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Morphological abnormalities in baseline ECGs in healthy normal volunteers participating in phase I studies

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***Background & objectives*: Morphological abnormalities in 12-lead electrocardiograms (ECGs) are seen in subgroups of healthy individuals like athletes and air-force personnel. As these populations may not truly represent healthy individuals, we assessed morphological abnormalities in ECG in healthy volunteers participating in phase I studies, who are screened to exclude associated conditions.**

***Methods*: ECGs from 62 phase I studies analyzed in a central ECG laboratory were pooled. A single drug-free baseline ECG from each subject was reviewed by experienced cardiologists. ECG intervals were measured on five consecutive beats and morphological abnormalities identified using standard guidelines.**

***Results*: Morphological abnormalities were detected in 25.5 per cent of 3978 healthy volunteers (2495 males, 1483 females; aged 18-76 yr); the presence was higher in males (29.3% vs. 19.2% in females; *P*<0.001). Rhythm abnormalities were the commonest (11.5%) followed by conduction abnormalities (5.9%), axis deviation (4%), ST-T wave changes (3.1%) and chamber enlargement (1.4%). Incomplete right bundle branch block (RBBB), short PR interval and right ventricular hypertrophy were common in young subjects (<20 yr) while atrial fibrillation, first degree atrioventricular block, complete RBBB and left anterior fascicular block were more prevalent in elderly subjects (>65 yr). Prolonged PR interval, RBBB and intraventricular conduction defects were more common in males while sinus tachycardia, short PR interval and non-specific T wave changes were more frequent in females.**

***Interpretation & conclusions*: Morphological abnormalities in ECG are commonly seen in healthy volunteers participating in phase I studies; and vary with age and gender. Further studies are required to determine whether these abnormalities persist or if some of these disappear on follow up.**

Key words Age distribution - clinical trials - electrocardiography - healthy population - sex distribution

Morphological abnormalities in the 12-lead electrocardiogram (ECG) may occur in healthy individuals. In 1962, Hiss and Lamb published data on 122,043 healthy male air force pilots aged 16 to 50 yr; they found that 5,773 subjects (4.72%) had electrocardiographic abnormalities[1]. De Bacquer *et al*[2] found major morphological ECG changes in 5.5 per cent of 47358 working individuals between 40 and 64 yr of age using data derived from four large epidemiological studies performed in Belgium

over a 30 year period. Pelliccia *et al* studied the prevalence of ECG abnormalities in 32,652 Italian athletes; and found that 12 per cent had morphological abnormalities[3]. However, these subjects do not really represent normal healthy individuals in the population. Physical fitness of the normal population may not be comparable to that of air force personnel and athletes. Sustained high level of exercise results in change in vagal tone, may also lead to structural cardiac changes which may manifest in the ECG as changes in rate, rhythm and QRS amplitude[4,5]. There are some studies in the general population. However, subjects in these studies are screened for co-morbid conditions by self-reporting or by a questionnaire[3]. On the other hand, healthy volunteers participating in phase I studies are screened rigorously to exclude associated conditions. Therefore, these individuals are more likely to represent healthy individuals than those in population-based studies.

There are two large studies on ECG intervals in healthy individuals participating in drug studies[6,7]. Dmitrienko *et al*[6] studied the reference ranges of the ECG intervals and heart rate in baseline ECG recordings from 13,039 subjects included in clinical trials. However, they did not study morphological ECG abnormalities. Mason *et al*[7] have reported on drug-free ECGs from 79,743 subjects in clinical trials with a focus on defining reference ranges for ECG intervals; in this study, the authors excluded 8455 (15.5%) subjects due to presence of morphological ECG abnormalities[7]. Since there is a paucity of data from healthy individuals, we studied the presence of morphological abnormalities in baseline ECGs in healthy volunteers participating in drug trials.

Material & Methods

ECG data pooled from 62 phase I studies conducted globally by different pharmaceutical companies between 2005 and 2009, where Quintiles Cardiac Safety Services, Mumbai was used as a central ECG laboratory were analyzed retrospectively. Only studies that included healthy normal volunteers were considered.

