JACC Vol. 20, No. 7
December 1992:1599–603

Early and Rapid Prediction of Patency of the Infarct-Related Coronary Artery by Using Left Ventricular Wall Thickness as Measured by Two-Dimensional Echocardiography

GARY H. FRIEDMAN, MD, FACC, MICHAEL S. LEE, MD, SCOTT L. ROTH, MD, ANDREW M. GRUNWALD, MD, FACC, MONTY M. BODENHEIMER, MD, FACC
New Hyde Park, New York

Objectives. **The aim of this study was to determine whether echocardiography can distinguish between persistent coronary occlusion and reperfusion.**

Background. **There are no adequate clinical or noninvasive laboratory markers to accurately predict successful reperfusion in an acute myocardial infarction.**

Methods. **In a closed chest swine model, the effect of reperfusion on myocardial wall thickness was studied by comparing a 150-min total coronary artery occlusion (group 1) with 120 min of occlusion followed by 30 min of reperfusion (group 2) in the area of risk as measured by echocardiography. Wall thickness was measured at baseline and at 90 and 150 min.**

Results. **In group 1 (n = 4), there was no appreciable change in mean wall thickness from 90 min to 150 min of occlusion at either end-diastole or end-systole (0.54 ± 0.02 to 0.52 ± 0.03 cm, 0.55 ± 0.03 to 0.54 ± 0.03 cm, respectively; p = NS). In contrast, in group 2 (n = 6), an increase in mean wall thickness from 0.53 ± 0.02 to 0.97 ± 0.05 cm at end-diastole and from 0.56 ± 0.04 to 1.04 ± 0.07 cm at end-systole was found from 90 min of occlusion to 30 min of reperfusion (p < 0.001). Reperfusion resulted in an increase in wall thickness of 83 ± 11% at end-diastole and 92 ± 17% at end-systole. In contrast, persistent coronary occlusion showed minimal changes of −3.0 ± 5% at end-diastole and −2.0 ± 6% at end-systole.**

Conclusions. **This study confirms the hypothesis that an increase in wall thickness can accurately distinguish between reperfusion and permanent coronary occlusion.**

(J Am Coll Cardiol 1992:1599–603)

Large scale clinical trials have demonstrated a significant reduction in mortality in patients with acute myocardial infarction treated with thrombolytic agents (1–3). Mortality is particularly low among patients treated within 3 h of the onset of symptoms (1,2). Several studies have shown that patency of the infarct-related artery was the most important predictor of late survival (4,5). Unfortunately, thrombolytic agents fail to restore myocardial flow in 30% to 40% of patients (6–9). Acute or "salvage" percutaneous coronary angioplasty has been shown to be effective in achieving rapid patency of the infarct-related vessel (10). However, to determine which patients require invasive therapy, it is necessary to rapidly determine whether patency was achieved with a thrombolytic agent.

Clinical markers for successful reperfusion, such as rapid resolution of symptoms, normalization of ST segment elevation, and reperfusion arrhythmias, have not proved to be either sensitive or specific (11). Early washout and time to peak of total creatine kinase (CK) or MB fraction of CK after thrombolytic therapy have been used to detect reperfusion (12). However, the delay of 4 to 8 h in detecting the peak precludes its use for determining the need for acute reperfusion (13).

Recent studies have shown that the MM_3 isoform of CK, which is converted to MM_2 and MM_1, is markedly elevated within 15 to 30 min of successful reperfusion. The assay for detecting this isoform, however, requires ≥90 min (14). In addition, although newer radioisotopes such as sestamibi can detect evidence of reperfusion, the methodology is time consuming and cumbersome (15).

