Body Surface Potentials Generated by the Heart of Normal Guinea Pigs

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Abstract

The objectives of this study were to describe (1) the form of body surface potentials for P, QRS and ST-T components using semiorthogonal ECG leads and vectorcardiograms (VCGs), (2) the instability of the QT using coefficient of variation compared with 3 other published methods, and (3) the frequency-domain characteristics of the QRS complex. Electrocardiograms were recorded and VCGs of P, QRS and ST-T loops were generated in frontal (X-axis versus Y-axis), sagittal (Y-axis versus Z-axis), and horizontal (X-axis versus Z-axis) planes. Frequency-domain components of the QRS complex were calculated using Fast Fourier Transform (FFT) algorithm. One of the 7 guinea pigs was placed in sternal recumbency in a 1.5 T whole body scanner to identify specific cardiac structures which produce the QRS and ST-T. In relation to human ECGs, the guinea pig ECGs showed higher HR, and shorter P, QRS, and QT durations. The result of VCGs of the body surface in the guinea pigs suggested that the maximum vectors for P, QRS and ST-T were oriented, spatially caudad, ventrad and leftward. From NMR imaging, the guinea pig's heart was situated in a more nearly vertical position than the human heart. Spectral analysis of QRS demonstrated that the frequencies which yielded the greatest powers were 44.8, 61.4 and near zero Hz in lead I, aVF, and V10, respectively.

บทคัดย่อ

ศักย์ไฟฟ้าบนพื้นผิวของร่างกายที่สร้างโดยหัวใจของหนูตะเภา

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การศึกษาครั้งนี้มีวัตถุประสงค์เพื่อ (1) อธิบายรูปแบบของความต่างศักย์ไฟฟ้าที่กำเนิดโดยหัวใจซึ่งทำการวัด ณ พื้นผิวของร่างกาย สำหรับตรวจวัดค่า พี คิวอาร์เอส และ เอสที-ที โดยใช้เครื่องมือวัดคลื่นไฟฟ้าหัวใจ และเวคเตอร์คาร์ดิโอแกรม (2) แสดงความไม่มั่นคงของค่า คิวทีด้วยวิธีวิเคราะห์ความแปรปรวนเปรียบเทียบกับวิธีอื่นๆ 3 วิธีที่มีการพิมพ์เผยแพร่ และ (3) วิเคราะห์ลักษณะคลื่นความถี่ของคิวอาร์เอส โดยใช้วิธีฟาสต์ฟูเรียร์ทราสฟอร์ม เก็บข้อมูลคลื่นไฟฟ้าหัวใจและเวคเตอร์คาร์ดิโอแกรมจากหนูตะเภา 7 ตัว และใช้เครื่องเอ็มอาร์ไอวิเคราะห์ ลักษณะทางโครงสร้างของหัวใจเปรียบเทียบกับช่องอก เมื่อเปรียบเทียบกับมนุษย์พบว่าหนูตะเภามีอัตราการเต้นหัวใจที่สูงกว่าและมีระยะพี คิวอาร์เอส และ เอสที-ที สั้นกว่า ผลของเวคเตอร์คาร์ดิโอแกรมแสดงค่าเวคเตอร์สูงสุดของพี คิวอาร์เอส และเอสที-ทีในทิศที่ชี้ไปด้านท้าย ลง ด้านล่างและค่อนไปทางซ้าย และจากภาพของเอ็นเอ็มอาร์พบว่าหัวใจหนูตะเภาในช่องอกอยู่ในลักษณะแนวตั้งมากกว่าหัวใจมนุษย์ จากการ วิเคราะห์คลื่นความถี่คิวอาร์เอสพบว่าค่าความถี่ที่ทำให้เกิดกำลังสูงสุดอยู่ที่ 44.8, 61.4 และ ใกล้ศูนย์ เฮิร์ต ในลีดหนึ่ง เอวีเอฟ และวีเท็น ตามลำดับ

