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EDITORIAL REVIEWS

Preservation of Cardiac Function by Coronary Thrombolysis During Acute Myocardial Infarction: Fact or Myth?

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Since the report by Rentrop et al. (1) showing that intracoronary thrombolysis with streptokinase is feasible in patients with acute myocardial infarction, emergency coronary thrombolysis and recanalization have challenged the traditional therapeutic regimen that has prevailed for the last quarter of a century. Coronary recanalization is about to revolutionize the treatment of acute myocardial infarction and has taken on forms that will extend this technique even to the primary care community hospital.

Several thousands of patients have undergone coronary thrombolysis, yet the question of long-term efficacy remains unanswered. Will it shorten or prolong life? Does it preserve myocardial function? Which patients, if any, benefit most? What is the best method to provide rapid, consistent coronary recanalization in the shortest possible time? Although these questions will only be answered after completion of large scale, randomized studies (2), considerable relevant experimental and clinical data are available. In this review, we address the available information and uncertainties dealing with the effects of coronary thrombolysis and recanalization on myocardial function.

Experimental Evidence That Coronary Recanalization Preserves Myocardial Function

The bulk of information gathered from diverse animal species overwhelmingly indicates that early reperfusion of ischemic myocardium leads to myocardial salvage and recovery of regional myocardial function. In those experiments, regional ventricular function was precisely quantified by implanted ultrasonic crystals, a sophistication that obviously is not possible in humans. The extent of recovery depends on the duration of myocardial ischemia. Reperfusion after 5 to 15 minutes of coronary occlusion in the dog leads to virtual complete salvage of myocardium and significant salvage is still possible even after 3 hours of occlusion (3). Essentially no improvement of regional function results when perfusion is restored after 3 hours of ischemia. In addition to the duration of ischemia, other factors play a role in the extent and rate of recovery of ventricular function. These include the size of the vascular bed perfused by the involved coronary artery, the coronary collateral flow and, in humans, the extent of disease in vessels other than that directly related to the area of damage. Despite salvage from irreversible injury, the previously ischemic myocardium does not function immediately. The "stunned myocardium" requires time to recover and this may range from several hours to days (3). Although reperfusion in the experimental animal clearly curtails the extent of irreversible injury and improves survival, there is evidence that reperfusion itself may also induce myocardial injury (4,5). In 1974 we reported (6) that reperfusion may increase myocardial damage. This finding has since been confirmed by several investigators (7,8). There is a clear-cut agreement among researchers that reperfusion is followed by temporary stunning of the myocardium, but whether further irreversible injury is induced by reperfusion remains controversial (9,10). The mechanism for the so-called postischemic stunning or delayed recovery of ventricular function remains unknown, the most recent suggestion being that reintroduction of oxygen to the ischemic cell generates toxic, oxygen free radicals (4,5,11). Many other factors, of course, have been postulated, including the no-reflow phenomenon.

Ventricular Function and Thrombolysis in Clinical Studies

Several clinical trials have now been performed using either intracoronary or intravenous streptokinase and, more recently, intravenous recombinant tissue plasminogen activator (rt-PA). The effect of reperfusion on left ventricular function in the observational trials that used intracoronary streptokinase (12–29) is shown in Table 1. A consistent observation in those trials was the lack of dramatic improvement in left ventricular ejection fraction and the wide range of ejection fraction values after thrombolysis. Striking improvement in left ventricular function was observed only occasionally. In the majority of these trials, which were

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Table 1. Effect of Intracoronary Thrombolytic Treatment on Ventricular Function (nonrandomized trials)*

