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研究室で撮影した本人のスナップ写真、及び発表論文のコピーを添付

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研究テーマ CHANGES OF SIGNAL AVERAGED ECG BY CLASS I ANTIARRHYTHMIC AGENTS IN PATIENTS WITH VENTRICULAR ARRHYTHMIAS

2．本年度の研究業績

(1) 学会・研究会等においての口頭発表 (有)・無 (学会名・内容)

第15回心電学会
「高分解能心電図を用いたピルジカイニドの薬効薬理の検討」

第9回日本医科大学留学者発表会
「高分解能心電図を用いたClass I 抗不整脈薬の薬效薬理の検討」

(2) 学会誌等に発表した論文 (有)・無 (雑誌名・論文名)

XXVth International Congress on Electrocardiology

≪時空間心電情報の新しい視点≫
－不整脈の治療における加算平均心電図の役割

3．今後の研究計画

高分解能心電図を使用して，各群抗不整脈薬の薬理作用，薬物動態等の研究引き続けています．

今回，心臓分泌のホルモンで ANP，BNPは，不整脈発生との関係，ペースメーカー植込　患者の心機能との関係等を研究始めました．年末に結果を発表予定です．

4．研究指導者の意見

呉医師は来日以来．循環器病学特に不整脈学の研修．研究に従事し．高分解能心電図を駆使した新しい研究領域において目覚しい成果をあげている．特に抗不整脈薬の薬理作用．薬物動態と心電図変化との関連性に関する研究は．数多くの学会発表を通して．注目を集め．この分野の研究の発展に大いに貢献しているところである．今後．生化学的手法を取り入れた新たな研究も予定されており．研究の更なる発展が期待される．

研究指導者氏名　加藤貴雄

5．研究報告

別紙形式を参考に、報告本文4000字以上で報告して下さい（枚数自由・ワープロ使用）

タイトル・要旨等は日本語で、KEY WORDS以下は日本語或いは英語で記入して下さい。

研究成果の発表予定がある場合は発表原稿・抄録集等を添付して下さい。

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CHANGES OF SIGNAL AVERAGED ECG BY CLASS I ANTIARRHYTHMIC AGENTS IN PATIENTS WITH VENTRICULAR ARRHYTHMIAS

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抗不整脈薬は心電図各成分に対し影響を及ぼすが、通常の 12 誘導心電図ではそれを詳細に検討することは困難である。我々は、高分解能を使用し I 群抗不整脈薬の効果と心電図高周波成分の変化の関連を検討します。対象は心室性期外収縮が認められる患者 37 名、内訳は disopyramide(DP)5 例、mexiletine(MX)11 例、flecainide(FL)7 例、propafenone(PF)6 例、pilsicainide(PS)8 例を経口投与、VPC が 75%以上減少したものを有効と判定した。I 群抗不整脈薬投与前後に NEC-SanEi 社製 Signal Processor 7T18 を用い SAE を記録した後、f-QRS、RMS40 を測定して、さらに薬剤投与前後の変化率△f-QRS、△RMS40 を求めました。結果：1)DP、FL、PF、PS は投与後 f-QRS が延長していましたが、ME ではほとんどかわりませんてした。2)DP、FL、PF、PL は投与後 RMS40 が減少しましたが ME ではほとんどかわりませんてした。3)DP、FL は投与前の f-QRS が 120msec 以上あるいは f-QRS が 20%以上延長した例で無効例が多く見られました。なお、PF、PS を経口投与した時には投与前の f-QRS が 100msec 以上の症例で無効例が多く見られました。結論：心電図高周波成分を詳細に検討することにより I 群抗不整脈薬の薬効を臨床的に評価することが可能であった。今回我々の行った検討は、薬剤有効例と無効例の比較、催不整脈作用の現れた例の検討等、抗不整脈薬を適切に使用するための指標として有用な方法となりうると思われた。

Key Words: Signal averaged ECG(SAECG), Class I antiarrhythmic drugs, Ventricular premature contractions(VPC)

INTRODUCTION

To date, the main clinical role of the signal averaged ECG (SAECG, SAE) was the

identification of patients at risk of sustained ventricular tachycardia and sudden death. Prediction of the efficacy of antiarrhythmic drugs represents another potential clinical application of this method[1-3].

It is important to search for new approaches to predict which drug will be most effective for a given patient with a particular arrhythmia. The same agent may be effective for one patient while it can fail for another. Empirically based antiarrhythmic treatment can be hazardous because of triggering dangerous proarrhythmias. But until now, only a few reports have examined the relation between drug induced SAE changes and antiarrhythmic efficacy.

