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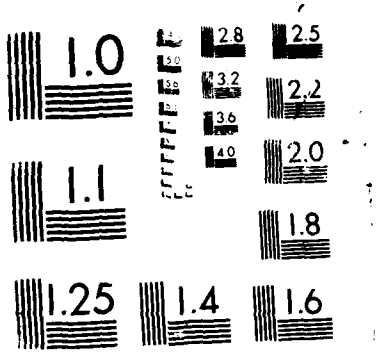

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Humoral Control of Regional Blood Flow in Hemorrhagic Shock in Non-Resuscitated and Resuscitated Animals

Annual/Final Report

J. Judson McNamara, M.D.

17 July 1987
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During the last 8 months of the contract, most of the time was devoted to data analysis and manuscript preparation. We reviewed all our data on visceral organ blood flow following hemorrhagic shock and prepared one manuscript for presentation at the American Association for the Surgery of Trauma which was published in the Journal of Trauma in May 1983.

We performed a pilot study in rabbits demonstrating pulmonary platelet trapping in the lungs of rabbits subjected to blunt trauma

Summary

The contract period covered in this contract started with work on microaggregate formation in stored blood and progressed to a careful, systematic evaluation of the clinical significance of microaggregates in animals. In conjunction with this, we evaluated clinical filtering systems for blood administration which removed particles from stored blood.

We proved the presence and nature of microaggregates in stored blood. We also showed ~~to~~ my satisfaction that quantities of microaggregates were negligible in terms of the effect of pulmonary structure or function. On the other hand, repeated blood filter testing showed that blood could be administered rapidly through blood ultrafilters that effectively removed microaggregate debris and not increase cost or flow rate.

We then studied blood flow in hemorrhagic shock and showed a prolonged reduction in visceral blood flow after successful hemodynamic resuscitation. In addition, total blood volume remained 15-20% below baseline.

In ancillary studies, we showed this change in blood volume and organ blood flow distribution was unrelated to catecholamines, renin release or thromboxane of prostacyclin production during shock. We examined local blood flow regulation in a hind limb perfusion model and showed that the changes induced on the peripheral vasculature by shocked blood was virtually all due to catecholamines.

The prolonged hypoperfusion of the abdominal viscera seen after resuscitation from hemorrhagic shock appears likely to be an "overshoot" of a teleologically important physiological mechanism for preserving blood flow to the most vital organs. The exact mechanism for this is unknown and deserved further study.

Foreword

In conducting the research described in this report, the investigator adhered to the "Guide for the Care and Use of Laboratory Animals", prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. [NIH] 78-23, Revised 1978).

A-1

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Body of Report

A. Microaggregates in Stored Blood

Our work on microaggregates fall into four major categories:

1. Identification and study of microaggregates
2. Evaluation of filtering efficacy
3. Investigation of the role of microaggregates in stored blood in the pathogenesis of ARDS
4. Miscellaneous related studies:
   a. Work on membrane oxygenation techniques
   b. Study of formation of microaggregates in vivo

1. Study of Microaggregates

We clearly determined that microaggregates formed in stored blood.[1,4,6,7,10,11,17] We developed methods for measuring and even counting microaggregates.[18,23] We did a lot of work, including electromicroscopy, that showed microaggregates to be primarily platelet aggregates and degenerating "sticky" white cells.[20]

2. Evaluation of Filtering Efficacy

Our studies on blood ultrafilters proved their efficacy[1,3,9,21] and recent unpublished data showed no disadvantage to ultrafiltration.

3. Investigation of the Role of Microaggregates in Stored Blood in the Pathogenesis of ARDS

Numerous studies of animals with and without shock showed no significant effect of massive microaggregate administration on lung structure or function.[2,12,13,15,19]

4. Miscellaneous Related Studies

a. ECMO. Our major contribution here was the importance of the axillary perfusion route in maintaining cardiac and upper body oxygenation in an ECMO system.[3,5,14,16]

b. In vivo Microaggregates. Major efforts were focused on identifying the presence of microaggregate formation in vivo in animals in shock.[18,19] The first efforts were directed at methods of preserving microaggregates, analogous to those which may be formed in vivo in shock. We used aggregates produced in vitro in fresh blood in response to addition of collagen, epinephrine, ADP or serotonin to study microaggregate preservation.