คำสำคัญ: หนูตะเภา หัวใจ คลื่นไฟฟ้าหัวใจ เวคเตอร์คาร์ดิโอแกรม

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Introduction

Guinea pig has emerged, as a mammalian surrogate for humans, to investigate potential toxic effects of drugs on the cardiovascular system (Hauser et al., 2005; Kagstrom et al., 2007; Gao et al., 2009). There are many benefits, and only a few limitations to use guinea pigs. They are inexpensive to house, tractable, highly predictable for torsadogenicity of drugs in humans, and are not afflicted with diseases communicable to human. Although they lack an I_{TO} channel (Mitcheson and Hancox, 1999; Ridley et al., 2003), this does not have limitation on predicting torsadogenicity in human. Many studies have been conducted in guinea pig models to explore effects of test articles on QTc, and attempted to predict torsadogenicity of the test articles for humans (Hamlin et al., 2004a; Hamlin et al., 2004b; Hauser et al., 2005; Kijtawornrat et al., 2005; Roche et al., 2005).

There are many publications describing the electrocardiograms (ECGs) of guinea pigs (Petelenz, 1971; Schwartze and Thoss, 1981; Cieslar et al., 1986). However, they were obtained using non-standardized electrocardiographs and lead systems, and none those publications has attempted to reconcile a putative cardiac activation process and topographical anatomy with the form of body surface potentials. Therefore, the objectives of this study were to describe (1) the form of body surface potentials for P, QRS and ST-T components using semiorthogonal lead ECGs and vectorcardiograms (VCGs), (2) the instability of the QT (beat-to-beat variability of repolarization) using coefficient of variation compared with 3 other published methods (Berger et al., 1997; Hondeghem et al., 2001; Thomsen et al., 2004), and (3) the frequency domain characteristics of the QRS complex using Fast Fourier Analysis.

Materials and Methods

Approvals: This study was approved by the Institutional Animal Care and Use Committee (IACUC) of QTest Labs, LLC and the experiment was conducted at QTest Labs except for the NMR study, which was conducted at The Ohio State University.

Animal preparation and ECG recording: A total of 7 male guinea pigs, weighing between 350 to 420 g, were used. All were judged to be in good health by their body conformation, activity, eating, and auscultation with normal heart sounds and breathing sounds. The animals were anesthetized with isoflurane (5% induction and 1% maintenance) in 95% to 99% oxygen at a rate of 400-500 ml/min. After clipping the hair from 4 legs and the dorsal region of thorax over the right or left 7th thoracic vertebra, the animals were placed in the right lateral recumbency and their thoracic limbs were kept at near right angles

to the long axis of the torso. ECG leads (subcutaneous needle electrodes) forming scalar semiorthogonal leads I (X), aVF (Y) and V10 (Z), were placed. Recordings of the scalar ECGs were obtained simultaneously on the Biopac MP100 Data Acquisition Unit for generation of vectorcardiograms (Biopac Systems, Inc., Santa Barbara, CA) and on an IOX version 1.7.0 for analysis of scalar ECGs (EMKA Technologies, Falls Church, VA). The high pass and low pass filters were set at 0.01 Hz and 500 Hz respectively, and signals were sampled at 1 kHz. Tracings were obtained for 5 minutes while the guinea pigs were asleep.

Magnetic Resonance Imaging (MRI): One of the 7 guinea pigs was anesthetized with ketamine (33 mg/kg) and xylazine (3.3 mg/kg). This guinea pig was placed in sternal recumbency in a 1.5 T whole body scanner (MAGNETOM Sonata; Siemens Medical Solutions, Erlangen, Germany) with commercially available coils (Machnet BV, The Netherlands). Images of the heart were obtained for the purpose of identifying specific cardiac structures, depolarization, and repolarization which are thought to generate body surface potentials.