First Author & Ref.	No. of Pts.	Time to Intervention (hours)	Assessment Technique	Before Intervention	Change in EF (units)		Regional Function
					Nonrecanalized	Recanalized	
Cowley (12)	11	5.5	Contrast	Done	−15†	10†	Improved
Ganz (13)	20	2.6	Nuclear	Not done	Not done	Not done	Improved
Rentrop (14)	55	<3.0 to >6.0	Contrast	Done	Not done	2.0†	Improved
Rentrop (15)	27	5.6	Contrast	Done	Not done	5.5†	Not done
Cernigliaro (16)	15	<3	Contrast	Done	Not done	8.0†	Improved
Schwarz (17)	27	0 to 8	Contrast	Done	−4.4	5.4	Improved
Smalling (18)	89	0 to 18	Nuclear	Done	1.0	8†	Not done
Cribier (19)	58	3.6	Contrast	Done	−12	2.0	Improved
Rentrop (20)	125	<2 to >6	Contrast	Done	−2.5	2.4†	Not done
Sheehan (21)	52	<3	Contrast	Not done	−7†	−4	Improved
Stack (22)	24	4.8	Contrast	Done	−4	3.0	Improved
Charuzi (23)	23	<3	Echo	Done	Not done	Not done	Improved
Ferguson (24)	77	<9	Nuclear	Not done	5	6	Not done
Murakami (25)	30	0 to >10	Contrast	Not stated	Not done	Not done	Improved
Saito (26)	30	2 to 8	Contrast	Done	1	15.6†	Improved
Sato (27)	38	<6	Contrast	Done	−6†	6†	Improved
Sheehan (28)	47	<3	Contrast	Not done	Not done	Not done	Improved
Timmis (29)	69	<5	Contrast	Not done	Not done	6.2†	Improved

*Only trials with information on left ventricular function are listed. †$p < 0.05$. Echo = echocardiography; EF = ejection fraction; Pts. = patients.

uncontrolled and nonrandomized, the disappointing results probably relate to the time interval from onset of symptoms to intervention, which was often >6 hours (Table 1). Restriction of analysis to patients with successful thrombolysis showed a consistent trend of improved left ventricular function. In several series (17,21,22), improvement in regional ventricular function in the infarct area was often documented, despite a lack of increase in global ejection fraction. There was also a definite trend indicating that the earlier the reperfusion, the more likely it was to be associated with improvement of left ventricular function (17,21,25).

Intracoronary versus intravenous streptokinase therapy. The results of the prospective, randomized trials (30–36) in which the thrombolytic agents were administered through the intracoronary route are summarized in Table 2. There was little or no improvement in the global ejection fraction of treated patients compared with that of the control group. However, in the two largest trials (33,34) left ventricular function was not assessed before and after the intervention; instead, the predischarge ejection fraction of the control and streptokinase groups were compared. Again, as in the nonrandomized trials, streptokinase therapy was not initiated until at least 3 hours after the onset of symptoms, which probably precluded any dramatic improvement in left ventricular function. The delay before the initiation of therapy was due primarily to time spent mobilizing personnel required for emergency cardiac catheterization. To overcome this difficulty, investigators initiated intravenous streptokinase therapy; results of those trials (37–44) are summarized in Table 3. Most of these trials, including the two randomized European trials, have shown only modest improvement in global or regional ventricular function. Will

Table 2. Effect of Thrombolytic Treatment on Ventricular Function (randomized trials)*

First Author & Ref.	No. of Pts.	Time to Intervention (hours)	Technique	Before Intervention	Change in EF (units)		Regional Function	Change in EF (units)	
					Nonrecanalized	Recanalized		Control	Treated
Anderson (30)	50	4	Nuclear, echo	Done	Not done	Not done	Improved	−3.0	3.9†
Khaja (31)	40	5.4	Nuclear, contrast	Done	Not done	Not done	Improved	+1	0
Leiboff (32)	43	4.8	Nuclear	Not done	−1.8	−1.1	Not done	−0.4	−2.8
Rentrop (33)	47	6.1	Nuclear	Done	Not done	Not done	Not done	−1.4	2.1
Ritchie‡ (34)	207	4.6	Nuclear	Not done	Not done	Not done	Not done	Not done	Not done
Raizner (35)	54	5.6	Nuclear	Done	−6	7†	Improved	2	3
Vermeer§ (36)	488	>4	Nuclear	Not done	Not done	Not done	Not done	Not done	Not done

*Only trials with information on left ventricular function are listed. †$p < 0.05$. ‡Difference in late ejection fraction between control and treated groups not significant. §Intravenous and intracoronary therapy used. Difference in late ejection fraction between control and treated group significant (43 vs. 50%, $p > 0.0001$). Abbreviations as in Table 1.

