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# Modifiable Predictors of Ventricular Ectopy in the Community

Tuomas Kerola, MD; Thomas A. Dewland, MD; Eric Vittinghoff, PHD, MPH; Susan R. Heckbert, MD, PHD; Phyllis K. Stein, PHD; Gregory M. Marcus, MD, MAS

**Background**—Premature ventricular contractions (PVCs) predict heart failure and death. Data regarding modifiable risk factors for PVCs are scarce.

**Methods and Results**—We studied 1424 Cardiovascular Health Study participants randomly assigned to 24-hour Holter monitoring. Demographics, comorbidities, habits, and echocardiographic measurements were examined as predictors of PVC frequency and, among 845 participants, change in PVC frequency 5 years later. Participants exhibited a median of 0.6 (interquartile range, 0.1–7.1) PVCs per hour. Of the more directly modifiable characteristics and after multivariable adjustment, every SD increase in systolic blood pressure was associated with 9% more PVCs (95% confidence interval [CI], 2%–17%;  $P=0.01$ ), regularly performing no or low-intensity exercise compared with more physical activity was associated with  $\approx 15\%$  more PVCs (95% CI, 3–25%;  $P=0.02$ ), and those with a history of smoking exhibited an average of 18% more PVCs (95% CI, 3–36%;  $P=0.02$ ) than did never smokers. After 5 years, PVC frequency increased from a median of 0.5 (IQR, 0.1–4.7) to 1.2 (IQR, 0.1–13.8) per hour ( $P<0.0001$ ). Directly modifiable predictors of 5-year increase in PVCs, described as the odds per each quintile increase in PVCs, included increased diastolic blood pressure (odds ratio per SD increase, 1.16; 95% CI, 1.02–1.31;  $P=0.02$ ) and a history of smoking (OR, 1.31; 95% CI, 1.02–1.68;  $P=0.04$ ).

**Conclusions**—Enhancing physical activity, smoking cessation, and aggressive control of blood pressure may represent fruitful strategies to mitigate PVC frequency and PVC-associated adverse outcomes. (*J Am Heart Assoc.* 2018;7:e010078. DOI: 10.1161/JAHA.118.010078.)

**Key Words:** population studies • predictors • premature ventricular beats

P remature ventricular contractions (PVCs) are associated with a worse prognosis among individuals with a variety of cardiac conditions.<sup>1,2</sup> Building on evidence that successful catheter ablation of PVCs can normalize reduced systolic function among patients with a high burden of ventricular ectopy,<sup>3</sup> our group demonstrated that community-dwelling individuals with more PVCs exhibited a higher risk of incident

systolic dysfunction, heart failure, and death.<sup>4,5</sup> More recently, we reported that a PVC from a single 12-lead ECG predicted incident heart failure both before and after adjusting for known heart failure risk factors in 2 different community-based populations.<sup>6</sup>

The cause of PVCs, and particularly varying frequencies of PVCs, remains largely unknown. Identifying modifiable behaviors or exposures that might influence the burden of ventricular ectopy may be useful. We therefore sought to leverage data collected from participants in the CHS (Cardiovascular Health Study) to identify predictors of PVC frequency.

## Methods

The authors will make the methods (codes for the statistical analysis) available to any researcher for purposes of reproducing the results. The data belong to the CHS, and the authors therefore do not have the authority to share the study data with investigators outside the University of California, San Francisco; however, investigators can submit an application to obtain the data directly from the CHS using their established processes.

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An accompanying Table S1 is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010078>

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## Clinical Perspective

### What Is New?

- In a community-based cohort, readily modifiable predictors of more frequent ventricular ectopy included a higher systolic blood pressure, less regular physical activity, and smoking.
- Over 5 years of follow-up, those with an increased diastolic blood pressure and history of smoking exhibited significantly larger increases in premature ventricular contraction counts.

### What Are the Clinical Implications?

- Optimizing blood pressure control, enhancing regular physical activity, and abstinence from smoking may all help reduce premature ventricular contraction frequency and consequently premature ventricular contraction-associated adverse outcomes.

## Study Design

The CHS is a prospective, community-based cohort study sponsored by the National Heart, Lung, and Blood Institute. Details regarding eligibility, enrollment, and follow-up have been previously published.<sup>7–9</sup> Briefly, 5201 subjects 65 years of age or older were recruited between 1989 and 1990 from a random sample of Medicare beneficiaries by 4 academic centers (Johns Hopkins University, Wake Forest University, University of Pittsburgh, and University of California, Davis). An additional 687 black patients were recruited between 1992 and 1993. All participants underwent a medical history, physical examination, laboratory testing, and 12-lead electrocardiography at enrollment. Participants were then followed with annual clinic visits and semiannual telephone contact for 10 years, with telephone contact continued every 6 months thereafter. Participants provided written informed consent, and the study protocol was approved by the institutional review board of each center.

## Study Population

Our analysis was restricted to the subset of 1424 participants randomly assigned to 24-hour ambulatory ECG (Holter) monitoring during their initial assessment and who were part of the initial recruitment cohort (those recruited between 1989 and 1990). Of these, 845 participants underwent a second 24-hour ambulatory Holter 5 years later.

## Holter Assessment

Holter data were analyzed at the Washington University School of Medicine Heart Rate Variability Laboratory using a

MARS 8000 Holter scanner (GE Medical Systems, Milwaukee, WI), and all PVCs were identified. The results were then manually reviewed to ensure accuracy. The PVC frequency was characterized as PVCs per hour, defined as the total number of PVCs divided by the duration of the Holter recording.

## Covariate Ascertainment

### *Demographics and anthropometric measurements*

Self-identified race was categorized as white, black, Asian/Pacific Islander, and other. Due to the small number of nonwhite participants, race was dichotomized as white versus nonwhite for the regression analyses. Self-identified sex was classified as male or female. Level of education was determined according to self-reported number of educational years. Anthropometric measurements included weight, height, and waist and hip circumferences. Blood pressure and heart rate were measured in the right arm of seated participants after a 5-minute rest period using an appropriately sized cuff, and the average of 2 measurements was used for analysis.

