AGE-RELATED CHANGES OF SINUS NODE FUNCTION
AND AUTONOMIC REGULATION IN SUBJECTS
WITHOUT SINUS NODE DISEASE

— Assessment by Pharmacologic Autonomic Blockade —

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To assess the relationship between aging and autonomic regulation of sinus node function, 56 subjects of various ages (range 14—75 years, mean 43±19 years) without sinus node disease were studied. Heart rate, corrected sinus node recovery time and sinoatrial conduction time were measured before (basic) and after (intrinsic) pharmacologic autonomic blockade (propranolol+atropine i.v.). Percent chronotropies of the above parameters were calculated by a modified Jordan’s method. Basic heart rate and basic corrected sinus node recovery time did not vary with age (r=−0.15, r=0.08, respectively), while basic sinoatrial conduction time tended to increase with age (r=0.32, p<0.05). Intrinsich heart rate decreased (r=−0.76, p<0.001), and intrinsic corrected sinus node recovery time and intrinsic sinoatrial conduction time both increased with age (r=0.55, p<0.001; r=0.56, p<0.001, respectively). The younger the subject, the more negative the percent chronotropies of the above parameters were, and the percent chronotropies correlated positively with age (r=0.68, p<0.001; r=0.52, p<0.001 and r=0.34, p<0.05, respectively). In conclusion, intrinsic sinus node functions deteriorated with age. Furthermore, parasympathetic tone on the sinus node functions decreased with age, which may compensate for age-related deterioration of intrinsic sinus node function.

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SINUS node function is determined by the balanced interaction of intrinsic sinus node automaticities, perinodal conduction properties and extrinsic factors!−3 Among the extrinsic factors, the autonomic nervous system has the greatest influence!−3 The diagnostic value of blocking sympathetic and parasympathetic activities, followed by determination of intrinsic sinus node function has been emphasized in previous reports!−4

Key words:
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garding the normal limits of corrected sinus node recovery time and sinoatrial conduction time in relation to age.

Cardiovascular sympathetic activity reportedly increases with age while parasympathetic activity decreases with age to compensate for age-related underlying functional defects. Similar age-related changes in the autonomic regulation of sinus node function have been reported in sick sinus syndrome. However, there have been very few reports which assess these age-related changes in subjects without sinus node disease.

Therefore, the purposes of the present study are, by using pharmacologic autonomic blockade, 1) to assess age-related changes in basic and intrinsic sinus node functions, 2) to assess age-related changes in the autonomic regulation of the sinus node function, and 3) to establish the normal limits of electrophysiologic variables of the sinus node function in relation to age in subjects with normal sinus node function.

METHODS

Patients

Electrophysiologic studies were performed on 56 subjects, 41 males and 15 females, ages 14—75 years (43±19 years, mean±standard deviation) who had experienced unexplained dizziness, loss of consciousness, palpitations or atrioventricular conduction defects. Loss of consciousness or dizziness was later determined to have been caused by epilepsy, orthostatic hypotension or vertigo, and not by sick sinus syndrome, based on repeated Holter ambulatory recordings and electrophysiologic studies.

Electrophysiologic studies

After the nature of the procedure was explained, informed consent was obtained from all patients. Patients were studied in a non-sedated, postabsorptive state in a cardiac catheterization laboratory. The electrophysiologic protocol used in this study has been reported previously. All cardioactive drugs and drugs known to interfere with sinus node function and autonomic nervous function were discontinued at least 48 h before the study. Using the standard intracardiac recording technique, 3 quadripolar pacing catheters with an interelectrode distance of 10 mm were introduced percutaneously under local anesthesia through the right femoral vein, advanced under fluoroscopic guidance, and positioned at the high right atrium, in the region of the tricuspid valve to record the His bundle electrogram, and in the right ventricular apex. The proximal poles of the atrial catheter were utilized for recordings and the distal poles were utilized for stimulations. Intracardiac electrograms at a frequency setting of 30 to 500 Hz and 3 surface leads (I, aVF, V1) were recorded concurrently on a photographic recorder (Electronics for Medicine, VR 12) at paper speeds of 50 or 100 mm/sec. Atrial stimulation was carried out with a programmable stimulator (Medtronic, Model 5325) using rectangular wave pulses of 1.8 msec in duration and at approximately twice the diastolic threshold.

