Influence of Age on the Electrocardiographic Waves in Taiwanese Lan-Yu Miniature Pigs

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Abstract | The purpose of the study reported here was to determine baseline information of the electrocardiogram (ECG) and the influence of age on cardiac function in Taiwanese Lan-Yu (TLY) miniature pigs. Non-anesthetized TLY minipigs (from birth to 6 months of age) were placed on a webbed stanchion, simulating a standing position, for acquisition of an ECG, using six limb leads (I, II, III, aVR, aVL, and aVF), with each as a single-channel ECG recorder. The P and T waves obtained from leads I, III, and aVL were useful in determining the subtle cardiac changes during maturation of TLY minipigs. Interestingly, changes in the QT interval analyzed from all 6 leads were almost indistinguishable. Shortening of the QT interval was induced ($p < 0.05$) between days 1 and 7 of postnatal life. The QT interval lengthened to a steady state at day 60, and paralleled pigs' physical maturation. The longer QT interval was conversely correlated to heart rate as pigs matured. In the QRS complex interval, only lead aVR was significantly decreased at day 7 ($p < 0.05$). Further changes in the QRS interval from day 21 were not observed in any lead. Because the duration of the ventricular complex represents the period required for the excitation front to reach the terminals of the Purkinje fibers in the ventricular myocardium, the increase in QRS interval observed within 21 days of birth could be attributed to an increase in the thickness of ventricular myocardium. The data suggest that cardiac maturation was achieved at 60 days of age, although the body weight of minipigs continued to increase beyond 60 days of age. Because the body weight of these newly developed TLY minipigs can be maintained within 25 to 30 kg at one year of age and their major ECG findings did not significantly differ from those of domestic pigs and humans, they may be useful as a model for cardiovascular and pharmacologic research. The similarity of ECG profiles between pigs and humans also was evaluated.

Certain characteristics of pigs that make them an excellent animal model for cardiovascular research include: spontaneous development of atherosclerosis (1), especially when cardiovascular endothelial cells are damaged; lipoprotein structures and functions similar to those of humans (2); anatomy of the coronary arterial system and morphologic changes of the arterial wall in the pathogenesis of thrombosis similar to those of humans (3, 4); and spontaneous development of hypertrophic cardiomyopathy almost identical to that of affected humans (5–11). Similarities to humans in cardiovascular physiology, size, anatomy, and perfusion distribution of blood make pigs better subjects than most other common laboratory species (12).

The ECG procedure is well established as a noninvasive and inexpensive technique to gain information about cardiac functions (13-17). Electrocardiographic parameters must be determined more systematically to evaluate heart rhythm and physiologic functions. In general (Figure 1), the P wave of the ECG represents depolarization of the atria, and its duration indicates the time required for an impulse to pass from the sinoatrial to atrioventricular node. The PR interval represents the time required for an impulse to travel from the sinoatrial node to the ventricles. If the PR interval varies from beat to beat, an arrhythmia or conduction disturbance could be responsible. Shorter conduction time is generally associated with faster heart rate. The QRS complex represents depolarization of the ventricle. Comparisons of the configurations of P and QRS can facilitate the analysis of arrhythmia. The ST segment measures the early phase of ventricular repolarization, and the T wave is the first major deflection after the QRS complex and represents repolarization of the ventricle. Although the QT interval is measured from the onset of the Q to the end of T wave, it is the summation of ventricular depolarization and repolarization and represents ventricular systole that varies inversely with heart rate. In veterinary medicine, the QT interval alone is not often helpful in diagnosis and should be compared with the other cardiographic segments (16, 18).

