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COMMENTARY

CORONARY THROMBOLYSIS: PHARMACOLOGICAL CONSIDERATIONS WITH EMPHASIS ON TISSUE-TYPE PLASMINOGEN ACTIVATOR (t-PA)*

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Although coronary thrombolysis offers promise for salvage of jeopardized ischemic myocardium, several constraints currently limit the clinical potential of this intervention. Progress in overcoming these constraints is likely, however, in view of increasing understanding of the pharmacology of activators of the fibrinolytic system, differentiation between systemic and clot specific fibrinolysis, and delineation of the dependence of myocardial salvage on the interval of ischemia preceding thrombolysis.

Thrombolysis is an attractive approach for treatment of evolving myocardial infarction (MI), in part because the frequency of coronary thrombosis is high in patients assessed early after the onset of symptoms of acute myocardial infarction [1]. Within the first 4 hr after the onset of symptoms, approximately 87% of patients exhibit complete occlusion of the vessel supplying the infarct zone. Thus, thrombosis early in the course of infarction is common as either a primary or contributing secondary event. Judging from the lower angiographically demonstrable incidence of thrombosis in patients evaluated at 12–24 hr after the onset of infarction, approximately 25% of the coronary occlusions appear to resolve spontaneously, presumably as a result of endogenous fibrinolysis [1].

A second key factor underlying enthusiasm for coronary thrombolysis is the increasing recognition that the extent of infarction is not fixed at the time of occlusion [2, 3]. Interventions instituted after the onset of occlusion may influence the ultimate extent of myocardial injury [4, 5]. However, the temporal constraints limiting the efficacy of coronary thrombolysis in man remain to be determined.

Effects of thrombolysis on the heart and long-term effects on the patient are likely to be markedly dependent on the rapidity of successful reperfusion with respect to the onset of preceding ischemia. Recovery of ischemic myocardium in dogs with coronary ligation is substantial when reperfusion is implemented within 20 min. However, if reperfusion is delayed for 6 hr, no significant salvage results [3]. Positron emission tomography demonstrates that reperfusion induced with streptokinase after ischemia induced by coronary thrombosis of 1- to 2-hr duration results in significant metabolic recovery of myocardium [6]. However, even though reperfusion after 6 hr of ischemia elicits substantial reflow, the reperfused myocardium does not respond metabolically to relief of ischemia [6]. Furthermore, although intracoronary streptokinase induces thrombolysis with clot present *in vivo* for as long as 14 hr, significant tomographically documentable metabolic salvage does not occur. The marked temporal dependence of recovery of myocardial metabolism is striking. Although the absolute intervals may differ in man compared with the intervals in experimental animals and although some late metabolic functional improvement may occur, the principle seems clear. Reperfusion must be prompt if it is to be optimally effective.

Effects of thrombolysis on the heart can be assessed definitively only with objective measurements that determine not only whether or not vascular patency is restored in large epicardial vessels but also whether or not nutritional tissue perfusion and metabolic activity are enhanced in the reperfused zone [7]. Unfortunately, many of the indirect indexes of salvage (such as changes in global or regional ejection fraction) may be influenced early after thrombolysis by altered tissue turgor, tissue edema, or changes in compliance in the reperfused zone and later by scar retraction. Furthermore, interpretation of such indexes is clouded by difficulties in delineating identical regional segments for sequential comparisons. Global ejection fraction may be insufficiently sensitive for assessment of the functional impact of segmental reperfusion. Tomographic indexes of myocardial perfusion and metabolism appear to be particularly useful for sequentially assessing the effects of thrombolysis on the heart in both experimental animals and in patients [8, 9].

Thrombolysis can be induced by the administration of activators of the fibrinolytic system via either the intracoronary (i.c.) or intravenous (i.v.) route. The incidence of successful lysis is higher (70–90%) after i.c. administration of activators, particularly when the clot is near the tip of the infusion catheter [10–12]. However, the i.c. route entails the disadvantages of requiring immediate availability of a highly

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trained catheterization team, cost, and some unavoidable risk. Lysis occurs in 50–60% of patients given activator intravenously [13]. However, thrombolysis may occur more slowly with conventional activators such as streptokinase administered i.v. rather than i.c. because the i.v. dose is limited by the risk of systemic fibrinogenolysis.

