# PROPERTIES OF THE BLOOD INTERFACE ESSENTIAL TO SUCCESSFUL ARTIFICIAL HEART FUNCTION

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There appears to be a tendency among investigators at the present time to feel that the development of the artificial heart field awaited the availability of special materials, in particular, materials which could be placed in intimate contact with blood without causing undue destruction or without initiating coagulation. The present authors are of the opinion that this is not the case, but rather that as in most scientific accomplishments, the important steps were: the development of the overall concepts, and the design and experimental studies undertaken to prove the practicality of these concepts. When the present authors initiated research in this field in 1955, their approach to the problem was to design a mechanical heart of extremely long mechanical life which would be compatible with the internal environment of the experimental subject, and which would fulfill the physiological requirements for completely maintaining a human subject[1-4]. The choice of materials for the mechanical heart was based on a number of factors, but with prime consideration given to long mechanical life and non-destruction of the blood elements. It is of considerable interest that the materials chosen for these early designs, namely, polished stainless steel, lucite, and polyethylene did not result in any undue destruction of blood elements. It is quite possible that the artificial heart field could have been brought almost to its present stage of development (that is, maintenance of an animal for a limited period of time) at a much earlier date had the concept been evolved, and the experimental work initiated. With an adequate design of the artificial heart, a number of materials might have fulfilled the required functions. This is not to say, however, that the choice of materials is not significant; on the contrary, the field of artificial heart research has now reached the stage where the problem of long term survival must be solved and to solve this problem basic studies of materials in relation to a number of physiological, biological, chemical and physical parameters must be undertaken.

Consideration of the problem of long term survival with an artificial heart indicates that one of the primary problems to be solved is the initiation of clot formation either in the prosthesis or in the natural vessel of the animal. Considerable research has been carried out by a number of investigators on the relation between blood coagulation and the material in immediate contact with the blood. This work can be reviewed here, but it is of interest to indicate that the research of Sawyer et al. on bioelectric phenomena[5], an ion metabolism[6, 7], and on electrochemical phenomena[8, 9] appears to be of immediate, direct value to the artificial heart field. In this regard it is also of interest to consider the theory of Copley et al. on coagulation and surface phenomena[10-14]. In recent years, with the increasing use of artificial heart valves, grafts and other prostheses, research has been initiated by a number of investigators on the relation between chemical and physical characteristics of materials and their effect on the biological system and the effect of the biological environment on the materials[14-18]. No attempt will be made here to discuss in detail the research involved in the review literature cited above except insofar as it is directly related to our experimental results outlined below.

Since much of the data of previous investigators on the interaction between the biological system and a non-viable material was obtained by implanting or grafting the material in the experimental animal, the present authors were interested in devising a different technique for studying the biological, chemical and physical parameters affecting blood coagulation when an artificial structure is incorporated into the biological system. Implantation techniques have yielded valuable data, but they offer some disadvantages when applied to the immediate problem of long term survival on artificial hearts. The simple implantation of a material such as plastic or metal into the experimental animal does not simulate the dynamic conditions under which this material will be used when incorporated into a mechanical heart, and does not, therefore, necessarily give the required data under such conditions. Ross et al.[19] did a most interesting study on the chemical structure and surface properties of a large number of synthetic polymers in relation to thrombosis. One of the techniques for determining and comparing the rapidity and extent of intravascular clot formation for each polymer was the implantation of probes constructed of the test materials into the superior vena cava of dogs. It is of interest to note that since maximum coagulation was obtained in a very brief period of time (5 to 7 minutes) after insertion of the pyrex glass,

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the presence of a clot subsequent to inserting the glass probe was used as the criterion for the presence of normal coagulation mechanism in the test animal. One question that can be asked regarding this technique is to what extent the geometric configuration of the probe affected the results obtained.

The present authors undertook to devise a technique for studying the relation between coagulation and the non-viable material in contact with the blood which would permit the following: study of the test material as an attachment to the normal vascular system of the animal; easy interchange of various geometric shapes and types of material within the vascular system; convenient accessibility of the test material for visual inspection and direct in vivo evaluation of the parameters under study; adaptability of the system to allow variation of blood flow in the test material.