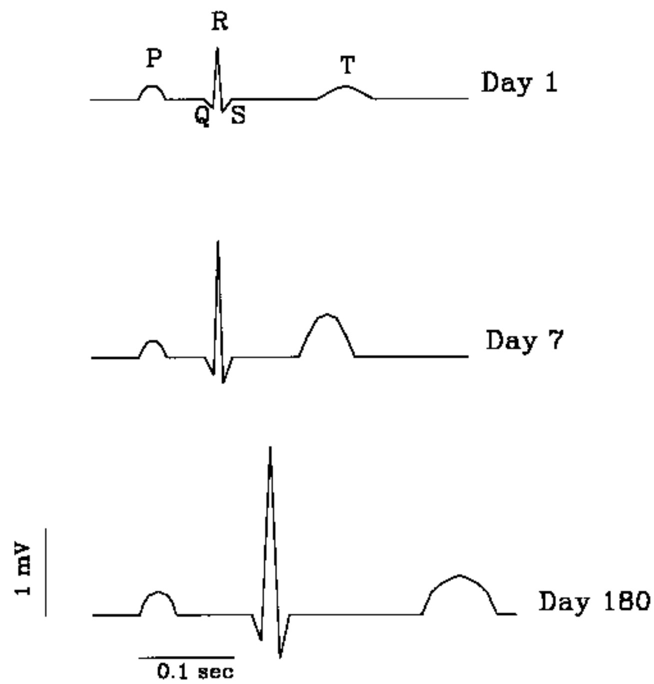

FIG. 1. Typical normal ECG waves (lead II) of Taiwanese Lan-Yu (TLY) pigs at 1, 7, and 180 days of age. Terms and their physiologic significance are described in the text. Paper speed was at 50 mm/s; 1mV = 1 cm.

Many cardiovascular research laboratories are now using swine as an animal model, but one of the major limitations is the physical size of this animal (19). Minipigs should, therefore, be more useful for cardiovascular research (19). Although the ECG data for conventional pigs (*Sus scrofa*) (20) and miniature pigs have been described (21), to the authors' knowledge, ECG profiles of Taiwanese Lan-Yu (TLY) miniature pigs have not been described.

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FIG. 2. Appearance of TLY miniature pigs at 6 to 8 months of age. The TLY minipigs are characterized as dark black, with a heavy coat. The ears are smaller than those of most domestic breeds. These animals are also known as TLY small-ear pigs.

The TLY minipigs (Figure 2) are characterized as dark black, with a heavy coat. The ears are smaller than those of most breeds. Often, they are known as TLY small-ear pigs. Under the support of National Science Council of Taiwan, the TLY pigs were first imported from the Lan-Yu Island of southeast Taiwan and have been bred at our Pig Research Institute Taiwan since 1987. Presently, pigs are available for export as long as arrangements meet the government regulations. The body weight of TLY minipigs is usually < 25 kg during the first six months of age, compared with 100 kg of other domestic pigs used for meat production. The TLY pigs weigh about 35 kg when they are sexually mature, and body weight increases to 50 to 60 kg at 2 years of age. These animals have been used in biomedical studies (22), and as an animal model for restenosis of coronary arteries (23). The study reported here was intended to determine the normal profiles of ECG waves in TLY minipigs and to evaluate the influence of age from birth to 6 months on their ECG characteristics.

Materials and Methods

The minipigs studied were selected from our breeding herd over a 2-year period. Mean (± SEM) litter size for the colony is 6 (± 1.3) piglets. Normal estrous cycle duration is 21 days, with a gestation period of 114 (± 1.6) days. Sexual maturity occurs at 17 to 18 weeks in males and females. Pigs were fed a corn (72.5%)- and soy bean (24.9%)-based chow (Tachung Co., Taiwan, R.O.C.) containing 3,000 Kcal of metabolizable energy/kg. Feed and water were available daily on an ad libitum basis. All minipigs were raised in a natural lighting environment in pens (3 x 5 m; each containing 6 pigs of the same sex). Management and medical treatment were conducted according to the guidelines established by National Science Council of Taiwan. Pigs were vaccinated against hog cholera, pseudorabies, atrophic rhinitis, swine erysipelas, and Japanese encephalitis. Parasite control programs were conducted by intramuscular administration of Ivomec (Merck Sharp & Dohme B.V., Haarlem, The Netherlands) twice a year. Pigs were observed daily. Necropsies were conducted by certified veterinarians when pigs died during the testing period. Presently, these Lan-Yu minipigs are available for use by any domestic research institute in Taiwan. Although these minipigs have not been exported from Taiwan, they can be exported as long as requests meet the government regulations.

