学位論文

Functional characteristics of left ventricular synchronization via right ventricular outflow-tract pacing detected by two-dimensional strain echocardiography

（2D ストレイン法を用いた経胸壁心エコー図における，右室流出路ペーシング時の左室機能に関する研究）

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Functional characteristics of left ventricular synchronization via right ventricular outflow-tract pacing detected by two-dimensional strain echocardiography

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Abstract

Background:

Recently, due to the detrimental effects on the ventricular function associated with right ventricular apical (RVA) pacing, right ventricular septal (RVS) pacing has become the preferred pacing method. However, the term RVS pacing refers to both right ventricular outflow-tract (RVOT) and mid-septal (RVMS) pacing, leading to a misinterpretation of the results of clinical studies. The purpose of this study was to elucidate the functional differences among RVA, RVOT, and RVMS pacing in individual patients with atrioventricular block.

Methods:

We compared the QRS duration, global longitudinal strain (GLS), and LV synchronization parameters at the three pacing sites in 47 patients. Also, the peak systolic strain (PSS) time delay between the earliest and latest segments among the 18 LV segments and standard deviation (SD) of the time to the PSS were calculated for the 18 LV segments at each pacing site using 2-dimensional (2D) strain echocardiography.

Results:

RVMS pacing was associated with a significantly shorter QRS duration as compared to RVA and RVOT pacing (154.4±21.4 vs. 186.5±19.9 and 171.1±21.5ms, P <0.001). In

contrast, RVOT pacing revealed a greater GLS (-14.69±4.92 vs. -13.12±4.76 and -13.51±4.81%, *P* <0.001), shorter PSS time delay between the earliest and latest segments (236.0±87.9 vs. 271.3±102.9 and 281.9±126.6%, *P* =0.007), and shorter SD of the time to the PSS (70.8±23.8 vs. 82.7±30.8 and 81.5±33.7ms, *P* =0.002) as compared to RVA and RVMS pacing.

Conclusions:

Those results suggest that the functional characteristics of RVOT pacing possess a greater possibility as an optimal pacing site than RVMS pacing, regardless of the pacing QRS duration in patients with AV conduction disorders.

Key words

Right ventricular apical (RVA) pacing; Right ventricular outflow-tract (RVOT) pacing; Right ventricular mid-septal (RVMS) pacing; 2D strain echocardiography; Left ventricular (LV) synchronization

1. Introduction

The implantation of permanent pacemakers has become an established technique for treating bradyarrhythmias, such as atrioventricular block (AVB), over the last several decades. In this procedure, right ventricular (RV) apical (RVA) pacing has been the typically applied method to preserve a desirable heart rate. However, several long-term observational studies have shown that RVA pacing may elicit an inappropriate ventricular function[1-5]. To avoid this disadvantage of RVA pacing, RV septal (RVS) pacing, which is comprised of RV mid-septal (RVMS)[6-9] and outflow-tract (RVOT) pacing[10-13], has been suggested as an alternative ventricular pacing method with a predominantly better cardiac function as compared to RVA pacing. Most investigations have compared the cardiac function between patient groups with RVA and RVOT or RVMS pacing. However, as the interpretation of the previous clinical studies has been misleading due to the lack of clarity as to which pacing method was employed[14, 15], it remains to be determined which pacing method is superior.

Previously, we compared the differences in the left ventricular (LV) function among the pacing sites in the same individual to avoid the above-mentioned problem[16]. However, the assessment of the LV function, and in particular, the assessment of the LV synchronization was not completed. In the present study, we compared the detailed LV synchronization parameters at three different pacing sites, in the RVA, RVOT, and RVMS, and clarified the functional characteristics at each pacing site with the aim to evaluate the superiority of a pacing site, in the same individual prior to a permanent pacemaker implantation in patients with AVB.

2. Material and Methods

2.1. Study population

The present study protocol was approved by the ethical committee of Hokkaido Cardiovascular Hospital. Subsequently, written informed consent was obtained after the patients received a full explanation of the study protocol from the investigators. The inclusion and exclusion criteria for the present study are shown in Table 1. Patient recruitment began on November 27, 2009, and ended on June 19, 2012 with 47 recruited patients.

2.2. Methods

Temporary pacing leads were applied in all patients prior to the study. In each patient, a temporary atrial pacing lead was positioned in the right atrial appendage (RAA), and a temporary ventricular lead was positioned according to the intended pacing site, in the RVA, RVMS, and RVOT in sequence.

2.2.1. Pacing lead positioning procedure

Each ventricular lead placement site was determined by guidance with both 12-lead surface electrocardiography (ECG) and fluoroscopy (Figures 1 and 2). The RVA lead was positioned in the RV apex. The method of lead positioning for the RVS (RVMS or RVOT) pacing was as follows: the tip of the electrode was advanced into the pulmonary artery through the pulmonary artery valve, withdrawing it carefully until the tip of the electrode was placed just below the pulmonary valve, and positioned at the RVOT. The RVMS is just below the septoparietal trabeculation and roof of the tricuspid valve[14,15], hence, the tip of the electrode was positioned between the RVOT and RVA, facing rightward on the septal wall as viewed from the 50° left anterior oblique fluoroscopy view, thereby distinguishing the septal wall from the RV free wall (Figure 2). The paced QRS morphology showed a narrower and smaller shape for RVMS pacing and a wider and taller shape for RVOT pacing, especially in the limb leads (Figure 1).

2.2.2. Pacing procedure

DDD pacing using temporary pacing leads was applied with an identical pacing rate of 20 beats per minute (bpm) above the sinus rate, identical pacing output, and identical AV delay time for each ventricular pacing position in each individual patient. After pacing for five minutes in each pacing position, the electrocardiography and echocardiography were demonstrated at each pacing position.

