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Cross-sectional Associations of Flow Reversal, Vascular Function, and Arterial Stiffness in the Framingham Heart Study

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Abstract

Objective—Experimental studies link oscillatory flow accompanied by flow reversal to impaired endothelial cell function. The relation of flow reversal with vascular function and arterial stiffness remains incompletely defined.

Approach and Results—We measured brachial diastolic flow patterns along with vasodilator function in addition to tonometry-based central and peripheral arterial stiffness in 5708 participants (age 47±13 years, 53% women) in the Framingham Heart Study Offspring and Third Generation cohorts. Brachial artery diastolic flow reversal was present in 35% of participants. In multivariable regression models, the presence of flow reversal was associated with lower flow-mediated dilation (3.9±0.2 vs. 5.0±0.2%, $P<0.0001$) and reactive hyperemic flow velocity (50±0.99 vs 57±0.93 cm/s, $P<0.0001$). The presence of flow reversal (compared to absence) was associated with higher central aortic stiffness (carotid-femoral pulse wave velocity 9.3±0.1 vs. 8.9±0.1 m/s), lower muscular artery stiffness (carotid-radial pulse wave velocity 9.6±0.1 vs. 9.8±0.1 m/s) and higher forearm vascular resistance (5.32±0.03 vs. 4.66±0.02 log dyne · s⁻¹ · cm⁻⁵), ($P<0.0001$). The relations of diastolic flow velocity with flow-mediated dilation, aortic stiffness and forearm vascular resistance were nonlinear with a steeper decline in vascular function associated with increasing magnitude of flow reversal.

Conclusions—In our large, community-based sample, brachial artery flow reversal was common and associated with impaired vasodilator function and higher aortic stiffness. Our findings are consistent with the concept that flow reversal may contribute to vascular dysfunction.

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Disclosures

The other authors report no conflicts.

Keywords

vascular function; epidemiology; endothelium; arterial stiffness

INTRODUCTION

Arterial blood flow is pulsatile in nature. Experimental studies demonstrate that endothelial cell phenotype and vascular function are strongly influenced by local shear stress, the frictional force exerted by flowing blood.^{1, 2} Blood flow can be either laminar or turbulent. Atherosclerosis preferentially develops at regions of disturbed flow, and this observation has been attributed to the effects of flow reversal on the vascular endothelium.^{3–6} Unidirectional laminar flow with pulsatility maintains endothelial health and suppresses inflammatory and thrombotic processes.^{7–9} Conversely, episodic flow reversal impairs nitric oxide production and generates a pro-atherogenic gene expression profile.^{10–12} In peripheral arteries, diastolic flow reversal may be present and is more prevalent with aging and sedentary behaviors.^{13–16}

Arterial stiffness may influence flow patterns, and increased stiffness of the central aorta has been proposed to be a determinant of flow reversal in peripheral arteries.^{17–20} Prior human studies suggest that induction of flow reversal acutely reduces endothelial vasomotor function.^{21–24} Therefore, we sought to investigate whether flow reversal in the brachial artery relates to measures of endothelial function, including flow-mediated dilation and hyperemic flow. Further, we examined the association of brachial flow reversal and aortic and peripheral arterial stiffness and forearm vascular resistance.

MATERIALS AND METHODS

Materials and methods are available in the online-only Data Supplement.

RESULTS

Participant Characteristics

The study sample included 5708 participants, mean age 47±13 years, 53% women. Clinical characteristics and vascular measures are shown in Table 1. Diastolic flow reversal was present in 35% of the participants. Representative examples of flow velocity waveforms are illustrated in Figure 1 showing an individual with unidirectional flow (Panel A) and flow reversal (Panel B).

Clinical Correlates of Flow Reversal

Clinical correlates of diastolic flow reversal in age- sex- and cohort- adjusted and multivariable-adjusted models are presented in Table 2. Increasing age and female sex were associated with higher prevalence of flow reversal. Among women there was a modest association of menopause with a lower prevalence of flow reversal in age-adjusted models, which becomes non-significant in multivariable adjusted models. Several cardiovascular disease risk factors, including higher heart rate, higher body mass index, higher total/HDL cholesterol ratio, and smoking were associated with a lower prevalence of flow reversal.

Participating in the walk test prior to vascular testing was associated with a lower prevalence of flow reversal.

