Arterial-Venous Perfusion Without Anticoagulation: The Impeller Centrifugal Pump

Roger A. Vertrees, B.A., C.C.P., Yan Yu, M.D., Charles Wacker, B.S., Aurel C. Cernaianu, M.D. and Anthony J. DelRossi, M.D.
The Division of Cardiovascular Surgery, Cooper Hospital/University Medical Center, Camden, N.J. 08103

Abstract
A study was designed to test the effects of the absence of anticoagulation in the extracorporeal circuit. Five swine were subjected to this experiment utilizing the impeller centrifugal pump during which neither heparin nor any other anticoagulant was used. The extracorporeal circuit consisted of polyvinylchloride tubing, a Centri-Med® pump and an external stainless steel heat exchanger that was primed with albuminized Ringer's solution. An arterial-venous circuit was employed with oxygenation supplied from the subject's lungs.

A series of blood aliquots were analyzed for coagulation at various times throughout the procedure. Following total body cooling using topically applied ice water, the subjects were rewarmed utilizing bypass. Within 10 minutes after the initiation of bypass, the circuits became clotted, rendering perfusion and subsequent warming ineffective.

The lab values indicated that intrinsically activated coagulation occurred upon exposure to the extracorporeal apparatus. Flow visualization studies revealed a source of stagnant blood flow in the area around the hub of the pump head. Blood clot was similarly located in this area, with clot extension throughout the return circuit being realized.

It is imperative that areas of stagnation be eliminated from extracorporeal circuits, since they may be potential sites for clot formation.

Introduction
By identifying a means of blood propulsion which would not require anticoagulation, a major source of morbidity that has been associated with extracorporeal technology may possibly be eliminated. The development of an extracorporeal circuit which would allow perfusion without anticoagulation was investigated.

In perfusion, two major classifications of blood pumps exist: the positive displacement (or roller) pump and the centrifugal flow pump. Of the latter group, there are two distinct philosophies which concern the production of energy necessary for blood flow: the constrained force vortex blood flow, which uses concentric cones and is marketed in the form of the Biomedicus® pump, and the impeller flow technology of which the Delphin® or Centri-Med® pumps are representative.

A previous study demonstrated that the constrained force vortex pump is capable of propelling blood for periods up to 75 minutes without using an active pharmaceutical drug for anticoagulation. In the clinical setting, this device has been successfully employed with no form of anticoagulation therapy given.

The centrifugal flow induced by the impeller pump differs from other modes of blood propulsion in that the energy generated by the centrifugal forces propels the blood. This centrifugal force is produced by the impeller fins or blades, which impart rotary motion or kinetic motion to the incoming blood. The blood is then directed through the outflow track and recovered in the form of pressure. Studies have shown that the hemolysis rate of this device favorably compares to that of the constrained force vortex pump.

This study was undertaken to determine the ability of the impeller flow pump to deliver blood flow without coagulation.

Materials and Methods
Five Yorkshire swine weighing 44.4 ± 3.5 kilograms were anesthetized with a preoperative intramuscular injection of Ketamine Hydrochloride (25-30 mg/kg IM) and Acepromazine (1 mg) and maintained intravenously with the pentobarbital sodium (20 mg/kg). An admixture of lidocaine (250 mg) in 250 cc of Ringer's solution was utilized to control arrhythmias. Once a patent airway was established, 100 percent oxygen was administered. Electrocardiograph leads were applied to the limbs for continuous monitoring. Rectal, skin and nasopharyngeal temperature probes were placed for continuous temperature assessment. For arterial pressure and blood sample access, an 18-gauge indwelling catheter was inserted in the left femoral artery. The femoral vein was used for the administration of intravenous
medications and fluids.

The perfusion circuit consisted of a Centri-Med® pump head, a stainless steel heat exchanger, modified 14 French catheters and 3/8-inch and 1/4-inch internal diameter (ID) polyvinylchloride (PVC) tubing. The arterial-venous (AV) circuit was oriented as follows: blood drained from the femoral artery into the pump head was propelled through the pump into the heat exchanger and then back into the swine's femoral vein. The perfusion circuit was primed with 12.5 grams of albumin and diluted in 500 cc of Ringer's solution. This solution was recirculated for 20 minutes to ensure purging of air and "coating" of the circuit with albumin. The drain line (femoral artery) and the return line (femoral vein) were clamped in anticipation of cannulation. Neither the prime nor monitoring solutions contained any anticoagulant.

