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Prediction of Left Ventricular Peak Ejection Velocity by Preceding and Prepreceding RR Intervals in Atrial fibrillation: A New Method to Adjust the Influence between Two Intervals

In atrial fibrillation, cardiac performance is dependent on both preceding RR (RR-1) and prepreceding RR (RR-2) intervals. However, relative contributions were not well defined. Left ventricular outflow peak ejection velocity (Vpe) was measured by echocardiography from 21 patients. The relation between RR-1 and Vpe could be divided into two zones; steep slope in short RR-1 intervals ($\leq$0.5 sec) and plateau in long RR-1 intervals (> 0.5 sec). RR-2 had a weak negative association with Vpe. The mean squared correlation coefficient (r^2) between RR-2 and Vpe was 0.15 $\pm$0.13 and improved to 0.29$\pm$0.21 (p<0.001), when coordinates with RR-1 $\leq$0.5 sec were excluded. The RR-1 was positively associated with Vpe. The mean r^2 between RR-1 and Vpe was 0.52$\pm$0.17 and improved to 0.72$\pm$0.11 (p<0.001), when adjusted by RR-2. Simple linear regression analysis showed that mean RR interval, age, fractional shortening (FS), and mean peak velocity were negatively correlated with modified r^2 between RR-2 and Vpe. Multiple stepwise regression analysis revealed that mean RR interval (r^2=0.32) and FS (r^2=0.16) were significant. In summary, simple modification could improve the relationship of both RR-1 and RR-2 with cardiac performance. RR-2 might play a more role in cardiac performance than previously expected, and when cardiac function was impaired.

Key Words : *Atrial Fibrillation; Electrocardiography; Echocardiography, Doppler, Pulsed; Stroke Volume*

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INTRODUCTION

Atrial fibrillation (AF) is the most common among cardiac rhythm disturbances with clinical significance (1, 2). It is often associated with congestive heart failure in elderly persons with diastolic dysfunction and in the patients with underlying heart diseases. Wide beat-to-beat variability in cycle length and left ventricular (LV) performance is characteristic of this arrhythmia. It may contribute to impaired cardiac function (3, 4) in addition to the loss of atrial contraction for ventricular filling and tachycardia-induced cardiac dysfunction especially, when ventricular rate is not controlled (1, 2, 5, 6). However, irregularity itself may have no effect on intrinsic contractility during acute stage (7).

Cardiac performance is mainly dependent on preceding RR interval (RR-1) in AF. Prepreceding RR interval (RR-2) is negatively associated. However, the relationship is not well defined and may be weak (8-12). There were few reports to quantify the relative contributions of RR-1 and RR-2 to cardiac performance (8, 12). Rawles reported that alteration of RR-1 could explain 58% of the variance of cardiac performance and RR-2 in 10% (8). In other studies, the relation between cardiac performance and RR-2 was obtained indirectly by comparing cardiac function according to categorized groups of preload or RR-2 (7, 10, 11). To our experiences, RR-2 seemed to play more roles to cardiac performance than the results of previous reports.

We aimed to reevaluate the relation between RR intervals and cardiac performance, and to calculate the relative contribution of RR-1 and RR-2 by developing a new method to adjust the influence between RR-1 and RR-2.

MATERIALS AND METHODS

Consecutive 21 patients with AF were studied prospectively. Fifteen patients were males and six were females. Mean age was 68.7 yr, ranged from 49 to 83 yr. Clinical characteristics of subjects, associated diseases and medications were illustrated in Table 1.

Two-dimensional and Doppler echocardiograms (Hewlett-Packard Sonos 2000, 2.5 MHz transducer) were performed in left lateral position. Dimensions were measured according to American Society of Echocardiography standards (13). Frac-

Table 1. Clinical characteristics of patients

Male/Female	15 (71.4%)/6 (28.6%)
Age	68.7±9.0 yr (Range 49-83)
Blood pressure	117.9±5.2/72.9±7.0 mmHg
Mean RR interval	0.77±0.15 sec
Duration of AF	40.4±43.4 months (Range 3days-150 months)
Associated Disease	
Hypertension	10 (47.6%)
Coronary artery disease	1 (4.8%)
Dilated cardiomyopathy	6 (28.6%)
Apical cardiomyopathy	2 (9.6%)
Chronic Lung Disease	1 (4.8%)
Mitral valvular disease	2 (9.6%)
Old hyperthyroidism	2 (9.6%)
No disease	5 (23.8%)
Medication	
Digoxin	16 (72.1%)
Calcium channel blocker	6 (28.6%)
Diuretics	11 (52.4%)
Beta blocker	1 (4.8%)
Nitrate	4 (19.0%)

