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Comparative Dipolar Electrocardiotopographic Study of Ventricular Activation in *Macaca mulatta* Monkeys and Man

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Summary

Electrocardiographic correlates of ventricular activation sequence were studied in 22 *Macaca mulatta* monkeys, aged 1-18 years, and 145 human subjects, aged 11-72 years, using the corrected orthogonal lead system of McFee-Parungao and the dipolar electrocardiotopographic (DECARTO) data presentation, where the time series of instantaneous spatial vectors are converted into time series of areas of activation on a spherical image surface enveloping the heart. Macaques had shorter ventricular activation time (61±11 vs. 97±11 ms) that could not be explained exclusively by their higher heart rate. Their DECARTO image of the resultant activation front occurred 10 ms after QRS onset (septal activation) identically with humans, but it attained a more anteriorly oriented maximum earlier than in humans (20 vs. 40 ms). The time course of the extent of the resultant activation front in old macaques (15-18 years) resembled to that observed in humans. On the average, female macaques had smaller DECARTO images of activation fronts throughout the QRS complex than males. This finding is in agreement with the known smaller QRS amplitudes in women than in men.

Key words
Electrocardiography • Ventricular activation • Macaques

Introduction

Electrophysiological mapping of the activation sequence in isolated mammalian and human hearts (Scher and Young 1957, Durrer *et al.* 1970) provided the basis for the idea that a sharply defined front moving at a defined velocity suffices for a gross description of ventricular activation. A dipolar double layer is thus a more-or-less convenient approximation of the ventricular activation wavefront. The double layer can be considered as a set of unit dipoles. Their vectorial sum is an equivalent dipole, and its vectorcardiographic representation is an instantaneous spatial vector, recorded by a physically corrected orthogonal lead system. Since the propagating wavefront spreads in an overall radial fashion, normally from the endocardium to epicardium, the magnitude of the resulting spatial vector provides a synthetic picture of its extent, and the spatial orientation of this vector indicates its predominant course.

In dipolar electrocardiotopography (DECARTO) proposed by Titomir, the time series of instantaneous spatial vectors, obtained by a physically corrected orthogonal lead system, are converted into time series of areas of activation on a spherical image surface enveloping the heart (Titomir and Ruttkay-Nedecký 1987, Titomir *et al.* 2001).

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Since the above-mentioned class of lead systems is well suited for interspecies comparative studies, and the DECARTO technique allows obtaining a comprehensible synthetic and quantifiable image of ventricular activation, it was utilized in the present study of electrocardiographic correlates of ventricular activation in *Macaca mulatta* monkeys and man.

Methods

This retrospective study is based on the evaluation of *x, y, z,* ECG tracings obtained in a sample of 22 *Macaca mulatta* monkeys (8 males and 14 females), consisting of a subgroup of 15 younger animals, aged 1-7 years, and another subgroup of 7 old animals, aged 15-18 years. All of them were reared at the former Primate colony of the Sukhumi Institute of Experimental Pathology and Therapy, U.S.S.R. Academy of Medical Sciences. The monkeys were studied at the same institution in the years 1964 and 1965, in the framework of a collaborative study on norms and physiological variability of the orthogonal electrocardiogram and vectorcardiogram of baboons and macaques (Ruttkay-Nedecký and Cherkovich 1977)

The recordings were made without anesthesia in the supine position of monkeys restrained on a board, handled and calmed down by their respective attendants. Their heart rate varied between 100-270 beats/min (mean±S.E.M. 234.2±6.6). Small subcutaneously inserted safety-pin electrodes served for simultaneous recording *x, y ,z* electrocardiograms with a paper speed of 50 mm/s and 1 mV=10 mm amplification on a VISOCARD vectorcardiograph (von Karajan, Austria), using the physically corrected axial lead system (McFee and Parungao 1961). After optical magnification of the tracings, the *x, y, z* components of the instantaneous spatial vectors were obtained at 10 ms intervals from the onset of the first, to the end of the last deflection in any of the three simultaneously recorded QRS complexes.

Human data were taken from previous studies (Ruttkay-Nedecký *et al*. 1988, Bachárová *et al.* 1991) on 145 human subjects (81 males, 64 females, aged 11-72 years, median value 35 years). Vectorcardiograms were recorded by a Vectorcardiograph 120A (Hewlett-Packard) in sitting subjects by means of the same lead system as in the macaques. The *x, y, z* coordinates of instantaneous QRS vectors were obtained manually at 10 ms intervals after optical enlargement of the left sagittal and horizontal plane VCG loop projections.

