Anesthesiology
71:870–877, 1989

Ancrod (Arvin®) as an Alternative to Heparin Anticoagulation for Cardiopulmonary Bypass

Vytas J. Zulys, M.D., F.R.C.P.(C), Sallie J. Teasdale, M.D., F.R.C.P.(C),† Ernest R. Michel, M.D., F.R.C.P.(C),* Richard A. Skala, M.D., F.R.C.P.(C),* Susan E. Keating, B.Sc.N.,§ Julia Rose Viger, B.Sc., D.Phys.,§ Michael F. X. Glynn, M.D., F.R.C.P.(C)‡*

Heparin is the anticoagulant used during cardiopulmonary bypass (CPB). Both the use of heparin and the reversal of its effect with protamine have well-documented complications. Ancrod is a defibrinogenating enzyme that has been used as an anticoagulant in humans, but its use as an anticoagulant for CPB has been limited to studies in animals. Twenty patients for elective aortocoronary bypass surgery were anticoagulated by means of an intravenous infusion of ancrod pre-operatively. Target plasma fibrinogen concentrations of 0.40–0.80 g/l were achieved within 13.3 ± 2.5 h using an average dose of ancrod of 1.65 ± 0.55 U/g. All perfusions were without incident. Postoperative blood loss (2286 ± 1311 cc) was compared to that of 20 matched controls (1737 ± 973 cc), as was blood product use; 4.1 ± 2.1 U of packed cells *versus* 2.5 ± 2.3 U ($P < 0.05$) and 5.6 ± 3.1 U of plasma *versus* 2.6 ± 2.9 U ($P < 0.05$) in the ancrod and heparin-treated groups, respectively. There were no differences in the postoperative courses or recovery periods of the ancrod-treated and control patients. This study confirms the efficacy and feasibility of ancrod as an alternative form of anticoagulation for CPB. (Key words: Blood, anticoagulants: ancrod. Surgery, cardiac: cardiopulmonary bypass.)

SINCE THE ADVENT of cardiopulmonary bypass (CPB), heparin has been the anticoagulant of choice. Its advantages include a rapid onset of action, relative clinical safety, and ease of neutralization when hemostasis needs to be restored after bypass. Nevertheless, there are complications associated with heparin itself and the antagonism of its effect with protamine sulphate.

There exists a group of patients intolerant of heparin and who therefore cannot undergo cardiac surgery with this method of anticoagulation. This group includes patients with a history of heparin-induced thrombocytopenia and thrombosis, or significant resistance to heparin, as in patients deficient in antithrombin III, the heparin cofactor. As well, protamine, a biological product, is intensely antigenic and can provoke severe allergic reactions.[1] When faced with patients with known anaphylactic reactions to protamine but needing cardiac surgery, we sought a substitute anticoagulant. Despite the acknowledged drawbacks to heparin and its neutralization, few efforts to find an alternative system of anticoagulation have been documented.

Ancrod is an anticoagulant derived from the venom of the Malayan pit viper (*Agkistrodon rhodostoma*), whose properties were first described by Reid *et al.*[2] Ancrod prevents the development of obstructive blood clots and thrombi by selectively depleting the plasma of fibrinogen. Experience with patients having congenital hypofibrinogenemia, as well as considerable data derived from animal experiments, shows that a concentration of fibrinogen of 0.2–0.6 g/l can support ongoing hemostasis, but effectively prevents spontaneous clotting or thrombosis. Ancrod-induced defibrinogenation has been successfully used in the treatment of peripheral vascular disease,[3] deep venous thrombosis,[4–6] central retinal vein thrombosis,[7] pulmonary embolism,[8] as well as an effective prophylaxis for thromboembolic events after surgery, especially orthopedic surgery.[8–10] When compared to heparin, the incidence of hemorrhagic complications was lower, while protection from thrombosis was equivalent.[8] Ancrod has also been used as a suitable alternative to heparin during hemodialysis.[11] Despite the potential for allergic reactions, there have not been any reports of such in the literature or to the pharmaceutical companies involved. There is also a specific antivenom available.

Ancrod has been used successfully in the long-term perfusion associated with extracorporeal membrane oxygenation in experimental animals.[12,13,**] We were, however, unable to find reports of its use in humans for this purpose. In view of the urgent situation of several of our patients with protamine allergies, and in the light of satisfactory experience with ancrod in similar clinical circumstances, we decided to proceed with CPB. Our initial successes led to this study, to document the safety and efficacy of ancrod anticoagulation of patients during CPB.

* Assistant Professor of Anaesthesia.
† Professor of Anaesthesia.
‡ Associate Professor of Medicine.
§ Research Assistant.

Received from the Departments of Anaesthesia and Medicine, Toronto General Hospital, Toronto, Canada. Accepted for publication August 1, 1989. Supported by Knoll Pharmaceuticals Canada, Inc. Presented in part at the Ninth Annual Meeting of The Society of Cardiovascular Anesthesiologists, Palm Desert, California, May 1987.

Address reprint requests to Dr. Zulys: Department of Anaesthesia, EC 2-306, Toronto General Hospital, 200 Elizabeth St., Toronto, Ontario, Canada M5G 2C4.

