Arterial Stiffness and Risk of Overall Heart Failure, Heart Failure With Preserved Ejection Fraction, and Heart Failure With Reduced Ejection Fraction

The Health ABC Study (Health, Aging, and Body Composition)

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Abstract—Higher arterial stiffness is associated with increased risk of atherosclerotic events. However, its contribution toward risk of heart failure (HF) and its subtypes, HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF), independent of other risk factors is not well established. In this study, we included Health ABC study (Health, Aging, and Body Composition) participants without prevalent HF who had arterial stiffness measured as carotid–femoral pulse wave velocity (cf-PWV) at baseline (n=2290). Adjusted Cox-proportional hazards models were constructed to determine the association between continuous and data-derived categorical measures (tertiles) of cf-PWV and incidence of HF and its subtypes (HFpEF [ejection fraction >45%] and HFrEF [ejection fraction ≤45%]). We observed 390 HF events (162 HFpEF and 145 HFrEF events) over 11.4 years of follow-up. In adjusted analysis, higher cf-PWV was associated with greater risk of HF after adjustment for age, sex, ethnicity, mean arterial pressure, and heart rate (hazard ratio [95% confidence interval] for cf-PWV tertile 3 versus tertile 1 [ref] =1.35 [1.05–1.73]). However, this association was not significant after additional adjustment for other cardiovascular risk factors (hazard ratio [95% confidence interval], 1.14 [0.88–1.47]). cf-PWV velocity was also not associated with risk of HFpEF and HFrEF after adjustment for potential confounders (most adjusted hazard ratio [95% confidence interval] for cf-PWV tertile 3 versus tertile 1 [ref]: HFpEF, 1.06 [0.72–1.56]; HFrEF, 1.28 [0.83–1.97]). In conclusion, arterial stiffness, as measured by cf-PWV, is not independently associated with risk of HF or its subtypes after adjustment for traditional cardiovascular risk factors. **(*Hypertension*. 2017;69:267-274. DOI: 10.1161/HYPERTENSIONAHA.116.08327.)** • **Online Data Supplement**

Key Words: arterial stiffness ■ ejection fraction ■ heart failure ■ hypertension ■ pulse wave velocity

Heart failure (HF) is a significant public health problem that affects an estimated 5.7 million American adults and is associated with increased morbidity, mortality, and health-care cost.[1,2] Despite important advances in medical and device therapies over the past 2 decades, outcomes associated with HF remain poor, highlighting the need for effective preventive strategies.[3,4]

An important first step in HF prevention is to identify the intermediate at-risk phenotypes that play a constitutive role in pathogenesis of HF and may be targeted with novel preventive therapies. Previous studies have demonstrated that progression from at-risk to symptomatic HF stage occurs through a series of intermediate cardiac phenotypes characterized by left ventricular (LV) remodeling (ie, concentric LV hypertrophy and eccentric LV hypertrophy), changes in systolic function (ie, ejection fraction [EF] and strain), and diastolic function.[5–11] Recently, there has also been an interest in characterizing the contribution of abnormal vascular remodeling with increased arterial stiffness and LV afterload toward development of HF and its 2 subtypes, HF with preserved EF (HFpEF) and HF with reduced EF (HFrEF).[12–15]

Higher carotid–femoral pulse wave velocity (cf-PWV), a well-established measure of arterial stiffness, is associated with increased risk of atherosclerotic cardiovascular disease

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(CVD) and mortality.[16–19] Furthermore, cross-sectional studies have demonstrated higher arterial stiffness among HF patients compared with hypertensive adults.[12,20–24] However, the contributions of increased arterial stiffness, independent of other established risk factors, on the risk of incident HF and its subtypes are not well established. This is largely because of conflicting findings from previous cohorts and lack of adequate power to assess HFpEF and HFrEF outcomes.[19,25] In this study, we evaluated the association between measures of cf- PWV and risk of HF, HFpEF, and HFrEF in a community-based cohort of well-functioning older adults.

Methods

Study Population

The Health ABC study (Health, Aging, and Body Composition) is a prospective cohort study of community-dwelling older adults that evaluated the impact of changes in weight and body composition on age-related physiological and functional changes. The details of the study design, participant eligibility criteria, and recruitment strategy have been reported previously.[26] Briefly, well-functioning adults aged 70 to 79 years who were free of life-threatening illnesses and could perform daily activities of living without difficulty were recruited between March 1987 and July 1998 from a random sample of white and all black Medicare beneficiaries residing around Pittsburgh and Memphis. The study participants underwent detailed examination at baseline and subsequent annual follow-up visits for first 6 years. Participants also had detailed telephone interviews every 6 months. All study participants provided written informed consent. Institutional Review Boards at the University of Tennessee and University of Pittsburgh approved the study protocols. Of the 3075 participants who were initially enrolled in the Health ABC study, baseline measures of cf-PWV were available in 2488 participants. For the present study, we further excluded 111 participants with prevalent HF and 87 participants with missing covariates of interest at baseline. The final study population consisted of 2290 participants. The baseline characteristics of study participants with versus without cf-PWV measures have been compared previously.[19]

Health ABC Baseline Examination and Covariate Definitions

Details about baseline examination, laboratory tests protocols, and variable definitions for the Health ABC study have been described previously.[26–28] Information on demographic characteristics, including age, sex, ethnicity, education level, smoking, and alcohol use, was self-reported. Prevalent comorbidities such as diabetes mellitus and hypertension were assessed based on self-reported physician diagnosis and confirmed by use of specific medications, or positive examination, or laboratory tests. Exercise and physical activity levels were also self-reported and estimated in kilocalories per week using a standardized questionnaire.[29] Prevalent CVD included coronary heart disease (CHD) identified based on history of myocardial infarction, angina, or coronary revascularization; cerebrovascular disease identified based on history of stroke, transient ischemic attack, or carotid endarterectomy; or peripheral vascular disease identified by history of intermittent claudication or peripheral vascular procedures.

Assessment of Central Arterial Stiffness

cf-PWV, a gold-standard measure of arterial stiffness,[30] was measured noninvasively using a well-established, highly reproducible technique that has been reported previously.[19,31] Higher measures of cf-PWV reflect higher central arterial stiffness. Nondirectional transcutaneous Doppler flow probes (model 810A, 9.0- to 10.0-MHz Probes; Parks Medical Electronics, Inc) were used to obtain Doppler flow signals from right carotid and femoral arteries. For each participant, the data were recorded for 3 runs, each with at least 10 pairs of simultaneous flow waves, and then averaged. A metal tape was used to measure the distance between the ipsilateral carotid and femoral artery above the body surface. cf-PWV was calculated as the ratio of the distance between the carotid and femoral arteries and the time differential between the onset of flow at carotid and femoral (defined as foot of the pressure tracing at each site) sites. The National Institute on Aging, Laboratory of Cardiovascular Science, Gerontology Research Center (Baltimore, MD) trained and certified all study personnel before data collection, read the waveforms, and evaluated data quality. As reported previously, cf-PWV measures demonstrated high degree of reproducibility with an interclass correlation coefficient of 0.88 between sonographers and 0.84 between readers.[32]

Heart Failure Outcomes Assessment

The study participants were contacted every 6 months to obtain information about interval adverse cardiovascular events.[26] Incident HF was identified by hospitalizations related to HF among participants without prevalent HF at baseline. The HF diagnosis was clinically adjudicated and confirmed based on the review of index hospitalization records using criteria similar to those from the Cardiovascular Health Study.[33] These criteria required a physician diagnosis of HF with documentation of HF symptoms and signs, supportive radiological findings, and medical therapy for HF, including use of a diuretic agent and either digitalis or vasodilator or β-blocker.[34] A subset of HF cases had EF data available, which was used to identify cases of incident HFpEF (EF >45%) and HFrEF (EF ≤45%).[35] The EF cutoff used for HFpEF and HFrEF diagnosis is consistent with that used in other longitudinal cohort studies and large-scale randomized controlled trials on HFpEF patients.[36–39]

Statistical Analysis

The study participants were stratified into tertiles of baseline measures of cf-PWV. Descriptive analyses were performed, and data are presented as mean (standard deviation) for continuous and percentage for categorical variables. Baseline clinical and demographic characteristics were compared across the 3 groups using the Chi-square test for categorical variables and Kruskal–Wallis test for continuous variables. Nelson-Aalen estimates of the cumulative hazard function were plotted to assess and compare the unadjusted cumulative risk of overall HF, HFpEF, and HFrEF across the cf-PWV tertiles. Multivariable adjusted Cox-proportional hazards models were constructed to determine the association between categorical (tertiles) and continuous measures of cf-PWV and different HF outcomes with adjustment for the following covariates: model 1—age and sex; model 2—model 1+ethnicity, heart rate, and mean arterial pressure; model 3—model 2+body mass index, prevalent CHD, antihypertensive use, education status, diabetes mellitus status, smoking, drinking status, physical activity, and renal function. Systolic blood pressure was not included as a covariate in the adjusted models because it is often a consequence of arterial stiffness in the pathogenesis of HF. Separate models were constructed for overall HF, HFpEF, and HFrEF outcomes. Proportional hazards assumption of the Cox models was assessed and satisfied for the study outcomes. Death was treated as a censoring event in these models. Owing to the skewed distribution of cf-PWV in the study population, the variable was log-transformed for continuous Cox-proportional hazards models.