Association of Flow Reversal with Vasodilator Function

To gain insight into the association of flow reversal with endothelial function, we compared mean values of vascular measures between participants with and without diastolic flow reversal. We used linear regression models adjusted for age, sex and cohort initially, and additionally adjusted for clinical covariates, including mean arterial pressure, heart rate, body-mass index, total/HDL cholesterol ratio, triglycerides, glucose, diabetes, current smoking, hypertension treatment, lowering lipid treatment, walk test, and prevalent CVD (Table 3). Both flow-mediated dilation and reactive hyperemia were lower in individuals with flow reversal compared to individuals without flow reversal. Further, we evaluated the continuous relation of diastolic flow and vasodilator measures using multivariable-adjusted spline analyses with knots at the 20th, 50th (0cm/s) and 80th percentiles of diastolic flow velocity (Figure 2). Lower diastolic flow velocity was associated with lower flow-mediated dilation; however, the relation was non-linear ($p<0.0001$). Greater degrees of flow reversal were associated with a steep decline in flow-mediated dilation. In contrast, the difference in flow-mediated dilation was more gradual with increasingly positive diastolic flow velocity (Figure 2A). A similar pattern was observed for reactive hyperemia (Figure 2B). Further, the association of diastolic flow velocity with flow-mediated dilation adjusted for hyperemic flow showed the same pattern (Figure I in the online-only Data Supplement).

As shown in Table 4, the associations of diastolic flow velocity with flow-mediated dilation and with hyperemic flow velocity were stronger in the presence of flow reversal compared to no flow reversal.

Further, there was evidence of effect modification by diastolic flow reversal of the association between hyperemic flow velocity and flow-mediated dilation (P-value for interaction=0.03). As shown in Figure 3, the presence of diastolic flow reversal is associated with lower flow-mediated dilation function for both individuals with high and low hyperemic flow. These findings suggest that the association of flow reversal and flow-mediated dilation is not simply reflective of lower stimulus for dilation.

Association of Flow Reversal with Arterial Stiffness

In multivariable models adjusting for clinical covariates, central aortic stiffness measured by carotid femoral pulse wave velocity was higher in individuals with flow reversal compared to individuals without flow reversal (Table 3). In spline analysis, the relation of diastolic flow velocity with carotid femoral pulse wave velocity was also non-linear (Figure 4). Increasingly negative diastolic flow velocity was associated with marked increase in carotid femoral pulse wave velocity consistent with greater aortic stiffness. The difference in carotid femoral pulse wave velocity was minimal with increasingly positive diastolic flow velocity above the median. As shown in Table 4, the association of diastolic flow velocity with carotid-femoral pulse wave velocity was stronger in the presence of flow reversal compared to no flow reversal.

In contrast, muscular artery stiffness measured by carotid radial pulse wave velocity was lower in the presence of flow reversal (Table 3). In spline analysis, the relation of diastolic flow velocity with carotid radial pulse wave velocity was also non-linear (Figure 4B). More negative diastolic flow velocity was associated with lower carotid radial pulse wave velocity consistent with lower muscular artery stiffness. The difference in carotid radial pulse wave velocity was minimal with increasingly positive diastolic flow velocity above the median. As shown in Table 4, the association of diastolic flow velocity with carotid-radial pulse wave velocity was stronger in the presence of flow reversal compared to no flow reversal.

Association of Flow Reversal with Vascular Resistance

Peripheral artery resistance may contribute to flow reversal. In both minimally and multivariable adjusted models, baseline forearm vascular resistance (FVR) was higher in individuals with flow reversal when comparing with individuals with non-reversal flow (Table 3). In spline analysis, the relation of diastolic flow velocity with forearm vascular resistance was non-linear (Figure 4). Greater degrees of flow reversal were associated with markedly higher FVR. As shown in Table 4, the association of diastolic flow velocity with FVR was stronger in the presence of flow reversal compared to no flow reversal. In age-, sex- and cohort-adjusted analyses, there was not a significant correlation of carotid-radial pulse wave velocity (partial $r=-0.013$, $P=0.31$).

DISCUSSION

In the present study, we investigated the relations of flow patterns in the brachial artery with vasodilator function and arterial stiffness. In a community-based study, we observed that flow reversal during diastole was present in more than a third of participants. In models adjusting for conventional risk factors, we noted that the presence of diastolic flow reversal was related to lower vasodilation in both the conduit brachial artery and forearm microcirculation. Diastolic flow reversal was associated with impaired flow-mediated dilation in individuals with low or high reactive hyperemic responses suggesting an independent association with conduit vasodilator function. Further, we demonstrated that an increasing magnitude of flow reversal was associated with a greater decrease in vasodilator function. Flow reversal related to higher carotid femoral pulse wave velocity and higher forearm vascular resistance, consistent with the possibility that reduced central arterial compliance alters flow patterns in the peripheral arteries. Conversely, muscular arterial stiffness was lower in the presence of flow reversal. Thus, our findings indicate that flow reversal in peripheral arteries is accompanied by vascular dysfunction and aortic stiffening.