The study was initially divided into two phases. The first phase involved use of one group of TLY miniature pigs (n = 18) to determine their ECG from birth to 180 days of age (Table 1a). The second phase independently involved use of a second group of TLY pigs (n = 176) at various ages for the ECG examinations (Table 1b). The subjects were evaluated by use of 6 limb leads (I, II, III, aVR, aVL, aVF) for as long as they remained healthy at intervals of 1, 7, 14, 21, 30, 60, 90, 120, 150, and 180 days of age.

The ECG were obtained from untrained pigs suspended on a webbed stanchion simulating a standing position. Chemical restraint was not used. A 5- to 10-min acclimation period preceded each ECG recording. Great care was taken to avoid electrical contact between adjacent electrodes when placing the electrodes and applying the paste. Each tracing was repeated, if necessary, until it was judged to be of good quality. Electrodes were placed on the inner surface of the hind limb between the knee and hock. Traces were inscribed by use of a single-channel electrocardiograph (FUKUDA 501A, Tokyo, Japan). The electrocardiograph was calibrated at a setting of 1 mV = 1 cm, and the trace was recorded, using a paper speed of 50 mm/s. All standard measurements of the ECG were made manually by averaging 3 to 5 consecutive heart cycles.

Statistical analysis:

Recordings were analyzed for P wave duration, PR interval, QRS duration, and QT interval. The amplitudes of the component deflections were calculated from each of six leads. Heart rate was recorded from lead II. The mean electrical axis containing 3 to 5 sequential waves was determined, using the values

Table 1a. Numbers of Taiwanese Lan-Yu (TLY) minipigs used for day-to-day ECG follow-up experiments

Age (d)	1	7	14	21	30	60	90	120	150	180
Male (n)	8	8	8	8	8	8	8	8	8	8
Female (n)	10	10	10	10	10	10	10	10	10	10
Body weight (kg)	0.62±0.09	1.43±0.21	2.41±0.36	3.29±0.49	4.37±0.70	8.56±1.25	14.46±2.11	20.23±2.05	22.51±2.19	24.39±2.24

More than 18 subjects were chosen at the beginning of the study. During the experimental course, animals that appeared ill and those that weighed < 80% of the average for the group were excluded. Body weight is expressed as mean ± SEM.

Table 1b. Numbers of TLY pigs from various age groups used in ECG experiments

Age (d)	1	7	14	21	30	60	90	120	150	180	Total
Male (n)	15	7	8	8	8	8	11	3	5	9	76
Female (n)	17	12	10	10	10	10	7	9	12	12	100
Total	32	19	18	18	18	18	18	12	17	21	176
Body weight (kg)	0.63±0.10	1.39±0.23	2.28±0.38	3.02±0.47	4.30±0.65	8.58±0.86	15.61±1.58	20.39±2.15	23.14±2.26	25.11±2.32	