Either i.v. or i.c. administration of conventionally used activators such as streptokinase and urokinase results in systemic activation of the fibrinolytic system. Consequently, a systemic lytic state is evident which may give rise to bleeding. Residual high grade stenoses are common after thrombolysis. Thus, subsequent angioplasty or surgical revascularization may be necessary. Such interventions are rendered more hazardous or precluded at least temporarily by the presence of a systemic lytic state.

Because successful thrombolysis is predicated to a large extent upon the rapidity with which the intervention can be implemented after the onset of ischemia, administration of the thrombolytic agent via a route that does not require cardiac catheterization and its unavoidable attendant delays would be desirable. Accordingly, attention has focused recently on i.v. infusion of streptokinase or urokinase and, most recently, on alternative activators.

PHYSIOLOGICAL THROMBOLYSIS

Fluidity of the blood without hemorrhage is maintained as a result of a physiological equilibrium between the coagulation and fibrinolytic systems and the dynamic interaction of the intrinsic and extrinsic pathways of plasminogen activation and inhibition (Fig. 1). Intrinsic activation of plasminogen involves circulating intravascular precursors. Extrinsic activation involves release of plasminogen activator from tissue or from endothelial cells. Under physiological conditions, plasma contains plasminogen (approximately 2.4 μM) which can be converted by endogenous or exogenous plasminogen activators to an active proteolytic enzyme, plasmin.

Plasminogen

This single chain glycoprotein (approximately 88,000 daltons) contains 790 amino acids and 2% carbohydrate. Multiple forms exist. The gene product (glu-plasminogen) has an amino-terminal glutamic acid, carboxy-terminal asparagine, and 24 disulfide bridges [14, 15]. "Glu-plasminogen" is converted readily by limited proteolytic digestion to modified forms with amino-terminal lysine, valine, or methionine. Conversion occurs by hydrolysis of the Lys-76-Lys-77, Lys-77-Val-78, or Arg-67-Met-68 peptide bonds.

Plasminogen has specific binding sites, called lysine binding sites (LBS), which interact intensely with lysine, 6-amino-hexanoic acid, and *trans*-4-amino-methylcyclohexane-1-carboxylic acid. LBS mediate the binding of plasminogen to fibrin [14, 16]. The role of these binding sites has been supported by results obtained with fibrin Sepharose affinity chromatography and by the observed inhibition of binding of plasminogen to fibrin by 6-amino-hexanoic acid [17, 18].

Lysine binding sites mediate the interaction of plasmin with α_2-antiplasmin as well [19]. Fibrin-bound plasmin is resistant to neutralization by α_2-antiplasmin because the LBS are occupied. In contrast, circulating plasmin is rapidly neutralized (Fig.

