

# Relationship between 24- hour Holter variables, chest discomfort and syncope: Does age matter?

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## Abstract

One hundred and forty four ambulatory, non-emergent human subjects from 20-88 years of age were investigated following routine 24 hour Holter monitoring referred by primary and tertiary care centers primarily for evaluation of palpitations and syncope. The patients were grouped into 3 different age categories: A) 20-59 years of age (16%), B) 60-69 years of age (26.4%) and C) > 70 years of age (57.6%). Heart rate profile, RR intervals, symptoms, frequency of premature supra ventricular and ventricular complexes were registered. The data show that though the occurrence and frequency of premature atrial and ventricular contractions over a period of 24 hours did not differ between the groups, the younger subjects documented more subjective discomforts during the Holter monitoring. Extra-systoles in excess of 1000 beats / 24 hour occurred incessantly throughout the registration. Patients with syncope and those without did not differ as regards the Holter variables. However, subjects with atrial fibrillation had acceptable rate control and had significantly lower incidence of syncope than those with sinus rhythm. The findings suggest that in a county setting, Holter monitoring for evaluation of syncope may not be the first hand mode of investigation in a non emergent setting. On the contrary, the modality appears to be valuable for monitoring patients with atrial fibrillation. Even mild symptoms in the elderly population may warrant closer clinical follow up to prevent cardiac events and/or syncope leading to serious physical injury.

**Key words:** Syncope, atrial fibrillation, Holter monitoring, ambulatory electrocardiography, premature atrial and ventricular contractions.

## Introduction

Continuous recording of cardiac rhythm over a period of 24-48 hour non-invasively using a digital device and subsequent computer software assisted electrocardiographic analysis (Holter ECG monitoring) plays a significant clinical role in the evaluation of arrhythmias in subjects with palpitations, subjective chest discomfort, as well as for evaluation of syncope. Holter electrocardiogram is also used to monitor the heart rate profile in patients with atrial fibrillation on antiarrhythmic medication to evaluate and monitor the effects of these medications. Subjective discomfort, if related to documented arrhythmia, is clinically very useful when diagnosing these patients. However, a clear cut dissociation between subjective symptoms with or without evidence of significant arrhythmia is clinically useful, particularly in the community setting.<sup>1</sup> In patients with syncope or near syncope without any identifiable cause or in patients with recurrent palpitation there is a class I recommendation for ambulatory Holter ECG monitoring.<sup>1</sup> Despite the recommendation, the cause of syncope is difficult to find since it can occur infrequently but has a large impact on patients' quality of life.

In individuals with apparently healthy hearts palpitations are often related to premature atrial (PAC) or ventricular contractions (PVC). Though PACs that arise from atrial focus could be benign, both the myocardial tissue and the specialized fibres in the myocardium can generate PVCs. Not only that ventricular tachycardia may originate from the same focus as does isolated PVC and may not only cause syncope but also may cause left ventricular dysfunction irrespective of age.<sup>2,3</sup> Therefore, for risk stratification accurate quantification of premature beats is necessary in symptomatic subjects using ambulatory Holter monitoring.

Because of demographic shift in the dynamics of cardiovascular illnesses considerable number of patients belong to subjects  $\geq 70$  years of age.<sup>4</sup> However, data are lacking in these increasingly large number of patient population. Therefore, one of the principal aims of the study was to investigate the heart rate and RR interval patterns in subjects  $\geq 70$  years of age (older adults) with or without syncope and/or atrial fibrillation and to compare these measures with younger adults. In addition, the occurrence of premature atrial and ventricular contractions and their relationship with subjective chest discomfort across a broad range of age group of subjects was also investigated.