## MATERIALS AND METHODS

The techniques used to fulfill the above outlined requirements consisted essentially of an adaptation of a commercially available Silastic-Teflon cannula system* (originally described by Quinton et al. (20-21) and Hegstrom et al. (22) to be used in conjunction with artificial kidney hemodialysis) and an electromagnetic instrument for measuring volume flow in the cannulated artery. The cannula system consists primarily of simple Silastic and Teflon shunts between an artery and vein of the patient which are designed to allow easy accessibility and maintenance over long periods of time with minimum trauma to blood vessels and tissue. This shunt system was used in our experiments between the femoral artery and vein in the upper thigh of a dog. Volumetric blood flow was measured by means of a square-wave electromagnetic flowmeter (Carolina Medical Products Co.) with the probe placed around the outside of the intact artery. No agents of any type were administered to the animal.

The following surgical approach is used on the dog for installation of the arteriovenous shunts. A 3" long incision is made in the skin of the medial aspect of the thigh. This incision is placed approximately midway between the knee and the external inguinal ring so as to lie in line with the course of the femoral artery as detected by finger identification of the pulse. The overlying muscle is separated and the femoral artery and vein are exposed along their length for approximately two inches. The method of insertion and fixation of the catheter to the femoral artery and vein is based on the Quinton technique as described in the Sweden Freezer Co. manual. A 10 mm. lumen circumference implantable electromagnetic probe is inserted around the femoral artery about 0.5" above the tip of the catheter. In order to modify the blood flow rates in the various shunting materials, an accurately controlled constriction is introduced in the Silastic tubing of the arteriovenous shunt complex. This constriction is produced by using a wide-face micrometer which clamps the Silastic tubing and changes its cross section shape and area. The internal area of the constricted cannula is accurately calibrated with respect to the micrometer reading by a combined photographic and planimeter method.

The preparation of the standard shunt materials for the arteriovenous bypass follows that outlined in the Sweden Freezer Co. manual for the Quinton cannula system. When other materials such as glass shunts are inserted in the bypass, these materials undergo a prescribed cleansing procedure. The glass is soaked in a detergent solution and a microscopic inspection is used to identify any remaining clinging particles which are recovered. A five minute high flow velocity wash in tap water followed by several rinses in distilled water is then used, and another microscopic inspection follows. The shunt is sterilized previous to insertion in the animal. Just prior to insertion, the shunt is rinsed with a sterile 6.0% gentran solution and then filled with the same gentran solution so that no air is left trapped in the cannula. The gentran solution is heparinized in a ratio of 0.1 ml. heparin to 500 ml. of gentran solution. The terminations of all shunts, and in particular, glass shunts, are carefully tapered so that on insertion into the Silastic tubing of the shunt complex the transition region will be as smooth as possible.

## EXPERIMENTS AND RESULTS

Glass cannula inserts. A number of experiments were conducted which indicated that with the proper experimental technique, blood flow could be maintained in the above described system in an unheparinized animal for longer periods of time (of the order of 24 hours) without thrombosis and that this flow could be accurately measured. It was also determined that if clot formation was initiated in the system that the presence and degree of clot could be deduced from the decreased blood flow. Investigations were also conducted on various techniques for maintaining the shunt in a conscious, unrestrained

*Sweden Freezer Mfg. Co., Seattle, Washington.

dog in such a manner that when experimental data was to be taken, the shunt was easily accessible without complex surgical procedures but with the added requirement that the easy accessibility did not result in damage to the shunt by the experimental animal during his normal conscious periods. The most appropriate and simplest technique is to surgically close the skin and muscle over the shunt and to protect the surface of the sutured incision with a cloth covering. Figure 1 shows the incision area; Figure 2 shows a dog with the shunt system inserted.

The general procedure followed was to establish normal blood flow in the Silastic-Teflon shunt system, then to insert a shunt made of the test material in place of the Teflon and to determine the presence of thrombi by the decreased volume of blood flow. The data discussed in this paper is primarily concerned with the results obtained with pyrex glass shunts.

One of the initial experiments consisted of insertion of a 3" length of curved pyrex glass cannula (I. D. 0.080") in substitution for the standard Teflon cannula and observation of the volumetric blood flow (Figure 3) in an unheparinized animal. As shown in Table I there was an increase in volumetric flow upon attaching the glass cannula followed by a decrease over the next 15 minutes. This decrease was apparently due to clot formation. However, presumably in response to the physical straining of the dog during a light anesthesia period, the clot formation broke loose after 15 minutes and unimpeded flow was resumed. The flow was both observed visually and recorded quantitatively over approximately the next six hours. There were some fluctuations in flow in the last four hours, but these fluctuations were not necessarily caused by clot formation since none could be observed by visual inspection of the glass cannula and since such variations in flow had been observed previously in anesthetized animals having the standard Silastic-Teflon shunt inserted. Approximately seven hours after the glass cannula had been attached, the muscle and skin were sutured over the glass Silastic cannula system. Twenty-four hours after the original attachment of the glass shunt, a blood flow reading was taken (without surgically opening the cannula area) and found to be essentially unchanged from that recorded when the wound was closed. The flow in this system was, of course, laminar flow with a calculated Reynolds number of 917.

