The Danger of Hemolysis in Shock

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Intravascular hemolysis is sometimes harmful and often fatal. Other times it is harmless. Dogs were paired and subjected to hemorrhagic shock. One of the pair was given 2 ml/kg of autologous hemolyzed blood before bleeding. The other of the pair was given 2 ml/kg of heparinized autologous blood. All of the animals given heparinized blood survived, whereas, all of the animals given hemolyzed blood died. The animals given hemolyzed blood developed coagulation changes indicative of Disseminated Intravascular Coagulation (DIC), whereas, the dogs given nonhemolyzed blood did not. It is concluded that hemolysis in the presence of shock (slow capillary flow) causes DIC and death. Hemorrhagic shock alone or hemolysis alone was harmless.

HEMOLYSIS MAY OCCUR as a result of a hemolytic transfusion reaction, massive tissue trauma,[2] as a result of distilled water intravenously, snake bite, malaria, various infections, extracorporeal circulation and many other situations. Severe hemolysis of blood is regarded as a dangerous event associated with renal failure, shock and death. However, it has been shown that the administration of distilled water intravenously is harmless to normal humans even though a marked hemolysis resulted.[1] It has been previously shown that[2] the administration of 100 ml. of autologous hemolized blood (frozen and thawed) to normal dogs was harmless. A transient coagulation deficit, noted only by laboratory tests, was the only result and these tests returned to normal within 4 hours. There was no mortality. It seems that on some occasions hemolysis is associated with dangerous complications and on other occasions is harmless. What conditions determine whether hemolysis is harmful or not?

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Materials and Methods

Fourteen mongrel dogs were divided into two groups, A and F. The dogs were paired and a Group A dog and a Group F dog were done on adjacent tables at the same

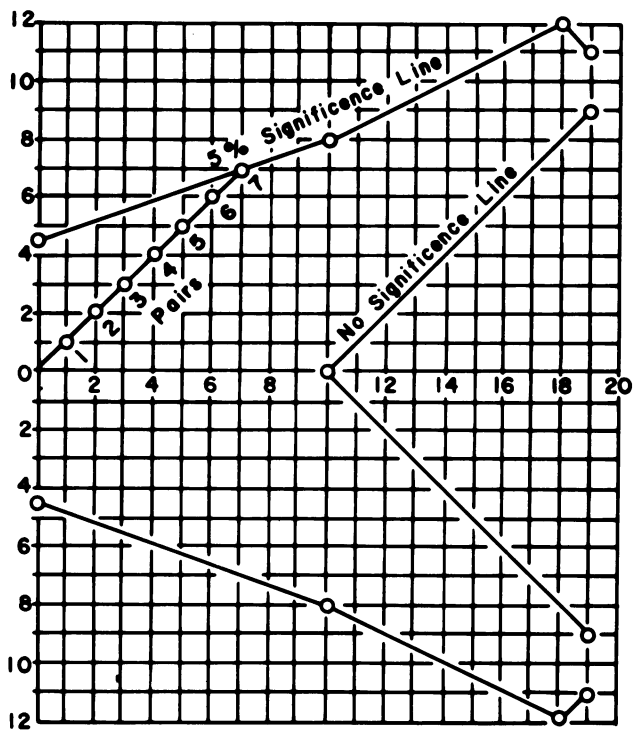

FIG. 1. Mortality of Groups "A" and "F" Dogs. This statistical analysis is suitable for paired experimental and control animals done at the same time and place. If a Group "A" dog survived and its paired "F" dog died, a line is drawn from point "O" upward and to the right one square. If both animals died or survived, no entry is made. If a Group "A" dog died and its paired "F" dog survived, a line would be drawn downward and to the right one square. If the resulting line crosses the 5% significance line, the data is significant at the 5% level. In this case every "A" dog survived and every "F" dog died, the resulting line crossing the 5% significance line in a minimum time.

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Submitted for publication: August 21, 1978.