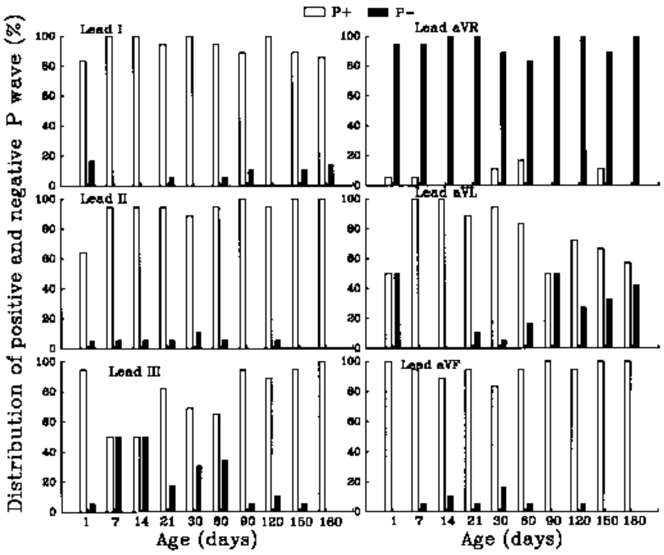

FIG. 3. Percentage distribution of positive and negative P waves over age, using 6 limb leads. Notice positive and negative values in the normal population. For positive P waves, lead III detected a significant decrease at day 7 of age, which returned to maximum at day 21. In lead aVR, however, negative waves predominated. Lead aVL indicated a significant decrease in negative P waves at day 7.

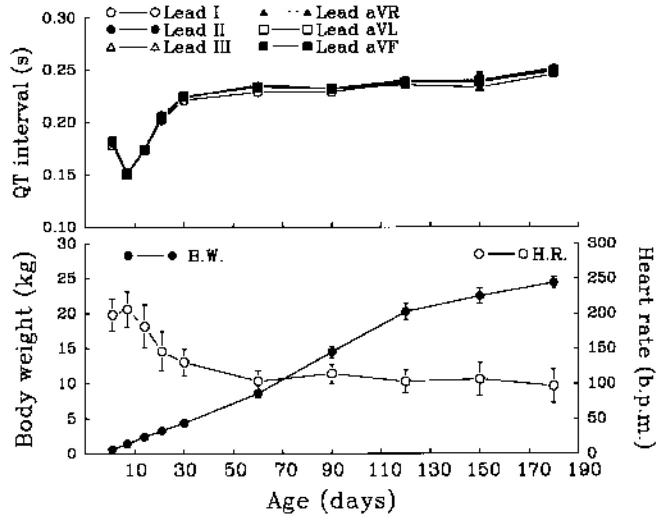

FIG. 5. Changes in QT interval (lead II), body weight, and heart rate over age, as determined by 6 limb leads. All measurements indicate a shortened QT induced ($p < 0.05$) between 1 and 7 days of postnatal life. From day 7, the QT interval underwent lengthening parallel to physical maturation up to 60 days of age. Such lengthening was conversely correlated to the heart rate. In general, high heart rate is required when the organ is small. The QT interval increases when thickness of the ventricular wall increases. Each bar represents the SEM.

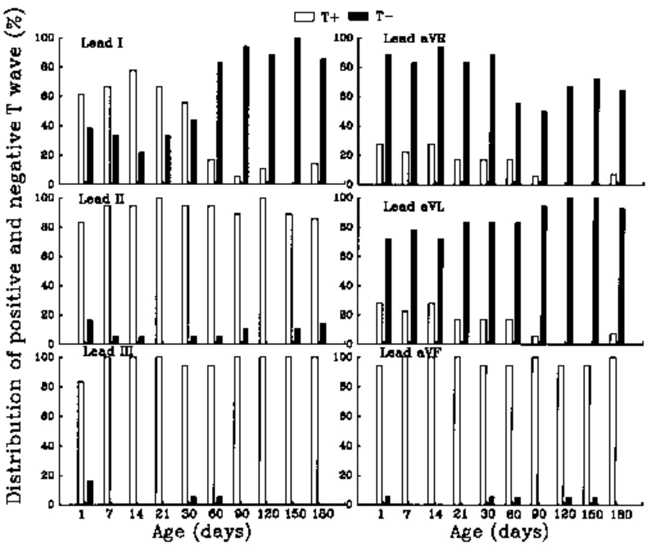

FIG. 4. Percentage distribution of positive and negative T waves over age, using 6 limb leads. Notice positive and negative values in the normal population over age. A significant decrease in negative waves was found at day 14, which progressively increased up to day 60 as detected by lead I.

from leads I and III in the charts according to the recommended procedures of the New York Heart Association (24). Data were analyzed by use of one-way analysis of variance and a computer statistical package (Proc GLM, SAS/STAT Guide for Personal Computer, Version 6. Edition, SAS Institute Inc., Cary, NC). In addition, the interaction among body weight, sex, and age was considered. Differences among means were determined by use of Duncan's multiple range test (25).