Sinus node recovery time (SNRT) was measured by atrial pacing at cycle lengths of 750, 667, 545, 461, 400 and 352 msec for 30 sec at each level. Sinus node recovery time was measured as the interval between the last pacing artifact and the onset of the first sinus escape beat on the high right atrial electrogram. Corrected sinus node recovery time (CSNRT) was calculated by deducting the mean sinus cycle length from the longest SNRT. Rest periods of at least 1 min were given between atrial pacings to allow the rhythm to return to the basic level.

Sinoatrial conduction time (SACT) was measured by the method described by Narula et al. Continuous pacing was performed for 8 beats at rates slightly faster (>10 beats/min) than the sinus rate. Thereafter, pacing was abruptly stopped. Sinoatrial conduction time was obtained by deducting the mean sinus cycle length from the interval between the last paced atrial deflection and the atrial deflection of the first escape sinus beat. The interval thus obtained represents the sum total of the conduction time into and out of the sinus node. Atrial pacing was performed similarly for at least 3 different pacing cycle lengths at decrements of 50 msec. The values of SACT during several repeated measurements were used to calculate the mean SACT to compensate for variations in the sinus cycle lengths.

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Fig.1. The relationships between age and basic HR (A), and between age and intrinsic HR (B). Basic HR did not correlate with age \( (r = -0.15, \text{N.S.)}. \) Intrinsic HR decreased with age \( (\text{IMR} = -0.65 \times \text{age} + 115, \ r = -0.76, \ p < 0.001). \) The shaded area indicates the 95% confidence normal limit of intrinsic HR proposed by Jose and Collison. Broken lines indicate 1 standard deviation of the normal limit proposed by the present study.

Fig.2. The relationship between age and percent chronotropy of heart rate \( (\% \text{CH HR}). \) Percent chronotropy of HR correlated positively with age \( (\% \text{ch HR} = 0.58 \times \text{age} - 44, \ r = 0.68, \ p < 0.001). \)

**Pharmacologic autonomic blockade**

After measurements in the basic state, pharmacologic autonomic blockade was achieved by using a modified protocol of Jose and Collison with propranolol, 0.2 mg/kg body weight, administered intravenously at a rate of 1 mg/min, and atropine sulfate, 0.04 mg/kg, administered over 2 min. After a stable sinus rate was achieved, usually 3 to 5 min after autonomic blockade, measurements of HR, CSNRT and SACT were repeated as in the basic state. The studies were completed within 30 min after autonomic blockade.

**Definitions**

The following definitions were used in this study

1. Basic heart rate (HR): The average heart rate calculated from 20 consecutive sinus cycles observed before autonomic blockade.

2. Predicted intrinsic HR: Predicted intrinsic HR was calculated using the linear regression equation derived by Jose and Collison \( (\text{predicted intrinsic HR} = 118.1 - 0.57 \times \text{age}) \)

3. Observed intrinsic HR: The average heart rate observed after autonomic blockade when a stable sinus rate was achieved. The 95% confidence normal limit of observed intrinsic HR was taken as \( \pm 14\% \) of the predicted intrinsic HR for patients 45 years of age or younger, and \( \pm 18\% \) of the predicted intrinsic HR for patients more than 45 years old.

4. Basic corrected sinus node recovery time (basic CSNRT): Basic CSNRT was calculated by deducting the mean sinus cycle length from the longest sinus node recovery time before autonomic blockade, without regard to the pacing cycle length at which it occurred.

5. Intrinsic corrected sinus node recovery time (Intrinsic CSNRT): Intrinsic CSNRT was calculated after autonomic blockade as in the basic state.

6. Basic sinoatrial conduction time (Basic SACT): The average SACT of several re-
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Fig. 3. The relationships between age and basic CSNRT (A), and between age and intrinsic CSNRT (B). Basic CSNRT did not correlate with age (r=0.08, N.S.). Intrinsic CSNRT increased with age (intrinsic CSNRT=3.15×age+143, r=−0.55, p<0.001). Broken lines indicate 1 standard deviation of the normal limit of intrinsic CSNRT in relation to age.