A sensitivity analysis was performed treating death as a competing risk, with additional adjustment for incident CHD on follow-up as a time varying covariate in model 3. Sensitivity analyses were also performed excluding participants with baseline CVD and without adjustment for heart rate and antihypertensive use because these characteristics may have a more mediatory role in the relationship between cf-PWV and incident HF. All statistical analyses were performed using SATA version 12 (Stata Corp, College Station, TX).

Results

We included 2290 participants in our study (53% women and 35% blacks). The baseline characteristics of the study participants are compared across tertiles of cf-PWV in Table 1. Higher cf-PWV was associated with black race, prevalent CVD, and prevalent CVD risk factors (hypertension and diabetes mellitus). Blood pressure, resting heart rate, and body mass index were also significantly higher among participants with higher cf-PWV. We observed 390 incident HF events over a median follow-up of 11.4 years, of which 41.5% were HFpEF, 37.2% were HFrEF, and 21.3% were unclassified HF.

Association Between cf-PWV Categories and Risk of Overall HF

In unadjusted comparisons, higher cf-PWV was associated with increased risk of HF (*P* value <0.0001; Figure 1), with the highest risk among tertile 3 participants. The cumulative hazard function curves indicate a threshold effect between tertiles 2 and 3 for HF risk. Table 2 shows the multivariable adjusted association between categorical measures of cf-PWV and risk of HF. After adjustment for age and sex, higher measures of cf-PWV were significantly associated with higher risk of HF (model 1). This association was slightly attenuated but remained significant after additional adjustment for ethnicity, heart rate, and mean arterial blood pressure (model 2). Further adjustment for additional risk factors attenuated this relationship significantly, such that cf-PWV was no longer associated with HF risk (model 3)

Association Between cf-PWV Categories and Risk of HF Subtypes

In unadjusted analysis, higher cf-PWV was associated with higher risk of both HFpEF and HFrEF (*P* value: 0.02 for both; Figure 2), with the highest risk among tertile 3 participants. In adjusted analysis, higher cf-PWV was significantly associated with higher risk of HFrEF and HFpEF after adjustment for age and sex (model 1; Table 3). This association attenuated significantly and was no longer significant after further adjustment for ethnicity, heart rate, mean arterial blood pressure (model 2; Table 3), and other risk factors (model 3; Table 3).

Association Between Continuous Measures of cf-PWV and Risk of HF Outcomes

The continuous association between cf-PWV and risk of HF, HFpEF, and HFrEF were assessed in separate Cox-proportional hazards models using log-transformed measures of cf-PWV. We observed a progressive attenuation in the association between cf-PWV and risk of HF, HFpEF, and HFrEF, with sequential adjustment for potential confounders, similar to that observed in categorical analysis. Higher cf-PWV was not associated with risk of HF outcomes in the most adjusted model (Figure 3). Furthermore, no significant interaction was observed between participant characteristics, such as body mass index, physical activity levels, and cf-PWV for risk of HF (*P* interaction >0.2 for all; Figure S1 in the online-only Data Supplement).

Sensitivity Analysis

Sensitivity analysis was performed to evaluate the association between measures of cf-PWV and risk of HF among participants without CVD at baseline and without adjustment for potential mediator characteristics, including hypertension status and heart rate, in the final model. The pattern of association between cf-PWV and risk of HF in this subgroup was not different from that of the overall study population, such that higher measures of cf-PWV were not significantly associated with HF risk after adjustment for potential confounders (hazard ratio [95% confidence interval] per $\log_2$ higher cf-PWV =1.12 [0.89–1.42]; Table S1).

Of the 2290 participants included in the analysis, 1027(44.8%) died during follow up. In sensitivity analysis treating death as a competing risk with additional adjustment for incident CHD as a time-varying covariate, categorical and continuous measures of cf-PWV were not significantly associated with risk of HF outcomes (Table S2).

Discussion

In the present study of community-dwelling elderly individuals, we observed that higher cf-PWV was associated with greater risk of overall HF and its subtypes, HFpEF and HFrEF.

Table 1. Baseline Characteristics of the Study Participants Across Pulse Wave Velocity Tertiles

Subject Characteristics	Tertile 1 (N=758); Low cf-PWV	Tertile 2 (N=764)	Tertile 3 (N=768); High cf-PWV	*P* Value
Age, y	73.4 (2.8)	73.8 (2.9)	73.9 (2.9)	<0.01
African Americans	35%	40%	43%	0.01
Body mass index, kg/m^2	26.5 (4.5)	27.6 (4.6)	27.8 (4.9)	<0.01
Systolic BP, mm Hg	131 (19)	136 (20)	142 (22)	<0.01
Hypertension	38%	49%	61%	<0.01
Antihypertensive use	43%	54%	63%	<0.01
CVD	23%	25%	29%	<0.01
Diabetes mellitus	9%	14%	21%	0.01
Physical activity kcal/kg per week	87.9 (66.5)	84.7 (71.3)	78.4 (70.4)	0.03
Heart rate, bpm	63 (10)	66 (11)	67 (12)	<0.01
Pulse wave velocity, cm/s	566.6 (91.4)	812.3 (75.2)	1329.7 (389.0)	NA

Data presented as mean (SD) or %. BP indicates blood pressure; cf-PWV, carotid femoral pulse wave velocity; CVD, cardiovascular disease; and NA, not applicable.

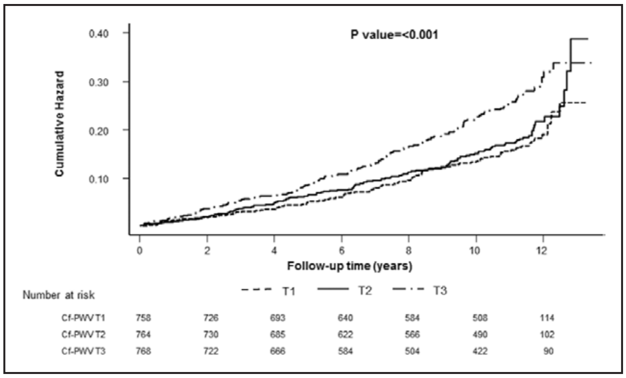

Figure 1. Cumulative risk of heart failure across different carotid–femoral pulse wave velocity–based study groups (cf-PW T1 through T3).

However, these associations were attenuated substantially after adjustment for CVD and its risk factors. Taken together, our study findings suggest that the association between vascular remodeling and increased arterial stiffness, as measured by cf-PWV, and HF risk in older adults may be related to the burden of coexistent CVD or risk factors.

Higher measures of arterial stiffness have been associated with greater risk of major adverse cardiovascular events, including MI, incident coronary artery disease, and mortality.[16–19] A previous analysis from the Health ABC study with 181 HF events demonstrated no association between cf-PWV and HF risk, even in unadjusted analysis.[19] In contrast, in the present study with 390 HF events, we observed significant inverse association after adjustment for age, sex, ethnicity, blood pressure, and heart rate. This could be related to greater statistical power and higher number of HF events in the present analysis.

The association between arterial stiffness, as measured by cf-PWV, and HF risk has been explored in other cohort studies. Chirinos et al[40] demonstrated that higher measures of cf-PWV were associated with greater risk of HF in a cohort of chronic kidney disease patients. Recently, in a secondary analysis from the FHS (Framingham Heart Study), Tsao et al[25] demonstrated a significant association between cf-PWV and HF risk (hazard ratio [95% confidence interval], 1.29 [1.02–1.64]; *P* value =0.04). Findings in our study are in contrast to that from Tsao et al[25] and could be related to several factors. First, there are significant differences in the population characteristics that may influence the observed associations between measures of arterial stiffness and HF risk. The FHS population is relatively younger and racially/ethnically homogenous as compared with the Health ABC study population. Second, the multivariable adjusted model by Tsao et al[25] did not account for many potential confounders, including heart rate, renal function, and physical activity levels. Thus, the observed association between cf-PWV and HF risk may be related to residual confounding. It is noteworthy that the association between cf-PWV and HF in the age- and sex-adjusted models was not different between the 2 studies. Finally, as noted previously, there were differences in the cf-PWV assessment methods between the Health ABC and FHS.[41] It is unclear if these differences in cf-PWV measurements may have influenced the study findings because its association with other cardiovascular outcomes is not different between the 2 cohorts.

Availability of EF information from index HF hospitalization in a substantial proportion of HF patients allowed us to evaluate the association between arterial stiffness and risk of HF subtypes, HFpEF and HFrEF. In age- and sex-adjusted models, cf-PWV was more strongly associated with HFrEF risk as compared with HFpEF risk. However, these associations were substantially attenuated and not significant after adjustment for blood pressure, heart rate, and other potential confounders. Tsao et al[25] had evaluated the association between cf-PWV and HF subtypes in the FHS and observed stronger association for HFrEF than for HFpEF, similar to our study findings. However, their study was limited in statistical power, with only 77 HFpEF and 61 HFrEF events. The present study with 162 HFpEF and 147 HFrEF events adds significantly to the existing literature, with adequate power to evaluate the association between cf-PWV and risk of HF subtypes.

