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Cardiac refractory periods extrastimulus technique
electrophysiology His bundle electrogram

The Influence of Age on Cardiac Refractory Periods in Man

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Extract

As age is a determinant of cardiac refractory periods, this communication describes changes of refractory periods in an age continuum of infants, children and adults, 7 months through 77 years. Seventy patients with evidence of normal A-V conduction on scalar electrocardiogram were included. The patients were divided into six age groups: <2 years, 3-5 years, 6-10 years, 11-15 years, 16-30 years, and >30 years. Extrastimulus technique was used to determine refractory periods in sinus rhythm or at longest cycle length assuring atrial capture, then at shorter cycle lengths. Cycle lengths (CL) for each age group were divided into ranges: CL₁, 1,000-600 msec; CL₂, 599-460 msec; CL₃, <459 msec. Refractory periods at the three CL's within each age group were determined. Full recovery times of the A-V node within groups of children were determined. Statistical significance of the data was found by analysis of variance. The younger group tended to have shorter values than the older groups ($F < 0.05-0.001$).

Speculation

These changes with age apparently reflect maturation of the conduction system and may explain the differences in susceptibility to and electrophysiologic manifestations of various arrhythmias in infants, children, and adults.

Standard cardiac catheterization studies have contributed much to understanding hemodynamic and myocardial functions in pediatric patients. Recent advances in clinical intracardiac electrophysiology have lead to better understanding of normal and pathologic atrioventricular conduction, primarily in adults (5, 6, 23, 24, 26). There is limited intracardiac electrophysiology data available for children (1-4, 21, 22). DuBrow *et al.* (7) recently demonstrated shorter atrial and A-V nodal refractory periods in juveniles compared with adults at similar heart rates. This paper will expand our previously reported observations by examining cardiac refractory periods in multiple age groups.

MATERIALS AND METHODS

PATIENT SELECTION

Studies were performed in 70 patients, whose ages ranged from 7 months through 77 years, during diagnostic cardiac catheterization. Only patients with evidence of normal A-V conduction on scalar electrocardiogram were included (sinus rhythm, normal P-R interval, and narrow QRS). Clinical status, electrocardiographic diagnosis, and intracardiac electrogram intervals were reported previously (5, 7, 26). Three additional children meeting the above criteria were included: two 8 year olds, one with a ventricular

septal defect, the other with a coarctation of the aorta; and a 2.5 year old with endocardial fibroelastosis.

ELECTROPHYSIOLOGIC PROCEDURE

Patients and parents were informed of the nature of the study and a signed consent was obtained. No child was receiving cardioactive drugs, and only two adult patients received cardioactive drugs within 1 week before study (procaine amide and digoxin). In both, the drugs were discontinued 48 hr before the study. Studies were performed in the postabsorptive, lightly sedated state in children and nonsedated state in adults after diagnostic cardiac catheterization.

Low atrial, His bundle, and ventricular electrograms were recorded with a multipolar catheter positioned across the tricuspid valve (24). High right atrial electrograms were recorded from the proximal electrodes of another multipolar catheter positioned in the high lateral right atrium, and distal electrodes of the same catheter were used for atrial pacing (5). Interelectrode distances