Fig. 4. The relationship between age and percent chronotropy of CSNRT (%CH CSNRT). Percent chronotropy of CSNRT correlated positively with age (%CH CSNRT=2.01×age−140, r=0.52, p<0.001).

The repeated measurements taken before autonomic blockade.

7. Intrinsic sinoatrial conduction time (Intrinsic SACT): The average SACT after autonomic blockade calculated as in the basic state.

8. Percent chronotropy: For the purpose of evaluating the magnitude and direction of autonomic chronotropic influences on sinus node function in the basic state, percent autonomic chronotropies of HR, CSNRT and SACT were calculated by the following formulas: 1) % chronotropy of HR=(intrinsic HR−basic HR/intrinsic HR)×100 (%); 2) % chronotropy of CSNRT=(intrinsic CSNRT−basic CSNRT/intrinsic CSNRT)×100 (%); and 3) % chronotropy of SACT=(intrinsic SACT−basic SACT/intrinsic SACT)×100 (%).

Thus, regulation of sinus node function by the autonomic nervous system was quantitatively represented. A positive value indicates that the sympathetic tone is predominant, while a negative value indicates that parasympathetic tone is predominant in the basic state.

Statistical analysis

Statistical evaluations were performed by the Student’s t-test for paired data. Regression analysis was performed using a computer program. A p value of 0.05 or less was considered to be significant. The data in this study are presented as mean±standard deviation.

RESULTS

Heart rate and age

Basic HR ranged from 46 to 94 beats/min (mean 67±11 beats/min). Basic HR did not correlate with age (r=−0.15, p=N.S.) (Fig. 1A). After autonomic blockade, intrinsic HR ranged from 55 to 119 beats/min (mean 87±16 beats/min) (Fig. 1B). Intrinsic HR decreased with age (intrinsic HR=−0.65×age+115, r=−0.76, p<0.001) (Equation-1). Forty-nine patients fell within the normal limit of intrinsic HR as proposed.
by Jose and Collison, while 7 patients were below the normal limit. One standard deviation of the normal limit was within ±16 beats/min of the values calculated by equation-1. The mean basic HR was less than the mean intrinsic HR. The younger patients showed more positive values of percent chronotropy of HR, whereas the elderly patients showed nearly zero values (Fig. 2). Percent chronotropy of HR correlated positively with age (percent chronotropy of HR = 0.58 × age - 44, r = 0.68, p < 0.001).

**Corrected sinus node recovery time and age**

Basic CSNRT ranged from 250 to 490 ms (mean 361 ± 70 ms). Basic CSNRT did not correlate with age (r = 0.08, p = N.S.) (Fig. 3A). After autonomic blockade, intrinsic CSNRT ranged from 115 to 490 ms (mean 279 ± 108 ms). Intrinsic CSNRT increased with age (intrinsic CSNRT = 3.15 × age + 143, r = 0.55, p < 0.001) (equation-2) (Fig. 3B). One standard deviation of the normal limit of intrinsic CSNRT in relation to age was within ±108 ms of the values calculated by equation-2. The mean intrinsic CSNRT was significantly less than the mean basic CSNRT (p < 0.001). The younger patients showed more negative values of percent chronotropy of CSNRT, whereas the elderly patients showed more positive values (Fig. 4). Percent chronotropy of CSNRT correlated positively with age (percent chronotropy of CSNRT = 2.01 × age - 140, r = 0.52, p < 0.001).

**Sinoatrial conduction time and age**

Basic SACT ranged from 107 to 300 ms (mean 211 ± 46 ms). Basic SACT tended to increase with age (basic SACT = 0.78 × age + 177, r = 0.32, p < 0.05) (Fig. 5A). After autonomic blockade, intrinsic SACT ranged from 60 to 233 ms (mean 140 ± 42 ms). Intrinsic SACT increased with age (intrinsic SACT = 1.23 × age + 87, r = 0.56, p < 0.001) (equation-3) (Fig. 5B). One standard deviation of the normal limit of intrinsic SACT was within ±42 ms of the values calculated by equation-3. The mean intrinsic...
SACT was significantly less than the mean basic SACT (P<0.001). The younger patients tended to show more negative values of percent chronotropy of SACT, whereas the elderly patients showed less negative values. Percent chronotropy of SACT correlated with age, but the correlation was weak (percent chronotropy of SACT=0.77×age−94, r=0.34, p<0.05) (Fig. 6).