Two-dimensional echocardiography is a very sensitive noninvasive method for detecting areas of ischemia and infarction. Experimental data have shown that the development of asynergy and the loss of systolic thickening are among the first manifestations of ischemia (16). These observations have been used to diagnose acute myocardial infarction in the emergency room setting (17). However, their role in detecting reperfusion has been limited. Indeed, it has been shown in an open chest dog model that despite reperfusion, asynergy and loss of systolic thickening persist, consistent with the concept of myocardial stunning (18). Yet the ease and ability with which echocardiography can be performed would make it an ideal test to detect acute reperfusion. Therefore, we used a closed chest swine model to determine whether myocardial wall thickness could dis-

From the Harris Chasanoff Heart Institute, The Division of Adult Cardiology, Long Island Jewish Medical Center, New Hyde Park, New York.

Manuscript received January 10, 1992; revised manuscript received June 1, 1992, accepted June 11, 1992.

Address for correspondence: Gary H. Friedman, MD, The Harris Chasanoff Heart Institute, The Division of Adult Cardiology, Long Island Jewish Medical Center, New Hyde Park, New York 11042.

0735-1097/92/$5.00

tinguish between persistent coronary occlusion and reperfusion.

Methods

Surgical protocol. Sixteen male Hampshire pigs matched for age and weight were randomly assigned either to permanent occlusion (group 1) or to a transient 2-h occlusion followed by 30 min of reperfusion (group 2). The study was approved by the Institutional Animal Care and Use Committee of the Long Island Jewish Medical Center. The animals were anesthetized with an initial intramuscular injection of ketamine followed by a continuous infusion of morphine sulfate and vecuronium. The pigs were intubated and attached to a Harvard pump respirator using room air. Under sterile technique, the right carotid artery and jugular vein were isolated. An 8F introducer was inserted into the carotid artery and a 5F Swan-Ganz catheter was inserted into the jugular vein for continuous monitoring of pulmonary capillary wedge pressure. Continuous electrocardiographic (ECG) monitoring was carried out with R2 defibrillator electrodes applied to the chest wall and attached to a Hewlett-Packard defibrillator.

Coronary angiography. Coronary angiography was performed with an 8F Amplatz guiding catheter. After the left anterior descending coronary artery was visualized, the animals were randomly assigned to either transient or permanent occlusion. *Transient occlusion* was carried out by negotiating an ACS ACK angioplasty catheter down the left anterior descending artery just distal to the first large diagonal branch. Once in position, it was inflated. Repeat contrast injection was performed to verify total occlusion. After 120 min of occlusion, the balloon was deflated and removed. Patency of the vessel was verified by repeat angiography.

Permanent occlusion was accomplished by passing a detachable silicon balloon (Interventional Therapeutics) down the left anterior descending artery; once positioned at the level just distal to the first large diagonal branch, the balloon was inflated and detached. Repeat contrast injection was performed to verify the maintenance of a complete occlusion throughout the protocol. All animals received a bolus dose of 5,000 U of heparin before occlusion.

Hemodynamics. Hemodynamic monitoring was performed by using a Statham transducer at baseline and every 30 min until the end of the protocol. Continuous ECG monitoring for ST segment elevation and arrhythmias was performed throughout the protocol. In swine that developed ventricular fibrillation, defibrillation was performed at an energy level of 200 J. Any pig requiring more than three defibrillations was excluded from the final analysis.

Two-dimensional echocardiography. Two-dimensional echocardiography was performed utilizing a Hewlett-Packard Sonos 500 with either a 3.5 or 5 MHz transducer. With the pig in the supine position, short-axis images from the right and left parasternal windows were obtained of the left ventricle at the level of the midpapillary muscles. These images were performed at baseline (before occlusion) and repeated at 90 min and at 150 min after baseline (or after 30 min of reperfusion for the transient occlusion group). All images were recorded on videotape.

All measurements were obtained in the area of the infarction as defined by a region of asynergy subtended by the left anterior descending artery. Utilizing the On-Line software of the HP Sonos 500, wall thickness was measured at end-diastole and end-systole in cm. End-diastole was defined as the frame that coincided with the onset of the QRS complex. End-systole was defined as the frame that had the smallest cavity area.

The percent change in wall thickness from 90 to 150 min after occlusion was calculated as percent change = (Wall thickness at 150 min − Wall thickness at 90 min)/Wall thickness at 90 min × 100. Systolic thickening at baseline and at 90 and 150 min after occlusion was expressed as the percent change in wall thickness from end-diastole to end-systole.

