Clinical Efficacy of Intracoronary Papaverine After Nicorandil Administration for Safe and Optimal Fractional Flow Reserve Measurement

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Summary

Fractional flow reserve (FFR) is considered the standard for assessment of the physiological significance of coronary artery stenosis. Intracoronary papaverine (PAP) is the most potent vasodilator used for the achievement of maximal hyperemia. However, its use can provoke ventricular tachycardia (VT) due to excessive QT prolongation. We evaluated the clinical efficacy and safety of the administration of PAP after nicorandil (NIC), a potassium channel opener that prevents VT, for optimal FFR measurement.

A total of 127 patients with 178 stenoses were enrolled. The FFR values were measured using NIC (NIC-FFR) and PAP (PAP-FFR). We administered PAP following NIC (NIC-PAP). Changes in the FFR and electrogram parameters (baseline versus NIC versus PAP) were assessed and the incidence of arrhythmias after PAP was evaluated. In addition, we analyzed another 41 patients with 51 stenoses by assessing the FFR using PAP before NIC (PAP-NIC). After propensity score matching, the electrogram parameters between 2 groups were compared.

The mean PAP-FFR was significantly lower than the mean NIC-FFR (0.82 ± 0.11 versus 0.81 ± 0.11, P < 0.05). The mean baseline-QTc, NIC-QTc, and PAP-QTc values were 425 ± 37 ms\textsuperscript{1/2}, 424 ± 41 ms\textsuperscript{1/2}, and 483 ± 54 ms\textsuperscript{1/2}, respectively. VT occurred in only 1 patient (0.6%). Although PAP induced QTc prolongation (P < 0.05), the PAP-QTc duration was significantly shorter in NIC-PAP compared to PAP-NIC (P < 0.05).

The administration of PAP with NIC may induce sufficient hyperemia and prevent fatal arrhythmia through reductions in the PAP-induced QTc prolongation during FFR measurement.

Key words: Ventricular tachycardia, QTc prolongation, Coronary artery stenosis, Vasodilator, Hyperemia
arrhythmia development, due to reductions in the rate of PAP-induced QTc prolongation. We aimed to investigate the changes observed in the FFR and electrocardiogram (ECG) parameters at baseline and the use of intracoronary PAP with NIC. Furthermore, we evaluated the occurrence rate of VT during FFR.

Methods

This study was approved by the Institutional Review Board of the University of Occupational and Environmental Health (UOEHCRB20-070) and was conducted in adherence with the guidelines of the 1975 Declaration of Helsinki.

Study participants: This retrospective study was conducted using data from a prospectively maintained database. Between November 2018 and September 2020, consecutive patients aged older than 20 years who had undergone coronary angiography and were diagnosed with intermediate coronary artery stenosis (> 50% stenosis) at The University of Occupational and Environmental Health were enrolled. They underwent FFR measurements to determine their indication of PCI. The exclusion criteria included any of the following: acute myocardial infarction; in-stent restenosis; severe arrhythmia; allergy to PAP or NIC; and stenosis of a previous bypass graft. A total of 127 patients with 178 stenoses measuring FFR with the University of Occupational and Environmental Health Board of the University of Occupational and Environmental Health (UOEHCRB20-070) and was conducted in adherence with the guidelines of the 1975 Declaration of Helsinki.

Catheterization and FFR measurement: Coronary angiography with 5Fr or 6Fr guiding catheters without side holes was performed using either the radial, brachial, or femoral artery approach. Coronary angiograms were recorded after the intracoronary administration of 2-3 mg of isosorbide dinitrate. A 0.014-inch diameter pressure wire (Pressure Wire Verrata, Volcano/Philips, Amsterdam, The Netherlands; Pressure Wire X, Abbott Vascular, Santa Clara, CA, USA; or Pressure Wire Comet, Boston Scientific, Marlborough, MA, USA) was externally calibrated and then advanced through the guiding catheter into the central aorta. Equalization of pressure between the aorta and pressure wire was performed. The pressure wire was advanced across the target stenosis lesion. The FFR was calculated as the mean coronary distal coronary pressure to the stenosis divided by the mean aortic pressure through the guiding catheter during hyperemia.

