Original article

Cardiac mortality of premature ventricular complexes in healthy people in Japan

Hideo Hirose (MD)a,*, Shizukiyo Ishikawa (MD)a, Tadao Gotoh (MD)a, Tomoyuki Kabutoya (MD)b, Kazunori Kayaba (MD)c, Eiji Kajii (MD)a

a Division of Community and Family Medicine, Jichi Medical University School of Medicine, Shimotsuke, Japan
b Division of Cardiovascular Medicine, Jichi Medical University School of Medicine, Shimotsuke, Japan
c School of Health and Social Services, Saitama Prefectural University, Koshigaya, Japan

Received 7 December 2009; received in revised form 18 January 2010; accepted 20 January 2010
Available online 25 February 2010

Summary
Background and purpose: Premature ventricular complexes (PVCs) are frequently encountered in healthy people. But the association between PVCs and cardiac events is not well established in Japan. We investigated the association of PVCs and cardiac deaths in people without cardiovascular disease in the Jichi Medical School (JMS) Cohort study.

Methods and subjects: We conducted a prospective cohort study in 12 districts in Japan as part of the JMS cohort study. Baseline data were obtained between April 1992 and July 1995. We excluded subjects who had myocardial infarction and stroke and those who had not received 12-lead electrocardiograms. Cox’s proportional hazard model was used to calculate the hazard ratios (HRs) of cardiac mortality of subjects with PVCs, using subjects without PVCs as reference.

Results: A total of 11,158 participants (4333 males and 6825 females) were analyzed. Participants were followed for an average of 11.9 years. PVCs were present in 1.4% of men and 1.1% of women. There were 92 cardiac deaths (47 males and 45 females) during the follow-up period. In crude cardiovascular mortality, HRs (95% confidence interval [CI]) were 5.29 (1.64—17.0) in males and 2.14 (0.29—15.5) in females. Age-adjusted HRs were 3.73 (1.16—12.0) and 0.98 (0.13—7.21), respectively. After further adjustment for body mass index, systolic blood pressure, total cholesterol level, high-density lipoprotein-cholesterol, and blood glucose, HRs were 3.98 (1.21—13.0) and 0.95 (0.13—7.11), respectively.

Conclusions: We conclude that PVCs are a predictive factor for cardiac death in men without structural heart disease.

© 2010 Japanese College of Cardiology. Published by Elsevier Ireland Ltd. All rights reserved.

* Corresponding author at: Division of Community and Family Medicine, Center for Community Medicine, Jichi Medical University School of Medicine, Shimotsuke, Japan. Tel.: +81 575 58 7394; fax: +81 575 44 0628.
E-mail address: hideohirose@h8.dion.ne.jp (H. Hirose).
Introduction

Premature ventricular complexes (PVCs) are frequently observed on standard 12-lead electrocardiograms in healthy people [1,2]. In patients with coronary heart disease, PVCs have been shown to be associated with a poor prognosis [3]. But the clinical importance of PVCs remains controversial in apparently healthy people. Kennedy et al. reported that asymptomatic patients with frequent or complex PVCs have a good prognosis [4]. In contrast, some prospective studies reported that incidental detection of PVCs is associated with all-cause mortality, myocardial infarction, and death due to coronary artery disease. The Framingham Heart Study demonstrated that men without coronary heart disease who had complex or frequent ventricular arrhythmias were at increased risk for all-cause mortality (relative risk 2.30) and the occurrence of myocardial infarction or death from coro-

na ry heart disease (relative risk 2.12) [5]. The Copenhagen Holter Study also reported that the detection of PVCs is an independent predictor of cardiovascular events (hazard ratio 2.6) [6].

In Japan, short-term 12-lead electrocardiogram is often used as a health care check to detect subclinical or clinical heart disease. PVCs are encountered in many healthy people. But the association between the presence of PVCs and cardiac events is not well established in Japan.

The Jichi Medical School (JMS) Cohort study is a large population-based prospective cohort study undertaken to clarify the risk factors for cardiovascular and cerebrovascu-
lar disease in Japan [7]. Thus, we investigated the association of PVCs and cardiac deaths in subjects without cardiovascular disease in this JMS cohort study.