## Subjects and Methods

Ambulatory and non-emergent subjects referred by the primary care physicians or by cardiologists for evaluation of arrhythmias using routine Holter ECG were included in the study. Referral reasons for Holter ECG were subjective chest discomforts in the form of palpitations, shortness of breath, chest pain related to palpitations, and history of recent syncope. In addition to that, subjects with atrial fibrillation referred for evaluation of heart rate response were also included in the study. Subjects with pacemaker or ICDs as well as acute cerebrovascular disease were not included into the study.

A 70-year cut-off was arbitrarily chosen to classify subjects as older adults in accordance with the Swedish registry of mortality from incident atrial fibrillation from 1995 to 2008 similar to the Danish healthy subjects with premature ventricular beats in the Copenhagen City Heart Study.<sup>5,6</sup>

Twenty four-hour Holter recordings were performed during the study period between April 2009 to June 2011. A commercially available two-channel digital device (Seer Light Extend, GE

**Table 1:** Age-wise distribution of clinical and Holter data in the entire cohort.

Clinical and Holter data	20-59 years (N=23)		60-69 years (N=38)		≥ 70 years (N=83)		P mean
	Mean	SD	Mean	SD	Mean	SD	
Chest pain, palpitations, shortness of breath (%)	48 %	11	39 %	15	26 %	21	0.09
Number of PAC: ≥ 1000/24 hours (%)	13 %	3	16 %	6	21 %	17	0.63
Number of PVC: ≥ 1000/24 hours (%)	30 %	7	11 %	4	20 %	17	0.15
Average heart rate (beats per minute)	73	7	71	11	69	11	0.31
Maximum heart rate (beats per minute)	133	23	126	20	129	26	0.56
Minimum heart rate (beats per minute)	47	6	48	8	47	9	0.93
Longest RR-interval: sec (median min-max)*	1.6	1.0-2.6	1.5a	1.0-3.2	1.7 a	1.0-3.1	0.008
Syncope (%)	43 %	10	37 %	14	42 %	35	0.83
Atrial fibrillation (%)	4 %	1	21 %	8	17 %	14	0.21

Proportions in % (N). Mean (SD) for normally distributed variables and median (max-min) for non-normal distributed variables

\* Kruskal-Wallis test

<sup>a</sup> Significant difference between 60-69 years and ≥ 70 years. P-value 0.024 (Bonferroni-corrected)

Health Care, USA) was used. All participants were given a time-activity diary to record symptom and were encouraged to continue their daily routine activities. Using a PC-based customized software (MARS version 7.2, GE health care, USA) average heart rate, maximum heart rate, minimum heart rate, number of pauses, pauses over 2 seconds, longest RR interval, number of PACs and PVCs were registered and were classified as either sporadic (20 of 24 hours free from extra beats) or incessant (extra beats registered during the entire period). From the time activity diary subjective symptoms were noted. For quantification of the burden of PVCs a cut-off of 1000 PVCs /24-hour was chosen, especially for evaluation of syncope, because with this much burden PVCs are unlikely to be associated with significant structural heart disease in contrast to 10,000 PVCs/24 hour that is often associated with advanced cardiac pathology such as heart failure.<sup>7, 8</sup> A similar cut-off was chosen for frequency of PACs (Adamec J and Adamec R, 2008).<sup>9</sup> Computer software generated Holter electrocardiogram data were edited if required.

## Statistical analysis

All quantitative data are presented either as mean ± SD or mean (95% CI), unless otherwise stated. For comparisons of continuous variables differences of means were evaluated using unpaired t-test for two groups and ANOVA for more than two groups. Chi-square test was used for the categorical variables. For continuous variables that were not normally distributed, Mann-Whitney U test was performed when comparing two groups, and Kruskal-Wallis test was used for comparisons between more than two groups. The Mann-Whitney U test with Bonferroni-correction was used as post hoc test using Kruskal-Wallis method. Logistic regression analysis was performed to generate the odds ratio for syncope in association with heart rate profiles, extra beats, atrial fibrillation, and longest RR intervals. A p-value of less than 0.05 was considered statistically significant. SPSS version 21 (IBM, USA) was used to analyse the data.