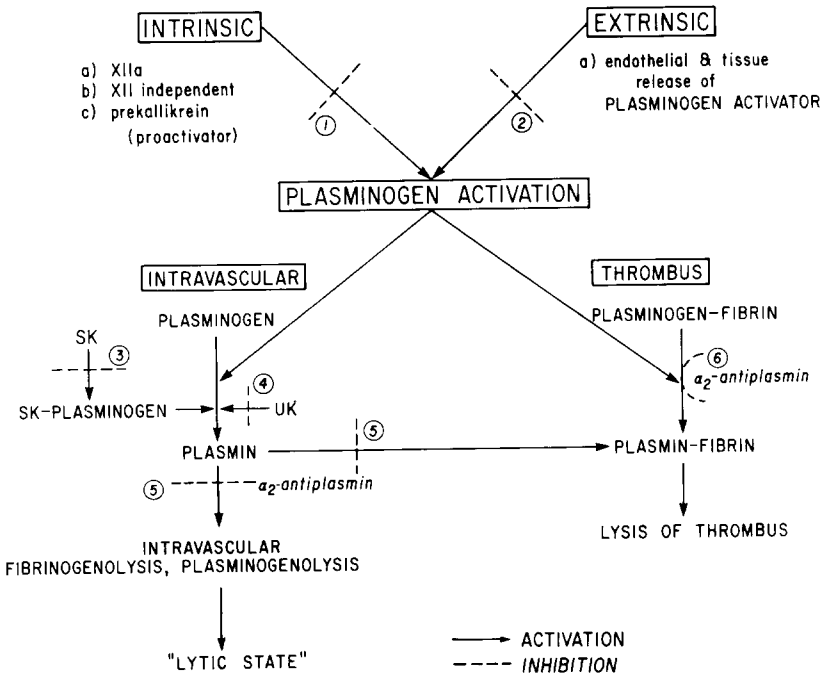

Fig. 1. Schematic representation of the fibrinolytic system. SK = streptokinase; UK = urokinase. Sites of action of inhibitors 1–6: (1) inhibitors of intrinsic activation of plasminogen including C1-inactivator, factor XIIa-related inactivator, heparin-antithrombin 3 complex, α_2-macroglobulin; (2) inhibitor of plasminogen activator; (3) antistreptococcal antibodies; (4) urokinase inhibitor; (5) α_2-antiplasmin in plasma ($T_{1/2}$ = 50–100 msec); and (6) α_2-antiplasmin in thrombus ($T_{1/2}$ = 10 sec).

1) with concomitant consumption of circulating α_2-antiplasmin [16].

Plasmin

Glu- or lys-plasminogen is converted to plasmin in a complex process of activation involving cleavage of a single Arg-Val bond at the 560-561 locus. In either case lys-plasmin is formed [16, 20]. Plasmin is an active protease that degrades either fibrinogen or fibrin leading to the formation of fibrin (or fibrinogen) degradation products. The two-chain plasmin molecule is composed of an α-chain conferring binding specificity to fibrin, which is derived from the amino-terminal portion of plasminogen, and a β-chain conferring proteolytic activity. The proteolytically active site is composed of His-602-Asp-645 and Ser-740 [21]. Activation of glu-plasminogen to plasmin by urokinase in purified systems occurs approximately twenty times more slowly than activation of lys-plasminogen [22]. Although plasmin has broad proteolytic specificity, *in vivo* its primary substrate is fibrin as a result of binding of its precursor, plasminogen, to fibrin.

Inhibitors of intrinsic activation of plasminogen

Inhibitors of intrinsic plasminogen activators in human plasma include C1-inactivator, factor XIIa related inhibitor, heparin-antithrombin 3 complex, and α_2-macroglobulin. However, a role for these inhibitors in regulation or control of fibrinolysis has not been established.

Alpha$_2$-antiplasmin, the physiological inhibitor of plasmin [23], forms a stable equimolar complex with plasmin. The complex is devoid of protease or esterase activity. Complex formation involves a very rapid, reversible second-order reaction followed by a slower, irreversible first-order reaction [19]. Free lysine binding sites and a free active site on the plasmin molecule contribute to the reaction with α_2-antiplasmin [16]. α_2-Macroglobulin appears to function as an inhibitor of plasmin only after saturation of the α_2-antiplasmin mechanism.

Alpha$_2$-antiplasmin interacts only weakly with the proenzyme plasminogen. Formation of the α_2-antiplasmin complex protects circulating fibrinogen from the proteolytic effects of plasmin (in contrast to the case with α_2-macroglobulin complexes) [24]. The concentration of plasmin in plasma is virtually undetectable because of the influence of circulating inhibitors, especially α_2-antiplasmin which forms complexes that are rapidly removed from the circulation.

Physiological activation of the fibrinolytic system

Activation of the fibrinolytic system may occur via an extrinsic pathway in which tissue-type plasminogen activator (t-PA) is released from the vascular wall (endothelial or vascular t-PA) or via intrinsic pathways, one of which involves activation of factor XIIa and prekallikrein. A factor XII-independent (C3) pathway and a platelet-dependent pathway may elicit plasminogen activation as well.

Extrinsic activation has been studied intensively since the 1930s. Cultures of normal and neoplastic cells liquefy fibrin clots, and activators have been extracted from diverse sources including endothelium, lymphatics, and epithelium from cornea, conjunctiva, uterus, vagina, and the urinary tract [25]. The biological properties of tissue plasminogen activators and those from plasma are similar if not identical. However, the properties of plasminogen activator differ markedly from those of urokinase [26].

