Prevention of ischemia during percutaneous transluminal coronary angioplasty by transcatheter infusion of oxygenated Fluosol DA 20%

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ABSTRACT Catheter balloon inflation performed during percutaneous transluminal coronary angioplasty (PTCA) results in temporary interruption of coronary blood flow and subsequent myocardial ischemia. This produces transient but profound regional left ventricular dysfunction. In an effort to mitigate this inflation-related dysfunction, oxygenated Fluosol DA 20%, a perfluorochemical oxygen transport fluid, was infused distal to the balloon through the central lumen of the dilating catheter during balloon inflation. Regional wall motion during PTCA was assessed by simultaneous continuous two-dimensional echocardiography and was quantified by computer analysis. During control inflations accompanied by no intracoronary infusion or by transcatheter infusion of Ringer’s lactate solution or nonoxygenated Fluosol DA 20%, there was profound regional left ventricular dysfunction with a greater than 90% decrease in regional contraction. In contrast, regional contraction during transcatheter infusion of oxygenated Fluosol DA 20% remained at normal levels throughout balloon inflation. Distal infusion of Fluosol DA 20% during balloon inflation is a useful adjunct to PTCA, allowing longer inflation times and perhaps permitting PTCA to be performed safely in patients with significant myocardium at ischemic risk or with limited left ventricular reserve for whom the procedure is currently believed to be too hazardous. Circulation 74, No. 3, 555-562, 1986.

PERCUTANEOUS transluminal coronary angioplasty (PTCA) is a procedure that has gained wide acceptance. However, balloon inflation during this procedure results in transient interruption of coronary artery blood flow and subsequent regional ischemia. Using two-dimensional echocardiography, we have demonstrated reproducible transient regional left ventricular wall motion abnormalities during balloon inflation in patients undergoing PTCA. Prevention of regional mechanical abnormalities incurred during balloon inflation may allow prolongation of the inflation period and expansion of the patient population currently deemed eligible for PTCA. Recent evidence suggests that prolonged inflation times result in superior primary success rates and lower residual gradients and angiographic stenoses. In addition, a subset of patients with large regions of myocardium at risk or limited contractile reserve caused by prior inflation are currently at high risk for hemodynamic instability as a result of profound contractile dysfunction during balloon inflation.

Efforts to mitigate regional ischemia during balloon inflation have involved intracoronary infusion of whole blood distal to the dilatation balloon. The viscosity characteristics of whole blood make its delivery via the distal lumen of the dilating catheter difficult and its infusion at high flow rates may potentially result in significant hemolysis. Fluosol DA 20% is a perfluorochemical emulsion that can deliver oxygen effectively to ischemic tissue at adequate flow rates and has been used as a blood substitute. Therefore we tested the hypothesis that delivery of adequate oxygen to obstructed coronary beds with oxygenated Fluosol DA 20% can prevent the profound regional left ventricular wall motion abnormalities that result from balloon inflation during PTCA. We further evaluated the importance of metabolite accumulation in the production of acute ischemic regional contractile dysfunction by examining the effect of byproduct “washout” with either oxygenated Ringer’s lactate or nonoxygenated Fluosol DA 20%.
Methods

Patients. Twenty consecutive patients with 70% or greater stenosis of the proximal left anterior descending coronary artery undergoing PTCA were studied. All had normal baseline global and regional wall motion, and none had angiographically visible collaterals. Informed consent, via an institutionally approved human investigation form, was obtained in all cases. Fourteen patients were men and six were women, ranging in age from 36 to 78 years (mean 62 ± 10). Five patients had class II angina, 13 class III, and two class IV. No patient had electrocardiographic evidence of prior myocardial infarction. Sixteen patients were receiving β-blocker therapy at the time of PTCA. Fifteen patients were being treated with calcium antagonists and 18 with nitrates.

PTCA procedure. PTCA was performed with USCI balloon dilatation catheter systems ranging in diameter from 2.5 to 3.5 mm. Balloon sizes were determined by examining normal regions of the coronary artery adjacent to the stenosis. Balloon inflation times ranged from 60 to 120 sec with balloon inflation pressures of 6 to 11 atm. Multiple inflations were performed on each patient (5.4 ± 2, mean ± SD) and 2 min was allowed between balloon inflations. Before the coronary artery was entered for balloon dilatation, pulmonary arterial pressure, pulmonary capillary wedge pressure, heart rate, and systemic arterial pressure were measured. After coronary angiography the steerable balloon dilating system was positioned across the stenosis and the initial pressure gradient was measured. After each inflation, a repeat transstenotic coronary gradient was determined.