Results

One of the purposes of this study was to evaluate the influence of age on the ECG of our newly developed TLY minipig line. The initial phase showing ECG changes from 0 to 180 days of age is presented in Table 1. Six limb leads were used to monitor the changes in P and T waves, QRS complex, and intervals of PR and QT during physical maturation. Typical ECG in pigs at days 1, 7, and 180 are shown in Figure 2.

Because P and T waves from normal pigs were found to have positive and negative values, the data in Figure 3 were presented as percentage distribution of the values. The P wave configuration over age in all 6 leads was observed. In positive P waves, lead III indicated a significant ($p < 0.05$) decrease at day 7 of age, returning to maximum at day 21. In lead aVR, however, negative waves predominated. Lead aVL indicated a significant ($p < 0.05$) decrease in negative P waves at day 7.

Figure 4 displays the 6-lead T waves in which a significant ($p < 0.05$) decrease in negative waves was found at day 14 and progressively increasing up to day 60, as detected by lead I. These data indicated that P and T waves obtained from leads I, III, and aVL may be used in determining subtle cardiac changes during the maturation of TLY minipigs.

Analyses of the QT interval measured by all 6 leads were almost indistinguishable (Figure 5). All measurements indicated that the QT interval shortened ($p < 0.05$) between days 1 and 7 of postnatal life. From days 7 to 60, the QT interval lengthened parallel to physical maturation. This change was conversely correlated to heart rate (Figure 5).

In the QRS complex interval (Figure 6), only lead aVR indicated a significant ($p < 0.05$) decrease at day 7. Further changes in all lead determinations from day 21 were not evident. Because duration of the ventricular (QRS) complex represents the time required for the excitation to travel from the terminals of Purkinje fibers through ventricular myocardium, the increase observed within 21 days could be attributed to an increase in the thickness of ventricular myocardium. To confirm this hypothesis, thickness of the left and right ventricles and ventricular septum was measured in the necropsy specimens from pigs of various ages. Table 2 shows the exponential increase of wall thickness within the first 21 days. The maximal thickness of right ventricle was almost reached by day 21, although thickness of the left ventricle increased slightly beyond day 21. There were no significant ($p > 0.05$) differences between male and female subjects for all of the aforementioned ECG waves and segments. The typical duration of QRS complexes in both sexes is shown

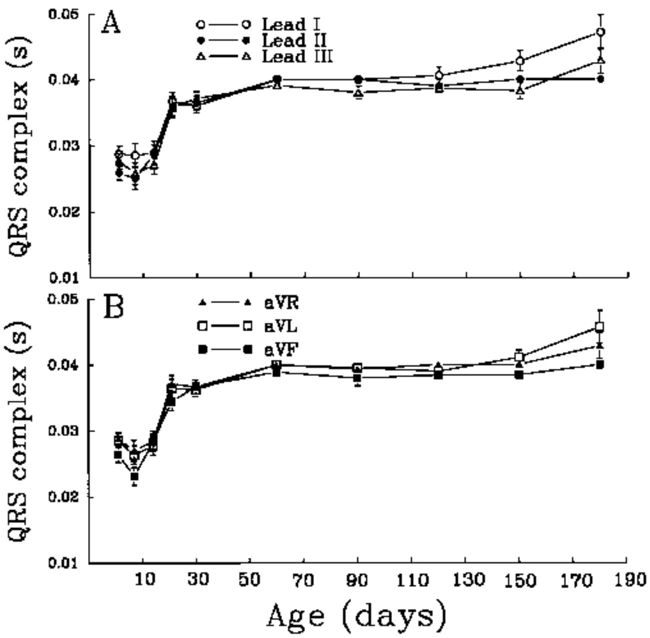

FIG. 6. Changes in amplitudes of the QRS complex over age, as determined by 6 limb leads. Only lead aVR indicated a significant ($p < 0.05$) decrease at day 7. Drastic changes from day 21 in all lead determinations are not evident. Panel A: leads I, II, and III; panel B, leads aVR, aVL, and aVF. The data indicate that lead aVR can be used for detection of a subtle change in cardiac maturation.

in Table 3.