REGULATION AND CONTROL OF FIBRINOLYSIS

Regulation and control of fibrinolysis appear to involve primarily: (a) release of plasminogen activator from the vascular wall, (b) fibrin-associated activation of plasminogen, and (c) inhibition by α_2-antiplasmin of plasmin activity formed in or released into the circulation.

Release of plasminogen activator (t-PA)

Release of t-PA can be triggered by physical exertion [27], venous occlusion [28, 29], or infusion of substances such as epinephrine, nicotinic acid, or histamine [30]. Anabolic steroids such as stanazolol and biquanidines appear to increase both the synthesis and release of plasminogen activator from the vessel wall [30]. Parenterally administered epinephrine liberates t-PA presumably by receptor-mediated action on endothelial cells [31, 32] and possibly centrally through release of vasopressin-like substances [33]. Many vasoactive drugs, including nicotinic acid, histamine, and vasopressin, enhance fibrinolytic activity transiently in blood [30, 34]. Exercise or electroshock releases t-PA by non-catecholamine- as well as catecholamine-mediated mechanisms.

The biological half-time of circulating t-PA is short. Activator appears to be cleared with a half-life of approximately 2 min after intravenous injection, 5 min after venous occlusion, 13 min after injection of nicotinic acid, and 20–30 min after exercise. The liver appears to be the primary site for clearance.

Cash [35] speculated that circulating levels of plasminogen activator may be controlled neurohumorally, with higher neurogenic centers playing an important role. Diverse modes of activation of plasminogen may reflect the association of fibrinolytic activity with activated macrophages participating in inflammation [36, 37], embryonic cells undergoing differentiation [38], granulosa cells during ovulation [39], and invading trophoblast.

It has been postulated [40, 41] that physiological fibrinolysis may be influenced centrally through regulation of vascular plasminogen activator levels by humoral or neural pathways and locally in response to clotting or ischemia with regulation involving vascular endothelial release of t-PA. The t-PA absorbs to fibrin and initiates fibrinolysis by activating fibrin-bound plasminogen.

Pharmacologic activation of plasminogen

Urokinase. In 1947, MacFarlane and Pilling [42] reported the presence of fibrinolytic activity in normal urine, known now to be attributable to urokinase, a trypsin-like protease. The high molecular weight (HMW) form of this enzyme is a double-chain protein linked by disulfide bonds [43] containing amino-terminal isoleucine. HMW urokinase can

be separated into two component chains (33,100 and 18,600 daltons). Urokinase cleaves plasminogen, its only known protein substrate, in a first-order reaction with splitting of a single arginyl-valyl bond [20]. The presence of fibrin appears to accelerate activation of plasminogen by urokinase modestly. Thus, kinetics of reactions with urokinase in the absence of fibrin cannot be directly extrapolated to conditions *in vivo*.

The kidney is the major site of synthesis of urokinase [44]. Urokinase differs from t-PA with respect to antigenic characteristics, proteolytic specificity, half-life in blood after intravenous injection (approximately 16 min for urokinase compared with 2 min for t-PA), and biological properties. Infusion of as little as 50×10^4 I.U. of urokinase per day is sufficient to deplete circulating α_2-antiplasmin levels to 60% of normal and induce a systemic fibrinolytic state [45]. Recently, the concept of oral fibrinolytic therapy with urokinase has been advocated [46]. However, administration of 30,000 I.U. of urokinase orally initiates a systemic fibrinolytic state reflected by elevated fibrinogen degradation products (FDP) [46].