Previous cross-sectional studies have reported higher arterial stiffness among patients with HFpEF as compared with hypertensive control patients.[12,20,42] However, there were significant differences in age, sex distribution, and other clinical characteristics that may have lead to the observed differences. In the present study, we observe that the contributions of arterial stiffness, as measured by cf-PWV, beyond differences in traditional risk factors toward risk of HF subtypes are not significant. Our findings are supported by the cross-sectional observations from Lam et al[43] who demonstrated that after adjustment for age, sex, and body size, measures of arterial stiffness were similar among HFpEF patients and hypertensive control participants.

It is noteworthy that the lack of association between cf-PWV and HF risk may not be generalizable to other measures of pulsatile hemodynamic afterload, such as reflected wave magnitude, aortic impedance, and total arterial compliance. Reflected waves and late systolic load have been associated

Table 2. Adjusted Association Between Categorical Measures of Pulse Wave Velocity and Risk of Heart Failure

Multivariable Adjusted Models	Hazard Ratio (95% CI), Tertile 1	Hazard Ratio (95% CI), Tertile 2	Hazard Ratio (95% CI), Tertile 3
Model 1: age and sex adjusted	Ref	1.09 (0.84–1.42)	1.55 (1.21–1.98)
Model 2: age, sex, ethnicity, heart rate, and MAP adjusted	Ref	1.00 (0.76–1.29)	1.35 (1.05–1.73)
Model 3: age, sex, ethnicity, heart rate, MAP, BMI, CHD, education status, anti-HTN use, diabetes mellitus, smoking, drinking status, physical activity, and renal function adjusted	Ref	0.88 (0.68–1.14)	1.14 (0.88–1.47)

Anti-HTN indicates antihypertensive medication; BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; and MAP, mean arterial pressure.

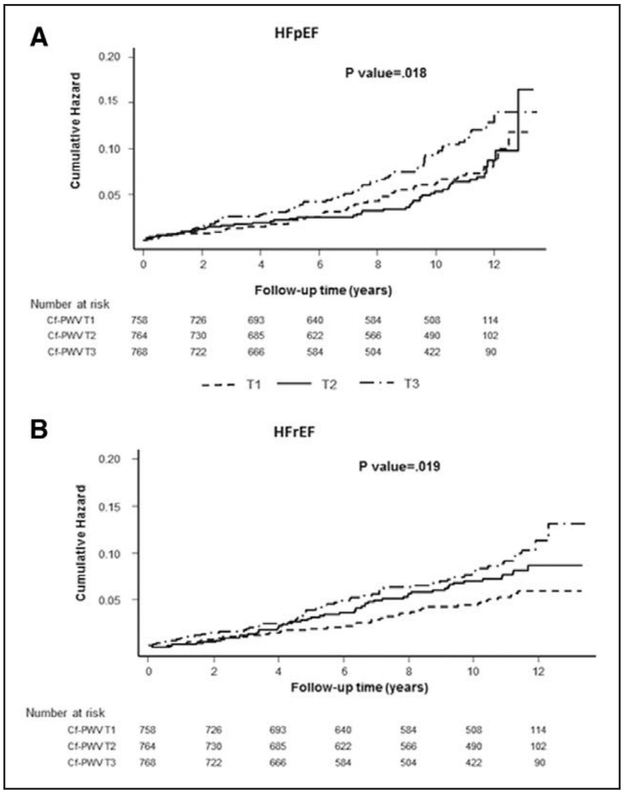

Figure 2. Cumulative risk of heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) across different carotid–femoral pulse wave velocity–based study groups (cf-PW T1 through T3).

with diastolic dysfunction and adverse myocardial remodeling in animal studies.[44,45] Similarly, several cross-sectional studies in humans have demonstrated the significant contribution of reflected waves and aortic characteristic impedance to LV systolic and diastolic dysfunction.[46–48] Furthermore, in a recent longitudinal cohort study among participants of the MESA (Multi-Ethnic Study of Atherosclerosis), Chirinos et al[49] demonstrated an independent association between reflection wave magnitude and incident HF risk. Future studies are needed to better assess the effects of afterload (reflected waves, aortic impedance, and total arterial compliance) measured directly via pressure flow relations on the risk of incident HF among older individuals.

Our study findings have important clinical implications. The higher incidence of HF outcomes among patients with elevated cf-PWV seems to be related to greater burden of CVD and its risk factors in these patients. Thus, higher arterial stiffness is an intermediate phenotype observed in at-risk individuals, but it may not contribute to development of HF, independent of other risk factors. Higher cf-PWV may be useful to identify individuals who are at increased risk of HF development and may benefit from aggressive risk factor modification. This is consistent with the hypothesis recently proposed by Paulus et al,[50] in which risk factors and comorbidity were identified as the primary determinants of HFpEF pathophysiology through their inflammatory effects.

Several important issues must be considered in regards to the overall null findings in our study. These include possibility of type II error, measurement of the exposure variable and outcomes of interest, and other potential biases. The large number of events (390 HF events) observed in our study ensures adequate statistical power to evaluate the association between cf-PWV and HF risk. Thus, a type II error is less likely in our study. The measures of cf-PWV in the Health ABC study are well established and previously validated.[19,32] Furthermore, cf-PWV has been shown to be strongly associated with cardiovascular mortality and CHD outcomes in the Health ABC cohort, similar to other population-based cohorts.[17–19] It is possible that the observed lack of association is related to the older age and higher burden of CVD and its risk factors in our study population. The strong associations of prevalent CVD and risk factors with HF risk in this older study cohort could mask our ability to observe an independent association for cf-PWV. Finally, there is a potential for survival bias in our study of older adults, such that individuals who were more susceptible to higher arterial stiffness–related HF risk or other adverse cardiovascular events may not have survived or met the eligibility criteria

Table 3. Adjusted Association Between Categorical Measures of Pulse Wave Velocity and Risk of HFpEF and HFrEF

Multivariable Adjusted Models	Hazard Ratio (95% CI), Tertile 1	Hazard Ratio (95% CI), Tertile 2	Hazard Ratio (95% CI), Tertile 3
HFpEF			
Model 1: age and sex adjusted	Ref	0.91 (0.61–1.36)	1.46 (1.01–2.11)
Model 2: age, sex, ethnicity, HR, and MAP adjusted	Ref	0.84 (0.56–1.26)	1.30 (0.89–1.89)
Model 3: age, sex, ethnicity, HR, MAP, BMI, baseline CHD, education status, anti-HTN use, diabetes mellitus, smoking, drinking status, physical activity, and renal function adjusted	Ref	0.72 (0.48–1.09)	1.06 (0.72–1.56)
HFrEF			
Model 1: age and sex adjusted	Ref	1.39 (0.91–2.14)	1.78 (1.17–2.70)
Model 2: age, sex, ethnicity, HR, and MAP adjusted	Ref	1.21 (0.78–1.86)	1.49 (0.98–2.27)
Model 3: age, sex, ethnicity, HR, MAP, BMI, CHD, education status, anti-HTN use, diabetes mellitus, smoking, drinking status, physical activity, and renal function adjusted	Ref	1.11 (0.72–1.71)	1.28 (0.83–1.97)

Anti-HTN indicates antihypertensive medication; BMI, body mass index; CD, coronary heart disease; CHD, coronary heart disease; CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; and MAP, mean arterial pressure.

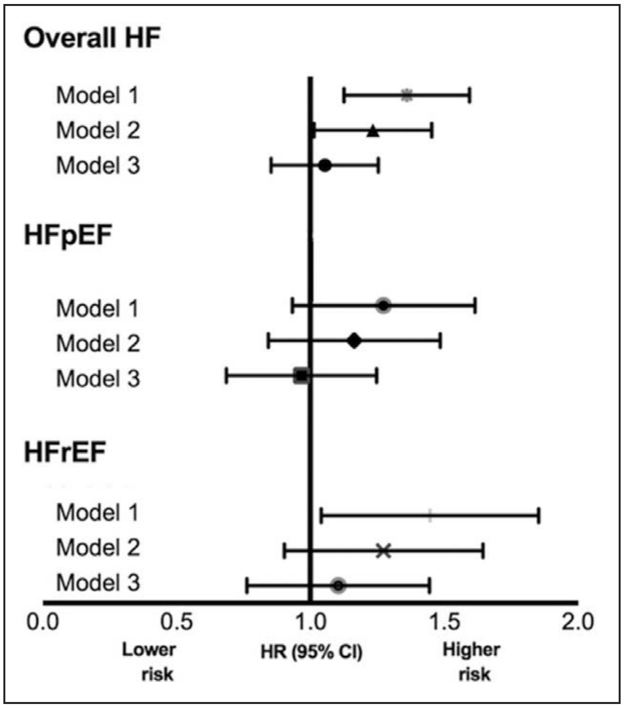

Figure 3. Continuous association between log-transformed carotid–femoral pulse wave velocity (cf-PWV) measures and risk of heart failure (HF), heart failure with preserved ejection fraction (HFpEF), and heart failure with reduced ejection fraction (HFrEF) in different multivariable adjusted Cox models. Model 1 is adjusted for age and sex. Model 2 is additionally adjusted for ethnicity, heart rate, and mean arterial blood pressure. Model 3 is adjusted for model 2 covariates+body mass index, prevalent cardiovascular disease, education status, antihypertensive use, diabetes mellitus, smoking, drinking status, physical activity, and renal function. CI indicates confidence interval; and HR, hazard ratio.

to be included in this study. Thus, the associations between arterial stiffness and HF risk may be stronger in a middle-age population.