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Table 3. Effect of Intravenous Thrombolytic Treatment on Ventricular Function

First Author & Ref.	No. of Pts.	Time to Intervention (hours)	Technique	Before Intervention	Change in EF (units)		Regional Function
					Nonrecanalized	Recanalized	
Schroder (37)	93	<6	Contrast	Done	−3	5	Improved
Rogers* (38)	63	7	Contrast, nuclear	Done	−12†	0	No change
Schwarz* (39)	55	<6	Contrast	Done	−5†	15†	Improved
Spann (40)	43	<6	Contrast	Done	−1	9†	Improved
Mathey* (41)	52	<3	Contrast	Not done	Not done	7	Improved
Valentine* (42)	164	6	Nuclear	Not done	3.8	9.5†	Not done
ISAM‡§ (43)	1,741	<6	Contrast	Not done	Not done	Not done	Improved
Simoohs*§ (44)	533	3.2	Nuclear‖	Not done	1.3	3.7†	Not done

*Series with both intracoronary and intravenous streptokinase or urokinase. †$p < 0.05$. ‡Late ejection fraction higher ($p < 0.005$) in treated than in control group. §Randomized series. In ISAM series, treated group had a higher ejection fraction than control patients at 4 weeks (56.8 vs. 53.9%, $p < 0.005$). ‖Radionuclide angiography done on days 2 to 4 and 10 to 20. Abbreviations as in Table 1.

the realization that "time is of the essence" naturally lead to improved ventricular function in future trials? Several factors must be taken into account, some prospectively, if we are to provide quantitative data on ventricular function.

Effect of Thrombolytic Therapy on Ventricular Function

Before we recommend to the medical community the routine use of intravenous thrombolytic therapy, we must demonstrate its efficacy not just in restoring coronary patency but also in reducing mortality and morbidity. Although long-term survival would be the most definitive end point for assessing the results of thrombolysis, it has several drawbacks. First, a sample size of several thousand patients would be required for a trial to unequivocably demonstrate or negate a beneficial effect on survival. Second, the increasing use of angioplasty in conjunction with or subsequent to thrombolysis may preclude assessment of the effect of thrombolysis itself, even on acute mortality. Ventricular function as an end point thus has great appeal because 1) it has been proved to be a reliable predictor of short- and long-term mortality; 2) it requires far fewer patients to demonstrate efficacy than does mortality; 3) the effect of thrombolysis can be determined acutely; and 4) it may be the only feasible and reliable end point to assess thrombolysis as such. In view of the recent Gissi trial (45) a placebo group is now an endangered species, as reflected in phase II of the TIMI trial, which was initiated in May 1986 after elimination of the placebo group. In future trials, the influence of thrombolysis or angioplasty, or both, on short- or long-term mortality will be assessed only in relation to historical or estimated future mortality rates. Therefore, a change in ventricular function, as assessed serially in each patient, appears to be the only trial end point, whether evaluating thrombolysis or angioplasty, that will be based on two or more values determined sequentially in the same patient.

In view of the Gissi trial (45), which demonstrated a 50% reduction in mortality in patients treated within the first hour, the reality of reduced mortality as the universal consequence of thrombolysis is likely to be near, as is improved ventricular function. How shall we best assess ventricular function? Early intervention in future trials will likely exclude any invasive assessment before therapy. Ventricular function will be assessed noninvasively, preferably before and after thrombolytic therapy, though initial assessment immediately after instituting therapy will likely be a reasonable compromise to avoid delaying treatment. Will the inherent limitation of the clinical trial or the imprecision of the methods used preclude one from demonstrating improved ventricular function?

Limitations Inherent in the Clinical Trial

Thrombolytic trials to date have given us at least two axioms: 1) acute transmural infarction is associated with coronary thrombosis (and this time the latter concept is here to stay); and 2) to salvage ischemic myocardium during evolving myocardial infarction, we must restore flow within 3 to 4 hours. There is also general agreement that the definitive statement on efficacy of thrombolytic therapy, whether for improving ventricular function or survival, must come from the large randomized trial analyzed on the basis of intention to treat. This form of analysis does not take into account several factors that would preclude or minimize the beneficial effect. All patients enrolled with suspected acute myocardial infarction will undergo a similar analysis. However, we know that even if ST segment elevation is required as an entry criterion, at least 15 to 20% of patients will not develop infarction. This is coupled with the fact that thrombolytic therapy will be successful in only 65 to 70% of patients receiving intravenous rt-PA and in 50% receiving streptokinase. Furthermore, patients presenting with subtotal coronary occlusion or having "spontaneous early reperfusion" may exhibit little depression in ventricular function.