In all studies, volunteers were screened by history, physical examination and laboratory tests. Haematological tests included haemoglobin, haematocrit, total and differential leukocyte counts and platelet count. Blood chemistry included serum bilirubin, transaminases, alkaline phosphatase, sodium, potassium, chloride, calcium, bicarbonate, blood urea nitrogen, creatinine, albumin and glucose. Appropriate tests for viral hepatitis (IgM for hepatitis A, antibody to core antigen for hepatitis B, hepatitis C antibody) and HIV were performed. Urine examination was done for protein, glucose, ketones, pH and microscopy (RBCs, WBCs, epithelials, and casts).

Subjects with history of long QT syndrome (personal or family) or other cardiac conduction disorder, or other clinically significant cardiac disease were excluded. Only normotensive subjects having resting blood pressure (>90 mm Hg and <140 mm Hg systolic; >60 mm Hg and <90 mm Hg diastolic) and normal resting heart rate (>50 bpm and <100 bpm) were included. Female subjects were included only if they were not pregnant (negative urine pregnancy test in women of childbearing age) or lactating. Only non-smokers or subjects who did not use any tobacco/nicotine products in the 6-month period preceding the screening visit were included. Individuals with a body mass index <18 or >30 kg/m^2, those with clinically significant abnormality at the screening medical assessment (history, physical examination, clinical laboratory tests, or ECG), or history of drug or alcohol abuse were excluded.

All subjects signed written informed consent forms for the respective study protocols and were able to understand and comply with the protocol requirements, instructions and protocol-stated restrictions. Age and gender of each subject was noted. Only a single drug-free baseline ECG from each subject was included in the present analysis.

ECGs were recorded using a digital electrocardiograph (Model Eli 250, Mortara Instrument Inc, Milwaukee, WI or Model MAC5000, GE Medical Systems, Freiburg, Germany) and were analyzed on-screen using digital calipers (CalECG Version 1.3, AMPS LLC, New York). For each ECG, PR interval, QRS duration, RR and QT intervals was the average of measurements made on five consecutive beats in lead II or V5. Morphology of the each ECG was interpreted in a standard sequence of rate, rhythm, conduction abnormality, hypertrophy/enlargement, axis, and or ischaemia/infarction. Standard diagnostic criteria were used to define various abnormalities (Table I). For each ECG, the reader could enter any number of diagnoses.

Statistical analysis: Chi-square test was used to compare prevalence of morphological abnormalities in males and females, and in various age groups.