Several other limitations to our study are noteworthy. The study population included older community-dwelling adults of black and white race, and our study findings may not be generalizable to younger population and other race/ethnicities. HF adjudication was based on inpatient hospitalization, and thus, we may have missed a proportion of HF events that were diagnosed in outpatient visits. Furthermore, we do not have baseline echocardiographic assessment in our study participants, and therefore, individuals with asymptomatic LV dysfunction or other cardiac structural abnormalities may have been included in the analysis.

Perspectives

We have demonstrated in a community-based sample of well-functioning older adults that higher arterial stiffness, as measured by cf-PWV, is not independently associated with increased risk of HF or its subtypes after adjustment for prevalent CVD and risk factors. These findings suggest that higher cf-PWV-associated risk of HF is largely mediated by coexistent disease or traditional risk factors. Future studies are needed to determine whether these findings are generalizable to other measures of LV afterload.

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Novelty and Significance

What Is New?

- Higher measures of arterial stiffness, as measured by carotid–femoral pulse wave velocity, identify individuals at greater risk of heart failure. However, this is largely related to the higher burden of established cardiovascular disease and its risk factors.

What Is Relevant?

- Higher carotid–femoral pulse wave velocity may be an intermediate phenotype observed in at-risk individuals, but it does not contribute to development of heart failure independent of other risk factors.
- Individuals with higher carotid–femoral pulse wave velocity may benefit from aggressive risk factor modification to lower heart failure risk.

Summary

Higher carotid–femoral pulse wave velocity is not independently associated with increased risk of heart failure in older individuals after adjusting for traditional risk factors. This observation is consistent in individuals with, as well as without, prevalent coronary artery disease. Future studies are needed to determine the contribution of other measures of left ventricular afterload toward heart failure risk in older individuals.

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Arterial Stiffness and Risk of Overall Heart Failure, Heart Failure With Preserved Ejection Fraction, and Heart Failure With Reduced Ejection Fraction: The Health ABC Study (Health, Aging, and Body Composition)

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SUPPLEMENTARY DATA

Arterial Stiffness and risk of Overall Heart Failure, Heart Failure with Preserved Ejection Fraction, and Heart Failure with Reduced Ejection Fraction: The Health ABC Study

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Table S1: Association between categorical and continuous measures of carotid-femoral pulse wave velocity and risk of heart failure among participants without cardiovascular disease at baseline

Outcome	Hazard Ratio (95% CI) Cf-PWV Tertile 1	Hazard Ratio (95% CI) Cf-PWV Tertile 2	Hazard Ratio (95% CI) Cf-PWV Tertile 3		Hazard Ratio (95% CI) per Log 2 higher Cf-PWV
Heart Failure	Ref.	0.81 (0.58 – 1.13)	1.11 (0.81 – 1.53)		1.12 (0.89 – 1.42)

Model adjusted for age, sex, mean arterial pressure, body mass index, education status, diabetes, smoking, drinking status, physical activity, and renal function

Separate multivariable adjusted models were constructed for categorical and continuous measures of pulse wave velocity

Table S2: Association between categorical and continuous measures of carotid-femoral pulse wave velocity and risk of heart failure outcomes after additional adjustment for interval incidence of coronary heart disease and treating death as a competing risk.

Outcome	Hazard Ratio (95% CI) Tertile 1	Hazard Ratio (95% CI) Tertile 2	Hazard Ratio (95% CI) Tertile 3	Hazard Ratio (95% CI) per Log 2
Overall HF	Ref.	0.88 (0.68-1.15)	1.06 (0.82-1.37)	1.04 (0.85-1.26)
HFpEF	Ref.	0.72 (0.48-1.09)	0.96 (0.64-1.42)	0.92 (0.66-1.28)
HFrEF	Ref.	1.12 (0.72-1.74)	1.15 (0.74-1.79)	1.04 (0.79-1.37)

HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction.

Separate multivariable adjusted models were constructed for categorical and continuous measures of pulse wave velocity and for each HF outcome

Models adjusted for age, sex, ethnicity, heart rate, mean arterial blood pressure, Body mass index, coronary heart disease at baseline, education status, anti-HTN use, diabetes, smoking, drinking status, physical activity, renal function, incident coronary heart disease on follow-up as a time varying covariate, and death as a competing risk

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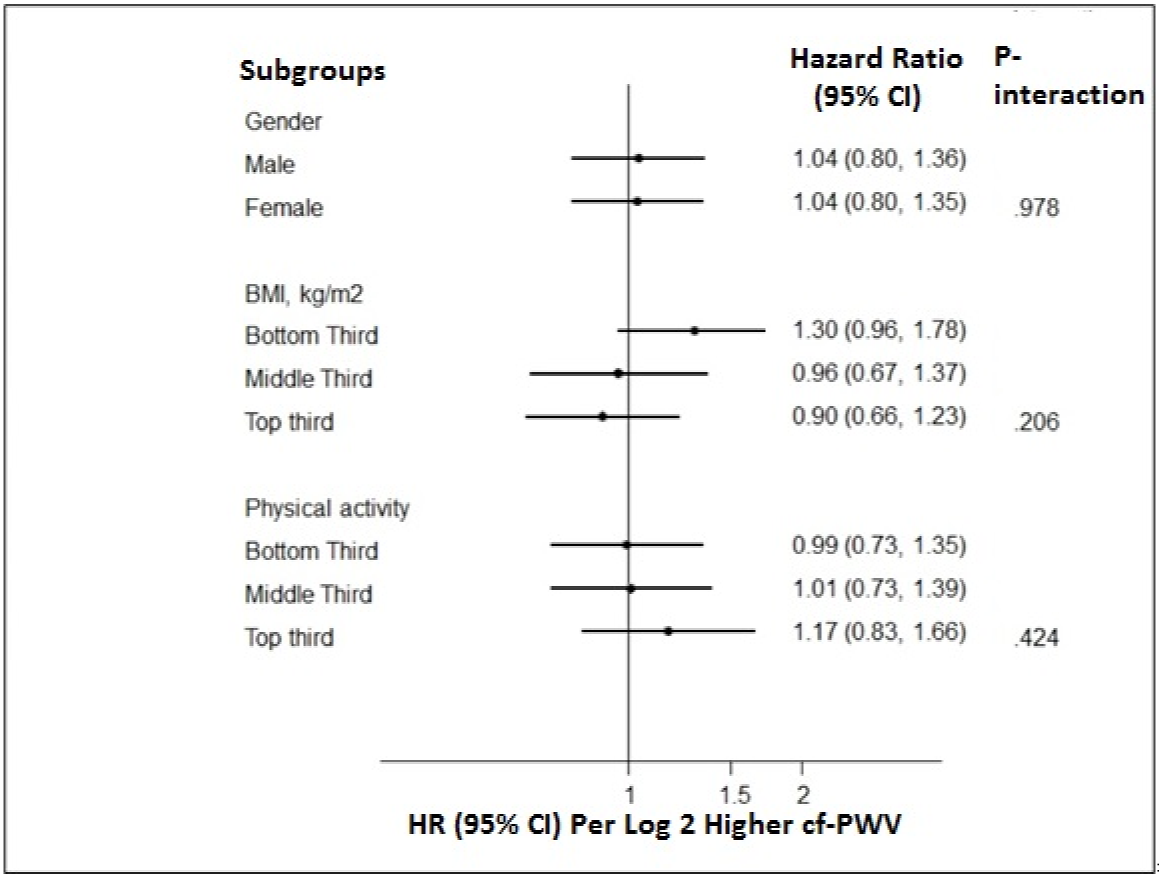
Figure S1: Subgroup analysis showing the association between carotid-femoral pulse wave velocity and risk of heart failure across sex, body mass index, and physical activity categories.



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Rigidez arterial y riesgo de insuficiencia cardíaca global, insuficiencia cardíaca con preservación de la fracción de eyección e insuficiencia cardíaca con reducción de la fracción de eyección

Estudio de salud ABC (Salud, envejecimiento y composición corporal)

Ambarish Pandey,* Hassan Khan,* Anne B. Newman, Edward G. Lakatta, Daniel E. Forman, Javed Butler, Jarett D. Berry