Once anesthesia was stabilized, control blood samples were collected at a baseline temperature of 37°C Centigrade. Subsequently, the subject was topically cooled by applying slush and administering cool intravenous solutions at a rate of approximately 30 drops per minute. A second blood sample was drawn just prior to cannulation for bypass. Once the rectal temperature reached 28-30°C, cannulation was accomplished and perfusion was begun. The blood flows were increased to the point of maximum flow (> 40 cc/kg/min) at 1500 RPMs and stabilized. Then rewarming commenced. These flows were sustained throughout the procedure or until clotting was observed. The flow rate, being dependent upon the blood return to the extracorporeal circuit, was optimized by the circuit design in that the arterial pressure helped to maintain an adequate blood flow by actively filling the pump head. This pre-load dependency was all the more important in the face of the increased viscosity of the cold blood. A third sample was collected approximately five minutes after the initiation of bypass, or when a 10°C difference existed between the blood temperature and the heat exchanger temperature. According to the protocol, a fourth sample was to be drawn once the rectal temperature reached the baseline value, and a fifth sample was to be drawn 15 minutes after the discontinuation of bypass. However, since rewarming was unsuccessful, samples #4 and #5 were drawn 30 and 60 minutes, respectively, after sample #3.

The following coagulation parameters were analyzed: activated clotting time (ACT), prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen level (Fib) and fibrin degradation products (FDP). A bleeding time (BT) was also performed with each sample. Additionally, the samples were analyzed for hematology findings: hematocrit (Hct) and platelet count (Plt). Upon completion of bypass, the circuit was gently rinsed with Ringer's solution and the residual material photographed and examined. Immediately following the procedure, the animals were euthanized and underwent necropsy to detect any presence of clot.

This protocol was approved by the Institutional Animal Care and Use Committee of the University of Medicine and Dentistry of New Jersey. During the experiment, all animals were handled in accordance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Institutes of Health (NIH publication No. 86-23, revised 1985).

Flow visualization studies were performed utilizing the Sams impeller pump. These studies are carried out by constructing a closed loop circuit which included the pump head and two pieces of 3/8-inch diameter tubing. The tubing was connected to the pump head and to each other with a 3/8-inch connector containing an integral side port. This circuit was primed with saline stained blue by the addition of a small amount of methylene blue. This allowed for color differentiation. Flow was established at a rate of 1,500 RPM and motor oil was slowly injected into the circuit through the connector side arm during the period of flow.

Results

In all cases, the animals failed to rewarmed after being successfully cooled. Upon inspection of the extracorporeal circuit, blood clot was located in all of the pump heads. This clot precluded the possibility of warm blood perfusion and consequent rewarming. Figures 1 and 2 represent the pump heads that were utilized. Due to this clot formation, forward blood flow ceased within 10 minutes in all experimental trials and none of the animals rewarmed.

The coagulation tests, which are depicted in Table 1, yielded the following results: baseline BT values were 2.5 ± 0.6 minutes. However, as the temperature declined, the BT began to extend. Sample #2 was 6.1 ± 1.4 minutes, which is an abnormally long time. At the coldest temperature (28°C), the BT was again extended to 8.75 ± 0.96 minutes. The recorded value became prolonged (10 minutes) at the last two sampling times. Another whole blood coagulation test, the ACT, was also analyzed. The activated clotting time, determined by the manner of Hattersley and analyzed by the Hemochron®, remained unchanged until active clotting was noted. Table 1 depicts the ACT results.

The PT values did not deviate and were always within normal limits throughout the procedure. The aPTT also appeared to be unaffected by the cold temperature. (See samples #1 and #2 at 30°C in Table 1) However, this value became adversely affected by the third sample, which was drawn at the time of active clotting. Sample #3 is greater than 100 seconds.

The fibrinogen level was affected by the cold temperature since the levels fell from 183.4 mg% ± 12.6 to 151 mg% ± 13.9. Additionally, the institution of bypass and the clotting of the

(a) Hemochron Model 400, International Technidyne Corp., Edison, NJ 08820

(b) Sarns/3M Health Care Group, Ann Arbor, MI 48103
(c) Gish Biomedical, Inc., Santa Ana, CA 92705
(d) Argyle Mfr. Trocar Catheter Stock # Mar 5610-14 Sherwood Medical Industries, Inc., St. Louis, MO 63103
(e) Ringer's Injection Code # 2B2304 Deerfield, IL 60015

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extracorporeal circuit, as would be expected, seemed to lower the fibrinogen levels. Sample #3 (150 mg% ± 24.4) fell to sample #4 (137 mg% ± 24.4). Fibrinogen samples #3, #4 and #5 have been corrected for the dilutional effect incident with extracorporeal circulation. Another value that needs to be corrected for dilution is the fibrin degradation products (FDP). This value remained unchanged throughout the procedures, as seen in Table 1.