Extensive experimental evidence links local flow disturbance to altered endothelial cell properties.² Multiple studies in cell culture and animal models have shown that oscillatory flow induces a pathologic endothelial state and flow reversal suppresses endothelial nitric oxide synthase expression and activation as well increases oxidative stress.^{4, 25–28} Prior human studies suggest an impact of flow patterns on endothelial vasodilator function. In coronary arteries, endothelial dysfunction is more pronounced at branch points, regions characterized by flow turbulence.²⁹ External counterpulsation therapy in patients with coronary artery disease improved flow-mediated dilation potentially through reduction of

brachial flow reversal in diastole.³⁰ Importantly, intervention studies by Thijssen et al provide compelling evidence that flow reversal impacts endothelial function acutely and over a two-week period.^{21, 23} In healthy volunteers, manipulation of brachial artery blood flow and shear to generate acute flow reversal lead reduced flow-mediated dilation.²³ Further, augmentation of retrograde flow with a compression sleeve worn for two weeks reduced flow-mediated dilation in young but not old men.²¹ Reduction of retrograde flow is related to the endothelial benefit of exercise interventions.^{31, 32} The association of flow reversal with vascular function and arterial stiffness in a community-based sample remains uncertain.

The current study evaluates flow reversal and vascular function in a large, unselected sample with comprehensive risk factor assessment. Flow-mediated dilation is a key physiologic regulator of blood flow that occurs in response to acute changes in shear stress through endothelial release of nitric oxide and other vasodilators.³³ Reactive hyperemia reflects microvessel dilation produced by ischemia-mediated vasodilator generation including nitric oxide.^{34–36} By evaluating average diastolic flow, we identified that more than a third of the participants had evidence of flow reversal, with mean diastolic flow 0. Consistent with prior reports, advancing age was associated with higher prevalence of flow reversal.^{13–15} Interestingly several cardiovascular risk factors were associated with a lower prevalence of flow reversal higher total/HDL cholesterol ratio, smoking and higher body mass index. We have previously demonstrated that a similar set of cardiovascular risk factors was associated with higher baseline forearm flow and reduced FVR potentially reflecting resting vasodilation or microvascular remodeling.^{36–39} Similarly, female sex was previously associated with lower resting flow and we now report a higher prevalence of flow reversal.³⁷ Higher resting flow with lower FVR may limit flow reversal.

We observed that brachial flow reversal was associated with impaired flow-mediated dilation and reactive hyperemia even after adjusting for risk factors suggesting that local flow dynamics alter vascular function. In addition, flow reversal was associated with impaired flow-mediated dilation both in individuals with low and high hyperemic responses consistent with an association flow reversal with endothelial dysfunction. Our findings support the possibility that flow reversal influences vascular function. Alternatively, abnormal endothelial function may contribute to the generation of diastolic flow reversal.¹⁴

Arterial stiffness may influence flow patterns in peripheral arteries. In the present study we observed elevated aortic stiffness in association with brachial flow reversal supporting an intersection of central arterial structure and peripheral arterial dynamics. Under physiological conditions, elastic recoil of the aorta helps maintain forward flow in peripheral arteries during diastole. Stiffening of the central aorta tends to increase systolic flow amplitude and induce diastolic flow reversal in the periphery.^{16, 40} Furthermore, several studies have suggested that elevated aortic stiffness may lead to increased peripheral resistance and have detrimental effects on microvessel structure and function that may augment flow reversal in the periphery.^{36, 37} Alternatively endothelial dysfunction may promote arterial stiffness that in turn influences peripheral flow patterns.^{41, 42} Central flow patterns in the aorta were not measured in the current study thus the contribution of aortic flow reversal to aortic stiffness cannot be assessed. However, prior studies indicate a

contribution of endothelial nitric oxide to functional aortic stiffness that may account for the association of carotid femoral pulse wave velocity with peripheral flow reversal.⁴¹ The cross-sectional nature of the present study precludes a precise determination of the temporal sequence of central arterial stiffening, endothelial dysfunction, and peripheral flow reversal. However, the observed association of carotid femoral pulse wave velocity and flow reversal is consistent with an intersection of central aortic properties and peripheral flow patterns.

Stiffness of the brachial artery may alter the effects of flow on the endothelium. We observed divergent patterns in the association of central and muscular artery stiffness with arterial flow patterns. In the presence of flow reversal, lower peripheral stiffness was associated with a greater degree of flow reversal; however, in the absence of flow reversal, there was no association between diastolic flow velocity and carotid-radial pulse wave velocity. Our finding of lower peripheral artery stiffness in the presence of flow reversal suggests complex interrelations of regional stiffness, flow patterns, and vascular function. In experimental models, local compliance modulates the effects of oscillatory flow on endothelial phenotype.⁴³ Circumferential stretch of the arterial wall, which occurs during systole, and relates to higher arterial distensibility, is associated with increased oxidative stress.¹⁴ Further, a stiffened central aorta accompanied by compliant muscular arteries permits increased forward wave penetration that may damage the microcirculation thereby augmenting resting flow reversal.^{37, 40, 44} Importantly, peripheral conductance measure as forearm vascular resistance does not associate with peripheral stiffness, confirming that forearm vascular resistance is largely determined at the arterial level. Thus, it appears that flow reversal is associated with higher small vessel resistance potentially related to microvascular vasodilator dysfunction (indicated by lower reactive hyperemia) but not with higher muscular artery stiffness. Lower muscular artery stiffness may promote small vessel damage by transmission of pulsatile forces into the microcirculation.³⁷