Resumen—La rigidez arterial más alta se asocia con mayor riesgo de eventos ateroscleróticos. Sin embargo, no está bien establecida su contribución al riesgo de insuficiencia cardíaca (IC) y sus subtipos: IC con preservación de la fracción de eyección (ICpFE) e IC con reducción de la fracción de eyección (ICrFE), independientemente de otros factores de riesgo. En este estudio, incluimos a los participantes del Estudio de Salud ABC (Salud, envejecimiento y composición corporal) sin IC prevalente, que presentaban rigidez arterial medida por la velocidad de la onda de pulso carotídeo-femoral (cf-PWV) al inicio del estudio (n = 2290). Se crearon modelos de riesgos proporcionales de Cox para determinar la asociación entre medidas continuas y categóricas derivadas de los datos (terciles) de cf-PWV e incidencia de IC y sus subtipos (ICpFE [fracción de eyección > 45%] e ICrFE [fracción de eyección ≤ 45%]). Observamos 390 eventos de IC (162 eventos de ICpFE y 145 de ICrFE) en 11.4 años de seguimiento. En el análisis ajustado, la cf-PWV más alta se asoció con mayor riesgo de IC tras el ajuste por edad, sexo, etnicidad, presión arterial media e insuficiencia cardíaca (razón de riesgos instantáneos [intervalo de confianza del 95%] para el tercil 3 de cf-PWV frente al tercil 1 [ref] = 1,35 [1,05-1,73]). Sin embargo, esta asociación no fue significativa después del ajuste adicional por otros factores de riesgo cardiovascular (razón de riesgos instantáneos [intervalo de confianza del 95%], 1,14 [0,88-1,47]). La cf-PWV tampoco se asoció con el riesgo de ICpFE ni de ICrFE después del ajuste por posibles factores de confusión (razón de riesgos instantáneos más ajustada [intervalo de confianza del 95%] para el tercil 3 de cf-PWV frente al tercil 1 [ref]: ICpFE, 1,06 [0,72-1,56]; ICrFE, 1,28 [0,83-1,97]). En conclusión, la rigidez arterial, medida por cf-PWV, no se asocia de manera independiente con riesgo de IC o de sus subtipos tras el ajuste por factores de riesgo cardiovascular tradicionales. **(Hypertension. 2017;69:267-274. DOI: 10.1161/HYPERTENSIONAHA.116.08327.) • Suplemento de datos en línea**

Palabras clave: rigidez arterial ■ fracción de eyección ■ insuficiencia cardíaca ■ hipertensión ■ velocidad de la onda de pulso

La insuficiencia cardíaca (IC) es un problema de salud pública significativo que se estima que afecta a 5,7 millones de estadounidenses adultos y se asocia con mayor morbilidad, mortalidad y costo de asistencia sanitaria.[1,2] Pese a los avances importantes en los tratamientos médicos y con dispositivos de las últimas 2 décadas, los resultados asociados con IC continúan siendo pobres, lo que destaca la necesidad de estrategias preventivas eficaces.[3,4]

Un primer paso importante en la prevención de la IC consiste en identificar los fenotipos de riesgo intermedio que desempeñan un papel constitutivo en la patogenia de la IC y pueden ser dianas de nuevos tratamientos preventivos. Estudios previos han demostrado que la progresión del estadio de riesgo de IC a IC sintomática tiene lugar a través de una serie de fenotipos cardíacos intermedios caracterizados por remodelado ventricular izquierdo (VI) (es decir, hipertrofia VI concéntrica e hipertrofia VI excéntrica), cambios de la función sistólica (es decir, fracción de eyección [FE] y deformación) y función diastólica.[5-11] Recientemente, también ha habido interés en caracterizar la contribución del remodelado vascular anormal con mayor rigidez arterial y poscarga VI a la aparición de IC y sus 2 subtipos, IC con preservación de la FE (ICpFE) e IC con reducción de la FE (ICrFE).[12-15]

La velocidad de la onda de pulso carotídeo-femoral (cf-

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PWV) más alta, una medida bien confirmada de rigidez arterial, se asocia con mayor riesgo de enfermedad cardiovascular (ECV) aterosclerótica y mortalidad.[16-19] Más aún, estudios transversales han demostrado mayor rigidez arterial en pacientes con IC que en adultos hipertensos.[12,20-24] Sin embargo, no están bien establecidas las contribuciones de la mayor rigidez arterial, independientemente de otros factores de riesgo confirmados, al riesgo de IC incidente y sus subtipos. Esto se debe, en gran medida, a los resultados contradictorios de cohortes previas y la falta de potencia adecuada para evaluar las variables ICpFE y ICrFE.[19,25] En este estudio, evaluamos la asociación entre medidas de cf- PWV y riesgo de IC, ICpFE e ICrFE en una cohorte comunitaria de adultos mayores con buen funcionamiento.

Métodos

Población de estudio

El estudio de Salud ABC (Salud, Envejecimiento y Composición corporal) es un estudio prospectivo de cohortes de adultos mayores residentes en la comunidad, que evaluó la repercusión de las modificaciones de peso y composición corporal sobre cambios fisiológicos y funcionales. Se han comunicado antes los detalles sobre diseño del estudio, criterios de elegibilidad de los participantes y estrategia de reclutamiento.[26] En resumen, entre marzo de 1987 y julio de 1998, se reclutó a adultos de 70 a 79 años de edad, con buen funcionamiento, sin enfermedades potencialmente fatales y capaces de realizar sin dificultad las actividades de la vida cotidiana, a partir de una muestra aleatoria de individuos de raza blanca y todos los beneficiarios de raza negra de Medicare que residían en los alrededores de Pittsburgh y Memphis. Los participantes del estudio fueron sometidos a un examen detallado al inicio del estudio y en las visitas de seguimiento anuales ulteriores durante los primeros 6 años. También se realizaban entrevistas telefónicas detalladas cada 6 meses. Todos los participantes del estudio dieron consentimiento informado por escrito. Los Consejos de Revisión Institucional de la University of Tennessee y la University of Pittsburgh aprobaron los protocolos del estudio. De los 3075 participantes enrolados inicialmente en el estudio de Salud ABC, se dispuso de medidas iniciales de cf-PWV en 2488 participantes. Para el presente estudio, excluimos además a 111 pacientes con IC prevalente y a 87 participantes de quienes faltaban covariables del interés al inicio del estudio. La población final del estudio consistió en 2290 participantes. Las características basales de los participantes del estudio con medidas de cf-PWV frente a aquellos sin medidas de cf-PWV se han comparado previamente.[19]

Examen inicial de Salud ABC y definición de las covariables

Se han descrito antes los detalles acerca del examen inicial, los protocolos de pruebas de laboratorio y las definiciones de las variables para el estudio de Salud ABC.[26-28] La información sobre las características demográficas, como edad, sexo, etnicidad, nivel de educación, tabaquismo y consumo de alcohol, fue referida por el propio participante. Las enfermedades concomitantes prevalentes, como diabetes mellitus e hipertensión, se evaluaron sobre la base del diagnóstico del médico informado por el participante y se confirmaron por el uso de medicaciones específicas o exploración o pruebas de laboratorio positivas. Asimismo, los propios participantes comunicaron los niveles de ejercicio y actividad física, estimados en kilocalorías por semana, utilizando un cuestionario estandarizado.[29] La ECV prevalente incluyó enfermedad coronaria (EC), identificada en función de los antecedentes de infarto de miocardio, angina o revascularización coronaria; enfermedad cerebrovascular, identificada en función de los antecedentes de accidente cerebrovascular, ataque isquémico transitorio o endarterectomía carotídea; o enfermedad vascular periférica, identificada por los antecedentes de claudicación intermitente o procedimientos vasculares periféricos.

Evaluación de la rigidez arterial central

Se midió de manera no invasiva la cf-PWV, la medida de referencia de rigidez arterial,[30] utilizando una técnica bien establecida, muy reproducible, que se ha comunicado con anterioridad.[19,31] Las medidas más altas de cf-PWV reflejan mayor rigidez arterial central. Se utilizaron sondas de flujo Doppler transcutáneas, no direccionales (modelo 810A, 9.0- to 10.0-MHz Probes; Parks Medical Electronics, Inc) para obtener señales de flujo Doppler de la carótida derecha y las arterias femorales. En cada participante, se registraron datos para 3 corridas, cada una de las cuales con por lo menos 10 pares de ondas de flujo simultáneas que, después, se promediaron. Se utilizó una cinta metálica para medir la distancia entre la carótida y la arteria femoral homolaterales sobre la superficie corporal. La cf-PWV se calculó como la razón de la distancia entre las arterias carótida y femoral, y la diferencia de tiempo entre el comienzo del flujo en los sitios carotídeo y femoral (definida como pie del trazado de presión en cada sitio). El National Institute on Aging, Laboratory of Cardiovascular Science, Gerontology Research Center (Baltimore, MD) capacitó y certificó a todo el personal del estudio antes de la recolección de datos, leyó las formas de onda y evaluó la calidad de los datos. Como se comunicó antes, las medidas de cf-PWV demostraron alto grado de reproducibilidad con un coeficiente de correlación interclase de 0,88 entre ecografistas y de 0,84 entre lectores.[32]

Evaluación de los criterios de valoración de insuficiencia cardíaca

Se contactó cada 6 meses a los participantes del estudio para obtener información acerca de eventos cardiovasculares adversos en el intervalo.[26] Se identificó IC incidente por hospitalización relacionada con IC en participantes sin IC prevalente al inicio del estudio. El diagnóstico de IC se adjudicó clínicamente y se confirmó por la revisión de los registros de la hospitalización índice aplicando criterios similares a los del Estudio de Salud Cardiovascular.[33] Estos criterios exigían un diagnóstico de IC realizado por un médico, con documentación de los síntomas y signos de IC, hallazgos radiológicos confirmatorios y tratamiento médico de la IC, como uso de un diurético y digital o vasodilatador o β-bloquenate.[34] Se conocían datos de la FE de un subgrupo de casos de IC, que se utilizaron para identificar casos de ICpFE (FE > 45%) e ICrFE (FE ≤ 45%) incidentes.[35] El valor de corte de la FE utilizado para el diagnóstico de ICpFE e ICrFE es compatible con el empleado en otros estudios de cohortes longitudinales y estudios aleatorizados controlados en gran escala en pacientes con ICpFE.[36-39]

