2) a time correspondence between these flow peaks (Figure S2). These findings are in accordance with a previous experimental study showing a reciprocal relationship (ie, ±180° out of phase) in the diastolic flow patterns between the descending aorta and brachiocephalic trunk in dogs.39 In addition, it has been shown that the aortic arch has the same reverse flow as that observed in the descending aorta in our patients.21 Therefore, by integrating these studies,21,39 it is clear that the reverse flow in the descending aorta supplies diastolic flow through the aortic arch up toward the carotid arteries. Our additional analysis suggests that, similar to the late-systolic flow,30 diastolic carotid flow is influenced by pressure wave reflection. Nevertheless, the relationship between aortic reverse and carotid diastolic flows seems to be direct and at least partially independent of the pressure wave reflection, because its significance remained even after adjustment for aortic augmentation index.

It has been shown that the risk of stroke (macro- and microvascular) is increased in the presence of aortic stiffening,26,7,13,12,14,15 and there is evidence suggesting that symptomatic stroke of undetermined origin can be attributed to retrograde plaque embolism from the thoracic aorta.20,22 Furthermore, aortic atherosclerosis is known to be one of the leading causes of embolic stroke, together with atrial fibrillation and carotid artery atherosclerosis.43 Our present study proposes an integrated explanatory mechanism for all of these observations. First, aortic stiffening exacerbated by atherosclerotic plaque lesions accelerates aortic flow reversal and then can cause any mobile complex plaques to detach from the aortic wall. The detached plaques can subsequently travel retrogradely into the carotid (or vertebral) arteries and can cause cerebral embolism. It should be of particular note here that aortic complex plaques (as a potential source of cerebral embolism) are much more prevalent in the descending aorta than in the ascending aorta or aortic arch.44 Clearly, this speculative mechanism needs further validation by investigating whether blood flow reversal corresponds with actual retrograde movement of embolic plaques.

The present study has several strengths. The use of suprasternal approach enabled us to obtain precisely the Doppler velocity signals without any need for angle corrections. The arterial (ie, aortic and carotid) blood flow profiles were evaluated with the mathematical generation of an ensemble-averaged waveform (during as long as 10 consecutive beats) and the automatic determination of the velocity parameters. This helped to provide quantitative information without any observer or data selection biases. In addition, measurement of the characteristic impedance enabled us to properly assess the descending aortic distensibility.

There are some limitations to this study. First, the recordings of the aortic and carotid flows were not completely simultaneous but rather successive, which might have biased the present results. However, the observed close agreement in the flow peak time (Figure S2) implies that such confounding influence was negligibly small. Second, the characteristic impedance was calculated based on the time domain rather than the conventional frequency domain analysis, although these analyses are known to yield comparable results.29–31 The descending aortic impedance was calculated from the estimated central pressure instead of the actual descending aortic pressure values, but the pressure waveforms can be regarded as virtually identical between the ascending and descending aorta.31 The use of flow data in the impedance calculation might have had partial influence on the observed association between aortic impedance and reverse/forward flow ratio. Third, most of our subjects were receiving antihypertensive medication, which could have affected the flow as well as pressure parameters, although the overall results presented here were unaltered even after controlling for drug effects. In addition, the peripheral vascular resistance (as well as central aortic stiffness or impedance), as modulated by vasodilators, could influence their pulsatile flow profile, although the steady pressure component (ie, mean arterial pressure) was considered for adjustment. Fourth, because of a lack of stroke patients in our cohort, we were unable to directly evaluate the possibility that the aortic flow characteristics differed between patients with and without prior cryptogenic stroke, which has been suggested by previous studies.20,22 Finally, because of the cross-sectional nature of this study, the suggested causal relationship among aortic stiffness, central flow dynamics, and cerebrovascular damage needs to be investigated further by prospective follow-up studies.

Perspectives
Hypertension is the leading risk factor for stroke, and severe aortic plaque is prevalent in as much as 20% of patients with...
stroke.41,43,44 Our present data suggest that aortic flow reversal plays a key role in the pathogenic mechanism by which aortic stiffening leads to ischemic stroke. Based on these premises, if the abnormally exaggerated aortic flow reversal in hypertensive patients with a stiffened aorta could be normalized (either directly through destiffening therapy or indirectly through certain types of antihypertensive therapy),5,6 the development of stroke could be effectively prevented. Future studies are clearly needed to explore the relationship between their potential efficacy on the central flow dynamics and therapeutic consequences.