On the basis of results of the trials to date, even if one abandons the intention to treat principle and assesses only those patients with complete occlusion who undergo successful thrombolysis, little improvement is expected in patients whose initial ejection fraction after the onset of symptoms remains in the normal range. It may well be that if damage is minimal to moderate and there is compensatory hyperkinesia of the noninvolved myocardium, the ejection fraction remains near normal. Reperfusion may be followed by withdrawal of the compensatory hyperkinesia and hence the ejection fraction does not change, despite improvement in the contraction of the ischemic myocardium. One is more likely to see greater improvement in patients with more severely depressed ventricular function, in whom compensatory mechanisms are inadequate to maintain a normal ejection fraction, such as those with extensive anterior infarction. So we must be concerned that patients exhibiting no effect from thrombolytic therapy because they did not have myocardial infarction or complete occlusion or in whom therapy was unsuccessful do not dilute the beneficial effects of successful therapy in appropriate patients.

The presence of collateral circulation also appears to afford greater recovery of function (*1,38,39*), presumably by maintaining cell viability until effective thrombolysis occurs. Conversely, it has been observed, though not well documented, that patients undergoing successful thrombolytic therapy who are left with residual high grade coronary stenosis exhibit less improvement in regional ventricular function (28).

Role of thrombolytic therapy combined with angioplasty or surgery. Assessment of the effect of thrombolysis, even acutely, may be complicated by available mechanical options for recanalization, such as angioplasty or surgery, which have a high likelihood of being used acutely in conjunction with thrombolytic therapy. On the basis of preliminary results of the recent TAMI trial (46), such combination therapy has been proclaimed superior to thrombolytic therapy alone, although the changes in ventricular function in patients undergoing emergent as opposed to elective angioplasty have yet to be reported in this study. It would be most applicable for the community needs if a thrombolytic agent could be administered and patency maintained so that angioplasty could be delayed for the 24 to 48 hours required to transport the patient to a larger medical center where appropriate angioplasty could be performed by experienced personnel. The complication rate of percutaneous transluminal coronary angioplasty in experienced hands during acute infarction has been generally low, the patency rate has been high and the severity of residual coronary stenosis has been decreased (47,48). However, the 20 to 30% restenosis rate after angioplasty will temper the long-term results. Initial trials, comparing thrombolytic therapy alone with coronary angioplasty (associated or not with thrombolytic agents), suggest greater improvement of left ventricular function when angioplasty is performed acutely (47,48). The precise interval during which angioplasty should be performed, namely, whether acutely or within days, is far from resolved and is now being assessed in phase II of the Thrombolysis in Myocardial Infarction (TIMI) Trial. Results in patients receiving angioplasty within 2 hours of thrombolytic therapy will be compared with those of patients undergoing angioplasty 18 to 48 hours after thrombolytic therapy.

Limitations Inherent in the Assessment of Ventricular Function

Left ventricular ejection fraction has been the functional variable most commonly assessed after coronary recanalization. However useful as an index of global left ventricular performance, it is importantly dependent on left ventricular preload and afterload, which are by no means constant in patients with acute infarction. Various medications such as diuretics and vasodilators, commonly used in patients with acute myocardial infarction, also affect these variables. Furthermore, although the ejection fraction affords a convenient variable to assess global function, it does not necessarily reflect regional myocardial function; yet myocardial infarction is almost always a regional disease. Quantification of regional function by radionuclide angiography as well as with contrast angiography or two-dimensional echocardiography is plagued by an unresolved problem, namely, rotation of the left ventricular center of gravity during cardiac contraction. Echocardiography, although the most readily available technique, still offers suboptimal endocardial edge definition, which hampers quantification of wall motion. Radionuclide angiography may be the best available means to quantify left ventricular ejection fraction, because it is the only technique that is independent of ventricular geometry. However, there is a pressing need for improvement in the quantification of regional ventricular function with radionuclide angiography.

