Papaverine-Induced Polymorphic Ventricular Tachycardia During Coronary Flow Reserve Study of Patients With Moderate Coronary Artery Disease
– Analysis of ECG Data –
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Background: Papaverine is useful for evaluating the functional status of a coronary artery, but it may provoke malignant ventricular arrhythmia (VA). The aim of this study was to investigate the incidence, and clinical and ECG characteristics of patients with papaverine-induced VAs.

Methods and Results: The 182 consecutive patients underwent fractional flow reserve (FFR) measurement of 277 lesions. FFR was determined after intracoronary papaverine administration by standard procedures. The clinical and ECG characteristics were compared between patients with and without ventricular tachycardia (VT: ≥3 successive premature ventricular beats (PVBs), or ventricular fibrillation (VF)). After papaverine administration, the QTc interval, QTUc interval, and T-peak to U-end interval were prolonged significantly. Single PVBs on the T-wave or U-wave type developed in 29 patients (15.9%). Polymorphic VT (torsade de pointes) occurred in 5 patients (2.8%), and of those, VF developed in 3 patients (1.7%). No clinical and baseline ECG parameters were predictors for VT or VF except for sex and administration of papaverine into the left coronary artery. Excessive prolongation of QT (or QTU), T-peak to U-end intervals and giant T-U waves were found immediately prior to the ventricular tachyarrhythmias (VTAs), which were unpredictable from the baseline data.

Conclusions: Intracoronary administration of papaverine induced fatal VTAs, although the incidence is rare. Excessive prolongation of the QT (and QTU) interval appeared prior to VTAs; however, they were unpredictable. (Circ J 2015; 79: 530–536)

Key Words: Coronary fractional reserve; Papaverine; QT interval; Ventricular tachyarrhythmia

Fractional flow reserve (FFR) measurement is considered the golden standard for assessing the physiologic status of moderate coronary artery stenosis, and is indispensable for decision making in coronary revascularization. FFR-guided percutaneous coronary intervention (PCI) has been shown to result in more favorable outcomes compared with angiography-guided PCI in patients with coronary artery disease.

To induce maximal hyperemia, which is mandatory for FFR measurement, adenosine, adenosine triphosphate (ATP), or papaverine is used. Flushing, chest pain, and vasospasm are reported as adverse effects of adenosine; ATP can cause bradycardia or an attack of bronchial asthma; papaverine is easy to administer into the coronary artery and induces a steady state of hyperemia with a duration >60 s, but this drug may provoke ventricular tachyarrhythmia (VTA).

Previously, we reported the ECG characteristics of patients who developed papaverine-induced ventricular fibrillation (VF) during FFR measurement. In this report, we present the incidence of papaverine-induced ventricular arrhythmias (VAs) and the characteristics of the patients who developed VA during FFR measurement at Tokyo Medical
University Hospital and an affiliated hospital, Toda Central General Hospital.

Methods

This study was approved by the Institutional Review Boards of Tokyo Medical University Hospital and Toda Central General Hospital.

Study Subjects

Among the patients who had undergone coronary angiography (CAG) and were shown to have significant stenotic lesion (≥75% stenosis) at Tokyo Medical University and Toda Central General Hospitals between January 2012 and February 2013, 182 consecutive patients were enrolled in the present study. All of them had additional lesion of moderate stenosis (50–75%) in the proximal site of the coronary artery and coronary flow reserve (FFR) measurements were performed to guide PCI.

Catheterization and FFR Measurement

After obtaining written informed consent, FFR measurement was performed as reported previously. Briefly, a pressure wire (PressureWire, St. Jude Medical, MN, USA; PrimeWire, Volcano Corp, CA, USA) was passed through the stenotic lesion, and papaverine was administered into the coronary artery: 12 mg to the left coronary artery (LCA) and 8 mg to the right coronary artery (RCA), which induced maximal dilatation within 15 s. At 15 s after papaverine administration, intracoronary blood pressure (BP) was measured by the pull-back method.

FFR was calculated as the mean coronary BP distal to the stenosis divided by the mean aortic pressure through the guiding catheter. An FFR value <0.80 was considered an indication for PCI. When papaverine had to be administered repeatedly, it was given at intervals of 2 min or longer.