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Disclosures

None.

References

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Aortic Stiffness and Central Blood Flow Reversal


What Is New?

This study is the first to systematically demonstrate the following in patients with uncomplicated hypertension:

- Substantial diastolic flow reversal exists in the descending thoracic aorta.
- The aortic flow reversal is primarily determined by aortic stiffness.
- The aortic reverse flow contributes to carotid diastolic antegrade flow.

What Is Relevant?

- Aortic stiffening caused by hypertension increases the aortic diastolic flow reversal.

- The exaggerated flow reversal can predispose hypertensive patients with aortic atherosclerosis to ischemic stroke through retrograde plaque embolism.

Summary

We found that aortic stiffness determines the diastolic flow reversal in the proximal descending aorta, which may mediate the pathophysiological link between the central and cerebral hemodynamics.
ONLINE SUPPLEMENT

Aortic stiffness determines diastolic blood flow reversal in the descending thoracic aorta: Potential implication for retrograde embolic stroke in hypertension

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Expanded Methods

Subjects
We consecutively studied adult patients with hypertension who were seen at Tohoku University Hospital. Patients were excluded from the analysis if they had the following concomitant disease(s): 1) heart failure (left ventricular ejection fraction < 40 %, or documented); 2) valvular heart disease including aortic regurgitation (ultrasound grade II° [mild]–IV° [severe]1, or documented); 3) aortitis syndrome or aortic coarctation; 4) thoracic or abdominal aortic aneurysm; 5) sustained atrial fibrillation; 6) carotid artery stenosis; or 7) previous history of symptomatic stroke events. Of the 359 patients who underwent aortic ultrasonography through the suprasternal window, 63 (17%) were excluded due to insufficient quality of B-mode images or Doppler signals. The remaining 296 patients (83%; 177 women and 119 men) were included in the final analysis. The rationale and design of this study were officially approved by the institutional ethics committee of Tohoku University, and all subjects gave written informed consent.

Aortic blood pressure and arterial function measurements
A series of blood pressure measurements were made in a quiet, temperature-controlled environment, as described previously.2,3 In brief, following 20 minutes of supine posture, the brachial blood pressure was measured twice using a validated cuff-oscillometric device (HEM-907, Omron Healthcare, Kyoto, Japan). The noninvasive technique of applanation tonometry was then applied to record pulsatile pressure signals from the radial, carotid and femoral arteries with a high-fidelity transducer (SPT-301, Millar Instruments, Houston, TX).

The recorded radial pressure pulse waveforms were ensemble-averaged for 11 seconds (s) and transformed to generate the corresponding aortic pressure waveform using a validated generalized transfer function (SphygmoCor version 8.2, AtCor Medical, Sydney, Australia). The averaged radial waveform was calibrated with the brachial cuff systolic and diastolic pressures to determine the mean arterial pressure from the area under the curve and thereby estimate the aortic systolic and pulse pressures. The calibrated aortic waveform was utilized to calculate the aortic incident pressure wave height ($P_{1h}$), augmented pressure and augmentation index (AIx, corrected for heart rate of 75 bpm), as reported previously.2,3 The aorta-to-radial and aorta-to-femoral pulse pressure amplifications were calculated as percentages from the integration of the respective (uncalibrated) pulse waveforms.2
The pulse wave velocity (PWV) was also determined between the carotid and femoral arteries and between the carotid and radial arteries, as described previously.\textsuperscript{2,3} The travel distance was estimated by body surface measurements from the suprasternal notch to pulse recording sites.\textsuperscript{4} The carotid-femoral PWV (PWV\textsubscript{C-F}) and carotid-radial PWV (PWV\textsubscript{C-R}) were considered as measures of elastic (aortic) and muscular (peripheral) artery stiffness, respectively. The aorta-to-peripheral stiffness gradient was also estimated as the ratio of PWV\textsubscript{C-F} to PWV\textsubscript{C-R}. The standardized PWV\textsubscript{C-F} was calculated by estimating the direct distance (between the carotid and femoral sites) from the subtracted distance and using a scaling factor of 0.8.\textsuperscript{5,6}

