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Reference ranges of PR duration and P-wave indices in individuals free of cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

In this brief report, we provide normal reference ranges for PR duration [unadjusted and heart rate adjusted] and P-wave indices [duration, amplitude and terminal force in V1] in individuals free of cardiovascular disease and its risk factors. We used automatically processed digital ECG data from 1252 US participants [mean age 59 (± 10) years, 738 women, 588 whites, 207 African-Americans, 217 Hispanics, 240 Chinese] from the Multi-Ethnic Study of Atherosclerosis [MESA]. In multivariable adjusted linear regression models with PR and each P-wave variable as a separate outcome, significant age, sex and race differences in these markers were observed. Subsequently, we report reference ranges for abnormal [2nd and 98th percentiles], borderline abnormal [5th and 95th percentiles] and mean [SD] values of PR and P-wave indices stratified by age [middle age (45–64 years) and seniors (65–84 years)], sex [men and women] and race [whites, African Americans, Hispanics and Chinese].

Keywords

P-wave indices; PR interval; MESA

INTRODUCTION

The idea that PR duration and P-wave morphology carry important prognostic information that could be utilized for prediction of cardiovascular disease [CVD] outcomes is gaining wide interest. Data from population studies showed that PR duration and P-wave indices [duration, amplitude and terminal force in V1] are strong predictors of atrial fibrillation,

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stroke and all-cause mortality (1–4). These findings have triggered several studies looking at associations and impact of different CVD risk factors on PR and P-wave indices (5–7), as well as examining their genetic background (8–10). These associations and determinants, however, would be better interpreted in the context of normal values expected in individuals free of CVD and its risk factors. Therefore, we used data from the Multi-Ethnic Study of Atherosclerosis [MESA], a US community-based cohort study, to establish age-sex-race specific reference ranges for PR (unadjusted and adjusted for heart rate; PRa) and P-wave indices in individuals free of CVD and its risk factors.

METHODS

The description of the MESA study is provided elsewhere (10). Briefly, between July 2000 and August 2002, 6,814 men and women aged 45 to 84 years old and free of clinically apparent CVD were recruited from six US communities: Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan and the Bronx, New York; and St. Paul, Minnesota. For the purpose of this analysis, we excluded individuals who were smokers or with diabetes, hypertension, dyslipidemia or obesity. We also excluded those with major ECG abnormalities as defined by Minnesota ECG classification (12). After all exclusions, 1252 individuals free of CVD and CVD common risk factors remained and were included in this analysis. All participants gave written informed consent and the study was approved by the Institutional Review Boards at the 6 Field Centers.

Electrocardiography

Standard 12-lead ECGs were digitally acquired using a GE MAC 1200 electrocardiograph [GE, Milwaukee, WI] at 10 mm/mV calibration and speed of 25 mm/s. ECG reading was performed centrally at the Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Winston Salem, NC. All ECGs were initially inspected visually for technical errors and inadequate quality. P-wave durations and amplitudes needed to calculate p-wave indices were automatically measured with the GE Marquette 12-SL program 2001 version [GE Marquette, Milwaukee, WI]. A global single measure of PR interval was calculated from the beginning of the P-wave to the beginning of the QRS. Heart rate corrected PR was calculated using Soliman-Rautaharju formula (13). P-wave duration and P-wave amplitude used in this report were the maximum value of these measures across the 12 leads. Finally, P-wave terminal force was defined as the duration in milliseconds of the terminal part [negative] of the P wave in lead V1 multiplied by its depth in microvolts.

Statistical analysis

Multivariable linear regression analysis was used to examine differences (Beta coefficient and 95% confidence interval) in PR and each of the P-wave variables across categories of age [middle age (45–64 years) vs. seniors (65 years or older)], sex [male vs. female] and race [whites vs. African Americans, Hispanics and Chinese, separately]. Reference ranges for abnormal values [2^{nd} and 98^{th} percentiles], borderline abnormal [5^{th} and 95^{th} percentiles] and mean [SD] across these categories were calculated.

RESULTS

This analysis included 588 whites [60.7% women], 207 African Americans [54.1% women], 217 Hispanics [57.6% women] and 240 Chinese [60.0% women]. Characteristics of the study participants stratified by race are detailed in Table 1.