0003-4932/79/0300/0373 $01.15

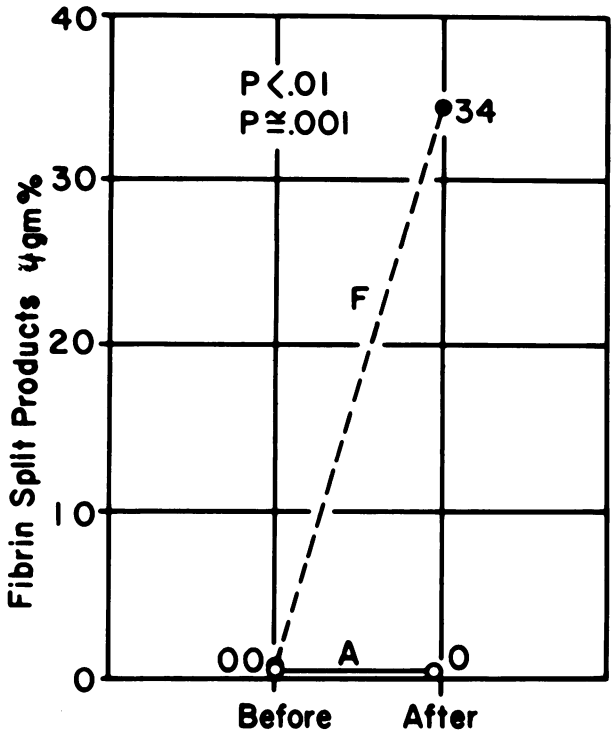

FIG. 2. Fibrin Split Products. None of the animals in either group had fibrin split products before shock. None of the animals in Group "A" had fibrin split products after shock either. However, Group "F" dogs had a mean level of fibrin split products after shock of 34 μ gm/ml. The difference was significant $p < .01$.

time. The designation as to group had been previously determined by the toss of a coin. *Group A* dogs were anesthetized with intravenous pentobarbitol and both femoral arteries catheterized, one for the recording of arterial blood pressure and the other for bleeding into a standard blood donor bag with sodium citrate. Two days previously 2 ml/kg of the dogs' blood had been withdrawn, anticoagulated with heparin and stored in a refrigerator. After catheterization of the femoral arteries, a 20 ml blood sample was taken and analyzed for 1) platelets 2) Prothrombin time 3) partial Thromboplastin time, 4) fibrinogen and 5) fibrin split products. Following this the previously withdrawn anticoagulated autologous blood was returned to the animal through the femoral artery catheter. The animal was then bled over a 15 minute period to a mean arterial blood pressure of 40 mmHg. Following this it was allowed to stabilize for 30 minutes during which time the mean arterial blood pressure usually rose from 40 mmHg to 60 or 80 mmHg. At the end of the stabilization period the animal was again bled to 40 mmHg per mean pressure over a 15 minute period. After this, the animal was kept at a mean arterial pressure of 40 mmHg for a one hour period by withdrawing small amounts of blood, or giving small amounts of normal saline intra-arterially. At the end of the hour period of shock a second blood sample was taken and analyzed as before. All the animal's blood was then restored by the intravenous route through a blood filter. The animal was observed for 24 hours. If the animal was alive at 24 hours, it was counted as a survivor.

Group F dogs were treated in a like manner except that the 2 ml/kg of heparinized blood which was withdrawn two days before the experiment, was frozen in dry ice, thawed, and then kept in a refrigerator until time for administration.

Results

Results were noted under the following headings.

Mortality

Of the 7 animals in Group A, none died. Of the paired seven animals in Group F, all died. This was plotted by

