Papaverine-Induced Polymorphic Ventricular Tachycardia in Relation to QTU and Giant T-U Waves in Four Cases

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Abstract

Objective Papaverine is used for the evaluation of functional status of the coronary arteries but it may provoke severe ventricular tachyarrhythmias (VTAs). This study compared the clinical and ECG characteristic of patients with papaverine-induced VTAs.

Materials and Methods The study involved 25 patients who underwent a fractional flow reserve (FFR) study. FFR was determined as the ratio of blood pressure at the distal and the proximal site of stenosis after intracoronary papaverine administration at 12 mg into the left and 8 mg into the right coronary artery. The QT and QTU intervals were measured manually in the limb leads and in the precordial leads, respectively and corrected by the R-R interval to obtain QTc and QTUc. The clinical and ECG data were compared between the patient groups with and without VTAs.

Results After papaverine administration into the left (20), right (3) or both coronary arteries (2), the RR interval shortened, but non-significantly however, the QT interval (and QTc) and the QTU interval (and QTUc) were significantly prolonged. VTAs developed in four women: torsade de pointes in 3 followed by ventricular fibrillation and ventricular premature beats in 1 patient. After papaverine administration, QTU and QTUc were more prolonged in women than men and in patients with VTAs compared to those without. Just prior to VTAs, giant T-U waves were observed.

Conclusion Intracoronary papaverine was used to determine FFR which may induce VTAs. VTAs developed only in women and they were closely related to prolongation of the QTU intervals with prominent T-U waves.

Key words: papaverine, QT interval, QTU interval, U waves, coronary artery stenosis

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Introduction

The coronary fractional flow reserve (FFR) is defined as the ratio of maximal flow in the stenotic territory to the maximal flow in the same area but without stenosis; it is also estimated from coronary artery pressure measurements (1). The vessel with FFR<0.80 is considered to be functionally impaired and an indication for percutaneous coronary intervention (PCI). After FFR-guided PCI, the one-year death rate, nonfatal myocardial infarction, and incidence of composite endpoint of revascularization reinforcement were significantly reduced (2-5).

To induce maximal hyperemia, adenosine, adenosine-triphosphate (ATP) or papaverine have been used (4, 6, 7). Papaverine hydrochloride is easy to administer intracoronary and results in a steady-state of hyperemia of durations up to 15 sec, however this drug may provoke ventricular tachyarrhythmias (VTAs) (6, 8-13). Recently we encountered 4 patients in which VTAs developed during the FFR study and
predictors of VTAs were analyzed from the clinical and ECG findings.

Materials and Methods

This study involved 25 (15 males) patients who underwent coronary angiography and were shown to have multiple vessel diseases. FFR was measured to determine the functional impairment and indications for PCI at the Tachikawa General Hospital, from February 2008 to August 2011. The mean age was 67.0 ± 11.2 years. All were diagnosed with angina pectoris and significant stenosis was observed in multiple vessels.

Catheterization and FFR study

After written informed consent was obtained, baseline coronary angiography was performed. Inclusion for the FFR study was when the patients had stenosis of 50-75% in either of the three coronary arteries. A pressure wire (Pressure Wire, Radi Medical Systems, Wilmington, MA, USA) was passed through the stenotic lesion and blood pressure was recorded by a pull-back method simultaneously with blood pressure at the ostium of the coronary artery through a guiding catheter.

Maximal dilatation was induced by papaverine hydrochloride given into the coronary artery: 12 mg into the left and 8 mg into the right coronary artery in 15 sec duration and at 15 sec after the end of administration, then blood pressure was recorded. FFR was calculated as the mean distal coronary pressure divided by the mean aortic pressure through the guiding catheter. FFR <0.80 was considered functionally impaired and an indication for stenting therapy.

ECG measurements

ECG was monitored during the whole study and any arrhythmias were recorded. The basic rhythm, the RR, QT and QTU intervals were measured at baseline and after administration of papaverine.

The QT intervals were measured manually in the standard manner in limb lead (usually in II) by two cardiologists. The QTU intervals were also measured in the precordial lead which showed the clearest U waves. The QT and QTU intervals were then corrected by the RR intervals for QTc and QTUc, respectively.

Data analysis

All baseline clinical parameters and FFR were obtained for each patient. The ECG parameters were compared before and after administration of papaverine and the incidence and type of arrhythmia was determined.

The patients were divided into two groups: those with and without VTA during the FFR study and the clinical data and ECG tracings were compared. Sub-analysis was undertaken among the female patients.

Statistical analysis

The numerical values were expressed as the mean ± SD and compared using the appropriate t-test. Categorical data was expressed as percentages and compared using the Chi-square test. P values that were less than 0.05 were considered significant.

For statistical analysis, we used JMP software (Statistical Discovery Software, version 5.0.1J. SAS Institute. Cary, NC, USA). This study was approved by the Institutional Review Board of the Tachikawa Medical Center.