** Bell W, White J, Buky B, Kehrer B. Prevention of thrombosis by ancrod for prolonged extracorporeal bypass (abstract). Clin Res 22: 498A, 1974.

Method

With approval from the hospital Research and Ethics Committee, informed written consent was obtained from 20 patients under 70 yr of age, NYHA classification I–III, and scheduled for elective aortocoronary bypass surgery. A companion group of 20 patients matched as to age, sex, and heart disease was used as a control and studied concurrently. Patients with primary disorders of hemostasis, as revealed by history or a hemostatic screen, were excluded, as were patients receiving heparin or coumadin. Patients scheduled for repeat cardiac surgery were also excluded from this study. The hemostatic screen included a prothrombin time (PT), partial thromboplastin time (PTT), thrombin time (TT), bleeding time (BT), platelet count, and fibrinogen concentration. Fibrinogen, as thrombin-clottable protein was determined with a Sherwood® fibrinogen analyzer. Samples of blood were drawn into tubes with a nonwettable surface, containing sodium citrate 0.15 M and either 0.05 ml of antivenom to neutralize any ongoing ancrod action, or 0.05 ml of protamine to prevent any further heparin effect in the control patients once they had received heparin during surgery.

Anticoagulation in the control group was carried out in the usual fashion using an initial dose of 300 U/kg of heparin/body weight and additional heparin as necessary to achieve and maintain an activated clotting time (ACT) of greater than 400 s. At the termination of bypass, the heparin was neutralized with protamine sulphate, using a dose of 1 mg/100 U of heparin used.

Ancrod (Arvin®, Knoll Pharmaceuticals, Markham, Ontario, Canada) is supplied in 1 ml ampoules containing 70 IU, an IU being defined as the weight of venom protein needed to clot a standard fibrinogen solution in the same time as 0.33 NIH units of thrombin. An infusion of ancrod was begun in the study patients, prior to the scheduled surgery at a rate of 8.4 U/h, (210 U in 500 ml D5W at 20 ml/h) using a constant infusion pump (IMED® 350 Controller, IMED Corp., San Diego, CA). Initially the infusions were begun 36 h prior to surgery, but later 12 h was found to be sufficient. The rate of infusion was altered according to the fibrinogen concentration, which was determined every 4 h, aiming for a concentration of 0.4–0.8 g/l at the time of surgery. Once the target fibrinogen concentration was reached, the infusion was stopped and the fibrinogen concentration was intermittently measured. If it rose above 0.8 g/l, the infusion was restarted at one-quarter the induction rate (2.1 U/h) and the concentration of fibrinogen measured again. This was only necessary in a few patients who had their surgery delayed and a period of more than 24 h had elapsed from the time the target fibrinogen was reached until their operation was scheduled.

During the perioperative period in both patient groups, fibrinogen concentrations, along with the other variables of a hemostatic screen, were determined at routine intervals. These were 1-h preoperatively, postinduction of anesthesia, during CPB when the patient was hypothermic and after rewarming, just prior to leaving the operating room and then hourly in the Intensive Care Unit (ICU) until hemostasis was assured. Although the PT, PTT, and ACT were measured in the ancrod treated patients, their results were noninformative. All three of these tests are dependent upon a mechanical end point, namely the conversion of fibrinogen into a thrombus, and are either extremely prolonged or infinite in the presence of hypofibrinogenemia.

Once in the operating room, 14-G iv and 20-G radial arterial cannulae were inserted after local infiltration before the induction of general anesthesia. All patients had pulmonary artery catheters inserted postinduction of anesthesia.

After CPB, coagulation status was assessed clinically by blood loss, inspection of vascular access sites and incisions for oozing, and by the results of the laboratory tests mentioned. If necessary, replacement fibrinogen was administered to the patient in the form of plasma or cryoprecipitate. Fibrinolysis was controlled by infusion of epsilon aminocaproic acid (Amicar®), initially as determined by clinical assessment of the individual patient and then later in the study, routinely, once the patient was separated from cardiopulmonary bypass and vital signs were stable. Postoperative chest tube drainage was returned to most patients by autotransfusion, according to routine in the ICU.

Cardiopulmonary bypass was carried out using a membrane oxygenator system consisting of polyvinyl chloride tubing, a venous reservoir, roller pump, and a hollow-fiber membrane oxygenator with an integral heat exchanger (Capiox® II 5.4, Terumo Corp, Tokyo). The occlusion of the roller pump was calibrated prior to every case. The standard prime was 2,000 cc Ringer's lactate solution, 100 cc 25% albumin, 100 cc 20% mannitol, and 100 ml 7.5% sodium bicarbonate solution. The cardiotomy suction return system consisted of polyvinyl chloride tubing and a polycarbonate hard shell filter reservoir (Model Card F-3L, Shiley Laboratories, Irvine CA). No arterial-tubing filters were used in the bypass system. Intraoperatively the pressure difference across the membrane oxygenator was measured continuously. Patient temperatures were reduced to 24–28° C and moderate hemodilution to a hematocrit of 0.28 ± 0.04 was used (mean ± SD).