Methods

Data were obtained between April 1992 and July 1995 in 12 districts in rural areas of Japan as part of the JMS cohort study. Mass screening for cardiovascular disease has been conducted in Japan since 1983 in accordance with health and medical service law for the aged, and we used this system to collect data for this study. The study design and some descriptive data have been presented previously [7]. The participants of this study were 12490 males and females. Past history of myocardial infarction and stroke was examined by questionnaire. If participants had a past history of these diseases, they were excluded. But drug use at baseline was not assessed. We also excluded participants who had not received 12-lead electrocardiograms at baseline. As a result, 11,158 participants (4333 males and 6825 females) were enrolled in the present study. The Institutional Review Board of Jichi Medical University of Medicine approved this study. Repeat examinations were used to follow most subjects every year. Those examined were asked whether they had any history of stroke and cardiovascular disease.

Statistical analysis

All statistical analyses were performed on a personal computer with the Statistical Package for Social Science® (SPSS for Windows (SPSS Japan Inc., version 11.5, Tokyo, Japan). Data are expressed as mean ± standard deviation (SD).

Cox’s proportional hazard models were used to calculate the hazard ratios (HRs) of cardiovascular mortality adjusted for age, body mass index, systolic blood pressure, total cholesterol level, HDL-cholesterol, and blood glucose.

A p-value less than 0.05 was considered to indicate statistical significance.

Results

A total of 11,158 participants (4333 males and 6825 females) were analyzed in this study. Table 1 presents a comparison of baseline characteristics for those with and without PVCs. Participants were followed for an average of 11.9 years from the time of baseline measurement until cardiac death. PVCs were present in 1.4% of men and 1.1% in women. Age in both sexes and systolic blood pressure in females were significantly higher in the PVCs group than in the non-PVCs group. Body mass index, total cholesterol, HDL-cholesterol, and blood glucose in both sexes and systolic blood pressure in males were similar in both groups.

There were 92 cardiac deaths (47 males and 45 females) during the follow-up period. Table 2 shows HRs calculated by Cox’s proportional hazard models with patients with PVCs, using patients without PVCs as reference. Crude cardiac mortality is 0.92/1000 person-year in males and 0.56 in females. In crude cardiovascular mortality, HRs with PVCs (95% confidence interval [CI]) were 5.29 (1.64–17.0) in males and 2.14 (0.29–15.5) in females. Age-adjusted HRs were 3.73 (1.16–12.0) and 0.98 (0.13–7.21), respectively. After further adjustment for body mass index, systolic blood pressure, total cholesterol level, HDL-cholesterol, and blood glucose, HRs were 3.98 (1.21–13.0) and 0.95 (0.13–7.11), respectively.
Cardiac mortality of VPCs in healthy people in Japan

Discussion

Our study demonstrates that apparently healthy men with PVCs had significantly increased cardiac mortality compared with participants without PVCs in this cohort study. Few reports have mentioned the association between PVCs and cardiac deaths in Japan, although the Niigata preventive medicine study reported PVC as risk factor of atrial fibrillation [8]. Our study also demonstrates that screening of PVCs on electrocardiograms may be beneficial for detecting individuals who are at high risk for cardiac death.

Our results are consistent with some other reports. The Framingham Heart Study, which examined a large free-living population, showed that men without coronary heart disease who had complex or frequent ventricular arrhythmias were at increased risk for all-cause mortality (relative risk 2.30) and the occurrence of myocardial infarction or death from coronary heart disease (relative risk 2.12) [5]. The Copenhagen Holter Study also reported that the detection of PVCs was an independent predictor of cardiovascular events (hazard ratio 2.6) [6]. A subanalysis of the Multiple Risk Factor Intervention Trial (MRFIT) noted that the finding of any VPCs on a 2-min rhythm strip, which was present in 4.4% of over 15,000 apparently healthy white men, was independently associated with a threefold increase in sudden cardiac death at seven year follow-up [9]. On the other hand, Kennedy et al. investigated the prognostic importance of complex or frequent ventricular arrhythmias in apparently healthy people. They reported no increase in all-cause mortality or myocardial infarction or death from coronary heart disease in people without coronary heart disease who had complex or frequent arrhythmias [4].

