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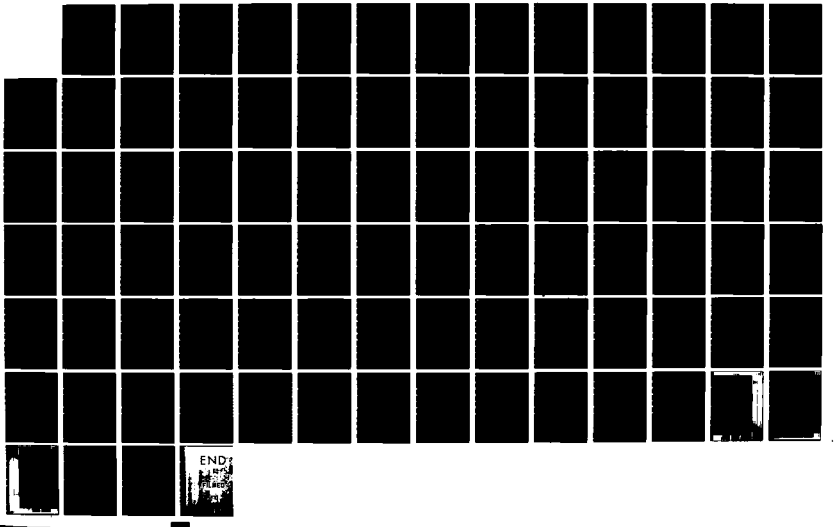

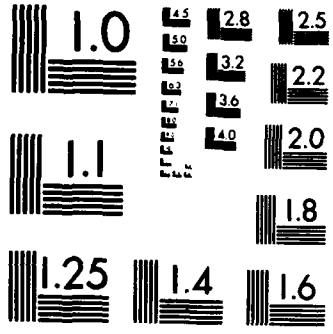

THE MECHANISM OF MICROCIRCULATORY FAILURE IN SHOCK

Annual Report

May 1979

J. Judson McNamara, M.D.

Supported by
U.S. Army Medical Research and Development Command
Fort Detrick, Frederick, Maryland 21701

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Work has progressed in 3 areas: 1) evaluating blood filtration, 2) assessment of shock in a rabbit and subsequently a baboon shock model, and 3) the influence of ischemia and shock blood in microvascular blood flow in an isolated limb perfusion system. We are currently halfway through a comprehensive in vitro evaluation of blood filters and are a year into a three-year project on the clinical evaluation of blood filters.

After conducting two sets of experiments in a rabbit shock model, we

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completed a preliminary set of experiments on baboons in shock which has allowed us to refine the protocol and demonstrate the feasibility of treating baboons, following resuscitation from shock, with nitroprusside in an attempt to restore visceral organ blood flow more quickly to normal.

We have established an isolated limb perfusion model in pigs and have completed one set of experiments showing an increase in vascular resistance in the limb perfused with shocked blood. We are planning to continue with isolated limb perfusion studies to try and define the role of the platelet in the genesis of these resistance changes.

A-1

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SUMMARY

Work has progressed in 3 areas: 1) evaluating blood filtration, 2) assessment of shock in a rabbit and subsequently a baboon shock model, and 3) the influence of ischemia and shock blood in microvascular blood flow in an isolated limb perfusion system. We are currently halfway through a comprehensive in vitro evaluation of blood filters and are a year into a three-year project on the clinical evaluation of blood filters.

After conducting two sets of experiments in a rabbit shock model, we completed a preliminary set of experiments on baboons in shock which has allowed us to refine the protocol and demonstrate the feasibility of treating baboons following resuscitation from shock, with nitroprusside in an attempt to restore visceral organ blood flow more quickly to normal.

We have established an isolated limb perfusion model in pigs and have completed one set of experiments showing an increase in vascular resistance in the limb perfused with shocked blood. We are planning to continue with isolated limb perfusion studies to try and define the role of the platelet in the genesis of these resistance changes.

FOREWORD

These studies represent an ongoing effort to elucidate basic mechanisms of cellular injury in shock and to discover methods of minimizing this injury and improving resuscitation in the whole animal.

In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal, Resources, National Academy of Sciences-National Research Council.

PROGRESS REPORT

During the previous year, we have had two major programs investigating the mechanisms of microcirculatory failure in shock and a continuation of some of our previous work in blood filtering.

Part I. Blood Filtering

Background: All filters evaluated to date (Bentley, Swank and Fenwal) have either been effective debris filters with limited capacity and flow rates or have been less effective filters, yet providing good flow rates (Pall). Preliminary data on the new J & J Intersept filter suggests excellent filtering characteristics with a larger capacity and good flow rates.(1)

The precise clinical significance of stored blood microaggregate infusion remains in doubt.(2) Few randomized clinical studies designed to address this problem have appeared. Virgilio, et. al.(3) demonstrated no effect of filtration in altering pulmonary stalis after massive transfusion but utilized a less efficient microaggregate removing filter (Pall). We propose to use the above filter to perform a randomized study on the differences in pulmonary stalis with and without blood ultrafiltration in massively transfused patients.

Progress: We have completed a study on filter efficiency which has been accepted for publication (Appendix A).

We are halfway through a concurrent in vitro evaluation of the following filters by the protocol contained in Appendix B: Fenwal 20 micron high capacity transfusion filter (Travenol Labs, Inc., Deerfield, IL), Bentley PFF-100 infusion blood filter (Bentley Labs, Inc., Irvine, CA), Ultipor(R) blood transfusion filter (Pall Corporation, Glen Cove, NY), Intersept(R) (Johnson & Johnson, New Brunswick, NJ), Swank IL-200 transfusion filter (Pioneer Filters, Inc., Beaverton, OR), and the standard V-2950 in-line blood filter (McGaw Labs, Glendale, CA). No significant data has yet been generalized.

We are about half-way through a clinical randomized study evaluation of the above six different filters in the clinical setting in patients requiring more than 3-unit transfusions. The protocol is in Appendix C. Filter use is randomized. We are accumulating data on:

1) Logistical problems of connecting filters.

2) Filtering capacity - numbers of units/filter.

3) Filtering effectiveness.

4) Filter flow rates, including maximal flow rates and administration times in an emergency.

5) Postoperative respiratory complications.

6) Comments by anesthesia and nursing staff.

An updated summary of this work is included in Appendix D.

Part II. We have looked at shock and trauma in three different experiments.

Background: Failure of nutrient blood flow to the tissue is the ultimate common denominator in shock. Compensatory mechanisms of the whole organism in shock redistribute blood flow to meet requirements of vital organs. Such redistribution is mediated to a large extent by smooth muscle cells controlling the caliber of peripheral arterioles, precapillary sphincters and postcapillary vessels. Venules provide the postcapillary resistance and venous system in turn makes up about 70% of the vascular reservoir.(4) It is, therefore, evident that venules are not only important in determining hydrostatic pressure and consequent transcapillary fluid exchange but by virtue of their influence on the venous reservoir, can influence cardiac output and tissue perfusion.

Under stress, such as shock, local mechanisms regulating blood flow are over-ridden by the necessity of maintaining central pressure and vital organ perfusion. The combined venular and arteriolar constriction increases venous return while (because of arteriolar resistance) decreasing capillary hydrostatic pressure, thus promoting transcapillary refill. As shock progresses, precapillary sphincters fail first resulting in increased capillary hydrostatic pressure, loss of fluid and decreased perfusion.(5)

Resuscitation from the shock state requires restoration of hemodynamic balance. In hypovolemic shock this principally involves replacement of volume. Indices involved in judging adequate volume replacement, however, do not necessarily relate to tissue perfusion but rather cardiac preload, afterload and cardiac output. Thus, persistent abnormalities in venous and arteriolar vascular tone can unfavorably influence tissue perfusion, yet allow normal central hemodynamic indices. That such changes can persist is evidenced by reduced blood volumes noted in battle casualties 24 hours after resuscitation at a time when central hemodynamics are normal.(6)

Progress: In a series of acute experiments in 30 rabbits we have assessed the influence of shock, trauma, and shock and trauma combined on platelet and pulmonary platelet trapping. We found that the combination of direct thoracic trauma and hemorrhagic shock was associated with significantly greater reduction in platelet count, more pulmonary platelet trapping and higher mortality than animals subjected to shock or trauma alone (Appendix F).

A series of 16 rabbits were studied in an attempt to assess organ blood flow distribution in animals in shock. It is our hypothesis that organ blood flow distribution remains abnormal for hours after resuscitation and that controlled vasodilator therapy may return organ blood flow distribution to normal much earlier than hemodynamic resuscitation alone.