ECG Measurement

ECG was continuously monitored and any arrhythmia was recorded during the study. The RR, PQ, QT, and T-peak to T-end intervals were measured at baseline and at the peak effects after papaverine administration. When papaverine resulted in formation of a T-U wave, QTU and T-peak to U-end intervals were measured (Figure 1).

QT interval was measured manually by tangent methods in limb leads (usually in II, but when inappropriate, in other leads). The QTU intervals were measured in the precordial leads that showed the maximal U-waves. To obtain corrected QT and QTU intervals, the QT and QTU intervals were corrected by the Bazett formula. The amplitudes of T-waves and U-waves were also measured (Figure 1). The ECGs were read by 2 cardiologists, and when there was a discrepancy in the diagnosis, it was discussed until agreement was reached.

Data Analysis

The baseline clinical characteristics, including the number and sites of stenotic lesions, were determined. Hypertension, diabetes mellitus, and dyslipidemia were diagnosed according to relevant criteria, or whether the patient was receiving treatment.

ECG parameters were measured and compared before and after the administration of papaverine, as well as compared between the sexes. The incidence of each VA was determined and the clinical features were compared between patients with and without ventricular tachycardia (VT) or VF.
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Table 2. ECG Parameters at Baseline and After Papaverine Administration in Patients Undergoing Fractional Flow Reserve Measurement (n=182)

| Parameter                          | Baseline        | After papaverine | P value |
|------------------------------------|-----------------|------------------|---------|
| R-R interval, ms                   | 960±87          | 941±89           | <0.001  |
| PQ interval, ms                    | 181±49          | 177±48           | 0.037   |
| QT interval, ms                    | 336±80          | 339±91           | 0.112   |
| QTc interval, ms\(^{1/2}\)         | 465±64          | 576±966          | 0.058   |
| QTU interval, ms\(^{1/2}\)        | 516±113         | 620±114          | <0.001  |
| QTUC interval, ms\(^{1/2}\)       | 536±12          | 640±104          | <0.001  |
| T-peak to U-end interval, ms       | 181±93          | 265±91           | <0.001  |
| T-wave amplitude, mV               | 0.382±0.362     | 0.317±0.371      | <0.001  |
| U-wave amplitude, mV               | 0.018±0.013     | −0.089±0.311     | <0.001  |

Table 3. Comparison Between the Sexes Regarding ECG Parameters at Baseline and After Papaverine Administration in Patients Undergoing Fractional Flow Reserve Measurement

| Parameter                          | Men (n=150) Before/After | Women (n=32) Before/After | Male/Female | Before/After |
|------------------------------------|--------------------------|---------------------------|-------------|-------------|
| R-R interval, ms                   | 960±87/941±90            | 960±85/940±81             | <0.001/0.003| 0.946/0.825 |
| PQ interval, ms                    | 181±50/177±49            | 173±44/177±46             | 0.007/0.204 | 0.299/0.926 |
| QT interval, ms                    | 450±67/504±570           | 428±60/456±95              | 0.147/0.069 | 0.052/0.577 |
| QTc interval, ms\(^{1/2}\)        | 469±65/593±105           | 447±58/487±99              | 0.073/0.19  | 0.040/0.498 |
| QTU interval, ms \(^{1/2}\)       | 512±112/596±114          | 538±120/636±109            | <0.001/0.001| 0.166/0.028 |
| QTUC interval, ms \(^{1/2}\)      | 533±109/633±105          | 562±125/676±94             | <0.001/0.001| 0.120/0.011 |
| T-wave amplitude, mV               | 4.15±3.72/3.58±3.57      | 2.08±2.38/1.09±3.78        | <0.001/0.060| 0.120/0.011 |
| U-wave amplitude, mV               | 0.27±0.09/−0.81±3.00     | −0.26±2.23/−1.32±3.8       | <0.001/0.055| 0.014/0.318 |
| T-peak to U-end, ms               | 175±93/258±88            | 211±87/302±97              | <0.001/0.001| 0.017/0.003 |

*Comparisons before and after papaverine in each sex. #Sex difference in ECG parameters before and after papaverine.

ship between VT/VF and the route of administration and dose of papaverine was also analyzed.