Hyperemic stimuli: After the confirmation of a suitable pressure wire position distal to the stenosis, the following hyperemic stimuli were administered successively (Figure 1): intracoronary NIC (2 mg to the left coronary artery and right coronary artery) and intracoronary PAP (12 mg to the left coronary artery and 8 mg to the right coronary artery). We first measured the FFR after NIC (NIC-FFR) administration. After blood pressure and heart rate returned to the baseline level, PAP was administered and a second FFR measurement was performed (PAP-FFR). After PAP use, the coronary pressure was measured by the pull-back method. Both NIC-FFR and PAP-FFR values were obtained at the minimal value, and a significant ischemic threshold was defined as that with a value ≤ 0.80.

Angiographic analysis: Quantitative coronary angiography analysis of target lesions after intracoronary nitroglycerin injection was performed using an auto-edge detection algorithm (CAAS QCA 2.0.1, Pie Medical Imaging BV, Maastricht, the Netherlands). The percent diameter stenosis (%DS) was calculated and the minimal luminal diameter (MLD) and the reference diameter (RVD) were measured.

ECG measurement: ECG parameters were continuously monitored, and any occurrence of arrhythmia was recorded during the study. The PQ, RR, QT, and QTU intervals were measured at the baseline and the time of maximal hyperemia achievement following intracoronary NIC and PAP use. The QT and QTU values were measured manually using limb leads (usually in lead II, but when inappropriate, in other leads showing maximal U waves) with the tangent method and the calculated intervals (QTc and QTUc). The QTc and QTUc intervals were corrected using the Bazett formula (QTc = QT/RR^1/2, QTUc = QT element/RR^1/2). The ECG findings were read by 2 cardiologists. If there was a discrepancy in the diagnosis, the cardiologists discussed the results to reach an agreement. QTc prolongation was defined as a QTc interval ≥ 450 ms for men and ≥ 460 ms for women. VT was defined as the presence of 3 or more successively occurring premature ventricular beats, and ventricular fibrillation (VF) as chaotic, random, and asynchronous electrical activity of the ventricle.

Endpoints: The primary endpoint was the comparison of the NIC-FFR and PAP-FFR values in intermediate coronary artery stenosis for the assessment of the effect of intracoronary PAP in the induction of further hyperemia compared to NIC. The secondary endpoints included: (1) changes in the ECG parameters after intracoronary NIC and PAP use, and (2) the incidence of VT after PAP use.

Propensity score matching for additional ECG analysis: We conducted an additional analysis of another 41 patients with 51 stenoses, which were assessed based on the FFR induced by the use of intracoronary PAP before NIC. In these patients, NIC-FFR measurements were performed following PAP-FFR measurements by switching the order of the hyperemic agents. The ECG parameters observed with the use of intracoronary PAP after NIC (NIC-PAP) and before NIC (PAP-NIC) were compared. We used pro-
pensity score matching for the adjustment of potential confounders. Variables included in the model for the comparison between the NIC-PAP and the PAP-NIC were age, sex, body mass index, history of hypertension, diabetes mellitus, dyslipidemia, smoking, acute coronary syndrome, levels of sodium, chloride, and potassium, echocardiographic left ventricular ejection fraction, %DS, MLD, RVD, and baseline ECG parameters for propensity matching. After propensity score matching, 45 pairs were created.

Statistical analyses: All continuous variables are presented as the mean and standard deviation (SD). Categorical variables are presented as counts and percentages and were compared using a chi-squared test. The significance of the differences in continuous variables with two different methods of hyperemia in the same patient group were assessed by the paired t-test. After propensity score matching, continuous variables between NIC-PAP and PAP-NIC were compared using Student’s t-test. A two-sided p value < 0.05 was considered statistically significant. The degree of agreement between the NIC-FFR and PAP-FFR values was analyzed using a Bland-Altman plot, which showed the differences between the FFR values and their means, with reference lines for the mean FFR difference. All statistical analyses were performed using JMP version 13.1.0 (Statistical Analysis System Institute Inc., Cary, NC, USA).