tional Shortening (FS) was measured using M-mode echocardiogram at the beat with the longest RR-1. Doppler images with measurable quality were obtained from all patients. A total 35-40 consecutive LV outflow ejection velocities were recorded with pulsed Doppler ultrasound from the apical 5-chamber view with sample volume positioned in the left ventricular outflow track, immediately proximal to the aortic valve at the paper speed of 50 mm/sec. Electrocardiogram was recorded simultaneously. LV peak ejection velocity (Vpe) and RR interval were measured.

Data were expressed by mean ±SD. The association between RR intervals and peak velocity was analyzed by the logarithmic regression analysis. The change of squared correlation coefficient (r^2) between Vpe and RR intervals was compared by the Wilcoxon signed ranks test. The associations of clinical, echocardiographic and electrocardiographic parameters with r^2 were assessed by the simple and multiple stepwise linear regression methods.

RESULTS

The representative example of the relation between RR-1 and Vpe was shown in Fig. 1A. The relationship was moderate (r^2=0.46, p<0.001). It could be divided into two zones; steep slope zone with better relationship (r^2=0.51) in short RR intervals (≤0.5 sec), and near plateau zone with worse relationship (r^2=0.26) in long RR interval (>0.5 sec) (Fig. 1B).

The RR-2 was negatively associated with Vpe, and the relation was very weak (r^2=0.08, p>0.05, Fig. 1C). If the coordinates with RR-1 ≤0.5 sec were excluded, the relationship became strong (r^2=0.61, p<0.001, Fig. 1D). The adjustment by the influence of RR-2 improved the relation between RR-1 and Vpe (r^2=0.77, p<0.001, Fig. 1E).

Table 2. Correlation of adjusted squared correlation coefficient between prepreceding RR interval and LV peak ejection velocity with clinical variables and parameters from electrocardiography and echocardiography by simple linear regression analysis

Variable	r^2	F value	p value
Age	0.22	5.48	0.03
Duration of AF	0.03	0.65	0.43
Mean RR interval	0.32	8.96	0.007
SD of RR interval	0.09	1.93	0.18
LA dimension	0.03	0.51	0.48
Aorta dimension	0.05	0.96	0.34
LVIDd	0.04	0.85	0.37
LVIDs	0.10	2.21	0.15
FS	0.16	3.53	0.075
Mean peak velocity	0.16	3.58	0.074
SD of peak velocity	0.09	1.93	0.18

SD; standard deviation, LA; left atrium, LVIDd: left ventricular diastolic dimension, LVIDs; left ventricular systolic dimension, FS; fractional shortening.

The mean r^2 between RR-2 and Vpe was 0.15±0.13. It was improved to 0.29±0.21 after the exclusion of coordinates with RR-1 ≤0.5 sec (p<0.001, Fig. 2B). The mean r^2 between RR-1 and Vpe was 0.52±0.17. It was improved to 0.72±0.11 after the adjustment by the effect of RR-2 on Vpe (p<0.001, Fig. 2A).

To evaluate the parameters that influence the relation between RR-2 and Vpe, clinical variables and values from electrocardiography and echocardiography were analyzed by simple linear regression analysis (Table 2). Mean RR inteval (r^2=0.32, p=0.007) and age (r^2=0.22, p=0.030) showed negative relationship with modified r^2. FS (r^2=0.16, p=0.075) and mean peak velocity (r^2=0.16, p=0.074) were associated negatively with borderline significance (Fig. 3). Multiple stepwise regression analysis with these variables revealed that the model including mean RR-1 and FS was the most significant (r^2=0.50, p=0.002).

DISCUSSION

In this study we demonstrated that simple modification could improve the model of the relation between RR intervals and cardiac performance, and that RR-2 might play more roles to determine the cardiac performance at least in the zone with RR-1>0.5 sec in AF than previously known.

In AF, cardiac function is impaired mainly by the loss of atrial contraction resulting in decreased ventricular filling, and by tachycardia-induced deterioration of LV function especially when ventricular rate is not controlled. Wide beat-to-beat variability in cycle length and ventricular performance is characteristic of AF and may contribute to impaired cardiac function (1-6), although there may be no effect of irregularity itself on intrinsic contractility (7).