The rabbit proved to be an impossible model for us for long-term (>12 hours) study. I included worksheets on all 16 animals indicating the reasons for failure. It was clear, however, even from this spotty data that hemodynamic resuscitation did not assure return to normal organ blood flow distribution or normal metabolic status (Appendix F). This led to a study in baboons:

To date five control animals resuscitated with shed blood and maintained with basal fluid replacement of 50 cc/hr and two nipride treated animals receiving the same therapy except one hour of post-resuscitation intravenous nitroprusside have been completed. A summary and graphs are included in Appendix G. It appears that nipride restores normal physiologic and metabolic hemostasis more rapidly than hemodynamic resuscitation alone. The data is still preliminary and a revised protocol has been adapted to more accurately verify this data.

Part III. Influence of ischemia (low perfusion), with and without shock blood perfusion, on platelet function, micro-vascular obstruction and limb metabolism in an isolated hind limb perfusion system.

Background: Platelets have been shown to aggregate in vivo in response to shock and even accumulation in certain organ systems has been demonstrated with tagged platelets during shock.[7,8,9] Furthermore, many of the substances released during shock stimulate platelet aggregation.[7] Whether aggregation of platelets contribute to the low flow state during shock is not known. It has been demonstrated that there is good reason to believe that the platelet is profoundly influenced during shock, not only because of the release of substances in the systemic circulation but also because of effects of shock on the vascular wall. It has been recently demonstrated that the capillary endothelium contains a prostaglandin (PGI_2) which is a potent inhibitor of platelet aggregation[10] and whose presence in the vascular wall is apparently responsible for prevention of platelet aggregation under circumstances of normal homeostasis.[11] Thus, shock may not only have systemic effects, but by producing local ischemia may alter the available inhibitory prostaglandin, thus predisposing platelet aggregation in the microvascular system specifically.

Another facet of platelet physiology which may link into micro-vascular function in shock involves recent information on a number of drugs which will to a large extent inhibit platelet function by interfering with the synthesis of thromboxane A_2. Thromboxane A_2 is an intermediate in the metabolic formation of prostaglandins from arachadonic acid. Furthermore, there is evidence which strongly suggests that thromboxane A_2 is the aggregation substance produced by platelets.[12,13]

Thus, the presence of thromboxane A_2, in fact the most potent vasoconstrictor yet known, would appear to further confound the peripheral circulation in shock by not only its effect on platelet aggregation but also by profound local peripheral vascular constriction and consequent further reduction in regional organ perfusion. One drug which will inhibit thromboxane A_2 and theoretically minimize these effects is aspirin. Current evidence indicates that it works by specific acetylation of prostaglandin synthelase.[14]

We have previously published evidence demonstrating accumulation of platelet in areas of ischemia following acute myocardial infarction in baboons and also demonstrated that the administration of aspirin will inhibit this platelet accumulation.[15] A similar widespread systemic and local response might be anticipated in shock and the present study intends to investigate this problem.

Progress: This experimental model has proven a long, hard, arduous struggle to perfect, particularly with the need to switch perfusion setups during the experiment. It has, however, evolved to a highly successful and sensitive model resulting in the successful completion of the last seven of these long and difficult experiments. An abstract resulting from these experiments and submitted to the Surgical Forum as well as a summary data flow sheet are included in Appendix G.

In brief, we have shown that:

1) None of the perfusions produced significant abnormality in circulating platelet function.

2) Low flow perfusion with shocked blood significantly reduced platelet count, increased vascular resistance and decreased oxygen consumption suggesting platelet aggregation and microvascular obstruction.

The next phase of the experiment will be to block prostaglandin synthesis, interfere with platelet function and measure this effect on the above altered physiological and metabolic parameters.

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APPENDIX A

FILTRATION OF DEBRIS FROM BANKED BLOOD

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Abstract

Commercially available filters will effectively remove microaggregates from stored blood. The combined results of screen filtration pressure (SFP), debris weight and particle size analysis offers a reproducible means of evaluating different filters.

The effectiveness of three blood filters (Fenwal, Bentley and Pall) is evaluated using SFP, debris weight measurement, particle size analysis and determinations of filter capacity. Of the filters studied the Fenwal filter provides the most efficient means of removing debris while maintaining adequate flow rates for relatively large volumes of blood. The filter appears comparable to the Swank filter in overall effectiveness and flow characteristics.

It is well documented that stored blood develops large quantities of microaggregates composed of platelets and white cells.[1,8,10] The physiological significance of this debris when infused into the circulation is unknown, although recent studies have implicated pulmonary microembolism of microaggregates in the pathogenesis of post-traumatic pulmonary insufficiency.[2,3,5,6] Commercially available micro-pore filters have been developed which remove microaggregates from stored blood with varying degrees of efficiency.[4,7] The present study evaluates the relative effectiveness of three commercially available filters in removing microaggregate material from 21-day old stored blood and is our first report of clinical evaluation of the Fenwal filter.

Materials and Methods

Outdated banked human blood (21-23 days old), stored in CPD bags at 4°C was obtained from the Blood Bank of Hawaii. All units were agitated by hand for one minute prior to testing. Multiple units of crossmatched blood were used for testing filter capacity and flow characteristics using both gravity flow and 150 mmHg pressure infusions with a Fenwal pressure infusion bag. Samples for testing was drawn from each 85 cc increment passing through the filter for the gravity flow studies and from each 100 cc increment for pressure infusion studies. Blood was continually passed through the filters up to 2,000 cc or until the flow rate was reduced to less than 1 cc/minute. All filters were initially primed to the point blood first appeared in the outflow tubing. Up to five filters were tested for gravity flow study. One pressure infusion study was performed for each filter.

Standard blood administration filters (V-2950 McGaw Laboratories, Division of American Hospital Supply Corporation, Glendale, California), with a 170μ

pore size, were placed in-line above each test filter. The filters compared were: 1) Bentley Infusion Blood Filter PF-127 (Bentley Laboratories, Inc., Irvine, California), 2) Pall Ultipore^{R} Blood Transfusion Filter (Pall Corporation, Biomedical Products Division, Glen Cove, Long Island, New York), and 3) Fenwal Microaggregate Blood Filter 4C2417 (Fenwal Laboratories, Division of Travenol Laboratories, Morton Grove, Illinois).

The Bentley utilizes a 260-300μ polyester screen followed by a depth filter consisting of three successive layers of polyester urethane of 150, 73 and 27μ pore sizes respectively. The Pall is a surface filter with a coarse clot screen, 127μ both above and below a pleated polyester fine mesh screen, 25μ in size. In the Fenwal, a 250μ filter screen precedes a 150μ capacity reticulated pore structure. This is followed by a depth filter of compressed fiber designed to retain particles of close to 20μ.

Particle size analyses were accomplished with a Coulter Counter Model TAII (Coulter Electronics, Inc., Hialeah, Florida).[9] The channels on the counter were set to cover a range of 3 to 80μ mesh spherical diameter using a 200μ aperture. A 1 to 100 dilution of blood in Isoton (Coulter Diagnostics, Hialeah, Florida) was used.

Debris weights and screen filtration pressures were done in a manner previously described.[8] Control samples were run repeatedly throughout the procedure. SFP is reported in mmHg/cc since most control samples were not able to pass an entire 10 cc increment through the SFP apparatus. Filtered samples are reported in mg/cc as well as for the sake of comparison.

Fifteen cc of blood was drawn from a point immediately preceding the test filter and another 15 cc was drawn from blood that had just passed through each filter.

Values obtained for gravity flow experiments were summated for each filter and graphs constructed from mean values of all 2,000 cc of blood tested for each filter. The numbers of determinations at each point decrease as larger volumes are passed through the filter indicating some small variation in debris load or filter capacity even within the same brand of filter.

Results

Control samples in these figures show high SFP's and debris weights, as well as a considerable accumulation of particles greater than 20μ (Figures 1b and 1c).

The Pall Ultipore^{R} 25μ is essentially the same design as the 40μ filter (SQ-40), except for a smaller screen size. It maintained the fastest flow rates for the largest volumes (Figure 1a). The Pall, however, was not nearly as effective in removing debris as the other filters studied (Figure 1c). Pressure studies were similar to results seen with gravity flow with regard to debris removal and flow rates. The Bentley filter would not accept 1,000 cc even with pressure infusion (Figure 3a).

The Pall displayed a relatively smaller change in SFP and a significant reduction in debris weight was not evident ($p>0.15$) (Figures 1b and 1c). Similar data was obtained for the Pall after pressure infusion (Figures 3b and 3c). Debris weights indicated that differences with pressure infusion between control and post filter values disappeared for the Pall filter after one unit of blood (Figure 3c).

Bentley and Fenwal filters showed substantial reductions in debris weight and SFP (all $p>0.05$) (Figures 1b-c and 3b-c). Flow rates for the Bentley, however, were lowest of the three filters studied (Figure 1a).