Therefore, in our research at Nippon Medical School, we focused on SAE changes caused by antiarrhythmic drugs and their possible use for prediction of antiarrhythmic efficacy.

To evaluate the different effects of Class I antiarrhythmic drugs on SAE, recording was made before and after the administration of Class I agents - disopyramide (Ia), mexiletine (Ib), flecainide (Ic), propafenone (Ic) and pilsicainide (Ic).

PATIENTS:

We studied 37 patients with ventricular premature contractions (VPC) for a whole day. Twenty-seven were male, ten were female, and the mean age was 60 years. The type of underlying heart disease was old myocardial infarction in two patients, dilated cardiomyopathy in six patients, and hypertrophic cardiomyopathy in one patient. In the remaining patients, any organic heart diseases were not clearly determined, and the cause of VPC was thought idiopathic.

The following Class I antiarrhythmic agents (AA) were administered per os; Disopyramide (DP) in 5 cases, mexiletine (MX) in 11 cases, flecainide (FL) in 7 cases, propafenone (PF) in 6 cases and pilsicainide (PS) in 8 cases.

METHODS:

After completing the basic evaluation of arrhythmias, each patient underwent control SAE recording. Then each patient was tested with the selected anti-arrhythmic agent. All recordings were performed at Nippon Medical School with the subject lying on the bed in a quiet environment.

SAE was recorded from X,Y and Z orthogonal leads using model 1000 DX recorder (San-Ei, NEC). The recordings prior to and on medication were obtained from the same

electrode position . A mean of 256 ±4 (range 179-356) cardiac cycles were averaged.
The skin of the patients was prepared with a mildly abrasive tape.
Then eight disposable electrodes were placed in the following positions:
1. the horizontal (X) electrodes at the right and left mid-axillary line at the fourth intercostal space,
2. the vertical (Y) electrodes at the manubrium and at the mid-axillary line on the eight-ninth rib and
3. the sagittal (Z) electrodes in V2 position and in the corresponding position posteriorly /on the back to the left of the vertebral column.
Two ground electrodes were also attached.
Before starting the recording, two minutes were allowed for stabilization, then the signals from X, Y, Z bipolar leads were recorded for 7 minutes. Signals were analysed with a band pass filter set at 50-250 Hz and recorded on a DAT tape. After amplification, averaging and filtering, the signals were combined into a vector magnitude $\sqrt{x^2+y^2+z^2}$ and three conventional parameters were calculated:
1. the duration of the total QRS complex (f-QRS)
2. the duration of the low amplitude (<40 uV) signals at the terminal portion of the QRS complex (LAS40)
3. root mean square voltage of the last 40 msec of the QRS complex (RMS40).
The result of the time domain SAE was considered abnormal when at least two of three parameters were beyond the normal range: the total QRS duration >120 msec, the duration of the low amplitude signals >40 msec, and the root mean square voltage of the last 40 msec of the QRS complex < 25uV.
SAE recordings were obtained after short-term maintenance therapy (DP 300 mg/d, MX 300 mg/d, FL 100 mg/d, PE 150 mg/d, PS 150 mg/d), when the AA was administered for at least two week.
Drug was consider effective if caused 75% reduction of VPC.
Blood samples were collected from patients in order to check serum concentration at the time of recording around 1.5-2 hours after administration of the drug.

RESULTS:

Changes of f-QRS and RMS40:

	DS	MX	FL	PE	PL
f-QRS (%)	9.1±9.6	1.8±5.9	7 .5±5	16.9 ±14.7	11.5±4.4
RMS40(%)	-10.5±67.7	-4.2±0.8	-29.3±28.6	-31.6±38.5	-30.8±17.4

1. We observed the significant prolongation of f-QRS after oral administration of disopyramide, flecainide, propafenone and pilsicainide. Mexiletine did not prolong f-QRS significantly.

2. The measurement of the RMS40 changes demonstrated that all class I AA except mexiletine markedly decreased RMS40 in most of the patients. Mexiletine decreased RMS40 slightly.

3. When we studied the cases in which the anti-arrhythmic treatment was not effective, we found that many of these patients were diagnosed with dilated cardiomyopathy (4 out of 6 DCM patients).