All studies were analyzed in blinded fashion by an independent observer. A study was included in the final analysis only if the endocardial and epicardial borders were clearly delineated by the observer.

Statistics. Data were analyzed by using the Student paired *t* test and analysis of variance for repeated measures where appropriate. All data are reported as the mean value ± 1 SEM. The null hypothesis was rejected at a level of 0.05.

Results

Study groups. Of the 16 randomized pigs, 6 were excluded: 1 pig because of refractory ventricular fibrillation and 5 pigs because of poor image quality. A total of 10 pigs—4 in group 1 and 6 in group 2—were included in the final analysis. All 10 of these pigs developed acute ST segment elevation immediately after occlusion of the left anterior descending artery. Ventricular fibrillation developed within 20 min of the occlusion in all pigs in the permanent occlusion group and in four of the six pigs in the transient occlusion group (p = NS). Defibrillation was successful in all animals.

Hemodynamics (Table 1). Mean arterial pressure, mean pulmonary capillary wedge pressure and heart rate were similar in both groups throughout the protocol.

Echocardiography. Baseline regional wall motion of the left ventricle was normal in both groups. Immediately after occlusion of the left anterior descending artery, an area of asynergy subtended by this artery was observed in all pigs. This abnormality persisted throughout the 150 min and 120 min of occlusion in group 1 and group 2, respectively. There was no improvement in wall motion after 30 min of reperfusion in group 2.

Figure 1 shows the changes in wall thickness in the infarct area for each animal. Wall thickness in diastole was similar at baseline and at 90 min in both groups. After coronary occlusion, systolic wall thickness decreased significantly in all animals in both groups. In the permanent occlusion

group, no significant change occurred from 90 to 150 min in either diastole or systole (Fig. 1, A and B). In contrast, in group 2, reperfusion was followed by a significant increase in thickness both in diastole and systole (Fig. 1, C and D, $p < 0.001$).

There was a clear separation in the mean percent change in wall thickness from 90 to 150 min between groups 1 and 2 (Fig. 2). At end-diastole, wall thickness in group 2 increased by 83 ± 11% compared with −3.0 ± 5% in group 1 ($p = 0.001$). Similarly, the mean percent change in wall thickness from 90 to 150 min was 92 ± 17% compared with −2.0 ± 6% at end-systole for group 2 and group 1, respectively ($p < 0.001$).

There was no significant difference between the groups at any time with regard to overall systolic thickening (Fig. 3). As expected, there was complete loss of systolic thickening at 90 min of occlusion for both group 1 and group 2 (2.0 ± 3.1% and 2.0 ± 4.0%, respectively, p = NS). This loss of systolic thickening persisted in group 1 at 150 min of occlusion. Similarly, in group 2, no improvement was seen after 30 min of reperfusion (3 ± 2.6% and 7 ± 2.5%, respectively, p = NS).

Table 1. Hemodynamic Data for the 10 Study Pigs

	Baseline	90 Minutes	150 Minutes
Mean Arterial Pressure (mm Hg)			
Group 1			
1	60	120	122
2	163	213	157
3	65	105	116
4	7*	100	106
Mean	90	135	125
SEM	24.5	26.5	11.1
Group 2			
1	103	87	87
2	110	127	117
3	76	108	120
4	55	110	107
5	94	121	113
6	73	84	123
Mean	85	106	111
SEM	8.5	7.1	5.3
Mean Pulmonary Capillary Wedge Pressure (mm Hg)			
Group 1			
1	6	12	10
2	10	8	7
3	4	8	12
4	4	10	9
Mean	6	10	10
SEM	1.4	0.9	1.0
Group 2			
1	16	20	20
2	8	7	9
3	8	17	18
4	5	12	10
5	6	11	15
6	8	8	8
Mean	9	13	13*
SEM	1.6	2.0	2.1
Mean Heart Rate (beats/min)			
Group 1			
1	76	94	76
2	100	74	72
3	107	110	110
4	110	98	94
Mean	98	94	88
SEM	7.7	7.6	8.6
Group 2			
1	56	92	150
2	108	84	150
3	96	80	98
4	104	130	110
5	56	58	90
6	100	52	95
Mean	87	83	116*†
SEM	9.8	11.4	11.2

*$p < 0.05$ compared with baseline value. †$p < 0.05$ compared with value at 90 minutes. Group 1 = pigs with permanent occlusion; Group 2 = pigs with 2 h of occlusion followed by 30 min of reperfusion.