Several limitations of the current study must be considered. The study design is cross-sectional. Thus, the directionality of the associations between flow patterns, endothelial function, and arterial stiffness cannot be determined. It is likely that flow patterns both alter and are altered by vasomotor function. However, the present study cannot evaluate the temporal sequence of these changes. We based our evaluation of diastolic flow patterns on mean diastolic flow velocity and did not measure minimum diastolic flow. Therefore, participants with transient, lesser degrees of diastolic flow reversal may have been assigned to the no flow reversal group. We would expect that misclassification of flow reversal would tend to make associations with vascular function measures more difficult to detect. Further, the spline analysis using diastolic flow velocity as a continuous measure confirmed the findings of the categorical analysis. The cohort consists of predominantly white participants potentially limiting generalizability to other racial and ethnic groups. Prior studies have suggested variability in flow-mediated dilation across the menstrual cycle and the scheduling of participant visits was not timed to menstrual cycle that may have introduced variability into the vascular measurements. Based on scheduling, some of the participants had a walk test performed prior to vascular testing that may influence flow patterns. We included an adjustment for this parameter in multivariable modeling. Given the community-based study design, we did not withhold medications or administer nitroglycerin to assess endothelium-independent vasodilation.

In summary, we provide evidence supporting a link between peripheral artery flow reversal and vascular function. Our observations are consistent with the hypothesis that flow reversal may influence endothelial function and impair vasodilator capacity. Taken together, our findings highlight flow reversal as an emerging vascular measure that relates to both central arterial stiffness and vasodilator function. Future longitudinal studies are required to evaluate the potential contribution of flow patterns to the risk for hypertension and cardiovascular events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Dr Mitchell is owner of Cardiovascular Engineering, Inc., a company that designs and manufactures vascular stiffness measurement devices.

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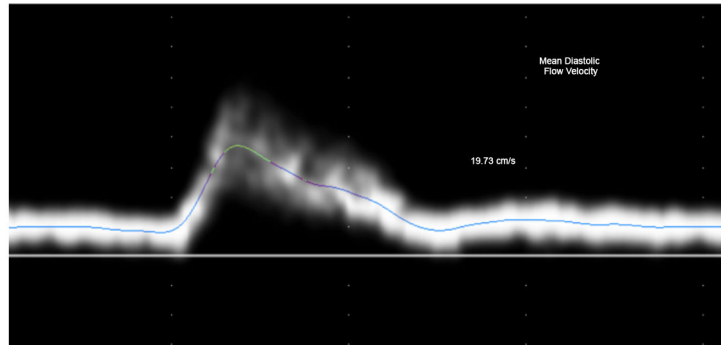
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Highlights

- Retrograde flow impairs endothelial cell function and phenotype. Arterial stiffness may contribute to peripheral flow reversal.
- We measured brachial diastolic flow patterns in a large community-based cohort. Flow reversal was present in more than a third of the participants and associated with advancing age.
- Greater degrees of flow reversal were associated with reduced flow-mediated dilation and reactive hyperemia flow velocity consistent with conduit and small vessel endothelial dysfunction.
- Brachial artery flow reversal was associated with higher central aortic stiffness, lower muscular artery stiffness and higher forearm vascular resistance.
- Our findings support a link between flow reversal in the peripheral arteries with impaired vascular function and higher central arterial stiffness, and are consistent with the hypothesis that flow reversal may contribute to endothelial dysfunction and impair vasodilator capacity.

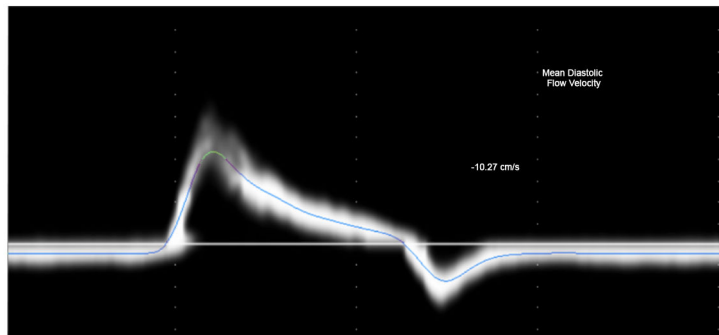
A

Non-flow reversal



B

Flow reversal

**Figure 1.**

A. Representative flow velocity tracing from a participant with no flow reversal B. Representative flow velocity tracing from a participant with flow reversal.