2.2.3. Electrocardiography

A 12-lead surface ECG was recorded using a 25 mm/s paper speed with a gain of 10 mm/mV at each pacing position. The paced QRS duration was calculated mainly from leads II, III, and aVF in order to clearly differentiate the characteristic QRS features of RVA, RVMS, and RVOT pacing.

2.2.4. Echocardiography

The global longitudinal strain (GLS), the time delay of the peak systolic strain (PSS) between the earliest and latest segments among the 18 LV segments, and standard deviation (SD) of the time to the PSS among the 18 LV segments were calculated using the 2-dimensional (2D) longitudinal strain method for each pacing position. All images were obtained using a Vivid E9 echocardiography machine (General Electric Healthcare, Horten, Norway), and all data were stored on an Echopac (General Electric Healthcare) for off-line analysis. The echocardiographer participating in the present study was well

trained for raw data analyses with no bias regarding the pacing position.

2.2.5. Statistical analysis

A one-way repeated measures analysis of variance with post-hoc Bonferroni pairwise comparisons was used to compare the means of the QRS, GLS, time delay of the PSS, and SD of the time to the PSS among the RVA, RVMS, and RVOT pacing groups. *P* values <0.05 were considered statistically significant. All calculations were conducted using IBM SPSS Statistics 20.0 for Windows software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

In total, 47 consecutive AVB patients (30 with complete AVB and 17 with non-complete AVB) were recruited with no randomization. The patient characteristics are shown in Table 2. Four patients with a baseline LVEF of <40% were included; one of the four patients had dilated cardiomyopathy and was undergoing regular hemodialysis.

3.2. QRS analysis on the ECG

RVMS pacing was associated with a significantly shorter QRS duration as compared to RVA and RVOT pacing (154.4±21.4 vs. 186.5±19.9 and 171.1±21.5 ms, n =47, P <0.001), and RVOT pacing was associated with a significantly shorter QRS duration as compared

to RVA pacing (171.1±21.5 vs. 186.5±19.9 ms, n = 47, P <0.001) (Table 3).

3.3. Echocardiographic analysis

When comparing the GLS at each pacing position, though one of the 47 patients was excluded from the analysis because of insufficient data, RVOT pacing yielded a statistically greater GLS as compared to RVMS pacing (-14.69±4.92 vs. -13.51±4.81%, n = 46, P =0.015) and RVA pacing (-14.69±4.92 vs. -13.12±4.76%, n = 46, P <0.001). On the other hand, no significant difference in the GLS was observed between RVA and RVMS pacing (-13.12±4.76 vs. -13.51±4.81%, n = 46, P =0.960) (Table 3). The 2D longitudinal strain imaging at each pacing position in the individual patients is shown in Figure 3. The LV wall was divided into 18 segments, each of which shows the individual time to the PSS (Table 4). Figure 4 shows the average time to the PSS in the 18 segments. These results illustrate the segmental spatial differences in the temporal differences to the PSS and the global changes in the LV synchronization among the RVA, RVMS, and RVOT pacing. A quantitative analysis of the time delay of the PSS between the earliest and latest segments or the SD of the time to the PSS in the 18 segments provided differences in the LV synchronization among each pacing site. The time delay of the PSS between the earliest and latest segments was significantly shorter with RVOT pacing than RVMS (236.0±87.9 vs. 281.9±126.6ms, n = 47, P =0.005) and RVA (236.0±87.9 vs.

271.3±102.9ms, *n* = 47, *P* =0.005) pacing, with no significant difference between RVA and RVMS pacing (271.3±102.9 vs. 281.9±126.6 ms, n=47, *P*=1.000) (Table 3). The SD of the time to the PSS in the 18 segments was significantly shorter with RVOT pacing as compared to RVA and RVMS pacing (70.8±23.8 vs. 82.7±30.8 and 81.5±33.7 ms, *n* = 47, *P* =0.007), with no significant difference between RVA and RVMS pacing (82.7±30.8 vs. 81.5±33.7 ms, n=47, *P*=1.000) (Table 3).

4. Discussion

4.1. Main findings

The purpose of the present study was to clarify the functional characteristics between RVMS and RVOT pacing in order to achieve optimal RV pacing as compared to RVA pacing in terms of a better LV function and LV synchronization. The main findings showed that RVOT pacing exhibited a greater GLS and better LV synchronization parameters than RVA and RVMS pacing. Interestingly, there were intriguing discrepancies between the QRS duration and LV synchronization parameters, namely, the QRS duration was the shortest with RVMS pacing, whereas the LV synchronization parameters were better with RVOT pacing. These RVOT pacing characteristics suggest that RVOT pacing possesses a greater possibility as an optimal RV pacing site as

compared to RVMS pacing, regardless of the pacing QRS width

In general, RVA pacing is thought to cause LV dysfunction due to minimal capture of the normal conduction pathway[17]. In contrast, it is believed that RVS pacing produces a narrower QRS duration and leads to a better LV function due to the maximum capture of the normal electrical pathway. Thus, the beneficial effect of RVS pacing is thought to be a result of the narrower pacing QRS duration[5]. To date, a number of studies on RVMS[6-9] or RVOT[10,12,13] pacing, have yielded a narrower pacing QRS duration and revealed a better LV function as compared to RVA pacing. Hence, RVMS pacing would be expected to achieve a better LV function and synchronization over RVOT pacing through the narrower pacing QRS duration. However, little data is available in regard to the functional differences between RVMS and RVOT pacing. Thus, we attempted to evaluate the differences between RVMS and RVOT pacing, based on the following description.