Discussion

The present study demonstrates that reperfusion causes an increase in myocardial wall thickness in the area of risk as measured by echocardiography. This increase was consistently seen 30 min after reperfusion. In contrast, no appreciable change in wall thickness was noted in the group with permanent occlusion. Indeed, the persistence of thinning in this group contrasted with the increase in wall thickness after reperfusion results in a clear separation between the two groups (Fig. 2). Not unexpectedly, other measures including wall motion did not discriminate between the two groups. To date, this is the first study to compare the effects of reperfusion and persistent coronary occlusion on wall thickness.

Mechanism of increased myocardial wall thickness. Several mechanisms have been proposed to explain the increased wall thickness after reperfusion. Gaasch and Bernard (19), and Heyndrickx et al. (16) described a transient increase in end-diastolic wall thickness early after short periods of reperfusion in the dog. The time course of this phenomenon paralleled the reactive hyperemic response. However, these transient hyperemic responses cannot explain the increased wall thickness after reperfusion with longer periods of occlusions when the hyperemic response is absent or minimal (20).

Another mechanism that may be responsible for an increase in wall thickness in reperfused myocardium is myocardial cell swelling. In a study of dogs exposed to prolonged ischemia, Whalen et al. (21) noted a sudden and explosive swelling of the myocardium on reperfusion. Much of this swelling occurred within 2 min of reperfusion and was associated with a marked increase in intramyocardial sodium and water in the reperfused tissue. Such swelling has been postulated to be due to the loss of the myocardial cell's capacity to regulate cell volume.

JACC Vol. 20, No. 7
December 1992:1599–603

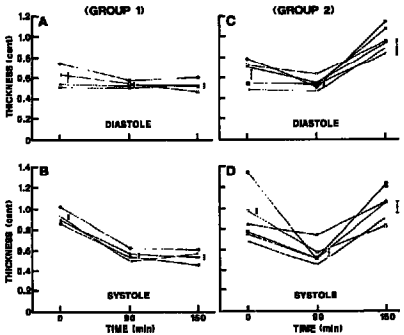
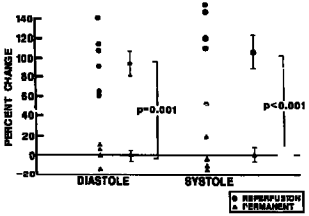


Figure 1. Change in wall thickness (in cm) from baseline to 150 min in the zone of infarction in systole and diastole for both group 1 (permanent occlusion, n = 4) and group 2 (2 h of occlusion + 30 min of reperfusion, n = 6). Mean values ± 1 SEM are shown at the right of each panel.

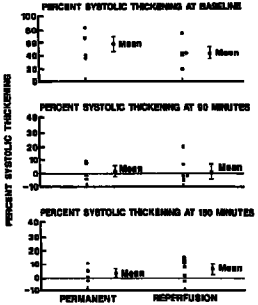
The role of microvascular damage has also been implicated in the genesis of myocardial cell swelling. Kloner et al. (22) noted a marked architectural disorganization caused primarily by massive myocardial swelling in the canine myocardium. The swelling was characterized by swollen mitochondria and intracellular vacuoles and by an increased separation of myofibrils. In addition, severe capillary damage resulting in large gaps in the capillary endothelium, interstitial fibrin deposits and extravascular red blood cells were noted. Microvascular damage, when severe, may lead to a marked myocardial hemorrhage. Reperfusion after 2 h of ischemia in pigs is associated with gross intramyocardial hemorrhage that is localized within the boundaries of the infarct (23). Such hemorrhage may contribute to an increase in wall thickness.

