ORIGINAL ARTICLE

Influences of Age, Gender, and Circadian Rhythm on Deceleration Capacity in Subjects without Evident Heart Diseases

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Background: Deceleration capacity (DC) is a newly found predictor of mortality after myocardial infarction. Age-, gender-, and circadian rhythm–related differences in DC may limit its predictive value, which should be considered in clinical settings.

Methods: DC, average heart rate, and HRV parameters, including 24 hours, awaking state (15:00–20:00) and sleeping mode (00:00–05:00) strips from 24 hours Holter recordings in 636 subjects without heart diseases were examined. Heart rate variability was analyzed in time domains (standard deviation of all normal-to-normal intervals [SDNN], normal-to-normal RR intervals in all 5-minute segments [SDANN], and root mean square successive difference [RMSSD]).

Results: The DC, SDNN, SDANN, RMSSD, and heart rate decreased with age. Deceleration capacity was significantly lower in patients greater than 50 years of age. The largest decrease of SDNN, SDANN, and RMSSD occurred in patients 30–39 years of age. The values of SDNN, SDANN, and DC of women were lower than that of men in the young and middle-aged groups, but age-related decrease of DC in men was greater than that in women. Heart rate of women was significantly higher than that of men in younger subjects, especially in a sleeping mode. There were higher values of DC and RMSSD during sleeping than that during a waking state.

Conclusions: The age, gender, and circadian rhythm may be useful when evaluating cardiac autonomic function and need to be considered when evaluating DC and HRV in clinical and scientific researches.

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autonomic nervous system; deceleration capacity; heart rate variability; age; gender; circadian rhythm

The autonomic nervous system plays an important role in cardiac regulation. Heart rate variability (HRV), which is the variability of normal sinus beat intervals, is believed to be a reliable measure of cardiac autonomic nervous system balance.[1] Impaired HRV indices are usually a manifestation of autonomic function imbalance, which is characterized by a predominance of adrenergic tone due to a depression of parasympathetic activity and/or an increase in sympathetic activity.[2] Decreased

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HRV is an unfavorable prognostic marker in cardiovascular diseases such as hypertension, myocardial infarction (MI), nonischemic dilated cardiomyopathy, and heart failure.[2–6] Experimental study suggested that a fall in parasympathetic activity significantly increases the risk of death.[7] However, measures of HRV, such as the standard deviation of all normal-to-normal intervals (SDNN), do not distinguish between parasympathetic and sympathetic effects on the heart.[1,8]

Deceleration capacity (DC) is a novel indicator of autonomic nervous system, characterized by the capacity to slow down the heart rate.[9] It is an integral measure of all deceleration-related periodic components of heart rate and provides a measure of cardiac parasympathetic modulation. Impaired DC was considered as a powerful predictor of death in post-MI patients, which would be more accurate than left ventricular ejection fraction (LVEF) and HRV.[9–11]

Previous studies have demonstrated that HRV was influenced by clinical factors such as age, gender, and so on, which should be considered when performing risk prediction.[12] The interaction between DC and above factors has not been well studied in healthy subjects. The aim of this study was to evaluate the effect of normal aging, gender, and diurnal variation on DC, HRV, and heart rate. We also explored the relationship between DC and spectral HRV in healthy subjects and DC-based risk stratification in different age groups.

METHODS

Study Population

Subjects admitted to the hospital for a routine medical evaluation or minor symptoms and 24-hour Holter monitoring were enrolled into the study. Six hundred thirty-six subjects aged from 18 to 70 years old without clinical evidence of organic disease by medical history, physical examination, and routine blood chemistry profiles were evaluated. There were 300 men and 336 women (Table 1). Healthy people were defined as those without clinical evidence of organic disease by medical history, physical examination, and routine blood chemistry profiles. Exclusion criteria were age less than 18 years or more than 70 years, Holter recordings <20 hours in duration, and Holter recordings demonstrating a nonsinus rhythm, sick sinus syndrome, atrioventricular block, or nonsinus beats comprising more than 10% of the total number of beats.

Heart Rate Variability and Deceleration Capacity

A 12-lead 24-hour Holter recording was performed on all the participants by using the DMS 300-4 Holter Recorder (Cardioscan Holter System; DMS, Stateline, NV, USA). Recordings were analyzed by Cardioscan 12, HRV Package system (version 12.5.0076a). QRS classifications (normal, ventricular ectopic, and supraventricular ectopic) were visually verified, manually checked and corrected if necessary. Measures the total heart rate of normal sinus RR intervals (SDNN), standard deviation of the averages of normal-to-normal RR intervals in all 5-minute segments (SDANN) and the root mean square successive difference (RMSSD) were calculated as a measure of HRV.[2] The RR intervals were exported and used in further analysis of DC.