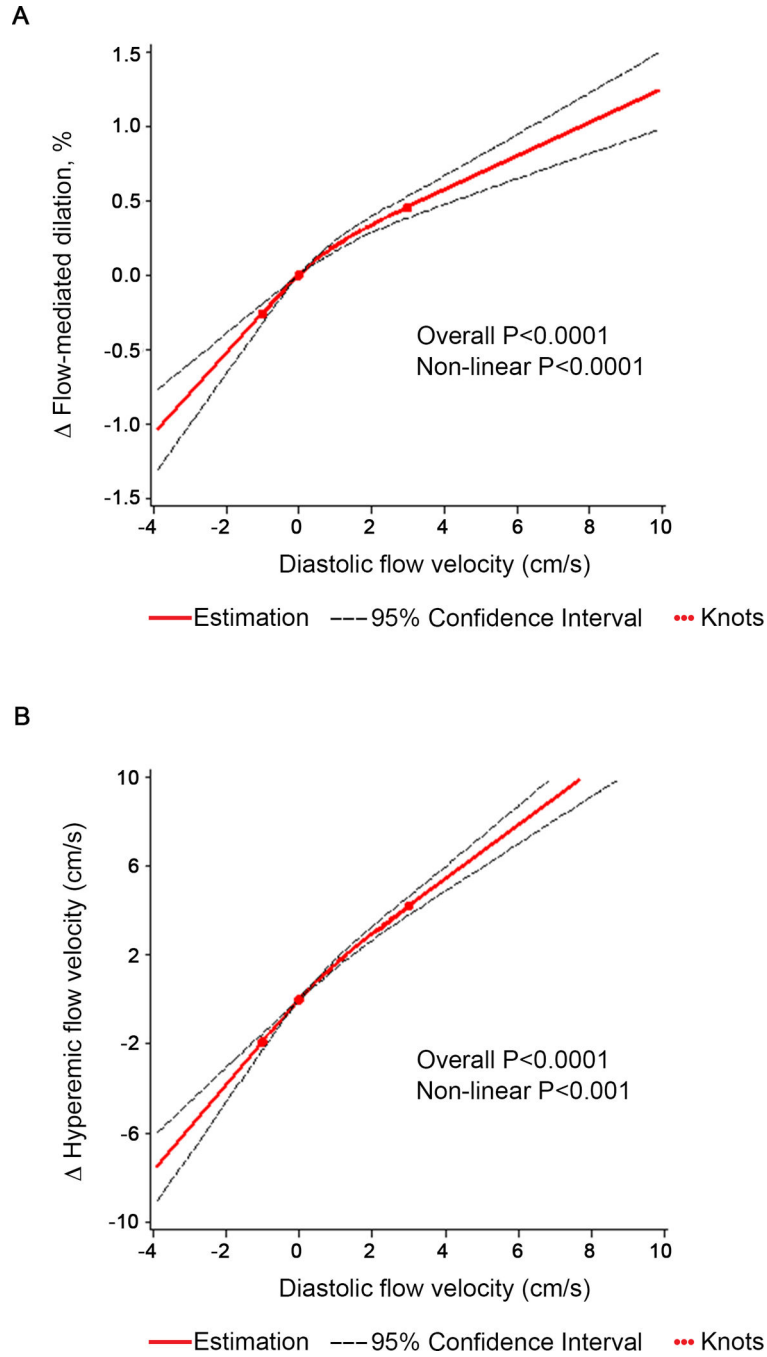


Figure 2. Multivariable-adjusted association of diastolic flow velocity and vasodilator measures (flow-mediated dilation and hyperemic flow velocity) using restricted cubic splines with 3 knots at diastolic flow velocity at the 20th, 50th, and 80th percentile. Analyses were based on the entire cohort; for visual display the range of mean diastolic flow shown on the x-axis was limited to the 5th to 95th percentile. The y-axis represents the difference in vasodilator response. The solid line shows the association of mean diastolic flow velocity and vasodilator measures. The dashed lines represent the 95% confidence interval.