Table I. ECG criteria for diagnosis of morphological abnormalities

Diagnosis	Criteria
Rhythm disturbances	
Sinus tachycardia[26]	Sinus rhythm with heart rate >100 bpm
Sinus bradycardia[5]	Sinus rhythm with heart rate < 50 bpm
Atrial extra systole: unifocal[27]	Atrial premature complexes originate from ectopic complexes in the atria. These may be unifocal or multifocal in origin. The P wave of the extrasystole is abnormal and different in configuration from sinus P wave and is premature in relation to the basic rhythm. QRS morphology typically unchanged unless functional BBB. Incomplete compensatory pause.
Atrial extra systole: multifocal[27]	
Ventricular extra systole: unifocal[27,28]	Ventricular extra systole also known as premature ventricular complex has its QRS complex that originates in the ventricles and is abnormally wide and accompanied by secondary ST-T changes. These beats are premature in relation to the expected beat of the basic rhythm. There is often a full compensatory pause following the PVC. Retrograde P wave due to retrograde ventriculo-atrial conduction may appear. PVCs originating from the same focus have constant coupling interval (interval between the PVC and the preceding beat of basic rhythm), except parasystole. According to the relation to basic beats, these may occur in various patterns such as bigeminy (relation 1:1), trigeminy (2:1), or can be in couplets when two PVCs follow in succession.
Ectopic atrial rhythm[5]	Presence of abnormal P waves and with a heart rate between 50 - 100 bpm.
Atrial fibrillation[28]	Complete absence of P waves. Rapid oscillation (“f” waves) may be seen varying in size, shape and timing. Irregularly irregular ventricular rhythm.
Junctional premature complex[28]	Junctional beat occurring earlier than the expected normal sinus P wave. P wave may follow, be superimposed on or rarely precede the QRS complex. Retrograde P waves, if present are : • Negative in leads II, III, aVF • Positive in leads I and aVR • Variable in precordial leads PR interval <120 ms. QRS complex is typically narrow (unless pre-existing BBB or aberrancy or pre-excitation)
Junctional escape complex[28]	Junctional beat occurring after a pause longer than normal PP interval
A-V block first degree [28]	PR interval >200 ms; each P wave is followed by QRS complex.
Incomplete right bundle branch block (IRBBB) [5,29]	QRS duration <120 ms but > 110 ms. Secondary R’ wave in right precordial leads V1 or V2 (usually rsr’, rsR’, rSR’).
Right bundle branch block (RBBB) [5,28]	QRS duration >120 ms. Secondary R’ wave in right precordial leads V1 or V2 (usually rsr’, rsR’, rSR’). Wide S wave in leads I, V5, V6 (more than 40 ms)
Left anterior fascicular block (LAFB)[28]	Frontal plane QRS axis of -45 to -90. qR morphology in leads I, aVL and rS morphology in leads II, III and aVF. QRS duration < 120 ms.
Intraventricular conduction delay (IVCD) [5,28]	QRS duration ≥ 110 ms. Criteria of LBBB or RBBB are not met.
Short PR interval[5]	PR interval <120ms
WPW syndrome[27,28]	PR interval <120 ms. Abnormally wide aberrant QRS complexes with duration of 110 ms or more. The presence of an initial slurring of QRS complex called Delta wave. Secondary ST segment and T wave changes.
Left atrial enlargement[5,27]	P wave duration in lead II >120 ms. Terminal negativity of P wave in lead V1 > 0.04 mV-sec.
Right atrial enlargement	Tall and peaked P wave with amplitude in lead II > 0.25 mV (in absence of tachycardia in amplitude).
Left ventricular hypertrophy with strain[5]	Classical ST and T wave changes (strain pattern) in LVH consists of ST segment depression with upward convexity and inverted T wave with a blunt nadir and asymmetric morphology in leads V4 to V6 and /or I, aVL.
Left ventricular hypertrophy by voltage only[5,27]	Voltage criteria (any one of the following) to be applied only to subjects >40 yr: • Amplitude of S wave in V1 + amplitude of R wave in V5 or V6 > 3.5 mV • Amplitude of R wave in aVL > 1.1 mV • Amplitude of R wave in aVL + amplitude of S wave in V3 is > 2.8 mV in men, > 2.0 mV in women

Contd...

Table I. (Contd.) ECG criteria for diagnosis of morphological abnormalities

Diagnosis	Criteria
Right ventricular hypertrophy[5]	• R:S ratio in V1 > 1 with R> 0.5 mV OR • rSR' in V1 with R' > 1.0 mV. • Right axis deviation > + 90º, if present is supportive of diagnosis
Left axis deviation[27]	- 30º< QRS axis < - 90º
Right axis deviation[27]	+ 90º< QRS axis < + 180º
North west Axis[30]	Axis between -90º & -180º or + 180º & + 270º
ST segment changes	
Non-specific ST change[5]	ST deviation not fulfilling the criteria for injury/ischaemia.
T wave abnormalities	
Non specific T wave changes[5]	T wave flattening/inversion/other T wave abnormalities like biphasic, notched, or asymmetric. Not meeting criteria for ischaemia.
T wave inversion suggestive of ischaemia[5,27]	Symmetrically and/or deeply inverted T waves in > 2 contiguous leads. ST depression with T wave inversion in > 2 contiguous leads.
U wave: abnormal[5,27]	Amplitude of U wave > 25 % of accompanying T wave amplitude in > 2 leads. U wave is negative in > 2 leads other then aVR & III.
Myocardial infarctions (MI)	
Old anterior MI[5,27]	Pathological Q waves (pathological q wave is > 40mS in duration and >25% of the ensuing R wave in amplitude) present on ECG in lead V1, V2, V3, V4, V5, V6
Old infero lateral MI[5,27]	Pathological Q waves (pathological q wave is > 40mS in duration and > 25% of the ensuing R wave in amplitude) present on ECG in lead II, III, avF, V5, V6 & or I, avL
Miscellaneous abnormalities	
Prolonged QT[21]	If QTc more than 430 ms in males and more than 450 ms in females
Low voltage QRS complex[26,27]	Total voltage (amplitude) of QRS in each of the limb leads < 5 mm and throughout the precordial leads < 10 mm