### *Cardiovascular comorbidities*

Hypertension was defined as either a reported history of physician-diagnosed hypertension combined with the use of antihypertensive medications or a baseline study visit systolic blood pressure  $\geq 140$  mm Hg or diastolic pressure  $\geq 90$  mm Hg. Diabetes mellitus was defined as use of an antihyperglycemic medication at baseline or a fasting glucose level  $\geq 126$  mg/dL. Congestive heart failure and myocardial infarction (MI) were identified by participant self-report and confirmed by medical record verification.<sup>9</sup> Coronary heart disease was defined as angina, previous MI, previous coronary artery bypass graft surgery, or previous angioplasty identified by participant self-report and confirmed by medical record verification.<sup>9</sup> Atrial fibrillation was defined as a reported history of atrial fibrillation at the first study encounter, on baseline 12-lead ECG, or on baseline Holter monitoring.

### *Physical activity*

Usual leisure-time activity was assessed using a modified, validated Minnesota Leisure-Time activity questionnaire.<sup>10</sup> The questionnaire evaluated frequency and duration of 15 different activities during the preceding 2 weeks, including gardening, mowing, raking, swimming, hiking, aerobics, tennis, jogging, racquetball, walking, golfing, bicycling, dancing, calisthenics, and exercise cycling. Each activity was defined as having an intensity value in metabolic equivalent task units, and participant responses regarding types, frequency, and duration of each activity were used to calculate weekly energy expenditure (kcal/week) from leisure-time activity. Usual exercise intensity was also separately assessed: based on the

highest-intensity leisure-time activity reported over the preceding 2 weeks, participants were categorized as having engaged in high, moderate, or low-intensity activity or none, where high-intensity activity was estimated to require >6 metabolic equivalent tasks.<sup>10</sup> To ascertain the association of at least moderately intensive exercise with PVC frequency, exercise intensity was dichotomized into no and low-intensity exercisers versus moderate- and high-intensity exercisers for regression analyses.

### Medications

Baseline angiotensin-converting enzyme inhibitor,  $\beta$ -blocker, and calcium channel blocker use were ascertained using an in-home medication inventory. Use of a particular medicine required a current prescription filled by a pharmacist or physician that was taken by the patient in the previous 2 weeks.<sup>11</sup>

### Habits

Self-reported usual consumption of the number of alcoholic drinks (1 drink was defined as a 12-ounce can or bottle of beer, a 6-ounce glass of wine, or a shot of liquor) was used to estimate weekly alcohol consumption. Smoking status was dichotomized as ever (current and former) versus never and was quantified as the average daily consumption of cigarettes when smoking, the length of smoking history in years, and average packs of cigarettes per day based on self-report. Smoking pack-years were calculated by multiplying the average packs of cigarettes per day by the duration of smoking in years.<sup>8</sup>

### Echocardiography

The echocardiographic assessment of participants in the CHS has been previously described.<sup>12</sup> In brief, 2-dimensional echocardiography, 2-dimensional targeted M-mode, and Doppler imaging were performed on each participant at baseline using Toshiba SSH-160A echocardiography machines (Toshiba Medical Systems, Tustin, CA) equipped with 2.5- and 3.75-MHz transducers. Imaging was performed at the highest Mhz that provided adequate tissue penetration for 2-dimensional imaging. Images were recorded and stored on Super-VHS videotape at the recruitment sites and then transferred to the University of California, Irvine, for central interpretation.<sup>12</sup> In all participants, left ventricular (LV) function was qualitatively assessed from the 2-dimensional imaging views, where at least 80% of the myocardium was visualized. Function was categorized qualitatively as normal, borderline, or abnormal, with 94% interreader agreement and 98% intrareader agreement of paired studies.<sup>12</sup> Because of the small number of participants with ejection fraction classified as “abnormal,” qualitative ejection fraction was dichotomized for regression analyses into (1) borderline or

abnormal versus (2) normal. In a subpopulation of 952 individuals, LV mass and fractional shortening were derived from M-mode measurements, using leading-edge-to-leading-edge methodologies per American Society of Echocardiography standards.<sup>13</sup> LV mass was calculated using the Devereux formula and indexed by dividing it by the body surface area.<sup>14</sup>

### Statistical Analysis

Continuous variables with a normal distribution are presented as mean $\pm$ SD and were compared using Student *t* tests. Non-normally distributed continuous variables are presented as medians with interquartile ranges and were compared using the Mann-Whitney U-test. Categorical variables are presented as numbers and percentages and were compared using the chi-square test.

Linear regression was used to estimate the associations of covariates with baseline PVC frequency, which was log base 2 transformed to meet normality assumptions. Most continuous covariates were expressed in units of standard deviation, and their regression coefficients ( $\beta$ s) were back-transformed using the standard formula  $100 \times [\exp(\beta \times \ln(2)) - 1]$  to obtain estimates of the percentage difference in PVC frequency for each SD increment in a normally distributed continuous predictor, or given the presence (versus absence) of a categorical predictor. To meet the assumption of model linearity kcal of activity, pack-years of cigarette smoking, and cigarettes per day were log base 2 transformed, which led to improved model fit. Back transformation using the same formula yielded the percentage increase in PVC frequency for each doubling of the predictor. Log base 2 transformation was chosen to remain consistent with the previous literature on the subject.<sup>4,15</sup> Because changes in PVC frequency between the baseline and follow-up Holter studies exhibited a long tail, they were divided into quintiles and analyzed using proportional odds models. Of the 3 highly collinear smoking variables, smoking status (as defined above) was selected as the primary covariate to represent smoking history; additional analyses substituting current smokers, ex-smokers, overall smoke pack-years, and cigarettes per day were also performed.