Calculation of DC was performed using the phase-rectified signal averaging (PRSA), which eliminates nonperiodic components, artifacts, and ectopic beats (The PRSA algorithm is accessible for noncommercial use from www.prsa.eu.). Heartbeat intervals that were longer than preceding intervals were defined as anchors. The RR interval changed beat by beat prolongations of more than 5% were excluded in order to avoid artifacts errors. Segments of interval data around the anchors that had the same size were selected and aligned with the anchors. The PRSA signals were calculated by averaging the signals within the aligned segments, that is, X_0 was the average of the RR intervals at all anchors, X_1 and $X-1$ were the averages of RR intervals immediately following and preceding the anchors, etc. Deceleration capacity was calculated as $[(X_0 + X_1) - (X - 1 + X - 2)]/4$, and divided into three groups, high-risk (DC $\leq$ 2.5 milliseconds), intermediate-risk (2.6–4.5 milliseconds), and low-risk (>4.5 milliseconds). Abnormal DC was defined as $\leq$4.5 milliseconds.[9] Twenty-four hour heart rate was also collected. Subjects were divided by age into three groups, a young group (18–39 years), a middle-aged group (40–59 years), and an elderly group (60–70 years). Average heart rate, DC, and HRV of the different age groups were compared. Two 5-hour periods from the 24-hour ECG daytime (15:00–20:00) and night-time (00:00–05:00) were examined to evaluate diurnal variation.

Table 1. Differences of DC and HRV among All Groups

Age (Years)	Men (N)	Women (N)	DC (Milliseconds)	SDNN (Milliseconds)	SDANN (Milliseconds)	RMSSD (Milliseconds)	HR (bpm)
18–29	30	29	7.52 ± 1.66	152 ± 32.0	137 ± 32.1	35.6 ± 11.3	77.7 ± 9.2
30–39	41	31	7.47 ± 1.79	137 ± 32.3[a]	124 ± 33.3[a]	27.6 ± 9.6[a]	78.6 ± 7.4
40–49	90	100	7.28 ± 1.63	133 ± 26.0[a]	120 ± 26.2[a]	26.7 ± 9.6[a]	74.3 ± 8.1[a,b]
50–59	79	103	6.61 ± 1.38[a,b,c]	127 ± 25.7[a,b]	115 ± 25.6[a,b]	24.6 ± 8.1[a,b,c]	72.8 ± 8.2[a,b]
60–70	60	73	6.18 ± 1.93[a,b,c]	121 ± 27.6[a,b,c]	111 ± 27.2[a,b,c]	23.8 ± 10.7[a,b,c]	71.4 ± 8.5[a,b,c]

Date are presented as mean ± SD. P values correspond to one-way ANOVA.
[a]$P < 0.05$, other age groups versus group 1 (18–29 years).
[b]$P < 0.05$, other age groups versus group 2 (30–39 years).
[c]$P < 0.05$, other age groups versus group 3 (40–49 years).

Statistical Analysis

Continuous variables were expressed as the mean ± standard deviation. Qualitative data were presented as absolute numbers and percentages. The two-way ANOVA test was used to compare multiple variables. An independent-sample *t* test was used to compare age-matched men and women and diurnal variation times. The 95% confidence limits were calculated for all regressions. Differences between qualitative data were examined using nonparametric tests. The relationship between variables was tested using Spearman correlations. $P < 0.05$ was considered statistically significant.

RESULTS

Effect of Age on 24-Hour Deceleration Capacity, Heart Rate Variability, and Heart Rate

Deceleration capacity and HRV determined by SDNN, SDANN, and RMSSD decreased with age ($P < 0.05$; Fig. 1). All measures showed a negative correlation with increasing age. Deceleration capacity decreased little at ages less than 50 years, and then greater with increasing age. The largest decreases of SDNN, SDANN, and RMSSD occurred between 30 and 39 years of age. Heart rate declined significantly above age 40 years (Table 1).