Results

The clinical characteristics

The clinical characteristics are shown in Table 1. Ten patients were female. Routine laboratory findings were all within normal ranges. Baseline coronary angiography showed significant stenotic lesions of the coronary arteries of >75% in all patients and the mean left ventricular ejection fraction was 49.0 ± 8.3%. Papaverine was administered into the left (n=20), right (n=3), and both coronary arteries (n=2). The mean FFR was 0.825 ± 0.121.

ECG changes and arrhythmias

The RR interval shortened slightly but non-significantly from 935 ± 178 ms to 876 ± 142 ms after papaverine administration (p=0.2033). Both the QT interval and QTc were normal at baseline but were significantly prolonged from 450 ± 47 ms/sec to 571 ± 111 ms and from 452 ± 46 ms to 611 ± 91 ms/sec respectively (p<0.0001 for both). The QTU and QTUc were significantly prolonged from 584 ± 113 ms to 667 ± 162 ms (p=0.0436) and from 608 ± 113 ms to 713 ± 143 ms/sec (p=0.0063), respectively. There was a significant gender difference in QTU and QTUc: 0.603 ± 0.106 ms vs. 0.730 ± 0.180 ms and 0.644 ± 0.088 ms/sec vs. 0.789 ± 0.142 ms/sec for males and females, respectively (p=0.0305 and p=0.0033).

VTAs developed in 4 patients following intracoronary papaverine into the left coronary artery. Torsade de pointes (TdP) developed in three patients and degenerated to VF in two which were successfully defibrillated (Fig. 1, 2). In another patient, premature ventricular beats up to couplets were observed (Fig. 3). Just prior to VTAs, the T and U waves were augmented and formed giant T-U waves (Fig. 1-3).

Predictors of VTA

Four female patients developed VTAs at the time of the peak action of papaverine. There was no difference in the clinical data except for body weight which was lighter in the patients with VTAs than those without: 50.5 ± 7.9 vs. 62.1 ± 10.0 Kg (p=0.0391). This would be due to the fact that VTAs developed only in females. The distribution of diseased coronary arteries or left ventricular ejection fraction
was not different between the two groups with and without VTAs. Among ECG parameters, QTU and QTUc were more prolonged in the patients with VTAs treated by papaverine (p=0.0136 and 0.0005, respectively) (Table 2).

Among female patients, diseased coronary arteries, the distribution pattern of diseases vessels, left ventricular ejection fraction, body weight and doses of papaverine were not different between the two female groups with and without VTAs. FFR was not different between them: 0.82 ± 0.0 vs. 0.87 ± 0.07 (p=0.3905).

At baseline, the QT and QTc were similar between the females with and without VTA and after papaverine, QTc was shorter in the former: 512 ± 36 ms\(^1/2\) vs. 624 ± 35 ms\(^1/2\) (p< 0.0226). The baseline QT and QTU were similar between the two groups and only QTUc was more prolonged after papaverine in the group with VTAs: 952 ± 224 ms\(^1/2\) vs. 730 ± 48 ms\(^1/2\) (p=0.0182).

Though, VTAs occurred when papaverine was given into the left coronary artery, the QT (QTc) and QTU (QTUc) and their responses were similar between the patients with papaverine given into the right or left coronary artery at baseline and after the drug.

### Discussion

Intracoronary papaverine prolonged the QT interval in every patient and polymorphic VT and VF occurred in 3 and couplets of ventricular premature beats in 1 out of 25 patients: in 4/25 (16%). The baseline clinical and ECG parameters were similar between the patients with and without VTAs, but the patients with VTAs were all female. QT and QTc were not different between the two subgroups with or without VTAs but, the patients with VTAs showed excessively prolonged QTU intervals and giant T-U waves. The

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**Table 1. Clinical Characteristics**

<table>
<thead>
<tr>
<th>Number of patients (male)</th>
<th>25(15)</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>67.0±11.2</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>60.7±10.5</td>
</tr>
<tr>
<td>Body height, cm</td>
<td>157±9</td>
</tr>
<tr>
<td>BMI</td>
<td>24.4±3.3</td>
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**Laboratory data**

| Na, meq/L                  | 140.9±1.9 |
| K, meq/L                   | 4.16±0.37 |
| Cl, meq/L                  | 104.4±2.8 |
| WBC, /μL                   | 5912±1555 |
| Hb, g/dL                   | 13.3±1.6 |
| CRP, mg/dL                 | 0.27±0.45 |

**Diseased vessels, number (% stenosis)**

| LAD                        | 22(72.5±20.8) |
| LCX                        | 15(72.7±20.1) |
| RCA                        | 16(64.0±24.9) |
| LM                         | 4(62.5±14.4)  |