In a multivariable linear regression model with PR and each of P-wave variables as separate outcomes and age, sex and race as covariates, significant differences in the distribution of PR and P-wave indices were observed across categories of these demographics. As shown in Table 2, participants younger than 65 years [middle age] compared to those 65 years or older [seniors] had significantly shorter PR, PRa and P-wave durations [p-value for each <0.01], lower P-wave amplitude [p=0.047] and smaller P-wave terminal force in V1 [p-value <0.01]. Men, compared to women, had longer PR, PRa and P-wave durations [p-value for each <0.01], but lower P-wave amplitude [p=0.04] and no significant difference in P-wave terminal force in V1. The most significant racial differences were between African Americans and whites. Compared to whites, African Americans had longer PR, PRa and P-wave durations, higher P-wave amplitude, and larger P-wave terminal force in V1 [p-value for each <0.01]. Given these age, sex and race differences, we provide reference ranges of PR, PRa and P-wave indices stratified by these demographics in Tables 3 and 4.

DISCUSSION

In a large multiracial population of adults without evidence of CVD or its risk factors, we report age-, sex- and race-specific normal reference ranges for PR and P-wave indices. With the increasing utilization of these easy-to-obtain ECG markers, there is need for reference values to distinguish normal from abnormal limits which would subsequently help in better interpretation of risk factor associations and impact of different diseases on these markers. The observed age, sex and race differences in the distribution of PR and P-wave indices in our study call for caution when setting a cut-point for abnormal values since what could be normal in one group may be actually abnormal in another. Nevertheless, given the small magnitude of these differences despite being statistically significant, it is not clear at this stage if these differences are of clinical importance or mirror potential differences in the prognostic significance.

The classical cut-points defining PR or P-wave abnormalities such as 200 ms for prolonged PR or 120 ms for prolonged P wave duration or 4000 μV.ms for large p-wave terminal force in V1 were derived with no consideration to age, sex, or race differences. They were also derived mostly using non-digital ECG data that were processed manually. As could be observed from our results, these classical cut-points are not similar to those derived from digital automatically processed ECG in multi-racial setting. With the availability of automated ECG interpretation systems, it should be feasible to consider age, sex and race differences in the definition of P-wave and PR abnormalities.

To our knowledge, this is the first report that establishes normal reference ranges for PR and P-wave indices utilizing digital ECG data collected from a large sample of individuals from 4 different ethnic/race groups. A previous report from the Framingham Heart Study provided reference ranges for PR, P-wave duration and P-wave dispersion (14). However, this was only in 295 whites, and more than half of the participants did not have all of the 12 ECG leads because of background noise that prohibited accurate measurement of P-wave indices. More importantly, P-wave indices in the Framingham study were measured by an operator and the process was not fully automated.

In our report we focused on the most commonly used P-wave indices as well as the recently developed heart rate corrected PR. We ignored P-wave area because of its rare use and inconsistency of the methods of its calculation using different automated software (15). We also ignored P-wave dispersion because of the conflicting reports about its prognostic significance (16, 17) and lack of consensus on what really dispersion in ECG represents (17, 18). There is no doubt that differences in the p-wave duration across leads exist, which is expressed as isolelectric interval in some leads due to different orientation. This isoelectric

interval is not necessary due to heterogeneous atrial conduction (claimed to be reflected by P-wave dispersion) but could be simply explained by different orientation of the ECG leads. Without solid grounds linking difference in the duration of P-wave in the 12 ECG leads (i.e. P-wave dispersion) to specific atrial conduction abnormalities beyond the expected differences due to lead orientation, we believe it is not yet the time to use. Similarly, we used the maximum value of P-wave amplitude in the 12 leads instead of using individual values in each lead. To reasonably compare different populations, using a more repeatable measure such as maximum P-wave in the 12 leads that is less prone to random measurement error is needed. Nevertheless, given the known variations in the P-wave amplitude in different ECG leads, looking at individual leads may be warranted and useful for other purposes. Per lead P-wave amplitude data are available upon request from the authors.

The reference ranges we provide in this report are based on digital ECG data that were processed automatically. If PR and P-wave indices are to be measured manually by an operator using magnifying loupe, it would be appropriate to approximate the values of durations and amplitudes to the nearest 5 ms or 25 μv, respectively, which are probably the smallest measurements that could be reasonably made using visual non-automated measurement. On a related point, we did not compare our reference values from GE-Marquette to other automated software. However, it is believed that these measurements should be highly repeatable especially if high quality ECGs such as those in our study, are used.

Limitations

The reported reference ranges are for individuals aged 45 years and older, and therefore, may not be applicable to younger individuals. Also, caution is needed when comparing the reference ranges in this report with those previously published that were mainly based on lead II or using manual measurements.

We did not validate the automatic measurements of P-wave indices and PR which we used in this report. However, a statement of validation and accuracy of the Marquette 12-SL has been published elsewhere (19). Further, the GE Marquette 12-SL program is an FDA approved software for interoperation of ECG, and subsequently the results that come out of it should be reasonably valid. Therefore, we feel that validating the measurements ourselves would be beyond the scope of this paper.