Effect of Gender on 24-Hour Deceleration Capacity, Heart Rate Variability, and Heart Rate

Gender affected the relationship between DC, HRV, and heart rate, with aging dependence. The values of SDNN, SDANN, and DC of women were lower than that of men in the young and middle-aged groups ($P < 0.05$). These gender differences were not found in the elderly group. The age-related decrease of DC in men occurred more rapidly than in women. No significant gender difference in RMSSD was found in the three age groups. Heart rate of women was significantly higher than that of men in the young group (80.1 ± 8.8 vs. 75.7 ± 8.0, $P < 0.05$). In the middle-aged group, the night-time heart rate of women was higher than that of men ($P < 0.05$). There was no gender difference both in daytime and night-time heart rate in elderly group (Fig. 2).

Effect of Diurnal Variation on Deceleration Capacity, Heart Rate Variability, and Heart Rate

We found that DC and RMSSD at sleeping were higher than during awakening in all three age groups, and declined with age in both the day and night evaluations (Table 2). In contrast, heart rate was much lower at night. Heart rate was significantly declined as age increased during the day while this was not seen at night.

Relationship between 24-Hour Deceleration Capacity and Age, Heart Rate Variability, and Heart Rate

Deceleration capacity was negatively correlated with and heart rate ($r = -0.313$), and positively correlated with SDNN ($r = 0.425$), SDANN ($r = 0.297$), and RMSSD ($r = 0.624$; Fig. 3).

Association of Gender and Age with DC in All 636 Subjects in this Study

Multiple linear regression analysis demonstrated that gender and age were independently associated

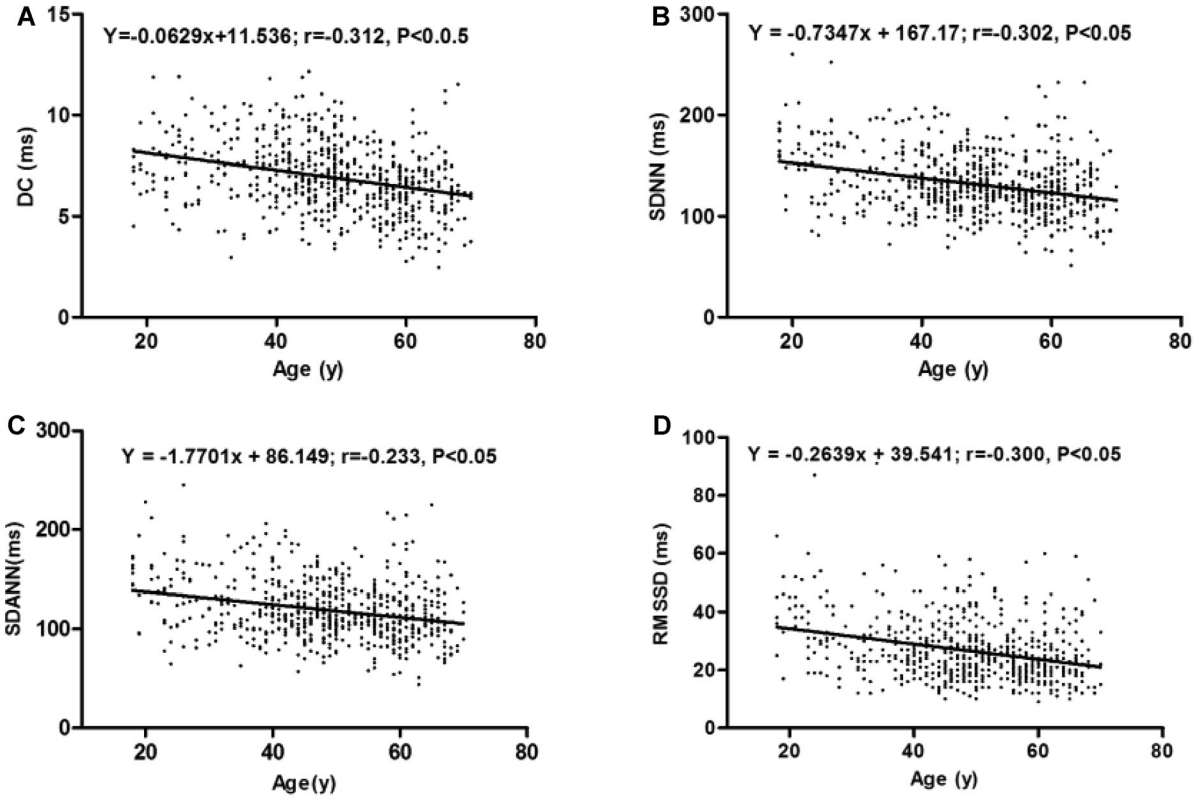

Figure 1. The influence of age on DC and HRV. (A) There is negative correlation between DC and age. (B) SDNN is decreasing with age. (C) Negative correlation is found between SDANN and age. (D) There is also negative correlation between RMSSD and age; n = 636.

