Pulse Pressure and Risk of New-Onset Atrial Fibrillation

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Atrial fibrillation (AF) is the most common chronic arrhythmia in adults and is associated with increased risk for mortality and stroke. An estimated 2.3 million adults in the United States have AF currently, and that number is expected to increase substantially as the population ages. The prevalence of AF increases markedly with age, with a substantial overall lifetime risk of approximately 1 in 4 for both men and women. Investigators have identified several key clinical risk factors for AF including advancing age, increased systolic blood pressure, diabetes, hypertension, heart failure, valvular disease, myocardial infarction, and obesity. Echocardiographic risk factors for nonrheumatic AF include left atrial enlargement, increased left ventricular wall thickness, and impaired left ventricular systolic function.

The exponential rise in AF incidence with age parallels a rapid age-related increase in aortic stiffness. The concomitant increase in pulse pressure adds to pulsatile load on the heart, thereby promoting ventricular hypertrophy, impaired ventricular relaxation, and increased left atrial size. Elevated left atrial size and pressure and impaired ventricular diastolic function may lead to fibrosis and electrical remodeling in the atrium, providing a substrate for the development of AF. Consistent with this causal pathway, echocardiographic measures of abnormal left ventricular diastolic function are associated with increased risk for developing AF.

Thus, age-associated increased pulse pressure may be a key determinant of the increasing incidence of AF in the elderly, and reduced pulse pressure will limit the growing incidence of AF.

Main Outcome Measures

Incident AF.

Prospective, community-based observational cohort in Framingham, Mass, including 5331 Framingham Heart Study participants aged 35 years and older and initially free from AF (median age, 57 years; 55% women).

Conclusion

Pulse pressure is an important risk factor for incident AF in a community-based sample. Further research is needed to determine whether interventions that reduce pulse pressure will limit the growing incidence of AF.

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PULSE PRESSURE AND ATRIAL FIBRILLATION

METHODS

Study Sample
The design and selection criteria of the Framingham Heart Study and the Framingham Offspring Study have been detailed previously. Participants attending the 16th examination of the original cohort (n=2351; 1979-1982) or the second examination of the offspring cohort (n=3863; 1979-1983) were eligible for the present investigation. These evaluations are referred to as the baseline examination for the present investigation. We excluded participants for the following reasons: age younger than 35 years (n=701); prior or current AF (n=127); or missing covariate or follow-up information (n=55), resulting in a sample of 5331 participants (2202 original cohort participants [41%]; 2946 women [55%]). All protocols were approved by the Boston University Medical Center institutional review board and participants provided written informed consent.

Clinical Evaluation and Definitions
Medical history, physical examination, and electrocardiography were routinely administered at each Framingham Heart Study examination. Blood pressure represented the average of 2 seated auscultatory blood pressure readings obtained by the physician at the time of each Framingham clinic examination. Pulse pressure was calculated as the difference between systolic and diastolic pressure. Mean arterial pressure was calculated as diastolic pressure plus one third of pulse pressure.

Height and weight were measured directly using a standardized protocol. Body mass index was calculated by dividing weight in kilograms by the square of the height in meters. Criteria for diabetes mellitus were a fasting glucose level of 126 mg/dL (7.0 mmol/L) or greater, random glucose level of 200 mg/dL (11.1 mmol/L) or greater, or use of insulin or medications used to treat hyperglycemia. Electrocardiographic left ventricular hypertrophy was defined as increased voltage with accompanying lateral repolarization abnormalities.

A standardized 2-dimensional guided M-mode echocardiogram was also performed at the baseline examinations. Left atrial diameter at end-systole was measured according to American Society of Echocardiography guidelines.

Medical records were obtained for all hospitalizations and follow-up physician visits related to cardiovascular disease and were reviewed by a committee of 3 investigators; events were adjudicated following written guidelines. Criteria for other cardiovascular events, including myocardial infarction and heart failure, have been described previously.

Atrial Fibrillation
Participants were diagnosed with AF if AF or atrial flutter was present on an electrocardiogram obtained from a hospital or physician chart or from a routine Framingham clinic examination (every 2 years in the original cohort and every 4-8 years in the offspring cohort). The electrocardiographic interpretation of AF was confirmed by 1 of 2 Framingham Heart Study cardiologists (D.L. or E.J.B.).