**Aortic blood flow measurements**

The blood flow velocity measurement was made using duplex ultrasonography equipped with a 3.5-MHz sector array transducer (Vivid i, GE Healthcare, Tokyo, Japan). Using a suprasternal approach, two-dimensional real-time B-mode and bidirectional pulsed Doppler signals were acquired from the proximal descending thoracic aorta. Specifically, the transducer was positioned in the suprasternal notch and aimed to cross the descending aortic arch in the long axis view, such that the angle of incidence with the blood flow was 0°. The Doppler shift signals were sampled at the center of the aortic lumen, since the velocity profile has been shown to vary little across the lumen.\textsuperscript{7} The wall (high-pass) filter was chosen to be as low as possible so that the slower moving flow would be included. The instantaneous velocity was calculated as the spatial average of the intensity-weighted Doppler signals within a sample volume of 5.5 mm. The spatially averaged instantaneous mean velocity was recorded continuously for 16 s, digitized, and stored as time-series data for further analysis. The luminal diameter of the descending aorta was also measured by B-mode imaging at the same site as that for the Doppler recording.

The 16-s flow velocity data were interpolated offline at 100 Hz (Mathematica version 4.0, Wolfram Research, Champaign, IL). The velocity pulse waveforms were then ensemble-averaged for 10 consecutive cardiac cycles using the foot of the systolic upstrokes as the fiducial point (BeatScope, BMEYE, Amsterdam), as described previously.\textsuperscript{2} The averaged waveform was plotted against time in a conventional manner for the Doppler flow, such that velocities toward the transducer are shown above and those away from the transducer below the baseline (Figure 1). The following parameters for the descending aortic flow waveform were thus measured in relation to the velocity and time: systolic forward (ie, downstream to the abdominal aorta) peak (maximum) velocity ($V_{Fwd}$); diastolic reverse (ie, upstream to the aortic arch) peak (minimum)
velocity ($V_{\text{Rev}}$); end-diastolic velocity ($V_{\text{ED}}$); time-averaged mean velocity ($V_{\text{M}}$); forward peak flow time ($T_{\text{Fwd}}$, the duration from the start of systolic flow to the systolic forward velocity peak); and reverse peak flow time ($T_{\text{Rev}}$, the duration from the start of systolic flow to the diastolic reverse velocity peak). The descending aortic reverse/forward flow ratio (R/F ratio) was thus calculated as a percentage:

$$\text{R/F ratio} = \frac{V_{\text{Rev}}}{V_{\text{Fwd}}} \times 100 \, \%.$$ 

The R/F ratio was used as an index of the aortic flow reversal, in consideration for the dependence of the aortic outflow (including the diastolic reverse flow) on the aortic inflow. The volumetric reverse and forward blood flows were also calculated from the integral of the flow velocity curve and the cross sectional area of the descending aorta.

The characteristic impedance of the descending aorta ($Z_0$) was determined as the ratio of the change in pressure to that in the volumetric flow under no influence of the wave reflection. Based on previous studies,8-10 $Z_0$ was computed in the time domain from the aortic forward peak flow velocity ($V_{\text{Fwd}}$), incident pressure wave height ($P_{\text{1h}}$) and aortic internal radius ($R$):

$$Z_0 = \frac{P_{\text{1h}}}{V_{\text{Fwd}} \times \pi R^2} \, (\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}).$$

**Carotid artery blood flow measurements**

Carotid duplex ultrasound was carried out with a 12-MHz linear array transducer (Vivid i). After the appropriate longitudinal image was obtained by B-mode scanning, the Doppler flow was recorded at the right common carotid artery 2 cm proximal to the carotid bulb. The sample volume was chosen to be large enough to encompass the entire lumen, and the insonation angle was maintained at 45-60°.2 In a manner similar for the aortic flow, data on the instantaneous, spatially-averaged mean velocities were processed to generate an ensemble-averaged pulse waveform for 10 consecutive beats. Because the carotid flow is normally unidirectional without flow reversal (Figure S1), we determined the following parameters: systolic maximum peak velocity ($V_{\text{Smax}}$); diastolic maximum peak velocity ($V_{\text{Dmax}}$); end-diastolic velocity ($V_{\text{ED}}$); time-averaged mean velocity ($V_{\text{M}}$); time from the start of systolic flow to the systolic velocity peak ($T_{\text{Smax}}$); and time from the start of systolic flow to the diastolic velocity peak ($T_{\text{Dmax}}$). The diastolic/systolic flow index (D/S index) was calculated as the percent ratio of the diastolic pulse height ($D$) to the systolic pulse height ($S$):

