Serum-Induced Thrombosis

Studies of its Induction and Evolution Under Controlled Conditions in Vivo

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A simple, reproducible, physiologic technic is delineated for the production and study of thromboembolism. The method is based on the observation that the infusion of serum, in striking contrast to plasma, induces massive thrombosis in vascular segments containing stagnant blood far removed from the site of infusion. Data are presented on the nature of the thrombosis-inducing activity of canine and human serum, on the effect of serum infusions on recipient animals, and on the morphology of the induced thrombus. The adaptability of this method to the study of a variety of thromboembolic phenomena in man is described.

Clinical approaches to thromboembolic phenomena have thus far been hampered by the lack of adequate criteria for recognizing the incipient or active thrombotic state. Pathologic observations have in turn been limited by the inability to assess accurately the age of thrombi and to determine, in many instances, whether clots found at necropsy were formed ante mortem. Clinical-pathologic correlations have frequently been unrewarding because of the inability to determine the extent to which thrombi fracture, dissolve, or propagate between the onset of the clinical episode and the time of pathologic examination.

Numerous experimental technics have been devised to produce thrombosis or vascular obstruction in animals. Some methods have depended on the production of marked intimal damage by mechanical, chemical, or electrical injury. Others have been based on the injection of thromboplastin or thrombin. Still others have utilized the infusion of extracorporeally formed fibrin, whole blood clot, or particulate foreign matter and several investigators have incorporated into the clot radioactive substances for subsequent identification of the thrombus or embolus. Many of these technics have been extremely unphysiologic, and were initially designed to study 1 or 2 aspects of thromboembolism. In almost all the procedures, the production of clot has been variable, and the ability to control or predict its size and shape has been limited. Data concerning the initial histopathology have frequently been meager and information concerning clot initiation, propagation, and embolization has been restricted by the nature of the technics themselves.

In the absence of an adequate clinical or laboratory test for intravascular thrombosis, a versatile experimental technic of thrombus formation would aid in evaluating discrepancies between clinical and pathologic aspects of thromboembolic phenomena and in correlating knowledge of the coagulation and lytic systems in vivo. Stimulated by the observations of Glenard and Baumgarten concerning the prolonged fluidity of a stationary column of blood in a vein occluded between 2 carefully applied ligatures, we at first studied the early changes in coagulation within isolated segments of the jugular veins of dogs.
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Although coagulation proceeded in this system, it was slow and incomplete for as long as 8 hours after the vein was isolated.\(^45\) An attempt was made, therefore, to accelerate coagulation by as physiologic an agent as possible without producing defibrination, seriously injuring the endothelium, or injecting extracorporeally formed clot. Serum, a natural product of the coagulation process itself, was selected for this purpose because it possesses clot-promoting activity in vitro\(^46-48\) and has been successfully used as a blood substitute in man.\(^49\) Moreover, Hayem\(^50\) and subsequently Feissly\(^51\) had demonstrated that serum could induce a clot in vivo.

It is the purpose of this report to describe this technic and to present some of the results that have derived from its use.

**METHOD**

The basic technic, as used in dogs, has been described previously.\(^52\) The animal is anesthetized with sodium pentobarbital, a segment of jugular vein 1 or more centimeters in length is freed from its surrounding tissues and its tributaries are ligated. Thirty milliliters of heterologous canine serum eluate,\(^*\) independent of the weight of the animal, are then infused into an antecubital vein in 30 seconds. Within 60 seconds after the completion of the infusion, the previously freed jugular vein segment is gently isolated with sersaffine clamps. A thrombus forming a cast of the occluded vein segment appears within several minutes after clamping (fig. 1). Thrombi also invariably form behind the distal occluding clamp. Stasis in this area is partial, since blood flow in the region of these thrombi continues by way of patent collateral venous tributaries and the fully patent distal continuity of the vein itself. Partial narrowing of the vein prior to the infusion of the serum eluate also produces thrombi distal to the narrowed zone.\(^52\)

A similar and more quantitative technic has also been developed for the infusion of human serum into rabbits.\(^53\) Human serum (1.32 ml. per Kg. of rabbit diluted with physiologic saline to a constant volume) is injected in 15 seconds into a contralateral rabbit ear vein. Within 15 seconds after completion of the infusion, the previously freed jugular segment is isolated. When, 10 minutes later, the isolated vein segment is opened, a clot forming a cast of the vessel is found.