The VCG data were fed into a PC and processed by means of Titomir´s mathematical model of image surface representation of ventricular activation. In this model, the instantaneous spatial vector is computed according to the Pythagorean theorem and centered in a sphere with the radius equal to the magnitude of the maximum spatial vector of the QRS complex under study. The projection of the instantaneous vector on the surface of this sphere becomes the center of a circle, the radius of which is proportional to the magnitude of the instantaneous vector. This circle then delineates an area representing the ventricular activation at a given instant of time. The image sphere was discretized into 264 points and unwrapped onto a rectangular planar surface in such a way that the distances along horizontal directions were proportional to latitudes and along vertical direction to polar distances of the spherical coordinate system. The left and right borders of the resulting rectangular map (decartogram) coincide with the meridian of the sphere, viewing the right mid-axillary line of the subject.

The set of points situated within the above mentioned area was labeled as activated. The relative frequencies of these activated points were computed on both composite macaque group decartograms (MGD) and human group decartograms (HGD). The characteristics of interest were: (i) the number of activated points, (ii) the position of the most frequently activated point, and (iii) the relative frequency of activation of this point. Chi-square test was used to evaluate the differences between frequencies, $p<0.05$ being accepted as significant.

Results

The ventricular activation time, as judged from the interval between the beginning of the first and the end of the last deflection in any of the three simultaneously recorded QRS complexes was significantly shorter in macaques than in humans (61±11 vs. 97±11 ms, $p<0.001$). This difference can be explained only partly by the higher heart rate of macaques and the known positive relationship between RR and QRS intervals. Namely, according to the linear regression model from our human sample (QRS interval = 82+0.02 RR interval), the QRS interval related to the average heart rate observed in our macaques (234 beats/min) should be 87 ms, but in fact it was only 61 ms.

The number of activated points on consecutive decartograms underwent changes with the evolution of ventricular activation fronts. The different timing of this

variable in the macaque and in the man is depicted in Figure 1 as percentages of activated points on MGDs and HGDs at consecutive 10 ms QRS intervals. While at 10 ms after QRS onset there was no difference, the extent of the activation front, as judged from the number of activated points, already reached its maximum in macaques at 20 ms, while in man as late as at 40 ms. The shorter ventricular activation time in macaque ventricles was then reflected in a more rapid decrease of the number of activated points towards the end of QRS.

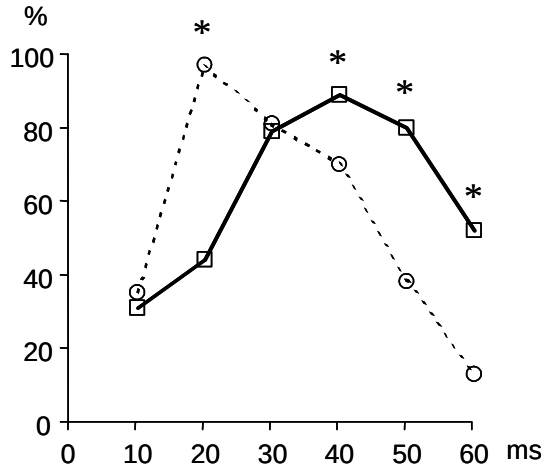

Fig. 1. Percentage of activated points in macaque (broken line) and human (full line) composite group decartograms at consecutive 10 ms time intervals of QRS. Asterisk indicates $p<0.05$.

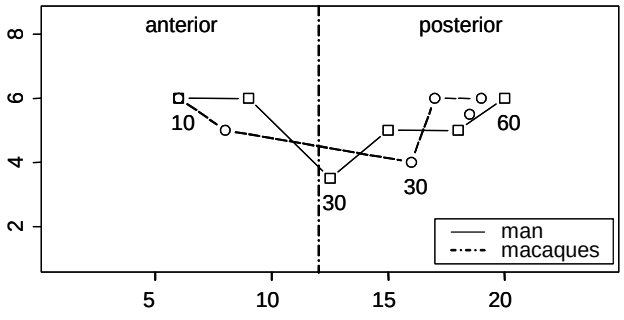

Fig. 2. Trajectory of points with maximum probability of activation in macaques (broken line) and man (full line). The unwrapped spherical image surface was discretized into 264 points given by the intersections of 11 rows and 24 columns (not shown). The left and right borders of the rectangle coincide with the meridian of the sphere, viewing the right mid-axillary line of the subject. Abscissa: rows, ordinate: columns. Columns 1–12 represent the anterior hemisphere.