Hematology reports revealed a mean 12 percent ±3.9 decrease in the hematocrit between samples #1 and #3 (28.0 ± 3, 23.6 ± 1.8, p<0.05). The platelet count was also monitored; mean values are displayed in Table 1. Corrected values are bracketed. The correction allows for the dilutional effect of bypass.

Chemical analysis of the blood gases seemed to indicate an increasing metabolic acidosis. This condition could be correlated to the length of time spent in a hypothermic state without the ability to rewarm.

Upon conclusion of the procedure, both animal and circuit were inspected grossly for clot genesis and extent (See Table 2). A clotted circuit and venous system were demonstrated in all animals. Extensive clot was found from the pump head prograde through the venous system to the lungs.

Discussion
The BT reflects disorders of platelet function and is basically independent of the coagulation mechanism. As exposure to cold temperatures increased, the BT became prolonged. It was also noted that the quantitative platelets were not substantially affected due to the cold temperatures (562,000 ± 55,000 vs. 515,000 ± 44,000, p>0.05). Activation of platelets depends on an enzymatic reaction and is temperature dependent. The rate of reaction will slow down due to the cold exposure. In this study, the platelet activity had been substantially delayed because of the reduced body temperature.

The ACT measures the coagulability of the blood and reflects the alteration of the blood coagulation time, as seen as a result of the effect of heparin anticoagulant therapy, specifically in the first stage of coagulation (thromboplastin generation). In our study, heparin was not used; this is substantiated by the lack of any change in ACT readings.

Prothrombin time is a measurement of the coagulant activity of the extrinsic system, specifically fibrinogen, prothrombin and factors V, VII and X. None of these tests were affected by the study, which may imply that neither the hypothermic conditions nor heparinless bypass had any affect on the extrinsic pathway. The aPTT results were rather complex, yet consistent. Initially, the aPTT was unaffected by the induction of the cooling phase. However, shortly after the initiation of bypass, sample #3 became prolonged, which coincided with the propagation of the clot. The aPTT detects deficiencies of the plasma coagulation factors, excluding platelets. As a result, the integrity of the intrinsic pathway is tested. At the time of drawing sample #3, the intrinsic pathway had become activate, as indicated by the prolonged aPTT.

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Investigation into the design of the impeller centrifugal pump has revealed that in flow visualization studies, stagnant areas were observed on or near the hub. These stagnant areas are contained within areas surrounded with a flow separation line. Our flow visualization studies confirmed these findings (see Figure 3). The same result was not appreciated when the constrained vortex pump was subjected to this analysis. In a flow visualization study, two immiscible fluids are added to a pump circuit and then perfused through a closed loop. Motor oil and water colored with methylene blue dye were utilized in this study. The lighter fluid (oil) should gravitate to and accumulate in the areas of lowest pressure and stagnant flow. It is apparent in Figure 3 that the motor oil accumulated around the hub of the pump head. This closely correlates with results found in previous flow visualization studies utilizing an impeller pump, and is strongly reminiscent of the first photographs of the location of the clotted blood...

It may be presumed that this area in question, after being exposed to the forces of the extracorporeal circuit, became, at first, a receptacle for stagnant blood flow with its attendant eddy currents and turbulence. In the face of an unaltered coagulation cascade, it became an eventual source of clotted blood. Blood in vitro, if it is stagnant, will clot in less than 10 minutes when exposed to foreign surfaces. Once the stagnant blood starts to clot, factors are released into the blood stream that will cause the intrinsic pathway to become involved, as revealed by the aPTT increases. Although the centrifugal pump is more advantageous than the roller pump in preventing the promotion of the intrinsic pathway, it may still be activated to a certain extent. As the intrinsic pathway became more involved, fibrin conversion and platelet activation finally occurred. Both of these values displayed abnormal results in response to the initiation of bypass. The clot which was then conceived at or near the hub grew outward with blood flow.