First, we determined that in human blood aggregates induced by any of the above agents are very susceptible to deaggregation and are uniformly deaggregated by the dilution necessary to obtain accurate aggregate counts in the model TA Coulter Counter.

Using varying concentrations of gluteraldehyde, having previously shown formalin to be unsatisfactory, we developed a satisfactory technique for stabilizing such microaggregates in human blood and initiated studies demonstrating the presence of in vivo microaggregates in humans in shock.

We then extended this work to animals and found wide variation in the ability to stabilize microaggregates induced in vitro in dogs and baboons. It was virtually impossible to stabilize microaggregates in baboons and results in dogs were quite variable.

Furthermore, in a series of baboons subjected to shock, no increase in vivo microaggregates could be demonstrated and again there was a wide variation in in vivo microaggregate production in dogs. This interesting observation relating to the variable stability of microaggregates and in vivo microaggregates in animals may in part explain the wide interspecies variation noted in different shock models in animals.

c. Fate of Platelets in Shocked Animals. We have completed a series of platelet survival studies in shocked baboons and demonstrated only slight decrease in platelet survival when compared with control animals, this decrease being not significant ($p > 0.05$). However, survival was significantly longer than that seen with 10-day old stored platelets ($p < 0.05$) (Fig. 1).

B. Studies of Regulation of Splanchnic and Peripheral Systemic Blood Flow in Hemorrhagic Shock

1. Several studies showed a profound reduction in visceral organ blood flow for over 18 hours after successful

resuscitation, by hemodynamic parameters, from hemorrhagic shock.

2. Evaluation of a number of humoral controls of vasomotor tone failed to implicate any of these in the observed splanchnic blood flow maldistribution.

3. Systemic peripheral circulation proved to be under catecholamine control in the shock state.

1. Reduced Blood Volume and Altered Visceral Blood Flow After Resuscitation From Shock

We have shown repeatedly[25,26] that after resuscitation from shock and for at least 18 hours thereafter visceral organ blood flow remains depressed as does blood volume. The mechanism for this is unclear.[26]

2. Neither catecholamines, renin/angiotensin or thromboxane/prostacyclin vascular regulatory mechanisms could be shown to be responsible for the observed prolonged alterations in blood volume or visceral blood flow after resuscitation from shock (See C-1).

3. A look at peripheral regulatory responses to shocked blood was carried out in a hind limb preparation.[24] Perfusion of an isolated pig hind limb with autologous hemorrhagic shock blood resulted in a significant increase in peripheral vascular resistance compared to perfusion with autologous normal (non-shock) blood. This increased resistance could be eliminated with phentolamine. However, oxygen consumption remained depressed during perfusion with shock blood in spite of normal flows ($p<0.05$, one tailed t test for paired data). Because of the small sample size (8 pigs) and the marginal statistical significance we continued the study to verify the findings and also measured blood transit time through the limb to evaluate the possible role of arterio-venous shunting during perfusion with shock blood.

Thirty-two limb perfusions were evaluated, including one dog and one calf. In a total of 15 controls, including the dog and calf, peripheral vascular resistance increased from 1.0 resistance units during perfusion with normal blood of 2.1 resistance units during perfusion with shock blood ($p<0.001$).

In a total of 17 phentolamine treated pig limbs blood transit time through the limb was evaluated by the dye dilution method using cardiogreen and a densitometer. Transit time was

evaluated by three methods: 1) time of first appearance of the dye in the venous effluent, 2) time of maximum dye appearance in the venous effluent, and 3) the mean transit time of the dye evaluated by using the best log fit for the downslope of the curve.

