Comparison of Intravenous Adenosine to Intracoronary Papaverine for Calculation of Pressure-Derived Fractional Flow Reserve

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For calculation of fractional flow reserve (FFR), simultaneous registration of both aortic pressure (P_a) and transstenotic distal coronary pressure (P_d) is necessary at steady-state maximum coronary hyperemia. The aim of the present study was to compare the maximum transstenotic gradient (ΔPmax) and pressure-derived myocardial fractional flow reserve (FFR_{myo}), observed during intravenous adenosine infusion, to ΔPmax and FFR_{myo} induced by intracoronary papaverine, which is considered to be the gold standard for induction of coronary hyperemia, but acts too short for steady-state hyperemic pressure recordings and is associated with QT-prolongation.

In 24 patients with coronary stenoses of various degrees, P_a and P_d were measured simultaneously by the diagnostic catheter and a high fidelity 0.018″ fiberoptic pressure monitoring guide wire, respectively. Excellent steady-state phasic intracoronary pressure recordings were obtained in all patients within 1 min after start of intravenous adenosine infusion at a rate of 140 μg/kg/min, and compared to ΔPmax obtained 30 sec after intracoronary administration of papaverine (12 mg LCA, 10 mg RCA).

ΔPmax was 24 ± 15 mmHg during adenosine infusion and 24 ± 15 mmHg after papaverine administration. Myocardial fractional flow reserve, calculated from these pressure recordings, was 0.75 ± 0.16 and 0.75 ± 0.15, respectively, with an individual difference of 0.02 ± 0.01 between both values (r = 0.99). No important side effects by intravenous infusion of adenosine were observed.

Thus intravenous adenosine infusion at a rate of 140 μg/kg/min is an excellent and safe alternative for induction of steady-state maximum coronary hyperemia and therefore is an ideal vasodilator for determination of fractional flow reserve based upon pressure recordings. © 1996 Wiley-Liss, Inc.

Key words: fractional flow reserve, coronary pressure, papaverine, adenosine

INTRODUCTION

Maximum coronary vasodilation must be achieved for several diagnostic techniques in coronary artery disease. Among these techniques are measurement of absolute coronary flow reserve (CFR) by an intracoronary Doppler guidewire [1–3] and calculation of fractional flow reserve (FFR) by intracoronary pressure recordings [4–9]. The concept of FFR was recently developed and validated [4,5]. Myocardial fractional flow reserve (FFR_{myo}) is defined as the ratio of maximum myocardial flow in the presence of a coronary stenosis to the maximum flow in the absence of this stenosis and can be calculated by:

$$FFR_{myo} = \frac{(P_d - P_v)}{(P_a - P_v)} \sim \frac{P_d}{P_a}$$

where P_a is the mean central aortic pressure, P_d the mean distal coronary pressure, and P_v the right atrial pressure, all measured at maximum coronary hyperemia [4]. Unique features of FFR are its independency of hemodynamic variations [4,10], the inclusion of collateral flow [4,6], its unequivocal normal value of 1.0 for every person and every coronary artery [7], a sharp cutoff point between values whether or not associated with inducible ischemia [7,8,9], and its simple calculation by steady-state hyperemic pressure recordings [4–9]. However, because steady-state hyperemia is a prerequisite for reliable calculation of FFR_{myo} and because P_a should be prefer-