4.2. Technical aspects and comparison with previous studies

First of all, the anatomical discrimination between the RVMS and RVOT is indispensable for accurate ventricular pacing lead positioning onto the true RVMS and RVOT. Although in one report by Alhous et al.[18] which referred to the predominance of RVMS and RVOT pacing as compared to RVA pacing in individual patients, the lead position on the RVMS was too close to the RVOT, resulting in the same

electrocardiographic appearance and LV performance, and thus differentiation between RVMS and RVOT pacing could not be clarified.

On the other hand, in our previous case report as a preliminary study, we clearly indicated the anatomical characteristics for the RVA, RVMS, and RVOT according to the fluoroscopic and electrocardiographic guidance in an individual patient[16], as referred to in previous reports by Hillock and Mond[14,15]. Also in the present study, we clarified the fine anatomical differences between the RVMS and RVOT in each patient; this is in contrast to most previous studies, which do not clearly define RVMS and RVOT.

Secondly, the quantification of the temporal difference in each LV segment by means of 2D longitudinal strain imaging would be useful as in the present study. The 2D strain imaging can distinctly divide the LV wall into 18 segments, and provide a superior spatial resolution. Previously, Nahum et al. reported the superiority of the GLS using the 2D longitudinal strain method over the LVEF to predict subclinical LV dysfunction and the outcome[19]. Further, Inoue et al. discussed less dys-synchronization and a better GLS with RVMS pacing as compared to RVA pacing[9]. Our case report also visualized better LV synchronization during RVOT pacing as compared to RVA and RVMS pacing using 2D longitudinal strain imaging[16]. To confirm the source of the differences in the LV synchronization, measurement of the GLS would be insufficient for the evaluation from

the viewpoint of comparing the extent of segmental dys-synchronization. Rather, a quantitative evaluation of the temporal difference in each of the 18 LV segments was considered to be necessary for a precise analysis among the pacing positions. Hence, we also calculated the time delay of the PSS between the earliest and latest segments and the SD of the time to the PSS among the 18 LV segments using 2D longitudinal strain imaging. With this methodology, we could easily quantify the segmental time differences from the first peak to last peak systolic strain among the 18 LV segments as shown in Figure 4; this made it possible to clarify the precise functional characteristics at each pacing site and to more specifically predict the optimal pacing position based on the changes in the LV synchronization.

4.3. The possible mechanism of the differences in the LV synchronization

Taking into account the results based on these analytical methods, the possible mechanism of the differences in the LV synchronization at each pacing site might be explained by the differences in the LV activation sequence limited by AVB. Recently, Laske et al. reported the differences in the myocardial activation sequences among sinus rhythm, RVMS pacing, and high postero-septal pacing in isolated swine hearts by using the non-contact mapping, EnSite® 3000 system[17]. They found a similarity in the activation sequence between sinus rhythm and RVMS pacing, namely, the depolarization

wave-front which propagated down the septal wall and activated the apical region, ascended up the lateral wall and terminated in the high posterolateral wall. However, the high posteroseptal pacing impulse primarily activated the anterior, septal, and lateral wall straight downward low on the lateral wall, which was in contrast to sinus rhythm and RVMS pacing. Laske et al. indicated that RVMS pacing has a greater likelihood of residing within the ventricular myocardium in close proximity to the intrinsic conduction system[17]. However, those models might not be applicable in AVB because of the condition requiring preserved atrioventricular electrical conduction pathways.

In patients with AVB, as the conduction of the AV node and His bundle is thought to be nearly completely impaired, the ventricular pacing impulse might be restricted from capturing the normal atrioventricular electrical conduction pathway. In that situation, the pacing impulse triggered by RVA, RVMS or RVOT pacing might directly activate the adjoining ventricular myocardium, and a depolarization wave-front may propagate through the proximal myocardium into the Purkinje fiber network in order, and then terminate opposite to each breakout site. As shown in Figure 4, although the temporal delay in the PSS at the basal-posterior (segment 1), basal-lateral (segment 12), and basal-anterior (segment 18) regions is particularly marked and common in RVA, RVMS, and RVOT pacing and facilitates LV dys-synchronization, RVOT pacing is expected to

diminish the temporal delay in those segments by tracing the different activation sequences, because the RVOT is relatively close to the basal-posterior, basal-lateral, and basal-anterior regions.

4.4. Possible mechanism for the discrepancy between the SD and QRS duration

One of the most interesting results in the present study is the existence of the discrepancy between the QRS duration and LV synchronization parameters in the RVMS and RVOT pacing. As mentioned above, the QRS duration was the shortest with RVMS pacing, whereas the LV synchronization parameters were considered better with RVOT pacing. As shown in Figure 4, the segment of the first peak strain is earlier in the RVMS pacing (segment 8) than the first peak in the RVOT pacing (segment 8). Those phenomena explained that RVMS pacing had a narrower QRS duration and could stimulate the septum more rapidly as compared to RVOT pacing. On the other hand, the segment of the last peak strain was earlier with the RVOT pacing (segment 1) as compared to the last peak with the RVMS pacing (segment 1). In addition, the time to the PSS at the lateral and posterior wall (segment 10, 11, 12, 17, 18) looked similar between RVMS and RVOT pacing. Those phenomena showed that LV conduction delays exist in RVMS pacing and not in RVOT pacing, and may explain the shortening of the time delay of the PSS between the earliest and latest segments, and the shortening of the SD of the time to the PSS,

resulting in the better synchronization parameters with RVOT pacing.

Based on the present study, together with the previous reports mentioned above[17], it is suggested that the prescriptive factor for clarifying the functional characteristics of RV pacing is not the diminishment of the QRS duration, but rather the pacing site, and RVOT pacing might allow preservation of the LV synchronization in the acute phase. In the case of choosing the RVOT for the permanent pacemaker lead implantation site, long-term observation of RVOT pacing might also clarify the usefulness and possibility of preventing complications such as the onset of heart failure.

