The Evolution of the Electrocardiogram in the Developing Heart

M. Irene Ferrer, M.D.
Cardiologist, Metropolitan Life Insurance Company; Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; Director, Electrocardiographic Laboratory, Columbia-Presbyterian Medical Center, New York, N.Y.

INTRODUCTION

The electrophysiologic events which together and in sequence produce the clinical electrocardiogram represent a sum of behaviors stemming from diverse and intrinsically quite different tissues. In order to understand the characteristics of the final product - namely the adult human electrocardiogram - one must be aware of the development of the contributing parts. The various anatomic components of the heart responsible for the generation of the electrocardiogram do not all develop at the same time in embryonic life, nor does the full maturation of each component proceed at the same rate.

Hence it is of interest to review the evolution of the structural and functional components of the various contributing parts of the electrocardiogram. The inscription of P, QRS and T complexes has its origin in the sequential contributions of the following tissues, the sino-atrial node and its surrounding approaches, the atrial myocardium and its specialized preferential intranodal pathways, the AV node and junctional tissue, the penetrating portion or common bundle of His and its branches, the Purkinje network and the ventricular myocardium.

The information relative to the development of these tissues is almost entirely anatomic. There is a paucity of electrophysiologic information. However, both will be reviewed.

The SA Node: The Primary Pacemaker.

The normal pacemaker of the heart, the sino-atrial node, does not control the cardiac rhythm from the onset of cardiac development in the embryo. Current anatomic information as recently reviewed1,2 reveals that at the very early stages of cardiac development, when the heart is in the "straight-tube" position, there is no sign of the SA node but there already is a differentiation of the specialized conducting tissues from working myocardial cells. This occurs by a separate migration of conducting cells from the myoepicardial mantle. Thus in the early stages of development there are probably two distinct populations of cells within the heart. Evidence is presented by these investigators2 that in the straight-tube stage "both phylogenetic and ontogenetic studies indicate that specialized zones of cells exist at the junctions between the primordial chambers of the heart tube". These are actually junctional rings of specialized tissues existing at the sino-atrial (between the sinus horn and atrium), atrio-ventricular, ventriculobulbar and bulbo-truncal junctions. These rings of tissue represent the primordia of conducting tissues.

During the first 6 - 7 weeks of life there is as yet no evidence of a discreet structure comparable to the definitive mature SA node2, the comma shaped island of tissues lying at the base of the superior vena cava in the adult heart. At this early stage only the primordia of the AV bundle and its ventricular branches are present astride the ventricular septum but the AV node as such is not yet formed. Hence it can be said that the specialized AV conducting tissues are not yet ready at 6 - 7 weeks for sinus rhythm, even if it existed; without a functioning AV node it could not reach the ventricles.

Information from fetal electrocardiograms indicates that definable complexes, usually only QRS complexes, first appear on the fetal electrocardiogram between 10 and 12 weeks of embryonic age3. This suggests that the cardiac rhythm in the early stages of development of the human embryo originates in junctional tissue, probably in the main AV bundle.

When the embryo is about 8 weeks old a structure approximating the mature SA node is first visualized2. By 10 weeks of age, when the right superior cardinal vein evolves to become the superior vena cava, the specialized tissue which remains at its base gradually becomes the normal pacemaker. The cells of the SA ring at the junction of the superior vena cava and the right auricle aggregate around a developing artery; by 10 weeks of age a discrete SA node is found surrounding this vessel. The tripartite cell population of the adult node - P cells, transitional cells, is seen at 10 weeks of age in the embryo, though the cellular arrangement is more dense, there is a tightly packed mass of small cells with more P cells and transitional cells than the typical adult pattern present by the time of birth2. Clearly then there are ongoing developmental changes in this SA node and these continue, especially with regard to increase in collagen in the node, until adult life4.

