Catheterization and Cardiovascular Diagnosis 14:150–153 (1988)

Changes in Epicardial Coronary Arterial Diameter Following Intracoronary Papaverine in Man

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The effect of intracoronary papaverine administration on epicardial coronary arterial diameter was examined in 18 male patients. Coronary-artery cineangiograms were acquired with a power injector before intervention, 20 sec after intracoronary saline (control), and 20 sec after administration of papaverine into either the left (12 mg) or right (8 mg) coronary artery. Absolute coronary arterial diameter of a normal-appearing segment was quantified using a previously validated, fully automated digital edge detection program with an ADAC digital radiographic unit. Baseline coronary arterial diameter of 3.1 ± 0.8 mm did not significantly change after saline administration (3.1 ± 0.9 mm) but did significantly increase ($p < .001$) to 3.4 ± 0.9 mm after papaverine administration. No significant percent change in diameter occurred in either the left anterior descending (−.5 ± 1.7%), left circumflex (−.2 ± 1.1%), or right (−3.0 ± 3.8%) coronary arteries with saline, but significant ($p < .001$) increases occurred with papaverine (7.2 ± 4.1%, 7.0 ± 4.5%, 6.8 ± 2.7%, respectively). The response of 7 coronary arteries examined immediately proximal to a significant lesion was not significantly different from the response of the remaining 11 coronary arteries. In conclusion, intracoronary papaverine causes a significant increase in coronary arterial diameter. This has clinical implications for assessing coronary flow reserve with devices that detect flow velocity.

Key words: coronary artery, digital angiography, vasodilators

INTRODUCTION

Coronary flow reserve, despite its limitations, is recognized as one measurement of the physiologic significance of a coronary stenosis [1,2]. In man, coronary flow reserve has been determined with devices that measure coronary blood-flow velocity at rest and following pharmacologically-induced hyperemia [3,4]. Extrapolation of absolute coronary blood-flow velocity measurements to obtain absolute coronary blood-flow volume requires knowledge of the arterial dimensions at the site of flow measurement. Intracoronary papaverine has gained popularity as a pharmacologic agent to induce hyperemia because of its short onset-to-peak effect, superior hyperemic effect, short duration of action (making it useful for repeated determinations in the same patient), and its lack of significant side effects compared to other available agents [5].

Current applications of coronary blood-flow velocity to measure coronary flow reserve assume that epicardial coronary arterial dimensions remain constant during papaverine administration [3,4]. Critical assessment of the clinical value and limitations of using papaverine to measure coronary flow reserve with devices that only measure coronary flow velocity must analyze the extent to which this assumption introduces error. This study examines the effect of intracoronary papaverine administration on epicardial coronary arterial diameter.

METHODS

All patients undergoing elective cardiac catheterization for angina pectoris at the Durham Veterans Administration Medical Center were eligible for inclusion in this study. Patients with left ventricular hypertrophy by electrocardiographic criteria, prior thoracotomy, valvular heart disease, cardiomyopathy, or rhythm other than normal sinus rhythm were excluded from analysis. Following routine right or left coronary angiography, the section of artery for analysis was chosen, prior to subsequent study angiograms, based on the ability of arterial sections to be visualized during diastasis in the same frame as the coronary catheter without overlying side branches. All analyzed arteries were patent. The view thought to be most optimal was selected for subsequent study angiograms. Three coronary-artery cineangiograms were acquired 5 min apart before intervention, 20 sec after intracoronary saline (control), and 20 sec after administration of papaverine (2 mg per cc of saline) into either

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Received June 20, 1987; revision accepted October 3, 1987.