Particle counting in gravity flow experiments showed significant ($p<0.05$) removal of particles by the Fenwal down to an 11μ mean spherical diameter and the Pall and the Bentley to 16μ (Figures 2a-c).

Discussion

Microaggregates of fibrin and aggregated platelets occur in banked blood as early as 2 days and becomes quite substantial after 10 days. This report evaluates the relative efficiency of three blood ultrafilters in removing microaggregate debris from stored human blood.

The Pall filter, though maintaining excellent infusion rates, was slightly less effective in removing debris as determined by SFP and debris weights but about the same as the other two when measured by actual particle counting. The present data again suggests that with multiple units of blood and pressure infusion, the Pall surface filters lose some of their efficiency apparently with the result that some of the accumulated debris may actually be blown off the screen back into the circulation as we have previously reported.[10]

Particle size analysis did provide an added dimension in allowing analysis of the smallest particles which each filter would remove effectively and is important in considering actual numbers of particles removed by each filter. The different techniques of monitoring filtering efficiency were in close agreement. In general, all three filters are efficient in removing debris but the Bentley has a much smaller, in fact, inadequate filtering capacity both with gravity flow and pressure infusion. Since numerous previous studies have compared the Swank filter with the Pall and Bentley filters, it was not included in this evaluation. Previous tests have established its general filtering superiority over either the Pall or Bentley

filters.[6,7] Based on previous studies it appeared slightly better but comparable to the Fenwal filter.[7]

Finally, no studies have measured the actual delay incurred in transfusing one or more units of blood through any of the microaggregate filters resulting not only from reduced flow rates but time spent hooking up filters, changing filters and priming filters prior to initiating the infusion. The need for determining the clinical importance of these filters if profound. We find ourselves frequently not using ultrafilters in massively bleeding patients because of the delays incurred by using any of the filters. It certainly appears that removal of microaggregates, of unproven clinical significance, should not be pursued to the point of slowing the rapidity of the blood transfusions needed to replace massive and continuing blood loss.

Of the filters studied, the Fenwal appeared to maintain the greatest filtering efficiency with a fairly adequate flow rate. It resembles the Swank filter in terms of flow and filtering efficiency. The Pall does slightly less filtering but maintains substantially better flow rates and for as many units of blood as were tested in this study. Since the pathologic significance of microaggregates remain uncertain, the Pall filter would seem the best in the massively bleeding patient as it interferes the least with infusion rate. Yet, if the filters are important, the wisdom of using a filter specifically because it is less effective is not self-evident. The real need is two-fold. First, to determine the pathologic significance, if any, of blood microaggregates and second, if microaggregates should be removed, to design a better filter.

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Legend

Figures 1a-c — Figure 1a shows a progressive fall off in flow rate with all filters with gravity infusion of three units of stored blood. Flow rates are best preserved with the Pall filter. Figures 1b and 1c demonstrate the efficiency of each filter in removing debris. Both methods show reduction of debris, is more effective with Bentley or Fenwal filters although the Pall produces substantial debris reduction as well.

Figures 2a-c — Figures 2a-c show effectiveness of the three filters as determined by electronic particle counting. All three filters significantly reduce the amounts of debris as evidenced by this data.

Figures 3a-c — Figures 3a-c are identical to the data in Figures 1a-c except that the blood is infused through the filters at 150 mmHg. With pressure infusion Pall sustains excellent flow rates and debris removal remains satisfactory.

Figures 4a-c — Debris removal is confirmed by electronic particle counting for all three filters.

GRAVITY I LOW RATE

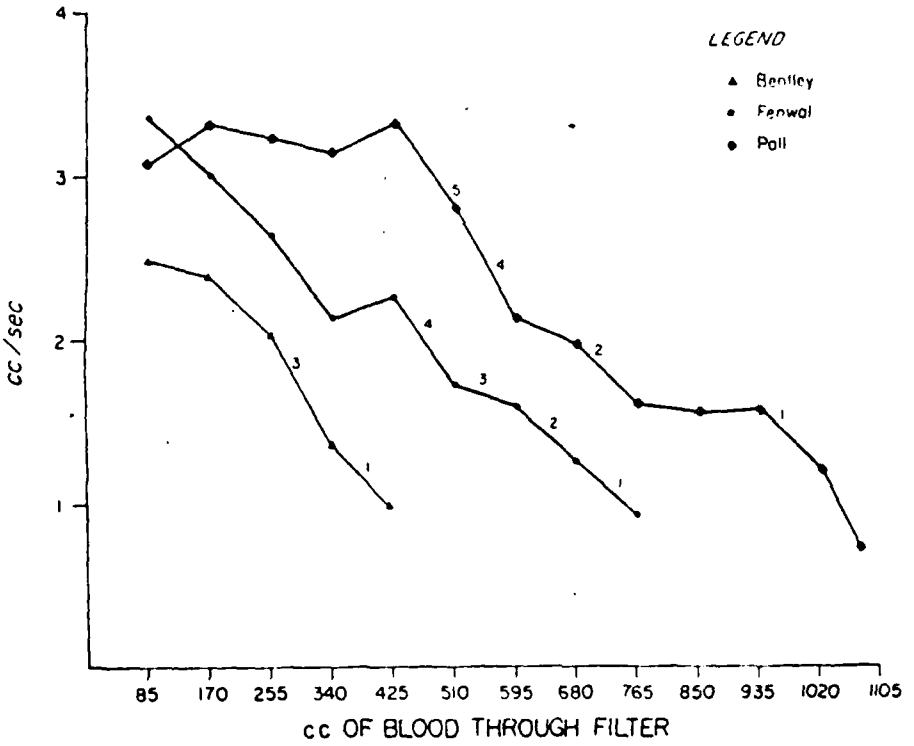
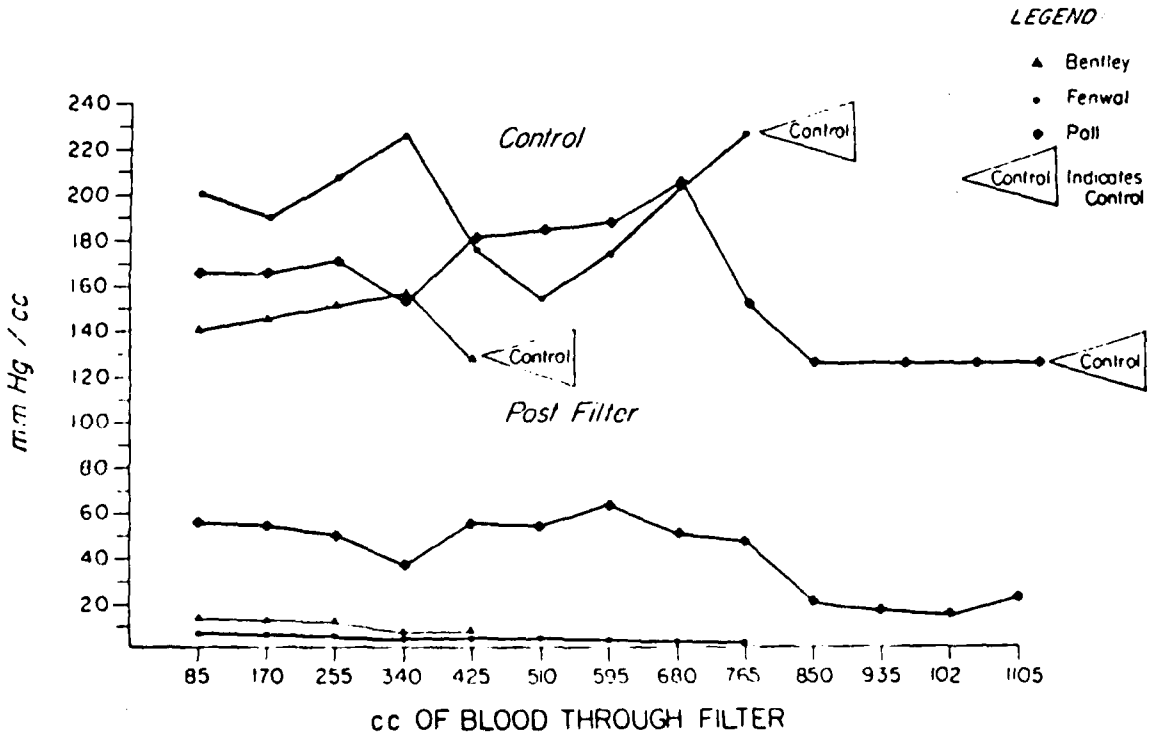
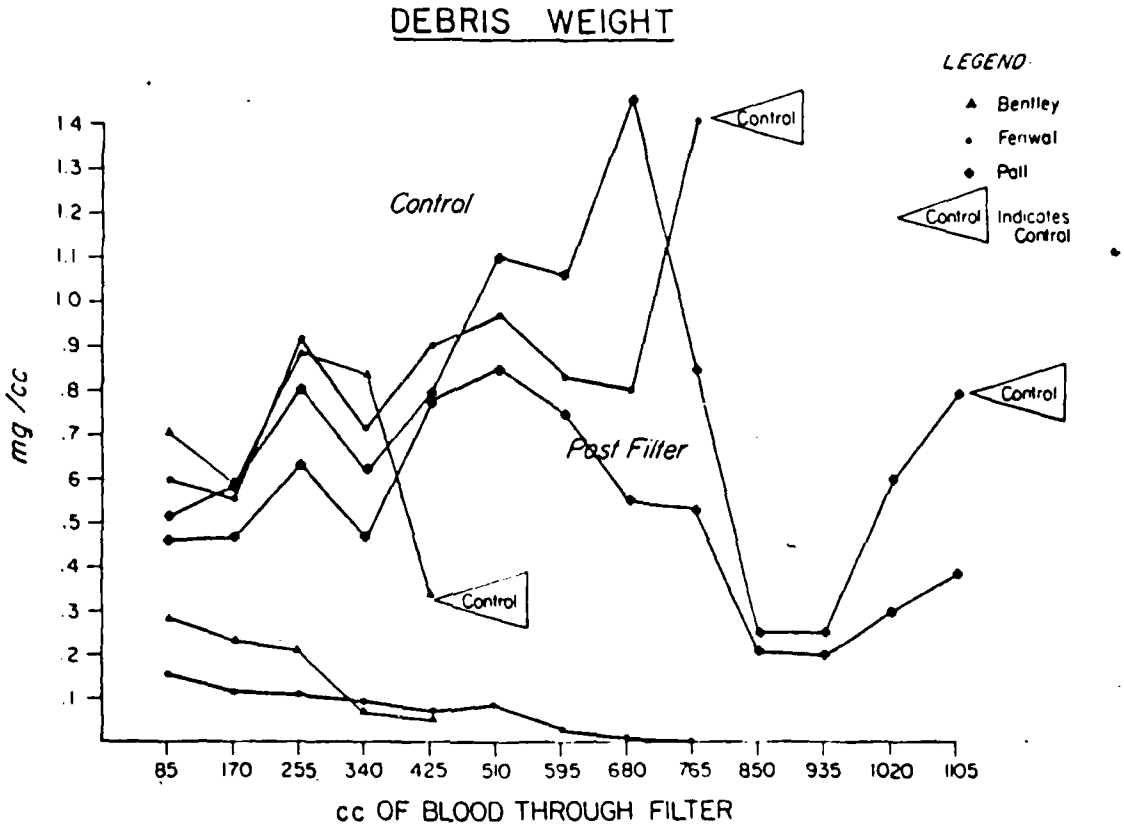


