Intracoronary Papaverine Induced Myocardial Lactate Production in Patients With Angiographically Normal Coronary Arteries

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Although intracoronary papaverine has been widely used for the measurement of coronary flow reserve, little is known concerning whether papaverine may produce deleterious metabolic changes in humans. We investigated the effect of papaverine on lactate metabolism in 28 patients with normal coronary arteries. We continuously monitored phasic coronary flow velocity in the proximal left anterior descending coronary artery using Doppler guidewire. We also obtained paired samples of arterial and coronary sinus blood for the measurement of lactate at control and at 1 min after administration of 10 mg of intracoronary papaverine. There were no serious side effects during papaverine infusion. Sixteen patients showed ST-T abnormalities after papaverine. The QTc interval increased from 450 ± 42 msec to 571 ± 58 msec ($P < 0.001$). Average peak velocity increased significantly (% increase: $198.5 \pm 87.8\%$, range: 27.8–374.1%) after papaverine. Although intracoronary papaverine produced no significant change in arterial lactate levels (8.5 ± 4.0–8.8 ± 5.0 mg/ml), it induced a significant increase in coronary sinus lactate levels (5.4 ± 3.2–15.3 ± 8.2 mg/ml, $P < 0.001$). Lactate extraction ratio decreased significantly (36.4 ± 18.4–$-82.2 \pm 58.4\%$, $P < 0.001$), and all patients showed net lactate production (-3.9–-198.0%) after papaverine. There was weak but significant correlation between lactate extraction ratio after papaverine and coronary flow reserve ($R^2 = 0.15$, $P < 0.05$). There was no correlation between lactate extraction ratio and QTc interval after papaverine. The mean value of lactate extraction ratio was not different in patients with ST-T abnormalities induced by papaverine compared to those without. These results demonstrate that intracoronary papaverine induces myocardial lactate production irrespective of the degree of coronary flow reserve and electrocardiographic changes in patients with normal coronary arteries. A safer and more reliable agent is needed for the measurement of coronary flow reserve. © 1996 Wiley-Liss, Inc.

Key words: Doppler guide wire, coronary flow reserve

INTRODUCTION

The measurement of coronary flow reserve is important to our understanding of the physiological significance of obstructive coronary artery disease [1–3], the results of coronary angioplasty [4,5], or the pathophysiology of microvascular angina [6–9]. The development of intravascular, catheter-based Doppler ultrasound devices have enabled us to measure with relative ease the coronary flow reserve in cardiac catheterization laboratories [10,11]. To produce maximum coronary vasodilatation, clinicians have used several different pharmacological agents. Intracoronary papaverine has been widely used for the measurement of coronary flow reserve, because it induces maximum vasodilatation and has a short duration of action [12]. A potential problem associated with papaverine is its propensity to induce significant electrocardiographic changes and sometimes serious side effects (e.g., ventricular fibrillation) [13–16]. In addi-

tion, intracoronary papaverine induced a significant increase in coronary venous serum lactate levels in a canine model [17], and this result suggests that papaverine may produce myocardial ischemia. However, little is known about the effect of papaverine on myocardial lactate metabolism in humans. The aim of this study was to investigate the effect of intracoronary papaverine on lactate metabolism in patients with normal coronary arteries.

METHODS
Patients

We studied 28 patients with angiographically normal coronary arteries who were undergoing diagnostic cardiac catheterization for the investigation of chest pain or abnormal noninvasive stress tests. Patients with previous myocardial infarction or valvular heart disease were excluded. The mean age was 52 ± 12 yr (range: 29–71 yr). There were 19 men and 9 women. All patients had normal sinus rhythms. Three patients had vasospasm of epicardial coronary arteries in response of acetylcholine. Six patients had echocardiographic evidence of left ventricular hypertrophy, and the other one had left ventricular dilatation with globally reduced wall motion. Hypercholesterolemia (total cholesterol >240 mg/ml) was present in six patients. There was one patient with diabetes. In this study group, seven patients were classified into normal subjects, because they had no coronary risk factors and no left ventricular hypertrophy with normal left ventricular systolic function. They also showed progressive increase in coronary blood flow in the response to graded dose of intracoronary continuous infusion of acetylcholine [18]. Cardiac medications were withheld for at least 24 hr before the study, which was approved by the Human Research Committee at our institution, and written informed consent was obtained from all patients.