Figure 7 indicates a tendency for the PR interval to increase with age and no significant ($p > 0.05$) difference among the 6 leads analyzed. In addition, regardless of choice of leads there was no significant ($p > 0.05$) difference in the mean axis of the P wave among ages, except among newborn pigs when leads III and aVL were used (Figure 3). The R-wave amplitudes in leads II, III, aVR, and aVF (Figure 8) increased over age except for a decrease at day 14.

Because these findings were obtained in day-to-day evaluation of newborn pigs until maturation, we next performed an identical study (Table 1b) using pigs (n = 176) of various ages to test whether the ECG changes over age may be simultaneously detected. All values including heart rate and body weight, P and T waves, QT and PR intervals, and QRS complex over age were comparable to those obtained in a day-to-day follow up study (data not shown).

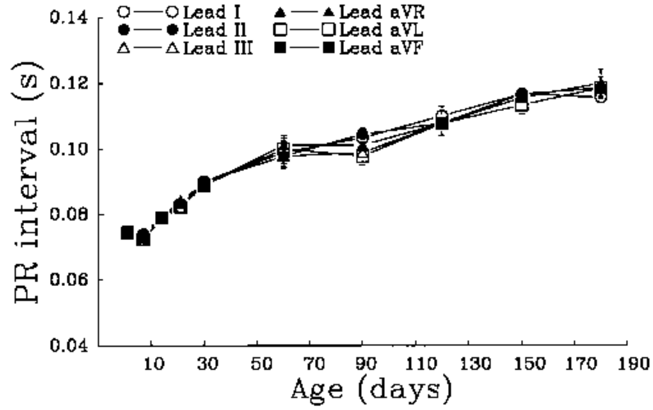

FIG. 7. Changes in PR intervals over age, as determined by 6 limb leads. There was a tendency of a continuously increasing PR interval with age and no significant ($p > 0.05$) difference among the 6 leads analyzed.

Discussion

It has been recognized for the last two decades that the cardiovascular system of pigs is similar to that of humans (26–33). Due to the large physical size of standard or agricultural domestic pigs, considerable effort has been made to use minipigs for cardiovascular research (34). One purpose of the study reported here was to determine the characteristics of ECG in newborn pigs and the influence of age on cardiac function of our newly developed TLY minipigs. This information may be relevant for future cardiovascular research, new drug intervention, and clinical care of TLY pigs.

Previous study of the same herd indicated that some common diseases (expressed in % of occurrence), such as porcine purulent bronchitis (26.7%), lung abscess (13.3%), interstitial pneumonia (13.3%), bronchopneumonia (11.1%), erysipelas (8.9%), *Escherichia coli* infection (4.4%), salmonellosis (4.4%), roundworm infection (2.2%), and *Sarcoptes scabiei* infestation (13.3%), were found in a group of 45 TLY pigs. Other diseases, such as gastric foreign body, cystitis, hemorrhagic fibrinous pleuropneumonia, peritonitis, and pleuritis, were rare. Further testing, such as examination of skin scrapings for external parasites, fecal examination for internal parasites, and clinical blood analyses for cell counts, plasma lipid content, liver function, thyroid hormone and glucose concentrations as criteria for general health, were routinely conducted and results were recorded. During this study, animals with infectious diseases that could possibly affect cardiac function and animals with low body weights (< 80% of average) were excluded (< 10% of the total pigs).