Results

Clinical characteristics: The patients’ characteristics are presented in Table I. Their mean age was 71.9 ± 9.8 years and 97 (76.3%) of the patients were men. Coronary angiography showed the presence of significant stenosis in 178 coronary sites, most often in the left anterior descending artery (60.7%). All laboratory data and left ventricular ejection fraction values were normal. Large percentages of the patients had hypertension (77.1%), diabetes mellitus (49.6%), and hypercholesterolemia (61.4%). A history of myocardial infarction was present in 22.8% of the patients.

FFR changes: The hemodynamic data obtained after the use of intracoronary NIC and PAP are shown in Table II. Heart rate increased after intracoronary NIC and PAP use compared to that at baseline. All the vasodilators produced a significant decrease in blood pressure, but the decrease was significantly more pronounced in association with intracoronary PAP use. The mean FFR after PAP use was lower than that observed following pre-administration of NIC (NIC-FFR 0.82 ± 0.11; PAP-FFR 0.81 ± 0.11; P < 0.001). Figure 2A shows a scatter plot of the FFR values. The NIC-FFR and PAP-FFR values showed a good correlation (r = 0.94, P < 0.001). Bland-Altman analyses were

| Variable | NIC-PAP, n = 178 |
|----------|-----------------|
| Number of patients, n | 127 |
| Number of lesions, n | 178 |
| Sex (male), n (%) | 97 (76.3) |
| Age, years | 71.9 ± 9.8 |
| BML, kg/m² | 18.9 ± 3.5 |
| Target vessel, n (%) | |
| LAD | 108 (60.7) |
| Non-LAD | 70 (39.3) |
| Laboratory data | |
| Hb, mg/dL | 12.7 ± 2.0 |
| Na, meq/L | 140 ± 2 |
| K, meq/L | 4.3 ± 0.5 |
| Cl, meq/L | 104 ± 3 |
| LVEF, % | 50.0 ± 10.3 |
| LVMI, g/m² | 117 ± 40 |
| Clinical diagnosis | |
| Stable angina, n (%) | 81 (63.8) |
| Silent ischemia, n (%) | 46 (36.2) |
| Clinical history | |
| Hypertension, n (%) | 98 (77.1) |
| Diabetes mellitus, n (%) | 63 (49.6) |
| Hypercholesterolemia, n (%) | 78 (61.4) |
| Smoker, n (%) | 23 (18.1) |
| Hemodialysis, n (%) | 26 (20.4) |
| Previous myocardial infarction | 29 (22.8) |
| Quantitative coronary angiography | |
| Minimal luminal diameter, mm | 1.4 ± 0.5 |
| Percent diameter stenosis, % | 52.7 ± 15.1 |
| Reference vessel diameter, mm | 2.9 ± 0.7 |

Values represent the mean ± standard deviation or n (%). BMI indicates body mass index; LAD, left anterior descending artery; Hb, hemoglobin; LVEF, left ventricular ejection fraction; and LVMI, left ventricular mass index.