Postoperatively the membrane oxygenator and cardiotomy reservoir used in four cases (two each receiving heparin or ancrod) were dismantled for examination with scanning electron microscopy. The samples were first

TABLE 1. Patient Characteristics and Operative Data*

Group	N	Gender M/F	Age (yr)	CPB (min)	Time to defibrinogenate (h)
Ancrod	20	17/3	57.9 ± 7.7†	92 ± 17	13.3 ± 2.5
Control	20	17/3	62.4 ± 6.5	92 ± 24	

CPB = Cardiopulmonary bypass time.
* Mean ± SD.
† $P < 0.05$ *versus* control.

fixed in Universal fixative *p*H 7.2 at 20° C. They were then rinsed with 0.1 M phosphate buffer, followed by postfixation with 1% osmium tetroxide at 20° C and *p*H 7.2 buffered with 0.1 M phosphate. The components were then rinsed again with the phosphate buffer and then taken through a gradient alcoholic series followed by critical point drying. The samples were mounted, gold coated, and examined with a JEOL 35 CF scanning electron microscope with accelerating voltages of 10–15 KV. Photo micrographs of various surfaces of the extracorporeal circuitry were examined and compared.

The two groups of patients were compared with respect to the clinical course of CPB, average blood loss, and use of replacement blood products. These results were compared using the Student's unpaired or paired *t* test. Their postoperative routine courses, both in the ICU and on the ward, were examined for any complications.

Results

Ancrod anticoagulation was instituted in 20 patients, 17 male and three female. Average fibrinogen concentrations before ancrod were 2.96 ± .47 gm/l (mean ± SD, $P < 0.001$ *vs.* control). Target fibrinogen concentrations (0.41 ± .20 gm/l) were achieved within 11.8 ± 2.5 h using an average dose of 1.65 ± 0.55 U/kg. Each patient underwent coronary artery bypass grafting, including the use of the left internal mammary artery in 15 patients. The average duration of bypass was 92 ± 17 min for the study group and 92 ± 24 min for the control group (table 1). The perfusions proceeded uneventfully in all cases. The perfusionist noted no changes in resistance across the oxygenator, the efficiency of gas exchange across the membrane, as judged by fresh gas flows and patient blood gases, or in the conduct of the perfusion in general.

The fibrinogen concentrations reached a nadir, in all patients, during hypothermia on CPB, but returned close to their preoperative values after the patients had been separated from CPB (fig. 1 and table 2). If volume was needed to permit separation of an ancrod-treated patient from CPB, either stored or fresh-frozen plasma was used, as opposed to albumin and/or saline in the control group. Post-CPB, if the fibrinogen concentration was low (< 0.4 g/l) and hemostasis judged to be inadequate, further fibrinogen was administered as plasma and/or cryoprecipitate. This would account for the increase in fibrinogen

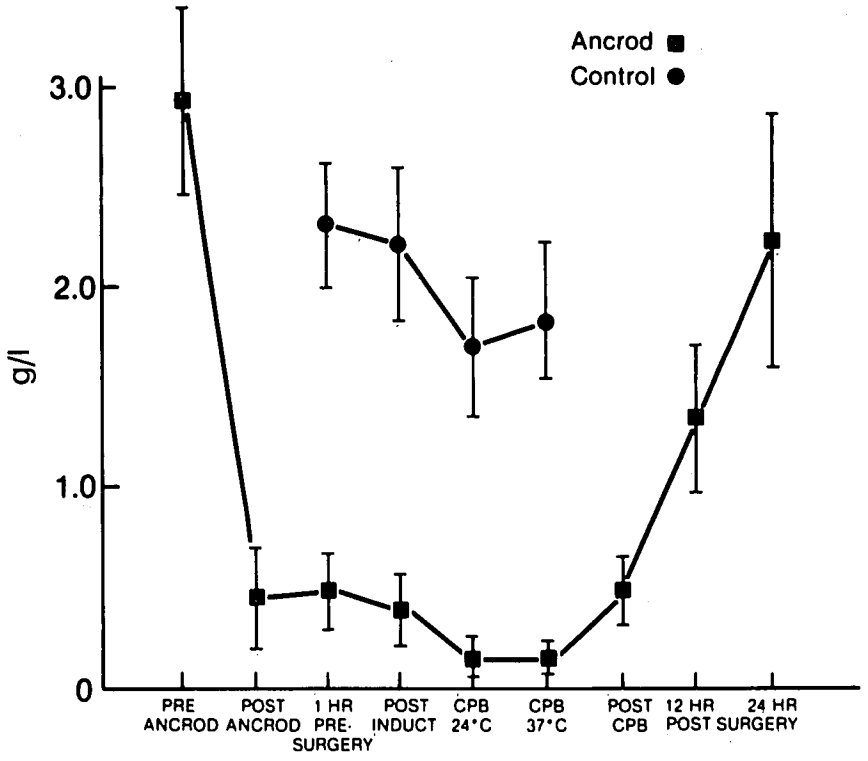

FIG. 1. Fibrinogen concentrations in ancrod and heparin anticoagulated patients.