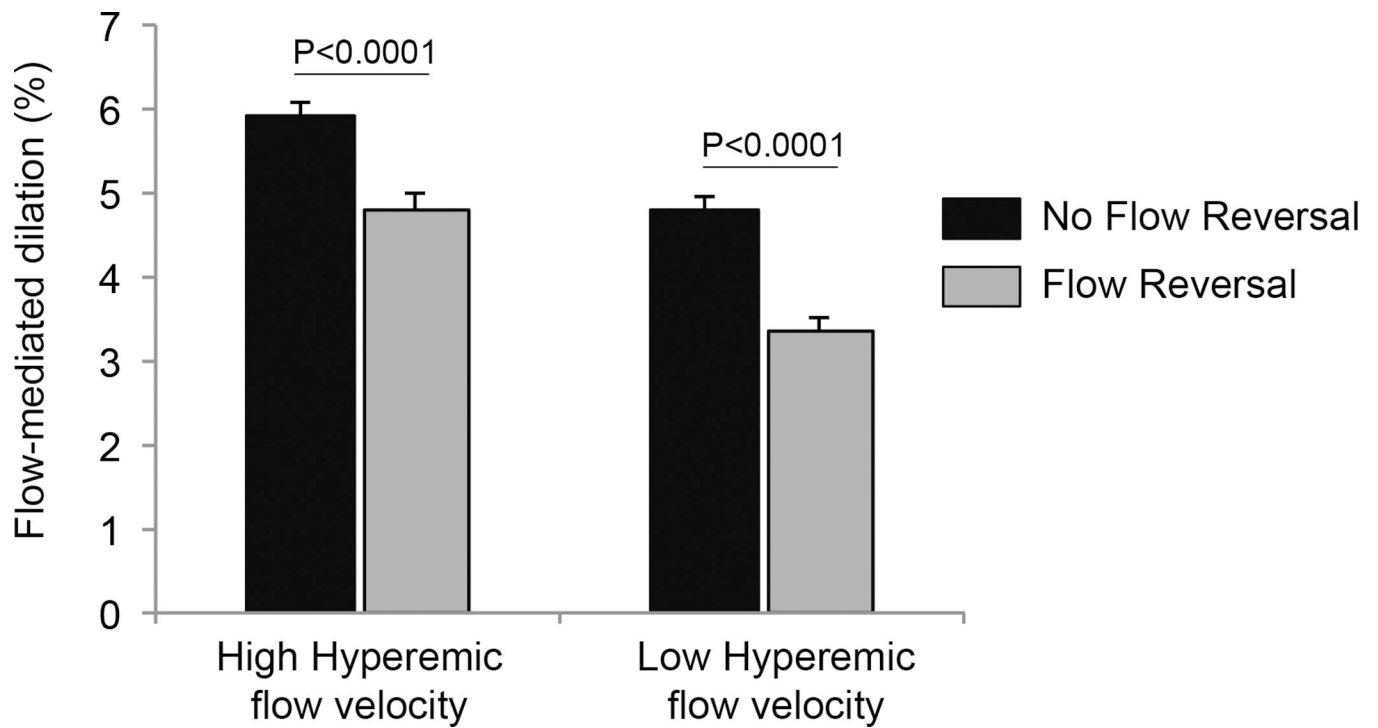


Figure 3. Multivariable adjusted least square means with standard error of flow-mediated dilation in high and low hyperemic flow velocity categories according to presence or absence of flow reversal. The hyperemic flow velocity categories are defined as high (hyperemic flow velocity above the overall median = 58 cm/s), and low (hyperemic flow velocity below the overall median < 58 cm/s).

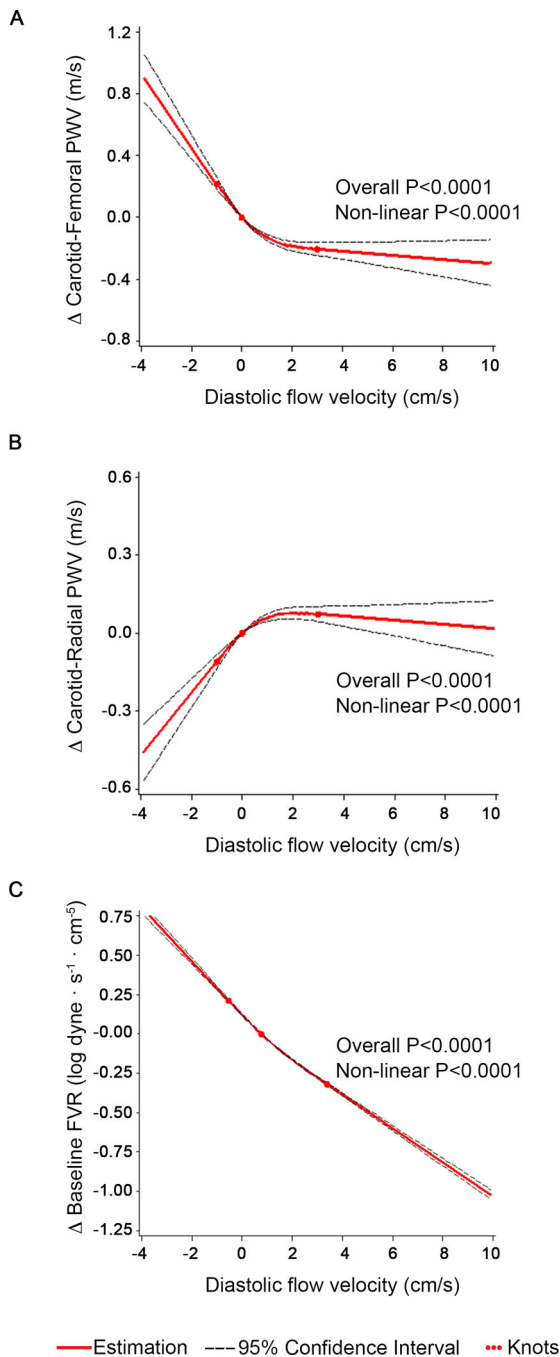


Figure 4.