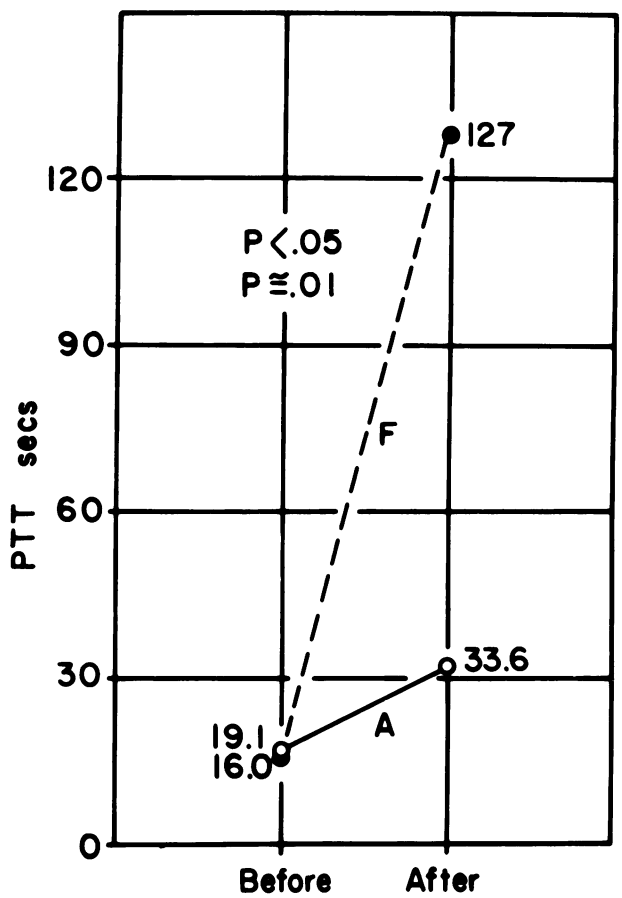

FIG. 3. Partial Thromboplastin Times. Group "A" animals had a mean PTT of 19 seconds before shock. This increased to 34 seconds after shock. Group "F" animals increased significantly more, from 16 seconds to 127 seconds $p < .05$.

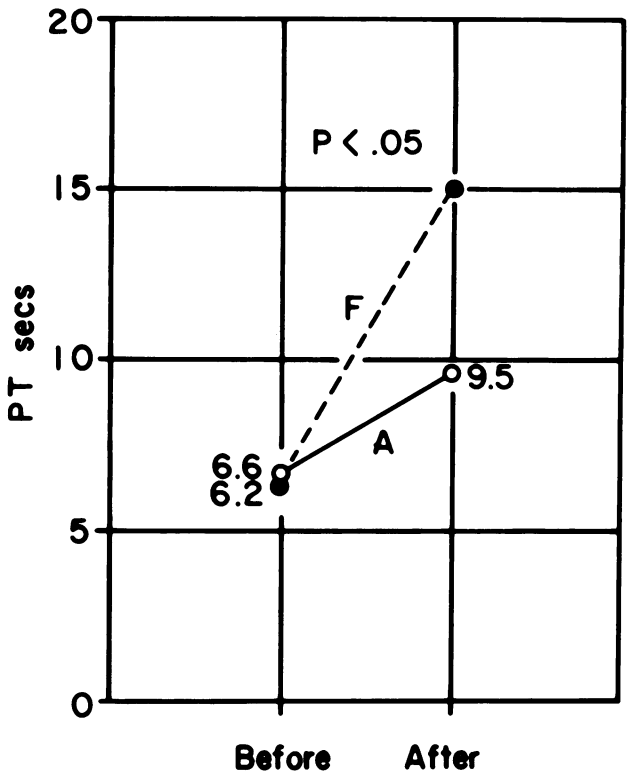

FIG. 4. Prothrombin Times. Group "A" animals had a mean PT of 6.6 seconds before shock. This increased to 9.5 seconds after shock. Group "F" animals increased significantly more from 6.2 seconds to 15.0 seconds $p < .05$.

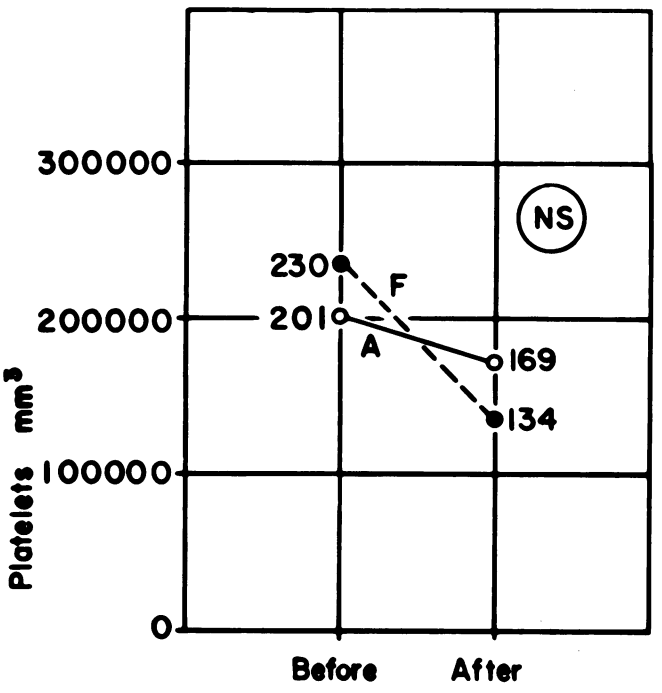

FIG. 5. Platelet counts fell much more in the "F" Group than in the "A" Group (96 vs 32 thousand) but this was not significant.