Data analysis: From the scalar ECGs, the following durations were measured automatically by the ECG-auto version 1.5.12.43 (EMKA Technologies, Falls Church, VA) for the final minute (approximately 200 beats) of 5 consecutive periods of recording in ms: RR, P, PQ, QRS, QT, QTc (F) and QTc (B), where F stands for correction of Fridericia and B for Bazett. Means, standard deviations (SD), coefficients of variation (C), maximal values, minimal values and differences between maximum and minimum values were calculated. QT Instability (QTI) was calculated from 200 consecutive QT intervals by 3 methods that were previously used (Berger et al., 1997; Hondeghem et al., 2001; Thomsen et al., 2004) and as the coefficient of variation. Firstly, the method of Hondeghem measures all QT interval, reorganizes them from the shortest to the longest, calculates the shortest and the longest 25%, and uses instability as the difference between the longest and the shortest (QTI = 75th percentile – 25th percentile). Secondly, the method of Berger applies the following equation: QT variability index (QTVI) = log10 [(QTʋ/QTm2)/(HRʋ/HRm2)], where QTʋ = variance of QT interval (ms), QTm = mean of QT interval (ms), HRʋ = variance of heart rate (bpm), and HRm = mean of heart rate (bpm). Finally, the method of Thomsen uses the following equation: short-term variability (STV) = ∑│Dn+1-

Dn│/[200x√2], whereas D = the duration of QT (ms). The coefficient of variation (%) of a set of values is calculated as 100*(SD/Mean). The QT interval was measured from the onset of Q wave to the end of T wave. The QT intervals were corrected for the preceding RR intervals using common exponential formulas (Bazett, 1920; Fridericia, 1920), which were suggested to be the best for correcting QT for RR interval in anesthetized guinea pigs (Hamlin et al., 2003).

Frequency components of the QRS complex were performed using a Fast Fourier Transform (FFT) algorithm and the frequencies, at which the peak power below the trivial power is present, were determined.

Vectorcardiographic P, QRS and ST-T loops were generated in frontal (X-axis versus Y-axis), sagittal (Y-axis versus Z-axis) and horizontal (X-axis versus Z-axis) planes. Loops were interrupted at 1 ms intervals. All vector loops were expressed by directions of inscription (clockwise, counterclockwise), and by magnitude and orientation of mean vectors in each plane.
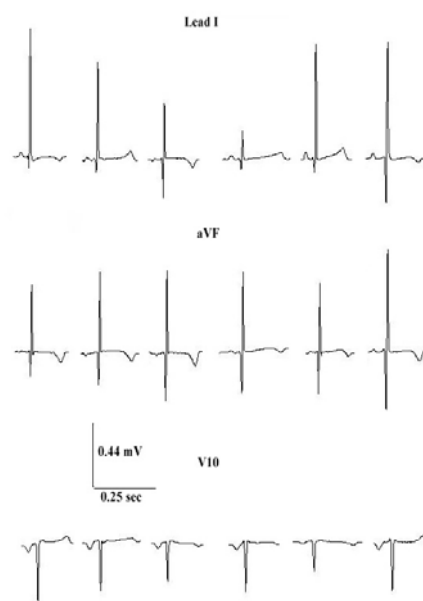
Results

Figure 1 Electrocardiograms recorded from scalar semiorthogonal leads (X: Lead I, Y: aVF, and Z: V10) were obtained from 6 anesthetized guinea pig.

Table 1 Measurements of individual parameters of the scalar ECG in anesthetized guinea pigs.