TABLE 2. Fibrinogen Concentration (g/l)

Time	Control Group	Ancrod-Treated Group
Preancrod	2.58 ± 0.50	2.91 ± 0.47*
Postancrod	—	0.38 ± 0.20
1 h presurgery	—	0.42 ± 0.16
Postinduction	2.62 ± 0.44	0.32 ± 0.16
CPB		
24° C	1.79 ± 0.50	0.14 ± 0.10
37° C	1.92 ± 0.48	0.14 ± 0.08
Post-CPB	1.97 ± 0.51	0.35 ± 0.17
Postsurgery		
1 h	2.07 ± 0.50	0.59 ± 0.18
12 h	2.23 ± 0.49	1.15 ± 0.40
24 h	2.76 ± 0.69	2.27 ± 0.64†

* $P < 0.05$ compared with control group.
† $P < 0.05$ compared with preancrod period in ancrod treated group.

concentration post-CPB and at 1–12 h postsurgery in the study group of patients. Twelve hours after surgery the fibrinogen concentrations had increased to 1.15 ± 0.40 g/l and at 24 h were 2.27 ± 0.64 g/l in the ancrod-treated patients. The latter value was without the further use of plasma or cryoprecipitate but was still less than that existing prior to administration of ancrod.

The average blood loss for the ancrod-treated patients was 2286 ± 1311 ml and 1737 ± 973 ml for the control group (NS). Perioperative blood product use is shown in table 3.

The average platelet concentration prior to ancrod was 230 ± 87 × 10^9/l. The concentrations after ancrod and after surgery were 207 ± 51 × 10^9/l and 87 ± 39 × 10^9/l, respectively. The control patient platelet concentrations pre and postsurgery were 253 ± 44 × 10^9/l and 139 ± 43 × 10^9/l (table 4). Three patients in each group required 6 U of platelets to achieve hemostasis.

One patient in each group was returned to the operating room for surgical evaluation of excessive bleeding. Discrete surgical sites of bleeding were found in each case and their data were not included in the preceeding calculations of blood loss and blood product use. Two patients in the treated group developed hematomas at the site where veins were removed from the lower extremity.

One patient who received ancrod developed a left-sided hemothorax 40 h postoperatively. The PT and PTT were normal; platelet concentration was 128 × 10^9/l, and the fibrinogen concentration was 4.6 g/l. This patient required 3 U of packed cells for replacement. This episode resolved without further intervention, and was not included in the above calculations.

The average duration of tracheal intubation and stay in the ICU was the same for both groups of patients. Mediastinal and pleural drains remained in place for 37.6 ± 11.8 h in the ancrod-treated group, on an average 1 day longer than the control patients. However, after 18 h the drainage was serous.

TABLE 3. Blood Loss and Blood Product Use

	Control Group	Ancrod-Treated Group
Chest tube drainage (ml)	1,737 ± 973	2,286 ± 1,311*
Packed Cells (U)	2.5 ± 2.3	4.1 ± 2.1†
Plasma (U)	2.6 ± 2.9	5.6 ± 3.1†
Cryoprecipitate (U)	1.5 ± 3.6	9.3 ± 16.3†
Albumin (U)	4.4 ± 2.8	2.4 ± 2.7†

Mean ± SD.
* $P = 0.15$.
† $P < 0.05$.

There was no significant difference in the incidence of perioperative myocardial ischemia or infarction, low cardiac output syndromes, use of inotropic drugs or vasopressors, respiratory or neurological complications between the two groups. There was no evidence of delayed wound healing, and no wound dehiscences or infections occurred in the patients given ancrod.

Using electron microscopy, we found less cellular deposition as well as less proteinaceous material on the surfaces of the bypass circuits from the patients given ancrod compared with those who received heparin. The nature and composition of the proteinaceous deposits were not determined (fig. 2).

Discussion

Ancrod is a proteinase obtained from a purified fraction of the Malayan pit viper venom. The active enzyme is composed of 17 amino acids and has a molecular weight of 37,000. Ancrod catalyzes the hydrolysis of an arginine-glycine sequence of the α chain of fibrinogen, thereby splitting off fibrinopeptide A but not the chemotactic fi-

TABLE 4. Platelet Concentrations (×10^6/l)

Time	Control Group	Ancrod-Treated Group
Presurgery/Preancrod	253 ± 44	230 ± 87*
Postancrod	—	207 ± 51
CPB		
28° C	147 ± 29	123 ± 27*
37° C	146 ± 25	139 ± 34
Post-CPB	122 ± 34	139 ± 42
12 h postsurgery	139 ± 43	87 ± 39*
24 h postsurgery	122 ± 31	87 ± 30*

Mean ± SD.
* $P < 0.05$ *versus* control.

