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Heart rate variability and its changes over 5 years in older adults

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Abstract

Purpose: to characterise the association between age, ageing and heart rate variability (HRV) in older individuals, 585 adults age >65 years with two 24-h Holter recordings in the Cardiovascular Health Study were studied.
Methods: heart rate (HR), ventricular premature contractions (VPCs), atrial premature contractions (APCs), frequency-domain, ratio-based and non-linear HRV and heart rate turbulence (HRT) were examined cross-sectionally by 5-year age groups and prospectively over 5 years. Analyses adjusted for gender, lower versus elevated cardiovascular (CV) risk and for the change in CV risk.
Results: HR declined, and VPCs and APCs increased per 5-year increase in age. Frequency-domain HRV decreased more at 65–69, less at 70–74 and minimally at ≥75 years, independent of CVD risk or change in CVD risk. Ratio and non-linear HRV continued to decline to ≥75 years old. Ratio HRV and HRT slope were more strongly related to CVD risk than frequency-domain HRV.
Conclusions: cardiac autonomic function, assessed by frequency-domain HRV, declines most at 65–70 and levels off at age >75. The decline is independent of CVD risk or change in CVD risk. Ratio-based and non-linear HRV and HRT slope continued to change with increasing age and were more closely related to CVD risk than frequency-domain HRV.

Keywords: *ageing, autonomic nervous system, heart rate variability, ambulatory ECG, elderly*

Introduction

Cardiac autonomic function can be assessed by heart rate variability (HRV) [1]. Although older age and ageing are believed to be associated with decreased HRV, there are few studies of HRV in older adults [2, 3] and they are mostly cross-sectional, with few >70 years of age. Only limited HRV measures have been assessed, and heart rate turbulence (HRT) has not been measured [3, 4]. These studies have not taken cardiovascular

disease (CVD) risk, which is associated with impaired autonomic function, into account [5].

The Cardiovascular Health Study (CHS), a population-based study of risk factors for CVD and stroke in people age ≥65 years, provides a unique opportunity to study age and HRV in older people. Holter monitoring (24 h) was performed at two time points (T1 and T2), 5 years apart, in 856 well-characterised older adults, and recordings were analysed to research standards. In order to gain perspective on the accuracy of prior cross-sectional studies of HRV and age, we compared information about HRV changes with age obtained from both cross-sectional and prospectively obtained recordings in the same participants. We also examined which HRV measures were affected by CVD risk and might therefore be useful for discriminating between healthy and potentially pathological ageing.

Methods

The CHS enrolled 5,888 community-dwelling adults >65 years old. The CHS has been described elsewhere [6, 7]. At baseline (T1), 1,421 underwent Holter monitoring. At T2, 5 years later in 1994/1995, 856 repeated Holter monitoring. Of these recordings, 585 pairs were adequate for HRV analysis (see the inclusion criteria below).

Cardiovascular risk category

Extensive clinical data were collected at T1 and collected on a more limited basis at T2. To adjust for CVD risk at T1 and T2 or changes in CVD risk from T1 to T2, a categorical variable—lower risk or increased risk—was created that incorporated measures available at both times. Lower risk for CVD at T1 or T2 had SBP ≤140 mmHg, DBP ≤90 mmHg, no beta blockers or anti-hypertensive medications, BMI ≤30, no history of MI, stroke, known CHD or CHF, fasting glucose <110 mg/dl and no hypoglycaemic medication use.

Analysis of Holter tapes

Tapes were recorded on Del Mar Avionics recorders and were processed by research technicians using a GE Marquette MARS 8000 Holter analyser (GE-Marquette, Milwaukee, WI, USA) using standard techniques. The scanner automatically detected and labelled each heartbeat (normal, ventricular ectopic, atrial ectopic). Automatically detected beats were over-read by the technicians and corrected if necessary. Undetected ectopic beats were inserted; however, undetected normal beats were inserted as 'unclassified' beats. Analyses were reviewed in detail by PKS. To be accepted for these analyses, recordings had to be in predominantly normal sinus rhythm with at least 18 h with ≥80% normal-to-normal (N–N) intervals. Both T1 and T2 recordings needed to be acceptable. HRV and ectopy counts were calculated from beat-to-beat files exported to a Sun Enterprise 450 server (Sun Microsystems, Santa Clara, CA, USA) using validated research software.