Table 2. Thickness of ventricular wall and septum in TLY minipigs

Traits	Age (d)					
	7 (n=20)	14(n=17)	21(n=15)	30(n=14)	120(n=12)	150(n=12)
Thickness of left ventricle (cm)	0.43 ± 0.04	0.56 ± 0.05	0.61 ± 0.06	0.71 ± 0.07	0.80 ± 0.08	0.80 ± 0.08
Septum (cm)	0.38 ± 0.04	0.53 ± 0.05	0.69 ± 0.07	0.66 ± 0.06	0.97 ± 0.10	0.95 ± 0.09
Thickness of right ventricle (cm)	0.17 ± 0.02	0.20 ± 0.02	0.27 ± 0.02	0.26 ± 0.02	0.30 ± 0.03	0.29 ± 0.03

Necropsy specimens were used for the measurements, which are expressed as mean ± SD.

Table 3. Comparison of the changes in QT intervals (mean ± S D, sec) between the sexes, using lead-II determinations

Sex	Age (d)									
	1	7	14	21	30	60	90	120	150	180
Male (n=8)	0.18±0.02	0.16±0.01	0.16±0.01	0.21±0.02	0.23±0.03	0.23±0.02	0.23±0.01	0.24±0.01	0.23±0.04	0.25±0.02
Female (n=10)	0.19±0.02	0.15±0.01	0.17±0.02	0.20±0.01	0.22±0.02	0.24±0.02	0.23±0.01	0.24±0.01	0.24±0.03	0.25±0.02

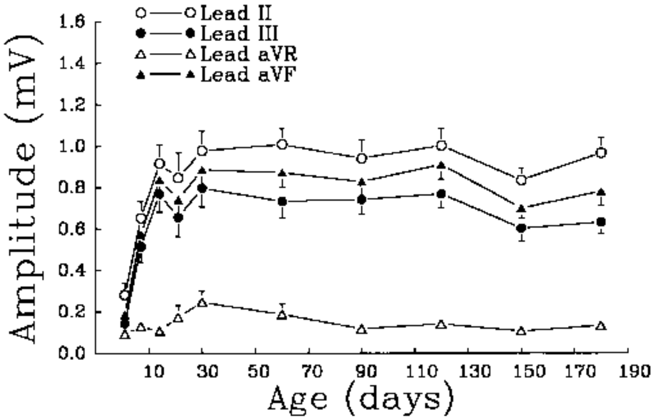

FIG. 8. Changes over age in amplitudes of R waves in leads II, III, aVR, and aVF. The amplitudes of ECG waves in leads II, III, and aVF had a tendency to increase with age. Measurement using lead aVR in R waves may not be suitable.

Routinely, limb lead II is used to evaluate heart rate and rhythm and duration or amplitude of the P, Q, R, S, and T waves during the cardiac cycle (20). The heart rate in all mammals decreases exponentially with growth (20). In this study, the heart rate of newborn TLY pigs was high, with a mean value of 193 beats/min, and increased during the first 7 days of life to a mean value of 206 beats/min (Figure 5). It then decreased gradually to 113 beats/min at 60 days. This result was similar to that reported by Larks (34), indicating that the heart rate of miniature pigs is relatively high at birth and decreases with age in accordance with the regression equation: heart rate = 205 − 0.27 × (age, days). It is noted that heart rate versus age is not absolutely linear. Miller and Ullrey (35) also found that heart rate decreased in normal pigs from the first to the fifth week of age, with significant increase in PR, ST, and QT intervals over this period. It would appear that the newborn pigs were under considerable stress during the transition from intrauterine to extrauterine life and that this period of stress lasts for about 2 weeks after birth (34).