In the cardiac electrophysiology literature, a high-burden of PVCs is considered relevant to cardiomyopathy risk (such as in determining optimal ablation candidates)<sup>3,16,17</sup>; we therefore performed additional analyses dichotomizing participants with more versus less than 5% and 10% PVCs. Although >20% or >10% PVCs are commonly used as thresholds for this purpose, no one exhibited more than 18% PVCs.<sup>3,16,17</sup> Because  $\beta$ -blockers are often empirically used to relieve symptoms related to PVCs, we performed secondary analyses comparing PVC frequency assessed from the baseline and 5-year Holter studies to the status of  $\beta$ -blocker use at each time

**Table 1.** Baseline Characteristics of Participants Exhibiting Below and Above the Median Number of PVCs per Hour (median=0.6)

Characteristic	≤Median PVCs/Hour (n=713)	>Median PVCs/Hour (n=711)	P Value
Age, y	71.5±4.8	72.4±5.1	0.001
Sex, male, %	270 (37.9)	392 (55.1)	<0.0001
Race,			
White, %	680 (95.4)	673 (94.7)	0.71
Black, %	28 (3.9)	35 (4.9)	
American Indian/Alaskan, %	2 (0.3)	1 (0.1)	
Asian/Pacific Islander, %	1 (0.1)	1 (0.1)	
Other, %	2 (0.3)	2 (0.3)	
Educational level, y	14.2±4.5	14±4.5	0.40
Height, cm	166.3±9.0	169.8±9.8	<0.0001
Weight, kg	71.1±13.0	74.3±13.2	<0.0001
Body mass index, kg/m <sup>2</sup>	26.6±4.3	26.7±4.0	0.60
Waist-to-hip ratio	0.91±0.10	0.93±0.09	0.001
Systolic blood pressure, mm Hg	133.6±20.4	135.4±21.3	0.11
Diastolic blood pressure, mm Hg	69.7±11.0	70.3±11.3	0.35
Heart rate, beats per minute	63.9±10.6	63.9±11.1	1.00
Hypertension, %	376 (52.8)	405 (57.0)	0.11
Diabetes mellitus, %	101 (14.2)	115 (16.3)	0.27
Coronary heart disease, %	124 (17.4)	161 (22.6)	0.01
Congestive heart failure, %	17 (2.4)	31 (4.4)	0.04
Myocardial infarction, %	56 (7.9)	102 (14.3)	0.01
Atrial fibrillation, %	13 (1.8)	19 (2.7)	0.28
Leisure-time physical activity, kcal/week (IQR)	1369 (557–2863)	1182 (478–1182)	0.03
Exercise intensity			
No exercise, %	32(4.5)	51 (7.2)	0.09
Low, %	327 (45.9)	342 (48.1)	
Intermediate, %	272 (38.2)	244 (34.3)	
High, %	81 (11.4)	74 (10.4)	
ACE inhibitors, %	35 (4.9)	52 (7.3)	0.06
β-Blockers, %	98 (13.7)	108 (15.2)	0.43
Calcium channel blockers, %	78 (10.9)	77 (10.8)	0.95
Alcohol consumption, units/week	2.3±5.6	2.6±6.0	0.22
Smoking status			
Never, %	359 (50.4)	291 (41.0)	0.002
Ex-smoker, %	289 (40.5)	349 (49.2)	
Current smoker, %	65 (9.1)	70 (9.9)	
Smoke pack-years (IQR)	0 (0–24.0)	6.6 (0–38.0)	<0.0001
Cigarettes per day (IQR)	0 (0–15)	8 (0–20)	<0.0001
Left ventricular ejection fraction			
Normal, %	670 (94.4)	617 (88)	<0.0001
Borderline, %	32 (4.5)	47 (6.7)	
Abnormal, %	8 (1.1)	37 (5.3)	
Left ventricular mass index, g/m <sup>2</sup> *	81.1±20.5	89.4±21.4	<0.0001
Left ventricular fractional shortening, %*	42.9±7.5	40.4±8.6	<0.0001

Data are presented as means±SD, medians (interquartile range [IQR]) or numbers (percentage). ACE indicates angiotensin-converting enzyme; and PVC, premature ventricular contraction. \*Available for 954 participants.

point; these analyses were repeated after adjusting for age and sex.

Multivariate models included sex and age, as well as covariates associated with the outcome at  $P < 0.10$  in unadjusted analysis and then retained by backwards selection with a retention criterion of  $P < 0.10$ . Multivariable-adjusted predictors were categorized as immutable (eg, age and height), potentially modifiable (eg, ejection fraction), and directly modifiable (such as conditions that could be modified with available medicines or habits that could, at least theoretically, change). Baseline PVC frequency was significantly associated with categorized change in PVC frequency and thus included as a covariate in the proportional odds models for this outcome, after log base 2 transformation to meet linearity assumptions.

Data were analyzed using SPSS<sup>®</sup> Statistics for Windows, version 23 (IBM Corp, Armonk, NY). A 2-tailed  $P < 0.05$  was considered statistically significant.

## Results

The mean length of the Holter recording was  $2.18 \pm 2.5$  hours, yielding a median hourly frequency of PVCs of 0.6 (interquartile range, 0.1–7.1). A total of 261 (18.3%) participants had no PVCs. The baseline characteristics of the participants are shown in Table 1. Those exhibiting above the median PVC frequency were older, were more often male, had greater height and weight, had more cardiovascular disease, engaged in less physical activity, and had a history of smoking. Unadjusted predictors of PVC frequency are included in Table 2. After multivariable adjustment, those who were older, taller, and with a lower ejection fraction had more PVCs. Of the modifiable predictors, systolic blood pressure, performing less than moderate-intensity physical activity and having ever (versus never) smoked were each independently associated with higher PVC frequency (Figure 1). While current smokers ( $n=135$ ) exhibited 20% more PVCs, this relationship did not achieve statistical significance (95% confidence interval, –5% to 55%;  $P=0.12$ ); in contrast, among the more numerous ex-smokers ( $n=638$ ), statistical significance was reached (18% more PVCs; 95% confidence interval, 2–36%;  $P=0.03$ ). No interactions with sex were observed.