Multivariable-adjusted association of diastolic flow velocity with arterial stiffness and resistance measures (carotid-femoral pulse wave velocity, carotid-radial pulse wave velocity and forearm vascular resistance) using restricted cubic splines with 3 knots at diastolic flow velocity at 20th, 50th, and 80th percentiles. Analyses were based on the entire cohort; for visual display the range of mean diastolic flow velocity shown on the x-axis was limited to the 5th to 95th percentile. The y-axis represents the difference in arterial stiffness measures or forearm vascular resistance respectively. The solid line shows the association of mean

diastolic flow velocity and stiffness and resistance measures. The dashed lines represent the 95% confidence interval.

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Table 1

Participant Characteristics and Vascular Measures

Characteristic	Offspring	Third Generation	Overall
	N= 2038	N = 3670	N = 5708
Clinical measures			
Age, years	61 ± 9	40 ± 9	47 ± 13
Female, %	54	52	53
Systolic blood pressure, mmHg	127 ± 19	116 ± 14	120 ± 17
Diastolic blood pressure, mmHg	74 ± 10	75 ± 10	75 ± 10
Heart rate, beats per minute	64 ± 11	62 ± 9	63 ± 10
Body mass index, kg/m ²	27.4 ± 4.5	26.5 ± 5.0	26.8 ± 4.9
Total/HDL cholesterol	4.0 ± 1.3	3.8 ± 1.4	3.8 ± 1.4
Triglycerides, mg/dl	134 ± 90	114 ± 89	121 ± 90
Glucose, mg/dl	103 ± 26	95 ± 18	98 ± 22
Diabetes, %	12	3	6
Smoking, %	13	17	16
Hypertension, %	44	15	26
Hormone replacement therapy, % women	37	5	16
Menopause, % women	85	14	40
Treatment of hypertensive, %	32	8	16
Treatment of Lowering-cholesterol, %	20	7	12
Walk test Before, %	39	0	14
Prevalent CVD, %	12	1	5
Vascular measures			
Baseline brachial diameter, mm	4.2 ± 0.9	4.1 ± 0.8	4.2 ± 0.8
Flow-mediated dilation, %	2.9 ± 2.8	5.9 ± 3.7	4.8 ± 3.7
Baseline Flow velocity, cm/s	8.05 ± 4.8	7.3 ± 4.2	7.6 ± 4.4
Hyperemic Flow velocity, cm/s	51.1 ± 21.5	62.1 ± 18.3	58.2 ± 20.2
Carotid-Femoral PWV, m/s	10.0 ± 3.5	7.0 ± 1.4	8.1 ± 2.8
Carotid-Radial PWV, m/s	10.1 ± 1.5	9.5 ± 1.5	9.7 ± 1.5
Flow reversal, %	54	24	35
Baseline FVR (log dyne · s ⁻¹ · cm ⁻⁵)	4.87 ± 0.73	4.99 ± 0.68	4.95 ± 0.7

Continuous variables expressed as mean ± sd

PWV: pulse wave velocity

FVR: forearm vascular resistance

Table 2

Relations of Flow Reversal with Clinical Characteristics

Characteristic	Flow Reversal			
	Age-Sex-Cohort		Multivariable	
	OR (95% CI)*	P	OR (95% CI)	P
Age	2.60 (2.36, 2.87)	<0.0001	2.79 (2.51, 3.09)	<0.0001
Sex, female vs. male	3.44 (3.03, 3.92)	<0.0001	2.94 (2.53, 3.40)	<0.0001
Mean arterial blood pressure	0.85 (0.79, 0.90)	<.0001	--	--
Heart rate	0.83 (0.77, 0.88)	<0.0001	0.90 (0.84, 0.96)	0.003
BMI	0.83 (0.77, 0.88)	<0.0001	0.63 (0.59, 0.68)	<0.0001
Total/HDL cholesterol	0.75 (0.69, 0.81)	<0.0001	0.90 (0.83, 0.98)	0.01
Triglycerides, mg/dL	0.80 (0.74, 0.86)	<0.0001	--	--
Fasting glucose, mg/dL	0.88 (0.82, 0.94)	0.0003	--	--
Diabetes	0.94 (0.73, 1.20)	0.61	--	--
Smoking	0.41 (0.34, 0.49)	<0.0001	0.39 (0.32, 0.48)	<0.0001
Hormone Replacement Therapy	0.86 (0.69, 1.07)	0.17	--	--
Menopause, yes vs no	0.74 (0.58, 0.96)	0.021	0.81 (0.62, 1.06)	0.12
Hypertension treatment	0.79 (0.67, 0.94)	0.009	--	--
Walk Test	0.71 (0.59, 0.87)	0.0007	0.69 (0.56, 0.84)	0.0003
Lipid lowering treatment	0.95 (0.78, 1.16)	0.61	--	--
Prevalent CVD	1.35 (1.03, 1.78)	0.03	--	--