Frequency-domain HRV

Traditional HRV can be measured in the time or frequency domain. Time HRV domain measures, which are statistical calculations, all have equivalent frequency domain measures [1]. Therefore, to avoid reporting an overwhelming and redundant set of results, only traditional frequency domain measures of HRV are reported here. Frequency-domain HRV is based on power spectral analysis [8] and quantifies the amount of variance in N–N intervals at different underlying frequencies (see the legend of Table 1). Power spectral analysis was performed using standard methods [8]. Ultra-low frequency (ULF) power reflects variance in heart rate (HR) with a period of between 5 min and 24 h and primarily reflects circadian HR patterns and long-term activities [9]. Very low frequency power (VLF, variations from 20 s to 5 min cycles) is believed to reflect the activity of the renin–angiotensin and parasympathetic systems, although it is exaggerated by periodic breathing patterns [10]. Low frequency power (LF, variations from 3 to 9 cycles/min) reflects the combined activity of the sympathetic and parasympathetic nervous systems [9]. Beat-to-beat HR changes are quantified by high frequency power (HF, variations at respiratory frequencies) and primarily reflect parasympathetic modulation of HR [9]. In addition, there are various ratio-based HRV measures that are proposed as measures of relative autonomic balance [9]. These include normalised low and high frequency power and the low-to-high frequency power ratio. More details are found in the legend for Table 1.

Non-linear HRV

Non-linear HRV quantifies the structure of the HR time series. The power-law slope characterises the fractal (i.e. self-similar) qualities of HRV occurring on time scales ranging from about a minute to several hours. More negative values are associated with worse outcomes among cardiac patients [11]. Detrended fluctuation analysis (DFA) quantifies the fractal scaling properties of the short-term R–R interval time series [12, 13]. DFA1 quantifies these properties on a scale of 4–11 beats. Higher values indicate less complexity and more periodicity in the HR time series, and lower values indicate more random fluctuations. Lower values for DFA1 are associated with worse outcomes in cardiac patients [14] and in the CHS [15].

Heart rate turbulence

HRT quantifies the response of the sinus node to ventricular premature contractions (VPCs) [16]. Normally, there is a brief sinus tachycardia after a VPC. Turbulence onset (TO) measures the magnitude of this tachycardia (if any) as the per cent change in the N–N interval of the two sinus beats after the VPC compared to the two before. Normally, TO is negative or zero, so TO >0 is abnormal (bradycardia or no tachycardia). TS quantifies the oscillation in HR (tachycardia, bradycardia then return to baseline) that follows a VPC as the largest fitted slope of the N–N intervals between any 5 beats

within 15 beats of the VPC. This requires five or more VPCs for calculation and is determined as a signal average of all of the VPCs on the recording, but participants having fewer than five total VPCs can be categorised as having normal HRT.

Statistical analysis

Frequency-domain HRV indices (ULF, VLF, LF and HF power), atrial and ventricular ectopy counts were skewed and natural log (ln) transformed before statistical analyses. *t*-tests compared age and Holter-based measures for lower and higher CVD risk at both T1 and T2. Age was then categorised by 5-year groups (65–69, 70–74, 75–79 and <80 years). The following comparisons were made:

differences in HRV between 5-year age groups at T1, adjusted for gender and CVD risk category at T1;
differences in HRV between 5-year age groups at T2, adjusted for gender and CVD risk category at T2;
pairwise changes in HRV between T1 and T2, adjusted for gender, CVD risk category at T1 and change in CVD risk category between T1 and T2.

Relationships of HRV with age group adjusted for gender, CV risk category, and potential interactions between them were tested using the UNIANOVA procedure in SPSS. Relationships of changes in HRV with age group, gender, baseline CV risk category and change in risk category were determined using a repeated measures ANOVA. *Post hoc* comparisons used Tukey's *post hoc* test with pre-planned contrasts of adjacent age groups only. Significance was $P < 0.05$. SPSS 14 (SPSS, Chicago, IL, USA) was used for this analysis.

Results

CHS participants with a T2 recording were younger (71 ± 4 vs. 73 ± 5 years, $P < 0.001$), more likely female (61 vs. 55%, $P < 0.001$) and at lower CVD risk (25 vs. 30% lower risk, $P = 0.006$) at T1 than those without a T2 recording. There were no other significant differences between those who did and did not have a second recording.