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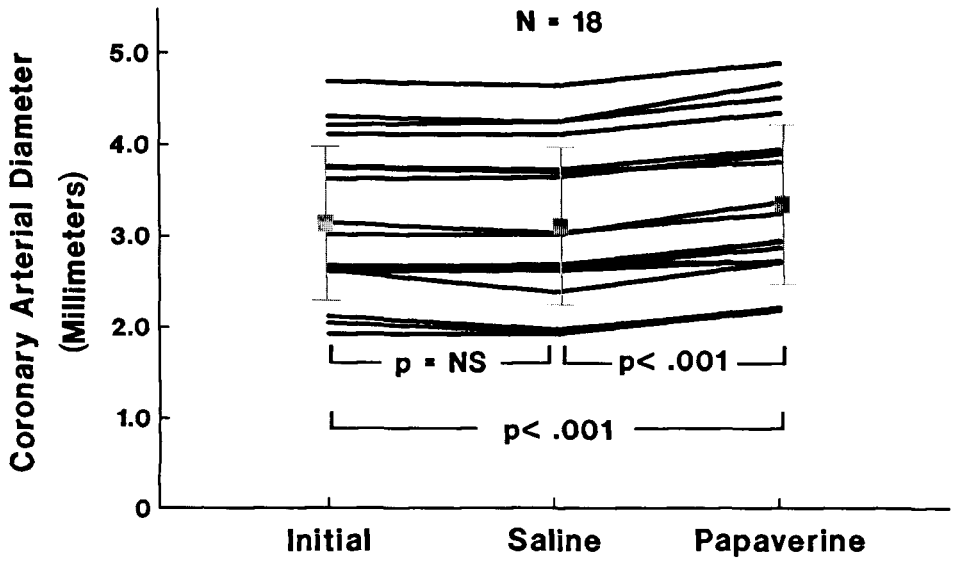

Fig. 1. Individual and group mean changes in absolute coronary arterial diameter during initial coronary-artery angiography, following intracoronary saline, and following intracoronary papaverine. The textured squares and bars represent the mean ± standard deviation, respectively.

the left (12 mg) or right (8 mg) coronary artery. No patient received atropine or supplemental vasodilators in the cardiac catherization laboratory. Informed written consent was obtained from all patients for a protocol approved by the Human Studies Subcommittee of the Institutional Review Board.

All study coronary-artery angiograms were acquired on cine film at 30 frames/sec using the 5" mode of the image intensifier. A power injector delivered 6–9 cc of meglumine diatrizoate at 3–6 cc per sec for each coronary-artery angiogram, with identical volumes and injection rates used for all three angiograms in each patient. Acquisition of each coronary-artery angiogram occurred during held inspiration without panning, making sure to keep the coronary catheter in the field of view. No movement of the image intensifier or the table occurred between coronary injections.

A single frame from each unsubtracted coronary-artery cineangiogram was selected during diastasis just prior to atrial contraction to ensure that coronary-artery diameter measurements occurred at the same time during the cardiac cycle. An ADAC digital radiographic unit digitized this frame on a 512 × 512 matrix with 256 gray levels. A previously validated, fully automated, center-line digital edge detection program [6] quantified absolute coronary arterial diameter. Calibration occurred by measurement of the catheter diameter. One normal-appearing proximal or midsection of one coronary artery was chosen for analysis from each patient, to prevent multiple measurements in the same patient from skewing the results.

All data are expressed as mean values ± standard deviation. Paired analyses used the Wilcoxon signed-rank test, and unpaired comparisons used the Wilcoxon rank-sum test.

RESULTS

The 18 male patients enrolled in the study had an average age of 61 ± 14 years and an average ejection fraction of 64 ± 15%. No patient had a recent myocardial infarction. Two patients had an old myocardial infarction remote from the myocardium supplied by the analyzed artery. The analyzed arteries did not supply angiographically visible collateral vessels to the infarcted myocardium. Thirteen patients had significant coronary artery disease, defined as a greater than 75% luminal-diameter narrowing in at least one vessel. Three-vessel disease was present in one patient, two-vessel disease in five patients, and single-vessel disease in seven patients. Five patients had insignificant coronary-artery disease, one of whom had angiographically normal coronary arteries. The response of papaverine was evaluated in five left anterior descending, six left circumflex, and seven right coronary arteries.