$$FFR_{myo} = {}^{98}\!/_{108} = 0.91$$

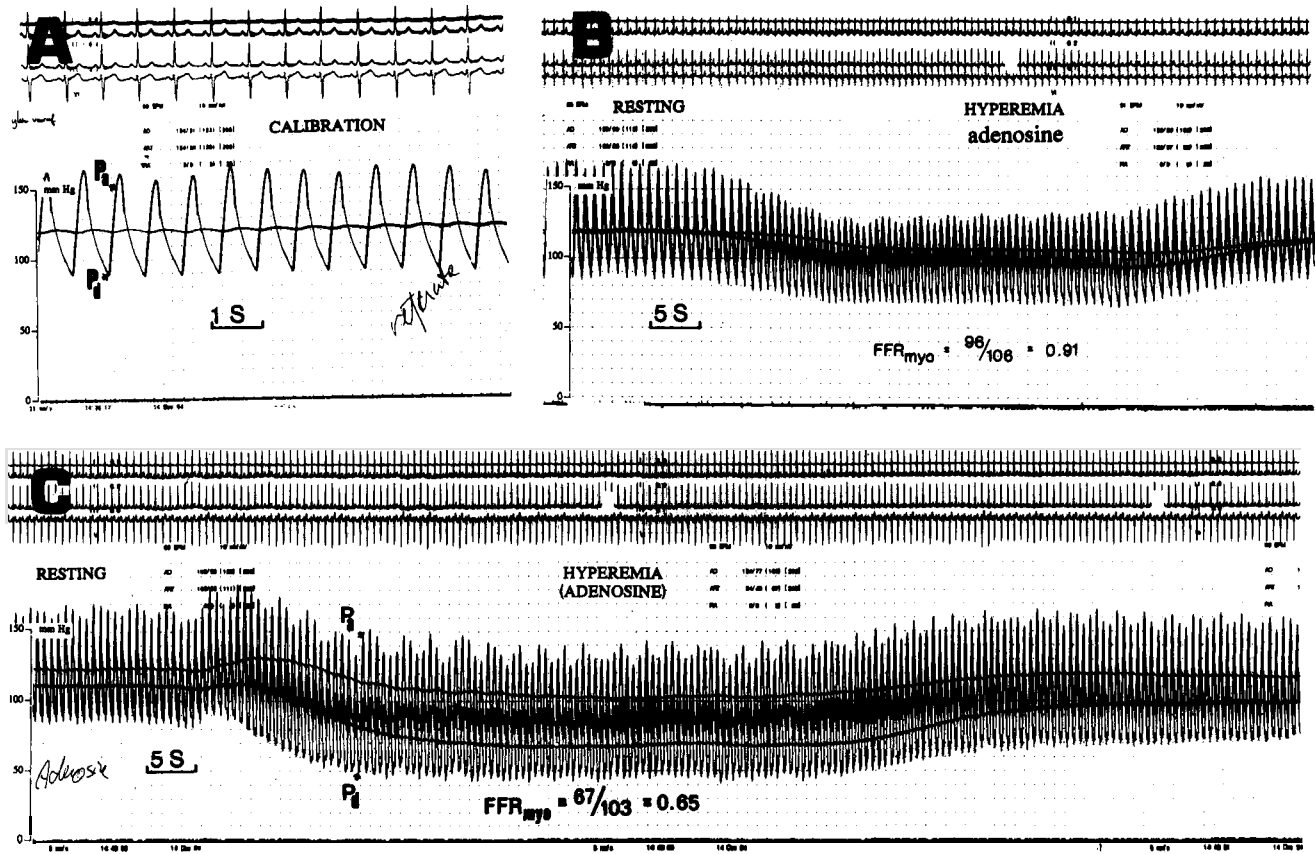$$FFR_{myo} = {}^{67}\!/_{103} = 0.65$$

Fig. 1. Some examples illustrating the induction of steady-state minimal distal coronary pressure achieved by i.v. adenosine. Minimum distal coronary pressure corresponds with maximum hyperemia and maximum translesional gradient. A. The fiberoptic wire is positioned at the tip of the coronary catheter to check equal pressures recorded at that site by the coronary catheter (Pa) and the fiberoptic wire (Pd), respectively. B. Pressure-recordings in a 58-year-old male with a 70% stenosis in the left anterior descending artery. C. Pressure recordings in a 49-year-old female with a 50% stenosis in the right coronary artery.

ably measured without interruption, continuous intravenous administration of a maximum vasodilatory drug would have some advantages compared to the more usual short-acting intracoronary administration of adenosine or papaverine.