Along with the changing anatomy of the specialized cardiac tissues one must also consider the development of the autonomic nervous

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system in relation to cardiac tissue. The fetal heart has varying rates before it develops autonomic innervation; the cardiac nerve supply develops rather late in cardiac development\(^1\). Once any neural control develops it is predominantly cholinergic\(^1,5\). Thus the sinus rate in the fetus and newborn is rapid and relatively unstable probably, in part at least, due to the unbalanced autonomic innervation. Adrenergic innervation appears later and is complete only some months after birth. It is now known that heart rate fluctuates widely in newborn infants\(^5\) and indeed is varying all the time. Immediately after birth it is 135-140/minute; during the first postnatal hour it lies between 75 and 200/minute, the third hour averages 115/minute and slowly increased to 120-140/minute at the end of the first 24 hours of extra uterine life\(^5\). The healthy premature infants during their first week of life the heart rate is labile and rapid, reaching 200/minute with slight stimuli and falling to 100/minute during sleep. Sinus arrhythmia occurs at any age and phasic variations in rate have even been seen in fetuses; however, fixed rates in sinus rhythm may occur quite suddenly, replacing variation, and the cause of this behavior is unknown. Equally unclear are the sudden periods of sinus bradycardia in healthy babies but these are usually short lived. Sinus tachycardia between 175 and 190/minute is seen between birth and one month of age, and rates of 200-220/minute can occur. There are reports of rates as high as 260/minute in neonates\(^5\). These tachycardias are probably due to increase in adrenergic activity. Sinus rates gradually decrease as the child ages and values range between 60 and 80/minute in adults at rest. The mechanism of this gradual decrease in intrinsic rhythmicity of the SA node has not been studied but is presumed related to or mediated by autonomic factors.

The Appearance of Sinus Rhythm.

The question should be asked, in view of our present knowledge, when does sinus rhythm finally become the controlling rhythm of the human heart? The answer should lie in recording fetal electrocardiograms. The information from fetal electrocardiograms unfortunately is very incomplete. The reason, of course, lies in the technical difficulties inherent in obtaining this fetal electrocardiogram. Recordings from the infant's scalp have been made but, of course, this is late in fetal life as they cannot be obtained until labor begins. Fetal electrocardiographic recordings via the mother's abdominal wall have been unsatisfactory because deflections are blunted and usually only QRS complexes can be found. However, there are now newer technologies being developed which can augment the fetal action potentials so that electrocardiographic recordings via the maternal abdomen are more accurate; when these are clinically available longitudinal serial observations of fetal electrocardiograms in utero will become possible. Similar augmenting techniques have recently successfully recorded the action potential intrinsic to and inside the SA node — the true "firing" of this pacemaker. This event, which precedes the P waves, is of course not visible on the clinical electrocardiogram. Once this pacemaker firing can be recorded details of the awakening of the SA node in the fetus and its take over as the dominant rhythm will be known.

At present, one can only opine that sinus rhythm begins early in the middle trimester of gestation. This opinion is reinforced by the fact that a definitive or completed AV node can be recognized only after 10 weeks in humans and only at midterm are definitive bundle branches recognizable even though these specialized tissues are distinguishable at 6 weeks\(^2\). Both these tissues are needed, of course, to convey sinus rhythm to the ventricles.

**Atrial Myocardium, Intemodal Tracts:**

**The P wave.**

The spread of the SA node impulse as it enters and then passes over the atrial myocardium creates the P wave. The intermodal tracts connecting the SA to the AV node offer direct access to the lower node from the pacemaker\(^6\); however, some investigators\(^2\) have questioned the special character of these tracts believing that conduction to the AV node is over homogeneous working atrial myocardium. The electrophysiologic studies, however, tend to support specific tracts between the nodes. There is no developmental data about them however.

The form of the atrial excitation wave (P) changes during early neonatal life. At birth the P wave is tall (3mm. or more) and narrow with a duration of 0.03 to 0.08 sec.\(^3\). Between one month and one year it measures 0.04 to 0.08 sec., between one and three years 0.06 to 0.09 sec., and after that slowly widens until it reaches adult values (0.08-0.11 sec.) somewhere between five and ten years of age. The height gradually lessens with age and by 10 years of age 3 mm. values are no longer seen. The development of a wider shorter P wave occurs during a normal increase in atrial size. There are no serial measurements of atrial conductivity during these developmental changes and these are needed to explain almost a doubling of atrial excitation time and a decline in P voltage with maturation.