The ethical committee of Umeå University, Umeå, Sweden, approved the study.

## Results

In all 144 patients were included into the study (79 female, 55% and 65 male, 45%). The subjects were subgrouped into three age categories: age 20-59 years, n = 23 (16%), age 60-69 years, n = 38 (26.4%) and age ≥ 70 years, n= 83 (57.6%). There was no significant difference in age distribution between men and women (p = 0.34).

Maximum, minimum, and average heart rates (beats per minute, bpm) respectively were 129 ± 24; 47 ± 8 and 70 ± 10 bpm in the entire cohort. The longest RR interval was 1.7 ± 0.4 seconds also in the entire cohort.

Clinical and Holter data for the groups are presented in Table 1 and Table 2. Subjective symptoms, as noted in the patients' diary such as palpitation, chest pain, and shortness of breath did not differ between the groups. However, subjects younger than 70 years of age reported significantly more symptoms than the older adults (p = 0.036, Table 2). The number of PACs and PVCs (over or under 1000/24 h), pretest occurrence of syncope, atrial fibrillation did not differ between the groups. In patients older than 70 years of age the RR interval was significantly longer (p = 0.008; Table 2).

Age-wise distribution of PACs and PVCs (cut-off frequency of the premature beats being 1000/24 h) are presented in Table 3. Chi-squared test showed uniform distribution of both the forms of premature extrasystoles across the 3 age groups (Chi-sq p = 0.63 for PAC, and Chi sq p = 0.15 for PVC).

## Timing of the premature beats

When the number of PACs were sub grouped into those occurring at ≤ 999/24 hour and ≥ 1000/24 hour, the latter were presented throughout the registration period in 92% of the subjects compared with 43% who had ≤ 999 PACs (p < 0.001). Similarly 96% of the subjects with ≥ 1000 PVCs/24 hour had the episode throughout the registration period compared with 34% of the subjects who had ≤ 999 PVCs/24 hour (p < 0.001).

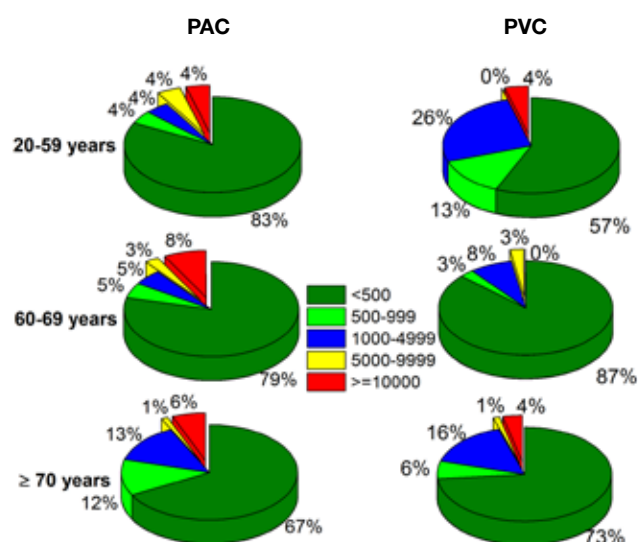
A vast majority of the subjects (57% to 87%) in all the three age categories had Holter registered PACs and PVCs < 500/24 hour (a magnitude often refereed as sporadic or infrequent)

**Table 2:** Clinical and Holter data under and over 70-year of age

Clinical and Holter data	20-69 years (N=61)		≥ 70 years (N=81)		P mean
	Value	SD	Value	SD	
Chest pain, palpitations, shortness of breath (%)	39 %	15	26 %	21	0.036
Number of PAC: ≥ 1000/24 hours (%)	15 %	6	21 %	17	0.36
Number of PVC: ≥ 1000/24 hours (%)	18 %	4	20 %	17	0.71
Average heart rate (beats per minute)	71	10	69	11	0.20
Maximum heart rate (beats per minute)	129	21	129	26	0.86
Minimum heart rate (beats per minute)	48	7	47	9	0.84
Longest RR-interval: sec (median min-max)*	1.5	1.0-3.2	1.7	1.0-3.1	0.008
Syncope (%)	39 %	24	42 %	35	0.73
Atrial fibrillation (%)	15 %	9	17 %	14	0.73

Proportions in % (N). Continuous values in mean (SD) for normally distributed data and median (max-min) for non-normal distribution of the measured variables.