The cohort was 97% white. At T1 there was a 29% prevalence of systolic and a 3% prevalence of diastolic hypertension, although 41% were on anti-hypertensive medications. Normal glucose tolerance was seen in 73% and 14% had diabetes. BMI ≥30% was found in 20%. Only 18% had clinical CVD. The proportion with increased CVD risk rose from 69% to 74% during follow-up, due primarily to increased use of anti-hypertensive medications (51% at T2) and an increase in the number diagnosed with clinical cardiovascular disease (26% at T2).

Table 1 shows Holter-based measures that differed by CVD risk category. HRs were decreased with increased CVD risk at T1, but differences narrowed at T2. The VPC count was not different by CVD risk at T1 but widened at T2. Most HRV measures were more abnormal with increased as compared to lower CVD risk. Differences in frequency-domain

Table 1. Holter-based measures significantly different by cardiovascular risk category for T1 or T2 (cross-sectional analyses)

	T1 Lower risk = 182 Higher risk = 403 (*n* = 585) Mean ± SE	T2 Lower risk = 153 Higher risk = 432 (*n* = 585) Mean ± SE
Age		
Lower risk	70 ± 0.3	75 ± 0.3
Higher risk	71 ± 0.2	76 ± 0.2
P-value	**0.001**	**0.022**
Heart rate (HR)		
Lower risk	75 ± 1	74 ± 1
Higher risk	73 ± 1	73 ± 1
P-value	**0.027**	0.054
Number of VPCs*		
Lower risk	10 [57]	12 [97]
Higher risk	13 [93]	32 [223]
P-value	0.180	**0.001**
Ln ULF		
Lower risk	9.5 ± 0.04	9.4 ± 0.1
Higher risk	9.3 ± 0.03	9.2 ± 0.03
P-value	**0.002**	**0.014**
Ln LF		
Lower risk	5.9 ± 0.1	5.7 ± 0.1
Higher risk	5.8 ± 0.04	5.6 ± 0.04
P-value	**0.019**	0.408
Normalised LF		
Lower risk	65 ± 0.8	63 ± 0.8
Higher risk	63 ± 0.5	59 ± 0.5
P-value	**0.002**	**<0.001**
Normalised HF		
Lower risk	22 ± 0.6	24 ± 0.7
Higher risk	24 ± 0.4	26 ± 0.5
P-value	**0.024**	**0.006**
LF/HF ratio		
Lower risk	4.8 ± 0.2	4.4 ± 0.2
Higher risk	4.4 ± 0.1	3.8 ± 0.1
P-value	**0.014**	**0.003**
DFA1		
Lower risk	1.10 ± 0.01	1.07 ± 0.01
Higher risk	1.06 ± 0.01	1.01 ± 0.01
P-value	**0.023**	**0.001**
	Lower risk = 147 Higher risk = 325 (*n* = 472)	Lower risk = 124 Higher risk = 379 (*n* = 503)
Turbulence slope		
Lower risk	7.7 ± 0.6	6.5 ± 0.5
Higher risk	6.6 ± 0.3	5.1 ± 0.2
P-value	**0.043**	**0.006**
Turbulence onset		
Lower risk	−0.015 ± 0.002	−0.012 ± 0.002
Higher risk	−0.011 ± 0.001	−0.008 ± 0.001
P-value	0.085	**0.047**

Heart rate (HR) beats/min = 60,000/average of normal-to-normal (N–N) intervals; ULF = ultra-low frequency power (1.15×10^{-5}–0.003–0.0033 Hz); VLF = very low frequency power (0.0033–0.04 Hz); LF = low frequency power (0.04–0.15 Hz), average of 5-min values; HF = high frequency spectral power (0.15–0.4 Hz), average of 5-min values; normalised LF (%) = LF/(TP−VLF), average of 5-min values; normalised HF (%) = HF/(TP−VLF), average of 5-min values; LF/HF ratio = LF/HF for average of 5-min values; DFA1 = short-term fractal scaling exponent; power-law slope = slope of a line fitted to a plot of log spectral power versus log of underlying frequency between 10^{-2} and 10^{-4} Hz; turbulence slope (TS) in ms/beat = maximum slope of any 5 beats in the 15-beat interval after a VPC; turbulence onset (TO) = average ratio of the difference in the N–N interval of the two beats before each VPC and the N–N interval of the two beats after each VPC divided by the N–N interval before each VPC. $P < 0.05$ in bold.