| Guinea Pig	Mean	S.D.	C (%)	Max	Min	Difference
RR (ms)	233.2	37.3	16.0	310.1	200.7	109.4
PQ (ms)	51.0	6.6	12.8	60.2	43.5	16.7
P (ms)	18.93	1.56	8.2	20.57	16.03	4.54
QRS (ms)	21.0	1.8	8.4	23.9	18.3	5.6
QT (ms)	147.1	16.0	10.9	176.1	129.4	46.7
QTc(F) (ms)	239.0	14.2	5.9	260.2	221.1	39.1
QTc(B) (ms)	304.3	12.1	4.0	320.0	288.0	32.0
QTVI$_{200}$ (ms)	0.78	0.55	69.9	1.31	-0.18	1.49
STV of QT (ms)	1.33	1.09	82.0	3.50	0.44	3.06
QT instability (ms)	3.04	2.20	72.5	6.00	1.00	5.00
C (%)	1.47	0.90	61.3	2.77	0.50	2.28
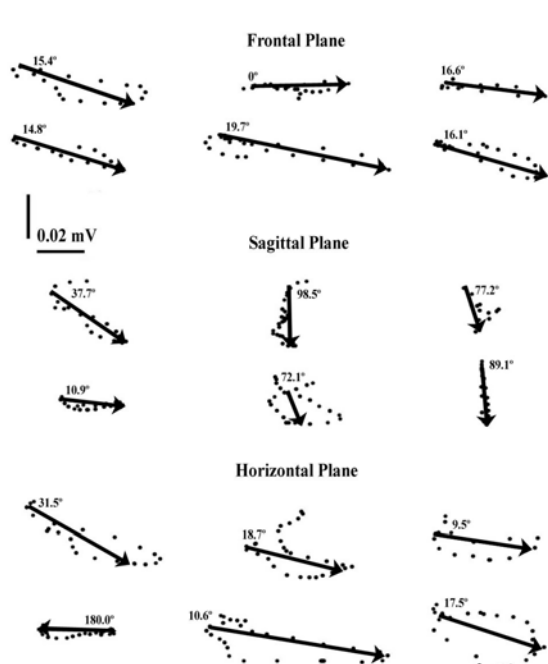
Figure 2 Vectorcardiograms (VCGs) recorded from 6 anesthetized guinea pigs shows the records of the P loops in each plane (Frontal/Ventral, Sagittal/left, and Horizontal/Coronal).

Figure 4 Vectorcardiograms (VCGs) recorded from 6 anesthetized guinea pigs shows the records of the ST-T loops in each plane (Frontal/Ventral, Sagittal/left, and Horizontal/Coronal).
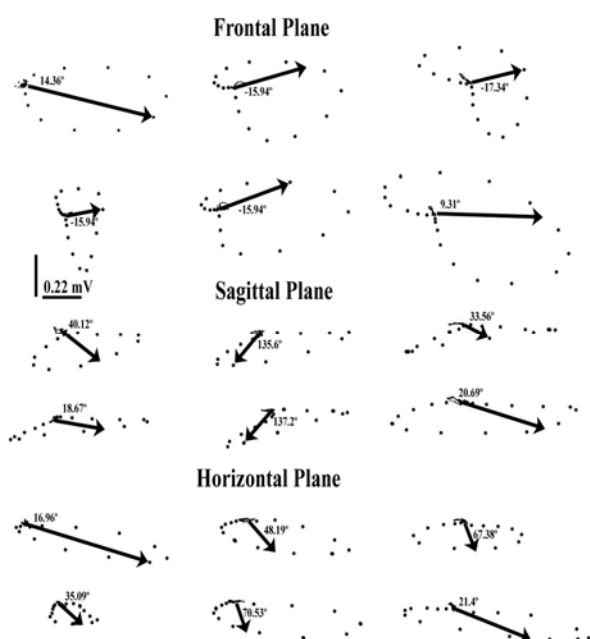