\* Mann-Whitney U-test



**Figure 1:** Pie chart distribution of premature supraventricular (PAC) and ventricular (PVC) contractions across the three different age groups. Frequency of extra beats is presented as < 500/24 hour to over 10000 extra beats/24 hour. A distribution of the extra beats at a cutoff of 999/24 hour is presented in Table 3.

**Table 3:** Distribution of premature atrial and ventricular extra systoles

Distribution of PVCs and PACs	Age groups						Chi Square
	20-59 years (N=23)		60-69 years (N=38)		≥ 70 years (N=83)		
	Mean	SD	Mean	SD	Mean	SD	P-mean
Number of PVCs ≥ 1000/24 hours (%)	30 %	16	11 %	34	20 %	66	0.15
Number of PACs ≥ 1000/24 hours (%)	13 %	20	16 %	32	21 %	65	0.63

(Fig 1, Table 3). Frequent or very frequent premature supraventricular or ventricular contractions (> 500 /24 hour) occurred in a very small population of subjects. No statistical significant differences were found between the age groups (Fig 1) (Chi-squared; p = NS).

With regards to syncope no difference was seen across the age range. The maximum heart rate was significantly higher in subjects with atrial fibrillation (AF) compared to those without AF (145 ± 28 vs. 126 ± 24 bpm; p = 0.012) (Fig 3). Average and minimum heart rate did not differ significantly. In older adults with AF the maximum RR interval tended to be longer compared with younger individuals (p = 0.058) (Fig 2).

The proportion of subjects with AF was higher among patients without reported symptoms of syncope (p = 0.012) (Fig 4). Logistic regression analysis also showed an inverse association between AF and syncope (Fig 5). All other variables including PACs and PVCs cut-off of 1000

beats/24h, and longest RR interval that were entered in the analysis did not show any significant association with syncope.