*P-values based on ln transformed values.

Table 2. Covariate-adjusted Holter-based measurements significantly different between 5-year age groups by cross-sectional analysis (Group 1: $n = 272$, Group 2: $n = 216$, Group 3: $n = 71$, Group 4: $n = 26$)

	T1 ($n = 585$) Mean ± SE	T2 ($n = 585$) Mean ± SE
Number of APCs		
Group 1 ≤70	30 [84]	
Group 2 70–74	51 [100]	62 [186]
Group 3 75–79	74 [264]	77 [175]
Group 4 ≥80	55 [270]	179 [628]
	P-value	*P*-value
	1:2 <0.001	
	2:3 = 0.026	2:3 = 0.208
	3:4 = 0.967	**3:4 = <0.001**
	($n = 585$)	($n = 585$)
ln VLF		
Group 1 <70	7.0 ± 0.04	
Group 2 70–74	6.9 ± 0.04	6.8 ± 0.1
Group 3 75–79	6.8 ± 0.01	6.8 ± 0.1
Group 4 ≥80	6.7 ± 0.1	6.7 ± 0.1
	P-value	*P*-value
	1:2 = 0.008	
	2:3 = 0.507	2:3 = 0.176
	3:4 = 0.405	3:4 = 0.323
ln LF		
Group 1 <70	6.0 ± 0.1	
Group 2 70–74	5.8 ± 0.1	5.8 ± 0.1
Group 3 75–79	5.8 ± 0.1	5.61 ± 0.1
Group 4 ≥80	5.6 ± 0.2	5.5 ± 0.1
	P-value	*P*-value
	1:2 = 0.002	
	2:3 = 0.698	2:3 = 0.103
	3:4 = 0.337	3:4 = 0.195
Normalised LF		
Group 1 <70	66 ± 1	
Group 2 70–74	64 ± 1	63 ± 1
Group 3 75–79	63 ± 1	61 ± 1
Group 4 ≥80	58 ± 2	59 ± 1
	P-value	*P*-value
	1:2 = 0.177	
	2:3 = 0.342	**2:3 = 0.011**
	3:4 = 0.038	3:4 = 0.253
ln HF		
Group 1 <70	4.8 ± 0.1	
Group 2 = 70–74	4.6 ± 0.1	4.6 ± 0.1
Group 3 = 75–79	4.6 ± 0.1	4.6 ± 0.1
Group 4 ≥80	4.6 ± 0.2	4.6 ± 0.1
	P-value	*P*-value
	1:2 = 0.036	
	2:3 = 0.853	2:3 = 0.918
	3:4 = 0.898	3:4 = 0.433
Normalised HF		
Group 1 <70	22 ± 1	
Group 2 70–74	23 ± 1	23 ± 1
Group 3 75–79	24 ± 1	25 ± 1
Group 4 ≥80	26 ± 2	26 ± 1
	P-value	*P*-value
	1:2 = 0.420	
	2:3 = 0.438	**2:3 = 0.048**
	3:4 = 0.165	3:4 = 0.601
LF/HF ratio		
Group 1 <70	4.9 ± 0.1	
Group 2 70–74	4.6 ± 0.2	4.5 ± 0.1
Group 3 75–79	4.7 ± 0.3	4.0 ± 0.2
Group 4 ≥80	4.0 ± 0.4	4.0 ± 0.2
	P-value	*P*-value
	1:2 = 0.173	
	2:3 = 0.943	**2:3 = 0.004**
	3:4 = 0.170	3:4 = 0.975
Power-law slope		
Group 1 <70	−1.28 ± 0.01	
Group 2 70–74	−1.32 ± 0.01	−1.32 ± 0.01
Group 3 75–79	−1.33 ± 0.02	−1.36 ± 0.01
Group 4 ≥80	−1.37 ± 0.03	−1.39 ± 0.02
	P-value	*P*-value
	1:2 = 0.005	
	2:3 = 0.275	**2:3 = 0.003**
	3:4 = 0.269	3:4 = 0.079
DFA1		
Group 1 <70	1.10 ± 0.01	
Group 2 70–74	1.08 ± 0.01	1.07 ± 0.01
Group 3 75–79	1.07 ± 0.02	1.03 ± 0.01
Group 4 ≥80	0.99 ± 0.03	1.02 ± 0.02
	P-value	*P*-value
	1:2 = 0.212	
	2:3 = 0.676	**2:3 = 0.015**
	3:4 = 0.021	3:4 = 0.475
	($n = 568$)	($n = 600$)
Turbulence slope		
Group 1 <70	7.1 ± 0.4	
Group 2 70–74	7.2 ± 0.4	6.8 ± 0.4
Group 3 75–79	6.4 ± 0.6	5.4 ± 0.4
Group 4 ≥80	5.4 ± 1.0	4.7 ± 0.5
	P-value	*P*-value
	1:2 = 0.912	
	2:3 = 0.270	**2:3 = 0.005**
	3:4 = 0.412	3:4 = 0.237