Figure 2. Percent change in mean wall thickness from 90 to 150 min in the zone of infarction in systole and diastole for group 1 (permanent occlusion [triangles], n = 4) and group 2 (2 h of occlusion + 30 min of reperfusion [circles], n = 6). Mean values ± 1 SEM are shown.



Relation between increased wall thickness and viability. The relation between an increase in wall thickness and myocardial viability remains unclear. Haendchen et al. (18) used two-dimensional echocardiography in dogs to show a marked increase in wall thickness of reperfused myocardium after 60 or 180 min of coronary occlusion. The extent of myocardial necrosis, as assessed by tetrazolium staining, correlated with the degree of increase in wall thickness observed after reperfusion. They concluded that the increased regional end-diastolic wall thickness after reperfusion may be an index of irreversibly damaged myocardium.

Figure 3. Percent systolic thickening in the zone of infarction from baseline to 150 min for group 1 (permanent occlusion [circles], n = 4) and group 2 (2 h of occlusion + 30 min of reperfusion [squares], n = 6). Mean values ± 1 SEM are shown.



No comparison group of permanent occlusion was studied. This conclusion, however, contrasts with the observations made by Murphy et al. (24). While studying the time course of myocardial damage in the pig, they found an increase in end-diastolic wall thickness of reperfused myocardium after 30 and 120 min of coronary occlusion. However, they did not attempt to correlate the changes in wall thickness with infarct size. Miyazaki et al. (23), using a similar model, found that 30 min of coronary occlusion results in only a small amount (11 ± 7%) of tissue necrosis in the risk area whereas 120 min of coronary occlusion results in near complete (96 ± 2%) necrosis of the risk area (22). Thus, an increase in wall thickness after reperfusion may not necessarily represent irreversibly damaged myocardium.

Limitations of the study. Several potential methodologic limitations exist in the present study. The exact duplication of anatomically defined short-axis planes may be difficult. However, we were careful to always use the original planes at the midpapillary muscle level. In addition, time interval to reperfusion was 2 h in our experimental model whereas this interval is variable in the clinical setting. Reperfusion after 2 h of occlusion in the pig results in near complete necrosis of the myocardium at risk. Thus, this finding should be applicable in patients with delayed reperfusion in whom only small amounts of myocardium are salvageable.

Reperfusion was achieved in a sudden manner in our model whereas reflow may be achieved more slowly in the clinical setting. Also, in contrast to our pig model, up to 10% to 20% of patients with coronary disease before infarction have good collateral flow (25). Although the nature of reperfusion in humans may be dissimilar from that in our experimental model, previous studies (16,19) have shown that the increase in wall thickness does not result from a transient increase in blood volume. Moreover, increase in wall thickness persists beyond the reactive hyperemic time period (15,16). Factors other than blood flow such as myocardial cell swelling and microvascular damage may be the principal causes of an increase in wall thickness (21,22).

Conclusions. Despite the increasing use of thrombolytic agents in patients with acute myocardial infarction, noninvasive identification of reperfusion has remained a significant challenge. Our study confirms the hypothesis that an increase in wall thickness can accurately distinguish between reperfusion and persistent coronary occlusion. Further studies in humans will be required to confirm whether two-dimensional echocardiography can be used to noninvasively predict patency of the infarct-related artery.

We thank Tarun Kumar for technical assistance.