Figure 1a

SCREEN FILTRATION PRESSURE

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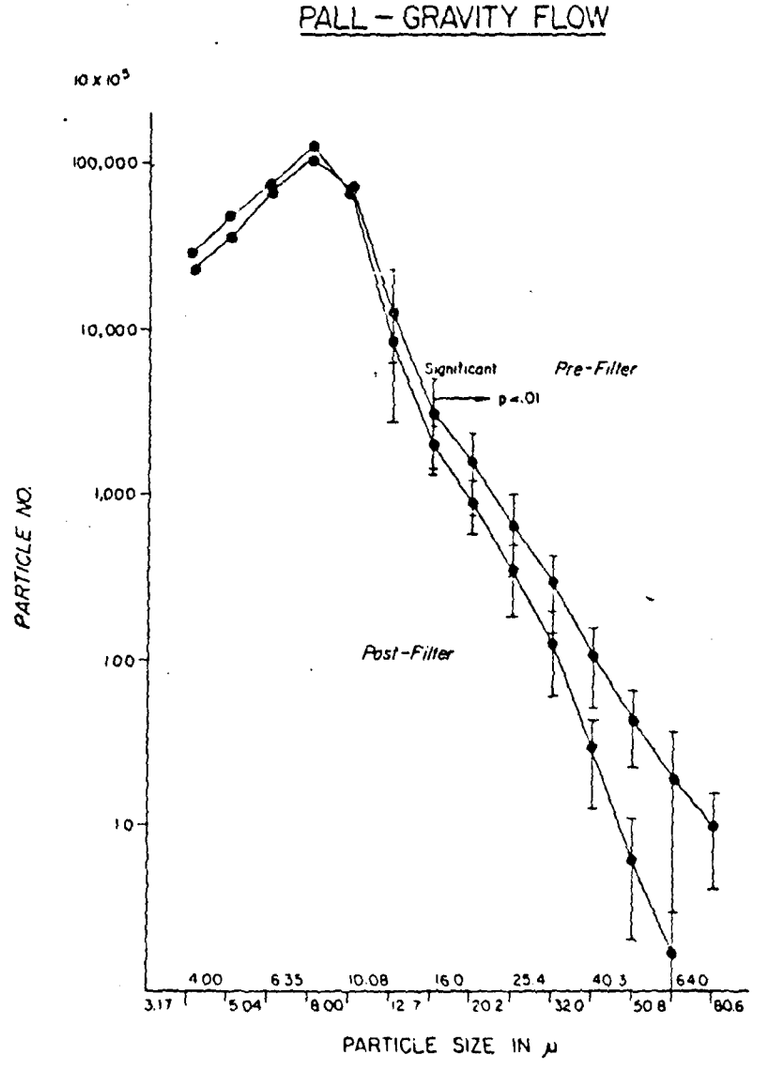
cc OF BLOOD THROUGH FILTER

Figure 1c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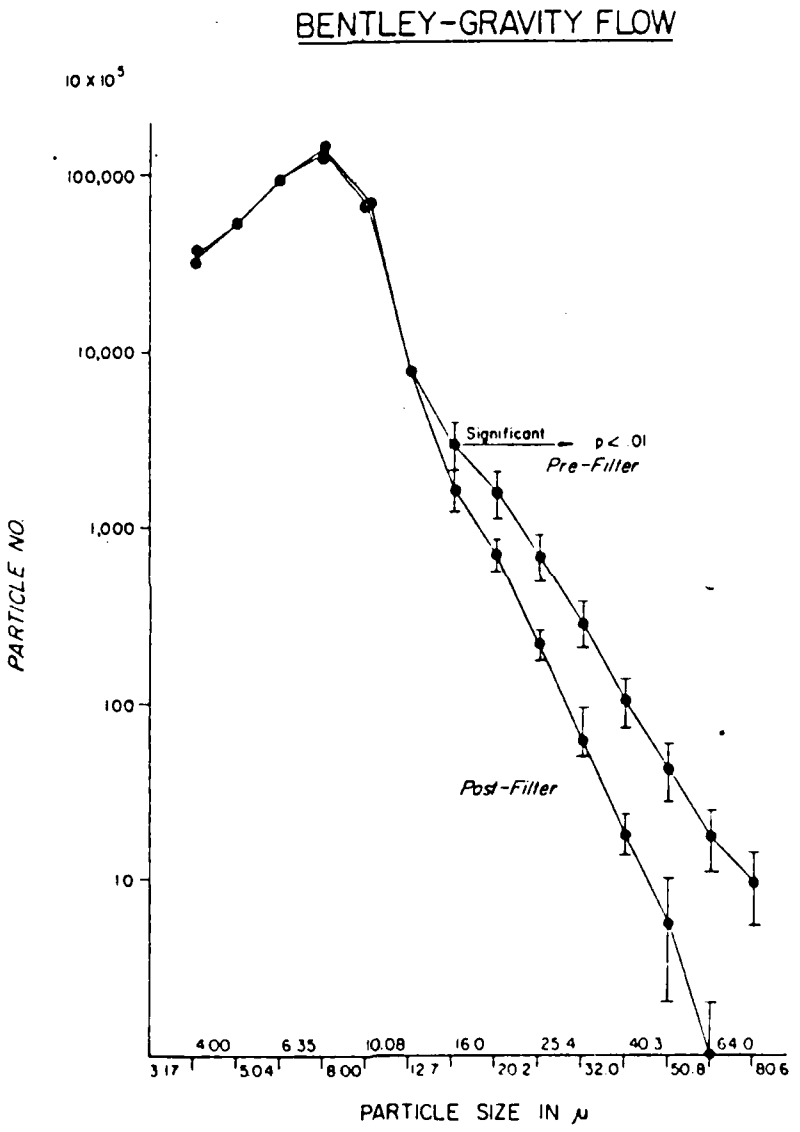
PARTICLE SIZE IN μ

Figure 2a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40.3
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32.0
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80.6
PARTICLE SIZE IN μ