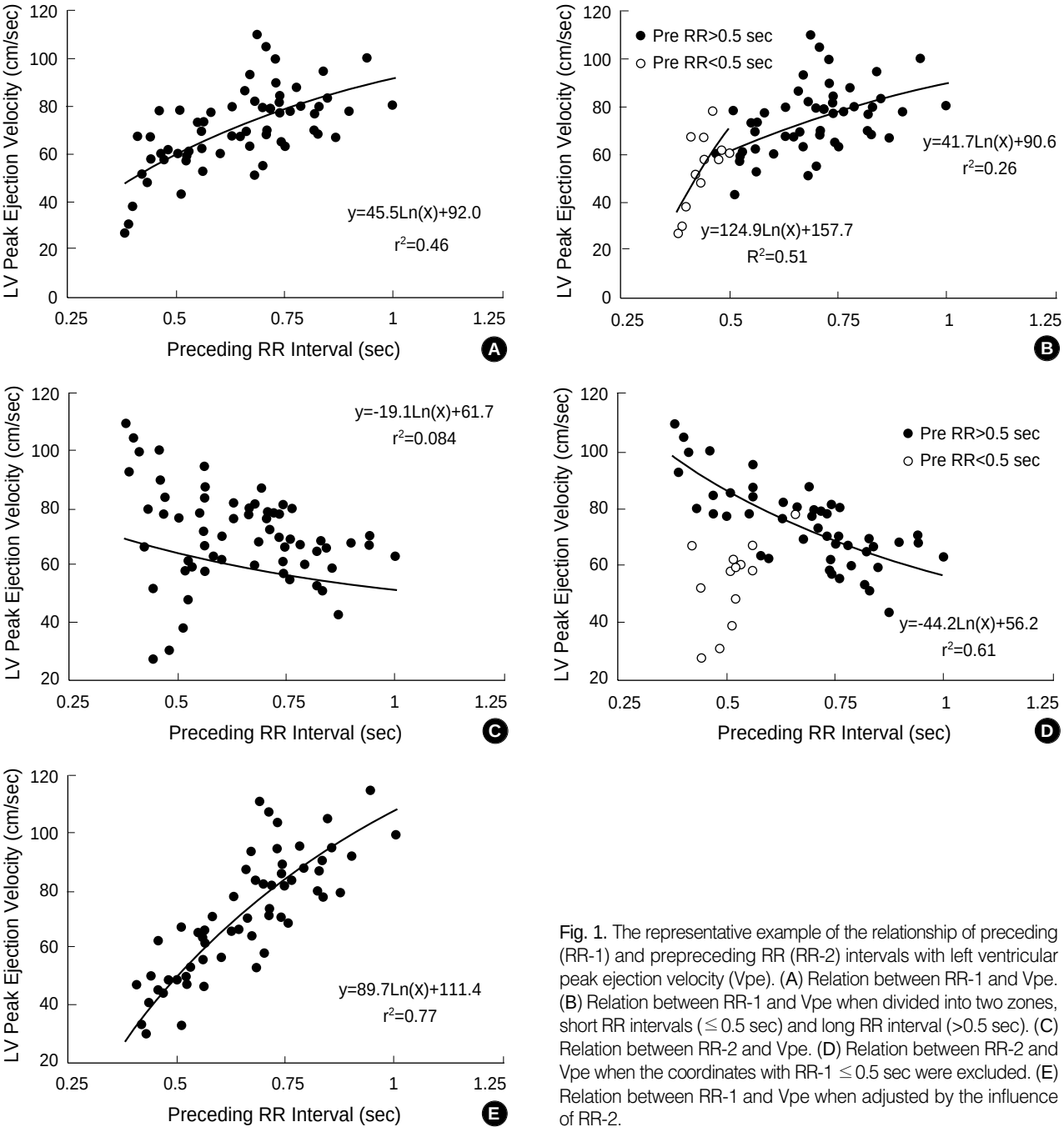

Fig. 1. The representative example of the relationship of preceding (RR-1) and prepreceding RR (RR-2) intervals with left ventricular peak ejection velocity (Vpe). (A) Relation between RR-1 and Vpe. (B) Relation between RR-1 and Vpe when divided into two zones, short RR intervals (≤0.5 sec) and long RR interval (>0.5 sec). (C) Relation between RR-2 and Vpe. (D) Relation between RR-2 and Vpe when the coordinates with RR-1 ≤0.5 sec were excluded. (E) Relation between RR-1 and Vpe when adjusted by the influence of RR-2.