All 20 patients underwent standard noninfusion balloon inflations followed by balloon inflations accompanied by infusion of oxygenated Fluosol DA 20%. During subsequent inflations, 11 of the 20 patients (11 inflations) received oxygenated Ringer’s lactate, and five patients (six inflations) received nonoxygenated Fluosol DA 20% in random order to evaluate the consequences of metabolite washout and to provide additional control data. Each patient’s last balloon inflation was performed without infusion to demonstrate the reproducibility of the regional dysfunction incurred with balloon inflation.

Before angiography, a test dose of 0.5 ml of Fluosol DA 20% was administered intravenously. All infusate solutions were at body temperature (37.8°C) and were administered at 60 ml/min (1 ml/sec) by an angiographic power injector (Medrad, Pittsburgh, PA) connected to the central lumen of the dilating balloon catheter. Fluosol DA 20% and Ringer’s lactate solutions were bubble oxygenated at 2 liters/min for at least 30 min before the procedure to maximize oxygen content. PO2 was determined with a Corning model 168 blood gas meter within 30 min of infusion. The mean PO2 values of the oxygenated Ringer’s lactate solution and oxygenated Fluosol DA 20% emulsion were 480 and 600 mm Hg, respectively.

Quantitative two-dimensional echocardiography. A two-dimensional echocardiographic imaging plane for each patient was determined by finding the best view for visualizing transient ischemic contractile dysfunction during balloon inflation. An apical long-axis view of the left ventricle was used to evaluate the anteroseptal and anterolateral left ventricular walls. The videotape record of the two-dimensional echocardiogram was reviewed at a computer work station and end-systolic and end-diastolic frames of individual beats at less than 20 sec intervals were manually traced and digitized. Regional wall motion was quantitatively assessed by a computer algorithm that constructs a centerline between end-diastolic and end-systolic contours (figures 1A and 1B). This technique was initially designed for assessing contrast left ventricular angiograms2 and the method for chord analysis was modified for use on two-dimensional echocardiograms. One hundred equidistant perpendicular chords are constructed between the boundaries, which represent motion of corresponding points of the left ventricular endocardium (figure 2). Chord shortening was normalized to the end-diastolic perimeter and reported as a dimensionless value. The average value of 10 adjacent chords centered in the region of initial maximal contractile dysfunction was determined, and these same 10 chords were evaluated serially during baseline, balloon inflation, and recovery periods.
The validity of the centerline technique for quantitating regional wall motion by two-dimensional echocardiography was established by the application of the technique to a cohort of eight patients with normal global and regional wall motion and eight patients with chronic anterior wall myocardial infarction who had undergone both contrast ventriculography and two-dimensional echocardiography. Analysis of regional chord shortening revealed a correlation coefficient of .74 with clear separation of the normal group from the group with anterior wall infarction (p < .01). Chronic anterior wall infarcts were chosen because of the analogy they provided to the regional wall motion abnormalities expected during PTCA of proximal left anterior descending coronary arteries.

Three types of variability in regional wall motion measurement with this technique were evaluated. To determine intraobserver variability, 15 end-diastolic frames and 15 end-systolic frames taken from apical long-axis recordings from five patients with coronary artery disease were traced by the same operator, with at least 2 days between tracings. Intraobserver variability in quantification of mean chord shortening of 10 chord groups in the septal and apical areas was 7 ± 4% and 10 ± 7% of mean motion, respectively.

To determine interobserver variability, the same 15 end-diastolic and 15 end-systolic frames were traced by different operators. Interobserver variability was 12 ± 6% in the septal region and 14 ± 7% in the apex. Beat-to-beat variability was determined in five patients with coronary artery disease continuously imaged by two-dimensional echocardiography for 3 min in a baseline resting state. Quantification of regional wall motion was performed by the same operator (on the same day) on 10 beats, each separated by 10 seconds. Beat-to-beat variability in mean chord shortening was 10 ± 5% in the 10 chord group in