Figure 2b

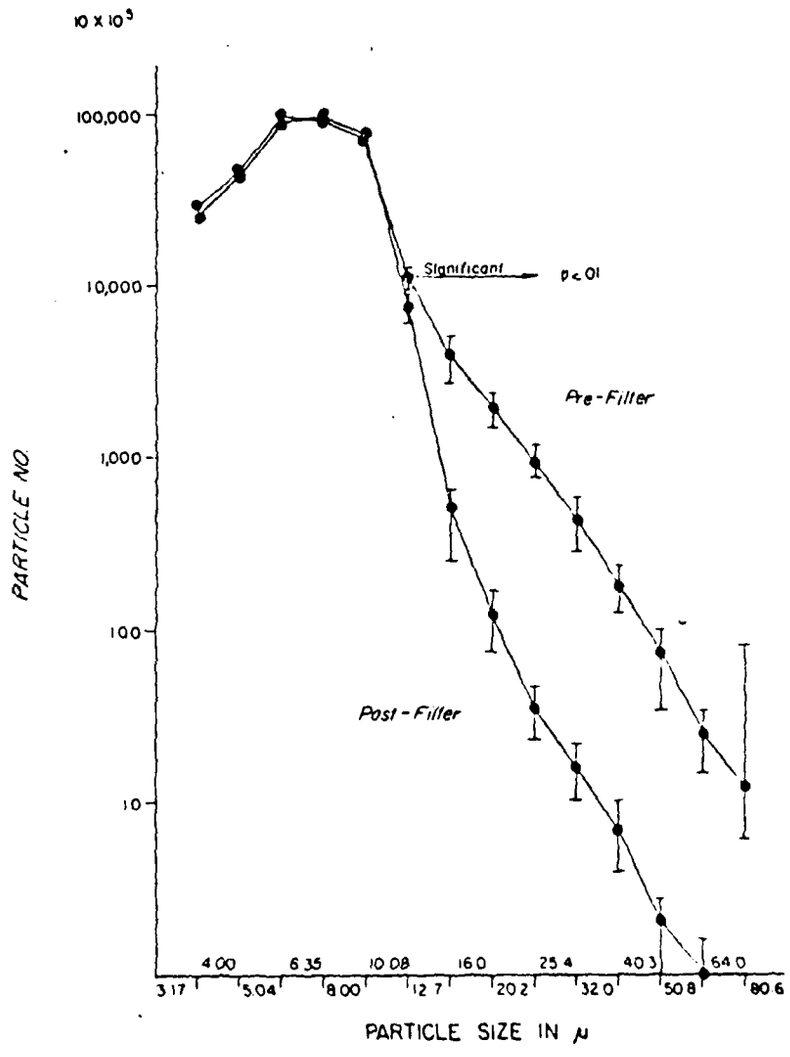

FENWAL – GRAVITY FLOW
10 X 10³
100,000
10,000
1,000
100
10
PARTICLE NO.
Significant
p < 01
Pre-Filter
Post-Filter
4 00
6 35
10 08
16 0
25 4
40 3
64 0
3 17
5 04
8 00
12 7
20 2
32 0
50 8
80 6
PARTICLE SIZE IN μ

Figure 2c

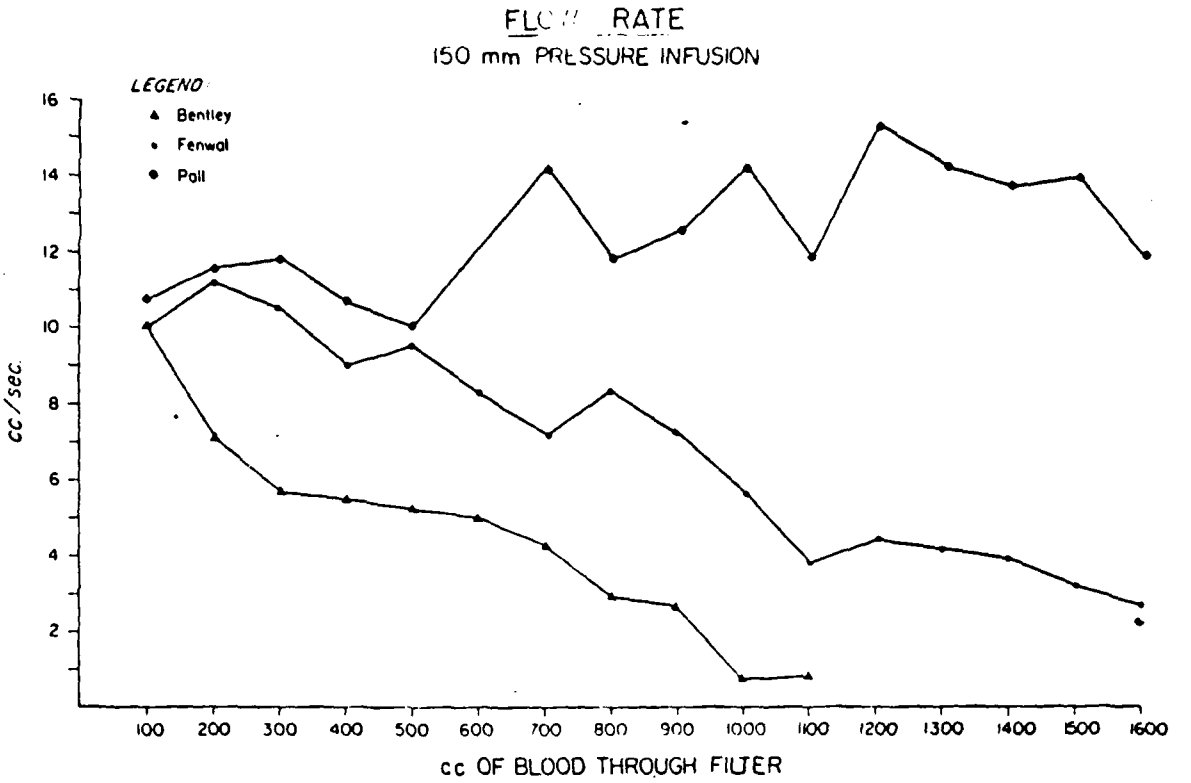
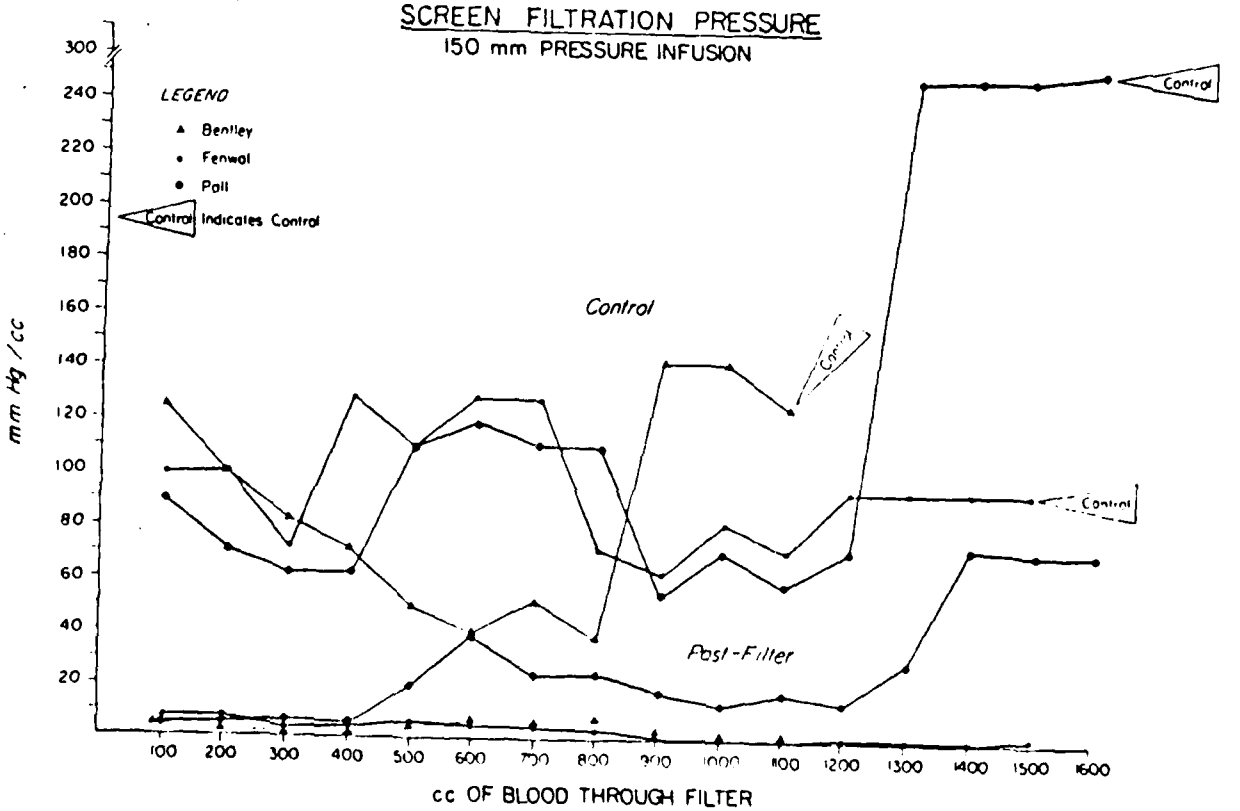