4.5. Limitations

The limitations of the present study were that RVA, RVMS, and RVOT pacing were demonstrated temporarily in the acute phase under conditions of almost a normal LV function, and the total number of cases was small. To define the mechanism of RV pacing, a combination of electrophysiological mapping and an echocardiographic analysis at each pacing site is needed. Furthermore, detailed studies, which evaluate the chronic phase with a large number of cases under the condition of a low LV function will also be necessary to adequately stratify the patients in order to utilize optimal RV pacing.

In addition, although we also compared the differences in the LVEF as one of the echocardiographic parameters among the RVA, RVMS and RVOT pacing, only a 0.6%

increase in LVEF could be shown in the RVOT pacing as compared to the RVMS pacing, which was not considered clinically significant (data not shown). Since the limitations of 2D strain echocardiography for evaluating dys-synchrony and predicting the efficacy of cardiac resynchronization therapy (CRT) have been reported in some clinical trials[20.21], it can be said that the difference regarding the hemodynamic advantages between RVOT pacing and RVMS pacing might be small. Further large scale studies will be needed to clarify these points.

5. Conclusions

The present acute phase study clarified the differences in the functional characteristics among RVA, RVMS, and RVOT pacing by two-dimensional strain echocardiography, and RVOT pacing was shown to have a functional superiority over RVMS and RVA pacing. Further investigation and long-term observation will be needed to judge the optimal pacing site for permanent pacemaker implantations.

Figure legends

Figure 1. Typical electrocardiographic appearance at each pacing site.

Right ventricular outflow-tract mid-septal (RVMS) pacing (QRS 140 ms) revealed a shorter QRS duration as compared to right ventricular apical (RVA) (QRS 165 ms) and right ventricular outflow-tract (RVOT) pacing (160 ms).

Figure 2. Fluoroscopic view of each pacing site (red circle).

The upper panels show the 0° anterior oblique view. The lower panels show the 50° left anterior oblique view.

Figure 3. This shows the 2D longitudinal strain echocardiography in an individual patient. The left ventricular (LV) wall was divided in 18 segments (No.1-18) and each segment revealed a longitudinal strain curve and an individual time to peak strain. Using this method, the differences in the LV synchronization could be easily quantified at each pacing site. The upper panels show the right ventricular apical (RVA) pacing images. The middle panels show the right ventricular outflow-tract mid-septal (RVMS) pacing images. The lower panels show the right ventricular outflow-tract (RVOT) pacing images.

APLAX, apical long-axis view; 4CV, four-chamber view; 2CV, two-chamber view.

Figure 4. The average time to peak systolic strain in each of the 18 segments.

The temporal delays for the peak systolic strain at the Basal-posterior (No. 1), Basal-lateral (No.12), and Basal-anterior (No. 18) regions were conspicuous at each pacing site. These segments caused a marked left ventricular (LV) dys-synchronization.

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Table 1. Inclusion and exclusion criteria

Inclusion criteria
1. Mobitzs Ⅱ AVB/comple AVB
2. Indication for a permanent pacemaker implantation
3. Age over 20
4. Obtained written informed consent
5. NYHA class I-II
Exclusion criteria
1. Unable to give informed consent
2. Age under 20
3. Atrial fibrillation/atrial flatter
4. Frequent, uncontrolled atrial tachyarrhythmias
5. NYHA class III-IV

AVB, atrioventricular block; NYHA, New York Heart Association.

Table 2. Patient characteristics (*n* = 47)

Age (years)	77.4 ± 7.8
Male	25 (53.1%)
Complete AVB	30 (63.8%)
Mobitz Ⅱ AVB	17 (36.2%)
Complications	
Hypertension	27 (57.4%)
Dyslipidemia	11 (23.4%)
Chronic renal failure	11 (23.4%)
Chronic heart failure	10 (21.2%)
Diabetes mellitus	9 (19.1%)
Coronary artery disease	7 (14.8%)
Valvular disease	5 (10.6%)
Cerebral infarction	2 (4.2%)
Dilated cardiomyopathy	1 (2.1%)
Sarcoidosis	1 (2.1%)
Hemodialysis	1 (2.1%)
None	6 (12.7%)
LVEF (%)	61.0 ± 9.9

Values are expressed as mean ± SD or number (%).

AVB, atrioventricular block; LVEF, left ventricular ejection fraction.

Table 3. Changes in the QRS duration, GLS, Peak to peak strain and standard deviation over time to peak systolic strain

	RVA	RVMS	RVOT	*P* *
QRS (ms)	186.5 ± 19.9	154.4 ± 21.4	171.1 ± 21.5	<0.001 [a]
GLS	-13.12 ± 4.76	-13.51 ± 4.81	-14.69± 4.92	<0.001 [b]
Peak to peak	271.3 ± 102.9	281.9 ± 126.6	236.0± 87.9	0.007 [c]
PSS-SD (ms)	82.7 ± 30.8	81.5 ± 33.7	70.8 ± 23.8	0.002 [d]

Values are expressed as mean ± SD.

