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RESEARCH LETTER

Duration of Hyperemia With Intracoronary Administration of Papaverine

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Fractional flow reserve (FFR) and pressure pullback gradient (PPG) are 2 hyperemic indices used in clinical practice to determine the hemodynamic significance of coronary stenoses and distribution of epicardial resistance. The PPG is calculated using FFR values along the coronary vessels during a pullback maneuver for determination of the pattern (eg, focal or diffuse) of coronary artery disease.[1] Insufficient hyperemia may minimize pressure … drops and affecting pressure gradients quantification.

Papaverine has been validated for FFR measurements in several studies.[2–4] However, despite its relatively long duration of action, a detailed analysis of the vessel-specific dose–response and steady hyperemic state duration stratified by severity of coronary artery disease is still lacking.

The data that support the findings of this study are available from the corresponding author upon reasonable request. This was a prospective, single-center study of patients undergoing coronary angiography with an indication for FFR measurement. Approval was obtained from the local Ethics Committee (OLV-74690), and the study protocol was in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients before enrollment in this study. A 6F guiding catheter was inserted through the femoral or radial artery. A pressure guidewire (PressureWire X, Abbott Vascular, USA) was advanced in the distal part of the vessel to obtain (distal mean coronary pressure [Pd]) at least 30 mm beyond the epicardial lesion. Pd/mean aortic pressure (Pd/Pa) values were recorded. The contrast was flushed from the guiding catheter and hyperemia was induced with intracoronary papaverine at a dose of 12 to 16 mg for the left coronary artery and 8 to 12 mg for the right coronary artery. The time to maximal hyperemia (time needed to reach 80% [T80] and 90% [T90] of the minimal value of Pd/Pa after the injection of papaverine) and plateau phase (time during which Pd/Pa remained at >90% of its minimal value) were computed (Figure A).[3] Variability during the plateau phase was assessed extracting 1 FFR value per second. Groups were stratified according to the FFR value of ≤0.80. Statistical comparisons between groups were performed using the Mann-Whitney *U* test.

Overall, 46 patients (51 vessels) were included. Vessel types were 32 left anterior descending coronary arteries, 11 left circumflex coronary arteries, and 8 right coronary arteries. The mean diameter stenosis was 43.5±13.0%. The mean pressure tracing recording time after papaverine injection was 1.72±0.65 minutes. The mean FFR was 0.82±0.09 and 23 vessels had an FFR ≤0.80. There were no adverse effects or complications observed during the administration of papaverine.

Median T80 and T90 were 9.2 (IQR 7.4–11.9) seconds and 11.4 (IQR 9.2–16.4) seconds, respectively. The plateau phase lasted for 40.5 (IQR 22.2–49.8) seconds. The changes of Pd/Pa value during the plateau phase was 0.001 (IQR −0.016 to 0.019; coefficient of variation of 11.4%).

The median plateau phase was significantly longer in vessels with an FFR value ≤0.80 compared with

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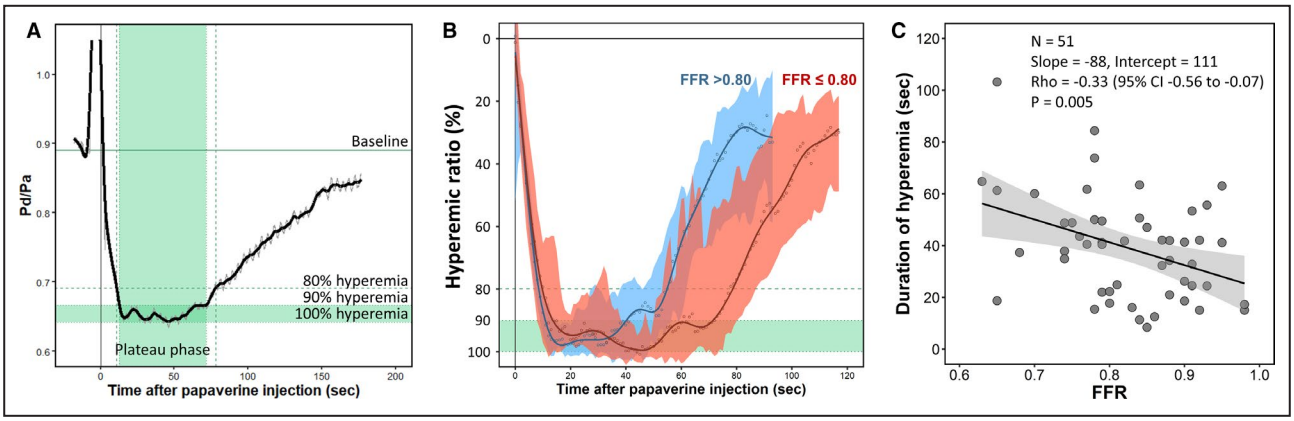