4. In case of propafenone and pilsicainide administration, patients who had f-QRS 100 ms before drug administration and/or excess prolongation of f-QRS(≧20%) after administration the antiarrhythmic efficacy tended to be low.
This effect was also observed in the case of the administration of disopyramide and flecainide, but in patients with initial f-QRS 120 ms and f-QRS prolongation (20%) after administration.
Mexiletine had no significant effect on f-QRS, and we could not find any relationship between f-QRS and the drug efficacy.

DISCUSSION:

In case of disopyramide, this agent caused significant prolongation of f-QRS in almost all cases. The RMS40 was also markedly decreased in most of the patients. These results correlate with the previous results of other authors. The magnitude of the drug-induced change in the SAECG is a reflection of the magnitude of the sodium channel blockade[4].
Already in 1992, Kulakowski studied the predictability of antiarrhythmic efficacy of procainamide, which is also a Class Ia agent. He stated that the change in the total QRS duration was similar in patients in whom arrhythmia became non-inducible and in patients in whom ventricular tachycardia was still inducible[4,5].
This is in contrary to our results, which suggests that the drug efficacy can be predicted by analyzing the changes of SAE findings.
Mexiletine, which dissociates rapidly from cardiac sodium channels seemed not to

change any of its time-domain parameters in our study. But the studies of other authors suggest that probably it depends on the heart rate. For example, J.K.Lee studied patients with implanted pacemakers[4]. At a heart rate less than 120, lidocaine (class Ib as mexiletine) had no significant effect on the QRS duration, however at higher pacing rates, prolongation of the QRS duration by lidocaine had occurred[4,9].
The administration of flecainide in our study prolonged the f-QRS and decreased the RMS40 more than disopyramide. Is important, as this agent shows a similar relationship to f-QRS as Ia class disopyramide - if f-QRS was longer than 120 ms prior to administration and/or excessively prolonged after the administration, the drug's efficacy would be lower. Therefore, in the cases of disopyramide and flecainide, the evaluation of drug-induced changes of SAE may be useful not only for categorizing the antiarrhythmic agent, but for predicting antiarrhythmic efficacy on VPC as well[8-10].
Also administration of propafenone caused marked changes in the parameters of signal-averaged electrocardiogram confirming that slowing of the intramyocardial conduction velocity is one of the effective mechanisms of this drug[11].

Pilsicainide is a lidocaine derivative that was developed in Japan. It suppresses the maximal rate of increase (V max) of the action potential in atrial and ventricular tissue. It has very slow kinetics (similar to flecainide) and increases both rest and exercise duration of QRS (Sadanaga). During exercise, this prolongation of QRS is rate dependent.
It is important to recall that particularly Ic antiarrhythmic drugs have been shown to induce proarrhythmias in an unpredictable number of patients. It has been reported by Cardiac Arrhythmia Suppression Trial (CAST), that pilsicainide and other Ic agents increased the rate of sudden death in patients with acute myocardial ischaemia (post-myocardial infarction patients)[1,5,7-10]. However, the majority of authors concluded that improved quality of life of patients treated by Ic drugs may outweigh the probable risk of reoccurence of lethal ventricular tachyarrhythmias.

CONCLUSION:

Initially, the main role of the signal-averaged ECG has been the identification of patients withpost-myocardial infarction who are at high risk of sudden death. In 1993, Greenspoon and Kidwell concluded that there is no SAECG parameter (either total QRS, late potential, or frequency content) that appears to be useful in predicting drug efficacy[5,12]. However, as stated above, lately it was discovered that there is predictive

value of this method. The evaluation of drug-induced changes of SAE may be useful not only for the categorizing of anti-arrhythmic agents, but also for predicting anti-arrhythmic efficacy of Class Ia and Ic agents on VPC.

Even now, the antiarrhythmic drugs are sometimes administered in "trial and error" fashion. Therefore, further research of the SAECG - antiarrhythmic agents relationships could be useful.