$$\text{D/S index} = \frac{D}{S} \times 100 = \frac{V_{\text{Dmax}} - V_{\text{ED}}}{V_{\text{Smax}} - V_{\text{ED}}} \times 100 \, \%.$$
Anthropometric and laboratory measurements

Body mass index was calculated as body weight in kilograms divided by height in meters squared. Venous blood samples were drawn to measure total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and fasting blood glucose by standard methods. Hemoglobin A1c was additionally measured in 287 subjects (97%). Hypercholesterolemia was defined as an LDL cholesterol $\geq 140$ mg/dl or use of cholesterol-lowering drugs, and diabetes mellitus as a fasting blood glucose $\geq 126$ mg/dl or use of anti-diabetic drugs.

Statistical analysis

All data analyses were performed with SPSS version 19.0 (IBM, Armonk, NY). Univariate comparisons among tertile or quartile groups were made using analysis of variance (ANOVA) with a post-hoc Bonferroni test, or $\chi^2$ test. Paired t-test was used to compare matched pairs data. Univariate correlations were evaluated with Pearson's coefficients, and the slopes of the regression lines were compared by analysis of covariance (ANCOVA). Multivariate linear regression analysis was used to evaluate independent associations between the aortic reverse/forward flow ratio and arterial stiffness parameters. Potential covariates for stepwise models were selected if there was a significant univariate association or previously recognized relation. Similar multivariate analysis was performed to assess the relationships between the aortic and carotid flow measures. Bland-Altman plots analysis was used to evaluate correspondences between the aortic and carotid flow peak time.11

Values are presented as mean ± SD or percentage, except as noted. A two-sided $P$ value of $< 0.05$ was considered statistically significant.

References


3. Hashimoto J, Ito S. Central pulse pressure and aortic stiffness determine renal hemodynamics: pathophysiological implication for microalbuminuria in
### Table S1. Patient Characteristics According to Descending Aortic Reverse/Forward Flow Ratio