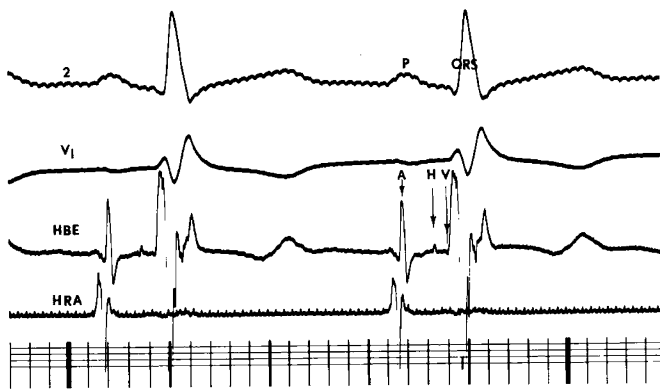


Fig. 1. Representative tracing from a 12-year-old child during sinus rhythm to demonstrate electrophysiologic events recorded at 200 mm/sec. 2 and V₁ are surface electrocardiogram leads. P and QRS waves are labeled. HBE is the tracing from the multipolar catheter lying across the tricuspid valve to record low right atrial (A), His bundle (H) and ventricular (V) electrograms. HRA is the tracing from the catheter placed at superior vena cava-right atrium junction. Atrial pacing and programmed extrastimuli are delivered via this catheter.

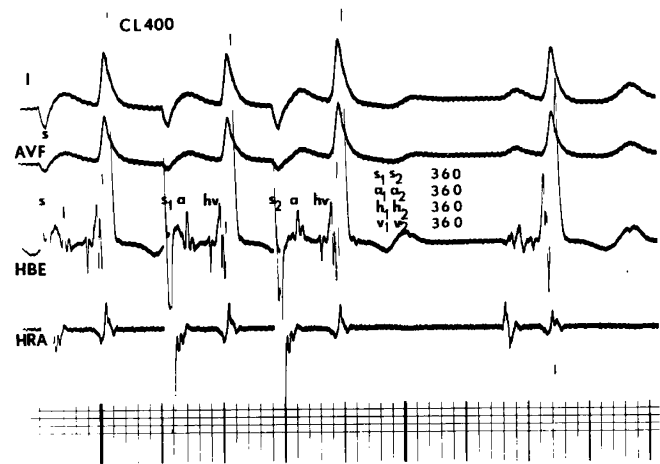


Fig. 2. Representative atrial extrastimulus tracing from a 2-year-old child at an atrial driving rate of 400 msec recorded at 100 mm/sec. I and AVF are surface electrocardiograms; HBE and HRA are as described in Figure 1. S is the pacemaker stimulus artifact; S₁ is the last stimulus before the programmed premature stimulus, S₂. Corresponding intracardiac electrograms (a, h, and v) follow S₁ and S₂. Early in the cycle scan S₂ is introduced 360 msec after S₁ (S₁S₂ 360) and a₁a₂, h₁h₂, v₁v₂ are 360 msec.

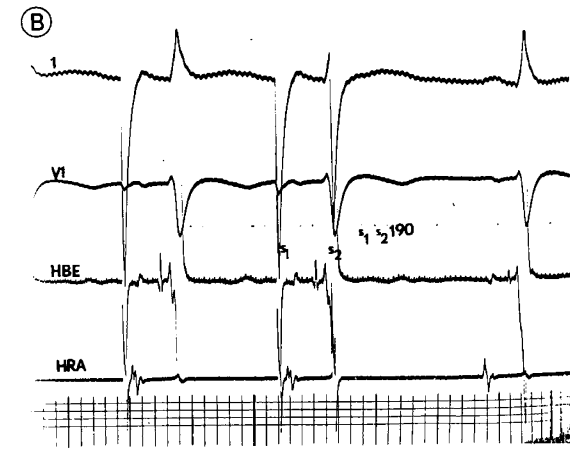
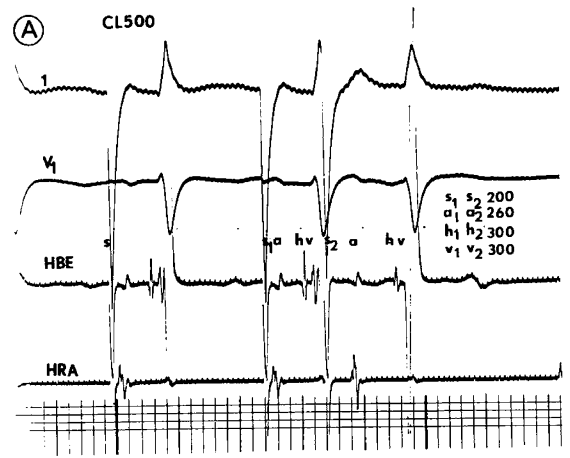