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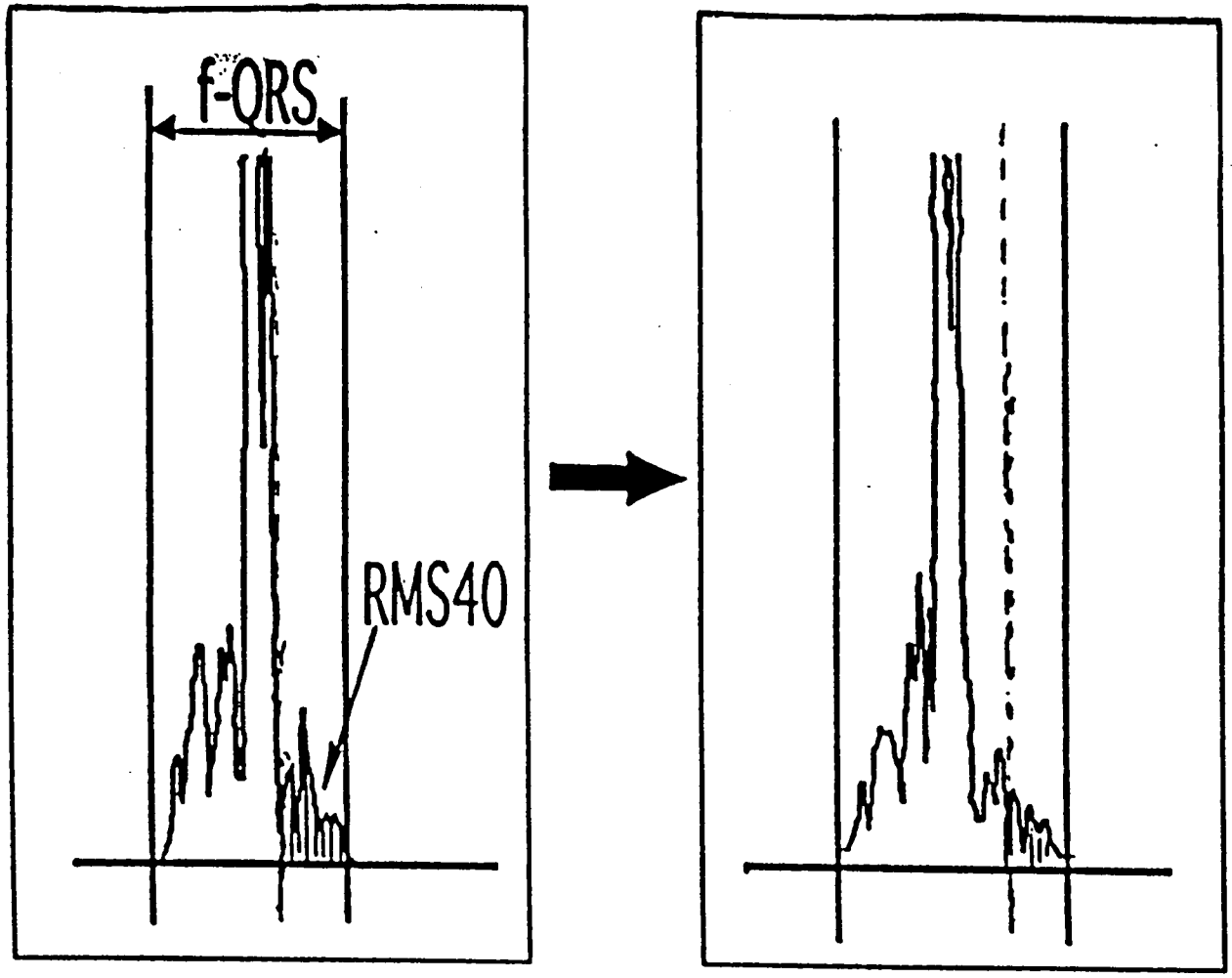
Figure 1. The SAE record obtained from a patient who was administered the DP. After DP administration, f-QRS prolonged from 99 to 114ms, RMS40 decreased from 325 to 254 uV.

Figure 2. The change of f-QRS before and after administration of Class I AA agents. (●) means that the drug was effective, (X) indices indicates ineffectiveness. After oral administration of DP, FL, PF and PS, the f-QRS was significantly prolonged. Such prolongation cannot be observed in case of MX.

Figure 3. The changes of RMS40 before and after administration of Class I AA agents. (●)means that the drug was effective, (X) indices ineffectiveness. After administration of DP, FL, PF and PS the RMS40 markedly decreased. In the case of MX, the decrease was only slight.