Figure. Case example of a pressure tracing after induction of hyperemia with papaverine and duration of hyperemic effect stratified by FFR.

A, An Pd/Pa tracing after the administration of intracoronary papaverine. The dashed green lines denote the plateau phase and 80%, 90%, and 100% of maximal hyperemia. The solid green areas represent the plateau phase. **B**, The duration of hyperemic plateau stratified by FFR 0.80. Pd/Pa values in the vessel with FFR ≤0.80 and FFR >0.80 are shown by red and blue curves, respectively; the shaded red and blue areas correspond to the 95% CIs. The solid green area represents the plateau phase. **C**, Correlation between distal FFR value and duration of maximal hyperemia. The gray area corresponds to the 95% CIs. FFR indicates fractional flow reserve; Pa, aortic pressure; and Pd, diastolic pressure.

vessels with FFR >0.80 (43.6 [IQR 36.1–60.7] seconds versus 32.6 [IQR 18.3–42.1] seconds, *P* value 0.027; Figure B). Distal FFR values were significantly correlated with the duration of the hyperemic plateau phase (ρ=−0.33 [95% CI −0.56 to −0.07]; Figure C).

Papaverine has been used as a hyperemic agent for the assessment of coronary flow reserve and FFR. Previous studies reported a mean time to onset of 17 to 23 seconds and the mean hyperemic duration of 22 to 51 seconds.[2,3] In the present study, using standardized papaverine doses, we found time to 90% of the hyperemic onset of 12.4 (IQR 8.8–19.2) seconds and a hyperemic plateau duration of 43.6 (IQR 36.1–60.7) seconds. We found an interaction between functional severity and time of microvascular dilation. The precise mechanisms behind this phenomenon remain to be elucidated. Concerns have been raised about the safety of intracoronary papaverine administration in terms of ventricular arrhythmias. Papaverine transitorily prolongs the QTc interval. Ventricular arrhythmias are observed in ≈1.4% of the cases.[5] In the present report there were no adverse events related to the use of papaverine.

The present analysis expands our knowledge by ascertaining that vessels with hemodynamically significant lesions, based on a contemporary criterion (ie, FFR ≤0.80), have similar time to hyperemic onset and longer stable-state hyperemic duration compared with vessels with nonsignificant lesions. These findings portray clinical implications given the increased use of the FFR pullbacks to evaluate the functional pattern of coronary artery disease using PPG and refine percutaneous coronary intervention indication and strategy. Recently, PPG was described as potentially influencing percutaneous coronary intervention outcomes. In clinical practice, vessels with an FFR ≤0.80 will be considered for PPG measurement. Based on the results of the present study, papaverine provides sufficient time to perform a pullback maneuver for at least 30 seconds under maximal hyperemic conditions. Therefore, the current study provides the foundations for the recommendation of a pullback technique using intracoronary papaverine administration.

Intracoronary administration of papaverine provides rapid onset hyperemia with a duration of steady-state sufficient for pullback maneuvers with minimal variability. The duration of steady-state hyperemia is longer in vessels with hemodynamically significant lesions.

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