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**FIGURE 2.** A. Computer representation of the chords connecting the end-diastolic (ED) and end-systolic (ES) boundaries of a normal baseline beat are illustrated (lengths normalized to the end-diastolic perimeter). B. The normalized chord shortening lengths (ordinate) of the 100 chords (abscissa) counterclockwise from the aorta to the mitral anulus are plotted for a baseline, pre-PTCA beat. The apex lies at approximately chord 50. C and D. Computer representation of left ventricular wall motion 30 sec after the onset of PTCA balloon inflation in the left anterior descending artery. The left ventricular anteroapical segment is shown to be dyskinetic, with chord shortening values that become negative (chords 25 to 70).
the septal area and 12 ± 7% in the 10 chord group at the apex. To account for these variabilities, a change in wall motion was considered significant only if there was a 25% decrease in chord shortening from baseline.

Statistics. Mean and standard deviation of summed data are reported. In each individual patient, chord shortening at 45 sec after the onset of balloon inflation during infusion of Fluosol DA 20% was compared with the temporally closest noninfusion or Ringer’s lactate infusion sequence by repeated measures of analysis of variance. Statistical significance was identified at p values <.05.

Results

All 20 patients underwent successful PTCA, with a reduction of angiographic stenosis from 88.5 ± 9% to 8 ± 12% after PTCA. The initial transstenotic gradient of 55.4 ± 19 mm Hg was reduced to 2.1 ± 5 mm Hg after the final balloon inflation. No patient experienced any complication of the PTCA procedure.

Balloon inflation during PTCA resulted in a reproducible pattern of regional left ventricular dysfunction. Temporal changes in chord shortening during routine infusions, infusions accompanied by infusion controls, infusions accompanied by Fluosol DA 20% administration, and during the final infusions without infusion are shown in table 1 in all 20 patients. Compared with baseline values, a statistically significant decline in chord shortening (p < .01) occurred in the group without infusion and the group receiving Ringer’s lactate within 20 sec after balloon inflation. Dysfunction persisted throughout balloon inflation, falling from a normalized 100% contraction at baseline to 5.7 ± 11.7% and 7.1 ± 5.1% of baseline chord shortening values, respectively. Regional chord shortening returned to baseline levels by 43 ± 17 sec after balloon deflation. During infusion of nonoxygenated Fluosol DA 20% a dysfunctional contractile pattern similar to that seen with Ringer’s lactate was noted. A decline in regional chord shortening to 12 ± 42% of baseline levels was observed at peak dysfunction. The onset of dysfunction occurred within 20 sec after balloon inflation, similar to the temporal changes found during balloon inflation without infusion or with infusion of Ringer’s lactate.

In marked contrast, regional left ventricular function was preserved when balloon inflation was accompanied by infusion of oxygenated Fluosol DA 20% for infusion as long as 120 sec (figures 3 and 4). Regional chord shortening at 20, 40, and 60 sec into balloon inflation sequences remained at 97 ± 16%, 98 ± 13%, and 94 ± 14%, respectively. After discontinuation of the infusion of oxygenated Fluosol DA 20% and despite the concomitant deflation of the balloon, there was an abrupt decline in regional chord shortening to 74 ± 26% of baseline values in the first 20 sec after balloon deflation (p < .01). Chord shortening returned to baseline levels by 40 sec after balloon deflation and discontinuation of oxygenated Fluosol DA 20%. The final balloon inflation with no infusion resulted in changes in chord shortening that were identical temporally and in magnitude to the initial control balloon inflation without infusion.

Hemodynamics. Baseline measurements of mean, systolic, and diastolic pulmonary arterial pressure were 17 ± 5, 26 ± 7, and 12 ± 5 mm Hg, respectively. Baseline pulmonary capillary wedge pressures were 10 ± 4 mm Hg, heart rate was 72 ± 17 beats/min, and arterial blood pressure was 127 ± 20/72 ± 13 mm Hg. Heart rate and arterial blood pressure were unchanged (p < .10, p = NS) after intracoronary infusions. Pulmonary capillary wedge pressure increased to 16 ± 5 mm Hg (p < .01) and mean, systolic, and diastolic pulmonary arterial pressures rose to 24 ± 7, 35 ± 12, and 17 ± 6 mm Hg, respectively (p < .01), after the final balloon inflation of the sequence.

Discussion

This study demonstrates that oxygenated Fluosol DA 20% (PO₂ greater than 600 mm Hg) infused

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<td>Percent regional chord shortening during PTCA sequences</td>
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Data expressed as percent chord shortening of an apical segment of the left ventricle (baseline functional contraction is 100%).