All patients remained on their anti-anginal and anti-platelet medications. The administration of these medications remained unaltered by the study. The medications being taken included beta blockers in 13, calcium channel antagonists in 12, long-acting nitrates in 9, and aspirin in 10 patients. One patient was not taking any medication, 5 patients were taking only one anti-anginal drug, and 12 patients were taking multiple anti-anginal drugs.

The absolute coronary-artery diameter following the initial, saline, and papaverine injections is displayed for all patients in Figure 1. No significant change in diameter

occurred between the initial (3.1 ± .8 mm) and saline (3.1 ± .9 mm) coronary injections. However, a significant increase in diameter occurred between the initial and papaverine (3.4 ± .9 mm) coronary injections. The percent change in coronary-artery diameter from the initial injection was not statistically significant following intracoronary saline (−1.4 ± 2.8%). Intracoronary papaverine administration, however, resulted in a significant ($p < .001$) 7.0 ± 3.5% increase in epicardial coronary arterial diameter. Analysis of the individual coronary arteries revealed no significant percent change in diameter in either the left anterior descending (−.5 ± 1.7%), left circumflex (−.2 ± 1.1%), or right coronary (−3.0 ± 3.8%) arteries with saline. However, similar and significant ($p < .001$) increases in coronary arterial diameter occurred with papaverine in all arteries (7.2 ± 4.1%, 7.0 ± 4.5%, 6.8 ± 2.7%, respectively).

The response of 7 coronary arteries examined immediately proximal to a significant lesion was compared to the response of the remaining 11 coronary arteries. In the group with a significant lesion, a −1.4 ± 3.5% change in diameter ($p = NS$) followed intracoronary saline, and a 5.9 ± 2.8% increase in diameter ($p < .001$) followed intracoronary papaverine. In the group without a significant lesion distal to the analyzed portion of the coronary artery, a −1.4 ± 2.5%change followed intracoronary saline ($p = NS$), and a 7.7 ± 3.9% increase in diameter ($p < .001$) followed intracoronary papaverine. The responses of these two groups were not significantly different.

DISCUSSION

This study revealed that administration of intracoronary papaverine, in the dosage used for evaluation of coronary flow reserve, results in approximately a 7% increase in epicardial coronary arterial diameter or a 14% increase in luminal area. The responses of the left anterior descending, left circumflex, and right coronary arteries were not significantly different. Likewise, the response of arterial segments analyzed proximal to a subtotal lesion was statistically comparable to the response of the remaining arterial segments.

This study used an automated quantitative digital angiographic analysis program, making the unblinded evaluation as objective as possible. Performance of all coronary angiographic injections with a power injector, set at a relatively high rate, avoided streaming and ensured adequate opacification of the arteries during hyperemia. Careful selection of single frames from the coronary artery cineangiograms for analysis ensured that coronary arterial diameter was measured at the same time during the cardiac cycle. Each patient in this study served as his own control, minimizing variability due to the effect of continuing medications. The effect of individual coronary vasoactive drugs on the magnitude of the observed change in coronary diameter could not be assessed due to the various combinations of medications in this patient population.

The physiologic significance of a coronary arterial obstructive lesion frequently does not correlate with the subjective interpretation of the coronary angiogram [7]. Although quantitative analysis of coronary arterial lesions in selected patient populations correlates more closely with their physiologic significance [8,9], alternative methods for evaluating the limitation in coronary flow reserve due to coronary arterial obstructive lesions have been sought.

Currently, coronary flow reserve in man may be determined from devices that measure coronary blood-flow velocity [3,4]. Devices that only measure coronary blood-flow velocity, and fail to account for increases in epicardial coronary arterial diameter with papaverine, will underestimate coronary blood-flow volume changes by an average of 14%. These changes, as well as individual variability, must be taken into account if precise measurement of coronary blood-flow volume are to be derived with intracoronary papaverine from devices that measure only coronary blood-flow velocity.

ACKNOWLEDGMENTS

We are grateful to Sherry Barker and Mary Lou Holman for their excellent secretarial assistance in the preparation of this manuscript.

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