| Table II. | FFR Values and ECG Parameters (NIC-PAP, n = 178) |
|-----------|-----------------------------------------------|
| Baseline | NIC | PAP | P value (Baseline versus NIC) | P value (Baseline versus PAP) | P value (NIC versus PAP) |
| HR, bpm | 70.0 ± 12.2 | 71.9 ± 12.8 | 73.2 ± 12.1 | <0.0001 | <0.0001 | 0.04 |
| Pd, mmHg | 87.0 ± 14.2 | 70.1 ± 14.8 | 65.1 ± 14.4 | <0.0001 | <0.0001 | <0.0001 |
| Pa, mmHg | 94.5 ± 13.4 | 85.4 ± 13.7 | 80.9 ± 15.3 | <0.0001 | <0.0001 | <0.0001 |
| FFR (Pd/Pa) | 0.92 ± 0.08 | 0.82 ± 0.11 | 0.81 ± 0.11 | <0.0001 | <0.0001 | <0.0001 |
| RR interval, ms | 883 ± 151 | 863 ± 162 | 843 ± 146 | 0.0004 | <0.0001 | 0.0007 |
| QT interval, ms | 397 ± 44 | 394 ± 44 | 441 ± 58 | 0.02 | 0.01 | 0.01 |
| QTc interval, ms¹/² | 425 ± 37 | 424 ± 41 | 483 ± 54 | 0.24 | 0.01 | 0.02 |
| QTU interval, ms | 466 ± 75 | 460 ± 78 | 542 ± 78 | 0.01 | 0.02 | 0.0006 |
| QTUc interval, ms²/² | 498 ± 65 | 497 ± 68 | 591 ± 63 | 0.69 | 0.0004 | 0.0005 |

Values represent the mean ± standard deviation or n (%). FFR indicates fractional flow reserve; ECG, electrocardiogram; NIC, nicorandil; PAP, papaverine; HR, heart rate; Pd, distal coronary pressure; and Pa, aortic pressure.
performed to evaluate the difference between NIC-FFR and PAP-FFR (Figure 2B). The mean difference and SD were 0.01 and 0.002, respectively. In most cases, PAP-FFR was equal to or lower than NIC-PAP, but in 19 lesions, the PAP-FFR value was higher than NIC-FFR. Of the negative NIC-FFR lesions, 9 (5.1%) were reclassified as having a positive status after PAP (Figure 3), while among the positive NIC-FFR lesions, none of the stenoses were reclassified as having a negative status after PAP. In 16 lesions (9.0%), PAP-FFR values decreased more than 0.05 compared to NIC-FFR. Half of them fell within their gray zone FFR values (0.75 to 0.85). Moreover, the PAP-FFR was lower compared to the NIC-FFR in the PAP-NIC group (NIC-FFR 0.85 ± 0.09; PAP-FFR 0.84 ± 0.09; P = 0.02).

**ECG changes and arrhythmias:** In the ECG parameter analysis of the 178 stenoses, the RR interval was significantly shorter following the use of intracoronary NIC and PAP than those at baseline (Table II). The mean baseline-QTc, NIC-QTc, and PAP-QTc intervals were 425 ± 37 ms$^{1/2}$, 424 ± 41 ms$^{1/2}$, and 483 ± 54 ms$^{1/2}$, respectively. The NIC-QTc was not significantly different from the baseline-QTc. However, PAP induced QTc prolongation (P < 0.05). Furthermore, the mean baseline-QTcN, NIC-
Figure 4. Changes in the ECG parameters with the infusion of hyperemic drugs. NIC administration shortened the QTc and QTUc intervals compared to those at the baseline. After PAP use, the QTc and QTUc intervals were slightly prolonged to 456 ms\(^{1/2}\) and 511 ms\(^{1/2}\), respectively. ECG indicates electrocardiogram; NIC, nicorandil; and PAP, papaverine.

Table III. Incidence of Arrhythmia

| Arrhythmia                          | NIC-PAP (n = 178) |
|-------------------------------------|-------------------|
| QT prolongation after PAP, n (%)    | 141 (79.2)        |
| Negative T wave, n (%)              | 42 (23.6)         |
| ST depression, n (%)                | 19 (10.7)         |
| Transient AV block, n (%)           | 0 (0)             |
| Premature ventricular beats, n (%)  | 4 (2.3)           |
| Ventricular tachycardia, n (%)      | 1 (0.6)           |
| Ventricular fibrillation, n (%)     | 0 (0)             |

NIC indicates nicorandil; PAP, papaverine; and AV, atrioventricular.