Table 2. Influence of Circadian Rhythm on Deceleration Capacity, Heart Rate Variability, and Heart Rate

Age (Years) and Time	DC (Milliseconds)	RMSSD (Milliseconds)	HR (bpm)
18–39 (N = 131)			
Day	6.70 ± 1.75[a]	25.4 ± 10.3[a]	84.7 ± 10.1[a]
Night	9.74 ± 2.80	41.7 ± 18.1	65.0 ± 8.5
40–59 (N = 372)			
Day	6.18 ± 1.74[b]	22.4 ± 8.9[b]	78.9 ± 10.4[b]
Night	8.68 ± 2.30[b]	31.2 ± 12.5[b]	63.1 ± 6.96[b]
60–70 (N = 133)			
Day	5.37 ± 2.02[b,c]	21.1 ± 11.9[b]	76.3 ± 10.0[b,c]
Night	7.85 ± 2.24[b,c]	27.4 ± 13.3[b,c]	62.4 ± 8.4[b]

Date are presented as Mean ± SD. P values correspond to one-way ANOVA.
[a]$P < 0.05$, day versus night in same age group.
[b]$P < 0.05$, other groups versus young group for the same time.
[c]$P < 0.05$, old age group versus middle age group for the same time.

with DC in all 636 subjects without evident heart diseases. DC is lower in the female than that in the male subjects (Beta = −0.4798, P = 0.0002). DC is decreasing with age (Beta = −0.04071, P < 0.0001) (Table 3).

Prediction of Mortality Risk by DC-Based Risk Stratification

Prediction of cardiac mortality was evaluated using DC-based risk stratification. In this study,

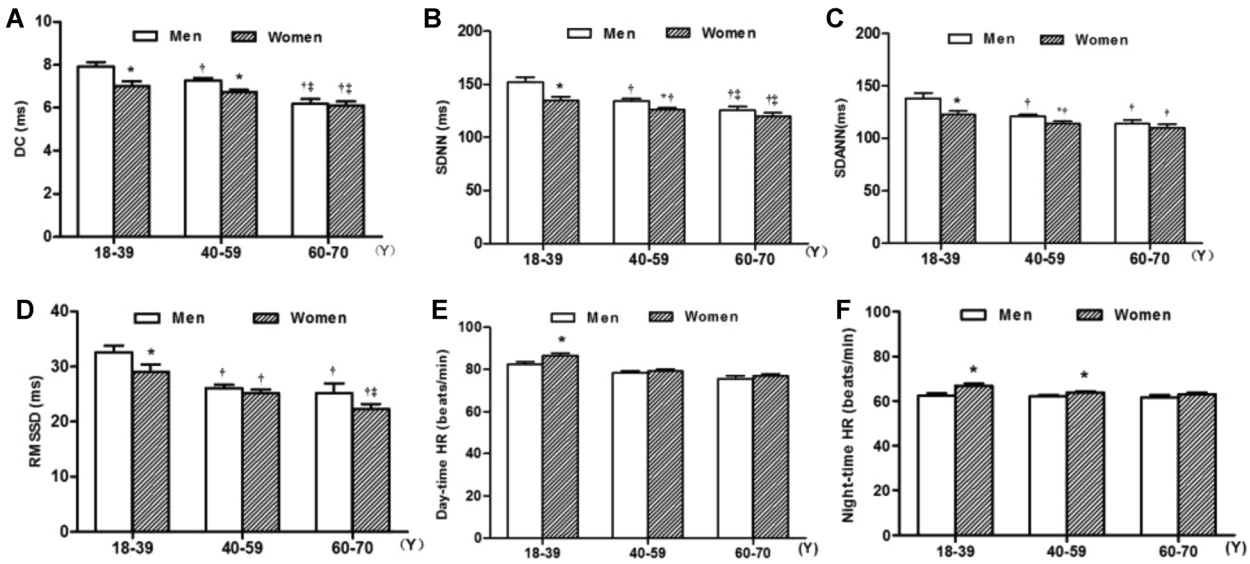

Figure 2. Variation of gender on DC, HRV, and heart rate. (A) Differences of DC among men and women in every group. (B–D) Changes of HRV including SDNN (B), SDANN (C), and RMSSD (D) between two gender. (E and F) The heart rate of women is higher whether on daytime (E) and night-time (F). Date are presented as mean ± SEM; P values correspond to one-way ANOVA. *P < 0.05, men versus women in same age group. †P < 0.05, other groups versus young group of same gender. ‡P < 0.05, old-aged group versus middle-aged group of same gender.