Superscript numbers indicate References

Results

A total of 3978 healthy volunteers (2495 males, 1483 females) who had participated in 62 phase I studies were included in this analysis. Age of these subjects ranged from 18 to 76 yr (31±14 mean ± yr). There were 803 subjects aged <20 yr, 2458 subjects between 21 and 45 yr, 634 subjects between 46 to 65 yr and 83 subjects were aged >65 yr.

Morphological abnormalities were seen in 1015 (25.5%) of 3978 subjects. The presence was higher in males (731 subjects, 29.3%) than in females (284 subjects, 19.2%; $P<0.001$). Rhythm abnormalities were present in 459 (11.5%) subjects (Table II), followed by conduction abnormalities (5.9%), axis deviation (4%), ST-T wave changes (3.1%) and chamber enlargement (1.4%) (Table III).

Individual abnormalities: The 10 most common morphological abnormalities were sinus bradycardia (7.8%), right axis deviation (3.3%), non specific T wave changes (2.5%), intraventricular conduction delay (IVCD) (2.3%), prolonged QT (2.3%), A-V block first degree (2.2%), ectopic atrial rhythm (2.1%), short PR interval (1.2%), left ventricular hypertrophy by voltage only (1.2%) and left axis deviation (0.8%). Multiple atrial premature complex, atrial fibrillation, junctional premature complex, junctional escape complex, right atrial enlargement, north-west axis, notched T wave, abnormal U wave and low voltage QRS complex were present in only one subject each.

Gender and age differences: On comparison between males and females (Tables II, III), sinus bradycardia (11%), first degree atrio-ventricular block (2.7%), right bundle branch blocks (0.3%), intraventricular conduction defects (3.2%), right axis deviation (4%) and left axis deviation (1%) were more common in males while sinus tachycardia (1.3%), short PR interval (1.7%), non specific T wave changes (3.5%) and flat T wave (1.1%) were more frequent in females.

Incomplete right bundle branch block (0.5%), short PR interval (1.6%), right ventricular hypertrophy (0.4%) and right axis deviation (5.5%) were most common in subjects <20 yr of age. Atrial fibrillation

Table II. Prevalence of rhythm and conduction abnormalities in baseline ECGs of 3978 healthy normal volunteers participating in 62 Phase I studies