FLOW RATE
150 mm PRESSURE INFUSION
LEGEND
Bentley
Fenwal
Pall
cc/sec.
16
14
12
10
8
6
4
2
100 200 300 400 500 600 700 800 900 1000 1100 1200 1300 1400 1500 1600
cc OF BLOOD THROUGH FILTER

Figure 3a


SCREEN FILTRATION PRESSURE
150 mm PRESSURE INFUSION
LEGEND
Bentley
Fenwal
Pall
Control Indicates Control
mm Hg / cc
300
240
220
200
180
160
140
120
100
80
60
40
20
Control
Control
Control
Post-Filter
100 200 300 400 500 600 700 800 900 1000 1100 1200 1300 1400 1500 1600
cc OF BLOOD THROUGH FILTER

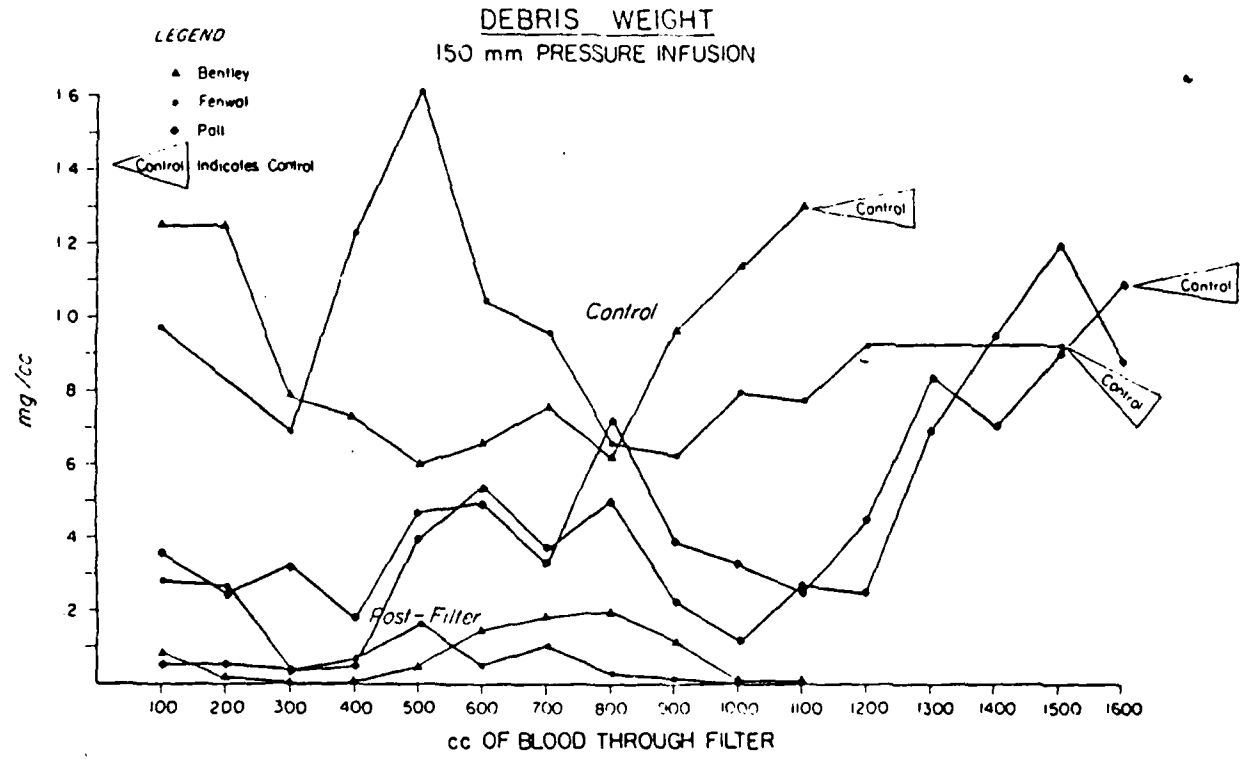

DEBRIS WEIGHT
150 mm PRESSURE INFUSION
LEGEND
Bentley
Fenwal
Pall
Control indicates Control
mg/cc
16
14
12
10
8
6
4
2
Control
Control
Control
Control
Post-Filter
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600
cc OF BLOOD THROUGH FILTER

Figure 3c

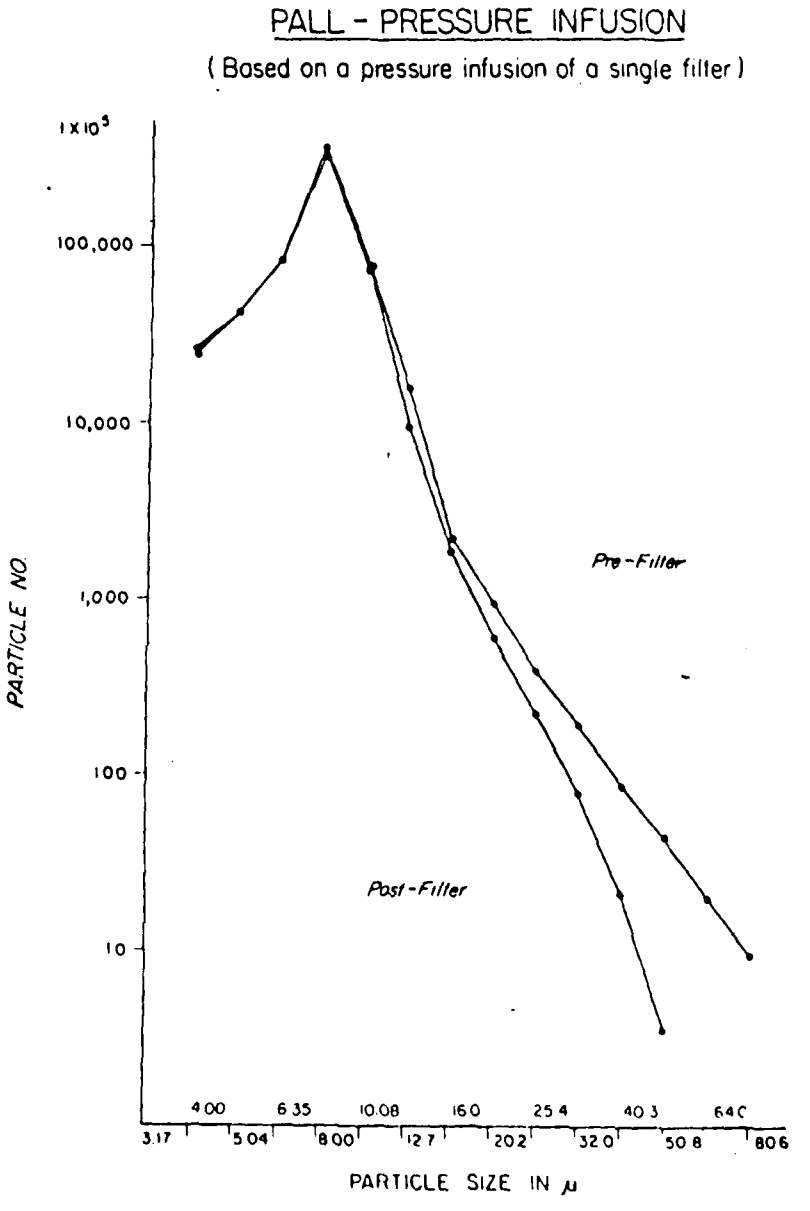

PALL - PRESSURE INFUSION
(Based on a pressure infusion of a single filter)
1 X 10⁵
100,000
10,000
1,000
100
10
PARTICLE NO
Pre-Filter
Post-Filter
4.00
6.35
10.08
16.0
25.4
40.3
64.0
3.17
5.04
8.00
12.7
20.2
32.0
50.8
80.6
PARTICLE SIZE IN μ