^p < .01 compared with no infusion, Ringer’s infusion, and nonoxygenated Fluosol DA 20%.

^p < .01 compared with 60 sec into balloon inflation in the oxygenated Fluosol DA 20% sequence.
FIGURE 3. A and B, A second baseline representation of left ventricular wall motion baseline 4 min after that shown in figure 2 in the same patient. Chord shortening is shown to be uniform. C and D. Left ventricular wall motion 30 sec after PTCA balloon inflation with Fluosol DA 20% infused at 60 ml/min into the left anterior descending artery through the central lumen of the catheter distal to the balloon occlusion. Normal wall motion is noted to be preserved, compared with the response shown in figure 2, C and D.

through the distal lumen of the dilating balloon catheter at 60 ml/min during balloon inflation prevents the regional dysfunction incurred during control balloon inflation without infusion. Administration of Fluosol DA 20% in total doses of less than 400 ml was safe and well tolerated in this patient population.

The salutary effects of myocardial contractile preservation during balloon inflation in PTCA may allow prolongation of balloon inflation times and affect the eligibility of patients previously at high risk because of limited contractile reserve or large regions of myocardium at risk. Prolongation of balloon inflation times may result in improved primary success rates, increased postdilatation lumen diameter, and lower residual transstenotic gradients. Although improvements in lumen diameter and transstenotic gradient have been demonstrated when 30 and 60 sec balloon inflations were compared, to date longer inflation times have not been evaluated. Thus it remains unclear what length of balloon inflation is optimal for maximal reduction of coronary obstruction. Recent data have linked lower residual stenosis and residual transstenotic gradients with reduced restenosis rates. The optimal inflation variables required have not been elucidated.

Distal coronary artery perfusion with oxygenated fluorocarbon during PTCA has recently been reported
by Anderson et al. A randomized crossover study with oxygenated Ringer’s lactate and oxygenated Fluosol DA 20% revealed minimal reduction of ST segment elevation and delay in the onset of angina during perfusion with fluorocarbon. That study evaluated prevention of regional ischemia by monitoring ST segment shifts in leads II, aVF, and V₅ and by the subjective analysis of the onset, severity, and duration of chest pain. We evaluated regional wall motion during balloon inflation, a variable that has been demonstrated to be a more sensitive indicator than electrocardiographic changes in assessing ischemia. Battler et al. demonstrated that echocardiographic evidence of regional myocardial dysfunction preceded electrocardiographic changes in dogs and concluded that regional contractile abnormalities are a better predictor of ischemia than ST segment changes. The time to onset of regional hypokinesia was 15 sec after occlusion in their study and is in close agreement with the time course of regional dysfunction in the control balloon inflation observed in our study. Other clinical studies under varying conditions of myocardial supply-demand imbalance support the sensitivity and advantage of monitoring contractile function rather than the electrocardiogram as an early and consistent indicator of ischemic change. We previously demonstrated wall motion abnormalities by two-dimensional echocardiography in 100% of patients undergoing PTCA for proximal stenoses of the left anterior descending coronary artery. ST segment changes occurred 20 sec after balloon inflation in only 36% of patients when monitoring limb leads and in 57% when lead V₅ was also monitored. More extensive electrode placement resulted in increased electrocardiographic sensitivity. Hauser et al. have demonstrated similar qualitative echocardiographic and electrocardiographic findings during myocardial ischemia induced by PTCA. We quantified regional wall motion as assessed by two-dimensional echocardiography in an effort to monitor more accurately the temporal sequence and extent of dysfunction and to permit greater objectivity when evaluating various interventions. We modified a centerline method previously applied to contrast left ventriculography that appears less subject to inconsistencies incurred by alternative methods that utilize selected or derived reference points.

The cause of early contractile dysfunction during regional myocardial ischemia remains controversial. ATP and creatine phosphate stores diminish, but not to levels that can account for the observed early mechanical dysfunction. Alternative events proposed to account for early mechanical dysfunction include regional accumulation of phosphate, lactate, and hydrogen ions. Cobbe and Poole-Wilson and others have noted a temporal relationship between the fall in intracellular pH and dP/dt in isolated muscle preparations.