Morphological abnormalities	All subjects (n=3978)	Female (n=1483)	Male (n=2495)	<=20 yr (n=803)	21-45 yr (n=2458)	46-65 yr (n=634)	>65 yr (n=83)
Rhythm abnormalities	459 (11.5)	108 (7.3)	351 (14.1)**	72 (9.0)	317 (12.9)	58 (9.1)	12 (14.5)
Sinus tachycardia	27 (0.7)	20 (1.3)	7 (0.3)**	9 (1.1)	15 (0.6)	3 (0.5)	0 (0.0)
Sinus bradycardia	312 (7.8)	38 (2.6)	274 (11.0)**	37 (4.6)	229 (9.3)	39 (6.2)	7 (8.4)
Atrial premature complex - unifocal	18 (0.5)	7 (0.5)	11 (0.4)	4 (0.5)	8 (0.3)	6 (0.9)	0 (0.0)
Atrial premature complex - multifocal	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Ventricular extra systole - unifocal	22 (0.6)	8 (0.5)	14 (0.6)	1 (0.1)	16 (0.7)	4 (0.6)	1 (1.2)
Ectopic atrial rhythm	84 (2.1)	34 (2.3)	50 (2.0)	23 (2.9)	50 (2.0)	8 (1.3)	3 (3.6)
Atrial fibrillation	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)**
Junctional premature complex	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Junctional escape complex	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Conductions	236 (5.9)	59 (4.0)	177 (7.1)**	47 (5.9)	140 (5.7)	39 (6.2)	10 (12.0)
A-V block first degree	88 (2.2)	20 (1.3)	68 (2.7)**	4 (0.5)	55 (2.2)	22 (3.5)	7 (8.4)**
Incomplete right bundle branch block (IRBBB)	5 (0.1)	1 (0.1)	4 (0.2)	4 (0.5)	1 (0.0)	0 (0.0)	0 (0.0)*
Right bundle branch block (RBBB)	8 (0.2)	0 (0.0)	8 (0.3)*	0 (0.0)	2 (0.1)	5 (0.8)	1 (1.2)**
Left anterior fascicular block (LAFB)	13 (0.3)	2 (0.1)	11 (0.4)	1 (0.1)	3 (0.1)	6 (0.9)	3 (3.6)**
Intraventricular conduction delay (IVCD)	90 (2.3)	11 (0.7)	79 (3.2)**	26 (3.2)	52 (2.1)	12 (1.9)	0 (0.0)
Short PR interval	48 (1.2)	26 (1.7)	22 (0.9)*	13 (1.6)	34 (1.3)	1 (0.2)	0 (0.0)*
WPW syndrome	2 (0.1)	1 (0.1)	1 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)

Figures in parentheses are percentages.*P<0.05; **P<0.005

(1.2%), first degree atrio-ventricular block (8.4%), complete right bundle branch block (RBBB) (1.2%), left anterior fascicular block (3.6%), left ventricular hypertrophy with strain (1.2%), left axis deviation (2.4%), T wave inversion suggestive of ischaemia (1.2%) were more common in elderly subjects (age >65 yr). Unifocal ventricular extrasystoles, first degree atrioventricular block, right bundle branch block, left anterior fascicular block, left axis deviation and T wave inversion suggestive of ischaemia showed a trend towards increasing frequency with increasing age. On the other hand, short PR interval (1.6%) and right axis deviation (5.5%) progressively decreased with increasing age. Sinus bradycardia, atrial premature complex - unifocal, and ectopic atrial rhythm showed no specific age-related differences.

Discussion

In a set of 3978 healthy volunteers participating in Phase I studies, who were rigorously screened to exclude associated co-morbid conditions, our study showed that morphological abnormalities in ECG were common; 25.5 per cent of subjects had an abnormal ECG. The prevalence was more frequent in male subjects (29.3% versus 19.2% in female subjects). This gender difference has also been reported by DeBacquer *et al* who found major morphological ECG changes in 6.0 per cent of men and 4.3 per cent of women in an epidemiological study in Belgium[2].

Sinus bradycardia (heart rate <50 beats/min) was seen in 7.8 per cent of our subjects. Mason *et al* found a heart rate of ≤47 in 2 per cent of healthy volunteers[7]. Sinus bradycardia may occur in healthy young adults during sleep, at rest or due to increased vagal tone[5]. It is more common in individuals performing regular exercise[5]. Sinus tachycardia was seen in only 0.7 per cent of volunteers as suggesting that sinus bradycardia is more common than sinus tachycardia in healthy individuals. We also found that sinus tachycardia was more common in women and sinus bradycardia in men. Previous studies have shown that the resting heart rate in women is faster than that in men, possibly

Table III. Prevalence of morphological abnormalities in baseline ECGs of 3978 healthy normal volunteers participating in 62 Phase I studies