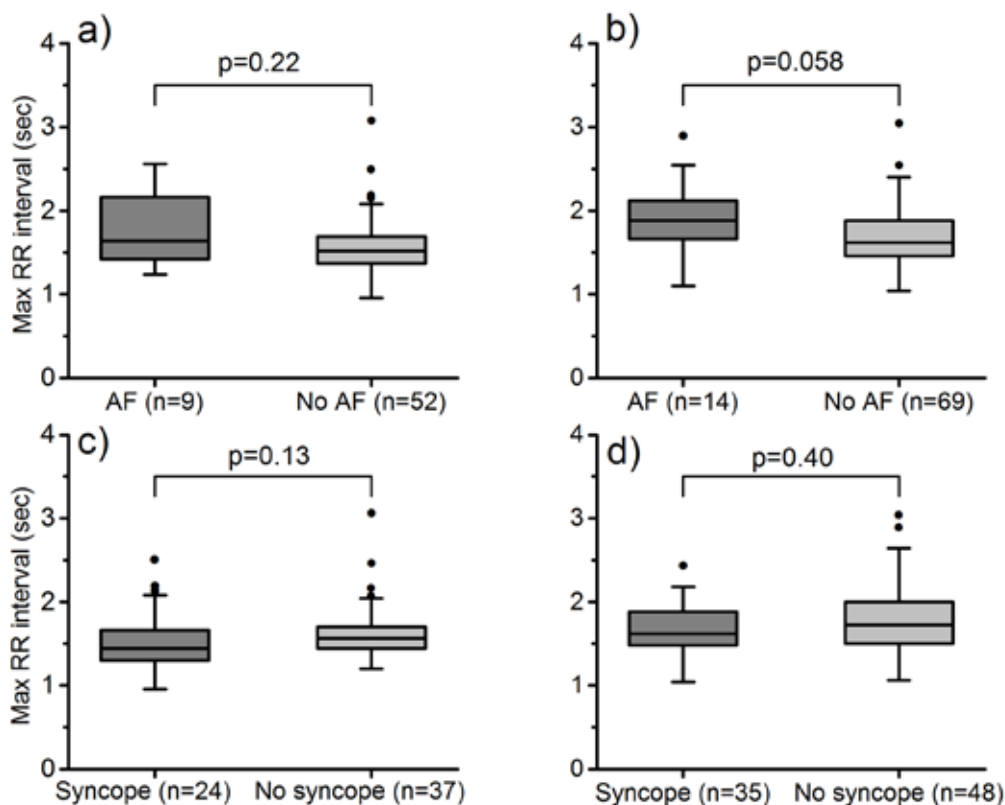
### Discussion

In the present study prevalence of atrial or ventricular ectopic beats did not differ between subjects over and under 70 years of age. Subjects younger than 70 years of age though experienced more subjective discomforts related to premature atrial or ventricular contractions. No significant association was noted between syncope and Holter variables. The latter finding could indicate that 24-hour Holter monitoring may not be an ideal or first hand choice for evaluation of syncope in a non emergent, outpatient setting. Furthermore, some of the the 24-hour heart rate profiles appear to be similar between subjects with sinus rhythm and those with AF signifying the fact that a rate control strategy was probably chosen in this population. Interestingly however, significantly more episodes of syncope was reported in subjects without AF. This inverse relationship between AF and syncope needs further evaluation.

The 24-hour heart rate profile (minimum, maximum, and average heart rates) and the circadian patterns of extrasystoles in the study closely resemble those presented in the Copenhagen City Heart Study.<sup>6</sup> However, unlike in the current study the relationships between Holter variables, subjective chest discomforts and syncope were not investigated in that study.

### Premature ventricular contractions (PVCs) and clinical significance

As regards quantification of PVCs an earlier study has shown that in subjects free of recognisable heart disease, verified by right- and left-heart catheterisation and coronary angiography, 39 out of 101 subjects had at least one PVC/24 h, four subjects had > 100/24 hours. Of those, five had > 5 PVCs in any given hour and four having multiform PVCs. Even frequent (> 60/h or 1 PVC/min) and complex PVCs may occur in apparently



**Figure 2:** Bar diagram (mean, 95% CI) showing longest RR intervals in subjects with atrial fibrillation (AF) and syncope compared with those without the either disease. a. c < 70 years of age; b,d ≥ 70 years of age.

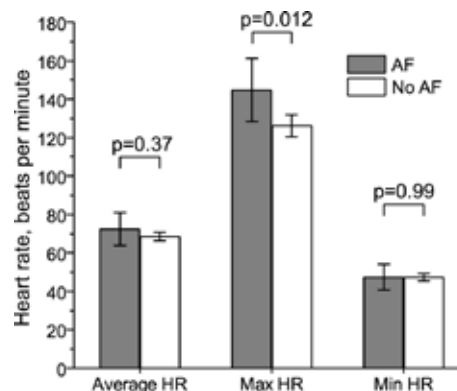
healthy subjects, with an estimated prevalence of 1 – 4 % of the general population with no excess mortality compared with the background population.<sup>10</sup> In our study 21 % of the subjects ≥ 70 years presented with PVC > 1000/24 h. In subjects aged 60 – 69 and 20 – 59 years the corresponding figures were 11 % and 30 % respectively. The burden of PVC in the current study did not differ between younger (< 70 years) and older (≥ 70 years) adults. Similar results were reported in a study by Ermis et al.<sup>11</sup> In the current study only 18 subjects had no detectable PVCs during the Holter registration while over three quarter of the subjects had less than 500 PVCs/24 hour irrespective of the age group (Fig 1), though PVC-related symptoms were significantly more common in younger subjects in our study.