Statistical Analyses
First, we examined the association between pulse pressure and the risk of developing new-onset AF using Cox proportional hazards regressions. We tested for an interaction between follow-up time and pulse pressure to determine whether the assumption of proportional hazards for prediction of AF was valid. Death was treated as a censoring event. Follow-up also was censored after 20 years, with the final participant censored in this manner in December 2004. Estimates were adjusted to account for competing risk from mortality during the follow-up period. Covariates selected for adjustment were based on prior reports and included the following at the baseline examination: age, sex, body mass index, regular use of cigarettes in the prior year, use of antihypertensive therapy, diabetes mellitus, electrocardiographic (ECG) left ventricular hypertrophy, history of myocardial infarction or heart failure, and valvular disease (defined as significant systolic murmur, grade 3 or greater out of 6, or any diastolic murmur identified at the Framingham clinic examination). In additional models, we examined whether pulse pressure predisposed to AF through an interim change in pulse pressure or any of the other clinical risk factors (considered as time-dependent covariates).

Second, we investigated relations between AF and the various components of blood pressure (systolic, diastolic, mean, and pulse pressure). Effect sizes in these models were per 20 mm Hg for systolic and pulse pressure and 10 mm Hg for diastolic and mean pressure, which is equivalent to approximately 1 SD for each variable. We assessed the significance of adding variables to blood pressure models using χ² tests based on changes in log likelihood.

Third, we explored whether the relation between pulse pressure and AF may be mediated by the influence of pulse pressure on left atrial or ventricular structure and function. To examine this, we constructed a multivariable model with adjustment for echocardiographic left atrial size, left ventricular mass, and fractional shortening measured at the baseline examination. Values for left atrial size, left ventricular mass, and fractional shortening were imputed if missing by using

don't have sufficient context to accurately represent the content of the document as if you were reading it naturally. However, I can provide a general understanding of the content.

The document discusses the association between pulse pressure and the risk of developing atrial fibrillation (AF). It outlines the design and selection criteria for the Framingham Heart Study and the Framingham Offspring Study, explaining that participants attending the 16th examination of the original cohort (n=2351; 1979-1982) or the second examination of the offspring cohort (n=3863; 1979-1983) were eligible for the present investigation. The evaluations are referred to as the baseline examination for the present investigation.

Participants were excluded based on age, prior or current AF, or missing covariate or follow-up information. The final sample included 5331 participants (2202 original cohort participants [41%]; 2946 women [55%]). All protocols were approved by the Boston University Medical Center institutional review board and participants provided written informed consent.

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linear regression on height and covar- 
irates from prior hazards models. Left 
artrial size had the least missing data so 
it was imputed first, left ventricular mass was imputed accounting for left 
artrial size (observed or imputed), and 
fractural shortening was imputed ac-
counting for left atrial size and left ven-
tricular mass (observed or imputed). A 
Cox model for onset of AF was refit-
ted with these additional echocardi-
ographic variables.

For descriptive purposes, we gener-
at adjusted cumulative incidence curves from estimated hazard func-
tions for AF and for survival (free of AF; 
free of mortality) in separate propor-
tional hazards models. Estimates were 
made at age 57 years for men and 
women separately and for each pulse 
pressure group. Components were re-
combined to estimate cumulative inci-
dence for each sex within each pulse 
pressure group and cumulative inci-
dence curves were averaged across sexes 
using the proportional distribution in 
the overall sample.

We tested for effect modification of 
pulse pressure with age (older or 
younger than median), sex, and obe-
sity (body mass index above or below 
30) by including interaction terms for 
these variables and pulse pressure in 
separate models that also adjusted for 
known risk factors for AF.

All analyses were performed using 
SAS version 8.1. A 2-sided P value <.05 
was considered statistically significant.

RESULTS
Study Sample
Baseline characteristics of the study 
sample grouped according to approxi-
mate quartiles of pulse pressure at the 
time of the initial examination are pre-

tised in Table 1. Mean age was 56 
(range, 35-90) years in men and 58 (35-
91) years in women. Mean pulse pres-
sure was 51 (SD, 15) mm Hg in men 
and 53 (SD, 18) mm Hg in women. 
Pulse pressure correlated highly with 
systolic pressure (calculated using Pear-
son correlation coefficient r = 0.87; 
P < .001), moderately with mean arte-
rial pressure (r = 0.53; P < .001), and 
weakly with diastolic pressure (r = 0.07; 
P < .001). Systolic pressure correlated 
moderately with diastolic pressure (r = 0.55; P < .001).