Eleven participants exhibited a PVC burden  $>10\%$ , and no statistically significant predictors of this PVC frequency were observed. Both older age (SD adjusted odds ratio, 1.43; 95% confidence interval, 1.09 to 1.90;  $P=0.001$ ) and lower exercise intensity (odds ratio for those with greater exercise intensity, 0.31; 95% confidence interval: 0.14–0.68,  $P=0.004$ ) were associated with a PVC burden  $>5\%$  (observed in 38 participants).

In the subset with available fractional shortening and LV mass index measurements ( $n=952$ ) older age, being taller,

**Table 2.** Unadjusted Relationships Between Baseline Covariates and PVC Frequency

Characteristic, Unit (SD)	Percent Increase (95% CI)*	P Value
<b>Immutable</b>		
Age, y (4.9)	16 (9 to 24)	<0.0001
Male	74 (52 to 99)	<0.0001
White race (vs nonwhite)	–19 (–41 to 10)	0.18
Height, cm (9.4)	33 (24 to 42)	<0.0001
<b>Potentially modifiable</b>		
Educational level, y (4.5)	–4 (–11 to 2)	0.19
Weight, kg (13.3)	22 (15 to 31)	<0.0001
Body mass index, kg/m <sup>2</sup> (4.2)	4 (–3 to 12)	0.25
Waist-to-hip ratio (0.10)	19 (10 to 28)	<0.0001
Heart rate, beats per minute (10.9)	0 (–6 to 7)	0.92
Hypertension	14 (–1 to 31)	0.06
Diabetes mellitus	11 (–9 to 34)	0.30
Coronary heart disease	29 (9 to 53)	0.003
Congestive heart failure	87 (28 to 172)	0.001
Myocardial infarction	64 (32 to 104)	<0.0001
Atrial fibrillation	36 (–14 to 115)	0.19
Ejection fraction below normal <sup>†</sup>	109 (65 to 165)	<0.0001
Left ventricular mass index, g/m <sup>2</sup> (20.9) <sup>‡</sup>	28 (19 to 37)	<0.0001
Left ventricular fractional shortening, % (8.0) <sup>§</sup>	–22 (–28 to –16)	<0.0001
<b>Directly modifiable</b>		
Systolic blood pressure, mm Hg (21.5)	10 (2 to 18)	0.01
Diastolic blood pressure, mm Hg (11.2)	6 (–1 to 14)	0.09
Leisure-time physical activity <sup>§</sup>	–2 (–4 to –1)	0.007
Exercise intensity <sup>  </sup>	–17 (–27 to –5)	0.009
ACE inhibitors	37 (3 to 82)	0.03
β-Blockers	18 (–3 to 43)	0.096
Calcium channel blockers	–2 (–21 to 22)	0.87
Alcohol consumption, units/week (10.8)	3 (–10 to 17)	0.70
Smoking status <sup>¶</sup>	31 (15 to 51)	<0.0001

ACE indicates angiotensin-converting enzyme; CI, confidence interval; PVC, premature ventricular contractions.

\*Percent increase in premature ventricular contractions PVC per hour per SD in continuous covariate/presence vs absence of dichotomous covariate.

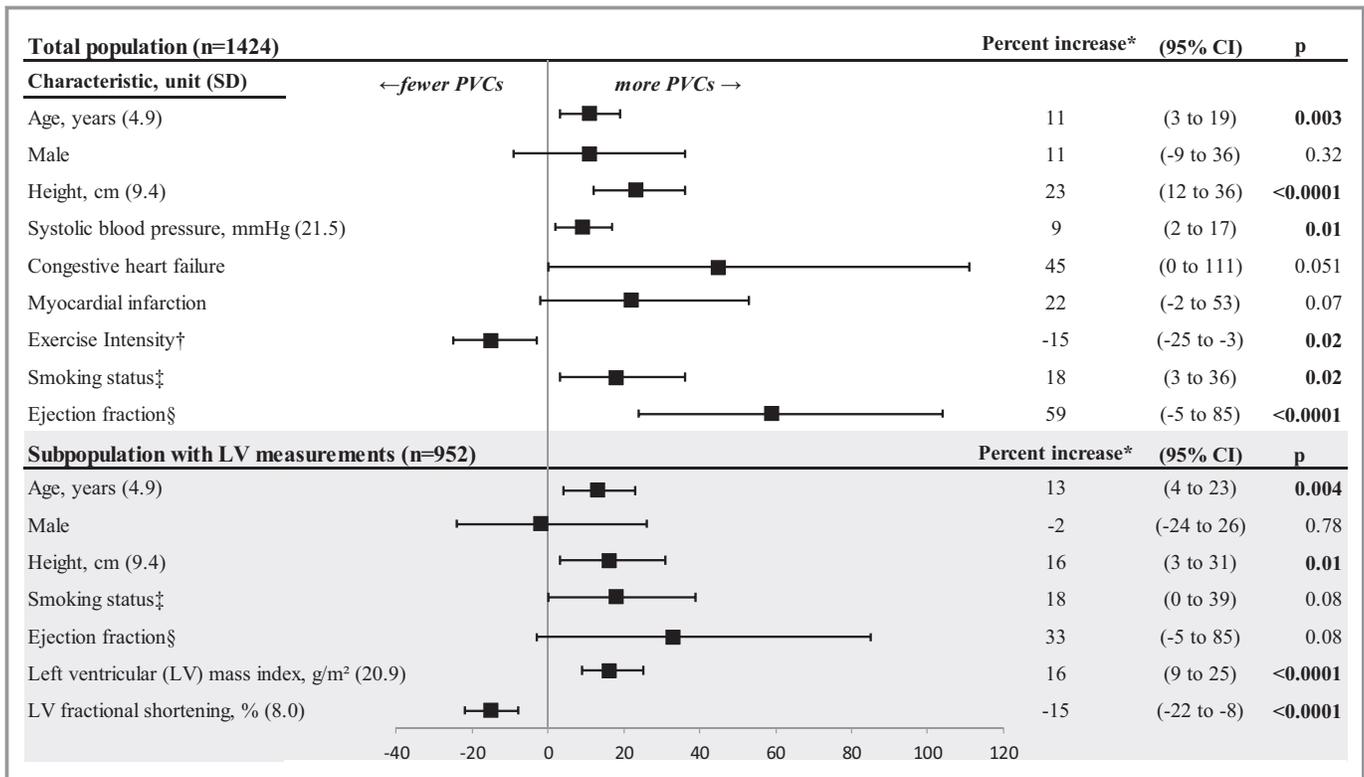
<sup>†</sup>Dichotomized into abnormal and borderline ejection fraction vs normal ejection fraction.