The aim of this study, therefore, was to investigate whether intravenous adenosine is equivalent to i.c. papaverine for induction of maximum coronary hyperemia as reflected by decline of distal coronary pressure. In other words, is the maximum transstenotic pressure gradient induced by i.v. adenosine comparable to the maximum gradient induced by i.c. papaverine, and are the accordingly derived FFR values identical?

METHODS
Patients

Included were 24 patients who were planned to undergo measurement of myocardial fractional flow reserve (FFR_myo). The study population consisted of 13 men and 11 women; mean age was 53.7 yr (range 44–72). All patients had complaints of angina and at a prior coronary angiography, an intermediate coronary artery stenosis between 50% and 70% in the proximal or mid-part of a coronary artery with a reference diameter of at least 3.0 mm. All patients had a normal AV conduction and a normal QT interval at the ECG.

Catheterization Protocol

A 6F large lumen diagnostic coronary catheter was introduced by the femoral artery and advanced into the ostium of the right or left coronary artery. Through that catheter, a high fidelity 0.018" fiberoptic pressure monitoring guidewire (RADI Medical Systems, Uppsala, Sweden) was advanced. Adequate calibration and verification of equal pressures registered by the coronary catheter and the wire when placed into the ascending aorta were performed as described elsewhere [7].

After advancing the pressure wire across the stenosis, both mean and phasic proximal pressure (P_a), measured

TABLE I. Patient Characteristics and Hemodynamic Variables at Baseline, During Intravenous Adenosine Infusion, and After Intracoronary Papaverine Administration

| Patient | Sex | Age | Artery | Adenosine | | | | | | Papaverine | | | | | |
				BP^a baseline (mm Hg)	BP^a hyperemia (mm Hg)	HR^b baseline (bpm)	HR^b hyperemia (bpm)	$\Delta Pmax^c$ (mm Hg)	$FFRmyo^d$ (−)	BP^a baseline (mm Hg)	BP^a hyperemia (mm Hg)	HR^b baseline (bpm)	HR^b hyperemia (bpm)	$\Delta Pmax^c$ (mm Hg)	$FFRmyo^d$ (−)
1	F	58	LAD	101	100	84	78	50	0.50	111	100	70	71	52	0.49
2	F	45	LAD	102	82	55	55	56	0.30	102	102	53	55	67	0.34
3	M	47	LAD	78	79	70	84	15	0.81	80	74	71	62	16	0.78
4	F	54	LAD	85	85	57	59	23	0.79	90	84	58	61	20	0.76
5	M	46	CX	86	85	77	70	14	0.84	85	81	85	90	12	0.85
6	F	54	RCA	115	111	78	91	44	0.61	111	100	87	88	35	0.66
7	F	63	LAD	73	69	60	73	2	0.97	70	70	68	72	2	0.97
8	M	52	LAD	92	85	58	73	5	0.94	80	82	60	64	7	0.91
9	M	56	RCA	105	82	66	70	17	0.79	102	92	58	52	18	0.80
10	F	61	LAD	93	79	62	89	17	0.78	90	95	59	59	18	0.79
11	F	51	LAD	110	97	57	62	36	0.63	105	100	59	59	38	0.62
12	M	59	LAD	60	58	57	76	25	0.60	56	62	66	69	26	0.57
13	M	57	LAD	102	97	70	70	20	0.79	103	97	72	76	23	0.77
14	F	47	IM	101	103	56	55	19	0.82	82	78	54	44	16	0.81
15	M	57	LAD	102	89	64	83	18	0.80	100	97	69	77	19	0.81
16	M	49	RCA	120	103	79	95	23	0.78	110	90	82	85	24	0.75
17	M	63	RCA	125	101	65	86	14	0.86	118	100	67	68	15	0.85
18	F	52	RCA	103	96	66	74	52	0.46	102	98	66	69	49	0.50
19	M	72	LAD	109	103	67	82	29	0.76	104	100	74	79	26	0.75
20	F	44	RCA	98	83	96	77	5	0.94	102	82	100	105	6	0.93
21	M	51	RCA	117	119	67	68	23	0.80	114	110	81	79	23	0.80
22	M	53	LAD	93	89	81	99	22	0.75	96	95	87	86	22	0.77
23	M	54	LAD	93	86	53	61	10	0.90	90	89	61	60	9	0.90
24	F	44	LAD	113	104	77	97	31	0.70	113	103	85	89	30	0.72
		mean		99.0	91.0	67.6	76.1	23.8	0.75	96.5	90.9	70.5	71.6	23.9	0.75
standard deviation				15.3	13.7	10.9	12.8	14.7	0.16	15.2	11.9	12.4	14.3	15.3	0.15