Streptokinase. Streptokinase (SK) is a 47,000 dalton protein produced by Lancefield group C β-hemolytic streptococci. It activates the fibrinolytic system only indirectly by reacting stoichiometrically with plasminogen to form a complex which unmasks an active site on the plasminogen constituent [47, 48]. The complex exhibits serine protease activity against numerous proteins. The SK–plasminogen complex does not bind to fibrin but catalyzes conversion of circulating plasminogen to plasmin. It gives rise to a series of intermediates with partially hydrolyzed SK and/or plasminogen constituents with differing proteolytic activities. Thus, the dose–response relationship is variable. The formation of plasmin in the circulation accounts for invariable depletion of circulating fibrinogen and circulating α_2-antiplasmin. Dosage regimens are complicated by a high prevalence of anti-SK antibodies in patients and consequent formation of antigen–antibody complexes which may or may not have activator activity [49]. In addition, immune responses such as anaphylaxis may be encountered. Because of the high prevalence of anti-SK antibodies probably as a result of previous exposure of the subject to β-hemolytic streptococci, initial dosage requirements for saturation of circulating antibodies may be high and vary from 25,000 to 3,000,000 units [49]. Anti-streptokinase titres rise soon after administration of streptokinase, limiting repeat applications in the same patient.

The binding of SK to plasminogen is highly species specific (with binding in human subjects and cats > dogs > rabbits and no binding to bovine plasminogen). Metabolism of streptokinase *in vivo* is not yet well understood. Clearance after i.v. administration is biexponential. A rapid component has a $T_{1/2}$ of 18 min, corresponding with binding of SK to antistreptococcal antibodies. A second, slower component ($T_{1/2}$ = 83 min) appears to reflect the rate of systemic clearance after antibody complex formation is complete. Administration of equimolar streptokinase–activator complex (SK plus plasminogen, plasmin, or β-chain plasmin) results in formation of immune complexes with a long biological half-life [50].

Effective clot dissolution *in vivo* requires a continuous supply of plasminogen and activator at the fibrin surface. Activators such as urokinase or streptokinase may deplete circulating plasminogen levels sufficiently to preclude the needed resupply. The result is a paradoxical refractoriness to increased doses of activator.

Although initial reports suggested that the development of a systemic lytic state was infrequent with streptokinase [51], it is now clearly apparent that even relatively low doses given selectively via the coronary arteries (201,000 ± 74,000 I.U.) elicit systemic fibrinolysis in approximately 88% of patients [52]. Fletcher *et al.* [53] have demonstrated that the fibrinolytic response to urokinase is proportional to dose. Nevertheless, substantial depletion of α_2-antiplasmin is common even with low doses [46, 54].

Administration of streptokinase or urokinase may result in systemic activation of the fibrinolytic system sufficient to exhaust circulating α_2-antiplasmin (normal concentration = 1 μM). Any excess of plasmin formed in or released into the circulation will then bind only to α_2-macroglobulin, forming a complex that retains proteolytic activity. Exacerbation of the systemic lytic state can be anticipated under such circumstances. Thrombolytic regimens incorporating high loading doses of streptokinase to overcome initial binding to antibody often result in extensive depletion of circulating fibrinogen, plasminogen and α_2-antiplasmin and elevation of fibrinogen degradation products that impair coagulation [49].

Tissue-type plasminogen activator (t-PA)

Activation of plasminogen and induction of fibrinolysis by exogenous t-PA occur through hydrophobic interactions between t-PA and fibrin and selective conversion of plasminogen bound to fibrin to plasmin [14, 55, 56]. Since the K_m of t-PA for free plasminogen is approximately 65 μM and the circulating concentration of plasminogen is approximately 2 μM, essentially no conversion of plasminogen to plasmin occurs in the circulation. Activation of plasminogen in the presence of fibrin occurs sequentially through binding of t-PA to the clot surface (K_d = 0.16 μM) and subsequent binding of plasminogen to form a ternary complex involving the lysine binding sites of plasminogen and resulting in high local concentrations of plasminogen at the fibrin surface in juxtaposition to activator [26, 57]. The result is "clot selective" activation without induction of a systemic lytic state.

Rijken, Collen and coworkers [58, 59] have recently purified t-PA from a Bowes human melanoma cell culture supernatant fraction. A two-chain form with comparable catalytic activity results from proteolytic degradation of the secreted 72,000 dalton one-chain molecule [26].