*One way repeated measure analysis of variance with post-hoc Bonferroni pairwise comparisons

[a] RVA vs. RVMS: *P*<0.001; RVA vs. RVOT: *P*<0.001; RVMS vs. RVOT: *P*<0.001

[b] RVA vs. RVMS: *P*=0.960; RVA vs. RVOT: *P*<0.001; RVMS vs. RVOT: *P*=0.015

[c] RVA vs. RVMS: *P*=1.000; RVA vs. RVOT: *P*=0.005; RVMS vs. RVOT: *P*=0.005

[d] RVA vs. RVMS: *P*=1.000; RVA vs. RVOT: *P*=0.007; RVMS vs. RVOT: *P*=0.007

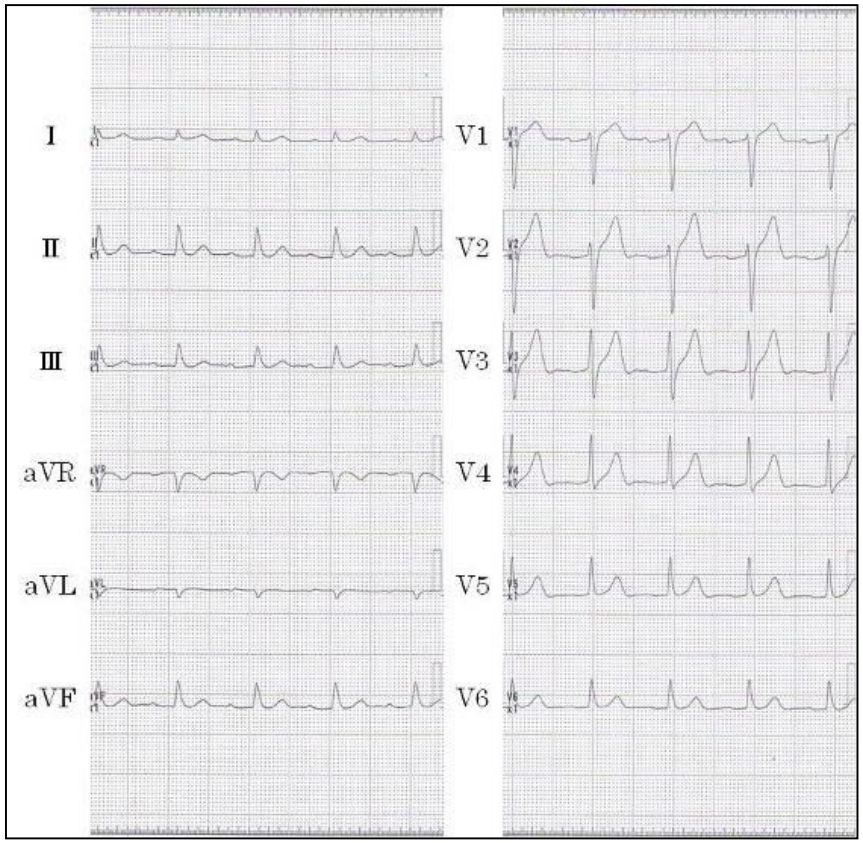
RVA, right ventricular apical; RVMS, right ventricular mid-septal; RVOT, right ventricular outflow-tract; GLS, global longitudinal strain; Peak to Peak, time delay of peak systolic strain between the earliest and latest segments; PSS-SD, standard deviation over time to peak systolic strain.

Table 4. Definition of 18 LV wall segments for quantification of the differences in the LV synchronization at each pacing site

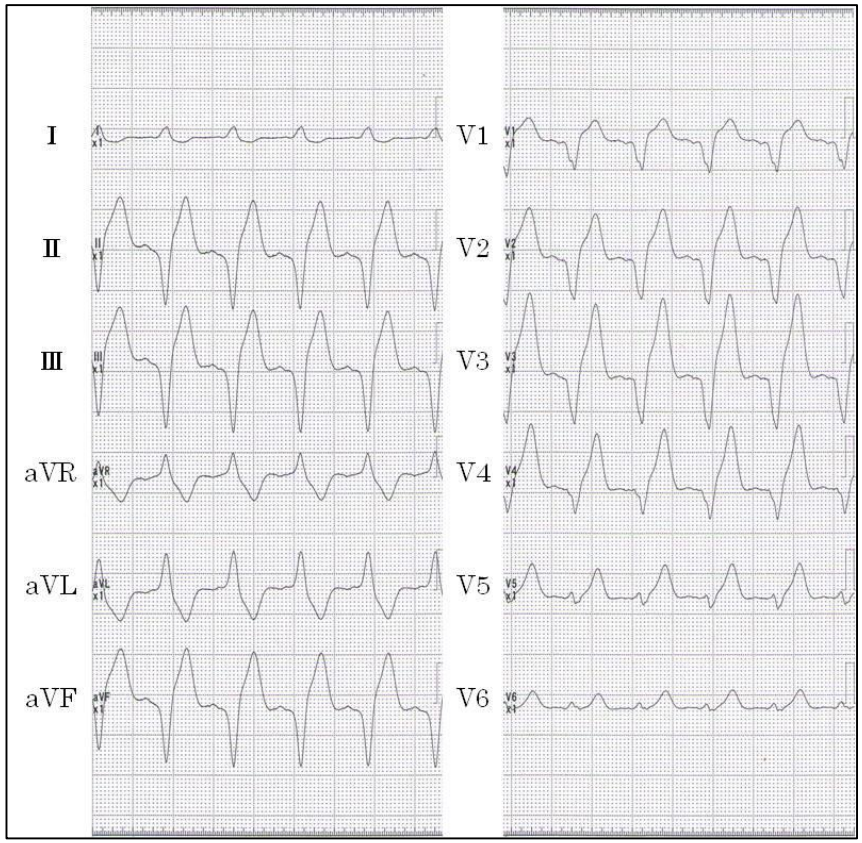
No.	View	Segment
1	APLAX	Basal-posterior
2	APLAX	Mid-posterior
3	APLAX	Apical-posterior
4	APLAX	Apical-anteroseptal
5	APLAX	Mid-anteroseptal
6	APLAX	Basal-anteroseptal
7	4CV	Basal-septal
8	4CV	Mid-septal
9	4CV	Apical-septal
10	4CV	Apical-lateral
11	4CV	Mid-lateral
12	4CV	Basal-lateral
13	2CV	Basal-inferior
14	2CV	Mid-inferior
15	2CV	Apical-inferior
16	2CV	Apical-anterior
17	2CV	Mid-anterior
18	2CV	Basal-anterior

LV, left ventricular; APLAX, apical long-axis view; 4CV, four-chamber view; 2CV, two-chamber view.