Incidence of Atrial Fibrillation
During a mean of 16 years of fol-
low-up (censored at 20 years), 363 men 
and 335 women developed AF with a 
median time-to-event of 12 years. The 
unadjusted cumulative 20-year inci-
dence of AF increased steeply across 
pulse pressure groups (Table 1). Prior 
to developing AF, 62 men and 33 
women experienced a myocardial in-
farction and 46 men and 41 women had 
experienced heart failure. During the 
follow-up period, 1956 participants 
(994 women) died, of whom 1523 (778 
women) were free of AF. There was no 
interaction between follow-up time and 
pulse pressure for prediction of AF in 
the primary Cox model, suggesting that 
the proportional hazards assumption 
was appropriate.

The FIGURE displays estimated cu-
mulative incidences of AF (adjusted for 
sex and baseline age, and accounting 
for competing risk of mortality), and 
shows that the probability of develop-
ning AF over time increased with in-
creasing pulse pressure.

Multivariable Analyses 
of Clinical Models
Results of Cox proportional hazards 
models relating pulse pressure to the in-
cidence of AF are shown in Table 2. In 
model 1, adjusting for age and sex, a 20 
mm Hg increase in pulse pressure was 
associated with a 34% increase in the 
risk for developing AF (95% confidence 
interval [CI], 22%-47%; P < .001). The 
association between pulse pressure and AF 
remained significant (P < .001) in model 
2, which further adjusted for mean ar-
terial pressure and clinical risk factors 
for AF; each 20 mm Hg increase in pulse 
pressure was associated with a 24% in-
crease (95% CI, 11%-39%; P < .001) in 
the risk for developing AF. In contrast, 
mean arterial pressure was not associ-
ated with increased risk for developing 
AF in model 2 (Table 2). Since el-

tuated pulse pressure may affect other 

covariates in the model, which then 
predispose to development of AF, we 
icorporated all variables in model 2 
as time-dependent covariates with es-
tentially unaltered results (model 3, 
Table 2).

In Table 3 we display the relative 
contribution of individual blood pres-
sure components and their change over 
time to risk for AF in the Cox model

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adjusted for clinical covariates (model 3, Table 2). If single blood pressure components were assessed, the associations between either systolic pressure or pulse pressure and AF were highly significant, whereas the associations between mean arterial pressure or diastolic pressure and AF were not significant (Table 3). If diastolic pressure was added to the systolic pressure model, the change (−2 log likelihood) was significant (χ² = 6.74; P = .01; Table 3). Both blood pressure components were related to risk for AF in this dual component model and the effects were opposite in direction, indicating that for a given systolic pressure, lower diastolic pressure (and hence, higher pulse pressure) was associated with higher risk for developing AF. In contrast, if diastolic pressure was added to the pulse pressure model, the change (−2 log likelihood) was not significant (χ² = 0.76; P = .38) and the hazard ratio (HR) for diastolic pressure did not differ significantly from 1 (Table 3).

**Multivariable Analyses of Echocardiographic Models**

We hypothesized that the observed relation between pulse pressure and risk for developing AF may be attributable in part to the effects of abnormal arterial stiffness on pulsatile load and left ventricular structure and function, leading to abnormal left atrial structure and function. To test this hypothesis, we next added baseline echocardiographic left ventricular fractional shortening, left ventricular mass, and left atrial diameter to model 3 of Table 2, which included time-dependent clinical variables, pulse pressure, and mean arterial pressure. Left ventricular fractional shortening and left ventricular mass were significantly related to incident AF in these models. Pulse pressure remained a significant predictor in this model (HR, 1.23; 95% CI, 1.09-1.39; P = .001). In a secondary analysis, we excluded people with imputed echocardiographic data, which reduced the number of AF events from 698 to 464. The pulse pressure effect was comparable in this model, although the P value was borderline because of reduced power (HR, 1.17; 95% CI, 1.00-1.38; P = .05).