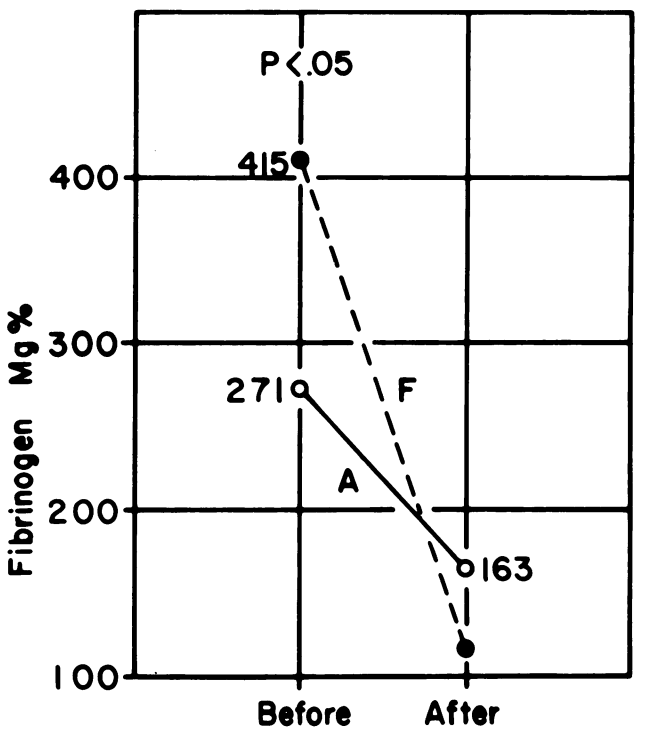

FIG. 6. Fibrinogen levels fell more in the "F" Group than in the "A" Group (296 mg/dl vs 108 mg/dl). This was significant $p < .05$.

the method of sequential sampling (Fig. 1) and the difference was found to be significant at the 5% level.

Fibrin Split Products

None of the animals in either the "A" or "F" groups had any fibrin split products before the shock. None of the animals in the "A" group showed any fibrin split products after the shock either. However, the mean level of fibrin split products after shock in the "F" group was 34 μg. This difference was significant, $p < .01$ (Fig. 2).

Partial Thromboplastin Time

Group "A" animals had a mean PTT of 19 seconds before shock. This increased to 34 seconds after shock. Group "F" animals increased significantly more, from 16 sec. to 127 seconds ($p < .05$) (Fig. 3).

Prothrombin Time

Group "A" animals increased from 6.6 to 9.5 seconds a rise of 2.9 sec. Group "F" animals increased from 6.2 to 15.0 sec. an increase of 8.8 sec. This was significant ($p < .05$) (Fig. 4).

Platelet counts fell much more in the "F" group than in the "A" group (96 vs 32 thousand) but this was not significant. (Fig. 5).

Fibrogen Levels

fell more in the "F" group then in the "A" group (296 vs. 108 mg%). This was significant $p < .05$ (Fig. 6).

Discussion

The results would tend to indicate that a small amount (2 ml/kg) of hemolysis, harmless in itself, was enough to significantly increase mortality and coagulation changes characteristic of DIC, when the animals were in a state of hemorrhagic shock. Much more autogenous hemolized blood (10 ml/kg) given to 13 normal animals had no effect and produced no mortality.[2]

It has been previously shown in a number of animal experiments[2–5] that pure hemorrhagic shock is relatively harmless and easily reversible by saline or blood. In contrast, hemorrhagic shock complicated by tissue injury, exposure of the extracorporeal blood to air or mechanical injury, resulted in an irreversibility to treatment with IV fluids or blood and high mortality associated with coagulation changes characteristic of Disseminated Intravascular Coagulation (DIC). It was postulated that for DIC to occur, two separate conditions must be present. 1) A slow moving, acid, capillary flow (hemorrhagic shock). 2) A thromboplastic agent gaining access to the blood stream. These would include bacterial toxins, thrombin and lysed red cells.

The thromboplastic effect of lysed red cells had been known for a long time.[6,7] It may be a red cell thromboplastin discovered by Quick,[8] or phospholypids liberated from the red cell or it may be merely the lysed cell membranes acting as particulate matter in the blood. Certainly it is not stroma-free hemogloben, which is actually anticoagulant, and which is harmless given intravenously.[9] In the present experiments, hemorrhagic shock produced the slow capillary flow but resulted in no mortality and minimal coagulation changes. However, adding a small amount of lysed red cells to the slow capillary flow situation resulted in a high mortality and coagulation changes characteristic of DIC.

Conclusion

Hemolysis occurring in a normal blood flow is relatively harmless. Hemolysis occurring in a shock situation (slow capillary flow) may produce DIC and death.

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