Protocol

After completion of diagnostic coronary angiography, a 6F Judkins type diagnostic catheter was introduced into the left main coronary artery, and a 0.014″ Doppler guidewire (Flowire, Cardiometrics, Mountainview, CA) was advanced into the proximal left anterior descending coronary artery via Y-connector attached to diagnostic catheter. The wire tip was carefully positioned in a straight segment of the vessel with adequate flow velocity signal, which could be imaged without overlap of vessels, thus allowing for quantitative measurement of the coronary artery diameter. A 6F CS catheter was inserted via right femoral vein into the junction of distal coronary sinus and the great cardiac vein for blood sampling. A Microtip catheter transducer (Millar Instruments) was advanced into the left ventricle to obtain pressure and dP/dt measurement. After stable control flow velocity was obtained, we measured hemodynamic variables, 12-lead ECG recordings, and obtained paired sample of arterial and coronary sinus blood for the measurement of lactate. Next we performed coronary angiography with nonionic contrast medium (Iopamidol, Schering, Tokyo, Japan). When the coronary flow velocity and systemic hemodynamics had returned to baseline values, we infused 10 mg of papaverine (1 mg/ml) into left coronary artery within

10 sec through the diagnostic catheter. Fifty sec after the administration of papaverine, we again obtained hemodynamic variables, ECG, and blood samples, after which we performed a second coronary angiography. We also obtained paired blood samples in 17 out of the 28 patients before and 1 min after 200 mcg of intracoronary nitroglycerine in order to investigate the effect on myocardial lactate turnover of this routine manipulation during catheterization. During the entire study period, coronary flow velocity was continuously monitored and recorded on VHS video tape for later analysis.

Measurement of Coronary Blood Flow and Diameter

Although the Doppler system automatically calculated on-line temporal flow velocity and other variables, it was not always accurate because of partial or complete failure of the detection algorithm. Therefore we performed manual tracing and calculation of these indices with an off-line system. The frames of control coronary flow velocity and peak hyperemic flow velocity after papaverine administration were digitized using a 714 × 512 bit pixel matrix from video tape, and transferred into a digital computer system (Kontron Cardio500, Kontron Instruments, Tokyo). Three to five consecutive cycles of coronary flow velocity were manually traced, and average peak velocity (APV: average of instantaneous spectral peak velocity throughout the cardiac cycle) and peak velocity integral (PVI) were calculated. For calculating coronary blood flow, coronary arterial diameter was measured in a 3 mm axial segment of vessel beginning 2 mm beyond the tip of the Doppler guidewire. Quantitative coronary angiography was performed with edge detection program (Kontron Cardio500). Cross-sectional area (CSA) was calculated from the corresponding diameter assuming a circular arterial cross section. Coronary blood flow (CBF) was calculated using the following formula: CSA × PVI × HR. Coronary flow reserve (CFR) was assessed by calculating the quotient of APV during papaverine-induced maximal hyperemia and APV at control (CFR-APV), and the quotient of maximum CBF during papaverine and CBF at control (CFR-CBF). Coronary vascular resistance (CVR) was also calculated using standard formula.

Measurement of Lactate

The plasma lactate concentration was measured with a calibrated lactate analyzer (Hitachi 7150). In addition to absolute lactate levels, we calculated lactate extraction ratio using the following formula: (arterial lactate level − coronary sinus lactate level)/arterial lactate level × 100 (%).

Statistics

Data were expressed as mean ± SD. The differences between mean of control and with papaverine were compared by using two-tailed paired t-test. Multiple comparisons between groups were made using ANOVA with Bonferroni's correction. Correlation between two variables were examined by simple linear regression analysis. The probability level $P < 0.05$ was considered as significant.