Morphological abnormalities	All subjects (n=3978)	Female (n=1483)	Male (n=2495)	<=20 yr (n=803)	21-45 yr (n=2458)	46-65 yr (n=634)	>65 yr (n=83)
Chamber enlargements	56 (1.4)	18 (1.2)	38 (1.5)	7 (0.9)	34 (1.4)	14 (2.2)	1 (1.2)
Left atrial enlargement	11 (0.3)	6 (0.4)	5 (0.2)	1 (0.1)	8 (0.3)	2 (0.3)	0 (0.0)
Right atrial enlargement	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Left ventricular strain / Ischemia	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)**
Left ventricular hypertrophy by voltage only	46 (1.2)	16 (1.1)	30 (1.2)	3 (0.4)	31 (1.3)	12 (1.9)	0 (0.0)*
Right ventricular hypertrophy	3 (0.1)	0 (0.0)	3 (0.1)	3 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)*
Axis	161 (4.0)	35 (2.4)	126 (5.1)**	46 (5.7)	95 (3.9)	17 (2.7)	3 (3.6)
Left axis deviation	30 (0.8)	4 (0.3)	26 (1.0)*	2 (0.2)	12 (0.5)	14 (2.2)	2 (2.4)**
Right axis deviation	130 (3.3)	31 (2.1)	99 (4.0)**	44 (5.5)	82 (3.3)	3 (0.5)	1 (1.2)**
North west axis	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
ST-T changes	124 (3.1)	67 (4.5)	57 (2.3)**	10 (1.2)	72 (2.9)	39 (6.2)	3 (3.6)
Non specific T wave changes	98 (2.5)	52 (3.5)	46 (1.8)**	6 (0.7)	60 (2.4)	30 (4.7)	2 (2.4)**
Non-specific ST change	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Flat T wave	23 (0.6)	16 (1.1)	7 (0.3)**	4 (0.5)	14 (0.6)	5 (0.8)	0 (0.0)
Inverted asymmetric T wave	5 (0.1)	3 (0.2)	2 (0.1)	1 (0.1)	4 (0.2)	0 (0.0)	0 (0.0)
Symmetric T wave inversion suggestive of Ischemia	5 (0.1)	1 (0.1)	4 (0.2)	1 (0.1)	3 (0.1)	0 (0.0)	0 (0.0)
Biphasic T wave	3 (0.1)	1 (0.1)	2 (0.1)	0 (0.0)	2 (0.1)	1 (0.2)	0 (0.0)
Notched T wave	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
U wave: abnormal	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
T wave inversion suggestive of ischemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	2 (0.3)	1 (1.2)*
Miscellaneous	91 (2.3%)	29 (2.0%)	62 (2.5%)	16 (2.0%)	33 (1.3%)	41 (6.5)	1 (1.2)
Prolonged QT	90 (2.3%)	28 (1.9%)	62 (2.5%)	16 (2.0%)	33 (1.3%)	40 (6.3)	1 (1.2)**
Low voltage QRS Complex	1 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2)	0 (0.0)

Figures in parentheses are percentages. *P<0.05; **P<0.005

due to differences in exercise tolerance, autonomic modulation and intrinsic properties of the sinus node[8].

An abnormal QRS axis was seen in 4.1 per cent of our subjects. Dmitrienko *et al* found an abnormal QRS axis in 5.8 per cent of healthy volunteers in drug trials. Left axis deviation was found in 0.8 per cent of our subjects. Its prevalence in other population-based studies varies from 2.6 per cent[9,10] to 4.9 per cent[11]. The QRS axis may shift leftwards in obese subjects and with increasing age[5,12]. Right axis deviation, on the other hand, is less common and has been observed in 0.1 to 1 per cent of the healthy population, especially in tall asthenic individuals[1]. Vitelli *et al* found that 2.2 per cent of the healthy population had left axis deviation and 0.1 per cent had right axis deviation[13]. The relatively high prevalence of right axis deviation in our study may be due to younger age of subjects (80% were aged ≤45 yr) as compared to population-based studies usually include a large number of elderly individuals in whom left axis deviation is common[2,11,13,14]. We also found that left axis deviation was more common in men (1%) than in women (0.3%). A Belgian[2] and an Australian population-based study too have observed a higher prevalence of left axis deviation on elderly males[14].