PVCs increased cardiac mortality in men, but not in women in our study. Pathophysiology of gender differences with respect to association between PVCs and cardiac mortality is not well known. One possible speculation is that the difference arises from sex differences in prevalence of left ventricular hypertrophy. Several previous studies have shown that left ventricular hypertrophy is an important risk factor for cardiovascular disease morbidity and mortality [10–14]. Bikkina et al. reported that in subjects with left ventricular hypertrophy, the presence of asymptomatic ventricular arrhythmia was associated with higher mortality [13] and a previous study reported that weight-adjusted left ventricular mass was greater in males than in females [14]. Thus, we speculate that the gender difference was a reflection of silent myocardial hypertrophy, although the echocardiogram was not demonstrated at baseline.

In Japan, short-term 12-lead electrocardiogram is often performed in health care check-ups. PVCs are common findings and occur in a broad spectrum of the population, including those without and with structural heart disease, irrespective of its severity.

With our results, doctors or public health nurses may inform people with PVCs of their increased risk. In the past, giving advice to patients with PVCs without structural heart disease has been difficult. But no evidence exists that antiarhythmic therapy in patients with asymptomatic ventricular arrhythmias improves cardiac mortality. Further investigation is needed to determine whether intervention is needed for healthy people with PVCs.

The present study has several limitations. First, the number of patients with PVCs is small, due to short-term measurement of electrocardiogram. Risk stratification, such as bigeminy, trigeminy, or frequency, was important in the point of cardiac death [15,16], but not demonstrated in this analysis. However, the sample size was still sufficient to demonstrate a statistical difference. Second, drug use at

Table 1  Baseline characteristics for those with and without PVC.

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any PVC</td>
<td>No PVC</td>
<td>p-Value</td>
<td>Any PVC</td>
</tr>
<tr>
<td>n (%)</td>
<td>59 (1.4%)</td>
<td>4274 (98.6%)</td>
<td>N.S.</td>
<td>74 (1.1%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.0 ± 9.3</td>
<td>54.8 ± 12.0</td>
<td>&lt;0.001</td>
<td>59.2 ± 11.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.9 ± 3.2</td>
<td>22.9 ± 2.9</td>
<td>N.S.</td>
<td>23.5 ± 3.3</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>135.1 ± 20.3</td>
<td>131.0 ± 20.4</td>
<td>N.S.</td>
<td>133 ± 23.9</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>179 ± 31.6</td>
<td>185 ± 34.3</td>
<td>N.S.</td>
<td>195 ± 36.2</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>47.4 ± 12.8</td>
<td>48.9 ± 13.4</td>
<td>N.S.</td>
<td>51.7 ± 12.9</td>
</tr>
<tr>
<td>BG (mg/dl)</td>
<td>111 ± 31.3</td>
<td>105 ± 30.7</td>
<td>N.S.</td>
<td>102 ± 30.6</td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± standard deviation (SD) for variables. PVC, premature ventricular complex (includes single, frequent, and complex PVCs); SBP, systolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; BG, blood glucose.

Table 2  Relationship of premature ventricular complexes and cardiac death.

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude HR</td>
<td>5.29 (1.64–17.0)</td>
<td>2.14 (0.29–15.5)</td>
</tr>
<tr>
<td>Age-adjusted HR</td>
<td>3.73 (1.16–12.0)</td>
<td>0.98 (0.13–7.21)</td>
</tr>
<tr>
<td>Covariate adjusted HR</td>
<td>3.98 (1.21–13.0)</td>
<td>0.95 (0.13–7.11)</td>
</tr>
</tbody>
</table>

Data are expressed as hazard ratio (HR) (95% confidence interval). Covariates included body mass index, systolic blood pressure, total cholesterol level, high-density lipoprotein-cholesterol, and blood glucose.
baseline was not assessed. Triggered activity is a more common mechanism for PVCs and such electrical activity may arise because of drug toxicity (such as digoxin, diuretics, or beta blockers) [17,18]. To our knowledge, there has been no study that has reported PVCs association with drug use, such as beta blocker and diuretics, in the general population. But in Japan, these drugs are less commonly prescribed than calcium channel blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers [19]. So we believe the effect of these drugs was small in our analysis. Third, variants of PVCs, i.e. monofocal or multifocal, or couplets/runs was not considered, because of the small sample size of multifocal, or couplets/runs.

This study was performed in Japanese subjects without known heart disease. We conclude that PVCs are a predictive factor for cardiac death in men without structural heart disease.

References