QTc, and PAP-QTc intervals were 498 ± 65 ms\(^{1/2}\), 497 ± 68 ms\(^{1/2}\), and 591 ± 63 ms\(^{1/2}\), respectively. PAP-induced QTc prolongation (P < 0.05). Figure 4 demonstrates a representative example demonstrating changes in the ECG parameters. In this study, the use of intracoronary PAP increased the number of premature ventricular beats in 4 patients (2.3%) (Table III). Of these patients, only 1 (0.6%) developed sustained VT after R on U, which resolved spontaneously. On the other hand, VT was observed in 3 patients during hyperemia with the use of PAP before NIC (5.9%). The incidence rate of VT tended to be lower in the NIC-PAP than in the PAP-NIC. PAP did not induce VF, regardless of NIC pre-administration. We compared the ECG parameters between NIC-PAP and PAP-NIC to evaluate the influence of NIC pre-administration (Table IV). The ΔQTc and ΔQTUc intervals in NIC-PAP were 56 ± 42 ms\(^{1/2}\) and 89 ± 51 ms\(^{1/2}\), respectively, while those in PAP-NIC were 125 ± 57 ms\(^{1/2}\) and 176 ± 84 ms\(^{1/2}\), respectively. The ΔQTc and ΔQTUc intervals were significantly shorter following NIC pre-administration (P < 0.05).

Discussion

The major findings of this study are as follows: (1) Maximal hyperemia was not achieved with intracoronary NIC use alone in all the lesions. The use of intracoronary PAP with NIC may be useful in the achievement of sufficient maximal hyperemia in daily clinical practice, and (2) the QTc interval was significantly shorter and incidence of VT was slightly lower for NIC-PAP compared to PAP-NIC. The administration of intracoronary PAP following NIC may prevent malignant arrhythmia development through reductions in the degree of PAP-induced QTc prolongation.

Hyperemic efficacy of NIC and PAP: The use of PAP induces a maximal hyperemic response in the coronary circulation without causing clinically important hemodynamic changes. Historically, PAP was used as a pharmacological agent in physiological assessments such as those pertaining to coronary flow reserve, but has been superseded by adenosine or ATP due to concerns pertaining to the development of VT. However, these agents were associated with the development of bronchial asthma or bradycardia, including atrioventricular block. In addition, caffeine intake attenuated the effects of adenosine and ATP, leading to the problem of false negatives. NIC has both nitrate-like and K+ATP-activating properties. By virtue of these mechanisms of action, NIC acts on both the microvascular and macrovascular systems as a coronary vasodilator. Previous studies have shown that the hyperemic ability of NIC is equivalent to that of adenosine or...
Intracoronary NIC is now widely used for FFR measurements owing to the associated safety and convenience, especially in patients who consume caffeine within 24 hours or have high risks or contraindications for adenosine or ATP. It has been reported that the effect of intracoronary NIC peaks at 1-2 minutes and returns to baseline 5-10 minutes after NIC administration. In our study, NIC use occasionally underestimated ischemic severity compared to PAP. Nicorandil dilates the macrovascular and microvascular systems through nitric oxide and potassium channels. In contrast, papaverine directly relaxes the vascular smooth muscle. We thought that the difference between pharmacological actions resulted in our findings. In 9 of the stenoses (5.1%), the ischemia diagnosis changed from negative to positive with additional PAP use; 8 of these had an FFR value in the gray-zone (0.76-0.80) and 1 had an FFR value ≤ 0.75. On the other hand, the reason why PAP-FFR was higher than NIC-FFR was considered to be the decrease in mean aortic pressure after PAP use. The FFR represents the gold standard for the assessment of ischemia-related lesions and is a valuable tool that can be employed to guide revascularization.