The relationships of both RR-1 and RR-2 with cardiac performance are curvilinear, and cannot be fit by simple mathematical equation (8-12) in AF. We used logarithmic equation because it was the best simple model. Although it could not fit exactly, the equation may be useful to compare the relationships before and after the adjustments. In previous reports, sophisticated (8, 9) or linear equation (10-12) was used. In this study, linear regression model revealed small but significant decrease in r^2 compared with logarithmic regression model in the relations between Vpe and RR-1 (0.46 ± 0.19 vs 0.52 ± 0.17, p=0.021) or RR-2 (0.13 ± 0.11 vs 0.15 ± 0.13, p=0.052). Therefore we believe that logarithmic regression analysis is better model than linear regression method. The difference was dominant in the cases with broad range of RR intervals as shown in Fig. 1. It was negligible in cases with almost all RR intervals limited either below or above 0.5 sec (data not shown).

RR-2 is negatively associated with cardiac performance in AF, although the relationship is not well defined and may be weak (8-12). Relatively higher cardiac performance is expected

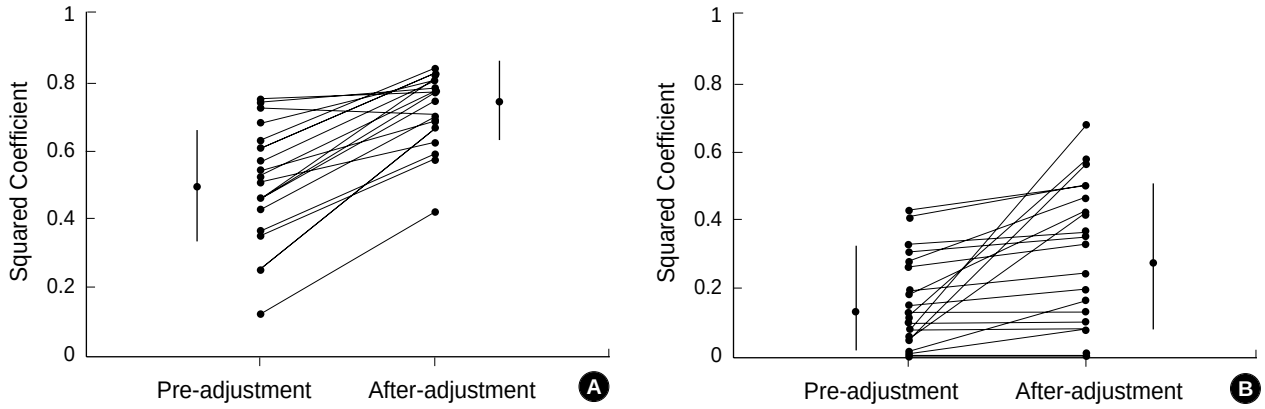

Fig. 2. Improvement of squared correlation coefficient after modification or adjustment. (A) Relation between preceding RR interval and left ventricular peak ejection velocity. (B) Relation between prepreceding RR interval and left ventricular peak ejection velocity.