Figure 1

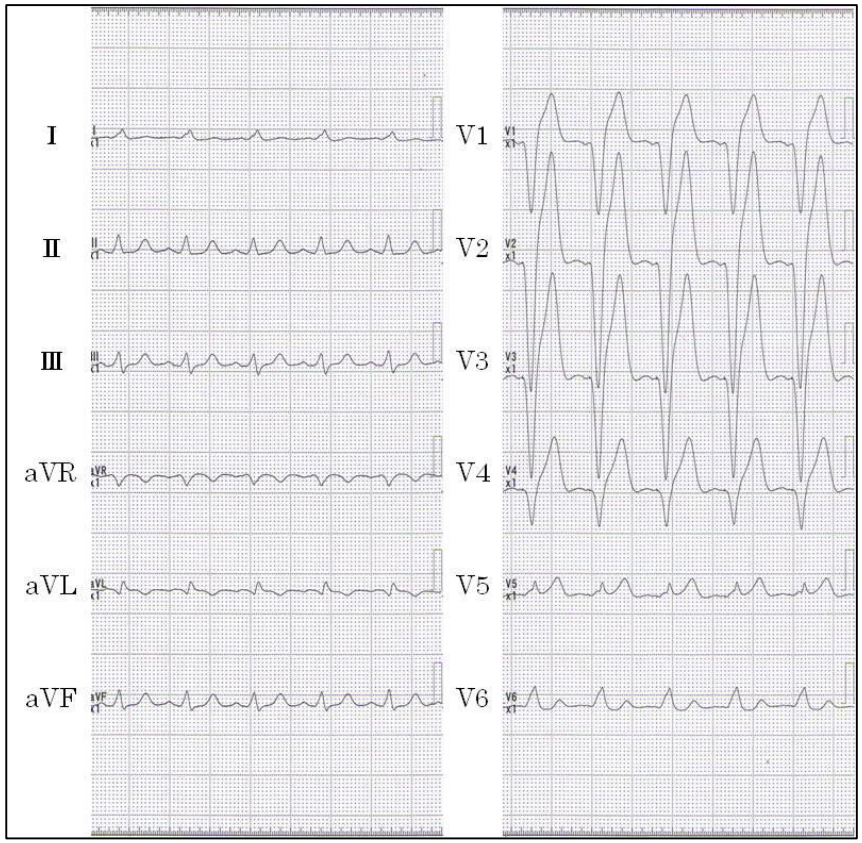


Control QRS 120ms

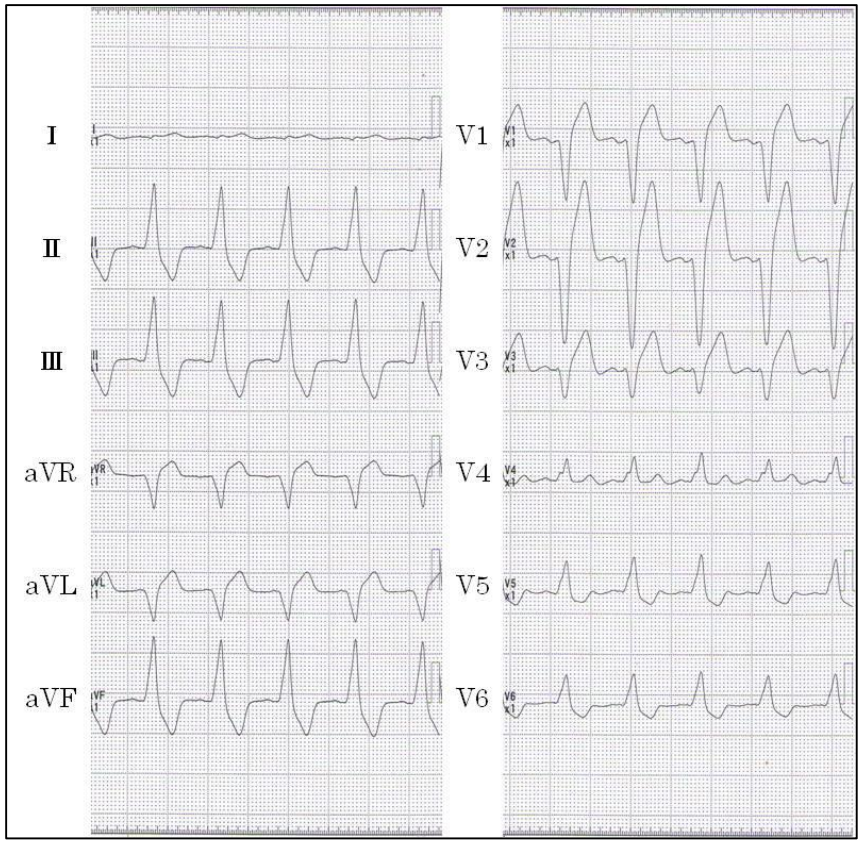


RVA QRS 165ms

Figure 1



RVMS QRS 140ms