TABLE I

MAINTAINED BLOOD FLOW IN SILASTIC-GLASS ARTERIOVENOUS SHUNT SYSTEM IN DOG WITH NORMAL CLOT TIME

| Type of Cannula | Time Interval Subsequent to Attachment of Glass Cannula | Volumetric Blood Flow ml. /min. |
|---|---|---|
| Silastic-Teflon | | 240 |
| Silastic-glass (I.D. glass cannula 0.080 in.) | 1 min. | 315 |
| " " | 2 min. | 270 |
| " " | 4 min. | 255 |
| " " | 6 min. | 225 |
| " " | 12 min. | 165 |
| " " | 14 min. | 158 |
| " " | 17 min. | 210 |
| " " | 25 min. | 225 |
| " " | 37 min. | 278 |
| " " | 46 min. | 308 |
| " " | 60 min. | 315 |
| " " | 1.5 hrs. | 315 |
| " " | 2.0 hrs. | 315 |
| " " | 2.5 hrs. | 300 |
| " " | 3.0 hrs. | 270 |
| " " | 4.0 hrs. | 270 |
| " " | 4.5 hrs. | 270 |
| " " | 5.0 hrs. | 255 |
| " " | 6.0 hrs. | 218 |
| " " | 24.0 hrs. | 225 |

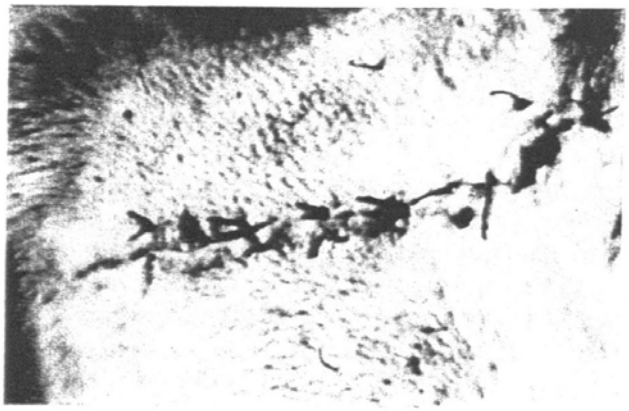

Figure 1. View of sutured skin covering arteriovenous shunt.

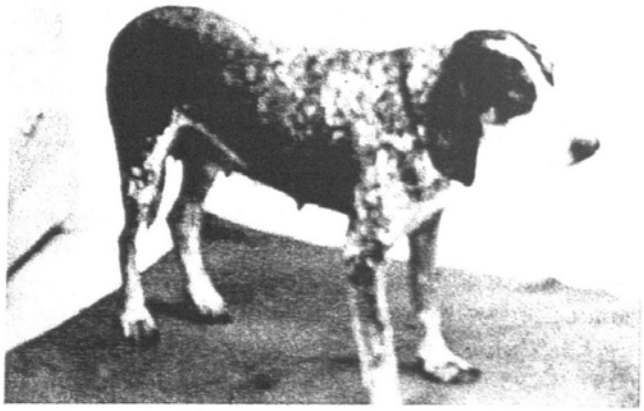

Figure 2. Dog with internal arteriovenous shunt.

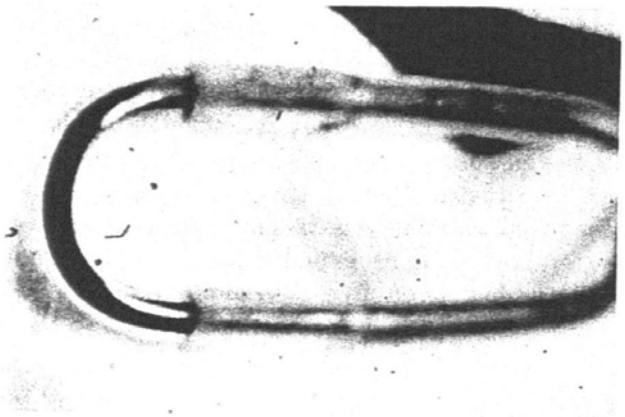

Figure 3. Glass-Silastic arteriovenous shunt.