**AV Node and His Bundle (Purkinje System): The PR Interval.**

Developmental anatomic studies have recently emphasized the individuality of this node, the penetrating bundle or common bundle of His, and the bifurcating bundle and its branches\(^2\). Each of these has a separate origin embryologi-
cally; hence different physiologic behaviors are no surprise. Specialized structures which can be considered analogous to both node and bundle are present in the earliest embryologic human specimens (5-6 weeks) which suggest development of both structures in situ. The final formation of the AV node in its adult form is a late event embryologically. The node is composed developmentally of two parts, the deep and the superficial. The deep component appears to be of AV canal origin while the superficial more atrial component is derived from the atrial venous valves. When the two parts are joined in the developmental shifts of atrial growth the definitive AV node is established. No electrophysiologic data yet exist at these early stages but it is likely that only the deep component of the node has pacemaker capability. This idea is reinforced by the fact, in terms of development, the penetrating bundle (an area also potentially of self excitation) and the deep nodal component are one and the same tissue structure. By 10 weeks the AV node is recognizable as a separate entity in the developing heart. The penetrating bundle is formed from invaginating AV ring tissue but the bundle branches probably arise from the bulbo-ventricular ring. These branches, though present at 6 weeks are still difficult to distinguish from myocardial cells until midterm when they are recognizable in their right and left positions.

To summarize, anatomic and electrophysiologic studies on human fetuses have recently shown that by 10 to 16 weeks of embryonic life the AV conducting system of the heart functions as it does in the adult heart. Very recent investigations on the development of normal impulse initiation and conduction in the Purkinje fibers have shown in fetal canine tissue that the action potential "undergoes a continuum of change from early fetal life through term." Increase in maximum diastolic potential, action potential amplitude and duration and $V_{max}$ all occur as the fetus ages. The changes in Purkinje fiber conduction are a consequence of membrane maturational changes, changes in cell size, shape and the variety and extent of intercellular connections. Since the Purkinje fiber system is the first clearly differentiated conduction tissue to function in fetal development (the SA and AV nodes develop later) such data are crucial to our understanding of arrhythmias.

The PR Interval.
This interval includes atrial activity (the P wave duration) and the AV node-His bundle conduction time to the ventricular myocardium (PR segment). The P wave changes have already been discussed above. Information concerning the total PR interval in infants and children reveals that it may be quite short at birth and during the first week (0.08 to 0.10 sec.) and later lengthens to 0.12 to 0.14 sec. by one to three years and 0.12 to 0.17 by five years or later. There are no data to state where this lengthening of conduction occurs — in the AV node, the main bundle or its fascicular branches.

Ventricular Myocardium: The QRS-T Complex.

QRS Duration. It has long been known that the duration of the QRS complex — the ventricular myocardial excitation complex — may measure 0.05 to 0.06 sec. at birth and yet at the end of the first, second, or third day of life the duration of this QRS may decrease by as much as 0.03 to 0.04 sec. Hence after age 2, 3, or 4 days the QRS complex is usually 0.05 to 0.06 sec. in duration. In view of recent work on the Purkinje fibers and their developmental changes in electrical properties, one looks for a solution of this unusual feature in the future as well as clarification of the cause for the larger QRS voltage in children as compared to adults. Perhaps these explanations will follow investigations concerning the electrocardiogram of premature infants which differ from normal ones in that the QRS voltage may be quite low and does not reach normal size until the first postnatal month. Noteworthy in this regard is the fact that studies of the developing working ventricular myocardial cells have shown that there are significant although transient differences in the quantitative internal composition of the myocyte itself as growth proceeds. If intracellular components in the myocyte are changing in early growth perhaps the membrane characteristics responsible for QRS generation also alter with development.

Electrical Axis. Changes in the frontal plane electrical axis of the QRS have long been known to be associated with the growth of the normal postnatal heart. These shifts from a right axis deviation at birth (+90° to +110°) leftward to the adult axis orientation (+30° to +90°) take place in the first half year of infancy and are completed usually by age 6-8 months. The classical explanation for the changing axis is a rotational one, noting a shift from vertical to a more horizontal position of the whole heart in the chest. Developmental changes within the myocytes of the ventricles as growth proceeds have recently become known and therefore the classical rotational concept may have to be reviewed.