In vivo a low concentration of circulating t-PA (approximately 0.1 M) is in equilibrium with t-PA promptly adsorbed onto fibrin. The effects of potential inhibitors of activation are reduced by adsorption of t-PA to fibrin. Thus, activation of plasminogen bound to fibrin through plasminogen lysine binding sites is localized to the fibrin surface (K_m = 0.14 μM),

fibrin is degraded, and the clot is lysed. Any plasmin released into the circulation is neutralized rapidly by α_2-antiplasmin ($T_{1/2} \simeq 100$ msec) [16, 60]. In association with fibrin, plasmin is inactivated by α_2-antiplasmin much more slowly than it is in the circulation ($T_{1/2} = 10$ sec rather than 50–100 μsec) since both the active site and the lysine binding sites are protected from the inhibitor (Fig. 1).

To quantitatively compare the thrombolytic effects of melanoma-produced t-PA with those of urokinase, Collen and colleagues [61] induced venous thrombi in rabbits. Local infusion was found to be more effective than systemic infusion for both agents. Systemic infusion of 100,000 units of t-PA induced 75% lysis of fresh clots and 30–50% lysis of clots 1- to 7-days-old. On a unit/unit basis, defined with the standard fibrin plate assay system, the thrombolytic activity of urokinase was five times less than that of t-PA. Infusion of t-PA did not deplete circulating fibrinogen, plasminogen, or α_2-antiplasmin. In contrast, urokinase produced significant thrombolysis only in doses that also induced a systemic lytic state.

In rabbits with experimentally induced pulmonary embolism, t-PA evoked thrombolysis at lower doses than urokinase without depleting circulating plasminogen or fibrinogen [62]. In dogs with experimentally induced femoral vein thrombosis, t-PA induced thrombolysis more effectively than urokinase without depleting circulating fibrinogen or α_2-antiplasmin [63].

In a preliminary clinical study, intravenous administration of t-PA (7.5 mg over 24 hr) induced complete lysis of a 6-week-old renal and iliofemoral thrombus in a renal allograft recipient. Thrombolysis was achieved without systemic fibrinolytic activation or hemostatic breakdown and was not associated with bleeding [64].

Acylated plasmin

Smith *et al.* [65] have demonstrated that acylated derivatives of plasmin and streptokinase/plasminogen complexes exhibit fibrinolysis *in vivo* after a lag period. Acyl plasmin is catalytically inert and, therefore, does not degrade circulating proteins. Furthermore, it does not react irreversibly with α_2-antiplasmin or α_2-macroglobulin. It appears to bind to fibrin because the lysine binding sites on plasmin are functionally separate from the catalytic center. Deacylation then appears to occur giving rise to fibrin bound plasmin which is proteolytically active. Unfortunately, however, the process of deacylation is slow, variable, and somewhat unpredictable. *p*-Anisoyl human plasmin has a half-life for deacylation of 96 min and *p*-anisoyl human plasminogen-streptokinase activator has a half-life for deacylation of 40 min. Thus, although the concept underlying development of these agents is attractive, their long half-lives prior to proteolysis limit their potential usefulness for coronary thrombolysis and myocardial salvage. They may well have applications, however, for treatment of peripheral arterial or venous thrombosis.

Implications for clinical induction of coronary thrombolysis

Until recently, streptokinase and urokinase were the only plasminogen activators available for clinical use. Their principle limitation is a lack of clot-selectivity with consequent induction of a systemic lytic state. The depletion of circulating fibrinogen, plasminogen, and α_2-antiplasmin has important implications. The risk of hemorrhage is substantial, especially at puncture sites. Accumulation of fibrin degradation products may exacerbate the lytic state by impairing coagulation. In addition, lysis of residual fibrin may be impaired paradoxically as a result of depletion of plasminogen.

Despite these limitations, in extensive clinical studies both streptokinase and urokinase have been shown to successfully induce thrombolysis in large epicardial coronary arteries. Results from the European Society of Cardiology Registry on Thrombolysis [11] and those from an International Registry on Intracoronary Streptokinase [12] indicate that early reperfusion may lead to improvement in myocardial function assessed by measurement of ejection fraction. Results from the five centers comprising the International Registry suggest a possible improvement in hospital mortality. However, the efficacy of reperfusion on myocardial salvage remains controversial, possibly because of delayed implementation of thrombolysis in many studies and high rates of reocclusion [10].