DISCUSSION

Influence of the autonomic nervous system on sinus node function

The sinus node and perinodal tissues are richly supplied with sympathetic and parasympathetic nerve endings\(^1\)\(^6\),\(^17\) and the autonomic nervous system exerts significant influence on sinus node automaticity\(^1\)\(^−\)\(^3\)\(^,\)\(^8\)\(^−\)\(^20\) and sinoatrial conduction\(^2\)\(^,\)\(^3\)\(^,\)\(^9\)\(^19\). Many functional changes in autonomic mechanisms have been shown to occur with age\(^12\)\(^,\)\(^21\)\(^,\)\(^22\) For example, an age-related increase in sympathetic nervous system activity has been reported\(^12\)\(^,\)\(^23\)\(^−\)\(^25\). Moreover, an age-related decrease in the R-R interval variation, which is consistent with a decrease in cardiac parasympathetic activity, has also been reported\(^12\). Neural control of the heart is extremely complex, primarily because of the dual innervation by the sympathetic and parasympathetic nervous systems. Hence, any interpretation of the activity of one division of the nervous system which is obtained by inhibiting the other is certainly incomplete and may in fact be misleading\(^26\). Accordingly, pharmacologic inhibition of both the parasympathetic and sympathetic nervous systems was used in this study.

Autonomic blockade, which was developed by Jose and Collison\(^8\)\(^,\)\(^27\) was used by Jordan et al\(^1\) to investigate the interaction between sinus node function and the autonomic nervous system. Since then, several other studies have also noted the importance of autonomic regulation in the evaluation of sinus node function\(^2\)\(^,\)\(^4\)\(^−\)\(^9\)\(^,\)\(^11\)\(^,\)\(^20\)\(^,\)\(^28\)\(^−\)\(^31\). Percent chronotropy of HR can be used to quantify the autonomic regulation of HR\(^1\) However, except for data regarding HR, little information is available concerning age-related changes in the autonomic regulation of sinus node function in subjects without sinus node disease\(^9\).

In the present study, calculation of percent chronotropy was applied to CSNRT and SACT, as well as HR, and age-related changes in the autonomic regulation of sinus node function were investigated quantitatively.

Sinus node function and aging

Intrinsic HR reportedly decreases with age in subjects without sinus node disease\(^8\)\(^,\)\(^9\)\(^,\)\(^13\). The fibrous stroma of the sinus node gradually increases with age, and there is a corresponding decrease in the number of nodal cells\(^32\)\(^−\)\(^34\). Accordingly, age-related deterioration of sinus node function is expected. Therefore, we conducted electrophysiologic studies in 56 subjects of various ages without sinus node disease and evaluated the age-related changes in HR, CSNRT and SACT before and after autonomic blockade.

Heart rate

In the present study, as in previous studies, basic HR did not change with age, but intrinsic HR increased with age\(^8\)\(^,\)\(^9\)\(^,\)\(^13\)\(^,\)\(^35\). In this study, intrinsic HR was described by the following regression equation: intrinsic HR=115−0.65×age (equation-1). This equation is almost identical to that proposed by Jose and Collison\(^8\) and most patients in the present study fell within the normal limit proposed by Jose and Collison\(^8\). Noting this correlation with age, equation-1 was used to determine the normal range of the observed intrinsic HR. The 90% confidence normal limit (±1 standard deviation) was considered to be ±16 beats/min of the value calculated by equation-1. Sinus heart rate of the pharmacologically\(^3\) or surgically\(^36\)\(^,\)\(^37\) denervated heart is more rapid than that of intact innervation. These observations suggest that vagal tone is predominant over sympathetic tone in HR at rest. However, in these previous studies, age-related changes in HR and autonomic regulation of HR were not considered.