Figure 4a

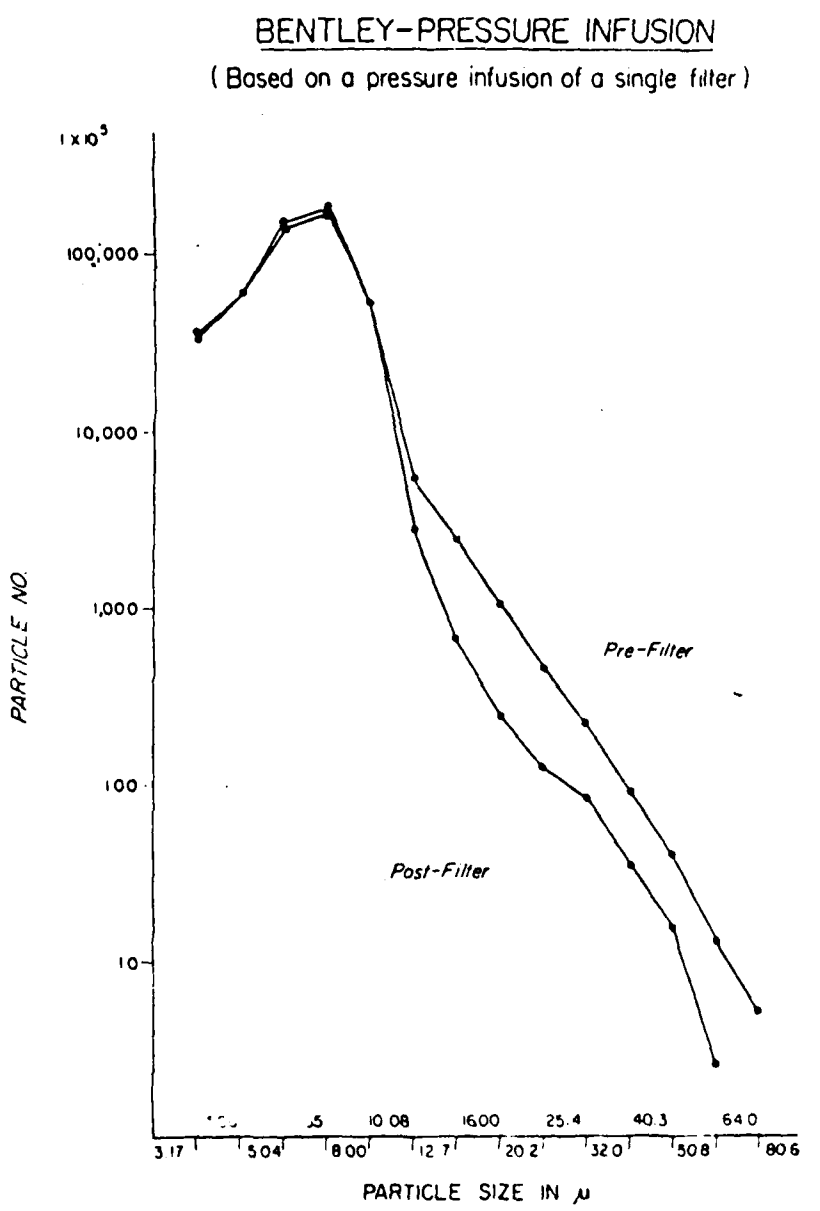

BENTLEY-PRESSURE INFUSION
(Based on a pressure infusion of a single filter)
1 x 10³
100,000
10,000
1,000
100
10
PARTICLE NO.
Pre-Filter
Post-Filter
10 08
16.00
25.4
40.3
64.0
3.17
5.04
8.00
12.7
20.2
32.0
50.8
80.6
PARTICLE SIZE IN μ

Figure 4b

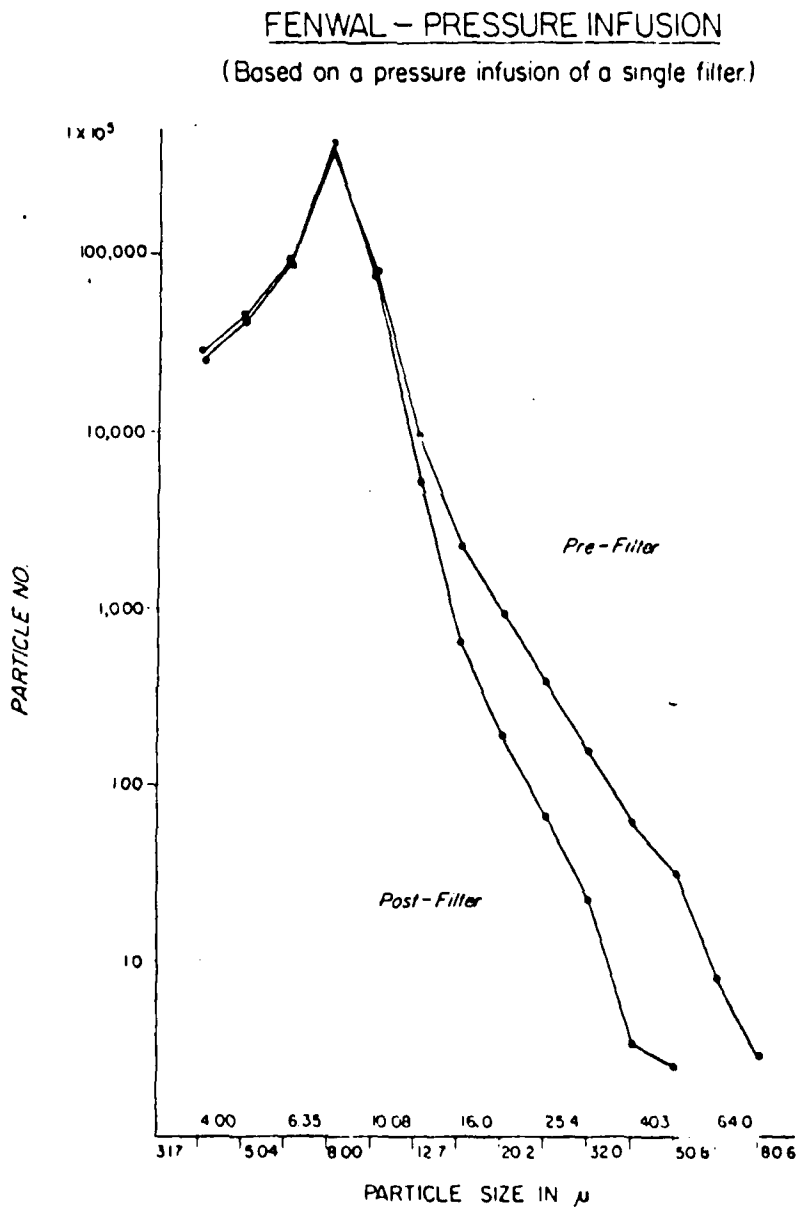

FENWAL – PRESSURE INFUSION
(Based on a pressure infusion of a single filter.)
1 x 10⁵
100,000
10,000
1,000
100
10
PARTICLE NO.
Pre-Filter
Post-Filter
4.00
6.35
10.08
16.0
25.4
40.3
64.0
3.17
5.04
8.00
12.7
20.2
32.0
50.6
80.6
PARTICLE SIZE IN μ

Figure 4c

APPENDIX B

CLINICAL FILTER EVALUATION

1) Hypothesis: It should be possible to determine which blood ultrafilter provides effective blood filtration while maintaining high flow rates with multiunit capacity, thus not endangering patient resuscitation.

2) Background: All filters evaluated to date (Bentley, J & J Intersept, Swank and Fenwal) have either been effective debris filters with limited capacity and flow rates or have been less effective filters, yet providing good flow rates (Pall).

3) Rationale and Relevance: As noted previously, the significance of microaggregate debris infusion which occurs with massive transfusion remains obscure. Last year's conference on microaggregates could document no causal relationship to clinical illness, but it was equally evident that microaggregate debris certainly does no good. It was concluded that if debris can be removed economically and effectively without affecting the adequacy of resuscitation of the patient, it should be done but that a filter which met these criteria was not on the market. One repetitive theme of that conference was the fact that the patients who would need filtration most are those who require massive amounts of blood over a short period of time and that the use of most effective blood filters will decrease the rate of blood infusion and interfere with rapid resuscitation. It was the concensus that such patients should not have blood ultrafiltered until a high flow effective ultrafilter was developed. We believe the Pall filter best meets these requirements.

4) Design and Methods of Approach: Outdated banked human blood (21-23 days old), stored in CPD bags at 4°C is obtained from the Blood Bank of Hawaii. All units are agitated by hand for [illegible] minute prior to testing. Multiple units of cross-matched blood are used for testing filter capacity and flow characteristics using both gravity flow and 150 mmHg pressure infusions with a Fenwal pressure infusion bag. Samples for testing are drawn from each 85 cc increment passing through the filter for the gravity flow studies and from each 100 cc increment for pressure infusion studies. Blood is continually passed through the filters up to 2,000 cc or until the flow rate is reduced to less than 1 cc/min. All filters are initially primed to the point blood first appeared in the outflow tubing. Up to five filters are tested for gravity flow study. One pressure infusion study is performed for each filter.