<sup>‡</sup>Available for 952 participants.

<sup>§</sup>Percent increase in PVCs per every doubling of leisure-time physical activity.

<sup>||</sup>Dichotomized into high and intermediate intensity exercisers vs low intensity and no exercisers.

<sup>¶</sup>Dichotomized into ever smokers vs never smokers.



**Figure 1.** Multivariable adjusted predictors of premature ventricular contraction (PVC) frequency. Multivariable models including all covariates listed for each population (please see the Methods section for selection of covariates). \*Percent increase in PVCs per hour per SD of continuous covariate or the presence (vs absence) of each categorical variable. †Dichotomized into high- and intermediate-intensity exercisers vs low-intensity and no exercisers. ‡Dichotomized into ever smokers vs never smokers. §Dichotomized into abnormal and borderline ejection fraction vs normal ejection fraction.

decreased fractional shortening, and increased LV mass index were each statistically significantly associated with a higher PVC frequency after multivariable adjustment (Figure 1).

Smoking remained statistically significantly associated with more PVCs whether analyzed as any history of smoking (versus none; Figure 1) or, as shown in Table 3, analyzed as total smoking pack-years or number of cigarettes smoked per day.

The median baseline PVC frequency among the participants with 2 Holter recordings was 0.5 (0.1–4.7) per hour, increasing to a median 1.2 (0.1–13.8) in the follow-up Holter 5 years later ( $P<0.0001$ ). The unadjusted predictors of the change in PVC frequency are shown in Table 4. Similar to the predictors of increased PVCs in the cross-sectional analyses, in unadjusted analyses, male sex, greater height and weight, prevalent cardiovascular disease, and history of ever smoking were all significantly associated with a greater increase in PVC frequency over time. In the multivariable analyses, potentially modifiable predictors of increasing PVCs included a history of MI and a reduced ejection fraction, whereas directly modifiable predictors of an increase in 5-year PVC frequency included increased diastolic blood pressure and a history of smoking (Figure 2). In the subset of participants with fractional shortening and LV

mass index measurements available, lower fractional shortening, a history of MI, and a history of smoking were each significantly associated with increasing PVC frequency.

When smoking was analyzed as a continuous variable, both greater pack-years and number of cigarettes smoked per day were associated with a greater change in PVC frequency, but statistical significance was reached only in certain multivariate models (Table 3).

We were unable to detect any statistically significant changes in PVC frequency with changing  $\beta$ -blocker use between the baseline and 5-year Holters (Table S1).

## Discussion

In this community-based cohort, a higher blood pressure, less physical activity, and smoking were each associated with more baseline PVCs after adjusting for relevant confounders and mediators. While different aspects of a higher blood pressure predicted both baseline PVCs (systolic blood pressure) and an increase in PVCs over time (diastolic blood pressure), smoking demonstrated the most consistent relationship with PVC frequency across several analyses.

**Table 3.** Relationship Between Continuous Measures of Smoking and PVC Frequency

		PVC Frequency		
		Percent Increase*	(95% CI)	P Value
Smoke pack-years				
Model 1	1		(0–2)	0.009
Model 2	1		(0–2)	0.03
Number of cigarettes smoked/day				
Model 1	1		(0–2)	0.01
Model 2	1		(0–3)	0.04
5-Year Change in PVC Frequency				
		Odds Ratio†	(95% CI)	P Value
Smoke pack-years				
Model 3	1.06		(0.99–1.14)	0.07
Model 4	1.08		(1.00–1.18)	0.04
Number of cigarettes smoked/day				
Model 3	1.07		(1.00–1.14)	0.047
Model 4	1.08		(1.00–1.07)	0.05

Model 1: Adjusted for age, sex, height, systolic blood pressure (BP), congestive heart failure, myocardial infarction, exercise intensity, left ventricular ejection fraction (EF); Model 2: Adjusted for age, sex, height, EF, left ventricular mass index, fractional shortening; Model 3: Adjusted for age, sex, height, diastolic BP, history of myocardial infarction, EF; Model 4: Adjusted for age, sex, height, history of myocardial infarction, EF, left ventricular mass index and fractional shortening. CI indicates confidence interval; and PVC, premature ventricular contractions.

\*Percent increase in PVCs per hour for each doubling of pack-years or cigarettes smoked per day.

†The odds ratio for a one-quintile increase in 5-year change in PVCs per hour between baseline and 5-year Holters, for each doubling of pack-years or cigarette smoked per day.