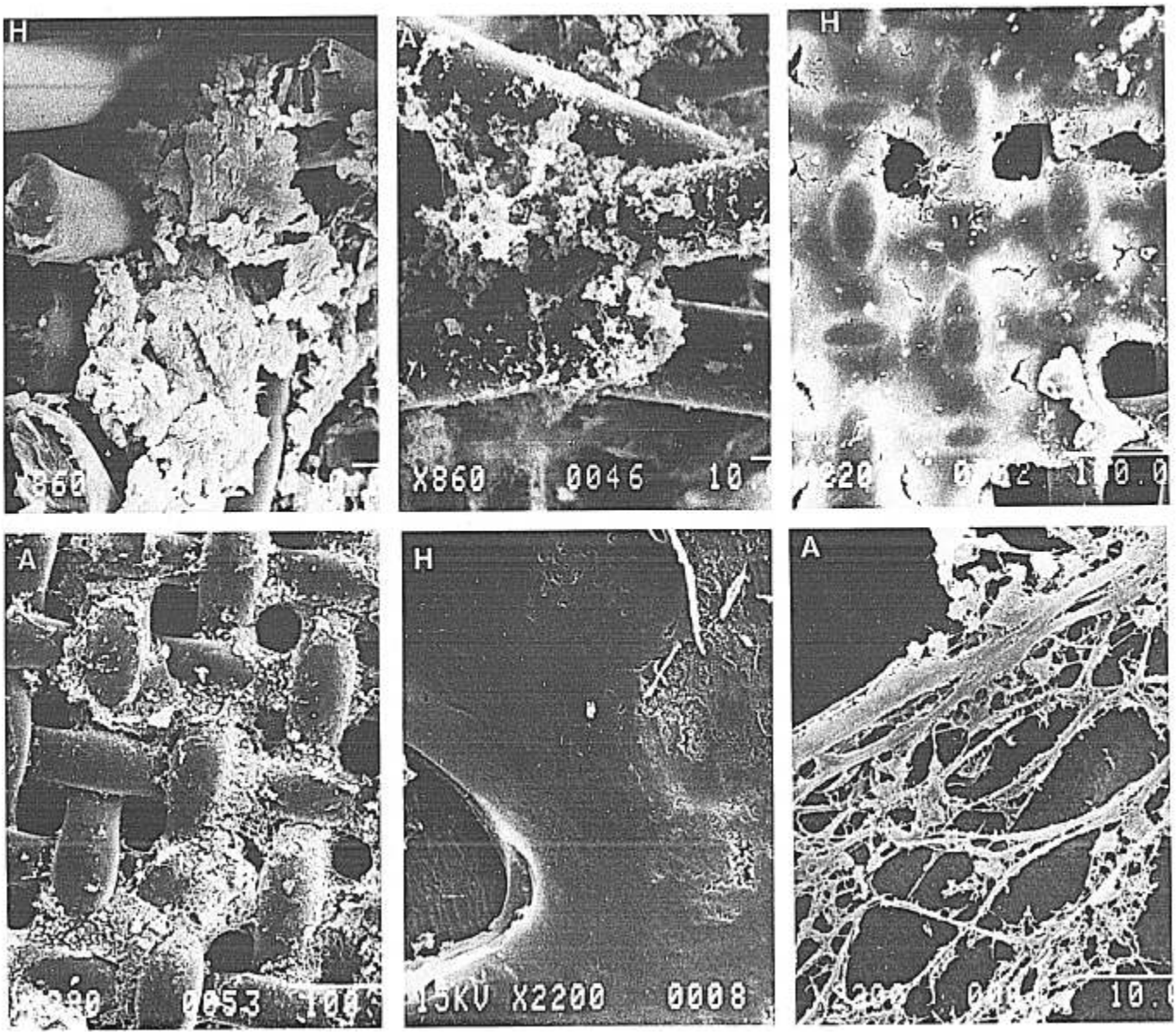

FIG. 2. Scanning electron photomicrographs of components of the CPB circuit in heparin (H) and ancrod (A) anticoagulated patients. The photomicrographs are from four patients—two each who received heparin or ancrod. Figures A (*top left*) and B (*top center*) show the fibers of the polypropylene depth media of the cardiotomy reservoir. Figures C (*top right*) and D (*bottom left*) show the mesh of the 43 μm polyester outer screen of the cardiotomy reservoir. Figures E (*bottom center*) and F (*bottom right*) show the cut inner surface of a polypropylene hollow fiber from the oxygenator. Note that in all cases in the heparin anticoagulated samples there is much more cellular and noncellular debris deposited on the surfaces examined. In figure E the entire surface of the membrane is covered by a sheet of proteinaceous material, the true membrane surface being visible only through a "pore" at the left edge of the photomicrograph, whereas in the ancrod-treated patient (fig. F), the entire surface of the membrane is visible, being covered only by some fibrillar strands.

brinopeptide B. The resulting monomers aggregate normally, but form unstable, friable, end-to-end linked, but not cross-linked, fibrin polymers, 1–2 μm in length.[14,15] These do not mature into tempered lattices but remain particulate, susceptible to normal fibrinolysis and phagocytosis by the reticulo-endothelial system (RES). In contrast, thrombin cleaves both the α and β chains, releasing fibrinopeptides A and B, allowing the formation of stable, cross-linked fibrin complexes (fig. 3). It is generally accepted that ancrod exerts a selective enzyme/substrate specificity for fibrinogen only and does not affect the level or activity of any clotting factors other than fibrinogen.[16,17] Ancrod stimulates fibrinolytic activity in established thrombus by the dose-dependent release of tissue plasminogen activator (tPA) from the vascular endothelium.[18] Tissue plasminogen activator has a high affinity