Right ventricular function in myocardial infarction. To date, radionuclide angiography has in general been performed to assess only left ventricular function after thrombolysis. The effect of this therapy on right ventricular function has only recently been addressed (49,50). Its importance lies in the observation that right ventricular infarction is quite frequent in patients with inferior wall infarction (51–58) and that right ventricular damage may be extensive, which with concomitant left ventricular damage may lead to cardiogenic shock and death (58,59). At the present time, it is difficult to quantify precisely the global right ventricular ejection fraction by either blood pool radionuclide angiography or echocardiography, let alone regional right ventricular function. Frequently, it is stated that thrombolysis appears less beneficial in inferior than in anterior infarction;

perhaps we should wait until we have assessed its effect on right ventricular function before making such judgment. Radionuclide angiography using the first pass technique and a multicrystal gamma camera is currently the best means to assess right ventricular function, but it is hampered by the high cost and limited portability of the multicrystal camera. A newly described, portable multiwire gamma camera (60), utilizing the short-lived radionuclide tantalum-178, provides high resolution first pass imaging of the right and left ventricle and may afford a means to conduct bedside quantitative assessment of right and left ventricular function.

Role of myocardial stunning and reinfarction. The interval over which left ventricular function should be assessed is unclear because stunning may recover in 24 to 48 hours or it may require several days; nevertheless, comparison of studies obtained on or shortly after admission and 7 to 10 days later should be satisfactory. Another major concern is coronary reocclusion with reinfarction. Follow-up studies in the TIMI trial (61), as well as in several other trials (32,33,62–65), have shown that the incidence of reinfarction from reocclusion, if no other intervention is performed, is in the range of 20 to 30%. This of course would cause further deterioration in ventricular function and, when combined with patients without reinfarction, the benefit from reperfusion would be diluted or even masked completely.

Recommendations for the Future

Coronary thrombolysis undoubtedly is a promising treatment modality for patients with acute myocardial infarction. However, because the risk of bleeding is considerable with this therapy, it is incumbent on investigators to prove conclusively that the benefits outweigh the risks. Short-term mortality has been shown to be decreased by thrombolytic treatment in recent randomized series (45,66). This beneficial effect on mortality will be easier to demonstrate in future trials if investigators focus on subsets of patients at high risk, such as those with extensive infarction or cardiogenic shock. Despite the somewhat disappointing results of the small randomized series reported thus far, the short-term effects of thrombolysis on ventricular function should be beneficial, provided that recanalization is achieved within 3 hours of coronary occlusion. To realize the full benefits of thrombolysis in the largest possible population with acute myocardial infarction, we must aim for the administration of thrombolytic agents by paramedic personnel in the patients' home or work site. In this regard, the report of Koren et al. (67) showing that patients treated < 1.5 hours after onset of pain had significantly higher global and regional ejection fractions than those of patients treated 1.5 to 4 hours after onset of pain is encouraging. This improvement in function, which may occur gradually over several days, is entirely consistent with the bulk of experimental data. To document improved performance, global left ventricular ejection fraction cannot be relied on as the sole variable but should be combined with quantitative assessment of regional function. Furthermore, in patients with inferior infarction the right ventricular function should be routinely assessed.

Definitive evaluation of the effects of reperfusion on the long-term mortality and on the preservation of left ventricular function—they must be intimately related—will have to await the results of large, long-term, randomized studies, in which the thrombolytic agent is administered within the first 2 to 3 hours of onset of myocardial infarction. The additional improvement that may result by combining thrombolysis with other interventions designed to improve myocardial reperfusion (by angioplasty or surgery), decrease myocardial oxygen demand (for example, beta-adrenergic blockade) or minimize reperfusion injury (for example, administration of free radical scavengers) also remains to be proved and will be fruitful areas for research in the years to come. Until then, we believe that preservation of cardiac function by coronary thrombolysis during acute myocardial infarction is a fact—but surely in need of confirmation.

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