Fig. 3. A: representative atrial extrastimulus tracing in a 5-year-old child during atrial pacing at cycle length 500 msec (CL500). 1 and V₁ are surface electrocardiograms. HBE and HRA, S₁, S₂, a, h, and v are as described in legends to Figures 1 and 2, S₁S₂ is 200 msec. The shortest a₁a₂ obtained was 260 msec (atrial functional refractory period). The 60-msec delay between S₁S₂ and a₁a₂ represents atrial latency. B: the next 10-msec extrastimulus decrement in the same patient at the same driving rate as in A. No atrial electrogram follows S₂. This is the longest S₁S₂ 190 msec that does not conduct to the atrium (atrial effective refractory period). In this patient the conduction system is atrial limited. A-V node and His-Purkinje system refractory periods are equal to or less than atrial functional refractory period.

were 1-0.5 cm. Intracardiac electrograms and at least two external ECG leads were displayed on an oscilloscope and recorded on a multichannel photographic recorder (Hewlett-Packard 4568C or Electronics for Medicine DR-16) at paper speeds of 100 and 200 mm/sec. Frequencies below 40 Hz and above 500 Hz were filtered for signal clarity. (Fig. 1). Pacing and premature stimuli were approximately twice diastolic threshold, 2 msec in duration, and delivered by a programmable digital stimulator (27) through a stimulus isolator unit.

Extrastimulus technique was used to determine refractory periods first in sinus rhythm or at longest cycle length assuring atrial capture, then at shorter cycle length(s). The extrastimulus (S₂) was introduced at 10-20-msec decrements after 8-10 sinus or driven (S₁) beats. Each patient had refractory periods determined at 1-5 cycle lengths.

Intervals were measured as previously described (5, 7, 26). A₁, H₁, V₁ represent atrial, His bundle, and ventricular electrograms of either spontaneous or S₁-driven beats. A₂, H₂, and V₂ represent atrial, His bundle, and ventricular electrograms of the premature beat induced by S₂ (Fig. 2).

DEFINITIONS

Atrial effective refractory period was the longest S_1 - S_2 at which atrial capture failed to occur. Atrial functional refractory period was the shortest A_1 - A_2 attainable. (Fig. 3, *A* and *B*). When the shortest coupling interval was too long to determine atrial effective refractory period or atrial functional refractory period, the value was said to be less than the shortest interval observed. Full recovery time (FRT) of the A-V node was the shortest A_1 - A_2 interval at which A_2 - H_2 was equal to A_1 - H_1 . A-V nodal effective refractory period was the longest A_1 - A_2 at which H_2 failed to occur. A-V nodal functional refractory period was the shortest H_1 - H_2 attainable. When atrial functional refractory period exceeded A-V nodal effective refractory period, the conduction system was said to be atrial limited and A-V nodal effective refractory period was tabulated as less than atrial functional refractory period. (Fig. 3*B*). Effective refractory period of the His-Purkinje system was the longest H_1 - H_2 at which conduction to the ventricles failed to occur. Refractory period of a bundle branch was considered the longest H_1 - H_2 at which the appropriate surface electrocardiographic pattern of bundle branch block occurred.

ANALYSIS OF DATA

The 70 patients were divided into six age groups: <2 years ($n = 10$), 3-5 years ($n = 11$), 6-10 years ($n = 14$), 11-15 years ($n = 12$), 16-30 years ($n = 8$), and >30 years ($N = 15$). In the youngest group the age range was 7 months to 2 years, 1.28 ± 0.46 (mean \pm SD). In the oldest group the range was 33-77 years, 52.2 ± 13.72 (mean \pm standard deviation). Cycle lengths for each age group were divided into ranges: CL_1 , 1,000-600 msec; CL_2 , 599-460 msec; CL_3 , <459 msec. Means and standard deviations of cycle lengths for each group within each CL were tabulated. Refractory periods at the three CL's within each age group were determined. Full recovery times of the A-V node within groups of children were determined. Means and standard errors of the means for data in each CL of each age group were tabulated and their statistical significance was found by analysis of variance.