RESULTS

There were no serious side effects during papaverine infusion. One patient developed nonsustained VT after papaverine. Sixteen patients showed ST-T changes after papaverine infusion. Intracoronary papaverine significantly increased the QTc interval from 450 ± 42 msec to 571 ± 58 msec ($P < 0.001$). Table I shows hemodynamic and coronary flow variables at control and with papaverine administration. Compared to control, APV (% increase: 198.5 ± 87.8%) and coronary arterial diameter (% increase: 15.2 ± 8.9%) significantly increased after papaverine. Mean coronary vascular resistance significantly decreased from 1.10 ± 0.41 mmHg/ml/min to 0.26 ± 0.11 mmHg/ml/min. The mean value of CFR-APV was 2.99 ± 0.88 (range: 1.28–4.74), and that of CFR-CBF was 4.18 ± 1.52 (range: 1.29–6.82), respectively. Although intracoronary papaverine produced no significant effect on arterial lactate levels, it induced a significant increase in coronary sinus lactate levels (Fig. 1). Compared to control, lactate extraction ratio significantly decreased from 36.4 ± 18.4% to−82.2 ± 58.4% after papaverine ($P < 0.001$), and all patients showed net lactate production (range −3.9−−198.0%). In addition, lactate extraction ratio significantly decreased from 35.0 ± 21.2% at control to −58.0 ± 54.0% after papaverine in a subgroup of seven patients who were classified as normal subjects. In contrast, there were no significant differences of lactate extraction ratio between before and 1 min after intracoronary nitroglycerine (31.0 ± 16.7% vs. 28.4 ± 26.0%, p = NS) in 17 patients with performing these measurements. We analyzed the data to see whether these lactate changes were correlated with CFR. There was weak but significant correlation between lactate extraction ratio after papaverine and CFR-CBF (R^2 = 0.15, $P < 0.05$). There was no correlation between lactate extraction ratio and QTc after papaverine. There was also no significant difference in lactate extraction ratio between patients with ST-T changes and those without (−96.7 ± 61.5 vs. −62.8 ± 49.8%, p = NS).

DISCUSSION

In the present study, we demonstrated that intracoronary papaverine induced myocardial lactate production
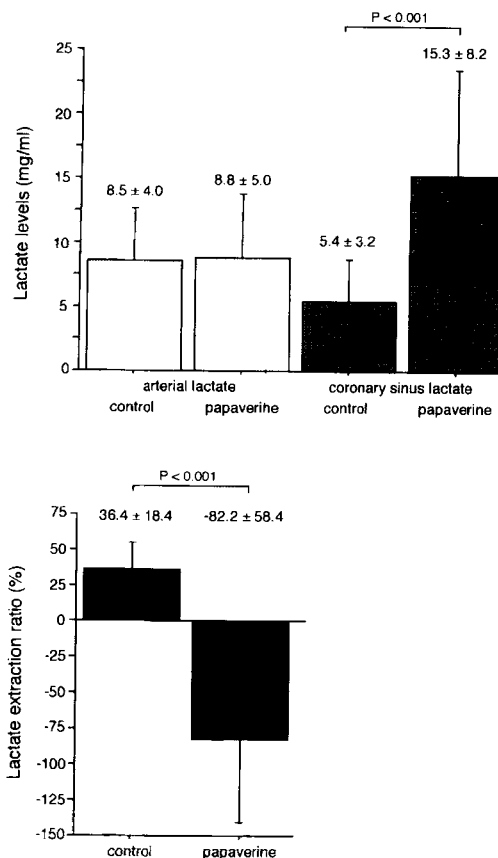

Fig. 1.   Bar graph of plasma lactate levels and lactate extraction ratio. Upper panel shows plasma lactate levels. There was no significant difference of arterial lactate levels, but coronary sinus lactate levels significantly increased after papaverine administration. Lower panel shows lactate extraction ratio. Lactate extraction ratio significantly decreased and showed net lactate production after papaverine.