Figure 3 Vectorcardiograms (VCGs) recorded from 6 anesthetized guinea pigs shows the records of the QRS complex loops in each plane (Frontal/Ventral, Sagittal/left, and Horizontal/ Coronal).
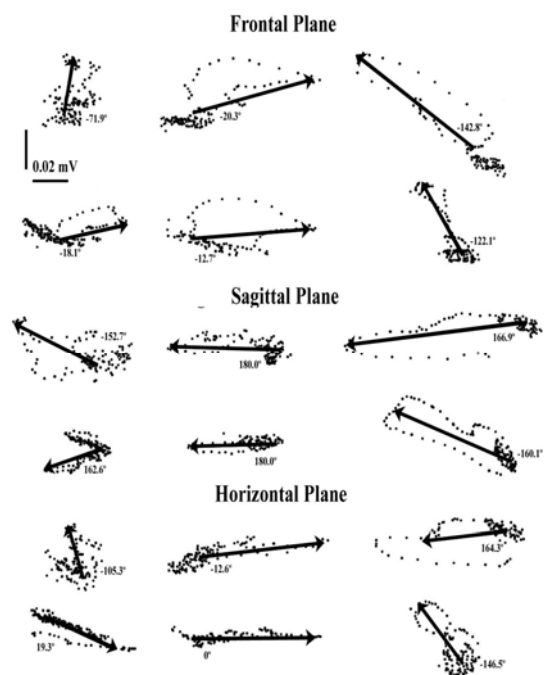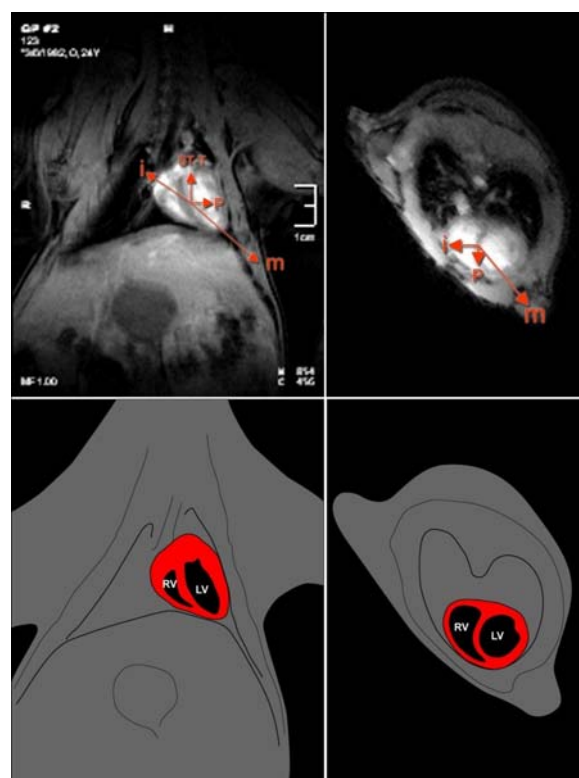

Figure 5 shows nuclear magnetic resonance (NMR) frontal (ventral), and horizontal (coronal) images of a representative guinea pig. For the ventral view, the animal's left is to the viewer's right; the animal's tail is at the bottom. For the coronal view, the animal's left is to the viewer's right. In the upper panels, i: The initial portion of the QRS complex vector, ST-T: The ST-T vector, p: The P wave vector, m: The major portion of the QRS complex vector. In the lower panel, RV: Right Ventricle and LV: Left Ventricle.

Table 2 Measurements of vectorcardiograms in anesthetized guinea pigs.

Guinea Pig		Length	Width	Ratio	Direction of inscription	Magnitude	Orientation
		millivolts				millivolts	degrees
Frontal Plane	P	0.052±0.004	0.017±0.002	3.29±0.43	CW	0.050±0.004	13.77±2.84
	QRS	0.80±0.12	0.45±0.04	1.81±0.30	CW	0.51±0.09	-6.90±5.98
	ST-T	0.065±0.010	0.039±0.005	1.77±0.33	CCW	0.054±0.008	-64.65±23.31
Sagittal Plane	P	0.022±0.005	0.024±0.003	1.24±0.49	CW	0.026±0.003	64.25±13.63
	QRS	0.86±0.07	0.20±0.01	4.55±0.67	CW	0.32±0.05	64.30±23.03
	ST-T	0.067±0.12	0.028±0.005	2.84±0.68	CW	0.058±0.008	62.78±69.38
Horizontal Plane	P	0.050±0.006	0.024±0.004	2.43±0.47	CW	0.047±0.006	44.61±27.27
	QRS	0.80±0.12	0.20±0.01	3.64±0.42	CW	0.37±0.10	43.26±9.28
	ST-T	0.064±0.010	0.026±0.004	3.24±1.01	CW	0.049±0.007	-13.46±44.35

CW: Clockwise, CCW: Counterclockwise

Scalar electrocardiograms (Fig 1) of excellent quality for interpretation were obtained from all guinea pigs. Vectorcardiograms of excellent quality for interpretation were generated from the scalar electrocardiograms (Figs 2-4). All animals maintained sinus rhythms with heart rates between 193 and 285 (mean 257) beats per minute.