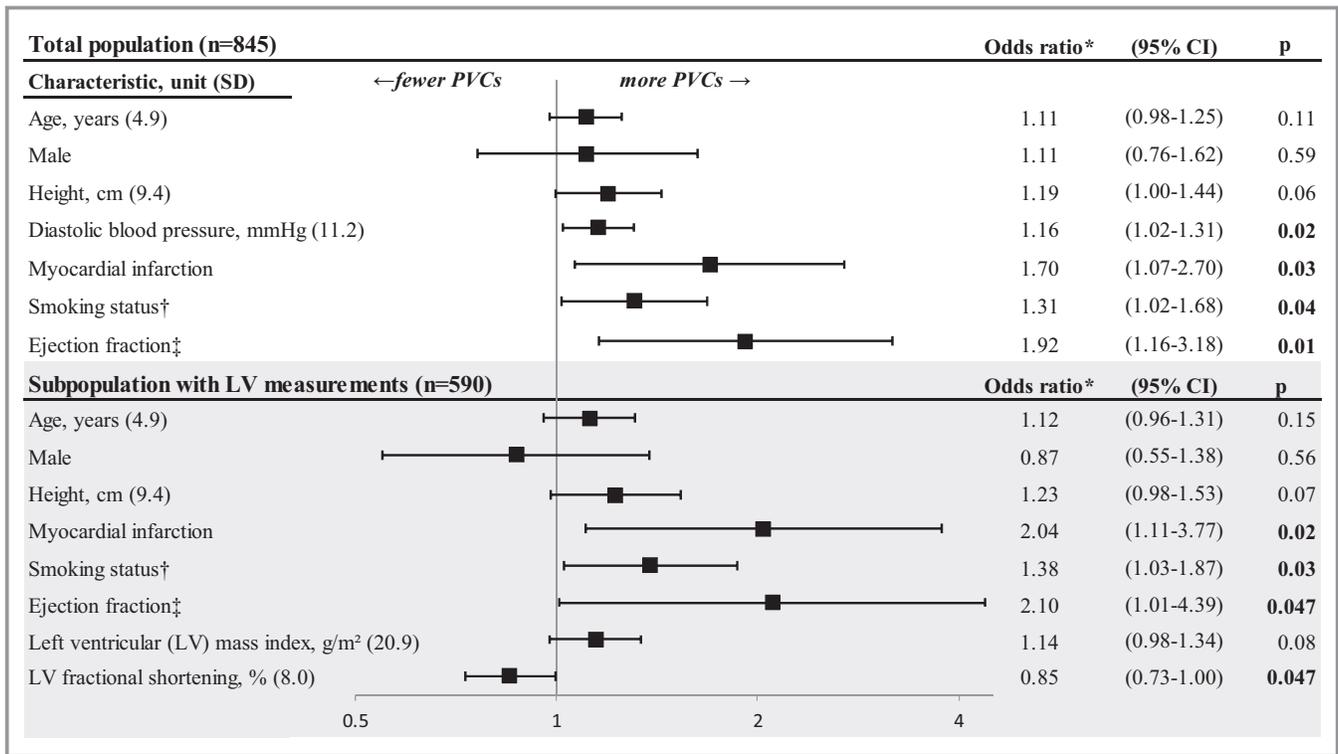
Smoking predicted both more PVCs at baseline and a significant increase in PVCs over time, whether analyzed as any history of smoking, number of pack-years, or number of cigarettes smoked per day. In the subset with all LV echocardiographic measurements available, an increase in LV mass index and a reduction in systolic function (as reflected by fractional shortening) were also found to be important predictors of more PVCs.

To our knowledge, this is the first community-based assessment of predictors of PVC frequency accompanied by echocardiography data as well as the first such study to evaluate predictors of changes in PVC frequencies over time. Previous literature has reported conflicting results regarding the relationship between cardiovascular risks factors and PVC frequency. An analysis of the ARIC (Atherosclerosis Risks in Community) study (including community-dwelling individuals enrolled at 45–65 years of age) found that male sex, black race, lower educational attainment, higher heart rate, presence of any heart disease, hypertension, and hypomagnesemia were each associated with at least 1 PVC during a

2-minute ECG recoding. The PVCs were not quantified and, unlike in the current analysis, alcohol consumption, a history of smoking, and echocardiographic measures were not included.<sup>18</sup> More recently, a study of 2048 young, healthy adults from the Principality of Liechtenstein found that, consistent with our current report, those with more PVCs were taller and generally performed less strenuous exercise.<sup>19</sup> While no statistically significant relationships between general smoking status and PVCs were observed, those who had a history of at least 15 pack-years of smoking did exhibit significantly more PVCs in one of their multivariable adjusted models. Neither systolic nor diastolic blood pressures were associated with PVC frequency in the Liechtenstein study. Although this study did not include some potentially important covariates, such as alcohol use or echocardiographic measurements or changes in PVC frequency over time, the disparate results with our current study may be attributable to the younger population in the Liechtenstein study. Specifically, perhaps smoking and a higher blood pressure require more time or perhaps involve other interactions with age, becoming manifest risk factors of PVC frequency only in older individuals.

