The Effect of Arvin Upon Cardiac Function[1] (34379)

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(Introduced by F. J. Stare)

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A new approach to the problem of thromboembolism, utilizing the principle of controlled defibrination, has recently been described (1). The therapeutic agent, called Arvin, is contained in a purified fraction of Malayan pit viper venom. Arvin converts plasma fibrinogen to a different fibrin monomer, designated Arvin-Fibrin (2), which is rapidly cleared from the circulation mainly by reticuloendothelial phagocytosis (3). Other than fibrinogen, the concentration and function of blood factors and platelets remains unaltered (1, 4). Blood is thereby rendered nonclotting, yet hemorrhage does not occur.

The therapeutic efficacy of Arvin has been established in patients with thromboembolic problems. Since such patients frequently have serious underlying cardiovascular disorders, it is important to determine whether Arvin exerts any adverse effect on cardiac function.

Material and Methods. Five mongrel dogs weighing 28–41 kg were anesthetized with 30 mg/kg sodium pentobarbital and ventilated with room air through a cuffed endotracheal tube coupled to a Bird Mark 14 respirator. Respirator rate was set at 12–18/min. Catheters were inserted via cut downs from the following sites: (1) a no. 7F Sones catheter passed into the left ventricle from the right carotid artery; (2) a no. 7F Cournand catheter placed in the abdominal aorta from the left femoral artery; (3) a PE no. 160 intracatheter placed in the abdominal aorta from the right femoral artery; (4) a no. 8F fiberoptic pressure catheter[2] positioned in the mid left ventricle from the left carotid artery; (5) a no. 5F bipolar pacing catheter passed into the right atrium from the right jugular vein.

Regular atrial pacing was achieved with a Medtronic 5834 stimulator set at 10–20 beats/min above each animal's intrinsic rate. Pressure tracings were taken on DC9 electronics for medicine recorder with a paper speed of 200 mm/sec. Cardiac outputs were performed by the indicator dilution technique using a Lexington computer. The first (dp/dt) and second (d2P/dt2) derivatives of left ventricular pressure were obtained from two analog differentiators in cascade using R-C networks and operational amplifiers. Details of this system and its calibration are cited elsewhere (5).

Left ventricular pressure and its derivatives were measured every 5 msec from the high-speed tracings of the fiberoptic catheter. Because of minimal but unpredictable baseline drift in the instrument, absolute end diastolic pressure was computed from the Sones catheter. Left ventricular stroke work (LV SW) in gm-m per beat and mean systolic ejection rate (MSER) in ml/sec were derived from standard formulae (6).

Myocardial mechanics were analyzed by the Hill model (7). Contractile element shortening velocity (CEV) was assumed to equal rate of elongation of the series elastic resistance during isovolumic systole. Because of constant heart size during this period, instantaneous pressure was related to instantaneous tension by a constant. CEV, therefore, was computed from end diastole to aortic valve

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[2] American Optical Company, Southbridge, Massachusetts.

opening utilizing the ratio dp/dt/P′ where P′=instantaneous pressure (8). Isovolumic force-velocity curves for the contractile element were constructed by plotting CEV against P′ and curve-fitting the data through the maximum observed point of CEV back to zero load, designated as V_{max} (9).

Arvin was prepared from 1.1 -ml sterile ampoules containing 80 units/ml[3]. One unit contains 2 μg protein dissolved in a 0.03 *M* sodium phosphate /0.13 *M* sodium chloride buffer at pH 6.8. Only one batch of Arvin (T114) was used during these experiments.

The Arvin stock supply was diluted with normal saline and given intravenously in a dose varying from 0.7–1.0 unit/Kg or 1.4–2.0 μg/kg body weight. A single infusion of 30 ml was administered intravenously over 30 min via a Harvard model 606 constant-infusion pump. This time interval was chosen so that the rate of Arvin-fibrin formation would not exceed the animal's capacity to dispose of it by fibrinolysis or through the reticuloendothelial system.

Plasma fibrinogen concentration was measured by a modification of the method of Ratnoff and Menzie (10). A semiquantitative rapid test for plasma fibrinogen in which serial dilutions of the animal's plasma were clotted with thrombin was also employed (11). Blood samples were collected in a solution of 15% potassium ethylene diamine tetraacetate and 10% epsilon amino caproic acid and measured in duplicate.

Results. Effect of Arvin on plasma fibrinogen. In five animals a single infusion of Arvin 1.4–2.0 mg/kg caused a prompt fall in plasma fibrinogen. Within 30–60 min fibrinogen levels had declined to nondetectable levels, remaining so for more than 24 hr (Fig. 1). During this time no excessive external bleeding or hematoma formation was noted at the cutdown sites, either during the experiment or subsequently when the dogs had returned to their cages. In three dogs fiberoptic catheters were left in place overnight. No fibrin clot could be detected on their caged tips for up to 18 hr.

Hemodynamic effects of Arvin. Assessment of myocardial performance was made before, immediately after, and, in some instances, during Arvin infusion. Results are listed in Table I. Left ventricular function was not influenced by Arvin, little change being observed in either stroke work or end diastolic pressure. Mechanics of isovolumic systole also remained unaltered. No significant change was noted in dp/dt or d2p/dt2 or in the ratio of dp/dt to a common isovolumic pressure. Analysis of left ventricular performance in terms of the isovolumic contractile element force-velocity relationship showed no alteration in either peak observed CEV or its extrapolate to zero load, V_{max} (Fig. 2).