in all patients with angiographically normal coronary arteries. In order to exclude the possibility that our findings may be the result of microvascular or endotherial dysfunction, we analyzed the lactate metabolism in a subgroup of seven patients who were classified into normal subjects and obtained the same results. We also showed that intracoronary nitroglycerine has no effect on myocardial lactate turnover. Although papaverine has been widely used for measurement of coronary flow reserve, potential arrhythmogenicity has been reported by several investigators [13–16]. We observed significant ST-T changes, QT prolongation, and occasional premature ventricular contractions with intracoronary papaverine in agreement to previous studies. We also observed that coronary sinus lactate levels significantly increased in all patients, and this occurred in concert with a >4.2-fold increase in coronary blood flow at the left anterior descending coronary artery.

Because lactate production is a byproduct of anaerobic

TABLE I. Hemodynamic, Angiographic, and Flow Variables at Control and Papaverine Infusion

	Control	Papaverine	P
HR (bpm)	70 ± 13	75 ± 14	0.001
SBP[a] (mmHg)	127 ± 22	118 ± 18	0.001
DP[b]	8,832 ± 2,147	8,821 ± 2,132	ns
LVEDP[c] (mmHg)	10.2 ± 4.4	11.9 ± 5.2	0.005
dP/dt (mmHg/sec)	1,543 ± 366	1,672 ± 458	0.005
CAD[d] (mm)	2.85 ± 0.54	3.27 ± 0.58	0.001
APV[e] (cm/sec)	20.2 ± 7.3	57.9 ± 18.1	0.001
CBP[f] (ml/min)	95.7 ± 36.8	384.5 ± 169.7	0.001
CVR[g] (mmHg/ml/min)	1.10 ± 0.41	0.26 ± 0.11	0.001

[a]Systolic blood pressure.
[b]Double product.
[c]Left ventricular end-diastolic pressure.
[d]Coronary arterial diameter.
[e]Average peak velocity.
[f]Coronary blood flow.
[g]Coronary vascular resistance.

glycolysis, its production by the heart and appearance within the coronary sinus are signs of myocardial ischemia [19]. There was no significant increase of arterial lactate levels after papaverine. These results suggest that the myocardium is the principal source for increase of coronary sinus lactate, and papaverine produces myocardial ischemia. Myocardial lactate production in relation to increased coronary blood flow after papaverine may seem paradoxical. Christensen et al. [17] have reported that intracoronary infusion of papaverine produced a significant increase of coronary sinus lactate levels and induced an abnormal contractile pattern despite increase in coronary blood flow in a canine model. They also showed that papaverine did not alter the endocardial to epicardial perfusion ratio compared to a control.

The above findings suggest that the vertical steal phenomenon is an unlikely candidate as the mechanism for the production of lactate by papaverine. They suggest that papaverine may be interfering with oxygen transport or uptake and in so doing may produce cellular hypoxia. Lactate production might also be caused by a shift in metabolism or a release of intracellular stores of lactate. We demonstrated that there was only weak correlation between lactate extraction ratio and coronary flow reserve, and there was no significant difference in lactate extraction ratio between patients with papaverine induced ST-T changes and those without. These results suggest that intracoronary papaverine may induce myocardial lactate production irrespective to the degree of flow reserve and ST-T changes.

As we know, there was only one report about the effect of papaverine on lactate metabolism in humans. Egashira et al. [18] have shown that intracoronary papaverine induced myocardial lactate production in patients with microvascular angina but not in control subjects.

The reason for the different results of lactate metabolism in our study and the study by Egashira et al. [18] is not known, but it may be partly related either to differences of study population or to differences in the timing of blood sampling. They had obtained blood sample 2 min after papaverine administration, which may have resulted in underestimation of lactate levels.

In conclusion, we suggest that intracoronary papaverine may produce deleterious metabolic and electrocardiographic changes in patients with normal coronary arteries. Intracoronary adenosine has been demonstrated to be no risk of ventricular arrhythmia as well as the equivalent vasodilator potency compared to papaverine [17,20]. Although we did not perform comparative study, our results suggest that adenosine may be a safer and more reliable agent for the measurement of coronary flow reserve.

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