Table IV. Baseline Characteristics and ECG Parameters in the Propensity Matched Groups

|                           | NIC-PAP (n = 45) | PAP-NIC (n = 45) | P value |
|---------------------------|-----------------|-----------------|---------|
| Number of patients (male) | 41 (37)         | 37 (32)         | 0.60    |
| Age, years                | 72.2 ± 9.5      | 71.7 ± 11.1     | 0.82    |
| BMI, kg/m²                | 19.1 ± 2.5      | 19.6 ± 3.7      | 0.45    |
| Target vessel, n (%)      |                 |                 | 0.83    |
| LAD                       | 27 (60.0)       | 26 (57.8)       |         |
| Non-LAD                   | 18 (40.0)       | 19 (42.2)       |         |
| Laboratory data           |                 |                 |         |
| Hb, mg/dL                 | 12.7 ± 2.0      | 12.6 ± 2.0      | 0.83    |
| Na, meq/L                 | 140 ± 2         | 140 ± 3         | 0.68    |
| K, meq/L                  | 4.1 ± 0.5       | 4.2 ± 0.5       | 0.53    |
| Cl, meq/L                 | 104 ± 3         | 104 ± 4         | 0.41    |
| LVEF, %                   | 51.0 ± 8.7      | 49.3 ± 7.6      | 0.33    |
| LVMI, g/m²                | 116 ± 38        | 125 ± 39        | 0.26    |
| Clinical history          |                 |                 |         |
| Hypertension, n (%)       | 32 (78.1)       | 28 (75.7)       | 0.80    |
| Diabetes mellitus, n (%)  | 15 (36.6)       | 15 (40.5)       | 0.72    |
| Hypercholesterolemia, n (%) | 26 (63.4)  | 23 (62.2)       | 0.91    |
| Smoker, n (%)             | 9 (22.0)        | 7 (18.9)        | 0.91    |
| Hemodialysis, n (%)       | 6 (14.6)        | 6 (16.2)        | 0.85    |
| Previous myocardial infarction | 16 (39.0) | 14 (37.8)       | 0.91    |
| Quantitative coronary angiography |     |                |         |
| Minimal luminal diameter, mm | 1.4 ± 0.5    | 1.5 ± 0.5       | 0.82    |
| Percent diameter stenosis, % | 50.8 ± 14.5  | 50.4 ± 11.5     | 0.88    |
| Reference vessel diameter, mm | 2.9 ± 0.6    | 2.9 ± 0.6       | 0.85    |
| ECG parameters            |                 |                 |         |
| Baseline                  |                 |                 |         |
| RR interval, ms           | 913 ± 140       | 887 ± 163       | 0.43    |
| QT interval, ms           | 398 ± 43        | 393 ± 34        | 0.62    |
| QTc interval, ms<sup>1/2</sup> | 417 ± 34   | 421 ± 35        | 0.64    |
| QTU interval, ms          | 467 ± 81        | 457 ± 75        | 0.53    |
| QTUc interval, ms<sup>1/2</sup> | 498 ± 67   | 486 ± 63        | 0.84    |
| After intracoronary PAP   |                 |                 |         |
| RR interval, ms           | 864 ± 156       | 868 ± 147       | 0.90    |
| QT interval, ms           | 438 ± 59        | 507 ± 72        | <0.0001 |
| QTc interval, ms<sup>1/2</sup> | 474 ± 51   | 546 ± 66        | <0.0001 |
| QTU interval, ms          | 537 ± 83        | 614 ± 71        | <0.0001 |
| QTUc interval, ms<sup>1/2</sup> | 579 ± 65   | 662 ± 63        | <0.0001 |
| ΔQT interval, ms          | 41 ± 423        | 113 ± 55        | <0.0001 |
| ΔQTc interval, ms<sup>1/2</sup> | 56 ± 42   | 125 ± 57        | <0.0001 |
| ΔQTU interval, ms         | 70 ± 54         | 157 ± 75        | <0.0001 |
| ΔQTUc interval, ms<sup>1/2</sup> | 89 ± 51   | 176 ± 84        | <0.0001 |

Values represent the mean ± standard deviation or n (%). ECG indicates electrocardiogram; eGFR, estimated glomerular filtration rate; NIC, nicorandil; PAP, papaverine; BMI, body mass index; LAD, left anterior descending artery; Hb, hemoglobin; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; and Δ, change due to papaverine use.
vascular events significantly increased when treatment was administered without revascularization. Therefore, the induction of maximal coronary hyperemia is required for reliable FFR measurement. PAP still has value in the cardiac catheterization laboratory when appropriate precautions are taken.