Conclusions

In individuals free of CVD and its risk factors, there are differences by age, sex and race in the distribution of PR and P-wave indices. In this brief report, we provide age, sex and race specific references ranges for these prognostically important ECG markers using data from the MESA study, one of the major cohort studies in the US.

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Table 1

Characteristics of the study participants

	All participants	Whites	African Americans	Hispanics	Chinese
	(n=1252)	(n=588)	(n=207)	(n=217)	(n=240)
Age, years	59.2 ± 10.2	60.2 ± 10.1	59.2 ± 10.2	57.7 ± 10.2	57.9 ± 10.1
45–64, n (%)	842 (67.2)	375 (63.8)	137 (66.2)	155 (71.4)	175 (72.9)
65–84, n (%)	410 (32.8)	213 (36.2)	70 (33.8)	62 (28.6)	65 (27.1)
Female Sex, n (%)	738 (59.0)	357 (60.7)	112 (54.1)	125 (57.6)	144 (60.0)
Body Mass Index, kg/m^2	24.6 ± 3.0	24.6 ± 2.8	25.6 ± 2.9	25.9 ± 2.7	22.7 ± 2.7
Fasting Glucose, mg/dL	86.0 ± 9.1	84.5 ± 8.8	86.1 ± 8.8	86.9 ± 8.9	88.9 ± 9.6
Diastolic Blood Pressure, mmHg	67.7 ± 8.8	66.3 ± 8.8	71.2 ± 8.1	67.2 ± 8.5	68.5 ± 8.5
Systolic Blood Pressure, mmHg	112.4 ± 13.3	111.5 ± 13.5	115.7 ± 12.9	112.0 ± 12.8	112.2 ± 13.4
HDL Cholesterol, mg/dL	57.9 ± 13.8	59.7 ± 14.9	60.0 ± 15.1	53.8 ± 10.7	55.5 ± 11.0
LDL Cholesterol, mg/dL	112.7 ± 23.6	113.0 ± 23.7	110.8 ± 25.1	115.2 ± 22.8	111.3 ± 22.6
Total Cholesterol, mg/dL	188.9 ± 25.0	190.8 ± 24.9	186.0 ± 26.9	189.0 ± 24.4	186.8 ± 23.9
Triglycerides, mg/dL	91.5 ± 36.5	90.3 ± 35.7	75.8 ± 30.0	100.1 ± 36.4	100.4 ± 38.6

Table 2

Multivariable adjusted age, sex and race differences in PR and P-wave indices*

	Age (middle age versus senior)**		Sex (men vs. women)		Race (Reference group = white)					
					African American		Hispanic		Chinese	
	Difference *(95%CI)*	p	Difference *(95%CI)*	p	Difference *(95%CI)*	p	Difference *(95%CI)*	p	Difference *(95%CI)*	p
PR duration (ms)	**−5.1** *(−7.8, −2.4)*	**0.001**	**9.6** *(7.0, 12.2)*	**<0.001**	**5.8** *(2.1, 9.4)*	**0.002**	**−4.3** *(−7.9, −0.7)*	**0.02**	**−4.7** *(−8.2, −1.2)*	**0.01**
PRa duration (ms)	**−4.3** *(−7.0, −1.6)*	**0.002**	**8.6** *(6.0, 11.2)*	**<0.001**	**6.1** *(2.5, 9.7)*	**0.001**	**−3.6** *(−7.2, −0.1)*	**0.05**	**−3.7** *(−7.2, −0.2)*	**0.04**
P-wave duration (ms)	**−5.8** *(−7.3, −4.4)*	**<0.001**	**6.1** *(4.7, 7.4)*	**<0.001**	**3.8** *(1.9, 5.7)*	**<0.001**	**−0.4** *(−2.3, 1.4)*	**0.65**	**−2.4** *(−4.2, −0.6)*	**0.01**
P-wave amplitude (μV)	**−4.1** *(−8.1, −0.1)*	**0.05**	**−4.0** *(−7.9, −0.2)*	**0.04**	**11.7** *(6.3, 17.1)*	**<0.001**	**−1.5** *(−6.8, 3.7)*	**0.57**	**4.1** *(−1.0, 9.2)*	**0.11**
PTF-V1 (μV.ms)	**−682.4** *(−871.7, −493.1)*	**<0.001**	**99.9** *(−80.3, 280.1)*	**0.28**	**580.9** *(328.4, 833.4)*	**<0.001**	**−23.7** *(−272.1, 224.6)*	**0.85**	**327.4** *(87.8, 567.0)*	**0.007**

*Differences calculated using multivariable linear regression model with each PR/P-wave variable as the outcome in separate models and age, sex, race as covariates in all study population