During regional ischemia, oxygen deprivation rapidly results in conversion from aerobic to anaerobic metabolism. Anaerobic metabolism results in lactate production, inefficient substrate utilization, and inefficient ATP synthesis. The major metabolic by-products that accumulate during regional ischemia include CO₂, lactate, and H⁺ ions. Thus potentially deleterious metabolic by-products increase regionally because of conversion to anaerobic pathways and interference with washout secondary to transient interruption of regional coronary flow. Our results indicate that adequate oxygen delivery is of greater importance than metabolite washout at infusion rates of 60 ml/min, as demonstrated by the ineffectiveness of both oxygenated Ringer’s lactate and nonoxygenated Fluosol DA 20% in preventing regional dysfunction during balloon inflation.

Alternative explanations for regional contractile protection during multiple balloon inflations may center on the findings from prior studies that have demonstrated the dynamic nature of collaterals during coronary angioplasty. In our study, the presence of collaterals was evaluated angiographically before PTCA but was not evaluated during balloon inflation. Prior studies in our institution have demonstrated no
change in the magnitude of regional dysfunction or temporal pattern between first and last balloon inflation sequences. Thus collaterals, if present, appear to have little influence on regional mechanical events. The temporal sequence of regional dysfunction and the magnitude of this dysfunction are again reproducible in the balloon inflation sequences without infusion in this study. Long-term use of medications was variable but would not be expected to influence the results of this study, since patients served as their own controls in a multi-inflation sequence.

Fluosol DA 20% has several favorable characteristics that are potentially responsible for its beneficial effects in preserving regional cardiac contraction during PTCA:

1. The perfluorocarbon emulsion has a linear oxygen dissociation curve, allowing it to deliver oxygen effectively to ischemic tissue. When oxygenated to a PO2 of greater than 600 mm Hg it has the capacity to deliver approximately 5.0 vol % of oxygen to ischemic tissue. This figure is similar to that found with whole blood at a hematocrit of 43%. Ringer’s lactate solution, on the other hand, when oxygenated by the same method is capable of delivering less than 2 vol % of oxygen.

2. Fluosol DA 20% has a CO2 affinity comparable to that of whole blood, allowing it to efficiently remove CO2 from ischemic regions.

3. The viscosity of Fluosol DA 20% is approximately 50% that of whole blood at body temperature. This feature, combined with its particle size of 0.1 to 0.2 μm (1/70 the volume of a red blood cell) may allow its delivery to capillary beds not normally perfused.

Prior animal studies have confirmed the effectiveness of fluorocarbons in protection against myocardial ischemia. Kloc, et al. evaluated the protective effects of intravenous administration of fluorocarbon in a canine preparation of myocardial ischemia. Myocardial ischemia during brief coronary occlusion was reduced when fluorocarbons were administered intravenously (40 ml/kg), as evidenced by smaller rises in intramyocardial CO2 and increased intramyocardial PO2. In animals receiving perfluorocarbons, prolonged occlusion resulted in infarction of 70 ± 5.4% of the myocardium at risk, compared with 103.6 ± 2.6% of the jeopardized myocardium in animals receiving salt solutions.

Additionally, Spears et al. have shown that distal infusion of oxygenated Fluosol during prolonged balloon coronary occlusion (>5 min) in dogs could be performed safely and resulted in protection against myocardial ischemia assessed electrocardiographically.

ly and hemodynamically by left ventricular end-diastolic pressure and dP/dt.

We have noted that cessation of intracoronary administration of Fluosol DA 20% at the end of balloon inflation results in an abrupt transient fall in regional FDP shortening (p < .01) despite concomitant balloon deflation. Possible explanations for this observation include the following: (1) Abrupt closure of capillary beds opened by the perfluorocarbon emulsion may have occurred after discontinuation of Fluosol DA 20%; (2) O2 delivery during administration of Fluosol DA 20% may have been more effective during infusion than blood reperfusion due to improvement in the O2 affinity characteristic of the blood-fluorocarbon mixture in ischemic tissue; (3) improved delivery of oxygen to ischemic border zones may have occurred because of the minute particle size and improved diffusion.

In summary, balloon inflation during PTCA results in transient but profound regional wall motion abnormalities that can be prevented by delivery of oxygenated Fluosol DA 20% through the distal lumen of the dilating catheter. Administration of oxygenated Fluosol DA 20% may be an important adjunct during coronary angioplasty, allowing more widespread utilization of the procedure and improved primary and long-term success.

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