Definitions
Premature ventricular beat (PVB) was defined as a single or couplet of PVBs. VT was defined as 3 or more successively occurring PVBs, and was classified as monomorphic or polymorphic by the QRS morphology. Sustained VT was defined as lasting more than 30s or requiring immediate termination because of hemodynamic deterioration. VF was fibrillation showing bizarre, chaotic electrical activity.

Statistical Analysis
Numerical data are expressed as mean±SD. The paired or unpaired t-test and the Whitney-Wilcoxon test were used for comparisons. Categorical data are expressed as percentages or absolute numbers and were compared by the chi-squared test. P<0.05 was considered to indicate a statistically significant difference between groups. The SPSS software (SPSS 19; IBM Corporation, Chicago, IL, USA) was used to perform statistical analyses.

Results
Clinical Characteristics of the Patients
The 182 patients underwent a FFR study for 277 lesions, and their clinical characteristics are shown in Table 1. The mean age was 68±10.7 years, and 150 (82.4%) were men. The patients’ laboratory data were normal, and the majority had hypertension, diabetes mellitus, or dyslipidemia. More than half the patients were current smokers. Their left ventricular ejection fractions were normal (62.3±9.6%). CAG revealed moderate stenosis of 50–75% in 277 coronary sites, most often in the left anterior descending (LAD) artery (n=217).

ECG Changes
After standard CAG, papaverine was administered into the LCA (n=217) or RCA (n=60) for measurement of FFR. The RR and PQ intervals were significantly shortened after papaverine administration (Table 2). QT and QTc, QTUC and T-peak to U-end interval were significantly prolonged after papaverine administration. The T-wave and U-wave amplitudes were increased after papaverine administration, and formation of a large T-U wave was observed in 73.7% and 44.7% of patients when papaverine was administered into the LCA and RCA, respectively, but more often in the LCA (P=0.011).

Differences Between the Sexes Regarding ECG Changes
After papaverine, RR interval shortened significantly in both sexes, and PQ in males (Table 3). QT did not alter significantly, but QTc, QTU, and QTUC were prolonged in both sexes. T- and U-wave amplitudes became smaller in males. T-peak to U-end interval was prolonged in both sexes. The baseline ECG parameters were not different between the sexes except for QTc, U-wave amplitude and T-peak to U-end interval. In females, QTU, QTU and the T-peak to U-end interval were more prolonged, and T-wave amplitude smaller after papaverine.
Papaverine-Induced VTAs

PVBs (all single) developed during FFR measurement in 29 of the 182 patients (15.9%): in the RCA (n=7) and in the LCA (n=22) (Figure 2A). Polymorphic VT developed in 5 patients (2.7%), and of those, 3 were female. VT degenerated into VF in 3 patients (1.6%) (Figures 2B,3). VT/VF developed after administration of papaverine into the LCA, but not into the RCA. The doses of papaverine were similar between patients with and without VT/VF: 0.194±0.034/kg with and 0.158±0.044/kg without VT/VF, respectively (P=0.127).

The baseline ECG parameters were not different between the patients with and without VAs. However, the QTU interval was longer after papaverine administration in the patients with PVBs (n=29) compared with those without PVBs (n=248), and was most prolonged in the 5 patients with VT/VF (Figure 4). The T-peak to U-end interval was significantly longer in patients with VT/VF than in those with single PVB and those without PVB. The U-wave was deeper in the VT/VF patients compared with the other 2 groups.

Discussion

We measured the FFR in 182 patients (277 lesions) with stable angina pectoris. At the time of the peak action of papaverine, a single PVB developed in 29 patients (15.9%). Polymorphic VT (≥3 beats) occurred in 5 patients (2.7%), 3 of whom were female, and followed by VF in 3 patients (1.6%). There was no baseline ECG predictor for VT/VF, but papaverine induced a remarkable, deep T-U wave formation in the patients with VT/VF. The QTU and T-peak to U-end intervals were most prolonged in patients with VT/VF. The QTU interval was also longer in the patients with PVBs compared with those without any VA. We should pay attention to these ECG features to avoid possible VT/VF when papaverine is administered into the LAD for FFR study.