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lowest &lt;28.93% (n=99)</th>
<th>Middle 28.93–38.50% (n=99)</th>
<th>Highest &gt;38.50% (n=98)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49 ± 13</td>
<td>54 ± 12</td>
<td>59 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>60 (61)</td>
<td>59 (60)</td>
<td>58 (59)</td>
<td>0.98</td>
</tr>
<tr>
<td>Height, cm</td>
<td>162 ± 9</td>
<td>161 ± 9</td>
<td>159 ± 9</td>
<td>0.08</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>64 ± 16</td>
<td>64 ± 14</td>
<td>65 ± 14</td>
<td>0.89</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.3 ± 4.3</td>
<td>24.7 ± 3.9</td>
<td>25.6 ± 4.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>192 ± 36</td>
<td>190 ± 43</td>
<td>189 ± 42</td>
<td>0.87</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mg/dl</td>
<td>51 ± 15</td>
<td>54 ± 15</td>
<td>50 ± 15</td>
<td>0.22</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mg/dl</td>
<td>114 ± 31</td>
<td>114 ± 37</td>
<td>111 ± 34</td>
<td>0.69</td>
</tr>
<tr>
<td>Fasting blood glucose, mg/dl</td>
<td>102 ± 24</td>
<td>104 ± 20</td>
<td>111 ± 43</td>
<td>0.08</td>
</tr>
<tr>
<td>Hemoglobin A1c, %*</td>
<td>5.5 ± 0.9</td>
<td>5.6 ± 0.8</td>
<td>5.8 ± 0.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>31 (31)</td>
<td>45 (46)</td>
<td>49 (50)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>17 (17)</td>
<td>26 (26)</td>
<td>35 (36)</td>
<td>0.01</td>
</tr>
<tr>
<td>Antihypertensive medication, n (%)</td>
<td>86 (87)</td>
<td>91 (92)</td>
<td>90 (92)</td>
<td>0.39</td>
</tr>
<tr>
<td>Brachial systolic blood pressure, mmHg</td>
<td>129 ± 20</td>
<td>129 ± 19</td>
<td>134 ± 20</td>
<td>0.14</td>
</tr>
<tr>
<td>Brachial diastolic blood pressure, mmHg</td>
<td>74 ± 11</td>
<td>74 ± 11</td>
<td>74 ± 12</td>
<td>0.88</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>93 ± 14</td>
<td>94 ± 13</td>
<td>95 ± 13</td>
<td>0.77</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>64 ± 10</td>
<td>64 ± 11</td>
<td>66 ± 11</td>
<td>0.49</td>
</tr>
<tr>
<td>Aortic systolic blood pressure, mmHg</td>
<td>118 ± 21</td>
<td>118 ± 19</td>
<td>123 ± 19</td>
<td>0.13</td>
</tr>
<tr>
<td>Aortic pulse pressure, mmHg</td>
<td>43 ± 15</td>
<td>44 ± 15</td>
<td>49 ± 16</td>
<td>0.01</td>
</tr>
<tr>
<td>Aortic augmented pressure, mmHg</td>
<td>12 ± 10</td>
<td>12 ± 9</td>
<td>14 ± 9</td>
<td>0.11</td>
</tr>
<tr>
<td>Aortic Aix adjusted for heart rate 75 bpm, %</td>
<td>20 ± 12</td>
<td>21 ± 11</td>
<td>24 ± 10</td>
<td>0.09</td>
</tr>
<tr>
<td>Aortic incident wave height, mmHg</td>
<td>31 ± 8</td>
<td>31 ± 8</td>
<td>34 ± 10</td>
<td>0.007</td>
</tr>
<tr>
<td>Aorta-to-femoral AMP, %</td>
<td>122 ± 14</td>
<td>123 ± 15</td>
<td>121 ± 16</td>
<td>0.10</td>
</tr>
<tr>
<td>Carotid-femoral PWV (PWV&lt;sub&gt;C-F&lt;/sub&gt;), m/s</td>
<td>7.5 ± 1.5</td>
<td>7.8 ± 1.8</td>
<td>8.4 ± 2.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Carotid-radial PWV (PWV&lt;sub&gt;C-R&lt;/sub&gt;), m/s</td>
<td>7.5 ± 1.0</td>
<td>7.6 ± 0.9</td>
<td>7.4 ± 1.0</td>
<td>0.56</td>
</tr>
<tr>
<td>PWV&lt;sub&gt;C-F&lt;/sub&gt;/PWV&lt;sub&gt;C-R&lt;/sub&gt; ratio</td>
<td>1.01 ± 0.21</td>
<td>1.04 ± 0.25</td>
<td>1.16 ± 0.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Standardized PWV&lt;sub&gt;C-F&lt;/sub&gt;, m/s</td>
<td>8.3 ± 1.6</td>
<td>8.7 ± 2.0</td>
<td>9.3 ± 2.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Aortic characteristic impedance, dyn·s·cm⁻⁵</td>
<td>305 ± 121</td>
<td>353 ± 155</td>
<td>406 ± 178</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Descending aortic diameter, mm</td>
<td>19.9 ± 1.8</td>
<td>20.2 ± 1.5</td>
<td>20.3 ± 1.6</td>
<td>0.20</td>
</tr>
<tr>
<td>Aortic reverse/forward flow ratio, %</td>
<td>23.9 ± 4.3</td>
<td>33.7 ± 2.7</td>
<td>46.6 ± 6.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic reverse flow, ml/s</td>
<td>6.0 ± 2.8</td>
<td>9.6 ± 3.8</td>
<td>14.2 ± 5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic forward flow, ml/s</td>
<td>34.1 ± 10.0</td>
<td>29.7 ± 9.5</td>
<td>27.8 ± 9.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Aix indicates augmentation index; AMP, pulse pressure amplification; PWV, pulse wave velocity. *Data available in 287 subjects.
Table S2. Independent Determinants of Descending Aortic Reverse/Forward Flow Ratio