**Left ventricular ejection fraction**

49.0±8.3

**Medical history,**

| Obesity (BMI ≥ 25kg/m\(^2\)) | 9(36.0) |
| Hypertension                | 22(95.7) |
| Diabetes mellitus           | 10(43.5) |
| Dyslipidemia                | 14(60.9) |
| Smoking                     | 16(69.6) |


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**Figure 1. Development of torsade de pointes (TdP).** The patient was a 67-year-old female. The control ECG shows normal sinus rhythm and normal atrio-ventricular and intraventricular conduction (control). Flat T waves were seen in limb and precordial leads. Small U waves are also seen in V3 and V4. After papaverine, prominent negative U waves appeared in leads I, aVL and V2 to V6 as indicated by the arrow (Papaverine-1). Ventricular tachycardia with changing QRS morphology developed (Papaverine-2) and led to ventricular fibrillation. Normal sinus rhythm was obtained by DC shock. The initial beat of ventricular tachycardia occurred at the ascending limb of the prominent U waves (arrowhead).
Figure 2. Prolonged QTU and development of torsade de pointes (TdP). The patient was a 76-year-old female. After papaverine, negative T and U waves were considered to be fusion in leads I and aVF. Lead II shows a positive U wave on the descending limb of T. The third QRS complex was not preceded by P wave and junctional escape beat by which the RR interval was prolonged. The T-U complex was prominent and was considered as pause-dependent augmentation. The first beat of TdP emerged at the ascending (I, aVF) or descending (II) limb of T-U waves. TdP was followed by ventricular fibrillation and the patient received DC shock delivery.

Figure 3. Prolonged QTU and development of a premature ventricular beat. The patient was 78-year-old female. Prolonged QT and QTU were evident. A pause following the premature atrial beat resulted in the prolonged RR interval which augmented the QTU and T-U waves. A premature ventricular beat emerged on the T-U waves (arrow).

Prolonged QTU and/or giant T-U waves can be a marker of VTAs during FFR studies using papaverine.

FFR-guided PCI has been shown to yield beneficial long-term outcomes in patients with multiple vessel disease and FFR studies have become popular (3-5). To obtain proper FFR, it is essential to induce maximal coronary flow and adenosine, ATP or papaverine have been used (14, 15). Among the three drugs, papaverine hydrochloride has some advantages; it can be administered intracoronary, resulting in a relatively steady-state of hyperemia (6, 7).

Intracoronary papaverine is known to prolong the QT interval and though infrequent, it may induce VTAs: TdP with or without subsequent VF (6-13). The incidence of VTAs was reported in the literature to range from <0.67% to 8.8% when papaverine was given intracoronary at doses of 6 mg to 20 mg (7-16).

Gender (female) (8, 9), hypokalemia and alkalosis (8, 12) have been suggested as risks for VTAs after papaverine administration but, the ECG characteristics of the patients who develop VTAs have been poorly elucidated to date. The pre-
sent study showed that excess prolongation of QTU or giant T-U waves was a risk for VTAs following intracoronary papaverine administration.

The genesis of U waves or the mechanism of its prolongation has not been fully elucidated (17), but the prolonged QTU interval is known to provoke bradycardia-dependent early after-depolarization (EAD) (18). Intracardiac catheter mapping has shown an intimate relationship between “humps” on the shoulder of monophasic action potential and EAD when the QT or QTU intervals are prolonged excessively (19-23). The first beat of TdP, a characteristic polymorphic ventricular tachycardia develops in association with the prolonged QT (or QTU) interval (24) and is considered to be “triggered activity” due to EAD (25).

Kirschhof et al found that the first TdP beat emerges from abnormal T-U waves which are larger than any other repolarization waves in the available ECGs and are not found before other types of premature ventricular beats (26). This was confirmed on the ECG tracings of patients with acquired or congenital long QT syndrome. Earlier workers (12, 15), found that papaverine induced U waves and in the present study, the drug was confirmed to induce TdP in association with marked prolongation of the QTU and prominent T-U waves.

Regarding safety, a dose-adjustment of papaverine might be recommended in females of small body weight and hyperkalemia or alkalosis should be excluded before the administration (8, 16). During the examination, ECG monitoring will be essential to avoid excessive prolongation of the QTU interval in the precordial leads.

**Limitation**

The number of patients who developed VTAs during the FFR study was small, but as common ECG findings, VTAs are often associated with excessive QTU prolongation or giant T-U waves (6-13). VTAs occurred more often in our FFR study than that of earlier workers (7-16) however the exact reason was not clarified. Whether the patients with papaverine-induced QT or QTU prolongation have a particular genetic background or not was not studied and a genetic screening test of these patients would be warranted (27).

## Conclusion

Intracoronary papaverine induced VTAs during the FFR study. VTAs developed only in females and were closely related to prolonged QTU or prominent T-U waves but not to the QT interval.

The authors state that they have no Conflict of Interest (COI).

## References

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