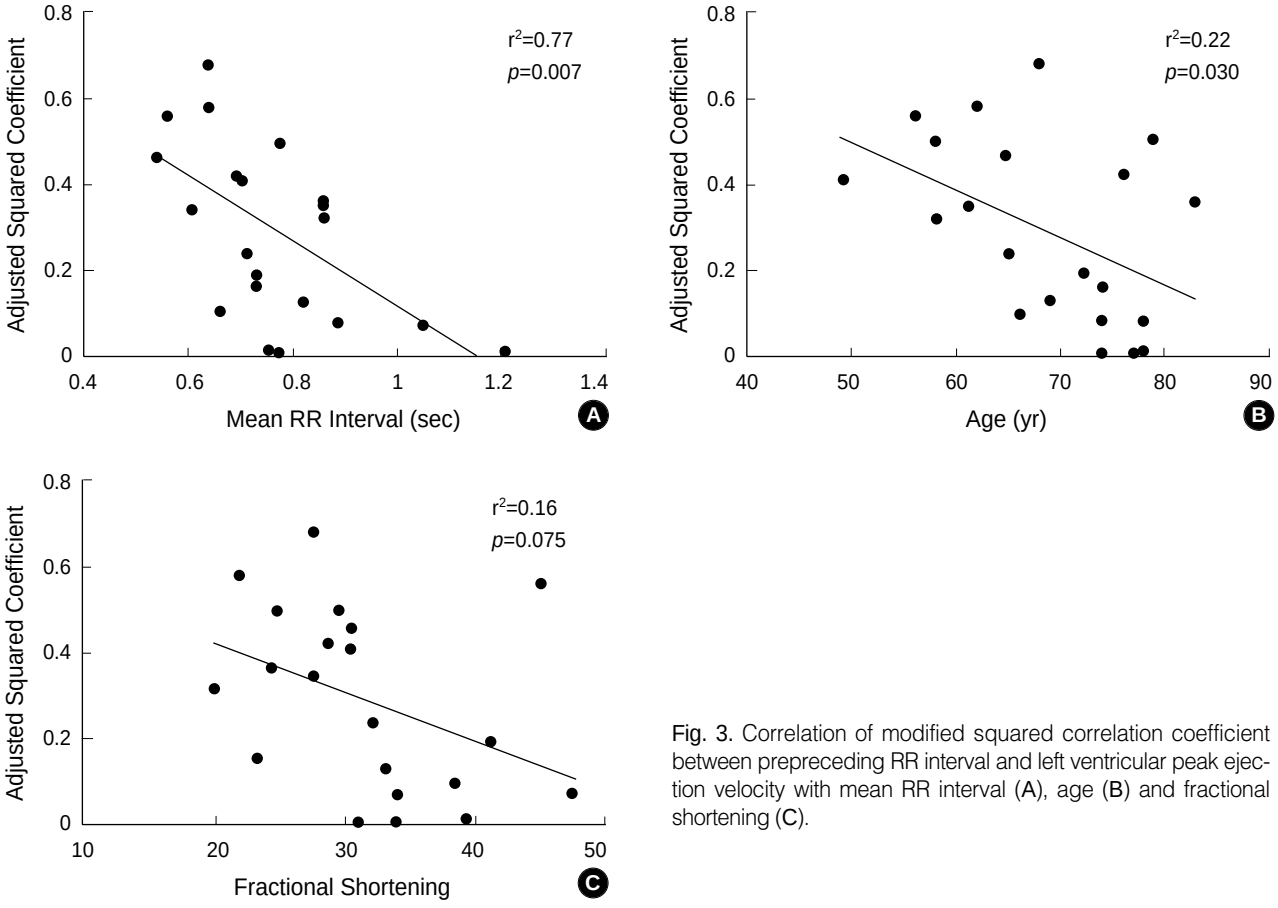

Fig. 3. Correlation of modified squared correlation coefficient between prepreceding RR interval and left ventricular peak ejection velocity with mean RR interval (A), age (B) and fractional shortening (C).

after shorter RR-2. It is related to higher preload by higher remaining ventricular volume and to lower afterload by lower aortic pressure with smaller preceding stroke volume relating to shorter RR interval, and to higher contractility by post-extrasystolic potentiation (14, 15). There were few reports to quantify the relative contribution of RR-2 to LV performance (8, 12). In this study, 15% of Vpe variation could be explained by alteration of RR-2 and it was consistent with the results of 10-21% in previous studies. In other studies, the relationship of cardiac performance with RR-2 was obtained indirectly by comparing the cardiac function according to categorized groups of preload or RR-2 (7, 10, 11).

We chose RR-1 $\leq$ 0.5 sec as an exclusion limit to adjust the relation between RR-2 and Vpe. It derived from the associa-

tions of both RR-1 and RR-2 with Vpe. The relation between RR-1 and Vpe could be divided into two zones. With short RR-1, the relation was steep and the deviation of Vpe from regression line was low (Fig. 1B). This finding implies that Vpe is mostly determined by the RR-1 and that other factors, including RR-2, have minor effect at this time interval. With long RR-1, the relation had a gentle slope and the deviation of Vpe from regression line was high (Fig. 1B). We tried wide ranges of RR-1 as an exclusion point to have the best fitting of the relation between RR-2 and Vpe, and finally decided to choose RR-1 $\leq$0.5 sec as an exclusion limit. This point was consistent with previous one that other reports adopted (7, 10) and at which mechanical restitution was complete in the interval-force relationship16.