First-degree A-V block was observed in 2.2 per cent of subjects in our study. It may occur in healthy individuals due to increased vagal activity[15] and was found 2 per cent of healthy subjects participating in pharmaceutical company-sponsored clinical trials[7]. As observed earlier[2], prolonged PR interval was more common in men than in women in the present study. Differences in atrio-ventricular nodal anatomy and

autonomic tone are possible explanations for the male preponderence[16].

The prevalence of right bundle branch block ranges from 0.2-1.6 per cent in the population. It was seen in 1.5 per cent of healthy volunteers by Mason *et al*[7], and in 1 per cent of athletes in a study by Pellicia *et al*[3]. We found RBBB in 0.2 per cent of our subjects; notably all these subjects were males. In contrast, LBBB is much less prevalent, and is seen in only 0.01 to 0.5 per cent of individuals; we did not find left bundle branch block in any of our subjects. In a study on 5360 Chinese healthy subjects aged 18 to 84 yr, 74 subjects had RBBB and four had LBBB[17]. We observed that RBBB was more common in men than in women; other studies have shown a male preponderance in the prevalence of RBBB with male: female ratio of 2.1 to 3.5:1; the prevalence of LBBB seems to be equal in both genders[2]. We also observed that the prevalence of bundle branch blocks increased with increasing age.

Intraventricular conduction delay (IVCD), was found in 2.3 per cent of the subjects in our study. Mason *et al*[13] found that 3.2 per cent of healthy volunteers participating in pharmaceutical clinical trials had QRS duration >110 ms and Vitelli *et al* found this in 2 per cent of the population. The QRS duration is influenced by gender and stature, being wider in males and in large, tall subjects[5]. Incomplete right bundle branch block was observed in only 0.1 per cent subjects in our study. It may be more common in athletes[3]. Left anterior fascicular block (LAFB) occurs in 0.5 to 1.5 per cent of healthy individuals and was seen in 0.3 per cent of subjects in our study[3,9,10].

Short PR interval was seen in 1.2 per cent of the subjects in our study, was more common in females and decreased with increasing age. Electrophysiologic studies have shown that both atrium-His and His-ventricular intervals are longer in men than in women[16]. The PR interval also depends on ventricular mass, which is also greater in men, and by female sex hormones levels.

Wolff-Parkinson-White Syndrome was seen only in two (0.1%) subjects (one male and female each) from our study. The prevalence of ventricular pre-excitation varies from 0.1 to 0.2 per cent[1-3,7]. In a study on 5360 healthy Chinese subjects, 10 (0.18%) had WPW syndrome[17]. Although a male preponderance is described[16], this was not evident in our study, probably due to a small number of individuals with this abnormality.

Left ventricular hypertrophy (LVH) by voltage was seen 1.2 per cent subjects with no gender preponderance. The prevalence of LVH in other studies has ranged from 0.6 to 0.9 per cent, and may be more prevalent in African Americans[13]. In one study, only 46 per cent of individuals with LVH by voltage criteria actually had left ventricular hypertrophy at autopsy[18]. Right ventricular hypertrophy (RVH) was seen in three (0.1%) of our subjects; all were aged 20 yr or less.

Nonspecific ST segment changes were seen in 3.1 per cent of our subjects and nonspecific T wave changes seen in 2.5 per cent. Both abnormalities were twice more prevalent in females than in males and increased with age. In a cohort study of 40-59 yr old European men, Rose and colleagues reported non-specific ST segment changes in 2.6 to 3.6 per cent of subjects and T wave abnormalities in 3.4 and 5.9 per cent[19]. Abnormalities of the T wave morphology such as flat, inverted, bifid or biphasic have been found in 0.5-2.0 per cent of persons in various population groups[5]. In participants of clinical trials, Dmitrienko *et al* found T wave abnormalities in 9.5 per cent of the subjects[6]. In the absence of heart disease, nonspecific T wave changes may occur with hyperventilation, electrolyte imbalance, postural change in heart position, vagally mediated reflexes, tachycardia and after food intake[5]. T wave inversion was seen in 10 (0.2%) subjects in our study. Of these, inverted asymmetric T wave change was seen in 5 subjects (3 males, 2 females) and symmetric inverted T waves suggestive of ischemia were seen in 5 subjects (4 males, 1 female). T wave inversions are often seen in athletes[3].