Figure 4. Here is displayed the f-QRS in combination with drug effectiveness. The X-axis represents the duration of f-QRS, Y-axis represents the change of f-QRS. (●) means that the drug was effective, (X) indices equals ineffectiveness. If f-QRS was more than 120ms before drug administration and/ or there was excess f-QRS prolongation 20% after administration, the therapeutic effectiveness tended to be low.



before DP
300mg p.o.
f-QRS 99msec
RMS_{40} 325 μV

after DP
300mg p.o.
f-QRS 114msec
RMS_{40} 254 μV

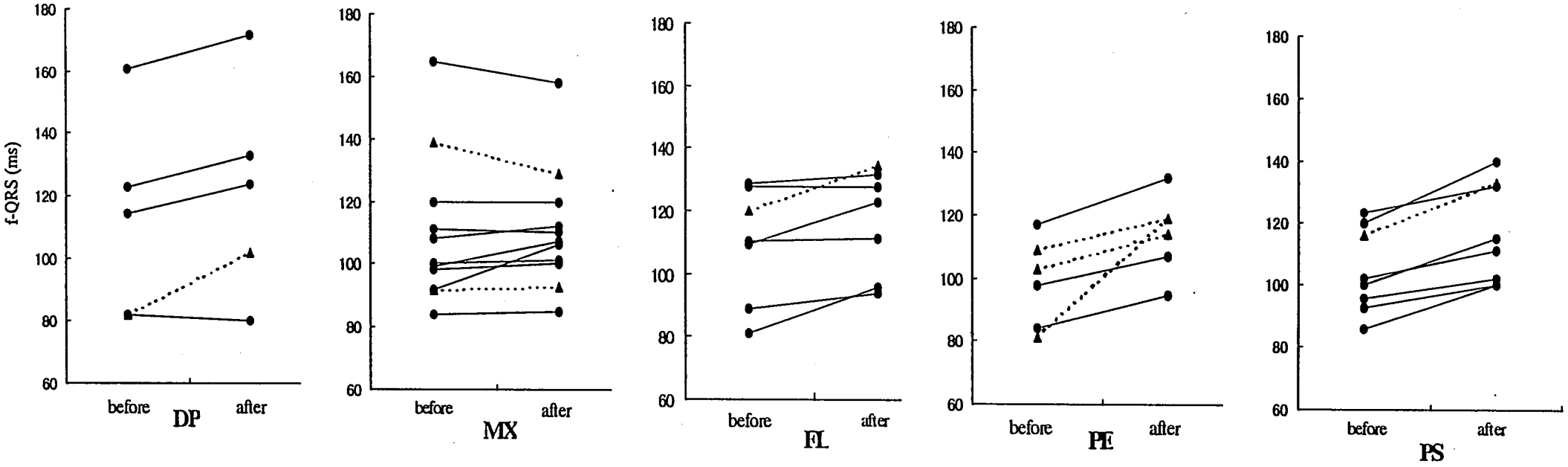


FIGURE 2.

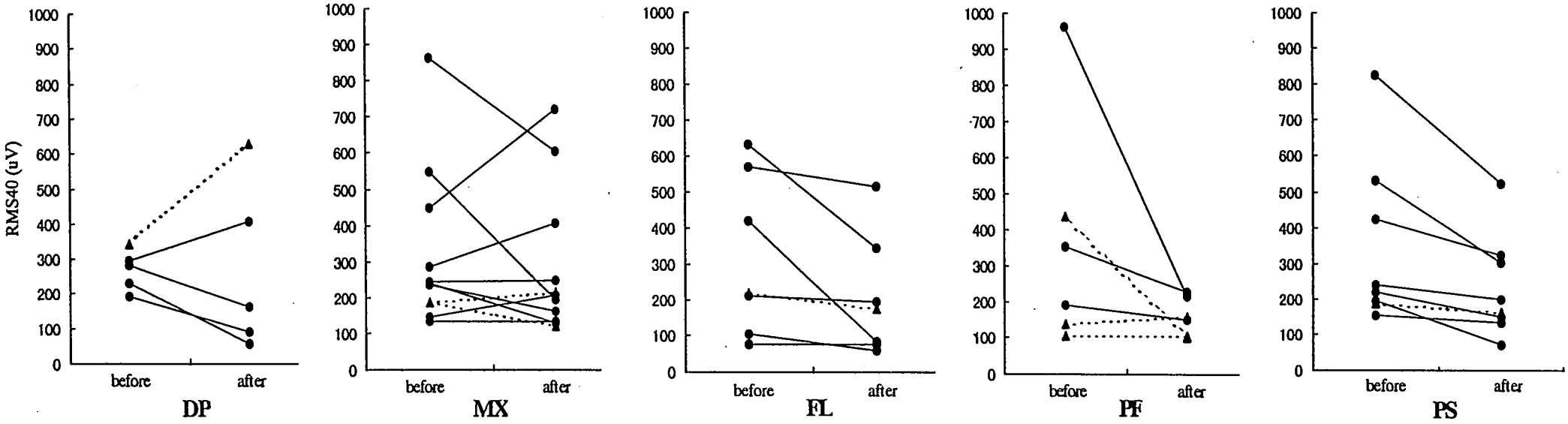

RMS40 (uV)
1000
900
800
700
600
500
400
300
200
100
0
before
after
DP
MX
FL
PF
PS

FIGURE 3.