Regression analysis utilizing linear, log X, log Y, and logs X and Y models was done on a programming calculator (Wang 700C series) coupled to an X, Y plotter (Wang 702 series). Refractory periods and A-V node full recovery times were the ordinates and age was the abscissa.

RESULTS

CYCLE LENGTHS

The mean values \pm 1 SDM of cycle lengths within cycle length ranges for the six age groups are listed in Table 1. There was no significant difference between groups at CL_1 and CL_2 ($F > 0.25$). Borderline significant difference was found at CL_3 ($F > 0.05$). The number of younger children who could be paced at slower rates, CL_1 , was smaller than older patients because of the faster resting

heart rates in the former. At faster rates, CL_3 , the number of older patients who could be paced was less than in the younger groups, as the former developed Wenckebach periods at slower rates than children.

REFRACTORY PERIODS

The mean values \pm 1 SEM of atrial effective and functional and A-V nodal effective and functional refractory periods are shown in Table 2. At CL_1 , the longest range, there were not enough observations in the two youngest groups for comparison. The younger groups tended to have shorter values than the older groups.

ATRIAL EFFECTIVE REFRACTORY PERIODS

Atrial effective refractory periods for each age group within each cycle length range were found to be significantly different from each other. At CL_1 , CL_2 , and CL_3 the F values were <0.001, <0.01, and <0.001, respectively (Table 2).

ATRIAL FUNCTIONAL REFRACTORY PERIODS

Atrial functional refractory periods for each age group within each cycle length range were significantly different from each other. At CL_1 , CL_2 , and CL_3 the F values were <0.025, <0.01, and <0.001, respectively (Table 2).

A-V NODE FULL RECOVERY TIMES

A-V node full recovery times were analyzed in patients less than 15 years old. Means \pm 1 SEM are listed in Table 3. There were not enough observations for analysis at CL_1 . At CL_2 there was borderline significant difference ($F < 0.05$) and at CL_3 the differences were significant ($F < 0.01$). The younger groups had faster recovery times.

A-V NODE EFFECTIVE REFRACTORY PERIODS

A-V node effective refractory periods for each age group within each cycle length range were significantly different from each other. At CL_1 , CL_2 , and CL_3 the F values were <0.01, <0.001, and <0.001, respectively (Table 2).

A-V NODE FUNCTIONAL REFRACTORY PERIODS

A-V node functional refractory periods for each age group were significantly different from each other within CL_2 ($F < 0.001$) and CL_3 ($F < 0.001$). Differences at CL_1 were not significant (Table 2).

There were not enough observations of His-Purkinje system or bundle branch refractory periods for analysis in age groups.

REGRESSION ANALYSIS

At CL_1 no fit was significant; however, the number of observations was small. At CL_2 atrial effective refractory periods were

Table 1. Cycle lengths within cycle length ranges¹

Cycle length ranges	Age, yr						<i>F</i>
	<2 (10) ²	3-5 (11)	6-10 (14)	11-15 (12)	16-30 (8)	30 (15)	
CL_1 , 1,000-600 msec		605	660 \pm 71	666 \pm 71	681 \pm 50	708 \pm 13	>0.25
<i>n</i>		(2)	(5)	(10)	(12)	(16)	
CL_2 , 599-460 msec	478 \pm 18	502 \pm 32	516 \pm 30	505 \pm 26	510 \pm 37	520 \pm 41	>0.25
<i>n</i>	(5)	(10)	(16)	(13)	(10)	(21)	
CL_3 , 459 msec	370 \pm 52	381 \pm 60	376 \pm 50	404 \pm 35	403 \pm 31	412 \pm 34	>0.05
<i>n</i>	(21)	(11)	(21)	(13)	(8)	(15)	

¹ Values of cycle lengths are listed as means in milliseconds \pm 1 SDM. *n*: number of observations.