References

1. Gruppo Italiano per lo Studio della Streptochinasi Nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic therapy in acute myocardial infarction. Lancet 1986;1:397–401.
2. AIMS Trial Study Group. Effect of intravenous APSAC on mortality after myocardial infarction: preliminary report of a placebo-controlled clinical trial. Lancet 1988;1:545–9.
3. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected myocardial infarction: ISIS-2. Lancet 1988;2:349–60.
4. Kennedy JW, Ritchie JL, Davis KB, Fritz JK. Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. N Engl J Med 1983;309:1477–82.
5. Dalen JE, Gore JM, Braunwald E, Borer J, Goldberg RJ, et al. Six and twelve month follow-up of the phase I Thrombolysis in Myocardial Infarction trial (TIMI) trial. Am J Cardiol 1988;62:179–85.
6. Rentrop KP. Thrombolytic therapy in patients with acute myocardial infarction. Circulation 1985;71:627–31.
7. Mathey DG, Schofer J, Sheehan FJ, Becher H, Tilsner V, Dodge HT. Intravenous urokinase in acute myocardial infarction. Am J Cardiol 1985;55:878–82.
8. The Thrombolysis in Myocardial Infarction (TIMI) Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase 1 findings. N Engl J Med 1985;312:932–6.
9. Topol EJ, Califf RM, George BS, et al. A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. N Engl J Med 1987;317:581–8.
10. Fung AY, Lai P, Topol EJ, et al. Value of percutaneous transluminal coronary angioplasty after unsuccessful intravenous streptokinase therapy in acute myocardial infarction. Am J Cardiol 1986;58:686–91.
11. Califf RM, O'Neil W, Stack RS, et al. Failure of simple clinical measurements to predict perfusion status after intravenous thrombolysis. Ann Intern Med 1988;108:658–62.
12. Gore JM, Roberts R, Bell SP, et al. Peak creatine kinase as a measure of effectiveness of thrombolytic therapy in acute myocardial infarction. Am J Cardiol 1987;59:1214–8.
13. Roberts R. Reperfusion and the plasma isoforms of creatine kinase isoenzymes: a clinical perspective. J Am Coll Cardiol 1987;9:464–6.
14. Garabedian HD, Gold HK, Yasuda T, et al. Detection of coronary artery reperfusion with creatine kinase-MB determinations during thrombolytic therapy: correlation with acute angiography. J Am Coll Cardiol 1988;11:779–34.
15. Freeman I, Grunwald AM, Hoory S, Bodenheimer MM. Effect of coronary occlusion and myocardial viability on myocardial activity of technetium-99m-sestamibi. J Nucl Med 1991;32:292–8.
16. Heyndrickx GR, Baig H, Nellens P, Leusen I, Fishbein MC, Vatner SF. Depression of regional blood flow and wall thickening after brief coronary occlusions. Am J Physiol 1978;234(suppl 6):H653–4.
17. Peels CH, Visser CA, Funke Kupper AJ, et al. Usefulness of two dimensional echocardiography for immediate detection of myocardial ischemia in the emergency room. Am J Cardiol 1990;65:687–91.
18. Haendchen RV, Corday E, Torres M. Increased regional end-diastolic wall thickness early after reperfusion: a sign of irreversibly damaged myocardium. J Am Coll Cardiol 1984;3:1444–53.
19. Gaasch WH, Bernard SA. The effect of acute changes in coronary blood flow on left ventricular end-diastolic wall thickness: an echocardiographic study. Circulation 1977;56:593–8.
20. Gaasch WH, Bing OHL, Pine MB, et al. Myocardial contracture during prolonged ischemic arrest and reperfusion. Am J Physiol 1978;235:H619–27.
21. Whalen DA Jr, Hamilton DG, Ganote CE, Jennings RB. Effect of a transient period of ischemia on myocardial cells. I. Effects on cell volume regulation. Am J Pathol 1974;74:381–97.
22. Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. J Clin Invest 1974;54:1496–508.
23. Miyazaki S, Fujiwara H, Onodera T, et al. Quantitative analysis of contraction band and coagulation necrosis after ischemia and reperfusion in the porcine heart. Circulation 1987;75:1074–82.
24. Murphy M, Chua FP, Kane JJ, Straub KD. Ventricular performance and biochemical alteration of regional ischemic myocardium after reperfusion in the pig. Am J Cardiol 1982;50:821–8.
25. Stadius ML, Maynard C, Fritz JK, et al. Coronary anatomy and left ventricular function in the first 12 hours of acute myocardial infarction: the Western Washington randomized intracoronary streptokinase trial. Circulation 1985;72:292–301.