Our most robust and consistent observation was that smoking was associated with more PVCs. There are several potential mechanisms that may underlie this relationship. First, smoking has known causal relationships with several of the phenomena identified in our study as risk factors for increased PVC frequency, including a higher blood pressure, a reduced ejection fraction and, in regards to increasing PVC frequency over time, MI.<sup>20</sup> Interestingly, however, smoking remained an important predictor of increased PVCs even after adjusting for those covariates, suggesting there may be a more direct proarrhythmic effect. In addition to enhancing the risk for those chronic cardiovascular diseases, smoking is known to acutely increase sympathetic tone, which might have an immediate effect on cardiac ectopy.<sup>21</sup> Indeed, in an ambulatory Holter study among 31 smokers, both premature atrial contractions and PVCs were more commonly observed during the same hours that participants reported smoking.<sup>22</sup> Nicotine, which itself may mediate sympathetic effects,<sup>23</sup> has also been shown to enhance myocardial fibrosis,<sup>24</sup> potentially contributing to a substrate more prone to automaticity<sup>25</sup> or micro-reentry.<sup>26</sup> Separately, carbon monoxide-induced hypoxia at the cellular level of the myocardium and oxidative stress produced by smoking are other possible direct mechanisms working either alone or in concert with the other described mechanisms predisposing smokers to arrhythmias.<sup>23</sup>

Higher blood pressure was the other directly modifiable characteristic associated with both baseline PVC frequency and an increase in PVCs over time. Although restricted to a smaller population in our study, the statistical significance of those relationships was lost after including LV shortening and



**Figure 2.** Multivariable adjusted predictors of 5-year change in premature ventricular contraction (PVC) frequency. Multivariable models including all covariates listed for each population (please see the Methods section for selection of covariates). \*The odds ratio for a 1-quintile increase in 5-year change in PVCs per hour, per increase of SD of each continuous covariate or the presence (vs absence) of each categorical variable. †Dichotomized into ever smokers vs never smokers. ‡Dichotomized into abnormal and borderline ejection fraction vs normal ejection fraction.

LV mass into the multivariable model, suggesting that such functional and structural LV changes might mediate this association. While only systolic blood pressure remained statistically significantly associated with baseline PVC frequency and diastolic blood pressure remained similarly associated with an increase in PVC frequency over time after multivariable adjustment, these findings are consistent with both the ARIC study mentioned above<sup>18</sup> and a previous case-control analysis wherein 50 hypertensive individuals exhibited more PVCs than did controls.<sup>27</sup>

A reduced LV ejection fraction was another consistent predictor of both more baseline PVCs and an increase in PVCs over 5 years. In our earlier study among the present cohort, we found individuals in the upper quartile (with more 100 PVCs/day) after adjustment to relevant confounders to have 48% higher risk of incident congestive heart failure during the follow-up when compared with those in the lowest quartile.<sup>4</sup> While some of this relationship might be explained by “reverse causation,” where the PVCs might actually contribute to a reduced ejection fraction,<sup>28</sup> the 5-year increase in PVCs among participants with a lower LV ejection fraction suggests that a bidirectional relationship may be possible. A history of MI also predicted a 5-year increase in PVCs, demonstrating that structural heart disease in the ventricle is likely

important. Again, fibrosis may play a role in these patients,<sup>29,30</sup> providing a substrate for insulated cardiomyocytes that may lose their normal electronic interactions with surrounding tissue and therefore depolarize and propagate to become a PVC<sup>31</sup> or provide an area of heterogeneous conduction and repolarization to facilitate reentry.<sup>26</sup>

In the cardiac electrophysiology literature, particularly high burdens of PVCs are often used to identify optimal candidates for ablation among patients with an established cardiomyopathy.<sup>3,15,16</sup> The number of participants with burdens in those ranges was relatively small in our current community-based study, although both older age and less exercise intensity were more common in those with at least 5% PVCs. It is important to emphasize, however, that we previously demonstrated both statistically significant and clinically meaningful enhanced risks of incident heart failure, reductions in LV ejection fraction, and death associated with relatively small increases in PVCs using this same cohort.<sup>4</sup>

While less cumulative leisure-time physical activity was associated with higher PVC frequency only in an unadjusted model, less regular exercise intensity exhibited statistically significant relationships with increased baseline PVC frequency both before and after multivariable adjustment. More physical activity may reduce PVCs through a variety of

**Table 4.** Unadjusted Predictors of 5-Year Change in PVC Frequency

Characteristic, Unit (SD)	Odds Ratio*	(95% CI)	P Value
<b>Immutable</b>			
Age, y, (4.9)	1.10	(0.97–1.26)	0.15
Male	1.73	(1.35–2.22)	<0.0001
White race (vs nonwhite)	1.41	(0.82–2.42)	0.21
Height, cm (9.4)	1.32	(1.17–1.51)	<0.0001
<b>Potentially modifiable</b>			
Educational level, y (4.5)	0.98	(0.87–1.11)	0.71
Weight, kg (13.3)	1.26	(1.09–1.42)	0.001
Body mass index, kg/m <sup>2</sup> (4.2)	1.09	(0.96–1.23)	0.17
Waist-to-hip ratio (0.10)	1.23	(1.09–1.38)	0.001
Heart rate, beats per minute (10.9)	1.06	(0.94–1.20)	0.39
Hypertension	1.24	(0.98–1.58)	0.08
Diabetes mellitus	1.14	(0.80–1.61)	0.47
Coronary heart disease	1.59	1.15–2.18)	0.005
Congestive heart failure	1.89	(0.76–4.72)	0.17
Myocardial infarction	2.19	(1.41–3.43)	0.001
Atrial fibrillation	1.42	(0.62–3.25)	0.41
Ejection fraction below normal†	2.36	(1.44–3.85)	0.001
Left ventricular mass index, g/m <sup>2</sup> (20.9)‡	0.79	(0.68–0.92)	0.003
Left ventricular fractional shortening, % (8.0)‡	1.22	(1.03–1.41)	0.02
<b>Directly modifiable</b>			
Systolic blood pressure, mm Hg (21.5)	1.02	(0.90–1.16)	0.72
Diastolic blood pressure, mm Hg (11.2)	1.16	(1.02–1.29)	0.02
Leisure-time physical activity§	0.98	(0.87–1.11)	0.69
Exercise intensity	1.04	(0.82–1.33)	0.73
ACE inhibitors	0.85	(0.49–1.46)	0.55
β-Blockers	0.88	(0.62–1.25)	0.47
Calcium channel blockers	0.97	(0.65–1.45)	0.89
Alcohol consumption, units/week (10.8)	1.14	(0.91–1.41)	0.17
Smoking status¶	1.40	(1.10–1.78)	0.007

ACE indicates angiotensin-converting enzyme; CI, confidence interval; PVC, premature ventricular contractions.