Table 3. Multivariate Analysis of Gender and Age Associated with DC in 636 Subjects

Independent Variable	β	Standard Error	P Values
Female	−0.4798	0.12726	0.002
Age	−0.04071	0.00521	<0.001

there were no high-risk subjects in healthy patients. About 6.67%, 5.35%, and 16.30% subjects were considered with intermediate-risk respectively in the three groups. There was no gender difference by risk stratification in the same age group. Women in elderly group had more intermediate-risk subjects than younger subjects (Fig. 4A, P < 0.05). Compared with the low-risk subjects, participants in intermediate-risk group showed a higher heart rate and lower values of SDNN, SDANN, and RMSSD (Fig. 4B, P < 0.05).

DISCUSSION

Many studies have demonstrated the effects of age, gender, and diurnal variation on cardiac autonomic function.[13,14] There is a great need for exploring the influence of these factors on DC and HRV, measures of cardiac parasympathetic, and sympathetic modulation. In this study, DC significantly decreased after age 50. Similarly, Lewek et al.[15] observed that lower DC was present in elderly patients with MI. Consistent with previous reports,[13,16] SDNN, SDANN, and RMSSD were also inversely associated with age. We believe that cardiac autonomic function becomes attenuated with age, especially the parasympathetic regulation. Clinical research has demonstrated that the incidence of cardiac death in acute myocardial infarction (AMI) was significantly higher for elderly.[17] Study suggested that sympathetic tone predominates and parasympathetic tone diminishes with age.[13] Increases in circulating levels of norepinephrine with age will increase sympathetic activity and might account for the reduction in parasympathetic activity with aging.[18]

We observed lower levels of parasympathetic activity in women in the young and middle-aged groups, as reflected by a lower DC, SDNN, and SDANN. The higher heart rate in younger women also supports this lower activity. The significant