See the Table 1 legend for HRV definitions. $P < 0.05$ in bold.

HRV between risk groups were unchanged over time. However, differences between lower and higher risk participants widened for normalised LF power, the LF/HF ratio, DFA1 and HRT slope. Ln VLF was not different between groups at either time point (data not shown).

Only measures that differed significantly for at least one age group compared to the next older group, after adjustment for gender and CV risk category, are shown in Table 2. At T1, the number of APCs increased up to 75–79 years. HRV decreased with increasing age for ln VLF, ln LF, ln HF and for power-law slope, but only differences between 65–69 and 70–74 years were statistically significant. There were generally no further differences in these measures with increasing age. On the other hand, normalised LF power and DFA1 were significantly lower in the ≥80-year-old group compared to 75–79.

At T2, there were no further cross-sectional differences in ln VLF, LF and HF between 70–74 and 75–79 years.

Table 3. Covariate-adjusted Holter-based measurements significantly different between 5-year age groups using pairwise comparisons[a]

Age at T1	T1 Mean ± SE	T2 Mean ± SE	*P*-value T1:T2
Heart rate			
<70	74 ± 1	74 ± 1	0.519
70–74	74 ± 1	73 ± 1	0.308
>75	72 ± 1	70 ± 1	0.089
All groups	74 ± 1	73 ± 1	**0.039**
Number of APCs[a]			
<70	30 [85]	62 [188]	**0.001**
70–74	52 [113]	84 [189]	**0.004**
>75	68 [255]	180 [625]	**<0.001**
All groups	42 [101]	86 [217]	**<0.001**
Number of VPCs[a]			
<70	11 [78]	15 [125]	0.206
70–74	12 [59]	31 [207]	**0.002**
>75	18 [108]	52 [332]	0.096
All groups	12 [78]	25 [175]	**0.001**
ln ULF			
<70	9.5 ± 0.04	9.3 ± 0.1	**0.001**
70–74	9.4 ± 0.1	9.3 ± 0.1	**0.010**
>75	9.3 ± 0.1	9.3 ± 0.1	0.986
All groups	9.4 ± 0.04	9.4 ± 0.04	**0.004**
ln VLF			
<70	7.0 ± 0.1	6.8 ± 0.1	**<0.001**
70–74	6.9 ± 0.1	6.8 ± 0.1	**0.042**
>75	6.8 ± 0.1	6.7 ± 0.1	0.580
All groups	6.9 ± 0.04	6.8 ± 0.04	**0.001**
ln LF			
<70	6.0 ± 0.1	5.8 ± 0.1	**<0.001**
70–74	5.9 ± 0.1	5.8 ± 0.1	0.137
>75	5.7 ± 0.1	5.6 ± 0.1	0.458
All groups	5.9 ± 0.1	5.7 ± 0.1	**0.002**
Normalised LF			
<70	66 ± 1	63 ± 1	**<0.001**
70–74	65 ± 1	61 ± 1	**0.000**
>75	63 ± 1	60 ± 2	**0.007**
All groups	65 ± 1	61 ± 1	**<0.001**
ln HF			
Group 1 <70	4.8 ± 0.1	4.6 ± 0.1	**0.026**
Group 2 70–74	4.7 ± 0.1	4.7 ± 0.1	0.477
Group 3 <75	4.5 ± 0.1	4.6 ± 0.1	0.481
All groups	4.7 ± 0.1	4.7 ± 0.1	0.991
Normalised HF			
<70	22 ± 1	23 ± 1	**0.014**
70–74	22 ± 1	25 ± 1	**<0.001**
>75	23 ± 1	25 ± 1	0.188
All groups	22 ± 1	24 ± 1	**<0.001**
LF/HF ratio			
<70	5.0 ± 0.2	4.6 ± 0.2	**0.001**
70–74	4.8 ± 0.2	4.1 ± 0.2	**0.000**
>75	4.6 ± 0.3	4.0 ± 0.3	**0.005**
All groups	4.8 ± 0.1	4.2 ± 0.1	**<0.001**
Power-law slope			
<70	−1.28 ± 0.01	−1.31 ± 0.01	**0.003**
70–74	−1.30 ± 0.01	−1.34 ± 0.01	**0.002**
>75	−1.34 ± 0.02	−1.38 ± 0.02	0.059
All groups	−1.31 ± 0.01	−1.34 ± 0.01	**<0.001**
DFA1			
<70	1.11 ± 0.01	1.07 ± 0.01	**0.005**
70–74	1.09 ± 0.02	1.03 ± 0.02	**0.000**
>75	1.08 ± 0.02	1.03 ± 0.03	**0.021**
All groups	1.09 ± 0.01	1.05 ± 0.01	**<0.001**
Turbulence onset			
<70	−0.014 ± 0.002	−0.014 ± 0.002	0.979
70–74	−0.012 ± 0.002	−0.006 ± 0.002	**0.047**
>75	−0.016 ± 0.003	−0.008 ± 0.003	**0.040**
All groups	−0.014 ± 0.001	−0.009 ± 0.001	**0.010**
Turbulence slope			
<70	7.2 ± 0.5	6.4 ± 0.5	0.182
70–74	6.9 ± 0.6	5.2 ± 0.6	**0.022**
>75	6.4 ± 0.7	5.1 ± 0.7	0.121
All groups	6.8 ± 0.4	5.5 ± 0.3	**0.003**