The time of first appearance was 23 seconds for normal blood compared to 24 seconds for shock blood. The time of maximum dye appearance was 49.3 seconds for normal blood and 47.5 seconds for shock blood, and mean transit time was 82.4 seconds and 79.4 seconds for normal and shock blood respectively. The corresponding values for oxygen consumption were 1.5 mL/min for normal blood and 1.4 mL/min for shock blood. None of these differences was statistically significant.

The findings show that phentolamine can eliminate the increased peripheral vascular resistance found in control limbs perfused with shock blood. They also suggest that there is no significant arteriovenous shunting occurring during perfusion with shock blood treated with phentolamine. In addition, the above results suggest that, in contrast to our previous findings, phentolamine can apparently also return oxygen consumption in the isolated limb perfused with shock blood to within normal or nearly normal values.

Although elevated catecholamines were documented in the shock blood, phentolamine is a direct vasodilator as well as alpha adrenergic blocking agent and thus could be producing effects other than merely blocking catecholamines.

This data also demonstrated that the hind limb preparation is a sensitive model for assessing the immediate neurohumoral (i.e., catecholamine) responses to shock.

C. During the last 16 months of the contract a series of pilot studies were done to look for new therapeutic modalities which might intervene in preventing the reductions in visceral blood flow.

1. We have now shown that neither catecholamines, renin-angiotensin system nor thromboxane/prostacyclin is involved in the persistance of these blood flow abnormalities as measurable levels of these substances in the serum are all back to normal within 4 hours, whereas the abnormality persists for at least 18 hours.

Furthermore, treatment with aspirin increased mortality significantly. This may be related to the fact that aspirin blocks thromboxane production and possibly for the first few minutes this is important in maintaining viability of the organism and that blocking thromboxane synthesis negatively affects early mortality and morbidity.

2. ATP-$MgCl_2$ increased survival of rabbits subjected to hemorrhagic shock.

3. Fluosol DA, a fluorocarbon oxygen carrier had no effect on survival of animals in shock.

4. Treatment with naloxone:

   a. Did not affect rabbits in hemorrhagic shock.

   b. Had little effect, as did morphine, on rabbit hemodynamics.

   c. Had profound beneficial effects on one primate studied.

1. This study clearly demonstrates the activity of platelets and thromboxane in the acute response to hemorrhage. Thromboxane peaks rapidly, but then quickly subsides to very low levels. In such a non-resuscitated model, presumably the same stimuli for the initial release would be operating throughout the experiment. If this is the case, then it is conceivable that the available pool of arachidonic acid becomes exhausted or that some feedback mechanism operates to inhibit production. The similarity in visceral perfusion despite significantly different concentrations of thromboxane suggest little physiologic in the regulation of vascular tone in this model. The reason for the reduced survival is unclear and it may be unrelated to the vasoactive and platelet aggregating properties of thromboxane. It is obvious from this work, however, that thromboxane cannot be important in the persistent vasoconstriction seen in shock.