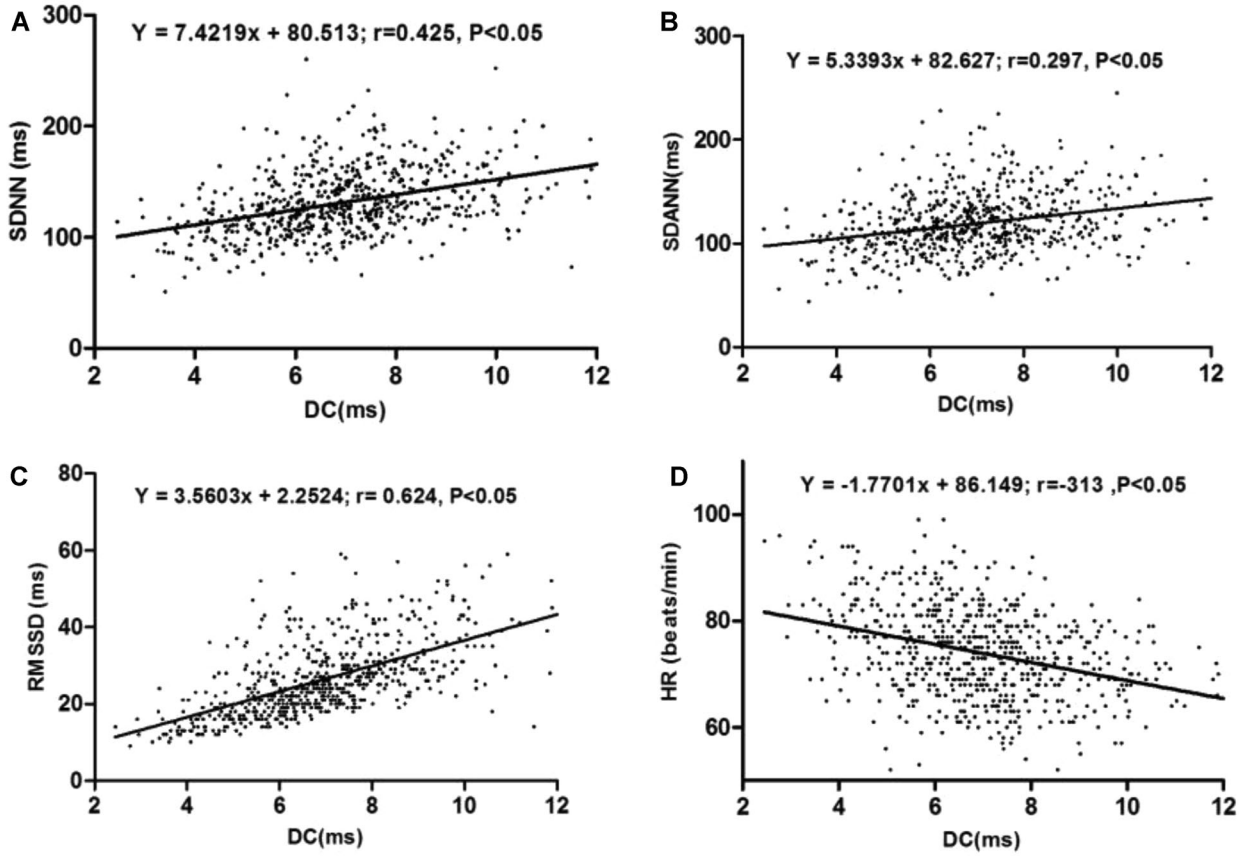

Figure 3. Correlation between DC and HRV parameters or heart rate. Deceleration capacity was positively correlated with SDNN (A), SDANN (B), and RMSSD (C). (D) Deceleration capacity was negatively correlated with heart rate. P values correspond to one-way ANOVA.

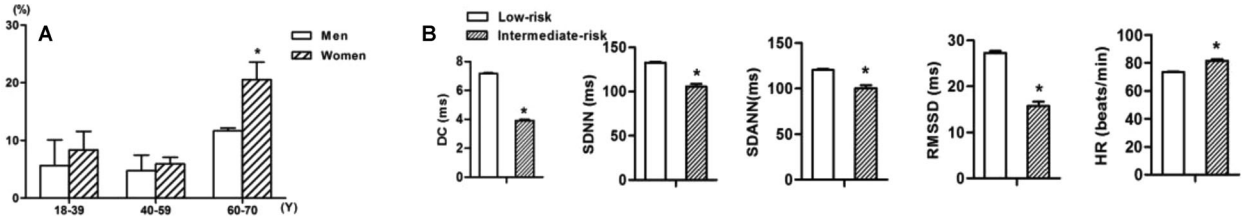

Figure 4. Deceleration capacity-based risk stratification. (A) Percentage of subjects with intermediate-risk by DC-based risk stratification. *P < 0.05, comparing 40–59 age group for the same gender. (B) Comparison of the DC, HRV parameters, and heart rate between low-risk group and intermediate-risk group determined by DC-based risk stratification. *P < 0.05, comparing to low-risk group.

gender-related differences of DC decreased with age. And multiple linear regression analysis in all our subjects without evident heart diseases showed that gender and age were independently associated with DC. Lewek et al.[15] also showed that women were associated with lower values of DC in patients with MI. Younger women have been reported to be with lower HRV than that of age-matched men, with gender differences decreasing above age 30 years until there was no difference above 50 years.[12] Clinical studies have demonstrated a higher mortality rate in younger women than younger men after AMI.[17,19,20] Ortolani et al.[20] found that younger women at age less than 50 years old both in the acute and postacute period had more than 3.6 higher risk of mortality compared

with men, but the mortality rate for elderly men and women was similar. The relationship between higher cardiac death for the women patients with AMI and lower parasympathetic activity in younger women was not clear. Further researches should be focused on the analysis of autonomic function in patients with AMI. In contrast, many studies have shown a higher HRV in women than in men.[13,21] The mechanism of gender differences in age-related changes of autonomic cardiac function is not clear. Estrogen and cytokine expression may play a role in the different autonomic modulation.[22] Men have been reported to have higher sympathetic tone with increased number of neurons in the sympathetic ganglion and high muscular sympathetic activity.[18]