[a]Grouped by age at time T1: <70 ($n = 256$); 70–74 ($n = 207$); >75 ($n = 90$).
**P*-values based on ln transformed values.
See the Table 1 legend for HRV definitions. $P < 0.05$ in bold.

However, ratio-based frequency HRV measures, normalised LF, normalised HF, power-law slope, DFA1 and HRT slope were all lower between 75–79 and 70–74 years.

Pairwise changes in HR, HRV and ectopy counts over 5 years were adjusted for gender, baseline CVD risk category and change in CVD from T1 to T2 [categorised as 'no change' ($n = 555$) or 'increased' ($n = 66$)]. The small group that changed from increased to low ($n = 32$) risk was excluded, and participants >75 years old at T1 were combined into a single group. When changes were examined without stratifying on age, there were significant declines in almost all autonomic measures in association with ageing 5 years (Table 3). When viewed by age group, declines in autonomic function were steepest between <70 and 70–74. Smaller declines between 70–74 and ≥75 were statistically significant in the pairwise analysis only (Table 3). Pairwise analyses revealed declines in ratio measures across all age groups, including beyond age 75. There were no significant effects of age group on HR (data not shown), and no significant effect of gender or change in CVD risk on age-related changes.

Discussion

In this cohort study of predominantly healthy, white older adults, we found that most HRV measures of autonomic function decreased with increasing age. The greatest decline was between 65–69 years and 70–74 years and was found on both cross-sectional and pairwise prospective analyses. More modest changes between 70–74 and 75–79 years were also found but were significant only on pairwise analysis. By age >75 years, there were few further changes in frequency-domain HRV with advanced or advancing age. Patterns were different for ratio-based and non-linear HRV, where significant pairwise changes over 5 years occurred in all age groups, including >75 years.

No age-group-related differences were observed for HR in the cross-sectional analysis, although a significantly lower 24-h averaged HR was observed in increased risk versus lower risk participants at T1. This could be a result of lower activity

levels in higher risk individuals. Prospectively, HR declined over 5 years when the cohort was examined as a whole, but consistent with the cross-section findings, changes within each 5-year age group were not significant. This suggests that changes in 24-h mean HR over 5 years are not a sensitive marker for the presence of CVD risk or of the ageing of the autonomic nervous system.