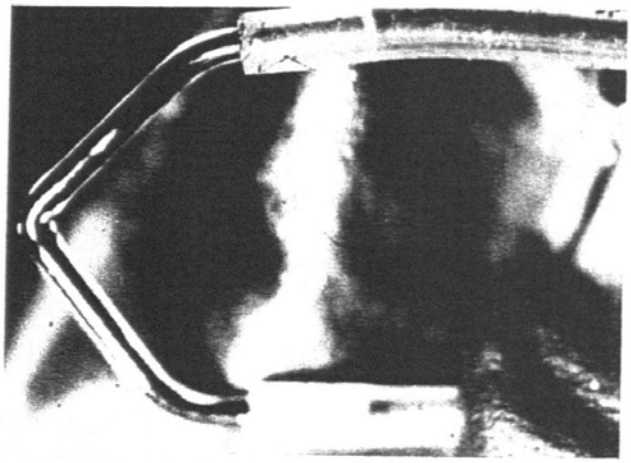

Figure 4. Right angle glass-Silastic arteriovenous shunt.

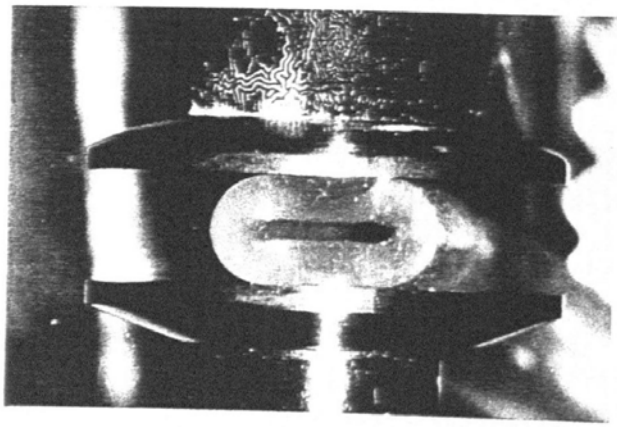

Figure 5. Constriction of Silastic cannula.

After additional experience was obtained with glass shunts, it was found that this initial appearance of clotting was not necessarily characteristic of the glass surface but associated with other technique factors. Table II, for example, shows the volumetric flow in the first 2 1/2 hours following insertion of a glass cannula. In this experiment the glass shunt was removed after seven hours of flow, and inspected. No deposit of any kind was visible on the walls of the glass shunt. Table III shows a number of hematological values recorded just prior to the insertion of the glass cannula, and at times periods of 7 and 20 hours after its insertion. The normal platelet count value, that is, the count taken prior to the insertion of the glass, appeared low, but there were no abnormal blood values after 20 hours of blood flow through the glass shunt. The glass cannula was removed after the 20-hour period and visually inspected. No clot formation or thrombi were observed.

TABLE II

MAINTAINED BLOOD FLOW IN SILASTIC-GLASS ARTERIOVENOUS SHUNT SYSTEM IN DOG WITH NORMAL CLOT TIME

| Type of Cannula | Time Interval Subsequent to Attachment of Glass Cannula | Volumetric Blood Flow (relative) |
|---|---|---|
| Silastic-Teflon | | 107 |
| Silastic-glass | 1 min. | 100 |
| (I. D. glass cannula 0.084. in.) | | |
| " " | 10 min. | 97.5 |
| " " | 15 min. | 97.5 |
| " " | 35 min. | 100 |
| " " | 50 min. | 100 |
| " " | 1 1/2 hrs. | 103 |
| " " | 2 1/2 hrs. | 103 |

TABLE III

BLOOD CHARACTERISTICS OF ANIMAL WITH SILASTIC-GLASS ARTERIOVENOUS SHUNT SYSTEM

| | 20 Minutes Prior to Insertion of Glass Cannula | Seven Hrs. after Glass Cannula Inserted | 20 Hours after Glass Cannula Inserted |
|---|---|---|---|
| Blood hemoglobin (g/100 ml.) | 16.1 | 16.3 | 13.7 |
| Hematocrit % | 49 | 49 | 45 |
| R.B.C. (millions/mm.$^3$) | 5.9 | 6.1 | 4.9 |
| W.B.C. (cells/mm.$^3$) | 14,100 | 24,100 | 19,900 |
| Platelets (/mm.$^3$) | 260,000 | 224,000 | 442,000 |
| Plasma hemoglobin (mg./100 ml.) | 14 | 4.5 | 12 |
| Osmotic fragility | normal range | no change | no data |
| Lee White clot time (min.) | 3.5 | 5.5 | 4.0 |