In search for intravenously effective thrombolytic agents, devoid of induction of a systemic lytic state, tissue plasminogen activator appears to be particularly attractive because it has such a high affinity for fibrin and exhibits clot-selective activation of plasminogen [16].

We have recently documented clot-selective coronary thrombolysis with t-PA administered intravenously in dogs. Coronary thrombosis was first induced with a copper coil advanced into the coronary artery [66]. Intravenous administration of t-PA resulted in lysis within 10 min in contrast with longer intervals required with streptokinase (intravenous SK requiring 85 ± 19 min, intracoronary SK requiring 31 ± 2 min). The percent salvage of jeopardized myocardium assessed by positron emission tomography with [^{11}C]-palmitate was $57 \pm 18\%$ with t-PA compared with $25 \pm 12\%$ with streptokinase. t-PA did not lower circulating α_2-antiplasmin nor induce a systemic lytic state in contrast to the case with streptokinase. Thus, t-PA administered intravenously elicited angiographically documented coronary thrombolysis with tomographically delineated restoration of regional myocardial metabolism and nutritional perfusion without induction of a systemic lytic state (Fig. 2).

Because of the desirability of production of large quantities of tissue-type plasminogen activator, the material has been synthesized by recombinant DNA technology (rt-PA) [67]. We have demonstrated recently that human rt-PA is biologically active. In dogs with coronary thrombosis, assessed angiographically and tomographically, we have obtained with this agent results virtually identical to those we had obtained previously with melanoma-derived material [68].