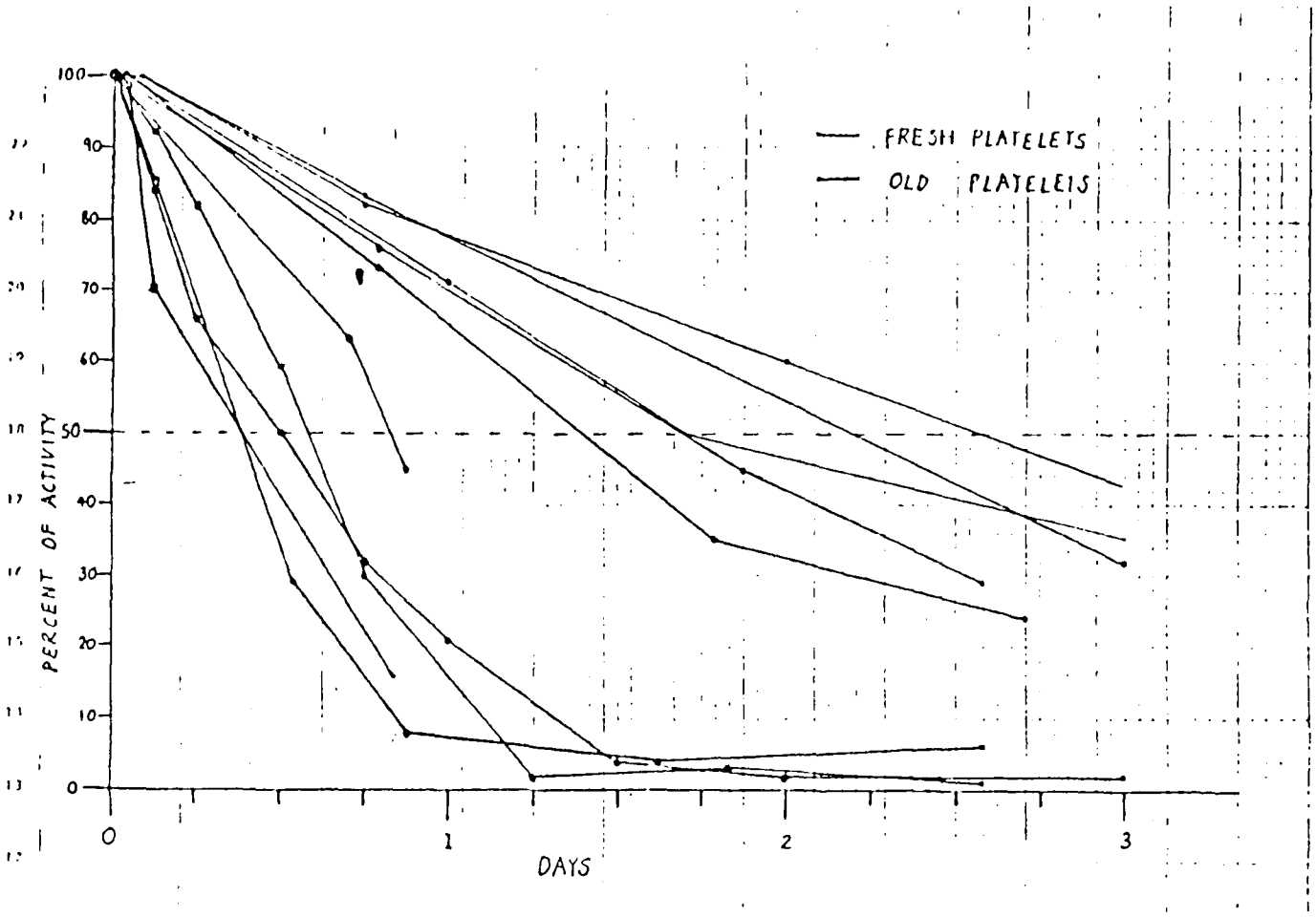
In this model, renin levels do not remain elevated, and in fact, return to baseline by 4 hours even without restoration of arterial pressure or blood volume. This suggests a finite capacity to produce renin acutely. Whether this is a function of depletion of substrate, profound renal ischemia, or feedback inhibition is unclear. But the use of a converting enzyme inhibitor to alleviate visceral congestion and to restore perfusion does not seem to be indicated.

It is important to continue the investigation of the biochemical basis for hemorrhagic shock. But the pathophysiology is very complex and the results are often difficult to define. Survival is the gold standard. What effect aspirin has on prostaglandin metabolism to cause that difference merits further work and thromboxane may be only a small part of the answer.