[a]Indicates mean arterial pressure.
[b]Heart rate.
[c]Maximum transtenotic gradient at i.v. adenosine infusion or after i.c. papaverine administration, respectively.
[d]Myocardial fractional flow reserve.

through the catheter, and the mean and phasic post-stenotic pressure (P_d), measured by the wire, were recorded simultaneously.

Transstenotic pressure gradient was defined as the difference of mean P_a and mean P_d. Central venous pressure was measured by a 6F multipurpose catheter in the right atrium.

Adenosine

At first, hyperemia was induced by i.v. adenosine, infused through the side arm of the femoral venous sheath, at a rate of 140 μg/kg/min. After a steady-state of all pressures had been achieved (Fig. 1), ΔPmax,aden. was calculated. Subsequently, the infusion was stopped and all hemodynamic variables were allowed to return to baseline.

Papaverine

Thereafter, papaverine was administered intracoronarily through the coronary catheter, 10 mg for the RCA, 12 mg for the LCA, followed by 3 cc of saline. Pressure recordings were obtained and ΔPmax,pap. was calculated as the maximum gradient during the subsequent hyperemia.

Myocardial Fractional Flow Reserve

During adenosine infusion and after i.c. papaverine administration, myocardial fractional flow reserve was calculated according to the equation in the introduction.