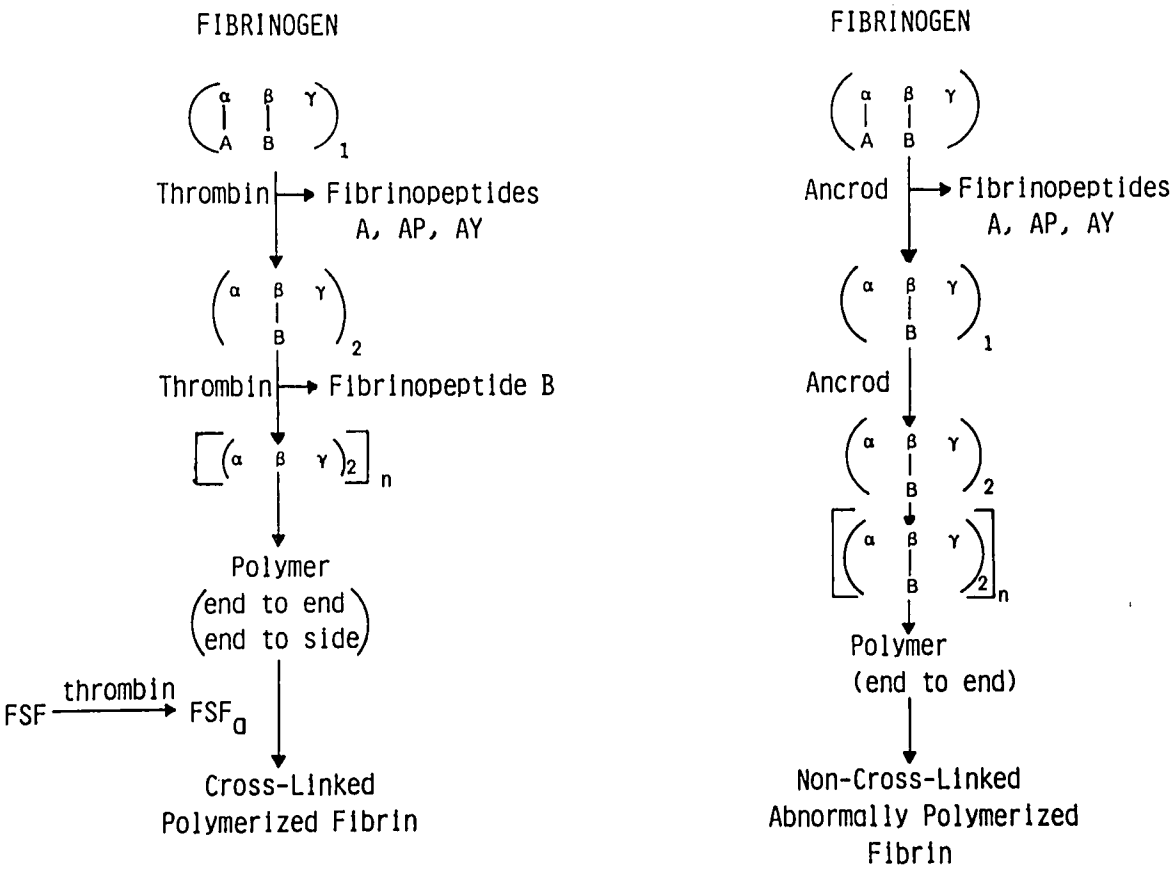

FIG. 3. A schematic representation of thrombin (left) and ancrod (right) proteolytic actions on fibrinogen.

for fibrin and fibrin-like materials and does not activate circulating plasminogen unbound to fibrin.

A constant feature in the elimination of ancrod from the plasma is the almost continuously changing rate of metabolism. This feature is characteristic of substances that depend on phagocytosis by the RES for their metabolism, since at lower concentrations there is a lower probability of particle-cell surface contact. The elimination of a labelled dose from the circulation follows a multiexponential function so that with increasing time the apparent half-life becomes longer and longer.[19] The initial rapid elimination ($t_{1/2}$ = 3–5 h in the first few hours) gradually slows, such that when 90% of the ancrod has been cleared at 4 days, the half-life has been prolonged to 9–12 days.

Therapeutic anticoagulation is achieved at a fibrinogen concentration of less than 0.7 g/l,[3] but the rate of defibrinogenation is also important. Defibrinogenation with 1–2 U/kg body weight of ancrod should not be carried out over less than 6 h to avoid overwhelming the capacity of the liver and the rest of the RES to harvest the imperfectly polymerized fibrin and hence prevent the excess being precipitated intravascularly, resulting in a hyperviscosity syndrome. We chose to administer ancrod as a constant infusion, allowing more precise control over the rate of defibrinogenation.

When ancrod is discontinued in patients who are in a normal physiologic state, the plasma fibrinogen returns slowly in a matter of days to the normal pretreatment value.[16] When fever, infection, or active underlying diseases are present, or noxious stimuli are given to animals, the fibrinogen concentration will return to pretreatment values, as part of a nonspecific stress response. This increase is measurable within hours and will return to normal values within 24 h. The etiology for the delay in the return of fibrinogen, in the absence of stress, is uncertain. It is not due to the presence of ancrod, since even the administration of the antivenom did not accelerate its return.[20] The fibrinogen concentrations in our patients returned to their normal preoperative value within 24 h of surgery. The initial increase (1–12 h postsurgery) was partly due to the use of blood products, but the increase in concentration from 12–24 h was purely due to hepatic regeneration.