We found that ST-T wave abnormalities were significantly more common in women than in men. In the Australian Busselton study (40-79 yr), prevalence rates of ST and T wave changes were 2.4 and 6.8 per cent in women and 0.5 and 4.6 per cent in men, respectively[14]. These differences were also observed in a study of healthy adults from Michigan[12], and in Belgian adults[2,20]. The reasons for these are not clear. Liao *et al* suggest that ST-T changes are more common in women due to hyperventilation; abnormalities of left ventricular wall motion related to mitral valve prolapse, and altered myocardial sensitivity to circulating catecholamines due to anxiety or emotion[9].

Using the mean 95% confidence limits of the QTc interval in healthy individuals Moss and coworkers defined the upper limit for QTc interval as 430 ms in males and 450 ms in females[21]. Consequently, 2.5

per cent of normal men and women will have QTc intervals that exceed these limits. Using the same criteria, prolonged QTc was seen in 2.3 per cent of the subjects in our study, but none had QTc >500 ms. The prevalence of prolonged QTc interval did not differ with age. Mason *et al* too found that 3.2 per cent of healthy subjects participating in pharmaceutical clinical trials had prolonged QTc interval[7].

As in previous studies, unifocal atrial premature complexes were seen in 0.5 per cent subjects in our study; the prevalence was equal in both the genders. Ectopic atrial rhythm was seen in 2.1 per cent of subjects; this was more common in individuals aged ≥65 yr[22]. Only one male subject aged 72 yr had atrial fibrillation in our study. The prevalence of atrial fibrillation in the general population ranges from 0.2 to 0.7 per cent[2,12]. There is a definite age-related increase in atrial fibrillation and it is often asymptomatic[5,22,23], as in our healthy volunteer. Ventricular premature complexes were seen in 0.6 per cent subjects; this was not influenced by gender or advancing age. This is similar to the 0.8 per cent incidence reported by Hiss and Lamb in healthy airmen, but is lower that reported in studies using ambulatory ECG monitoring[22,24].

One of the limitations of this study is that the subjects were not randomly selected from the population, but were volunteers participating in Phase I clinical studies. Secondly, Phase I studies generally tend to include a fewer elderly subjects. In this sense, our subjects do not represent a cohort from a particular geographic region. However the strengths include a rigorous screening by clinical examination and laboratory tests to exclude co-morbid conditions, ensuring that these individuals are truly healthy and analysis of ECGs in a central ECG laboratory where stringent quality control processes are in place to ensure consistency and accuracy of ECG interpretation[25].

In conclusion, the present study showed that morphological ECG abnormalities were common in this population. There was a definite age and gender difference. Abnormalities like sinus bradycardia, first degree atrioventricular block, right bundle branch block, intraventricular conduction defects and left axis deviation were more common in males while sinus tachycardia, short PR interval and nonspecific ST segment and T wave changes were more seen in females. While the prognostic significance of some of these abnormalities has been well characterized, other abnormalities may only represent normal variations and their possible occurrence in healthy individuals must be kept in mind when these are encountered during routine health check-ups.

Our observations are especially relevant when interpreting data from phase I drug trials where normal healthy volunteers are administered new drug entities. Volunteers with ECG abnormalities like sinus bradycardia or tachycardia, conduction disorders or prolonged QT interval during the screening visit were excluded. However, in the baseline ECG recorded a few weeks later, some of these abnormalities appeared *de novo* in a few healthy volunteers, suggesting that some of these abnormalities may be transient. Further studies are required to determine whether these morphological abnormalities persist or whether some of these are only transient phenomena and disappear on further follow up.

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