\(^*\)Preparation of this eluate has been previously described in detail.\(^52\)

Fresh thrombi formed in vessels occluded following the infusion of serum or serum eluate are not adherent and are readily moved by the stream of fluid blood when the obstructing clamps are removed. By this means, in the dog, emboli have been released to the portal venous bed, the tibial arteries, and the pulmonary arteries. By applying simultaneous stasis to various vascular systems after the infusion of serum, multiple thrombi of the same histologic composition can be produced in different areas of the circulation at the same time. In certain areas, such as the femoral or jugular veins, comparable simultaneous thrombi have been formed bilaterally, permitting release of 1 thrombus as an embolus while the contralateral thrombus is maintained in situ as a control. When large amounts of thrombi are desired, the infusion and clamping may be repeated as often as every 10 minutes; in this fashion a large volume of thrombi may be sent to a specific vascular area such as the lung. In addition to releasing varying amounts of freshly formed thrombi, it is also possible to permit thrombi to age in situ, thereby undergoing varying degrees of alteration for hours or days prior to their release.

Although complete absence of endothelial injury at the site of thrombus formation is difficult to establish,\(^54\) a variety of experiments has demonstrated that vascular obstruction per se does not cause endothelial damage sufficient to produce thrombosis by the method used.\(^52\) In any event, the release of thrombi to distant vascular areas, such as the pulmonary arteries, permits study of the response of previously uninjured vessel wall to the presence of the contained thrombus.

Thrombi were prepared for microscopic study by fixation in 10 per cent formalin in isotonic saline, and sections were stained with hematoxylin and eosin. A few thrombi were also fixed in hypotonic solutions, such as 5 per cent and 10 per cent aqueous formalin.

Tidal volume, minute volume, and rate of respiration were recorded on a kymograph attached to a Tissot spirometer. Arterial blood pH was measured with a Radiometer glass electrode. The carbon dioxide content and the oxygen content and capacity of arterial blood were measured by the technic of Van Slyke and Neill.\(^55\) The arterial carbon dioxide tension was measured by applying the arterial pH and plasma carbon dioxide content to the line chart of Van Slyke and Sendroy.\(^56\) After collection of the expired air in a Douglas bag, oxygen consumption and carbon dioxide production were measured in a 0.5-ml. Scholander apparatus.\(^57\) The right ventricle was catheterized through the right external jugular vein. Electrocardiographic tracings and right ventricular pres-
in a multichannel recorder. Platelet counts were performed by the method of Rees and Ecker; clotted times by the method of Lee and White; thromboplastin generation by the method of Biggs and Douglas; 1-stage prothrombic activity by the method of Rosenfield and Tuft; prothrombin, factor V and factor VII activities by the methods of Owren; and "Stuart" factor activity by the method of Bachmann, Duekert, and Koller. Platelet-poor plasma was prepared by the method of Brinkhaus.

RESULTS

Single infusions of 30 ml. of canine serum eluate into a series of 200 dogs resulted in thrombi forming a complete cast of the isolated vein lumen in 198 animals. When veins were clamped without prior infusion of serum eluate, no macroscopic clot was observed for periods ranging from 20 to 90 minutes after clamping. Following infusion of serum eluate on the other hand, visible clot developed within 60 seconds after the vein was isolated. The thrombus increased rapidly in size and, after 5 minutes, formed a complete cast of the isolated segment. A high degree of reproducibility could also be demonstrated with the infusion of human serum into rabbits; thrombi were formed in the jugular veins of 23 of 24 animals following serum infusion. The thrombosis-inducing activity of serum was transient. Under the experimental conditions used, a delay of 2 to 10 minutes in the dog and 30 to 60 seconds in the rabbit between infusion and clamping the vein segment resulted in variable-sized thrombi. With greater delays, no thrombi formed.

The size and shape of the thrombus are determined by the caliber of the vessel and the length of the isolated segment. Thus, single clots varying from 0.5 to 15 cm. in length and from 0.1 to 0.8 cm. in diameter have been produced in the dog. The occlusion of a vein by a single clamp produces variable lengths of clot, often as great as 30 to 40 cm. (fig. 2).

The location of the thrombi is determined by the sites of vessel isolation. Thrombi of predetermined size can thus be formed in the femoral, renal, and portal veins, as well as in the jugular venous system. In similar fashion, thrombi can be induced in the femoral, renal, coronary (fig. 3), and carotid arteries. In addition, thrombi can also be formed in the inferior vena cava, the abdominal aorta (fig. 4), and the atrial appendages (fig. 5).