RESULTS

Hemodynamic Observations

The hemodynamic variables at baseline conditions and during intravenous adenosine infusion and after i.c. administration of papaverine are shown in Table I. During intravenous administration of adenosine, there was a decrease in blood pressure of 8 ± 8 mmHg and an increase in heart rate of 8 ± 11 b.p.m. After intracoronary papaverine administration, there was a blood pressure decrease of 6 ± 7 mmHg, with heart rate increase of 1 ± 4 b.p.m.
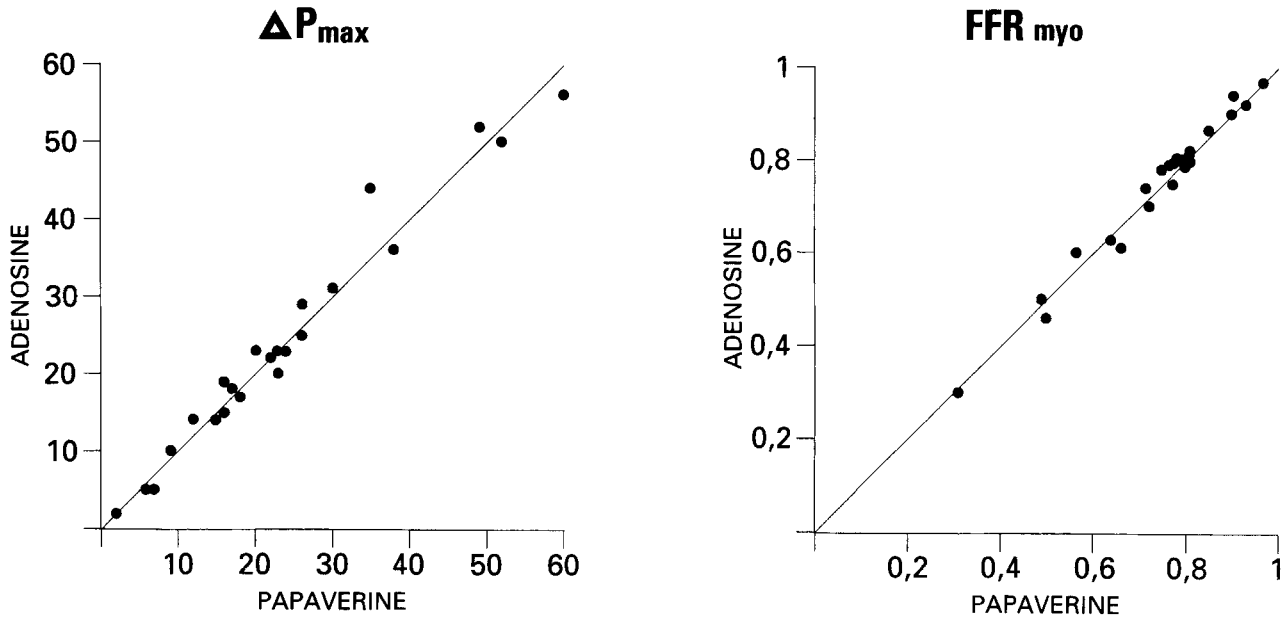
Fig. 2. Maximum transstenotic pressure gradient (left) and myocardial fractional flow reserve (right) after intracoronary administration of papaverine (horizontal axis) and during intravenous adenosine infusion (vertical axis).

At i.v. adenosine infusion, the maximum pressure gradient was 24 ± 15 mmHg (range 5–56 mmHg). Intracoronary administration of papaverine resulted in a maximum pressure gradient of 24 ± 15 mmHg (range 2–67 mmHg). The absolute value of the individual differences was 2.2 ± 2.6 mmHg (9 ± 11%). FFR_{myo} at adenosine infusion was 0.75 ± 0.16 vs. 0.75 ± 0.15 after papaverine (Fig. 2). The absolute value of individual differences of FFR_{myo}, not influenced by the change in driving pressure, was 0.02 ± 0.01 (3 ± 1%). In those six patients with FFR_{myo} < 0.75 PTCA was performed subsequently and successfully.

Side Effects

During and after adenosine infusion, there were no important side effects, especially no detectable second or third degree AV block. Most patients had a burning, anginalike sensation in the chest or neck, which was not severe and disappeared rapidly after stopping the infusion.

After papaverine injection, some prolongation of the QT time was observed in most patients. However, this did not result in ventricular tachycardia, or other rhythm disturbances in any of our patients. No other side effects of any drug were observed.

DISCUSSION

Decrease of coronary arteriolar and myocardial resistance causes an increase of blood flow and thereby in-

creases the transstenotic pressure gradient across an epicardial stenosis [11]. The maximum achievable gradient after administration of a pharmacologic agent presumably corresponds with maximum vasodilation. From animal studies it is well known that intracoronary administration of papaverine is the most potent pharmacologic vasodilator, producing the highest increase in coronary blood flow, comparable with reactive hyperemia after 20″ of occlusion. This also has been confirmed in humans by measuring blood flow velocity by Doppler catheters and wires [2,12]. Therefore, intracoronary papaverine is considered as the "gold standard" to achieve maximum coronary hyperemia [13,14]. Intracoronary adenosine, intravenous adenosine, and intravenous dipyridamole have been investigated as alternative hyperemic stimuli [11,15,16].

For the specific purpose of steady-state maximum hyperemic pressure recordings in the coronary circulation, it would be desirable to use intravenous drug infusion as a stimulus for maximum coronary hyperemia for a sufficiently long and easily steerable time. Because of the rapid onset of action, its stable steady-state, its short half-life, and the lack of significant side effects, intravenous adenosine seems appropriate for this purpose.