**Middle age= 45–64; Senior 65 and older

PRa= Heart rate adjusted PR duration

PTF-V1= absolute value of P-wave terminal force in V1

Table 3

Age, sex and race specific reference ranges for PR interval

		Age group	Whites		African Americans		Hispanics		Chinese	
			Men (n=231)	Women (n=357)	Men (n=95)	Women (n=112)	Men (n=92)	Women (n=125)	Men (n=96)	Women (n=144)
PR duration (ms)	**Mean (SD)**	*Middle*	167 (25)	155 (23)	174 (24)	165 (22)	159 (19)	155 (21)	162 (19)	154 (18)
		Senior	176 (32)	162 (22)	178 (31)	160 (19)	162 (17)	163 (18)	160 (24)	158 (19)
	5%→95%	*Middle*	134→212	120→194	144→228	134→208	131→197	120→196	124→198	124→188
		Senior	132→234	132→202	130→248	136→186	138→190	138→200	130→212	128→198
	2%→98%	*Middle*	132→244	114→214	140→240	122→210	128→206	114→212	120→204	120→192
		Senior	128→246	124→212	128→260	134→218	130→196	136→204	128→220	124→214
PRa duration (ms)	**Mean (SD)**	*Middle*	163 (25)	153 (22)	170 (24)	162 (22)	157 (19)	153 (21)	160 (19)	152 (18)
		Senior	171 (33)	159 (22)	175 (32)	157 (18)	159 (17)	161 (18)	157 (24)	156 (19)
	5%→95%	*Middle*	130→207	118→189	137→224	131→205	130→193	119→197	124→194	121→188
		Senior	128→225	132→198	128→245	134→181	135→186	139→197	126→207	124→196
	2%→98%	*Middle*	130→241	113→213	136→238	120→206	126→200	112→208	118→199	118→189
		Senior	120→246	120→209	125→252	133→210	125→190	138→204	124→220	122→210

Middle age= 45–64; Senior 65 and older

PRa= Heart rate adjusted PR duration

Table 4

Age, sex and race specific reference ranges for P-wave indices

		Age group	Whites		African Americans		Hispanics		Chinese	
			Men (n=231)	Women (n=357)	Men (n=95)	Women (n=112)	Men (n=92)	Women (n=125)	Men (n=96)	Women (n=144)
P-wave duration (ms)	**Mean (SD)**	*Middle*	104 (14)	98 (13)	108 (13)	103 (10)	105 (10)	97 (12)	104 (10)	94 (10)
		Senior	111 (13)	105 (13)	112 (14)	106 (9)	108 (12)	105 (10)	106 (11)	104 (10)
	5%→95%	*Middle*	78→124	80→120	84→130	86→120	88→122	78→114	88→116	76→110
		Senior	90→130	83→125	96→144	84→122	88→128	90→122	92→124	86→128
	2%→98%	*Middle*	72→144	76→126	84→130	84→124	86→122	72→116	86→136	72→112
		Senior	82→136	78→138	72→146	84→122	84→134	88→126	78→126	82→128
P-wave amplitude (μV)	**Mean (SD)**	*Middle*	111 (29)	119 (36)	127 (38)	127 (37)	115 (28)	111 (27)	122 (33)	119 (35)
		Senior	114 (31)	123 (38)	124 (43)	138 (36)	120 (34)	121 (26)	122 (37)	122 (33)
	5%→95%	*Middle*	63→161	73→185	73→205	78→205	81→175	78→161	73→180	78→185
		Senior	68→170	78→190	87→229	92→239	83→185	78→161	73→205	73→205
	2%→98%	*Middle*	53→170	63→200	63→219	73→214	78→180	68→175	58→195	63→229
		Senior	68→195	63→200	78→268	78→239	58→224	68→170	63→205	73→214
PTF-V1 (μV.ms)	**Mean (SD)**	*Middle*	1507 (1519)	1350 (1510)	1954 (1900)	2049 (1424)	1680 (1513)	1238 (1198)	1769 (1489)	1538 (1487)
		Senior	1932 (1810)	2143 (1849)	2766 (1604)	2431 (1964)	1804 (1920)	2137 (1714)	2786 (1725)	2557 (1131)
	5%→95%	*Middle*	0→4410	0→4410	0→5976	0→4095	0→4551	0→3120	0→4347	0→4399
		Senior	0→4788	0→5905	0→5976	0→5772	0→5694	0→5229	0→5610	0→4399
	2%→98%	*Middle*	0→5146	0→5168	0→6612	0→4836	0→4891	0→3969	0→4420	0→5810
		Senior	0→6351	0→7812	0→7081	0→6059	0→7387	0→5304	0→7084	0→4453

Middle age= 45–64; Senior 65 and older

PTF-V1= absolute value of P-wave terminal force in V1