The position of the most frequently activated point (Fig. 2) was identical on the HGD and MGD respectively, at 10 ms after QRS onset and close at 20 ms. In macaques it was thereafter quickly shifted to the posterior upper quadrant, while in man it proceeded much slowlier in the lower posterior quadrant to became close to the macaque point at 60 ms of QRS.

The maximum values of relative frequencies, observed at the most often activated points, are shown in Figure 3. While at 10 and 20 ms of QRS the values did not differ significantly, they decreased thereafter in the macaque group dramatically, speaking for a gradual decay of a prevailing orientation of the summary activation front.

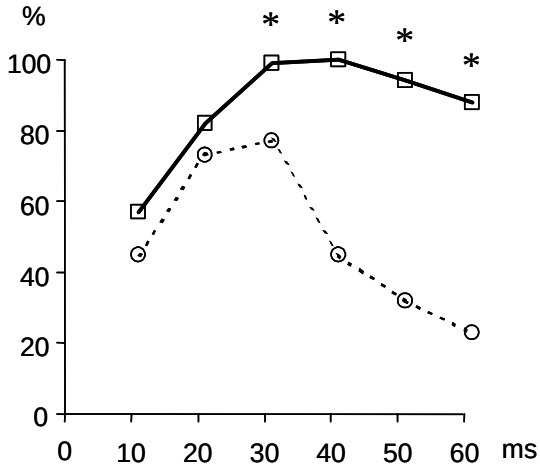

Fig. 3. Maximum values of relative frequencies, expressed as percentage (ordinate) at most often activated points of macaque (broken line) and human (full line) composite group decartograms at consecutive 10 ms time intervals of QRS (abscissa). Asterisk indicates $p<0.05$.

In general, ECG amplitudes have been found to be lower in women than in men, especially in young adulthood (Macfarlane and Lawrie 1989). Gender differences in the time course of the percentage of activated points on MGDs of 7 males and 8 females, aged 1-7 years, are shown in Figure 4. The generally lower percentage of activated points reached statistical significance ($p<0.05$) at 10, 40, 50 and 60 ms of QRS.

The age-dependence of most human ECG variables is well known. In our human group, the linear regression model of the maximum spatial QRS vector on age had a negative slope ($p<0.001$), i.e. that QRS deflection amplitudes tended to decrease with advancing age. A comparison of the percentage of activated points on MGDs of the subgroup of 15 younger animals (1-7 years, 7 males, 8 females) versus the subgroup of 7 old animals (16-18 years, 1 male, 6 females) has shown lower values at 10 and 20 ms, and higher values at 30-60 ms of QRS in old animals (Fig. 5).

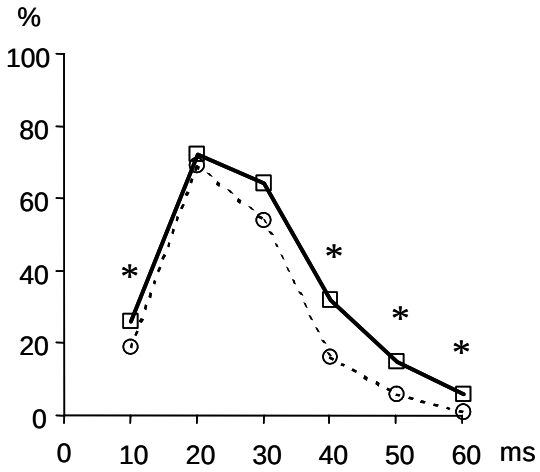

Fig. 4. Percentage of activated points on male macaque (broken line) and female macaque (full line) composite group decartograms at consecutive 10 ms time intervals of QRS. Asterisk indicates $p<0.05$.