Measurements from scalar ECGs of all animals are shown in Table 1 with measurement of vectorcardiograms in each plane are shown in Table 2. Both P and ST-T loops amplitudes were rather small and their directions of inscription were indeterminated. On the other hand, QRS loops were relatively large in amplitude, and were inscribed clockwise in all planes. The QRS loops had length:width ratios that were greatest in the sagittal plane (i.e., the loops are more open). Vectors representing mean QRS were approximately 0.5, 0.3, and 0.3 mV in the frontal, sagittal and horizontal planes respectively, and their orientations were approximately -6, 64, and 43 degrees in the frontal, sagittal, and horizontal planes, respectively.

Fig 5 shows nuclear magnetic resonance (NMR) of frontal (ventral) and horizontal (coronal) images of a guinea pig. Notice the shape of the guinea pig's chest and orientation of the heart within the chest. The orientation in frontal and horizontal planes of "typical" P, QRS and ST-T vectors are shown.
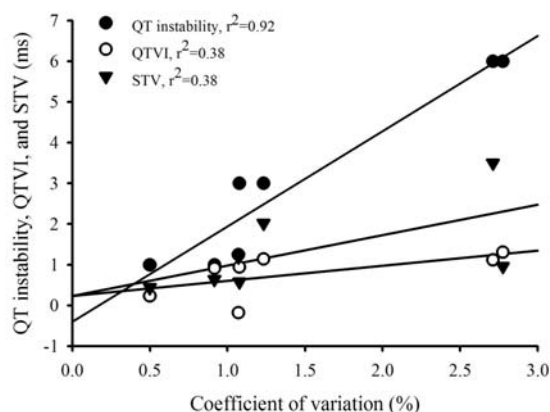
Fig 6 shows Bland-Altman plots for each index of QT instability versus coefficients of variation, in which the difference in QT was plotted (ordinate) against the QT variability (abscissa) in all 3 methods (i.e. QTI, QTVI, and STV). This method of plotting demonstrated the coefficient of correlation among each method. It could be noticed that 92% of the variability of QT instability calculated using the method of Hondeghem could be explained by the coefficient of variation, but only 38% of the variation could be explained by coefficient of variation using the methods of Berger and Thomsen.

Fig 7 shows spectral analysis of QRS complex from each X (Lead I), Y (aVF), and Z (V10) lead. The frequencies at which powers are greatest are 44.8, 61.4 and near zero Hz in lead I, aVF, and V10, respectively. The frequencies below which power is trivial (i.e., <5%) are 275, 225, and 175, for leads I, aVF and V10, respectively.

Discussion

From the scalar ECGs, all values obtained in our study are consistent with previous reports in guinea pigs (Petelenz, 1971; Cieslar et al., 1986). In relation to human electrocardiograms, guinea pig ECGs show a higher heart rate (shorter RR intervals), and shorter PQ and QT durations, which were 830 ms, 160 ms, and 350 ms, respectively in humans (Guyton and Hall, 1996; Ghista et al., 2010). This was fully expected based upon the smaller size of the guinea pig with shorter pathways for depolarization and
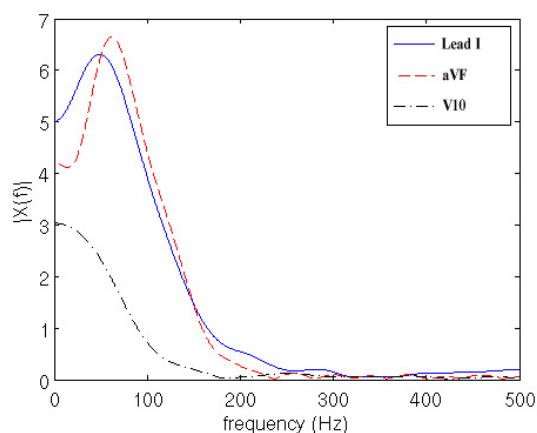

Figure 6 Plots of QT instability (Hondeghem), QT variability index (QTVI) (Berger), and short-term variability (STV) (Thomsen) against coefficient of variation of QT. Each point is the mean of QT Instability calculated from 200 consecutive QT intervals.