The ECG from normal animals usually indicates positive P and T waves in the standard bipolar limb leads (35). The change in P waves appears not to be related to the change in the anatomic position of the heart (20). Likely, it was associated with the influence of a variable degree of autonomic discharge, as is associated with a respiratory-heart rate response. The T wave in six leads was similar to that of Dukes and Szabuniewicz's report of other strains of swine, including a miniature pig and a mixed breeding of Yorkshire, Hampshire, and Duroc (20). In that study, the T wave of lead II in the ECG of newborns and during early postnatal life was, in general, large and positive. After a year of life, the T wave of lead II values was large and was negative (34). However, these results are not consistent with those obtained by us. The difference was possibly due to the animal strain.

The patterns of the QRS complex in the various leads from TLY pigs were in agreement with those reported for other pig breeds (12). The patterns of QRS complexes were present in leads: I, qR patterns; II and III, qRs patterns; aVR, rS patterns; aVL, QR patterns; and aVF, qR patterns. Only lead aVF patterns were different. Alterations in QRS complexes could be due to the elevation or depression of the ST segment. This happens frequently, particularly in young pigs (34). In the study reported here, we found that the change in QRS complex was not related to elevation or depression of the ST segment.

Compared with normal ECG standards for infants and children (18), the heart rate in pigs increased within the first 7 days of age and decreased sharply between days 10 and 30 (Figure 5). Steady state was reached beyond day 30. Heart rate in humans increases within the first 30 days of age, and gradually decreases within the next 16 years, then tends to continuously decrease. Such heart rate changes are present in both species. Likewise, characteristics, such as the changes of P and R waves and PR, QT, and QRS intervals over age, were found to be similar in TLY pigs and humans. The major significant differences were in the time course of the ECG changes. These differences in duration between minipigs and infants and children are summarized in Table 4. In general, most of the ECG changes reached steady state at or after 60 days of age in our pigs regardless of the increase in body weight (Table 1). We suspect that the steady state of ECG profiles is associated, in part, with the growth of the heart. Postmortem measurements of the ventricular wall thickness in the TLY pigs (Table 2) suggest that the exponential changes of the ECG were associated with heart growth. Body weight after day 60, however, did not play a major role in cardiac function; it was maintained between 10 and 20 kg without major changes in the ECG during 60 to 120 days. Pigs of this size are sufficiently small to permit experimental handling.

In conclusion, our study indicated that markedly different P and T waves were obtained when measured by use of different leads. There are consistent patterns in PR interval and QRS complex regardless of the choice of leads. From all intervals and waves analyzed, the data suggest that cardiac maturation was mostly achieved by 60 days of age in TLY minipigs, although body weight increased beyond 60 days of age. Because body weight of these newly developed TLY minipigs can be maintained

Table 4. Comparison of the changes in ECG over age between TLY pigs, infants,* and children*

	Pigs	*Infants and children
Heart rate	Increased within days 0 to 7 and sharply decreased from 225 to 100 bpm at day 60	Increased within days 0 to 30 and gradually decreased from 145 to 85 bpm within years 1 to 16
P wave amplitude	Negative amplitude was often found within days 7 to 60, using lead III and days 60 to 180, using lead aVL, and was always found, using lead aVR	Positive amplitude was often found within 16 years, using lead II
T wave amplitude	Negative amplitude was always found through days 0 to 80, using leads I, aVR, and aVL	Positive amplitude was found at birth, but became negative within three days, using leads V3R and V1
PR interval	Gradually and identically increased from days 7 to 180 in all leads (up to 120 ms)	Gradually increased from days 60 to 90 (up to 135 ms)
QT interval	Sharply decreased within days 0 to 7 and increased from days 7 to 30 (up to 250 ms)	Progressively decreased within days 0 to 30 and stable within days 30 to 360. Continuously increased from years 1 to 16 (up to 340 ms)
QRS interval	Sharply increased from days 7 to 21 and almost stable from days 60 to 180 (up to 40 to 45 ms)	Quite stable from birth to year 16 (50 to 60 ms)

*Data summarized from reference 18.

within 25 to 30 kg at one year of age and their major ECG findings did not significantly differ from those of humans and domestic pigs, they are well suited as an animal model for cardiovascular and pharmacologic research.

Acknowledgments

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