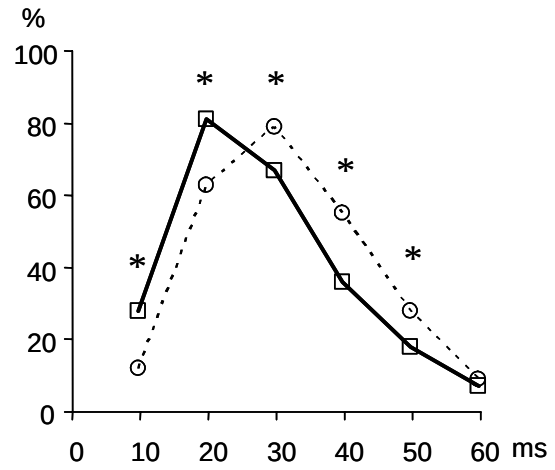

Fig. 5. Percentage of activated points in younger macaque (broken line) and old macaque (full line) composite group decartograms at consecutive 10 ms time intervals of QRS. Asterisk indicates $p<0.05$.

Discussion

Studies of the normal macaque electrocardiogram were focused in the past on quantitative data of the standard lead ECG intervals and amplitudes. Their striking similarity (especially that of the QRS measurements) to human values was noted (Kokaja 1954, Atta and Vanace 1960).

The concept behind physically corrected orthogonal lead systems, based on theoretical and modeling studies, was to produce an electrode network providing equal magnitude and mutually perpendicular lead vectors. This is advantageous in comparative studies, especially those involving humans. In contrast to man, mammals (including monkeys) have a chest which is virtually as large along the anterior-posterior axis as along the transverse axis. Even if the correction provided by the resistor network of the lead system, attenuating the effect of differences in cardiac surface to body surface geometry, cannot be expected to be perfect, the residual confounding factor may affect only the orientation and the absolute value of the spatial magnitude of instantaneous vectors, but not the timing of their maximum. Physical modeling of the cardiac electric field, using electrolytic tanks fashioned from plaster casts on the thorax of adult male and female macaques and baboons (Szathmáry *et al.* 1985) showed a better performance of the McFee-Parungao lead system in lower primates than that of the Frank lead system.

Normal values of the physically corrected Frank lead system vectorcardiograms were reported in 15 macaques (Bristow and Malinow 1965). Our earlier comparative study of vectorcardiographic data in 82 macaques and 53 baboons, using the corrected orthogonal lead system of McFee and Parungao (Ruttkay-Nedecký and Cherkovich 1977) showed significantly smaller differences between human and macaque VCG characteristics of the cardiac electric field, than between humans and baboons. Macaques had smaller absolute values of to the left oriented, and greater values of the anteriorly oriented maximum QRS vectors than humans. Statistically evaluated comparative data on the time course of QRS vectors in monkeys and man are lacking.

The present study introduces DECARTO as a novel technique of visualization of the QRS complex of orthogonal ECG, designed to promote a better understanding of interspecies differences in ventricular activation. It shows differences in relative values during evolution of the extent of resulting ventricular activation fronts (Fig. 1). The most striking difference is the earlier maximum in macaques, at 20 ms, as compared to the later maximum in humans, at 40 ms of the QRS complex. This is in agreement with the earlier observation (Nelson *et al.* 1965) of a maximum of spatial magnitude of the resultant dipole vector, obtained by body surface potential integration, at 12-20 ms after QRS onset in a 27 kg monkey of undetermined species. The above finding is also corroborated by the results of epicardial mapping in two *Macaca rhesus* monkeys (Harris 1941) and by intraventricular mapping in eight macaques (Scher 1965). Harris (1941) emphasized the irregular and widespread area on the ventricular surface that received excitation

within 14 ms, including the whole right ventricle (except the conus region), the apex and the right half of the left ventricle. Patters of intramural excitation of the macaque heart in the work of Scher (1965) showed that epicardial excitation was completed practically within 20-25 ms.

Macaques have a shorter ventricular activation time and a much smaller heart than humans. It follows that relatively large portions of their ventricular muscle mass are excited earlier. Since their epicardial activation during this period is confined mainly to the right ventricular and anterior left ventricular surface, the overall direction of the resultant activation front is at 20 ms after QRS onset anterior.

Gender differences were also observed in our above quoted study, in that female macaques and baboons had a smaller x (transverse) and *z* (antero-posterior) lead QRS amplitudes than males. This finding in monkeys supports the existence of true sex differences in the electrogenesis of ventricular activation, since mammae of monkeys do not alter the shape of the thorax to such an extent as in the case of humans.

Regarding the influence of age, it should be noted that macaques cease to grow after 10 years and our 15 to 18- year-old animals were close to the end of their natural life span. The time course of the number of activated points in old macaques was similar to that observed in humans.

Acknowledgements

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