Nature of the Thrombosis-Inducing Activity of Serum

In contrast to the formation of thrombi following infusions of canine serum or serum eluate in dogs, infusion of 100 ml. of physiologic saline solution into each of 5 dogs, 100 ml. of distilled water into each of 5 additional dogs, and 100 ml. of carefully collected plasma into another group of 10 animals, failed to induce thrombus formation in the standard test system.

Thrombi have been repeatedly induced not only in the dog and rabbit, but also in the guinea pig by infusions of homologous and heterologous serum of each species respectively, and by human serum. Thrombi in both the dog and rabbit have in addition been produced by the infusion of sera from cow, lamb, and pig.
As noted above, 23 of 24 rabbits receiving 1.32 ml. of normal human serum per Kg. developed thrombi forming a cast of the isolated jugular vein segment. Sixteen of 23 rabbits receiving 1.32 ml. of normal platelet-rich recalcified human plasma formed comparable thrombi. Thrombi also formed when platelet-poor recalcified plasma was used as the infusate. In sharp contrast, human plasma collected in the cold with siliconized equipment completely failed to induce thrombosis in rabbits. Thus, 20 infusions of normal human plasma (1 part 0.1 M sodium oxalate to 9 parts of whole blood) at a dose of 1.32 ml. per Kg. and 10 infusions at twice this standard dose did not cause thrombosis. Human plasma collected with 1 part of 3.2 per cent sodium citrate to 9 parts of whole blood, or with 1 part of a 10 per cent solution of the disodium salt of ethylenediaminetetraacetic acid to 9 parts of whole blood, also failed to induce thrombi. Unless plasma is processed according to the prescribed technic, partial and occasionally complete thrombus formation may occur. Plasma less carefully collected, although reflecting the presence of the thrombosis-inducing activity of serum, nevertheless showed normal thromboplastin generation, normal prothrombic activity, and normal prothrombin, factor V, factor VII, and "Stuart" activities.

The thrombosis-inducing activity of normal human serum is destroyed at 4 C. for 96 hours, but is retained for weeks at -20 C. The active moiety is completely adsorbed on barium sulfate and recovered from the adsorbate by elution with citrate.

Systemic Response of Recipient Animal to Serum and Serum Eluate Infusions

In 14 dogs the infusion of heterologous canine serum eluate produced in the recipient animal no significant alteration in body temperature, tidal volume, minute volume or rate of respiration, arterial blood pH, arterial carbon dioxide content or tension, arterial oxygen content or capacity, oxygen consumption, or carbon dioxide production. There were also no changes in cardiac rate, rhythm,
electrocardiographic configuration, or right ventricular pressure.

In 8 dogs infused with heterologous canine serum and in 6 rabbits infused with normal human serum, neither thrombocytopenia nor visible hemolysis of the plasma was observed in blood samples obtained from the recipient animals 30 seconds, 5, and 30 minutes after infusion of serum or serum eluate.

The clotting time of the recipient animal in untreated and in siliconized glass tubes was transiently but significantly decreased immediately following serum infusion. There was also a marked impairment in thromboplastin generation, but the 1-stage prothrombic activity, prothrombin, and convertin concentrations remained normal.

Whereas the infusion of serum via a peripheral vein invariably induced thrombus formation in any vessel where blood flow was retarded, the infusion of the same amount of normal human serum into the portal vein of 8 rabbits failed to induce thrombus formation in a systemic vein. In 4 animals thrombi were successfully induced in systemic veins by an infusion of serum into the marginal ear vein before and after an unsuccessful portal vein infusion.

**Morphology of the Serum-Induced Thrombus**

Thrombi from 31 dogs were examined 10 minutes to 24 hours after their formation. The thrombi formed under conditions of complete stasis were red, smooth, firm, flexible, complete casts of the isolated vein segments. Microscopic examination revealed a fine meshwork of fibrin in which red cells were trapped (fig. 6). The erythrocytes were sharply defined, densely packed, often in rouleaux formation; white cells were distributed at random. The fibrin strands were usually difficult to see among the densely packed red cells, but became readily apparent when the peripheral erythrocytes had been partially laked by hypotonic fixatives such as 10 per cent aqueous formalin (fig. 7). Small hyaline foci from which fine fibrin strands appeared to radiate, and around which a thin...

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**Fig. 6 Top.** Photomicrograph of 10-minute, complete stasis clot formed in jugular vein of dog. × 128. Note absence of lines of Zahn.