* OR = odds ratio; CI = Confidence interval.

Continuous variables expressed per 1 SD change; see table 1 for SD values

Table 3

Relations of Vascular Measures with Brachial Artery Flow Reversal

Measurement	Age-Sex-Cohort				Multivariable*				
	Flow Reversal		Flow Reversal		Flow Reversal		Flow Reversal		
	Yes N=1994	No N=3714	Yes N=1994	No N=3714	Yes N=1994	No N=3714	Yes N=1994	No N=3714	
	LSM (SE)**	LSM(SE)	P	LSM (SE)	LSM(SE)	P	LSM (SE)	LSM(SE)	P
Baseline brachial diameter, mm	4.11 (0.01)	4.22 (0.01)	<0.0001	4.16 (0.03)	4.20 (0.03)	<0.01	4.16 (0.03)	4.20 (0.03)	<0.01
Flow-mediated dilation, %	3.9 (0.08)	4.9 (0.06)	<0.0001	3.9 (0.17)	5.0 (0.16)	<0.0001	3.9 (0.17)	5.0 (0.16)	<0.0001
Hyperemic Flow velocity, cm/s	53 (0.46)	60 (0.33)	<0.0001	50 (0.99)	57 (0.93)	<0.0001	50 (0.99)	57 (0.93)	<0.0001
Carotid-Femoral PWV***, m/s	8.3 (0.05)	8.1 (0.04)	0.0016	9.3 (0.10)	8.9 (0.09)	<0.0001	9.3 (0.10)	8.9 (0.09)	<0.0001
Carotid-Radial PWV, m/s	9.5 (0.03)	9.8 (0.02)	<0.0001	9.6 (0.07)	9.8 (0.06)	<0.0001	9.6 (0.07)	9.8 (0.06)	<0.0001
Baseline FVR (resting), (log dyne · s ⁻¹ · cm ⁻⁵)	5.38 (0.01)	4.64 (0.01)	<0.0001	5.32 (0.03)	4.66 (0.02)	<0.0001	5.32 (0.03)	4.66 (0.02)	<0.0001

* Multivariable model adjusted for age, sex, cohort, mean arterial pressure, heart rate, body-mass index, total/high density lipoprotein cholesterol ratio, triglycerides, glucose, diabetes, current smoking, hypertension treatment, lowering lipid treatment, walk test (before), prevalent CVD.

** LSM = least squares mean, SE = standard error.

*** PWV = pulse wave velocity.

Table 4

Multivariable-Adjusted Association of Diastolic Flow Velocity with Vascular Function Measures by Flow Reversal Status

	Flow Reversal		No Flow Reversal		P [‡]
	Est. β^* (SE)	P	Est. β (SE)	P	
Flow-mediated dilation, %	0.23 (0.04)	<0.0001	0.13 (0.01)	<0.0001	0.04
Hyperemic flow velocity, cm/s	1.87 (0.23)	<0.0001	1.27 (0.08)	<0.0001	0.02
Carotid femoral PWV δ , m/s	-0.26 (0.02)	<0.0001	-0.02 (0.02)	0.004	<0.0001
Carotid radial PWV, m/s	0.14 (0.02)	<0.0001	-0.01 (0.01)	0.62	<0.0001
Log baseline FVR (resting), (dyne · s ⁻¹ · cm ⁻⁵)	-0.15 (0.01)	<0.0001	-0.12 (0.01)	<0.0001	<0.0001

Multivariable model adjusted for age, sex, cohort, mean arterial pressure, heart rate, body mass index, total/hdl cholesterol ratio, triglycerides, glucose, diabetes, current smoking, hypertension treatment, lowering lipid treatment, hormone replacement therapy, walk test (before), prevalent CVD.

* β -represents the slopes of outcome variable versus diastolic flow velocity.

[‡] Difference in β estimates comparing flow reversal to no flow reversal ($\beta = \beta$ (no flow) - β (flow)).

[‡] For comparison of β for the association of diastolic flow velocity with vascular measures for flow reversal compared to no flow reversal, from test of Ho: $\beta = 0$.

δ PWV denotes pulse wave velocity