2. ATP-$MgCl_2$, an energy rich molecule, has been shown to improve survivability after hemorrhagic shock. Twenty-five anesthetized New Zealand rabbits underwent shock by exsanguination until mean femoral artery pressure ($\overline{FAP}$) was 60 mmHg for one hour and 40 mmHg for a second hour. Resuscitation with the shed blood followed immediately. Ten rabbits were then treated with 30 mg/kg of ATP-$MgCl_2$ infused at a rate of 0.206 mL/min. Hemodynamics indicate no significant difference between the control and treated groups in heart rate at any time during the 6-hour monitoring period. In all rabbits heart rate was significantly lowered after 2 hours of shock. At 20 minutes post ATP-$MgCl_2$ infusion, $\overline{FAP}$ was 36.7 ± 12.2 mmHg (mean ± SD) for the treated group and 83.9 ± 10.0 mmHg for the control. Survival at 72 hours post-shock significantly improved from 33% in the control to 80% in the treated group ($p<0.01$). After one week 27% of the control and 80% of the treated rabbits survived ($p<0.005$). Animals surviving for at least one week were sacrificed. The average survival time was greatly increased from 71.6 ± 64.4 hours in control to 139.5 ± 60.1 hours in the treated group ($p<0.025$). These results demonstrate the benefit of exogenous ATP-$MgCl_2$ administration in hemorrhagic shock. Although the exact mechanisms for ATP-$MgCl_2$ intervention in shock have not been elucidated, this study is strong evidence for the involvement of ATP-dependent reactions and metabolic factors in shock.

3. Perfluorochemical compounds have the capacity to transport oxygen and have been used extensively experimentally as blood substitutes. They have also been infused in resuscitation from hemorrhagic shock. Twenty-two anesthetized New Zealand rabbits underwent shock by exsanguination until $\overline{FAP}$ was 60 mmHg for one hour and 40 mmHg for a second hour. Fifteen rabbits, comprising the control group, were resuscitated with the shed blood and crystalloid. Resuscitation with a volume of Fluorocarbon-43 (perfluorotributlyamine) Emulsion equal to the amount of shed blood followed in 7 treated rabbits. The treated group was further divided: 4 rabbits received additional 5% dextrose in lactated Ringer's solution (5% DLR) to replace a large urine output engendered by apparent osmotic diuresis (Treated II) and the other 3 rabbits received only a maintenance volume (8-10 ml/hr) of 5% DLR (Treated I). Hemodynamics indicated a significant reduction in $\overline{FAP}$ immediately in the treated group (63.4 ± 12.1 as compared with 78.6 ± 8.6 mmHg (mean ± SD) in the control ($p<0.01$). A decreased $\overline{FAP}$ in the treated groups persisted for the entire 4 hours after resuscitation. The heart rate was significantly lower in the Treated II group 2 hours after shock (122.1 ± 17.1/min vs. 156.7 ± 18.0/min in the control, $p<0.005$) and 6 hours after shock (127.5 ± 29.9/min vs 177.8 ± 25.4/min, $p<0.01$). Arterial blood gases

in treated rabbits suggest profound metabolic acidosis 2 hours after shock (pH 7.074, pO_2 96.8, pCO_2 33.2) and a less severe acidosis 2 hours after FC-43 infusion (pH 7.22, pO_2 201.0, pCO_2 36.8). Hematocrit values in the treated groups decreased from 29.8% before shock to 18.7% 2 hours after shock and 11.6% one hour after FC-43 infusion (3 hours post-shock). Hematocrit increased to 20.8% by 24 hours after shock. Survival at 72 hours decreased significantly from 33% in the control to 0% in both treated groups ($p<0.005$). The average survival time was also reduced significantly from 71.6 hours in the control to 24.9 hours in the treated rabbits ($p<0.025$). FC-43 resuscitation from shock induced a significant hypotension and apparent fluid shifts raising hematocrit levels rapidly and had decreasing survival in rabbits.



The decrease of radioactivity of Cr^{51}-labeled platelets is shown in percent of the radioactivity of the first blood sample after infusion. Survival curves of platelets from blood stored for 10 days (old platelets) are definitely different than curves of fresh platelets. As the most suitable measure of platelet survival, the platelet half-time is selected. Fresh platelets have a mean half-time of 47±9 hours (n=5). The half-time of old platelets is considerably shortened to 13±3 hours (n=5, $p < 0.01$), however, 50% of the platelets from 10-day old blood are still circulating 13 hours after transfusion.

Fig. 1

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