The necropsy analysis supported this observation. Clot was universally found on the outlet side of the pump in all of the animals through inferior vena cava up to the level of the right atrium. It must be noted that the clot was not seen in the blood or vessels draining the superior vena cava and that the animal’s arterial system remained clot-free as well. It is from these observations that the genesis of the clot was recognized to have originated from within the extracorporeal circuit. No clotting was observed in the tubing or cannula which connected the femoral artery to the pump’s inlet port, again clarifying that the genesis must be within the pump head.

Conclusion
The stagnant area of blood flow which was identified in the flow visualization studies ultimately contained clotted material in all of the subjects. The blood that accumulated in the stagnant area formed a clot which then caused the activation of the intrinsic pathway and more clotting. Fibrin conversion and
platelet activation finally occurred (being slowed in response due to the hypothermia of the protocol) with the clot growing in the direction of the blood flow.

This study helps to focus attention on the fact that stagnant blood flow is deleterious and supports Toomasian's contention that stagnant areas of blood flow must be actively avoided. Indeed, it may be surmised that eventually, all areas of stagnant blood flow will clot. Therefore, it would be in the patient's best interest if the attention was directed toward actively seeking a design to eliminate stagnant areas.

References


Fig. 1: Inferior view of clotted Centrimed® pump head.

Fig. 2: View of clotted material.

Fig. 3: Result of flow visualization study. Arrow identifies the boundary between the immiscible fluids.
### Table 1

**Results of Coagulation Testing**

<table>
<thead>
<tr>
<th>Test</th>
<th>#1-37°C</th>
<th>#2-30°C</th>
<th>#3-28°C</th>
<th>#4-(28°C)</th>
<th>#5-(28°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct</td>
<td>28.0 ± 2.37</td>
<td>27.5 ± 2.12</td>
<td>23.575 ± 1.76</td>
<td>24.7 ± 2.8</td>
<td>22.4 ± 0.9</td>
</tr>
<tr>
<td>ACT 80-140 sec.</td>
<td>126 ± 18.7</td>
<td>118 ± 18.7</td>
<td>102.8 ± 16.3</td>
<td>111.6 ± 19.2</td>
<td>11.75 ± 1.0</td>
</tr>
<tr>
<td>PT 11-13 mins.</td>
<td>11.3 ± .8</td>
<td>11.2 ± .9</td>
<td>10.9 ± .8</td>
<td>11.0 ± .9</td>
<td>11.75 ± 1.0</td>
</tr>
<tr>
<td>aPTT &lt;38 sec.</td>
<td>14 ± 2.2</td>
<td>14.6 ± 2.9</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Fibrinogen 170-410 mg%</td>
<td>183 ± 12.6</td>
<td>151.4 ± 13.9</td>
<td>(132 ± 15.7)</td>
<td>(114.5 ± 11)</td>
<td>(111 ± 29.6)</td>
</tr>
<tr>
<td><em>These values corrected for dilutional effect of the asanguinous prime.</em></td>
<td>100</td>
<td>100</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDP 10</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Platelets x103</td>
<td>562 ± 55.2</td>
<td>515 ± 44</td>
<td>450 ± 59</td>
<td>371.7 ± 119</td>
<td>362 ± 96</td>
</tr>
<tr>
<td><em>Formula: Value noncorrected X Hematocrit original / Hematocrit dilution = Value</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2

**Gross Morphology Results**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Anatomic Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FV  IVC RA RV PA SVC AO PA PV PH AL VL HE AC VC</td>
</tr>
<tr>
<td>2</td>
<td>+ + + + + + + + + + + + + + + + + + + + + + +</td>
</tr>
<tr>
<td>3</td>
<td>+ + + + + + + + + + + + + + + + + + + + + + +</td>
</tr>
<tr>
<td>4</td>
<td>+ + + + + + + + + + + + + + + + + + + + + + +</td>
</tr>
<tr>
<td>5</td>
<td>+ + + + + + + + + + + + + + + + + + + + + + +</td>
</tr>
</tbody>
</table>

(+ *) denotes presence of visible clot; (-*) denotes no visible clot

FV=femoral vein  IVC=inferior vena cava  RA=right atrium  RV=pulmonary vein  PA=pulmonary artery  SVC=superior vena cava  AO=aorta  PV=pulmonary vein  PH=pump head  AL=arterial line (from animal)  VL=venous line (to animal)  HE=heat exchanger  AC=arterial cannula  VC=venous cannula

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