**Fig. 7 Bottom.** Photomicrograph of 10-minute, complete stasis clot formed in jugular vein of dog and fixed in hypotonic 10 per cent aqueous formalin. × 128. Note fibrin mesh in areas of red cell lysis at surface.
collar of leukocytes was occasionally noted, were scattered through the clot; these apparently consisted of centers of fibrin formation and possibly platelets. These hyaline foci also became more evident when the red cells had been partially laked (fig. 7). There was no evidence, however, of the anastomosing strands rich in platelet material (the lines of Zahn) generally associated with thrombi formed at sites of endothelial injury. Significant variation in gross or microscopic appearance was not noted when such thrombi were examined after periods ranging from 20 minutes to 4 hours from the time of formation.

The complete stasis thrombus showed no essential difference from the red clot produced by withdrawing blood from the animal and allowing it to clot in vitro or from postmortem clot removed from the chambers of the left side of the heart after the death of the animal.

Thrombi formed under conditions of partial stasis behind the distal occluding clamp were frequently bizarre in shape, varied greatly in length, and usually failed to form complete casts of the venous lumen. Side-arm extensions corresponding to connecting venous tributaries were often seen. Grossly, a small amount of gray-white surface accretion was noted on some of these thrombi, more frequently on the distal "tail" of the thrombus or on the side-arm extensions. Microscopic examination revealed that these thrombi were similar in all respects to those formed by complete stasis except for variable amounts of fibrin, leukocytes, and hyaline platelet material on the surface corresponding to the accretion noted grossly. Only minute amounts of this material were noted after 20 minutes, but it became increasingly evident on the surface of most thrombi followed in situ for periods up to 4 hours or longer.

Complete stasis thrombi released to areas of narrowing in more proximal portions of the vein also tended to show this accretion in the majority of instances up to periods of 4 hours and invariably after 24 hours. The same was true of such thrombi released into the systemic circulation and recovered from the right ventricle or pulmonary arteries after periods of 20 minutes or longer; the amount of such accretion on emboli tended to be greater than on thrombi of comparable age confined to the vein of origin (fig. 8). The accretion appeared morphologically identical to the material comprising the lines of Zahn in human thrombi and was usually limited to zones at or near the surface of the thrombus. In some instances, however, narrow zones could be observed extending for variable distances between clot laminations as though layers had been formed at different times (fig. 9). On the other hand, no evidence of accretion, either on the surface or between the layers of thrombus could be observed on postmortem clot or in clot permitted to form in vitro.

**DISCUSSION**

The method described in this communication affords a simple, reproducible, physiologic technic whereby one or more thrombi of uniform composition and predetermined size can be produced in any selected vessel without significant systemic side effects. These thrombi may be produced in a variety of experimental animals and can be studied in situ or released to vascular beds initially free of endothelial injury. With this technic observations can be made on factors relating to the initiation, propagation, dissemination, and dissolution of intravascular thrombi.

The lack of significant systemic side effects from the infusion of serum suggests that the thrombotic activity of serum acts through a specific pathway upon the coagulation mechanism of the recipient animal rather than through other physiologic alterations.

The identity of the thrombosis-inducing activity of human serum remains obscure, but it is not an artifact. It arises, directly or indirectly, as a consequence of the coagulation process itself, has been demonstrated in platelet-poor recalcified plasma, and is distinct from tissue thromboplastin, factor V (ac-globulin), factor VII
FIG. 8 Top. Photomicrograph of clot released to lung and recovered 10 minutes later. X 128. Note heavy surface accretion of fibrin, leukocytes, and platelet material.

Fig. 9 Bottom. Photomicrograph of clot released to proximal area of narrowing and removed 70 minutes after formation. X 10. Note “tail” and coating of accretion with inclusion into clot to resemble lines of Zahn.

(convertin), factor VIII (antihemophilic globulin), and “Stuart” factor.66 On the other hand, it is related to at least 3 specific clotting factors essential for the first phase of coagulation: factor IX (plasma thromboplastin component, PTC), Hageman factor, and plasma thromboplastin antecedent (PTA).66 It is possible that the initiation of experimental thrombosis with human serum may be dependent on the presence of these factors in “activated” form, or on the formation of the complex termed “intrinsic thromboplastin.” The failure to produce systemic thrombi when serum was infused through the portal vein suggests that this thrombotic moiety is inactivated in the liver.

The level of the thrombosis-inducing activity in normal human serum can be determined quantitatively by a bioassay based on a direct relation between in vivo thrombosis in rabbits and the quantity of serum infused.53 This assay of human serum thrombosis-inducing activity may eventually serve as a guide to its isolation, purification, and characterization.