CONCLUSIONS

Most recently, we have been able to induce throm-

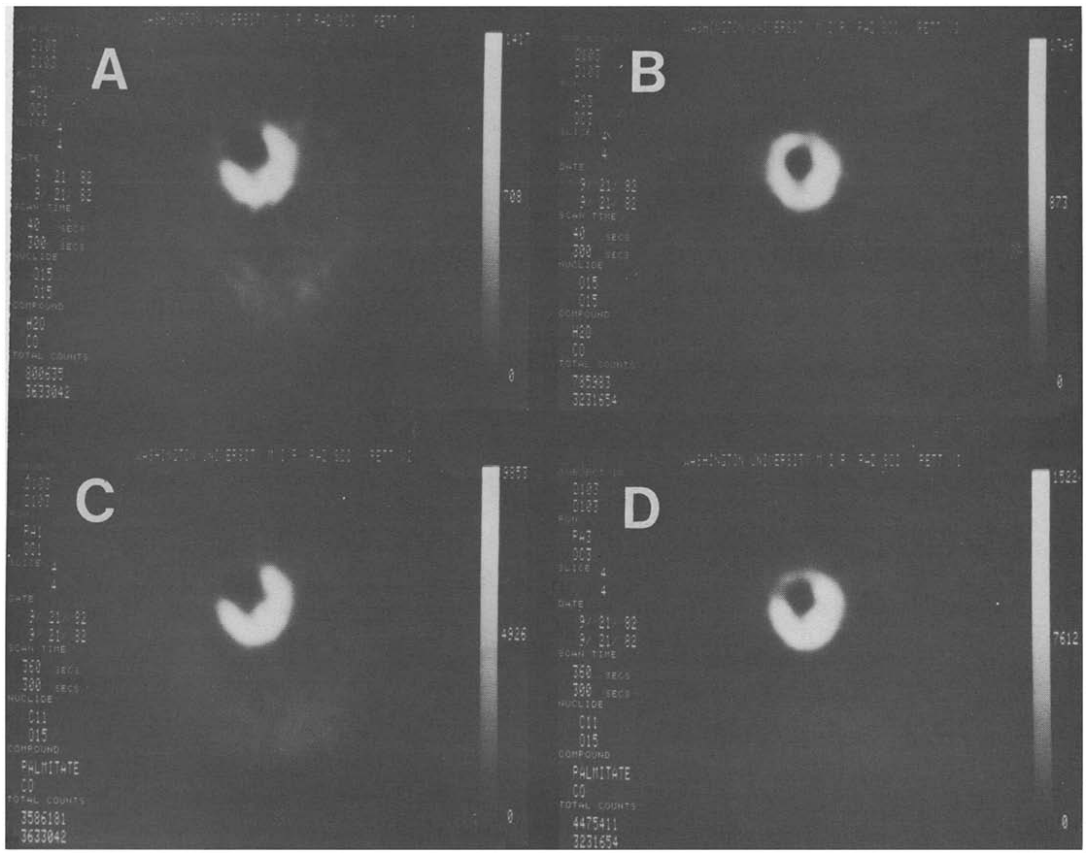

Fig. 2. Reconstructions from a single mid-ventricular transverse slice obtained with positron emission tomography before (A and C) and after (B and D) thrombolysis in one dog treated with intravenous t-PA. In these tomograms, anterior is to the top, posterior is to the bottom, and the free lateral and septal walls of the left ventricle are to the reader's left and right respectively. The right ventricle is not visualized because of its thin size. Perfusion scans were obtained after a bolus injection of $H_2{}^{15}O$ with correction for vascular pool activity with $C^{15}O$-labeled red blood cells (A) before and (B) after thrombolysis. Metabolism scans were done after the administration of [^{11}C]palmitate (C) before and (D) after thrombolysis. The [^{11}C]palmitate tomograms were corrected analogously for radioactivity in the blood pool by using $C^{15}O$-labeled red blood cells to identify the vascular space. The initial tomograms (A and C) were obtained 1.5 hr after induced coronary thrombosis and show a large anterior defect in both (A) perfusion and (C) metabolism scans. The post-thrombolysis scans (B and D) were obtained 1.5 hr after the first scan and approximately 80 min after thrombolysis following a second administration of $H_2{}^{15}O$, $C^{15}O$, and [^{11}C]palmitate. Restoration of perfusion is virtually complete in B. Significant restoration of [^{11}C]palmitate accumulation occurred, but a residual metabolic defect persisted in the center of the initially ischemic zone (D). (Published with permission of the American Association for the Advancement of Science [66] copyright 1983.)

bolysis in patients given t-PA intravenously as well as intracoronarily. The feasibility of coronary thrombolysis is unequivocal. End points for unambiguous determination of myocardial salvage are, however, elusive. Conventional interpretation of the electrocardiogram, myocardial enzyme release, global ejection fraction, and regional wall motion analyses may not apply in the setting of thrombolysis. Judging from our initial results in experimental animals and patients, we believe that quantification of myocardial perfusion and metabolism before and after thrombolysis by positron emission tomography is a promising approach for objective assessment of the effects of coronary thrombolysis on the heart.

Selection of pharmacological agents for induction of coronary thrombolysis has been determined largely by availability. Unfortunately, both streptokinase and urokinase induce a systemic lytic state with depletion of circulating fibrinogen, plasminogen, and α_2-antiplasmin, and accumulation of fibrin degradation products. All of these factors conspire to set the stage for hemorrhage with a risk of serious bleeding. Intravenous administration of these agents is limited by a lower success rate, in part because the upper bound of dose is constrained by the risk of inducing a severe systemic lytic state.

The probability that progress in recombinant DNA technology will lead to widespread availability of tissue-type plasminogen activator is particularly exciting because of the clot specific properties of t-PA. For coronary thrombolysis its potential advantages include: safety and efficacy of intravenous adminis-

tration of high doses; effective clot lysis without induction of a systemic lytic state; prompt implementation without the need for extensive characterization of the coagulation and fibrinolytic systems in each patient prior to and during therapy; avoidance of frank allergic reactions or variations in dose–response relations due to immune complex formation; ease of minute-by-minute adjustment of dosage and prompt termination of fibrinolysis when needed because of the short biological half-life of t-PA and the lack of induction of a systemic lytic state. These factors are particularly important for fibrinolysis in patients with evolving infarction and/or residual stenoses who may require urgent invasive intervention. The possibility of prompt intravenous administration of a fibrinolytic agent with consequent prompt fibrinolysis enhances the potential for improved salvage of myocardium. The recent synthesis of t-PA by recombinant DNA technology offers particular promise for the widespread availability in the near future needed for large scale clinical evaluation of this attractive agent in patients with evolving infarction.

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