Análisis estadístico

Se estratificó a los participantes del estudio en terciles de medidas iniciales de cf-PWV. Se realizaron análisis descriptivos, y los datos se presentan como media (desviación estándar) para las variables continuas y como porcentajes para las variables categóricas. Se compararon las características clínicas y demográficas iniciales entre los 3 grupos mediante la prueba de Ji al cuadrado, para las variables categóricas, y la prueba de Kruskal–Wallis, para las variables continuas. Se graficaron las estimaciones de Nelson-Aalen de la función de riesgo acumulada para evaluar el riesgo acumulado no ajustado de IC global, ICpFE e ICrFE en todos los terciles de cf-PWV. Se crearon modelos de riesgos proporcionales de Cox multivariados para determinar la asociación entre medidas categóricas (terciles) y continuas de cf-PWV, y diferentes variables de IC, con ajuste por las siguientes covariables: modelo 1, edad y sexo; modelo 2, 1 + etnicidad, frecuencia cardíaca y presión arterial media; modelo 3, 2 + índice de masa corporal, EC prevalente, uso de antihipertensivos, nivel de educación, diabetes mellitus, tabaquismo, nivel de consumo alcohólico, actividad física y función renal. La presión arterial sistólica no se incluyó como covariable en los modelos ajustados, porque a menudo es una consecuencia de la rigidez arterial en la patogenia de la IC. Se crearon modelos separados para las variables de IC global, ICpFE e ICrFE. Se evaluó la presunción de riesgos proporcionales de los modelos de Cox, que fue satisfactoria para las variables del estudio. En estos modelos, la muerte se trató como un evento censor. Debido a la distribución sesgada de la cf-PWV en la población de estudio, la variable se transformó logarítmicamente para los modelos de riesgos proporcionales de Cox continuos.

Se llevó a cabo un análisis de sensibilidad que trató la muerte como un riesgo competitivo, con ajuste adicional por EC incidente en el seguimiento como una covariable que variaba en el tiempo, en el modelo 3. Asimismo, se efectuaron análisis de sensibilidad con exclusión de los participantes con ECV inicial y ajuste por frecuencia cardíaca y uso de antihipertensivos, porque estas características pueden tener un papel más mediador en la relación entre cf-PWV e IC incidente. Todos los análisis estadísticos se llevaron a cabo con SATA versión 12 (Stata Corp, College Station, TX).

Resultados

Nuestro estudio incluyó a 2290 participantes (53% mujeres y 35% negros). En la Tabla 1, se comparan las características iniciales de los participantes del estudio entre los terciles de cf-PWV. La cf-PWV más alta se asoció con raza negra, ECV prevalente y factores de riesgo de ECV prevalentes (hipertensión y diabetes mellitus). La presión arterial, la frecuencia cardíaca en reposo y el índice de masa corporal también fueron significativamente más altos en los participantes con cf-PWV más alta. Observamos 390 eventos de IC incidente durante una mediana de seguimiento de 11.4 años, de los cuales el 41,5% correspondió a ICpFE; el 37,2%, a ICrFE; y el 21,3%, a IC no clasificada.

Asociación entre categorías de cf-PWV y riesgo de IC global

En comparaciones no ajustadas, la cf-PWV más alta se asoció con mayor riesgo de IC (valor $P < 0{,}0001$; Figura 1), con máximo riesgo en los participantes del tercil 3. Las curvas de función de riesgo acumulado indican un efecto umbral entre los terciles 2 y 3 para el riesgo de IC. La Tabla 2 muestra la asociación ajustada por múltiples variables entre las medidas

Tabla 1. Características iniciales de los participantes del estudio en todos los terciles de velocidad de la onda de pulso

Características del sujeto	Tercil 1 (N = 758); cf-PWV baja	Tercil 2 (N = 764)	Tercil 3 (N = 768); cf-PWV alta	Valor *P*
Edad, años	73.4 (2.8)	73.8 (2.9)	73.9 (2.9)	<0,01
Afroamericanos	35%	40%	43%	0,01
Índice de masa corporal, kg/m^2	26,5 (4,5)	27,6 (4,6)	27,8 (4,9)	<0,01
PA sistólica, mmHg	131 (19)	136 (20)	142 (22)	<0,01
Hipertensión	38%	49%	61%	<0,01
Uso de antihipertensivos	43%	54%	63%	<0,01
ECV	23%	25%	29%	<0,01
Diabetes mellitus	9%	14%	21%	0,01
Actividad física kcal/kg por semana	87,9 (66,5)	84,7 (71,3)	78,4 (70,4)	0,03
Frecuencia cardíaca, lpm	63 (10)	66 (11)	67 (12)	<0,01
Velocidad de la onda de pulso, cm/s	566,6 (91,4)	812,3 (75,2)	1329,7 (389,0)	NA

Datos presentados como media (DE) o %. PA indica la presión arterial; cf-PWV, velocidad de la onda carotídeo-femoral; ECV, enfermedad cardiovascular; y NA, no aplicable.

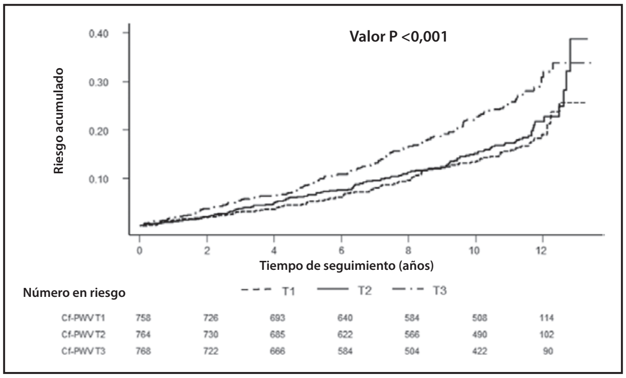

Figura 1. Riesgo acumulado de insuficiencia cardíaca en grupos de estudio basados en la diferente velocidad de la onda de pulso carotídeo-femoral (cf-PW, T1 a T3).

categóricas de cf-PWV y el riesgo de IC. Tras el ajuste por edad y sexo, las medidas más altas de cf-PWV presentaron una asociación significativa con riesgo más alto de IC (modelo 1). Esta asociación fue ligeramente atenuada, pero continuó siendo significativa, después del ajuste adicional por etnicidad, frecuencia cardíaca y presión arterial media (modelo 2). El ajuste adicional por otros factores de riesgo atenuaron de manera significativa esta relación, de manera que la cf-PWV ya no se asoció con riesgo de IC (modelo 3)

Asociación entre categorías de cf-PWV y riesgo de subtipos de IC

En el análisis no ajustado, la cf-PWV más alta se asoció con mayor riesgo tanto de ICpFE como de ICrFE (valor *P:* 0,02 para ambas; Figura 2), con el riesgo más alto en los participantes del tercil 3. En el análisis ajustado, la cf-PWV más alta mostró una asociación significativa con riesgo más alto de ICrFE y ICpFE después del ajuste por edad y sexo (modelo 1; Tabla 3). Esta asociación se atenuó de manera significativa tras el ajuste adicional por etnicidad, frecuencia cardíaca, presión arterial media (modelo 2; Tabla 3), y por otros factores de riesgo (modelo 3; Tabla 3).

Asociación entre medidas continuas de cf- PWV y riesgo de IC

Se evaluó la asociación continua entre cf-PWV y riesgo de IC, ICpFE e ICrFE en modelos separados de riesgos proporcionales de Cox utilizando medidas de cf-PWV transformadas logarítmicamente. Observamos una atenuación progresiva de la asociación entre cf-PWV y riesgo de IC, ICpFE y ICrFE, con el ajuste secuencial por posibles factores de confusión, similar a la observada en el análisis categórico. La cf-PWV más alta no se asoció con riesgo de IC en el modelo más ajustado (Figura 3). Más aún, no se detectó ninguna interacción significativa entre las características de los participantes, como índice de masa corporal, niveles de actividad física y cf-PWV, y riesgo de IC (*P* de la interacción > 0,2 para todos; Figura S1 del Suplemento de datos solo en línea).

Análisis de sensibilidad

Se llevó a cabo un análisis de sensibilidad para evaluar la asociación entre medidas de cf-PWV y riesgo de IC entre participantes sin ECV al inicio del estudio y sin ajuste por posibles características mediadoras, como nivel de hipertensión y frecuencia cardíaca, en el modelo final. El patrón de asociación entre cf-PWV y riesgo de IC en este subgrupo no fue diferente del de la población global de estudio, de manera que las medidas más altas de cf-PWV no mostraron una asociación significativa con riesgo de IC después del ajuste por posibles factores de confusión (razón de riesgos instantáneos [CI de confianza del 95%] por $\log_2$ de cf-PWV más alta = 1,12 [0,89-1,42]; Tabla S1).

De los 2290 participantes incluidos en el análisis, 1027 (44,8%) murieron durante el seguimiento. En el análisis de sensibilidad que trató la muerte como un riesgo competitivo con ajuste adicional por EC incidente como una covariable que variaba en el tiempo, las medidas categóricas y continuas de cf-PWV no se asociaron significativamente con el riesgo de IC (Tabla S2).