During extracorporeal circulation, platelets have an increased tendency to aggregate and an increased adhesiveness, both of which lead to platelet accumulation in the lungs and on the surfaces of the extracorporeal cir-

cuitry.[21] Past work has shown that in spite of an initial decrease in platelet concentrations with defibrinogenation, these tendencies are less pronounced in ancrod-treated than in animals receiving heparin and that platelet function and levels were preserved to a greater extent in ancrod-treated animals.[13] Our results also showed an initial decrease in platelet concentration with defibrinogenation and that platelet counts were maintained throughout surgery in both groups. Postoperatively, however, platelet counts fell in the ancrod-treated patients. This may represent the dilutional effect of the autotransfusion of the mediastinal drainage, which is platelet-free due to the filters in the system, combined with the other fluids used for volume replacement in the postoperative period.

Delayed wound healing has been reported in several experimental animal models and has been ascribed to the role that fibrinogen plays in normal wound healing.[22] However this has never been confirmed in patients in the postoperative period and there were no apparent problems with our patients. All authors uniformly reported that wounds remained moist with drainage of a serosanquinous fluid for a prolonged period in patients given ancrod compared to those given heparin. Our findings support these data, the chest drainage tubes draining serous fluid 12–24 h longer.

Drainage from the mediastinal drains postoperatively was felt to be higher in the ancrod-treated group, although statistically this was not the case. The higher losses, especially in the first few hours postsurgery, were compensated for by the autotransfusion system employed. This bias probably accounted for the slightly higher, statistically significant, use of blood products in the ancrod-treated patients. This was especially true in the first half of the study, and with experience, blood product use decreased. There were no differences in the peri- and postoperative courses of the two patient populations and there were no complications that could be directly attributed to the use of ancrod, other than two-leg hematomas at vein harvesting sites.

Consideration of the properties of ancrod anticoagulation, as well as the results of this study, suggest that defibrinogenation for CPB may have advantages. Fibrinogen is the plasma component primarily responsible for plasma viscosity, and there is a parallel reduction in blood viscosity as fibrinogen concentration falls. With defibrinogenation blood flow increases across stenoses and through the microcirculation accounting for its therapeutic efficacy in symptomatic, inoperable peripheral vascular disease.[23],†† Intuitively, defibrinogenation may help hemodilution offset the increase in viscosity induced by hypothermia during CPB. Whether it may also aid the perfusion of areas of myocardium distal to coronary artery stenoses prior to CPB at the present time remains speculative. However, one of our patients, with a severe heparin resistance that had lead to the intraoperative cancellation of his cardiac surgery at another center, was having angina at rest despite maximal medical therapy including iv nitroglycerin. He had a complete resolution of his symptoms when ancrod anticoagulation was begun, such that the nitroglycerin could be discontinued. He later underwent percutaneous transluminal coronary angioplasty, in a defibrinogenated state, without complications.

The finding that the surfaces of the CPB circuit of the patients in the ancrod group consistently had less fibrin and cellular deposition is consistent with reports of similar depositions on membranes used with experimental animals.[13] It also suggests another possible advantage of ancrod during cardiac surgery. This animal work showed that less cellular elements accumulated in the lungs. In view of the implicated role of leukocytes, platelets, and fibrin in the pathophysiology of low-pressure pulmonary edema ("pump lung") seen post-CPB,[24–26] it may be reasonable to speculate that the decreased deposition of these circulating elements during the intraoperative period might well decrease the incidence of postoperative pulmonary dysfunction caused by increased capillary permeability. There were no episodes of low-pressure pulmonary edema in either group of this study, and the number of patients in each group was too small for the evaluation of this problem.

We have now used ancrod in six patients requiring CPB who had known protamine-induced anaphylactic reactions and two patients with heparin-induced thrombocytopenia and thrombosis without complication. There is still no readily available alternative to protamine in North America, but its use can be avoided during CPB by not reversing the heparin at the end of the procedure or using coumadin anticoagulation; however, each is associated with difficulties.[27] Alternatives to heparin for CPB also exist. Coumadin, low-modecular weight heparin,‡‡ low molecular weight dextrans,‡‡ extreme hemodilution with hypothermia, and more recently prostacyclin analogs[28,29] combined with heparin have all been successfully used, but again each with its own problems and disadvantages.

In summary, we have shown that defibrinogenation using ancrod is an effective and manageable method of anticoagulation for CPB. More experience is needed before it can be recommended for routine use, however, we feel that it is a definite alternative in cases where heparin or protamine are contraindicated or heparin is ineffective.

†† Ehringer H, Dudczak R, Lechner K. Rhealogical and hemodynamic actions of Arvin in patients with arterial occlusive disease (abstract). Fourth Congress of the International Society on Thrombosis and Hemostasis. Washington, DC. 1:415, 1973.

‡‡ Schwatz AJ, Howie MB. Case conference. Journal of Cardiothoracic Anesthesia. 1:577–583, 1987.

The authors wish to thank the members of the Department of Cardiac Surgery at Toronto General Hospital for their cooperation, as well as the nursing staffs of the cardiac operating rooms and the cardiovascular intensive care unit, and the perfusionists at our hospital for their ongoing patience and help. Our thanks also to Linda Westecott for the preparation of this manuscript.