Incidence and Mechanisms of VA

The incidence of papaverine-induced VT-VF has not yet been clarified. Some of the previous reports are only case reports, and in others, the incidence of VT/VF ranges from 2.3% to 8.8% when papaverine was administered into the coronary artery at 6–20 mg. In one of these reports, papaverine was administered for FFR study in 102 patients and polymorphic VT was induced in 3 (1.9%); QT interval prolongation and poor coronary reserve were considered risks for VT. The incidence of VF in the present study was similar to that reported earlier: 3 (1.6%) among 182 patients.

Following intracoronary papaverine administration, prolongation of the QT and QTU intervals was common, and PVBs might lead to polymorphic VT showing the characteristics of torsades de pointes (TdP) which is known to occur in association with prolongation of the QT (or QTU) interval.
sic action potential. Papaverine-induced PVB or VT is thought to be caused by the same mechanism as in acquired or congenital long QT syndrome.

Knowledge of the electrophysiological action of papaverine

Figure 3. Torsades de pointes followed by ventricular fibrillation. Baseline QT and QT intervals of 380 ms and 450 ms are greatly prolonged to 530 ms and 625 ms, respectively. T-waves and U-waves merge to form giant T-U waves.

Figure 4. Papaverine-induced changes in QTUs, T-peak to U-end interval, and U-wave amplitudes in patients with and without ventricular tachyarrhythmia (VTA). At baseline, there is a non-significant difference in the QTU, T-peak to U-end interval, and U-wave amplitude. After papaverine administration, these parameters are significantly different among the groups, and the QTU was more prolonged in the patients with VTA compared with those without.

Development of PVB or TdP induced by excessive QT prolongation is considered to be attributable to early after-depolarization (EAD) and a close relationship is observed between EAD and “humps” on the shoulder of the monophasic action potential. Papaverine-induced PVB or VT is thought to be caused by the same mechanism as in acquired or congenital long QT syndrome.

Knowledge of the electrophysiological action of papaverine
on cardiac ion channels is limited; however, papaverine does inhibit the rapid component of the delayed rectifying potassium current: IKr.33 Recently, we encountered a patient demonstrating papaverine-induced long QT and VF, who had a history of bepridil-induced QT prolongation.39 Bepridil is known to exert an inhibitory action on IKr.40 Therefore, it is likely that papaverine acts similarly to class III antiarrhythmic agents, and inhibits IKr of the myocardium.

Predictors of Fatal VT/VF

In the literature we located 27 patients who developed VF by intracoronary papaverine administration.12–21 Of these, 18 (66.7%) were women. All VF’s were induced when papaverine was administered into the LCA, as confirmed in the present study. This suggests that papaverine acting on a larger cardiac mass and at a relatively larger dose are requisites for the occurrence of VT/VF. Another requisite for VT/VF occurrence would be excessive prolongation of the QT(U) and T-peak to U-end intervals, and deep T(U) wave (Figures 2–4). Such excessive QT prolongation is considered to precipitate EAD and VTA.35 Though the baseline QTc, U-wave amplitude and T-peak to U-end intervals were larger in females, but they were not predictors of VT/VF. These ECG parameters were more prolonged by papaverine in females compared with males, and the excessive prolongation of the QTU and T-peak to U-end intervals and the deep T(U) waves in females were associated with VT/VF.

From the reports in the literature and the present study, we might be able to list the parameters that put patients at risk for papaverine-induced VTAs: sex (female), and hypokalemia and alkalosis at baseline. A relatively slow heart rate can be another risk. These parameters are known to be risks for VT or VF in patients having acquired or congenital long QT syndrome.36,37 A history of antiarrhythmic drug-induced QT prolongation might be another risk for papaverine-induced VT/VF.39

Study Limitations

This study involved a limited number of patients. However, we treated the largest number of patients, and the results are comparable to those reported to date. It is unknown whether the patients with papaverine-induced QT prolongation or VT/VF have underlying mutations of cardiac ion channels, particularly in IKr,38 because genetic analysis was not performed.

Conclusions

Intracoronary papaverine administration induced QT (and QTU) prolongation and VF. Excessive prolongation of QT (and QTU) and VT/VF were unpredictable from the baseline data.

Disclosures

None.

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