In the present study, percent chronotropy of HR was negative (basic HR< intrinsic HR) in the younger patients, positively correlated with age, and was almost zero (basic HR=intrinsic HR) in the elderly patients. These observations suggest that, regarding HR, the parasympathetic tone is
predominant in younger patients, parasympathetic activity decreases with age, and that sympathetic tone and parasympathetic tone are almost equilibrated in elderly patients.

Corrected sinus node recovery time

Different investigators have reported different normal values of intrinsic CSNRT. One possible cause of this discrepancy seems to be the different age distributions of the patients studied. Accordingly, the normal range of intrinsic CSNRT should be established in relation to age.

There have been few systematic studies concerning age-related changes in CSNRT and SNRT. In subjects without sinus node disease\(^4\) basic CSNRT does not change with age and intrinsic CSNRT increases with age. The findings of the present study correspond to those of previous studies. In this study, intrinsic CSNRT was described by the following regression equation: intrinsic CSNRT = 3.15 × age + 143 (equation-2). The 90% confidence normal limit (±1 standard deviation) is considered to be ±108 ms of the value calculated by equation-2. Because of the wide interindividual variance of the data, the normal limit is also relatively wide.

Corrected sinus node recovery times of denervated transplanted\(^37\) and pharmacologically denervated\(^4\) hearts are shorter than that of an intact innervation. It has been reported that, without regard to age-related changes, vagal tone is predominant over the sympathetic tone on sinus node automaticity at rest. We also observed in the present study that the mean CSNRT was significantly shortened by autonomic blockade. Moreover, percent chronotropy of CSNRT was negative in younger subjects, nearly zero in elderly subjects, and correlated positively with age. These results suggest that with regard to CSNRT, the parasympathetic tone is predominant in younger subjects, the parasympathetic and sympathetic tones are equilibrated in elderly subjects, and there is an age-related decrease in the predominance of parasympathetic activity. These age-related changes in CSNRT were similar to those of HR.

Sinoatrial conduction time

Unlike previous studies\(^9,10\) we found a positive relationship between age and basic SACT, which was weak but still significant. Furthermore, we found a positive relationship between age and intrinsic SACT. These electrophysiological findings may correspond to the pathological observation that fibrosis in the sinus node and the perinodal tissues progresses with age\(^32-34\) Some uncertainties still exist concerning the normal limit of SACT. In the normal limit proposed previously, age-related changes were not considered. In the present study, intrinsic SACT was described by the following regression equation: intrinsic SACT = 1.27 × age + 84 (equation-3). Taking account of this age-related change, the 90% confidence (±1 standard deviation) normal limit is within ±43 ms of the value calculated by equation-3. A shortening of SACT by pharmacologic autonomic blockade\(^2,28-30\) and in the transplanted heart\(^36\) also suggests that the parasympathetic tone is predominant in SACT. In the present study, percent chronotropy of SACT was negative in younger subject (basic SACT > intrinsic SACT), almost zero (basic SACT = intrinsic SACT) in elderly subjects, and correlated positively with age. These findings suggest that with regard to SACT, the parasympathetic tone is predominant in younger subjects, parasympathetic and sympathetic tones are almost equal in elderly subjects, and there is an age-related decrease in the predominance of parasympathetic activity.

Clinical implications and limitations

Several studies have suggested that intrinsic electrophysiological variables of the normal sinus node may vary with age. Furthermore, age-related changes in the intrinsic HR, intrinsic CSNRT and intrinsic SACT were observed in th present study. However, except for that of intrinsic HR, there have been no reports concerning normal limits in relation to age. The normal limits of CSNRT and SACT in relation to age which have been proposed in this study are expected to improve the specificity and sensitivity of diagnoses of sinus node dysfunction.

A hyperadrenergic state is reportedly not provoked during invasive electrophysiologic study\(^38\) However, the subject's apprehension regarding the study is not completely avoidable.\(^39\) The associated increase in sym-
pathetic activity may bias the evaluation of the autonomic activity. To avoid these limitations and possible bias, investigations in asymptomatic individuals without apparent heart disease, using a non-invasive method such as esophageal pacing, seem to be indicated for more accurate evaluation of the influence of the autonomic nervous system on the sinus node functions.

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