² Number of patients.

Table 2. Refractory periods within cycle length ranges and age groups¹

Refractory period Cycle length range	Age, yr						F
	<2	3-5	6-10	11-15	16-30	>30	
AERP							
CL ₁			164 ± 17	201 ± 18	211 ± 16	250 ± 12	<0.001
n			(5)	(9)	(7)	(16)	
CL ₂	176 ± 18	181 ± 15	206 ± 8	212 ± 13	213 ± 10	240 ± 13	<0.01
n	(5)	(11)	(16)	(13)	(10)	(21)	
CL ₃	144 ± 8	151 ± 7	185 ± 8	193 ± 7	188 ± 8	205 ± 8	<0.001
n	(21)	(1)	(21)	(14)	(8)	(16)	
AFRP							
CL ₁			230 ± 8	259 ± 17	243 ± 19	295 ± 11	<0.025
n			(5)	(9)	(7)	(16)	
CL ₂	210 ± 9	235 ± 15	245 ± 5	250 ± 1	255 ± 10	278 ± 12	<0.01
n	(5)	(11)	(15)	(13)	(10)	(21)	
CL ₃	195 ± 6	208 ± 11	218 ± 6	229 ± 11	240 ± 9	258 ± 9	<0.001
n	(21)	(12)	(21)	(14)	(8)	(16)	
AVNERP							
CL ₁			236 ± 13	283 ± 12	261 ± 21	313 ± 10	<0.01
n			(5)	(9)	(7)	(16)	
CL ₂	212 ± 10	240 ± 17	276 ± 13	280 ± 13	319 ± 17	334 ± 13	<0.001
n	(5)	(11)	(16)	(13)	(10)	(21)	
CL ₃	205 ± 6	213 ± 13	231 ± 7	266 ± 9	286 ± 14	293 ± 14	<0.001
n	(21)	(12)	(21)	(13)	(6)	(11)	
AVNFRP							
CL ₁			428 ± 26	423 ± 16	412 ± 29	416 ± 9	NS
n			(5)	(7)	(5)	(16)	
CL ₂	316 ± 9	327 ± 21	362 ± 13	399 ± 18	432 ± 19	401 ± 12	<0.001
n	(5)	(11)	(16)	(12)	(10)	(21)	
CL ₃	286 ± 6	280 ± 16	311 ± 12	345 ± 10	353 ± 15	348 ± 10	<0.001
n	(20)	(12)	(21)	(10)	(3)	(11)	

¹ AERP: atrial effective refractory period; AFRP: atrial functional refractory period; AVNERP: A-V nodal effective refractory period; AVNFRP: A-V nodal functional refractory period; CL₁: cycle length range 1,000-600 msec; CL₂: cycle length range 599-460 msec; CL₃: cycle length range <459 msec; n: number of observations; NS: not significant. All values are listed in milliseconds ± 1 SEM.

Table 3. A-V nodal full recovery time¹

Cycle length range	Age, yr					F
	<2	3-5	6-10	11-15	16-30	
CL ₂	376 ± 27	445 ± 12	436 ± 19	463 ± 8		<0.05
n	(5)	(12)	(14)	(9)		
CL ₃	310 ± 10	341 ± 19	351 ± 11	384 ± 15	370	<0.01
n	(17)	(8)	(9)	(10)	(2)	

¹ CL₂: cycle length range 599-460 msec; CL₃: cycle length range <459 msec; n: number of observations. All values are listed in milliseconds ± 1 SEM.

significant as follows: linear, $P < 0.02$; log X, $P < 0.05$; log Y, $P < 0.01$; log X and Y, $P < 0.02$. Atrial functional refractory period fits were not significant. A-V node full recovery times were significant as follows: linear, $P < 0.02$; log X, $P < 0.01$; log Y, $P < 0.02$, log X and Y, $P < 0.01$. A-V node effective and functional refractory periods were significant at $P < 0.001$ for each equation. At CL₃ all variables were significant at $P < 0.001$ for each equation.