Since it was obvious that blood flow could be maintained in glass shunts for extended periods of time without clotting, preliminary investigations were made on the effect of geometric configuration on the initiation of the clotting phenomenon. A pyrex glass cannula bent in the form of a right angle with a sharp 90° turn on the inside surface was inserted in the previously described shunt system and the volumetric blood flow recorded (Figure 4). It was observed over a period of 1 1/2 hours that the blood flow was erratic, continuously varying in the first 15 minutes between minimums as low as 118 ml./min. to maximums of 216 ml./min. After the first 40 minutes, there was a general decline of flow with the result that in 1 1/2 hours the volumetric flow was decreased by approximately 60%. Further, visual observation of the glass cannula soon after its insertion clearly showed the phenomenon of clot formation followed by breaking away of the clot from the glass wall; in the later stages the gradual build-up of a clot on the inner wall surface could be observed. Substitution of another right angle glass shunt of the same dimensions but with the right angle bend of the inner surface being rounded-over instead of sharp resulted in no decrease in flow and showed no evidence of clotting when the glass shunt was visually inspected after its removal from the animal. It is apparent, therefore, that the geometric configuration of the glass surface is an essential factor in the coagulation of blood on glass surfaces.

Technique for controlled variation of in vivo volumetric blood flow. Paramount to the problem of determining ways to prevent thrombi formation when blood is in contact with in vivo, non-viable surfaces of various materials and configurations is control of the rate of blood flow. In the present investigation, a simple technique is being used to control the volumetric blood flow in the shunt system described above. As indicated in the Materials and Method section, a micrometer is used to quantitatively depress the outside surface of the Silastic cannula in series with the artery and thus decrease the blood flow by restricting the inside surface area of the Silastic (Figure 5). The essential question, however, is whether under such circumstances the volumetric flow measured represents a linear response to the decreased area, uncomplicated by artifacts such as thrombi formation at very low flow rates. The results of one experiment are shown in Table IV. It is evident that this technique can be used to accurately control rate of blood flow.

TABLE IV

CONTROL OF VOLUMETRIC BLOOD FLOW
BY QUANTITATIVE CONSTRICTION OF SILASTIC CANNULA

| Micrometer Setting | Lumen Area of Silastic Cannula (cm.$^2$) | Volumetric Blood Flow during Time Interval of Constriction of Cannula (ml. /min.) | | |
|---|---|---|---|---|
| | | 1/2 min. | 5 min. | 10 min. |
| No constriction | 0.0455 | 270 | 270 | 270 |
| 0.113 | 0.0165 | 202 | 195 | 195 |
| 0.1044 | 0.0103 | 120 | 127 | 127 |
| 0.1005 | 0.0073 | 75 | 85 | 83 |
| 0.0975 | 0.0058 | 42 | 42 | 41 |
| 0.0955 | 0.0068 | 20 | 21 | 22 |
| 0.0940 | 0.0045 | 7.5 | 7.9 | 7.9 |
| No constriction | 0.0455 | 270 | 270 | 270 |

## DISCUSSION

It is of basic interest that in this study blood flow was maintained in a glass cannula for periods of the order of 20 hours without any evidence of clotting or thrombi formation in the glass. The choice of a glass cannula was not based on any assumption that this might be a desirable material for artificial internal prostheses, but was chosen in order to try a new approach to the problem of occurrence of blood coagulation when blood is brought in contact with foreign surfaces. Since glass is apparently universally considered to be an inappropriate material for contact with blood, the most difficult case was chosen for initial study. It is of interest in this regard to compare the results obtained in the present study with those of Ross et al. [19], mentioned earlier in this paper. Ross et al. found maximum coagulation on pyrex glass probes within 5 to 7 minutes after insertion in the blood stream. Mirkovitch et al. in a similar experiment found that glass and quartz probes were covered with thrombi within five minutes after insertion to the extent that they occluded the blood vessel, while plastic probes and probes coated with colloided graphite were covered only with a thin membrane[23].

## SUMMARY

It has been demonstrated that a glass cannula may be inserted as part of an arteriovenous shunt system in an unheparinized experimental animal for long periods of time (hours) without any clotting of the blood or thrombi formation.

The significance of the geometric form of a prosthesis in relation to blood clotting is demonstrated.

A technique is described for quantitatively controlling blood flow rate in an arteriovenous shunt system.

The above results are discussed in relation to the problem of designing an artificial heart capable of maintaining a subject for long term periods.

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