**Secondary Analyses**

The association between baseline pulse pressure and incident AF did not vary significantly by age, sex, or presence of obesity (P>.05 for the interaction terms if added to model 2 of Table 2). We also evaluated pulse pressure as a categorical variable by creating pulse pressure groups based on approximate quartiles. Increasing pulse pressure category was significantly predictive of incident AF in this model (HR, 1.19 for the trend across the 4 pulse pressure groups; 95% CI, 1.08-1.31; P<.001).

**COMMENT**

Our study evaluated relations between pulse pressure and incident AF during 2 decades of prospective follow-up in the Framingham original and
PULSE PRESSURE AND ATRIAL FIBRILLATION

Table 3. Cox Proportional Hazards Models for Components of Blood Pressure as Predictors of Development of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Blood Pressure Component</th>
<th>Hazard Ratio (95% Confidence Interval)†</th>
<th>P Value</th>
<th>–2 Log Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic pressure</td>
<td>0.97 (0.88-1.06)</td>
<td>.44</td>
<td>10561.3</td>
</tr>
<tr>
<td>Change in diastolic pressure</td>
<td>0.98 (0.90-1.06)</td>
<td>.56</td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>1.05 (0.97-1.13)</td>
<td>.26</td>
<td>10561.4</td>
</tr>
<tr>
<td>Change in mean arterial pressure</td>
<td>1.01 (0.94-1.09)</td>
<td>.75</td>
<td></td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>1.14 (1.04-1.25)</td>
<td>.006</td>
<td>10554.4</td>
</tr>
<tr>
<td>Change in systolic pressure</td>
<td>1.05 (0.97-1.14)</td>
<td>.27</td>
<td></td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>1.23 (1.11-1.37)</td>
<td>&lt;.001</td>
<td>10548.0</td>
</tr>
<tr>
<td>Change in pulse pressure</td>
<td>1.08 (0.98-1.19)</td>
<td>.14</td>
<td></td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>1.23 (1.11-1.37)</td>
<td>&lt;.001</td>
<td>10547.7</td>
</tr>
<tr>
<td>Change in systolic pressure</td>
<td>1.07 (0.98-1.18)</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>0.87 (0.78-0.96)</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>Change in diastolic pressure</td>
<td>0.95 (0.86-1.05)</td>
<td>.28</td>
<td></td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>1.23 (1.11-1.37)</td>
<td>&lt;.001</td>
<td>10547.2</td>
</tr>
<tr>
<td>Change in pulse pressure</td>
<td>1.08 (0.98-1.19)</td>
<td>.14</td>
<td></td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>0.96 (0.88-1.05)</td>
<td>.39</td>
<td></td>
</tr>
<tr>
<td>Change in diastolic pressure</td>
<td>0.98 (0.90-1.06)</td>
<td>.64</td>
<td></td>
</tr>
</tbody>
</table>

*All models include age, sex, and time-dependent body mass index, smoking, valvular disease, myocardial infarction, heart failure, diabetes, electrocardiographic left ventricular hypertrophy, and hypertension treatment.
†Hazard ratios expressed per 20 mm Hg for systolic and pulse pressure and per 10 mm Hg for diastolic and mean arterial pressure.

offspring cohorts and showed that pulse pressure is an important predictor of incident AF even after considering other clinical variables known to be associated with AF (including baseline echocardiographic measures of left atrial size, left ventricular mass, and left ventricular fractional shortening). Thus, arterial stiffness, as evidenced by elevated pulse pressure, represents a potentially modifiable risk factor for AF.

Our analysis of the components of blood pressure indicates that the relation between blood pressure and incident AF is potentially related specifically to the pulsatile component of blood pressure as assessed by pulse pressure. Incident AF was unrelated to mean arterial pressure. Furthermore, model fit improved significantly if both systolic and diastolic blood pressures were considered together as compared with either being considered alone. These findings underscore a potential weakness of simply concentrating on systolic pressure and ignoring diastolic and pulse pressure. Our data suggest that systolic and diastolic pressure should be considered together, or more logically, pulse pressure should be considered if interpreting blood pressure relations with various end points including risk for developing AF.