DISCUSSION

There is a paucity of information regarding pediatric intracardiac electrophysiology. Many of the studies in the literature describe basic intracardiac intervals and compare the data to adult values. Basic intervals are shorter in children and have been shown to be related to age and heart rate (1-4, 22). Abella *et al.* (1)

demonstrated an age-related continuum of basic intracardiac intervals. The present communication expands previous observations on the refractory period relationship to various age groups, infants through adults (7). The population was divided arbitrarily into six groups large enough for meaningful analysis of variance.

As heart rate is inversely related to age (16, 21), and as refractory periods are related to heart rate (5, 20), faster heart rates in children could account for the shorter refractory periods. Friedman *et al.* (10) demonstrated shorter refractory periods in isolated lamb ventricular myocardium compared with adult sheep, suggesting that age may be an additional factor. We controlled cycle length variable by pacing the age groups at equivalent rates and found atrial effective and functional and A-V nodal effective refractory periods of all age groups to be significantly different. A-V nodal functional refractory periods were significantly different at CL₂ and CL₃. Refractory periods of younger groups were shorter than older groups, and differences were greater through groups 6-10 years. Differences from 11-15 years through >30 years were less marked. A-V node full recovery times in the groups examined showed similar trends.

The purpose of this analysis was not to predict refractory periods or A-V node full recovery time with age, as there was not enough data. Pilot regression analysis in the children, however, did show significant fits to the mathematical models tested for each variable at CL₃ and all but atrial functional refractory periods at CL₂. CL₁ was not significant; however, numbers of observations were smaller than in other ranges. As there were multiple significant fits, further data presently being collected in our laboratory should elucidate which equation will best describe the observed variables. In the mean time, we feel that tabular form and analysis of variance are useful to see the trends.

James (14) has demonstrated progressive histologic changes in the conduction system of the human fetus, infant, and young child through 2-3 years of age. He has postulated that the observed remodeling may have electrophysiologic correlates (15). With further aging, Erickson and Lev (8, 18, 19) have shown degenerative changes in the conduction system. Our demonstration of the changes in refractory periods with age, particularly in children, is consistent with the concept that electrophysiologic functional changes are related to architectural changes of the conduction system during the aging process.

In addition, there is evidence indicating that fetal newborn, and young mammalian hearts are more sensitive to the chronotropic and inotropic influences of catecholamines. This is felt to be due to the progressive innervation of the young heart and the development of the sympathetic intraneural enzyme systems controlling uptake, binding, and synthesis of norepinephrine in the postnatal period. The β -receptors respond equally to isoproterenol in fetal, young, and adult animals; however, the response to norepinephrine, the endogenous neurohumor, is exaggerated in fetal, infant, and young animals compared with adults (9-13). Krayer *et al.* (17) demonstrated that epinephrine shortens effective and functional refractory periods of atrioventricular conduction in the heart-lung preparation of dogs, and Siebens *et al.* (25) have shown that epinephrine and norepinephrine shorten the refractory periods of atrium and ventricle in the dog. Our findings relate to increased catecholamine sensitivity in juvenile hearts.

In conclusion, this study suggests that atrial and A-V nodal refractory periods and A-V nodal full recovery time increase with age. Previous observations suggest that A-V conduction intervals, A-H and H-V, also are age related (1-4, 20). These changes in conduction times and refractory periods with age apparently reflect maturation of the conduction system and may explain the differences in susceptibility to and electrophysiologic manifestations of various arrhythmias in infants, children, and adults.

SUMMARY

An age-related progression of cardiac refractory periods, independent of cycle length, was observed using atrial extrastimulus technique in 70 patients (age range 7 months to 77 years). The changes with age apparently reflect maturational changes in the conduction system and may explain differences in susceptibility to and electrophysiologic manifestations of various arrhythmias in infants, children, and adults.

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