Figure 7 shows the fast Fourier transform (FFT) for QRS complexes in leads I, aVF and V10 for one representative guinea pig.

repolarization. From VCGs, the mean vectors of atrial depolarization were oriented between $0°$ to $+180°$, the mean vectors of the ventricular depolarization were between $-17.34°$ to $+137.2°$, and the mean vectors of the ventricular repolarization were between $-148°$ to $+180°$. This enormous variability when compared with dog or human is consistent with the inexplicable variabilities for cat, mouse, and rat (Coulter and Calvert, 1981; Tseng et al., 1989). These variabilities may be due to changes in gross structural anatomy, position of the heart within the torso, homogeneities of the body as a volume conductor, electrode placement; or they may be due to altered pathways of depolarization and repolarization. Moreover, it may be due to differences in distributions of specialized conductile tissue (i.e., Purkinje fibers for the ventricles, internodal pathways for the atria) in guinea pig compared to humans.

The results of VCGs of the body surface from all guinea pigs suggest that the maximal vectors for P are oriented leftward and ventrad, but neither craniad nor caudad. For QRS, they are oriented equally leftward, caudad, and ventrad. For T they are oriented caudad, but neither leftward nor rightward and neither dorsad nor ventrad.

As shown by anatomical investigation from NMR imaging (Fig 5), the guinea pig's heart is situated in a more nearly vertical position than human heart (Anderson et al., 2004). The heart is in intimate contact with sternum, and the greatest mass is to the left of the midline. Schwartze and Thoss (1981) reported that two-thirds of the ventral surface of the heart was directly adherent to the middle and caudal parts of the sternum, and one-third of the heart was adherent to the apex slightly to the left of the midline.

Temporal heterogeneity of ventricular repolarization, demonstrated as beat-to-beat variability of QT interval, has been suggested as a valuable parameter in evaluation of pro-arrhythmia in isolated perfused rabbit hearts, in intact dogs with complete AV block, and in telemetered dogs (Hondeghem et al., 2001; Thomsen et al., 2004; Schneider et al., 2005). Increased temporal instability was correlated with increased proarrhythmic and torsadogenic risk of repolarization retarded agents (Eckardt et al., 2002). Beat-to-beat variability in QT was quantified by Thomsen et al. (2004) using Poincaré plots. These are plots of QT for 1 beat against QT for the following beat. Berger et al (1997) and Hondeghem et al. (2001) utilized mathematical expression of differences in QT's equations. From this study, the instability could be expressed simply and as accurately by merely calculating coefficient of variation of QT for 200 beats utilizing EMKA software. This requires virtually no effort, and, as shown by the results, expresses instability with little difference from that expressed by the method of Hondeghem.

The QRS complex contains, clearly, the highest frequency components of any portion of the electrocardiogram, therefore the high-frequency characteristic of the electrocardiogram should be determined by the frequency components in the QRS complex. The relative powers of these frequency components were determined by the FFT, which breaks the deflection into sine and cosine waves of differing frequencies, and measures their relative amplitudes. Thus, the "true" ECG signal can be resynthesized using a combination of these sine and cosine waves. This study demonstrated that for each lead components greater than 175 and 275 Hz contained virtually no power, therefore the low pass filter for an electrocardiograph is necessary to record, faithfully, QRS complexes in guinea pig electrocardiograms should be approximately 200 Hz. It can be observed that maximal power (Y-axis) for leads I and aVF is between 50 and 100 Hz, therefore a filter imposed to minimize 60 Hz interference may well diminish amplitude of QRS complex in those leads but not in lead V10, in certain disease states (e.g. hypertrophy, infarction) higher frequency components may develop, but they usually contribute minimally to the electrocardiogram and are highly unlikely to be important in safety pharmacological studies. The American Heart Association recommends for human electrocardiography a high-pass filter of 0.01 Hz, i.e., the lowest frequency that is recorded faithfully. Since the guinea pig electrocardiogram contains frequencies higher than in man, then a high-pass filter of 0.01 or even 0.1 Hz should be acceptable.

Acknowledgements

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