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient ±SE</th>
<th>Standardized coefficient</th>
<th>Partial $r^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: Aortic $Z_0$ and covariates*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic $Z_0$, $10^2$ dyn·s·cm$^{-5}$</td>
<td>1.27 ± 0.46</td>
<td>0.19</td>
<td>0.037</td>
<td>0.006</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.13 ± 0.05</td>
<td>0.17</td>
<td>0.028</td>
<td>0.02</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>0.37 ± 0.14</td>
<td>0.15</td>
<td>0.023</td>
<td>0.009</td>
</tr>
<tr>
<td>Aortic diameter, mm</td>
<td>0.79 ± 0.40</td>
<td>0.12</td>
<td>0.015</td>
<td>0.047</td>
</tr>
<tr>
<td>Model 2: PWV$_{C-F}$ and covariates*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PWV$_{C-F}$, m/s</td>
<td>0.75 ± 0.36</td>
<td>0.13</td>
<td>0.017</td>
<td>0.04</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.18 ± 0.05</td>
<td>0.23</td>
<td>0.051</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>0.43 ± 0.13</td>
<td>0.17</td>
<td>0.030</td>
<td>0.002</td>
</tr>
<tr>
<td>Model 3: PWV$<em>{C-F}$/PWV$</em>{C-R}$ ratio and covariates*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PWV$<em>{C-F}$/PWV$</em>{C-R}$ ratio</td>
<td>5.98 ± 2.75</td>
<td>0.15</td>
<td>0.023</td>
<td>0.02</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.16 ± 0.05</td>
<td>0.20</td>
<td>0.040</td>
<td>0.004</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>0.41 ± 0.13</td>
<td>0.17</td>
<td>0.028</td>
<td>0.003</td>
</tr>
</tbody>
</table>

SE indicates standard error; $Z_0$, characteristic impedance; PWV$_{C-F}$, carotid-femoral pulse wave velocity; PWV$_{C-R}$, carotid-radial pulse wave velocity. *Covariates in the stepwise linear regression models included age, sex, height, body mass index, diabetes, hypercholesterolemia, mean arterial pressure, heart rate, descending aortic diameter, use of vasodilators, diuretics and β-blockers. Estimated $R^2$ was 0.15 for model 1 and 0.13 for models 2 and 3, respectively.
### Table S3. Independent Determinants of Carotid Diastolic/Systolic Flow Index

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient ± SE</th>
<th>Standardized coefficient</th>
<th>Partial $r^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic reverse/forward flow ratio, %</td>
<td>0.17 ± 0.05</td>
<td>0.20</td>
<td>0.040</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.09 ± 0.04</td>
<td>0.14</td>
<td>0.019</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>0.14 ± 0.04</td>
<td>0.21</td>
<td>0.046</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>−0.23 ± 0.05</td>
<td>−0.27</td>
<td>0.072</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of β-blockers</td>
<td>−5.21 ± 1.56</td>
<td>−0.18</td>
<td>0.033</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Abbreviations are the same as Table S2. Covariates in the stepwise linear regression model included age, sex, height, body mass index, diabetes, hypercholesterolemia, mean arterial pressure, heart rate, descending aortic diameter, carotid artery diameter, use of vasodilators, diuretics, β-blockers, and aortic reverse/forward flow ratio. Model $R^2$ was 0.18.
Figure S1. Representative example of ensemble-averaged carotid artery flow velocity waveform. $V_{S\text{max}}$ indicates systolic maximum (peak) velocity; $V_{D\text{max}}$, diastolic maximum (peak) velocity; $V_{\text{ED}}$, end-diastolic velocity; $S$, systolic velocity pulse height; $D$, diastolic velocity pulse height. Diastolic/systolic flow index (D/S index) was calculated as follows: D/S index = $D \div S \times 100 = \frac{|V_{S\text{max}} - V_{\text{ED}}|}{|V_{D\text{max}} - V_{\text{ED}}|} \times 100$ (%).
Figure S2. Bland-Altman histogram of relationship between carotid diastolic flow peak time ($T_{\text{Dmax}}$) and aortic reverse flow peak time ($T_{\text{Rev}}$). The x-axis indicates the mean (ie, $[T_{\text{Dmax}}+T_{\text{Rev}}]/2$); y-axis, difference (ie, $T_{\text{Dmax}}-T_{\text{Rev}}$); z-axis, observation numbers. The 2SD of difference was 0.08 s.