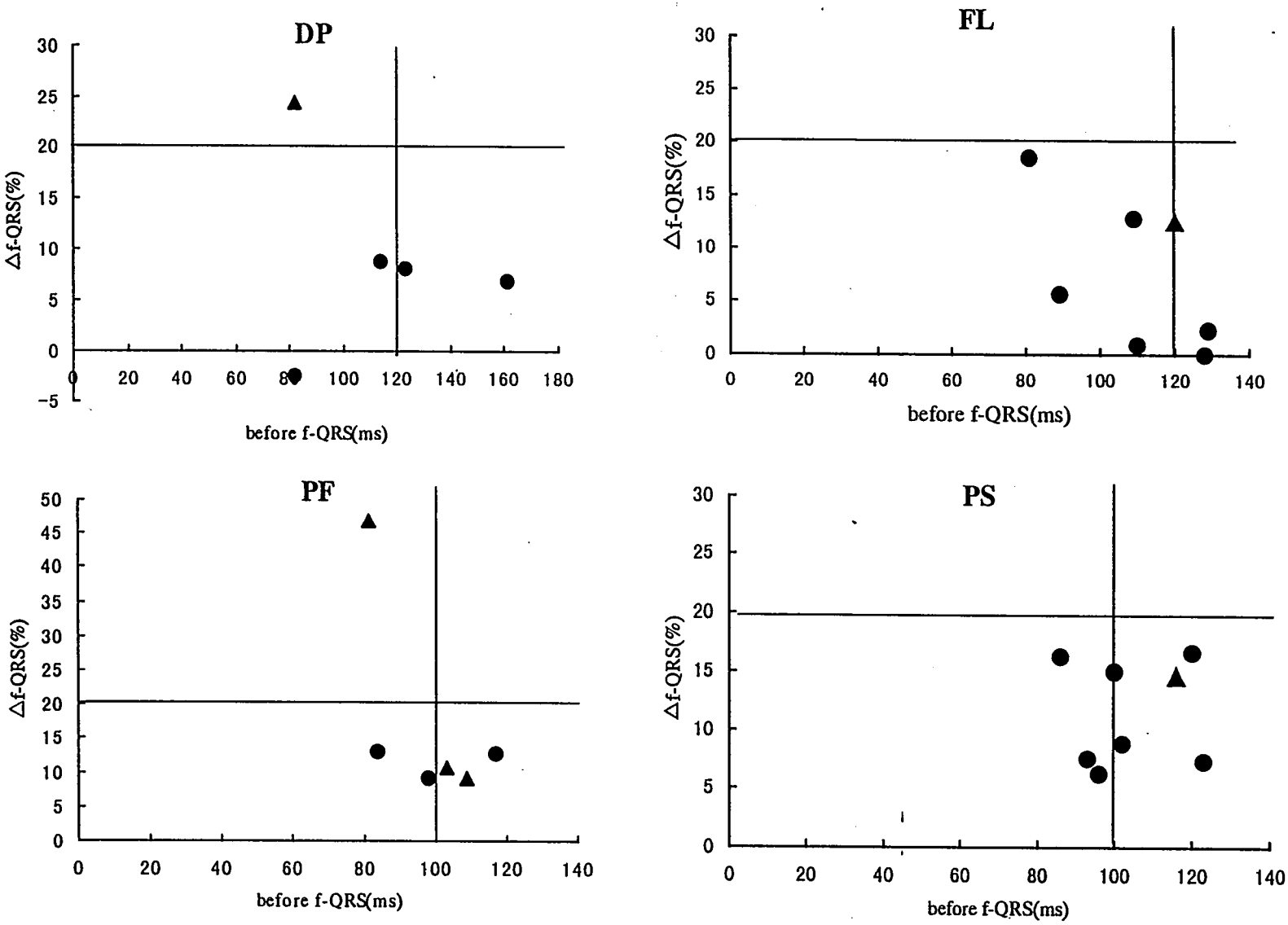


FIGURE 4.