In some previous Doppler studies, adenosine, given by intravenous infusion was slightly less hyperemic than intracoronary papaverine [12]. However, in a recent study by Kern et al. [16], intravenous infusion of adenosine at a rate of 100 or 150 μg/kg/min. produced an

increase of coronary flow velocity comparable to i.c. papaverine.

As far as we know, there has been no comparative study of coronary vasodilators using the magnitude of inducable transstenotic gradient or the decline of transstenotic distal coronary pressure as an endpoint. As outlined in the introduction, however, such investigations are relevant for physiological assessment of coronary artery stenosis by pressure measurements. Therefore, we decided to compare intravenous infusion of adenosine to intracoronary administration of papaverine, with respect to measuring maximum transstenotic gradient and accordingly calculated FFR_{myo} induced by both stimuli.

In our experiments, only small differences were observed between transstenotic gradients at adenosine-induced and papaverine-induced hyperemia. For FFR_{myo}, which also takes into account the mean arterial pressure at which the gradient is calculated, the differences were even smaller. There were no patients in whom a submaximal response to adenosine was observed, as was the case in some former studies [9,14]. Therefore, it can be concluded that in the assessment of FFR_{myo} by pressure recordings, i.v. adenosine at a rate of 140 µg/kg/min can be used as a sufficient stimulus to produce a maximum transstenotic pressure gradient or maximum decline of distal coronary pressure.

In this study, both agents appeared to be safe, and no significant side effects were observed. A slight decrease of arterial blood pressure was induced by adenosine, without clinical consequence. No second or third degree atrioventricular block was observed. After administration of intracoronary papaverine, the QT interval was slightly prolonged in most patients, but no arrhythmias were observed. In earlier studies in larger groups of patients, serious ventricular rhythm disturbances after intracoronary administration of papaverine have been described, with an incidence of 0.7–2.7% [17–19]. Torsade the pointes was the most frequently occurring rhythm disturbance, more often in women than men (4.4 vs. 0.3%) [19], but also severe sinus bradycardia has been described [18]. In our small series, none of these side effects was observed.

Limitations

Adenosine is rapidly inactivated by whole blood and has a correspondingly short half-life. Therefore, to avoid inactivation before reaching the coronary circulation, the drug should be administered by a large vein and a sufficiently well running infusion. In our catheterization laboratory, we always use a 4-5F femoral sheath for that purpose. In this particular study, such a sheath was needed to measure P_v, but for routine clinical use of FFR_{myo}, it is not necessary to measure P_v [5,10]. If one prefers to use a large cubital vein, it is advisable to prepare the adenosine solution in such a way that the flow rate of the infusion is at least 10 ml/min to ensure that the drug reaches the central compartment before being inactivated and to guarantee maximum coronary vasodilation. To measure myocardial fractional flow reserve, it is necessary to cross the stenosis with the pressure-monitoring guidewire, which is also available at present as a floppy 0.014″ wire. As extensively demonstrated before, this is a safe technique, also in diagnostic angiography [7].

Conclusions

For the purpose of determining fractional flow reserve by pressure recordings, an adequate vasodilator should fulfill the next conditions: (1) the coronary vasodilation should be maximal, (2) the agent can be given intravenously to prevent interruption of the arterial pressure signal as would be the case at intracoronary injection, (3) the agent should have a rapid onset and steady-state and a short duration of action, in order to regulate the duration of maximum hyperemia, and (4) the agent should have no important side effects.

Intravenous infusion of adenosine at a rate of 140 µg/kg/min, in our opinion, fulfills these conditions and therefore is an excellent vasodilator for measurement of fractional flow reserve by intracoronary pressure recordings and potentially also for other techniques in which steady-state maximum coronary hyperemia is needed.

ACKNOWLEDGMENTS

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