Precordial Leads. Right sided predominance in the ventricles at birth and its subsidence later on is demonstrated by the developmental changes that occur in the precordial leads of the electrocardiogram. The large R wave seen at birth in the right V leads gradually decreases in size and this change may begin around 6 months or one year of age and continues gradually over the first 4 to 6 years of life. Cellular and electrophysiologic data are not yet available to clarify all these changes but it likely that simple hemodynamic changes will not fully explain them.
T Wave Changes. There are constant changes in T waves during early cardiac development. Electrophysiologically the T wave is the resultant of the recovery phase of the action potential as it returns to resting potential. The well known transmembrane ionic shifts (sodium, potassium, calcium) have elucidated much of the formation of this wave in cellular preparations. However, there are as yet no data to explain the marked changes in T direction or polarity in the clinical electrocardiogram with growth. In the first 24 hours of life the T waves may be almost flat in contour in all leads and then become larger in a few days. The T wave in the right V leads may be upright in the first 24 hours but after the first few days, or occasionally even as late as 3 weeks after birth, the T waves in the right V leads normally become quite negative and remain so up to approximately one year of age. Thus after age 3 weeks and up to one year the normal T wave is negative in the right and positive in the left precordial leads. It is usual for the negative T waves in V1-V3 to become upright in the early years of life, but the change may not take place until the late teens or early twenties, the persistence of the “juvenile” pattern. The details of this developmental shift are unknown.

Note on Abnormal Rhythms.
In view of our present knowledge of the continuum of change occurring in the developing heart’s specialized tissues, the evaluation of the effects of disease and drugs becomes difficult. The same pathologic process may conceivably produce quite different effects depending on the stage of development existing in the tissues. The effect of drugs has recently been shown to be diametrically opposite depending on the age of the tissues being treated. A study (in dogs) of amrinone, a substance in the adult shown to have a positive inotropic action, demonstrated that the effects of the drug on ventricular muscle contractility were age-related. There was a decrease in contractility in the newborn (0-3 days old) and by day 4-10 the medication increased contractility. There was no difference in the action potential plateau in these two ages. The effects of amrinone in the young dog are most likely different due to a difference in membrane composition and function compared to the adult animal, and not to differences in intra-cellular composition.

With regard to the generation of arrhythmias very little is known of fetal and infant electrophysiology. Instability of the sinus rate in early life has been noted. Furthermore, remnants or “rests” of primordial or Purkinje-like tissues noted in such places as the central fibrous body and analus fibrosus and in both atrial and ventricular tissues conceivably could become self-excitatory pacemakers under certain circumstances especially with catecholamine influences. Re-entrant tachycardias may travel over accessory AV bundles which remain functional instead of being absorbed during cardiac development. Recent studies using 2-D real-time and M mode echocardiography to record atrial and ventricular rates and rhythms and supra-abdominal fetal electrocardiograms, appear to offer the most useful current means for diagnosis of arrhythmias.

The Electrocardiogram of Twins
The stability of the electrocardiogram once it has fully evolved in the normal adult heart is remarkable. Indeed one can use the electrocardiogram as a clear identifier of any one individual and the tracing remains identical when done again and again. Hence an interesting aspect of the development of the electrocardiogram is that concerned with twins. Although investigation into this subject is still scanty, some rather unexpected facts have come to light. The incidence of twins is 1 in 86 pregnancies and of the total number of twins about one-third are identical twins (monozygotic). The electrocardiograms in monozygotic twins are identical in only 52% with dissimilar tracings in 48%. In dizygotic or non-identical twins the electrocardiograms are identical 42% and in 58% the tracings are different. Thus identical electrocardiograms are seen in both identical and non-identical twins. This has suggested an indepth genetic evaluation of these subsets using all the modern genetic approaches in order to learn what makes for an identical electrocardiogram in twins. In this connection it is interesting to note that fingerprints are considered the best means of establishing identity and yet the fingerprints of identical twins are not the same. Each one has his or her own individual fingerprints. The ridges and furrows of fingerprints are now thought to be due to external positional pressures on the skin of the fingers in utero. The positions of twin fetuses is constantly shifting and are not identical for each fetus.

In summary, we are entering a new phase of understanding of the evaluation of the electrocardiogram in the developing heart by virtue of the present ability to examine electrophysiology at the heart cell level. It will be exciting to watch the unfolding of this knowledge as observations continue on the minute details of myocardial and specialized tissue growth and development.

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References