**Premature atrial contractions**

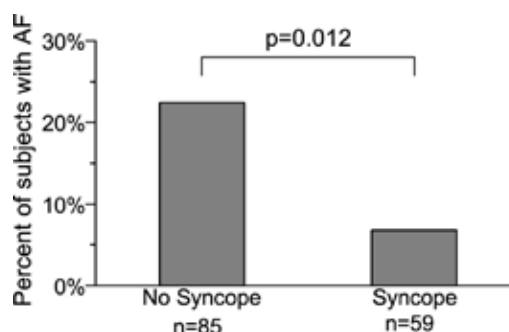
In our study PACs occurred in 97 % of the subjects, a prevalence similar to what was found in a recent study though we did not observe any age dependent association with occurrence of premature atrial contractions.<sup>12</sup> Though quite common in general population and considered to be benign in isolation, PACs could be a risk factor for incident atrial fibrillation.<sup>13</sup> It is however beyond the scope of the current study to investigate this association.

**Syncope: To Holter or not to Holter**

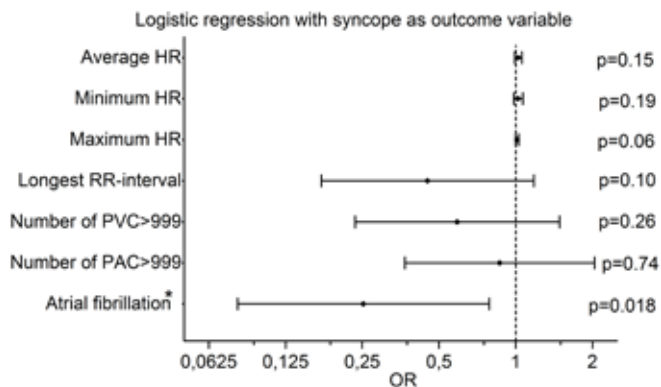
Syncope is defined as a sudden loss of consciousness with the inability to maintain postural tone, not related to anesthesia or a seizure disorder, with spontaneous recovery reported by the patient or an observer. This excludes cardiac arrest, which requires resuscitation.<sup>14</sup> Syncope is common with a similar incidence in men and women. The incidence increases with age, especially after 70 years and is bimodal with peaks at



**Figure 3:** Bar diagram (mean, 95% CI) showing average, maximum (max) and minimum (min) heart rates during 24 hour Holter registration in subjects with atrial fibrillation (AF).



**Figure 4:** Proportion of subjects with atrial fibrillation with or without syncope. Comparison were made by Chi-sq test.



**Figure 5:** Logistic regression analysis showing association between syncope and Holter variables. \* Denotes  $p < 0.05$ .

20 and 80 years of age.<sup>15</sup> A total of 59 subjects (41%) in the current study had syncopal attacks as noted in the referral requests. Although cardiac arrhythmias are one of the major triggers of syncope only 4 subjects (3 %) with syncope had coexistent AF.<sup>16</sup> The logistic regression analysis has therefore identified AF having the lowest odd of association with syncope (OR = 0.25; 95 % CI : 0.08 - 0.8;  $p < 0.05$ ). Heart rate profiles, supraventricular and ventricular extra beats in excess of 1000/24 hour had no significant association with reported syncope episode. We can only presume that the subjects in the cohort most probably suffered from neurally mediated syncope, since this is the most common form of syncope, irrespective of age.<sup>17, 18</sup>