Discusión

En el presente estudio de individuos ancianos residentes en la comunidad, observamos que la cf-PWV más alta se asociaba con mayor riesgo de IC global y sus subtipos, ICpFE e ICrFE.

Sin embargo, estas asociaciones se atenuaron de manera sustancial tras el ajuste por ECV y sus factores de riesgo. En conjunto, los resultados de nuestro estudio sugieren que la asociación entre remodelado vascular y mayor rigidez arterial, medida por cf-PWV, y riesgo de IC en adultos mayores puede estar relacionada con la carga de ECV o factores de riesgo coexistentes.

Tabla 2. Asociación ajustada entre medidas categóricas de velocidad de la onda de pulso y riesgo de insuficiencia cardíaca

Modelos multivariados ajustados	Razón de riesgos instantáneos (CI 95%), tercil 1	Razón de riesgos instantáneos (CI 95%), tercil 2	Razón de riesgos instantáneos (CI 95%), tercil 3
Modelo 1: ajustado por edad y sexo	Ref	1,09 (0,84-1,42)	1,55 (1,21-1,98)
Modelo 2: ajustado por edad, sexo, etnicidad, frecuencia cardíaca y PAM	Ref	1,00 (0,76-1,29)	1,35 (1,05-1,73)
Modelo 3: ajustado por edad, sexo, etnicidad, frecuencia cardíaca, PAM, IMC, EC, nivel de educación, uso de anti-HTN, diabetes mellitus, tabaquismo, nivel de consumo alcohólico, actividad física y función renal	Ref	0,88 (0,68-1,14)	1,14 (0,88-1,47)

Anti-HTN indica medicación antihipertensiva; IMC, índice de masa corporal; EC, enfermedad coronaria; CI, intervalo de confianza; y PAM, presión arterial media.

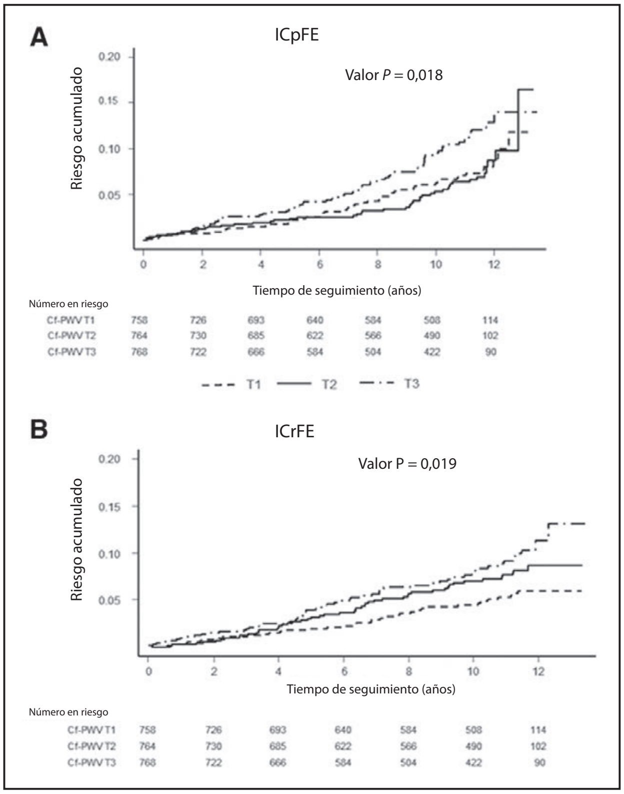

Figura 2. Riesgo acumulado de insuficiencia cardíaca con preservación de la fracción de eyección (ICpFE) y de insuficiencia cardíaca con reducción de la fracción de eyección (ICrFE) en grupos de estudio basados en la diferente velocidad de la onda de pulso carotídeo-femoral (cf-PW, T1 a T3).

Las medidas más altas de rigidez arterial se han asociado con mayor riesgo de eventos cardiovasculares adversos mayores, como IM, enfermedad coronaria incidente y mortalidad.[16-19] Un análisis previo del estudio de Salud ABC con 181 eventos de IC no demostró ninguna asociación entre cf-PWV y riesgo de IC, ni siquiera en el análisis no ajustado.[19] En cambio, en el presente estudio con 390 eventos de IC, observamos una asociación inversa significativa tras el ajuste por edad, sexo, etnicidad, presión arterial y frecuencia cardíaca. Esto podría estar relacionado con la mayor potencia estadística y el número más alto de eventos de IC en el presente análisis.

La asociación entre rigidez arterial, medida por cf-PWV, y riesgo de IC se ha explorado en otros estudios de cohortes. Chirinos et al[40] demostraron que las medidas más altas de cf-PWV se asociaban con mayor riesgo de IC en una cohorte de pacientes con enfermedad renal crónica. Recientemente, en un análisis secundario del FHS (Framingham Heart Study [Estudio cardiológico de Framingham]), Tsao et al[25] comunicaron una asociación significativa entre cf-PWV y riesgo de IC (razón de riesgos instantáneos [intervalo de confianza del 95%], 1,29 [1,02-1,64]; valor $P = 0,04$). Los hallazgos de nuestro estudio se contraponen a los Tsao et al[25], lo que podría estar relacionado con varios factores. En primer lugar, hay diferencias significativas en las características de la población que pueden influir en las asociaciones observadas entre medidas de rigidez arterial y riesgo de IC. La población del FHS es relativamente más joven y homogénea desde el punto de vista racial/étnico que la población del estudio de Salud ABC. En segundo lugar, el modelo ajustado por múltiples variables de Tsao et al[25] no tuvo en cuenta muchos factores de confusión potenciales, como frecuencia cardíaca, función renal y niveles de actividad física. Por consiguiente, la asociación observada entre cf-PWV y riesgo de IC puede estar relacionada con confusión residual. Cabe destacar que la asociación entre cf-PWV e IC en los modelos ajustados por edad y sexo no fue diferente entre los 2 estudios. Por último, como se mencionó antes, hubo diferencias en los métodos de evaluación de la cf-PWV entre el estudio de Salud ABC y el FHS.[41] No se ha esclarecido si estas diferencias de las mediciones de la cf-PWV pueden haber influido en los

Tabla 3. Asociación ajustada entre medidas categóricas de velocidad de la onda de pulso y riesgo de ICpFE e ICrFE

Modelos multivariados ajustados	Razón de riesgos instantáneos (CI 95%), tercil 1	Razón de riesgos instantáneos (CI 95%), tercil 2	Razón de riesgos instantáneos (CI 95%), tercil 3
ICpFE			
Modelo 1: ajustado por edad y sexo	Ref	0,91 (0,61-1,36)	1,46 (1,01-2,11)
Modelo 2: ajustado por edad, sexo, etnicidad, frecuencia cardíaca y PAM	Ref	0,84 (0,56-1,26)	1,30 (0,89-1,89)
Modelo 3: ajustado por edad, sexo, etnicidad, frecuencia cardíaca, PAM, IMC, EC, nivel de educación, uso de anti-HTN, diabetes mellitus, tabaquismo, nivel de consumo alcohólico, actividad física y función renal	Ref	0,72 (0,48-1,09)	1,06 (0,72-1,56)
ICrFE			
Modelo 1: ajustado por edad y sexo	Ref	1,39 (0,91-2,14)	1,78 (1,17-2,70)
Modelo 2: ajustado por edad, sexo, etnicidad, frecuencia cardíaca y PAM	Ref	1,21 (0,78-1,86)	1,49 (0,98-2,27)
Modelo 3: ajustado por edad, sexo, etnicidad, frecuencia cardíaca, PAM, IMC, EC, nivel de educación, uso de anti-HTN, diabetes mellitus, tabaquismo, nivel de consumo alcohólico, actividad física y función renal	Ref	1,11 (0,72-1,71)	1,28 (0,83-1,97)

Anti-HTN indica medicación antihipertensiva; IMC, índice de masa corporal; EC, enfermedad coronaria; CI, intervalo de confianza; ICpFE, insuficiencia cardíaca con preservación de la fracción de eyección; ICrFE, insuficiencia cardíaca con reducción de la fracción de eyección; IC, insuficiencia cardíaca; y PAM, presión arterial media.