References

1. Harrow JC. Protamine: A review of its toxicity. Anesth Analg 64: 348–361, 1985
2. Reid HA, Chan KE, Thean PC: Prolonged coagulation defect (defibrinogenation syndrome) in Malayan viper bite. Lancet 1: 621–626, 1963
3. Dormandy JA, Reid HL: Controlled defibrination in the treatment of peripheral vascular disease. Angiology 29:80–88, 1978
4. Bell WR, Pitney WR, Goodwin JF: Therapeutic defibrination in the treatment of thrombotic disease. Lancet 1:490–493, 1968
5. Sharp AA, Warren BA, Paxton AM, Allington MJ: Anticoagulant therapy with a purified fraction of Malayan pit viper venom. Lancet 1:493–499, 1968
6. Davis JA, Sharp AA, Merrick MV, Holt JM: Controlled trial of ancrod and heparin in the treatment of deep vein thrombosis of the lower limb. Lancet 1:113–115, 1972
7. Bowell RE, Marmion VJ, McCarthy CF: Treatment of central retinal vein thrombosis with ancrod. Lancet 1:173–174, 1970
8. Latallo ZS: Report of the task force on clinical use of snake venom enzymes. Thromb Haemost 39:768–774, 1978
9. Barrie WW, Wood EH, Crumlish P, Forbes CD, Prentice CR: Low-dosage ancrod for the prevention of thrombotic complications after surgery for fractured neck of femur. Br Med J 4: 130–133, 1974
10. Lowe GDO, Morrice JJ, Fulton A, Forbes CD, Prentice CR, Barbenel JC: Subcutaneous ancrod after operation for fractured hip. A dose ranging and feasibility study. Thromb Haemost 40: 134–143, 1978
11. Hall RJC, Young C, Sutton GC, Campbell S: Anticoagulation by ancrod for haemodialysis. Br Med J 4:591–593, 1970
12. White J, Bell W, Matthews P, Buky B: Arvin anticoagulation for prolonged extracorporeal membrane oxygenation. Anaesthesist 25:526, 1976
13. Berglin E, Hansson HA, Teger-Nilsson AC, William-Olson G: Defibrinogenation as an alternative to heparinization during prolonged extracorporeal circulation in the dog. Thromb Res 9: 81–93, 1976
14. Stocker K, Fischer H, Mercer J: Thrombin-like snake venom proteinases. Toxicon 20:265–273, 1982
15. Ewart MR, Hatton MWC, Basford JM, Dodgson KS: The proteolytic action of Arvin on human fibrinogen. Biochem J 603–609, 1970
16. Esnauf MP, Tunnah GW: The isolation and properties of the thrombin-like activity from Agkistrodon rhodostoma venom. Br J Haematol 132:581–90, 1967
17. Barlow GH, Halleman WH, Lerand L: The action of Arvin on fibrin stabilizing factor (factor XIII). Res Commun Chem Pathol Pharmacol 1:39–42, 1970
18. Soszka T, Kirschbaum NE, Stewart GJ, Budzynski AZ: Direct effect of fibrinogen clotting enzymes on plasminogen activator secretion from human endothelial cells. Thromb Haemost 54:164–169, 1985
19. Regoeci E, Bell WR: *In Vivo* Behaviour of the Coagulant Enzyme from Agkistrodon rhodostoma Venom Using ^{131}I-'Arvin'. Br J Haematol 16:573–587, 1969
20. Bell WR, Regoeczi E: Isotopic studies of therapeutic anticoagulation with a coagulating enzyme. J Clin Invest 49:1872–1877, 1970
21. Mielke Jr CH, de Leval MD, Hill JB, Macur MF, Gerbode F: Drug influence on platelet loss during extracorporeal circulation. J Thorac Cardiovasc Surg 66:845–854, 1973
22. Sharp AA: Clinical Use of Arvin. Thromb Diath Haemorrh (suppl) 45: 69, 1971
23. Ehrly AM: Influence of Arvin on the flow properties of blood. Biorheology 10:453–458, 1973
24. Galuser FL: The uncertain role of the neutrophil in increased permeability pulmonary edema. Chest 88:601–607, 1985
25. Rinaldo JE, Rogers RM: Adult respiratory distress syndrome: Changing concepts of lung injury and repair. N Engl J Med 300:900–909, 1982
26. Dalton RC, Edmunds Jr HL, Hutchinson JC, Benson BR: Platelet aggregate emboli produced in patients during cardiopulmonary bypass with membrane and bubble oxygenators and blood filters. J Thorac Cardiovasc Surg 67:258–262, 1974
27. Smith JP, Walls JT, Muscuto MS, McCord ES, Worth ER, Curtis JJ, Silver D: Extracorporeal circulation in a patient with heparin-induced thrombocytopenia. ANESTHESIOLOGY 62:363–365, 1985
28. Kraenzler EJ, Starr NJ: Heparin associated thrombocytopenia: Management of patients for open heart surgery. Case reports describing the use of iloprost. ANESTHESIOLOGY 69:964–967, 1988
29. Kappa JR, Horn D, McIntosh CL, Fisher CA, Ellison N, Addonizio VP: Iloprost (ZK 36374), a new prostacyclin analogue, permits open cardiac operation in patients with heparin-induced thrombocytopenia. Surg Forum 36:285–286, 1985