Since the patients were ambulatory and non emergent, it maybe argued that either the subjects with syncope did not have cardiac causes of syncope (ventricular tachyarrhythmias, severe left ventricular systolic dysfunction) in which case either the patients were hospitalized according to the ESC guideline or were transferred to tertiary care centre.<sup>18</sup> Therefore, it is not surprising that the elderly subjects in the study who had syncope did not have Holter variables significantly different from those who did not have syncope. However, occurrence of excessive premature ventricular ectopics by Holter may be a predictor of abnormal electrophysiological study in high risk subjects, thereby necessitating the use of Holter in syncope, though it may not be the 1st line choice in subjects with normal resting ECG.<sup>19</sup> Head-up tilt test is clearly the modality of choice as a class 1B indication according to the European Society of Cardiology guideline in otherwise healthy individuals.<sup>18</sup>

### Atrial fibrillation and rate control status using Holter ECG

Atrial fibrillation has previously been shown to be age dependent.<sup>20</sup> In all twenty three subjects had AF in our study and only two of them were younger than 65 years. Twenty-one of them belonged to the age category of 65 -86 years of age. Although the inclusion of AF subjects was not intended a priori in the our study the maximum heart rate was significantly higher in subjects  $\geq 70$  years of age with AF compared with those  $< 70$  years of age. However, no significant difference could be found as regards minimum heart rate and average heart rate compared with the subjects in sinus rhythm. Such rate control strategy in subjects with AF have been reported to reduce incidence of stroke equivalent to adapting rhythm control

strategies along with anti-coagulation therapy.<sup>21</sup> Maximum RR interval was however marginally longer in AF but never exceeded 2 seconds (a cut-off that may necessitate pacemaker implantation or medication adjustment).

### Clinical implications

On the basis of the findings in this study, it is intriguing to suggest that 24 hour Holter monitoring may not be a 1st hand modality of choice for evaluation of syncope, especially in the low risk population. Head-up tilt testing not only is useful in this situation but may also guide therapy such as vagal denervation or pace maker implantation in some subjects with cardio inhibitory response.<sup>22, 23</sup> However, pace maker is incapable of overcoming the vasodepressor component of the reflex, universally present to some degree in neurally mediated syncope.<sup>15</sup> It maybe mentioned here that since the diagnostic yield of Holter monitoring is low risk stratification of the patients is necessary to select appropriate diagnostic tests.<sup>15</sup> In low risk patients, such as those with an isolated episode of syncope, only reassurance is recommended without further investigation.<sup>18</sup> Despite the low diagnostic yield of the Holter monitoring the modality may play a "gold standard" role in cardiac syncope secondary to ventricular tachy- or bradyarrhythmias. Absence of such arrhythmias in subjects with syncope such as in this study may help limit hospitalizations in subjects with reflex variant of syncope, the commonest cause of syncope that generally has favourable prognosis.<sup>24</sup> According to a scientific statement from the American Heart Association, Holter monitoring is indicated only in recurrent episodes and that even after echocardiography, exercise tolerance tests, and ischemia evaluation.<sup>25</sup> Since our data suggest that the average heart rate profile was similar to that in the strict control arm of the population in the RACE II registry, Holter ECG continues to be very useful to monitor heart rate profile in subjects with AF.<sup>26</sup>

### Study limitations

The major limitation in the study is the lack of follow up and outcome data. Background co-morbid conditions and orthostatic data (in those that had syncope) were also not available. We could not provide the medication data such as beta blockers that could have impacted the occurrence of premature extra beats and duration of RR intervals. It is also not known if those subjects with  $> 1000$  PVCs/24 hour underwent echocardiographic investigation to rule out structural heart disease resulting in syncopal episodes. Since 16% of the study population had AF and since all of them had minimum and average heart rate profile comparable to those without AF it is reasonable to believe that these patients were on antiarrhythmic medication. The time lapse between the Holter registration and the referral from the primary care center is quite variable which is why a clear cause and effect relationship between the referral reason for syncope and the Holter findings could not be clearly established. Despite this limitations we are convinced that the current Holter data provide a real world scenario in a community setting similar to the Copenhagen City Heart Study.<sup>6</sup>

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