After the exclusion of coordinates with RR-1 $\leq$0.5 sec, r^2 between RR-2 and Vpe became strong from 0.15$\pm$0.13 to 0.29$\pm$0.21 (p<0.001), and was superior to those of reports described previously (8, 12). This finding suggests that RR-2 plays a significant role in cardiac performance when RR-1 is over 0.5 sec, and has negligible effect when RR-1 is below 0.5 sec. In the zone with RR-1 $\leq$0.5 sec, we could not obtain the relation between RR-2 and Vpe because the number of coordinates was too small to calculate the regression equation in many cases. Although it seemed to be insignificant, further study may be needed.

Cardiac performance is mainly dependent on RR-1 in AF. Relatively higher cardiac performance is observed after longer RR-1. It is related with higher preload by enough time to fill the ventricle, more complete restitution by the interval-force relationship (16), and lower afterload by lower aortic pressure with long diastolic period. In previous reports, the alteration of RR-1 could explain 50-58% of the variance of cardiac performance (8, 12) and those were consistent with our result of 52%.

After the adjustment by the relation between RR-2 and Vpe, r^2 between RR-1 and Vpe was improved from 0.52$\pm$0.17 to 0.72$\pm$0.11 (p<0.001). This value was at least as good as 0.67 derived from sophisticated equation including RR-1 and RR-2 in previous study (8). In the equation of that study, cardiac performance decreased with very long RR-1 and we could not observe the phenomenon. As described above, the equation derived from RR-2 and Vpe was limited to Vpe with RR-1 >0.5 sec. As this zone had a wide deviation of Vpe from regression line, the adjustment by the influence of RR-2 might improve the relation between RR-1 and Vpe. Considering variations from intrinsic autonomic tones, measurement errors and inadequate equation model of regression, we think that almost all measurable alterations of Vpe can be explained by the changes of RR-1 and RR-2.

The influence of RR-2 on cardiac performance in the zone with RR-1 >0.5 sec was prominent when mean RR interval was short and LV function was impaired. The effect of mean RR interval could be expected from Fig. 1D. The slope was steep when RR-2 was short and this phenomenon might make the relationship better. The effect of LV function was very interesting. When LV function was normal, RR-2 had minor effect on cardiac performance. As LV function deteriorated, RR-2 played more important role in determining Vpe. There were few reports that compared the relations between RR intervals and cardiac performance according to LV function (12, 17). Kerr et al. reported that the relations between RR intervals and cardiac performance did not differ for patients with normal and impaired LV function (12). Nagahama et al. reported that the increase of Vpe following the short RR-2 was greater in patients with impaired LV function than in those with normal LV function (17).

Possible explanations for the discrepancy among the studies may be the differences in study subjects and statistical methods. We divided the subjects into two groups by FS and compared the relationship following the method of Kerr et al. The difference was quite evident and r^2 between RR-2 and Vpe was 0.14$\pm$0.17 in higher FS group (n=10) and 0.42$\pm$0.13 in lower FS group (n=11, p<0.001). Therefore, the difference in statistical method could not explain the discrepancy. Compared with previous studies, we used mutivariate analysis to rule out the effect of other variables, such as mean RR interval of each subject. We also used total range of RR-2 instead of the comparison between arbitrary high and low ranges of RR-2. In several reports, they displayed data without statistical assessment (10).

There are several limitations in this study. We used Vpe to show cardiac performance. Although there were several studies that used Vpe (7, 10, 15), most studies adopted stroke volume, cardiac output (3, 4), velocity-time integral (6) or ejection fraction (11). As the scattergrams looked alike among these studies, we believed that the difference might be insignificant. In contrast, Vpe may have several advantages, such as less time consuming and less variation of measurement than other parameters. In this study, we assumed a logarithmic relation between RR intervals and Vpe. As described previously, it could not exactly fit all coordinates.

In summary, simple modification by RR-1 could improve the relation between RR-2 and Vpe. Adjustment by modified relation between RR-2 and Vpe could improve of the relation between RR-1 and cardiac performance, at least to the degree obtained by sophisticated equation. Almost all alteration of Vpe might be explained by the changes of RR-1 and RR-2. RR-2 might play more role to determine the cardiac performance at least in the zone with RR-1>0.5 sec than previously expected. The effect of RR-2 was more prominent when LV function was impaired.

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