\*The odds ratio for a one-quintile increase in 5-year change in premature ventricular contractions (PVC) per hour, per standard deviation (SD) increase in each continuous covariate or the presence (vs absence) for each categorical variable.

†Dichotomized into abnormal and borderline ejection fraction vs normal ejection fraction;

‡Available for 952 participants.

§Odds ratio for a 1-quintile increase in 5-year change in PVCs per hour, per each doubling in leisure-time physical activity.

||Dichotomized into high- and intermediate-intensity exercisers vs low-intensity and no exercisers.

¶Dichotomized into ever smokers vs never smokers.

mechanisms, including via reducing blood pressure (although this relationship was independent of blood pressures ascertained as part of the study)<sup>32</sup> or through more generalized effects such as reducing general inflammation<sup>33</sup> or reducing weight.<sup>10,34</sup> It is also possible that those with more PVCs did not tolerate more physical exertion precisely because of their frequent PVCs, and hence in this cross-sectional aspect of the study we once again must acknowledge the possibility of reverse causation.

Consistent with previous data,<sup>18,19</sup> taller individuals exhibited a greater PVC frequency, both before and after multivariable adjustment (including adjustment for sex). Although height displayed a trend toward greater PVC over time, this did not reach statistical significance, suggesting that this more fixed quality may be associated with a certain increase in PVCs that then remains stable over time. Taller height has similarly been shown to predict premature atrial contractions<sup>35</sup> and atrial fibrillation,<sup>36</sup> suggesting that taller stature may reflect a general propensity to arrhythmias rather than some pathophysiology specific to ectopy arising from the ventricles alone.

In addressing this common arrhythmia recently shown to predict important cardiovascular outcomes and mortality,<sup>4</sup> the current study has several strengths. First, we employed 24-hour Holter monitoring, considered the gold standard in quantifying PVCs, in a community-based population. To our knowledge, this is the only community-based cohort in the United States with such published Holter data and the only community-based study in the world with published serial Holter measurements. The CHS also employed particularly meticulous ascertainment of the covariates considered for inclusion in our models. Finally, to our knowledge, this is the first community-based study to include echocardiographic measurements in considering predictors of PVCs. Indeed, ejection fraction, LV mass index, and LV fractional shortening each proved to be significantly associated with ventricular ectopy.

Several limitations of our study should be acknowledged. As the study involved only those 65 years of age and older, and the population was predominantly white, extrapolation of our findings to younger individuals and to nonwhites should be done with caution. The observational nature of our study does not allow any conclusions about causality between the parameters observed and PVC frequency. We were also unable to comment on the relationship between acute exposures (such as alcohol or smoking) and immediate effects on PVCs. The results of the present study are attributed to baseline measurements, and therefore we are unable to comment on how the change in several exposures influences the change in PVC frequency. There was likely substantial mediation between the covariates included in the multivariable models (eg, smoking and a higher blood pressure increase the risk for a reduced ejection fraction and MI), so that we may have underestimated the strength of

some associations. Finally, as with any observational study, we cannot exclude either residual confounding or additional confounding by unmeasured (or unknown) factors.

In conclusion, several common and potentially modifiable risk factors, including a higher systolic blood pressure, less physical activity, and smoking, were each associated with a greater baseline PVC frequency, while a higher diastolic blood pressure and smoking predicted an increased PVC frequency over time. Therefore, optimizing blood pressure, increasing physical activity, and smoking cessation may all represent useful strategies in reducing PVC frequency and potentially avoiding the harms of PVC-induced adverse outcomes.

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# **SUPPLEMENTAL MATERIAL**

**Table S1. Median (interquartile range) of PVC frequency according to status of 5-year beta-blocker usage among individuals *using/not using* beta-blockers at baseline.**

<b>Using beta-blockers at baseline (n=117)</b>			
	<b>Continued beta-blockers (n=82)</b>	<b>Beta-blockers discontinued (n=35)</b>	<b>p</b>
PVCs per hour at baseline	1.0 (0.1 to 7.6)	0.9 (0.1 to 15.6)	0.95
PVCs per hour in five years	0.8 (0.1 to 8.5)	4.6 (0.1 to 45.5)	0.09

<b>Not using beta-blockers at baseline (n=728)</b>			
	<b>Continued without beta-blockers (n=691)</b>	<b>Beta-blockers started (n=37)</b>	<b>p</b>
PVCs per hour at the baseline	0.4 (0.1 to 4.4)	0.5 (0.1 to 5.6)	1.00
PVCs per hour in five years	1.3 (0.1 to 12.0)	1.0 (0.1 to 20.6)	0.74

p values are based on Mann-Whitney U test

Ordinal regression analyses regarding changing beta-blocker use and change in PVC frequency among individuals *using* (n=117)/ *not using* (n=691) beta-blockers at baseline.

<b>Using beta-blockers at baseline</b>			
	<b>Odds ratio</b>	<b>95% CI</b>	<b>p</b>
unadjusted risk of cessation vs. continuing beta-blockers	1.79	0.87 to 3.68	0.11
sex and age adjusted risk of cessation vs. continuing beta-blockers	1.8	0.87 to 3.70	0.11

<b>Not using beta-blockers at baseline</b>			
	<b>Odds ratio</b>	<b>95% CI</b>	<b>p</b>
unadjusted risk of commencement vs. never use of beta-blockers	1.18	0.66 to 2.13	0.57
age and sex adjusted risk of commencement vs. never use of beta-blockers	1.22	0.67 to 2.20	0.51

The odds ratio for a one-quintile increase in 5-year change in PVCs per hour. All analyses additionally adjusted for baseline PVC frequency