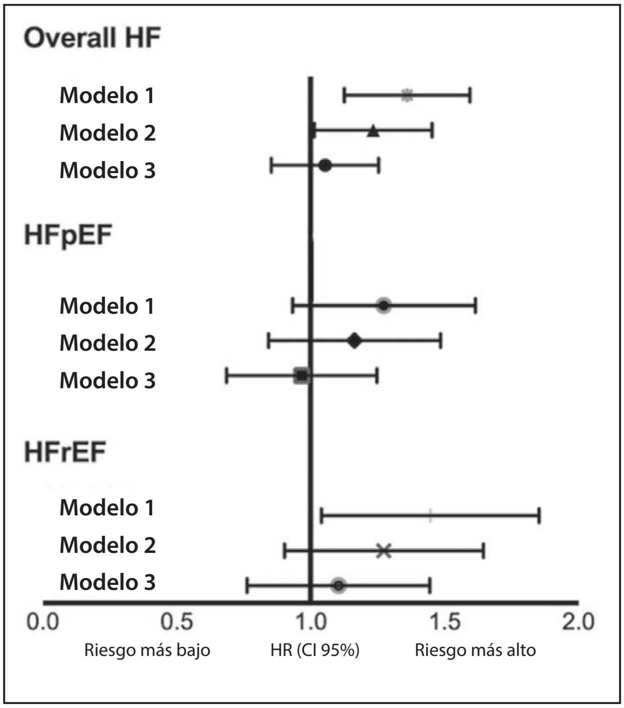

Figura 3. Asociación continua entre medidas transformadas logarítmicamente de la velocidad de la onda de pulso carotídeo femoral (cf-PWV) y riesgo de insuficiencia cardíaca (IC), insuficiencia cardíaca con preservación de la fracción de eyección (ICpFE) e insuficiencia cardíaca con reducción de la fracción de eyección (ICrFE) en diferentes modelos de Cox ajustados por múltiples variables. El modelo 1 está ajustado por edad y sexo. El modelo 2 está ajustado, además, por etnicidad, frecuencia cardíaca y presión arterial media. El modelo 3 está ajustado por las covariables del modelo 2 + índice de masa corporal, enfermedad cardiovascular prevalente, nivel de educación, uso de antihipertensivos, diabetes mellitus, tabaquismo, nivel de consumo alcohólico, actividad física y función renal. CI indica intervalo de confianza; y HR, razón de riesgos instantáneos.

resultados del estudio, porque su asociación con otras variables cardiovasculares no es diferente entre las 2 cohortes.

El acceso a información de la FE de la hospitalización índice por IC en una proporción sustancial de pacientes con IC nos permitió evaluar la asociación entre rigidez arterial y riesgo de subtipos de IC, ICpFE y ICrFE. En los modelos ajustados por edad y sexo, la cf-PWV se asoció más firmemente con riesgo de ICrFE que con riesgo de ICpFE. Sin embargo, estas asociaciones se atenuaron de manera sustancial y dejaron de ser significativas tras el ajuste por presión arterial, frecuencia cardíaca y otros posibles factores de confusión. Tsao et al[25] habían evaluado la asociación entre cf-PWV y subtipos de IC en el FHS, y observaron una asociación más firme para ICrFE que para ICpFE, similar a los resultados de nuestro estudio. Sin embargo, su estudio tenía limitada potencia estadística, con solo 77 eventos de ICpFE y 61 de ICrFE. El presente estudio con 162 eventos de ICpFE y 147 de ICrFE se suma significativamente a la bibliografía existente, con potencia adecuada para evaluar la asociación entre cf-PWV y riesgo de subtipos de IC.

Estudios transversales previos han comunicado rigidez arterial más alta en pacientes con ICpFE que en pacientes control hipertensos.[12,20,42] Sin embargo, hubo diferencias significativas en la distribución por edad y sexo, y otras características clínicas que pueden haber determinado las diferencias observadas. En el presente estudio, observamos que las contribuciones de la rigidez arterial, medida por cf-PWV, más allá de las diferencias de los factores de riesgo tradicionales de subtipos de IC no son significativas. Nuestros resultados son avalados por las observaciones transversales de Lam et al,[43] que demostraron que tras el ajuste por edad, sexo y tamaño corporal, las medidas de rigidez arterial fueron similares entre pacientes con ICpFE y participantes control hipertensos.

Cabe destacar que la falta de asociación entre cf-PWV y riesgo de IC quizá no se pueda generalizar a otras medidas de poscarga hemodinámica pulsátil, como magnitud de la onda reflejada, impedancia aórtica y distensibilidad arterial total. Las ondas reflejadas y la carga telesistólica se han asociado con disfunción diastólica y remodelado miocárdico adverso en estudios en animales.[44,45] De modo similar, varios estudios transversales en seres humanos han demostrado la contribución significativa de las ondas reflejadas y la impedancia aórtica característica a la disfunción VI sistólica y diastólica.[46-48] Más aún, en un estudio de cohortes longitudinal reciente entre participantes del MESA (Multi-Ethnic Study of Atherosclerosis [Estudio multiétnico de aterosclerosis]), Chirinos et al[49] demostraron una asociación independiente entre magnitud de la onda de reflexión y riesgo de IC incidente. Se requieren futuros estudios para evaluar mejor los efectos de la poscarga (ondas reflejadas, impedancia aórtica y distensibilidad arterial total) medidas directamente a través de relaciones de flujo y presión sobre el riesgo de IC incidente en individuos mayores.

Los resultados de nuestro estudio tienen importantes implicaciones clínicas. La incidencia más alta de IC en pacientes con cf-PWV elevada parece estar relacionada con mayor carga de ECV y sus factores de riesgo en estos pacientes. Por consiguiente, la rigidez arterial más alta es un fenotipo intermedio observado en individuos en riesgo, pero puede no contribuir a la aparición de IC en forma independiente de otros factores de riesgo. La cf-PWV más alta puede ser útil para identificar a individuos con mayor riesgo de IC, que se pueden beneficiar con una modificación más agresiva de los factores de riesgo. Esto es compatible con la hipótesis postulada hace poco por Paulus et al,[50] en la que identificaron factores de riesgo y comorbilidad como los determinantes primarios de la fisiopatología de la ICpFE a través de sus efectos inflamatorios.

Se deben considerar varios aspectos importantes respecto de los hallazgos nulos globales de nuestro estudios. Estos comprenden la posibilidad de error de tipo II, medición de la variable de exposición y los resultados de interés, y otros posibles sesgos. El gran número de eventos (390 eventos de IC) observados en nuestro estudio garantiza una potencia estadística adecuada para evaluar la asociación entre cf-PWV y riesgo de IC. Por consiguiente, hay menos probabilidad de un error de tipo II en nuestro estudio. Las medidas de cf-PWV en el estudio de Salud ABC están bien establecidas y han sido validadas con anterioridad.[19,32] Más aún, la cf-PWV ha mostrado tener una firme asociación con mortalidad de origen cardiovascular y EC en la cohorte de Salud ABC, como en otras cohortes poblacionales.[17-19] Es posible que la ausencia de asociación observada se relacione con la edad más avanzada y la carga más alta de ECV y sus factores de riesgo en nuestra población de estudio. En esta cohorte de estudio de edad más avanzada, las firmes asociaciones de ECV y factores de riesgo prevalentes con riesgo de IC podrían enmascarar nuestra capacidad de detectar una asociación independiente para cf-PWV. Por último, hay un posible sesgo de supervivencia en nuestro estudio de adultos mayores, de manera que los individuos que eran más susceptibles al riesgo de IC relacionado con rigidez arterial u otros eventos cardiovasculares adversos pueden no haber sobrevivido o cumplido con los criterios de elegibilidad para este estudio. En consecuencia, las asociaciones entre rigidez arterial y riesgo de IC pueden ser más sólidas en la población de mediana edad.

Cabe destacar varias otras limitaciones. La población de estudio incluyó a adultos mayores residentes en la comunidad de raza negra y blanca, y los resultados de nuestro estudio tal vez no se puedan generalizar a una población más joven y de otras razas/grupos étnicos. La adjudicación de IC se basó en la hospitalización, y por consiguiente, podemos haber perdido una proporción de eventos de IC diagnosticados en consultas ambulatorias. Más aún, no contamos con evaluación ecocardiográfica inicial de los participantes de nuestro estudio y, por lo tanto, se puede haber incluido en el análisis a individuos con disfunción VI asintomática u otras anomalías cardíacas estructurales.

Perspectivas

En una muestra comunitaria de adultos mayores con buen funcionamiento, hemos demostrado que la rigidez arterial más alta, medida por la cf-PWV, no se asocia independientemente con mayor riesgo de IC ni de sus subtipos después del ajuste por ECV y factores de riesgo prevalentes. Estos resultados sugieren que el riesgo de IC asociado con cf-PWV más alta es mediado, en gran medida, por enfermedad o factores de riesgo tradicionales coexistentes. Se necesitan futuros estudios para determinar si estos hallazgos se pueden generalizar a otras medidas de la poscarga VI.

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Declaración de conflictos de interés

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Novedad e importancia

¿Qué es nuevo?

- Las medidas más altas de rigidez arterial, determinadas por la velocidad de la onda de pulso carotídeo-femoral, identifican a individuos con mayor riesgo de insuficiencia cardíaca. Sin embargo, esto está relacionado, en gran medida, con la carga más alta de enfermedad cardiovascular establecida y sus factores de riesgo.

¿Qué es relevante?

- La velocidad más alta de la onda de pulso carotídeo-femoral puede ser un fenotipo intermedio observado en individuos en riesgo, pero no contribuye a la aparición de insuficiencia cardíaca independientemente de otros factores de riesgo.
- Los individuos con velocidad más alta de la onda de pulso carotídeo-femoral se pueden beneficiar con la modificación agresiva de factores de riesgo para reducir el riesgo de insuficiencia cardíaca.

Resumen

En individuos mayores, la velocidad más alta de la onda de pulso carotídeo-femoral no presenta una asociación independiente con mayor riesgo de insuficiencia cardíaca después del ajuste por factores de riesgo tradicionales. Esta observación es uniforme en individuos con enfermedad coronaria prevalente o sin ella. Se necesitan futuros estudios para determinar la contribución de otras medidas de la poscarga ventricular izquierda al riesgo de insuficiencia cardíaca en individuos mayores.