Having increased risk of CVD was associated with more abnormal values of most HRV on cross-sectional analysis. Notably, however, the non-linear HRV measure power-law slope was not related to CVD risk at either time point. Differences in 5-year follow-up between those with lower and increased CVD risk widened for some Holter-based measures and were unchanged for others. Wider differences were seen in ventricular ectopy counts, ratio-based and non-linear HRV values (normalised LF power, the LF/HF ratio, DFA1). From this, it may be speculated that a steeper decline in these HRV markers among those at increased CVD risk may reflect declining CV health, while CVD-risk-independent declines in frequency domain measures of HRV between T1 and T2 may be better markers of the 'ageing' of cardiovascular (CV) autonomic control *per se*.

This is the first study to report on the relationship of HRT with CVD risk and with age and ageing in population-dwelling older adults. HRT quantifies the response of the CV system to the BP perturbation associated with a VPC and is believed to reflect baroreceptor functioning [17]. Although the HRT slope (TS) decreased with increasing age, most cross-sectional and pairwise differences over 5 years were non-significant, and none were significant for HRT onset (TO). Thus, HRT measures were not strongly related to 5-year changes in age, although the pairwise analysis did reveal a modest increase (worsening) in TO over 5 years in all groups older than 70. On the other hand, TO and TS were more abnormal in higher risk participants at both T1 and T2 and the difference between lower and increased risk patients widened at T2 for TS, suggesting a relationship of TS with CVD progression.

Age-related values for HF power, a measure of parasympathetically modulated respiratory sinus arrhythmia, declined both cross-sectionally and prospectively in 70–74 years compared to 65–69 years of age. However, no further decline with increasing age was seen. Results might suggest that the age-related decline of parasympathetic control of the heart levels off at age 70, a finding consistent with another study measuring 24-h HRV at baseline and 16 years later in 41 elderly subjects aged 69 $\pm$ 4 years [18]. However, another explanation is likely. We observed, as did the previously mentioned study, that decreases in the short-term fractal scaling exponent (DFA1) continued with advancing age. Decreasing DFA1 reflects increased randomness of HR patterns, i.e. an increase in a sinus arrhythmia that is not of respiratory origin [19]. This increase in randomness of HR patterns may be due to the ageing of the atrial conduction system and/or the ganglionic network that controls the pacemaker of the sino-atrial node [20]. Thus, while HF power due to parasympathetically modulated respiratory sinus arrhythmia may be decreasing with advancing age, in some participants HF power is increasing, because of an increase in randomness of HR patterns. As a result, the continuing age-related decline in parasympathetic control of HR, as measured by HF power, is likely to be masked by an increase in the prevalence of sinus arrhythmia of non-respiratory origin that elevates HF power.

A large number of HRV variables were analysed in this study. Although different measures of HRV tend to correlate to some degree, only 24-h ln TP and ln ULF can be considered surrogates, as both are primarily influenced by circadian changes in HR. Although it is true that people with excellent cardiac autonomic function will have good values for all HRV measures and that people with extremely poor autonomic function will have abnormal values for all measures, the different components of frequency-domain and non-linear HRV reported here all reflect different underlying autonomic processes, as previously described in the Methods section, and no HRV measure adequately characterised the entire system.

Limitations

Multiple statistical tests were performed in order to generate these results, and although Tukey *post hoc* testing was used for pairwise comparisons, there is no agreed upon method for correcting analyses that involve the full set of HRV measures. Findings are limited by the small number of participants categorised as having lower CVD risk at T1 with increased CVD risk at T2. Furthermore, few had CVD events during the 5-year time frame of this study, so that results cannot be generalised to older adults with clinical CVD. This has the advantage, however, of permitting the examination of the effect of ageing on HRV function unimpeded by the confounding effect of clinical CVD.

Implications

Results suggest that, in older adults, declines in traditional frequency-domain HRV measures may slow at age 70 years, whereas non-linear and ratio-based measures of autonomic function decline continuously throughout advancing age. Declines in the latter measures also appear to be more affected by the presence of CVD than are declines in traditional frequency-domain HRV measures.

Key points

- HR, HRV (reflecting autonomic function), atrial and ventricular ectopy over 24 h examined cross-sectionally and prospectively over 5 years in 585 community-dwelling adults $\geq$65 years.
- Age-related changes are different across measures.
- Atrial and ventricular ectopy continued to increase with advancing age.
- Frequency-domain HRV declined most between 65–69 and 70–74 years, with minimal declines after 75 years, independent of CV factors.

- Continuing decline with age of 'ratio' and 'non-linear' HRV measures with greater decline in cases of increased CV risk.

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Conflicts of interest

There are no conflicts of interest to disclose.

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