RVOT QRS 160ms

Figure 2

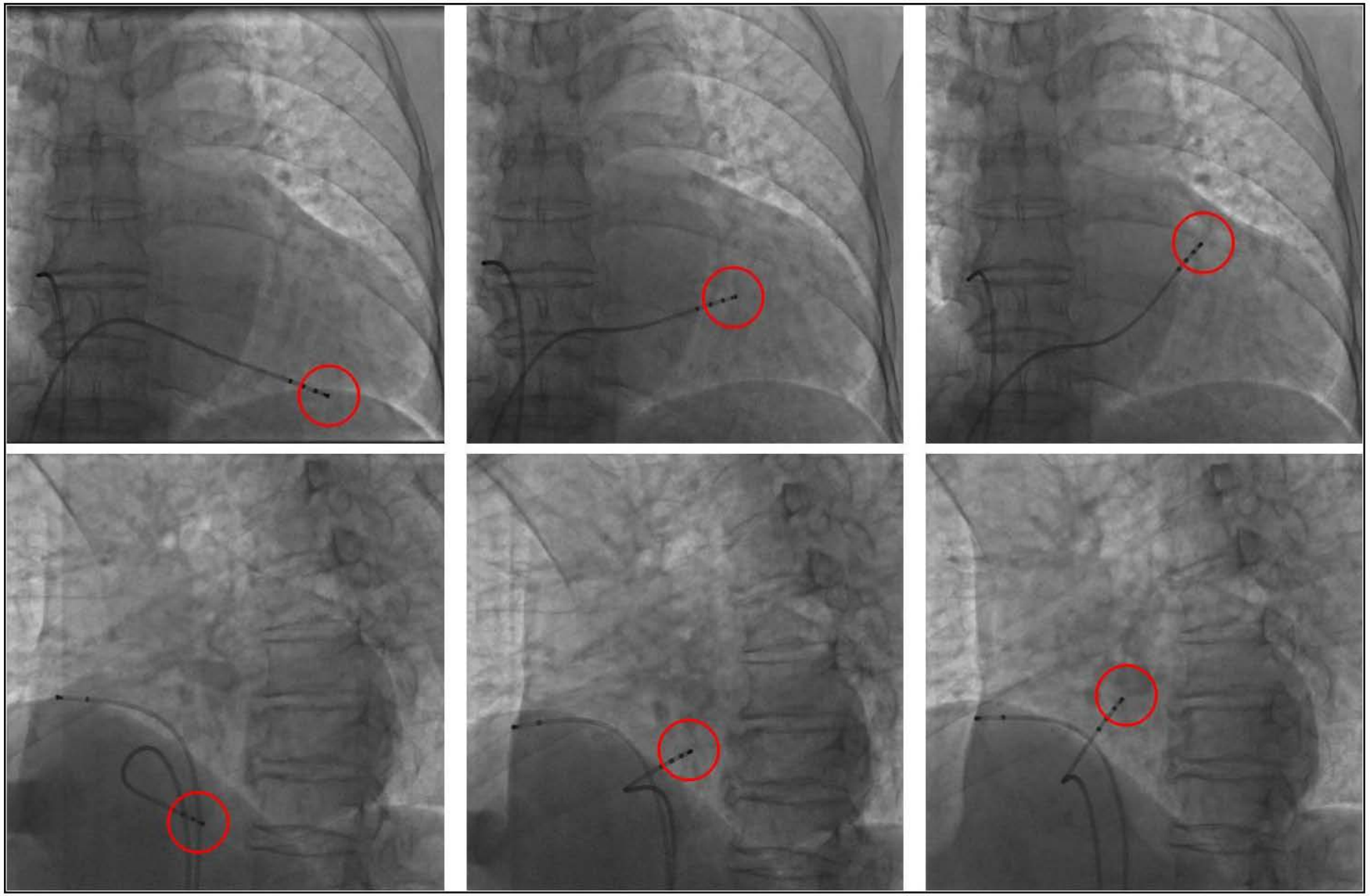


Figure 3

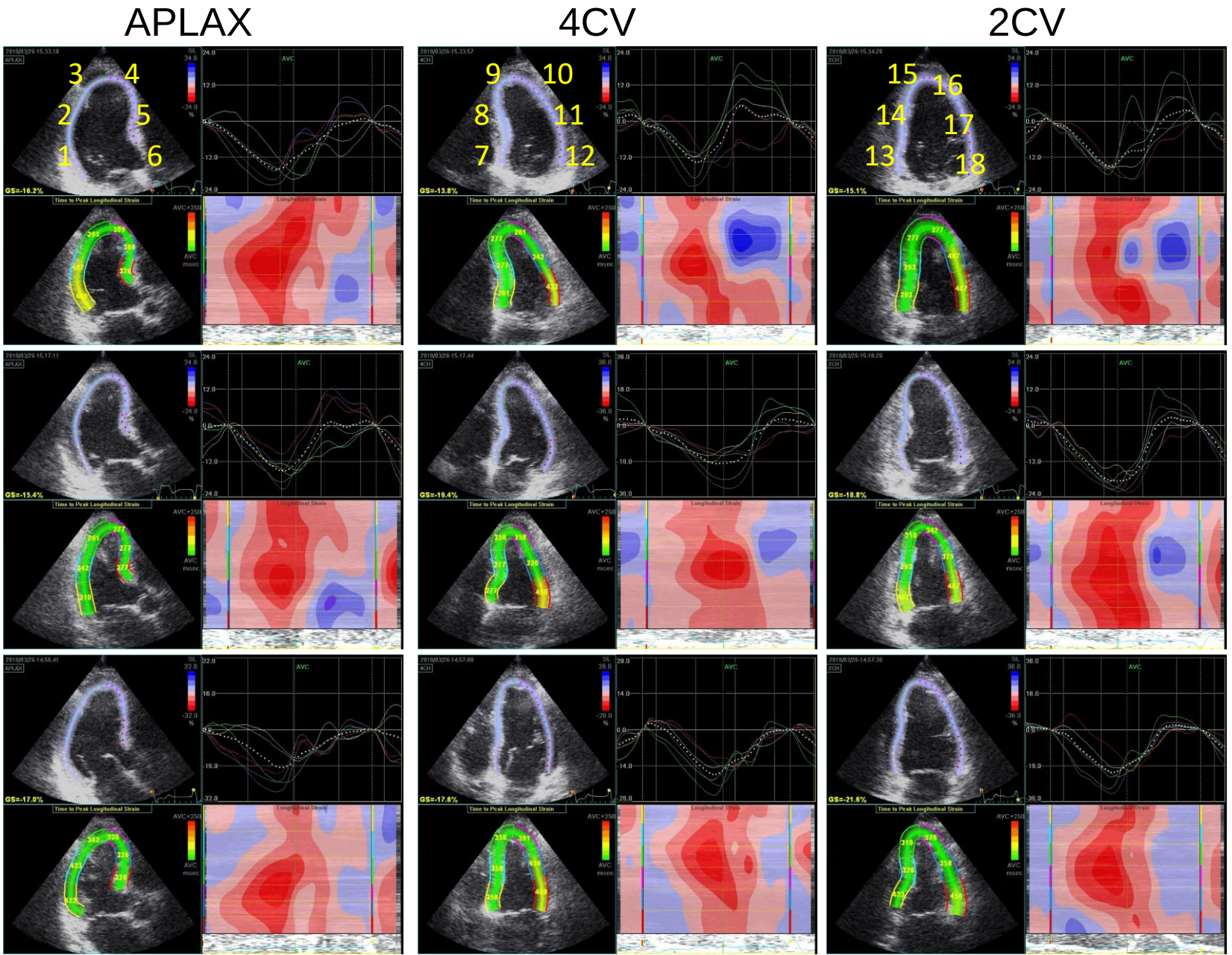
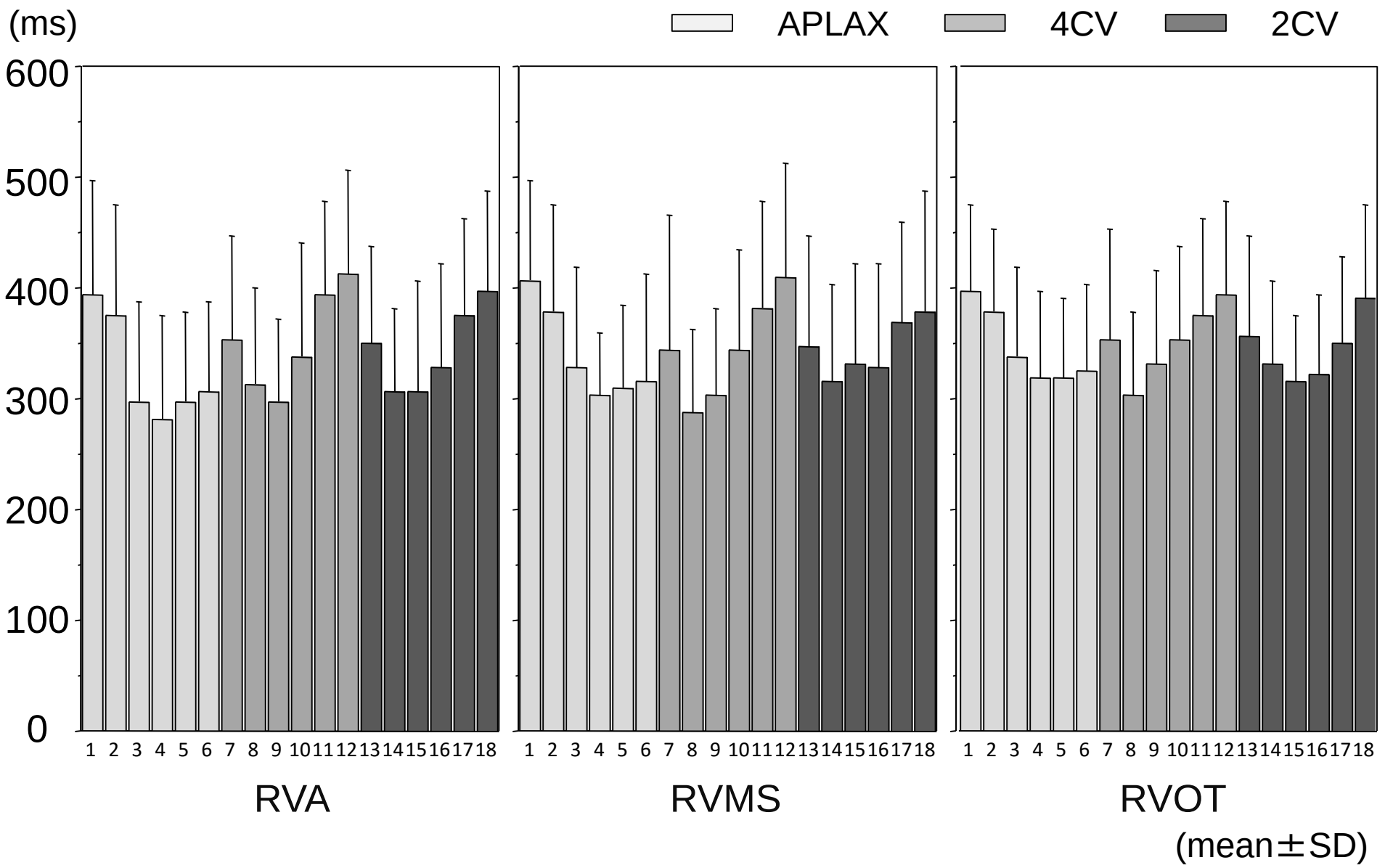


Figure 4


(ms)
APLAX
4CV
2CV
600
500
400
300
200
100
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
RVA
RVMS
RVOT
(mean±SD)