Morphologic studies of the thrombi produced by this method indicate that they are in no way distinguishable from postmortem or in vitro clots when stasis is complete. When stasis is partial, however, or when the thrombus is exposed to rapid blood flow, as in passage to the lung, variable amounts of eosinophilic hyaline accretion of fibrin, leukocytes, and platelets accumulate on the surface, apparently in direct relation to the amount and duration of blood flow. Such accretion may, in fact, be included in the substance of the thrombus as it propagates, eventually becoming indistinguishable from the lines of Zahn. This sequence is an established mechanism in the instance of a thrombus propagating from the white platelet nidus formed at a site of endothelial injury.67-69 It would appear that, in the dog at least, a similar sequence may be initiated by a red, serum-induced, stasis thrombus formed in areas of retarded flow where endothelial injury is absent or so minimal that thrombus
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formation will not form in the absence of serum infusion.\textsuperscript{52}

No species specificity to the serum infused, or to the recipient animal has yet been found. This uniformity of response suggests that thrombosis resembling the experimental serum-induced complete stasis thrombus may be initiated in areas of retarded blood flow free of endothelial damage under appropriate conditions in man. Such thrombi, hours after their formation, might be difficult to distinguish from thrombi originating as a platelet nidus at a site of local endothelial injury. Although no evidence has yet been uncovered demonstrating that the mechanism of serum-induced thrombosis has a counterpart in man, sufficient data have been accumulated to encourage further investigation of such a hypothesis.

The technic of serum-induced thrombosis, in our hands as well as in those of others, has provided data on the response of the intact animal to peripheral arterial,\textsuperscript{70, 71} coronary arterial,\textsuperscript{72} and pulmonary arterial emboli,\textsuperscript{73} in addition to observations concerning the effectiveness of anticoagulant\textsuperscript{74, 75} and lytic\textsuperscript{71, 72, 76} agents. Finally, a standard method of thrombus induction has been developed that may prove extremely helpful in clarifying some of the conflicting results obtained by different laboratories studying experimentally various aspects of thromboembolic disease.

**SUMMARY**

A method of serum-induced thrombosis has been described whereby thrombi of predetermined size can be formed in 1 or more vascular beds singly or sequentially.

The thrombosis-inducing activity is present in platelet-poor recalcified plasma as well as in serum, but is absent, in an active form, from carefully collected normal plasma. The thrombotic activity arises, directly or indirectly, as a result of the coagulation process itself and is not species specific.

The red, serum-induced thrombus cannot be distinguished from in vitro or postmortem clot at the time of its formation. When exposed to flowing blood, however, a surface accretion of fibrin, leukocytes, and platelet material forms that is similar in appearance to the lines of Zahn. The extent of this accretion is in direct relation to the amount and duration of blood flow.

In addition to providing a versatile technic for experimental study of thromboembolism, the observations herein reported indicate that thrombi produced by this method may eventually become indistinguishable from those arising at sites of endothelial injury. The accumulated data raise the possibility that a similar mechanism of serum-induced thrombosis may be operative in man.

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**SUMMARIO IN INTERLINGUA**

Es describibe un metodo pro le induction de thrombose per sero, permittente le formation de thrombos de dimensiones predeterminate in un o plure vasculaturas, individual-o sequentialmente.

Le activitate thrombopoietic es presente in sero e etiam in plasma recalcificato que es povre in plachettas, sed illo es absent in cautemente collectionate plasma normal. Le activitate thrombotic se manifesta, directe-o indirectemente, como resultato del processo coagulatori mesme e non es specific al specie.

Le thrombo rubie que es induceite per sero non pote esser distinguite al tempore de su formation ab un coagulo formate in vitro o post morte. Tamen, quando illo es exponite al effecto de sanguine currente, illo disveloppa un accretion superficial de fibrina, leucocytes, e plachettas. Iste accretion exhibi un apparentia simile al lineas de Zahn. Le magnitude de illo es relationate directemente al quantitate e al duration del fluxo de sanguine.

Le hic-reportate observationes provide un technica versatile pro le studio experimental de thromboembolismo. Illos indica que throm-
bos producere per iste methodo pote, in le curso del tempore, devenir indistinguibile ab thrombos formate in sitos de injuria endothelial. Le accumulate datos subleva le posibilidad que un simile mecanismo de induction de thrombose per sero es presente in le homine.

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