**ECG parameters and VT incidence:** PAP increases the risk of VT caused by prominent QT prolongation, while PAP inhibits the rapid component of the delayed rectifier potassium current of the myocardium and prolongs the action potential. Following intracoronary PAP use, the early afterdepolarization (EAD) caused by the excessive prolongation of the action potential duration may lead to VT development. NIC has K+ATP-activating properties with a nitric donor. This may increase the strength of the potassium current, thereby abolishing EAD in PAP-induced QT prolongation. In this study, intracoronary NIC use did not shorten the QTc interval compared to those at baseline. However, the QTc interval was significantly shorter for NIC-PAP compared to PAP-NIC. The incidence of VT/VF ranged from 1.3% to 8.8% when PAP was administered into the coronary artery at a dose of 6-20 mg. In the present study, PAP-induced VT occurred in only 1 case (0.6%), and the rate of VT development was slightly lower than that related to the use of PAP before NIC. The present findings suggest that NIC pre-administration suppresses the development of PAP-induced VT due to reductions in the rate of PAP-induced QTc prolongation.

Furthermore, NIC use alone can aid in the achievement of sufficient hyperemia during FFR measurement in most cases. Therefore, the routine injection of intracoronary PAP with NIC in daily clinical practice may not be viable due to the procedural complexity and associated high costs. If the achievement of optimal hyperemia for reliable FFR measurement cannot be ensured with NIC use alone, the addition of PAP may be effective and safe in the assessment of the severity of coronary stenosis, especially in cases with a gray-zone physiological index (FFR value of 0.81-0.85). Although the additional dose of intracoronary nicorandil may be one of the simple and reliable FFR measurement cannot be ensured with NIC. PAP still has value in the cardiac catheterization laboratory when appropriate precautions are taken.

**Study limitations:** There are several limitations to this study. First, it had a single-center design and enrolled a relatively small sample size from the Japanese population. Second, the administration order of PAP was not randomized. Therefore, we compared the study population with a nitric donor. This may increase the strength of the potassium current, thereby abolishing EAD in PAP-induced QTc prolongation. If the achievement of optimal hyperemia for reliable FFR measurement cannot be ensured with NIC use alone, the addition of PAP may be effective and safe in the assessment of the severity of coronary stenosis, especially in cases with a gray-zone physiological index (FFR value of 0.81-0.85). Although the additional dose of intracoronary nicorandil may be one of the simple and safe ways for confirmation of maximal hyperemia, it was reported that an additional 4 mg dose of nicorandil was not associated with a greater decline in the FFR than a 2 mg dose of nicorandil.99

**Study limitations:** There are several limitations to this study. First, it had a single-center design and enrolled a relatively small sample size from the Japanese population. Second, the administration order of PAP was not randomized. Therefore, we compared the study population with a retrospective population of patients who received intracoronary PAP before NIC. Third, patients with papaverine-induced QT prolongation or VT have underlying gene mutations in the cardiac ionic channels, particularly IKr.99 We did not analyze these genetic data. Fourth, we did not perform electrophysiological evaluations for the assessment of the EAD caused by the excessive prolongation of the action potential.

**Conclusion**

The administration of PAP with NIC may induce sufficient hyperemia in optimal FFR measurement. Our study suggests that the use of PAP after NIC can aid in the prevention of VT development during FFR measurement through reductions in the rate of PAP-induced QTc prolongation.

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**Disclosure**

**Conflicts of interest:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**IRB information:** This study was approved by the Ethics Committee of the University of Occupational and Environmental Health, Japan.

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