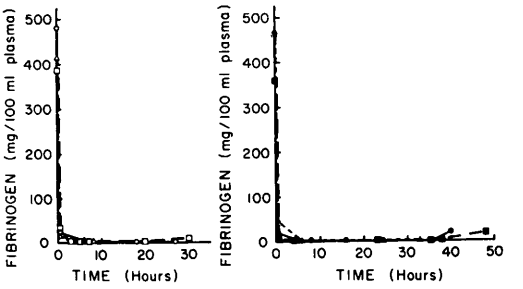

FIG. 1. Time course of changes in circulating fibrinogen in six dogs given Arvin, 1.4–2.0 μg/kg over a 30-min period.

Discussion. Long-term hemodynamic monitoring is being increasingly utilized in the rational therapeutic management of patients with serious cardiovascular derangements. Fiberoptic monitoring catheters have been developed which offer several advantages over conventional fluid-filled catheter systems. The fiberoptic catheter samples continuously and thereby obviates the need of withdrawing blood. It can be adapted for measurement of pressure (5) or blood flow, either total cardiac output (12) or regional circulation (13). A major deterrent to its application in man, however, has been the tendency for the caged tip shielding the glass fibers to accumulate fibrin, thereby damping the signal. Without anticoagulation a fibrin clot in the cage forms within 10 min. Heparin in therapeutic doses postpones clot development until 30–60 min have elapsed. In animals, only massive doses of heparin insures a prolonged period during which the fiberoptic catheter tip remains free from fibrin clot.

[3] Supplied by Prof. F. A. Robinson, Twyford Laboratories, London, N. W. 10, England.

TABLE I. Hemodynamic Effects of Arvin.[a]

Study	C.O. (liters /min)	LV_{sm} (mm Hg)	LVEDP (mm Hg)	Rate	LVSW (g-m/bt.)	dp/dt (mm Hg/sec)	d^2P/dt^2 (mm Hg/sec^{-2})
B	5.0	120 ± 5	3 ± 1	150	54	2252 ± 170	133,800 ± 450
A	6.0	117 ± 4	3 ± 1	150	63	2350 ± 52	136,450 ± 210
B	3.0	110 ± 4	4 ± 1	130	49	2242 ± 210	193,560 ± 550
A	3.4	110 ± 4	3 ± 1	130	52	2140 ± 110	191,480 ± 230
B	3.1	140 ± 6	1 ± 1	168	36	2337 ± 120	148,000 ± 800
D	3.3	144 ± 6	1 ± 1	168	39	2459 ± 140	164,300 ± 500
A	3.0	150 ± 4	1 ± 1	168	38	2622 ± 110	169,300 ± 615
B	4.2	118 ± 6	5 ± 2	144	46	2400 ± 235	172,800 ± 690
A	4.4	120 ± 6	4 ± 2	144	50	2450 ± 210	173,940 ± 840
B	3.9	130 ± 5	5 ± 3	152	47	2340 ± 205	152,640 ± 475
A	3.8	128 ± 5	5 ± 3	152	46	2384 ± 226	154,760 ± 520

[a] B = before, D = during, and A = after Arvin; C.O. = cardiac output; LV_{sm} = left ventricular systolic mean pressure; LVEDP = left ventricular end diastolic pressure; LVSW = left ventricular stroke work; dp/dt = first derivative and d^2P/dt^2 = second derivative left ventricular pressure.

In the present study, Arvin was used to circumvent the problem of clot formation while avoiding possible side effects of bleeding consequent to excessive anticoagulation. A single 30-min infusion of Arvin extended the useful monitoring life of the fiberoptic pressure catheter to more than 10 hr. The abnormal fibrin monomer created by Arvin's action on fibrinogen was adequately disposed of by fibrinolytic and reticuloendothelial systems. Hence, no fibrin was deposited in the interstices of the catheter cage tip, either during or for 18 hr after the completion of Arvin infusion when circulating fibrinogen remained nondetectable. At the same time, no excessive external bleeding was noticed in any of the animals despite the presence in each of several cutdown sites. Reports of Arvin used in man indicate a similar lack of bleeding problems (1, 4).

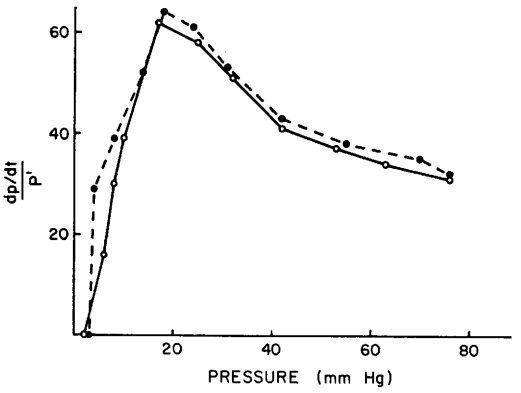

FIG. 2. Representative study of the effects of Arvin upon force velocity relationships of the contractile element (CE) during isovolumic systole. Solid line is the control state. Dashed line is immediately after a 30-min Arvin infusion, (dp/dt)/P' in sec^{-1} depicts CE velocity.

Arvin approaches the ideal in anticoagulant therapy because of rapidity of onset of action, long duration of effect, freedom from side effects of bleeding, and prompt reversal with specific antidotes (14). The present work indicates that Arvin in no way impairs myocardial function and holds forth the possibility that Arvin may find useful application in shock syndromes accompanied by fibrin deposition within the microcirculation.

Summary. Arvin, a therapeutic agent which prevents clotting by means of controlled defibrination, was evaluated in five dogs in conjunction with long-term fiberoptic hemodynamic monitoring. Cage-tipped catheters remained free of fibrin clot for more than 18 hr during which time no significant bleeding was noted from cutdown sites. Arvin did not cause any significant changes in left ventricular function, both tension gen-

erating and velocity shortening attributes remaining unchanged.

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