Heart rate variability also has a diurnal rhythm, which can reflect the autonomic nervous system balance.[23] In the study, we observed that DC and RMSSD had significantly higher values during sleeping in subjects without evident heart diseases. Deeping of sleep is associated with progressive parasympathetic dominance.[24] There is evidence to suggest that both sleep and circadian processes modulate the cardiovascular system, and could prevent adverse cardiac events at night.[14] An increased incidence of cardiovascular diseases such as ischemia, stroke, and sudden death has been associated with the circadian changes in the autonomic activities.[25] The occurrence of AMI also showed a circadian rhythm, with a morning peak.[26] The early hours after waking are coincidental with maximal increase in hormones secretion such as cortisol and plasma catecholamine levels, which would potentially contribute to the adverse cardiovascular events.[24,27]

We also observed the changes of heart rate in our study and demonstrated that heart rate decreased slowly with age, after age 40. Women had a higher heart rate than age-matched men in young and middle-aged groups in a sleeping mode. Epidemiological studies have shown that heart rate during sleeping is a predictor of all-cause mortality and cardiovascular mortality in subjects without diagnosed cardiovascular disease.[28] Heart rate is regulated by neural and endocrine mechanisms. It has been demonstrated that the cardiac nervous system consists of sympathetic and parasympathetic neurons, and that interconnecting local circuits play a role in regulating heart rate. Parasympathetic mediated changes in heart rate occur much faster than sympathetic mediated effects.[3,29] Although the parasympathetic activity declines with age, endocrine factors including thyroxin, reproductive hormones, and rennin–angiotensin levels are reduced, and circadian hormonal and temperature rhythms lose amplitude with age.[18,23,30,31] There is also a progressive decline in sino-atrial conduction and sinus node recovery time with age.[32] All of these factors would influence heart rate in healthy subjects without evident heart diseases.

The ISAR-Risk trial found that a LVEF $\leq$30% in AMI survivors was the best predictor of mortality and sudden cardiac death (SCD) at 5 years.[10] However, the majority of MI survivors had a normal or only moderately reduced LVEF. The greatest number of SCD events occurred in relatively lower-risk group, compared with the small group of patients with severely depressed LVEF that comprised the high-risk group.[33] Bauer et al.[10] found that impaired DC was a powerful predictor of total mortality in post-MI patients, especially those with LVEF >30%. Deceleration capacity was a sensitive and specific predictor of SCD after MI. In addition, for long-term (around 1 minute) heart rate dynamics, which is independent of DC for beat-to-beat short-term heart rate dynamics, decrease in DC also has great predictive power for post-AMI mortality.[34] These findings suggest DC may be useful in evaluating parasympathetic function and predicting cardiovascular risk.

Evaluation of DC has mainly been used in patients with AMI. In this study, we found impairments in cardiac autonomic function in subjects who have no evident heart diseases with lower values of DC and HRV parameters, especially in the elderly group. Percentage of subjects with intermediate risk by DC-based risk stratification is increasing with aging, especially that of women in elderly group. Deceleration capacity which was considered as an inexpensive and noninvasive method to assess autonomic function in the general population would be an early indicator for cardiac death or correspond to the generally higher risk of death for elderly and lead to earlier prophylactic interventions.

There were several limitations to our study. Subjects enrolled in our study were younger than 70 years. Because subjects without evident heart diseases older than 70 are usually in a subclinical state, our finding cannot be extrapolated to the elderly. Additional large studies that include more

age groups are needed. The number of subjects was not evenly distributed among the different age groups and genders. There were more subjects in the middle aged group than in the other groups. The disproportionate distribution of subjects could have affected the statistical analysis of age-based data. The 24-hour HRV is known to be influenced by activity level. We did not standardize activity levels, which would influence the age-related decline in DC and HRV, particularly in the elderly group. Different levels of activity could also contribute to the finding of a lower DC and HRV in women, compared with the age-matched men in the young and middle aged groups. Finally, the small number of subjects with abnormal DC and short follow-up time did not allow adequate evaluation of DC-based risk stratification. Further studies are needed in large populations in order to identify the significance of DC in the general population and its use as a predictor of cardiac death.

In summary, DC and HRV were significantly affected by age, gender, and diurnal variation, at a varying rate and degree. Heart rate of women was higher than that of men in younger subjects. Subjects without evident heart diseases were observed to have abnormal DC (≤4.5 milliseconds), especially women in the elderly group. These dates suggest that the clinical factors should be taken into consideration when evaluating DC and HRV for cardiac risk stratification.

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