Elevated pulse pressure, a surrogate measure for increased proximal aortic stiffness, is associated with advancing age, higher body mass index, and prevalent diabetes, as was evident in our sample (Table 1). In addition, elevated pulse pressure predisposes to myocardial infarction, heart failure, left ventricular hypertrophy, impaired ventricular relaxation, and increased left atrial size. In our multivariable models, the association between pulse pressure and AF risk persisted in models that included echocardiographic left ventricular mass, left ventricular fractional shortening, left atrial size, time-dependent change in echocardiographic left ventricular hypertrophy, and other established strong risk factors for AF. Our analysis, including time-dependent change in echocardiographic left ventricular hypertrophy (shown to predict incident AF), suggests that increased risk for AF associated with elevated pulse pressure cannot be explained fully by changes in electrocardiographic left ventricular hypertrophy.

Episodic increases in systolic and pulse pressure in individuals with a stiff aorta may contribute to relations between pulse pressure and incident AF independently of effects on left atrial size or left ventricular mass. Acute increases in pulsatile load likely increase left atrial distending pressure, which may provide the substrate for initiation of AF. Alternatively, our relatively simple measure of left atrial dimension at baseline may inadequately characterize the full impact of elevated pulse pressure on left atrial structure and function or the elevation of pulse pressure may ameliorate left atrial enlargement. Importantly, regardless of whether increased pulse pressure induces a substrate conducive to development of sustained AF through effects on atrial or ventricular structure or function, interventions known to reduce pulse pressure, such as blockade of the renin-angiotensin system, have been shown to reduce the incidence of new or recurrent AF. Thus, increased pulse pressure and the downstream pathways leading from elevated pulse pressure to AF are potentially reversible.

There are several alternative mechanisms whereby elevated pulse pressure could be associated with increased risk for AF. Pulse pressure may be a surrogate for age or elevated blood pressure, which are known risk factors for AF. However, our multivariable models adjusted for age, hypertension requiring treatment, and observed mean arterial pressure. Furthermore, we have shown that pulse pressure is the single blood pressure component most predictive of future development of AF. Indeed, mean arterial pressure considered alone or in combination with pulse pressure was unrelated to development of AF. Thus, the pulsatile component of blood pressure appears to be specifically related to risk for developing AF. Various cardiovascular disease risk factors predispose to arterial stiffening and increase the risk for AF. However, our analyses, which included clinical risk factors (age, diabetes, obesity, and smoking) as covariates, indicate that pulse pressure conveys additional risk for AF beyond the risk that is attributable to

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these risk factors. Other potential mechanisms include the possibility that increased pulse pressure predisposes to neurohumoral activation\(^1\),\(^7\),\(^38\) or a generalized cardiovascular inflammatory response\(^1\),\(^39\),\(^40\) which, in turn may contribute to the development of AF.\(^41\)

Several potential limitations of our study merit consideration. We evaluated echocardiographic measures at a single examination. Consideration of change in echocardiographic measures over time during follow-up may have provided more robust prediction of risk for incident AF and may have indicated that increased risk for AF associated with elevated pulse pressure is mediated by subsequent effects of elevated pulse pressure on cardiac structure or function. We lacked power to analyze paroxysmal vs chronic AF or atrial flutter separately, so cannot comment if pulse pressure was more specifically related to subgroups of individuals with AF. Also, our cohort is predominantly white, middle-aged to elderly, and has normal or moderate elevations of blood pressure; thus, our findings may not be generalizable to younger individuals, other races/ethnicities, or individuals with severe hypertension. Finally, whereas the HRs associated with pulse pressure were statistically significant, the estimated effect size was modest. It remains to be determined whether interventions that alter pulse pressure will alter AF risk.

In summary, we have shown that increased pulse pressure, a simple and readily accessible if somewhat indirect measure of arterial stiffness, is likely an important risk factor for development of AF in a community-based sample. Arterial stiffness increases with advancing age, even in a relatively healthy sample.\(^31\) However, increased arterial stiffness with advancing age is not inevitable and appears to be modifiable.\(^42\) As a result, increased arterial stiffness may represent a major modifiable risk factor for development of AF. Given the aging of the population, further research is needed to determine whether interventions aimed at reducing pulse pressure or preventing the increase in pulse pressure with advancing age effectively reduce the incidence of AF. In light of the variable and often substantial increase in pulse pressure that accompanies advancing age, lifestyle modifications or therapy aimed specifically at reducing or limiting the increase in pulse pressure with advancing age may markedly reduce the substantial and rapidly growing incidence of AF in our aging society.


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Scepticism the tonic of minds, the tonic of life, the agent of truth—the way of art and salvation.
—Joseph Conrad (1857-1924)