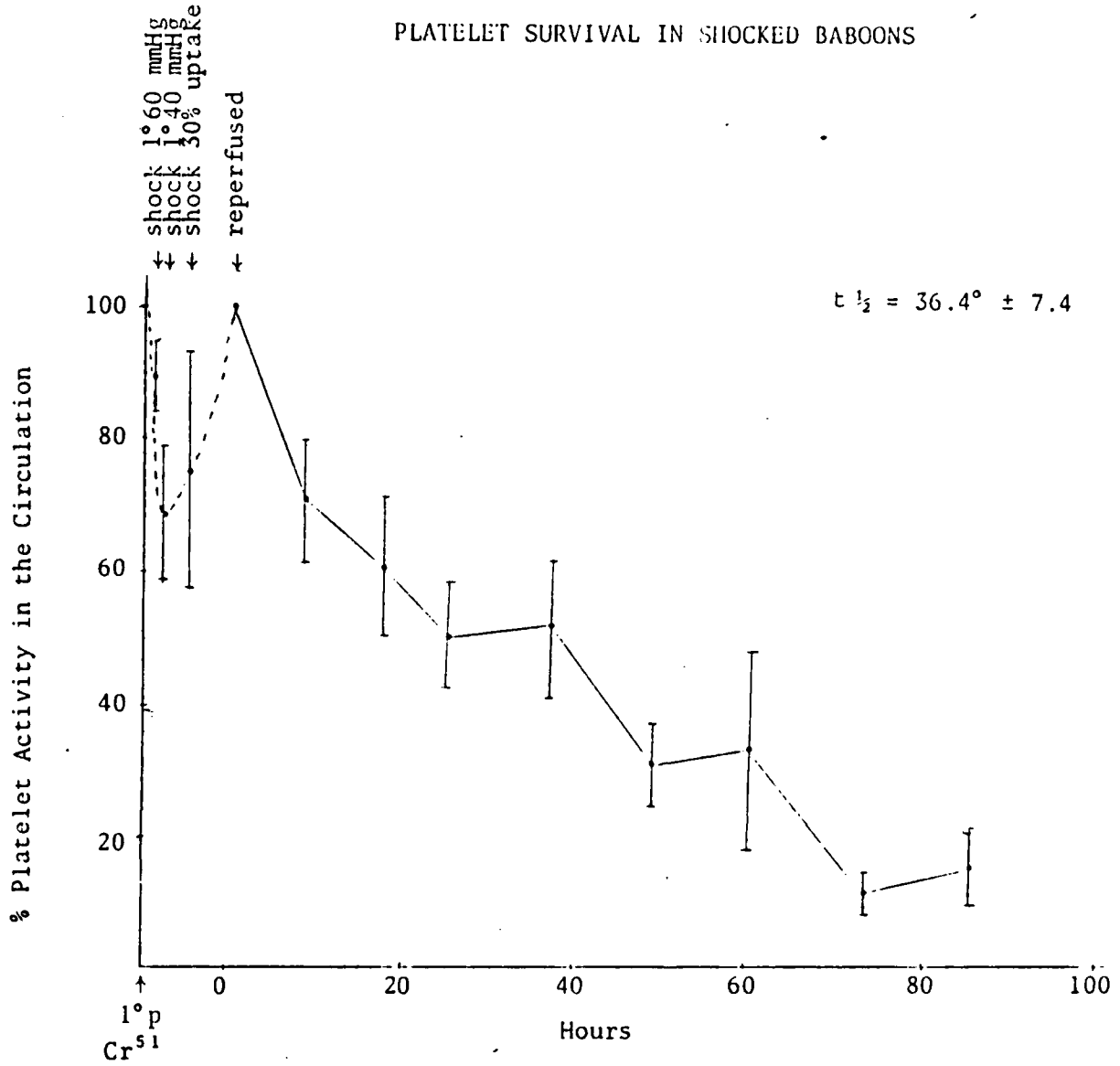
Particle size analyses are accomplished with a Coulter Counter Model TAII (Coulter Electronics, Inc., Hialeah, Fla.). The channels on the counter are set to cover a range of 3 to 80μ mesh spherical diameter using a 200μ aperture. A 1:100 dilution of blood in Isoton (Coulter Diagnostics, Hialeah, Fla.) is used.

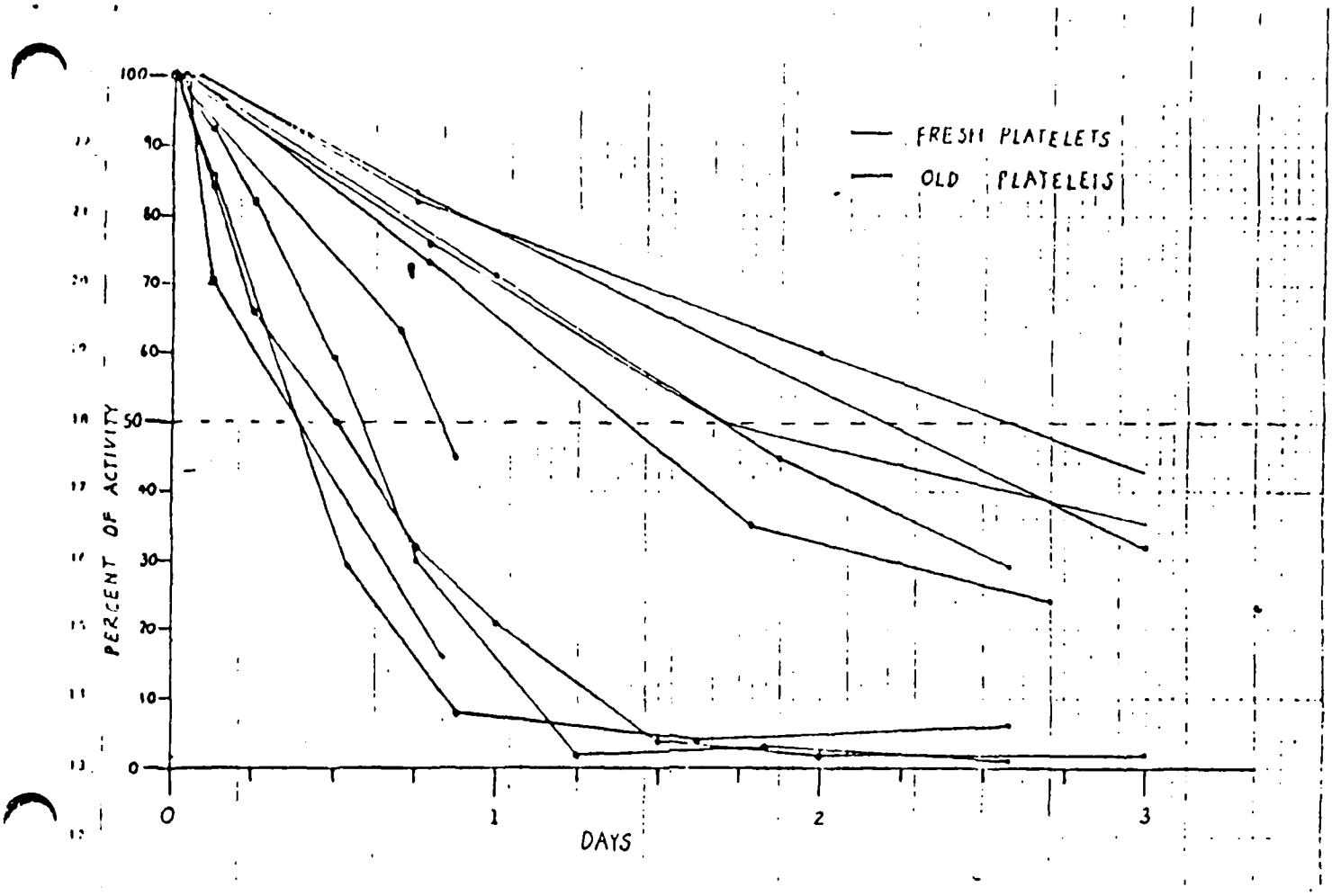
Debris weights and screen filtration pressures (SFP) are done in a manner previously described. Control samples are run repeatedly throughout the procedure. SFP is reported in mmHg/cc since most control samples are not able to pass an entire 10 cc increment through the SFP apparatus. Filtered samples are reported in mg/cc as well as for the sake of comparison.

Fifteen cc of blood is drawn from the point immediately preceding the test filter and another 15 cc is drawn from blood that has just passed through each filter.

Values obtained for gravity flow experiments are summated for each filter and graphs constructed from mean values of all 2,000 cc of blood tested for each filter. The numbers of determinations at each point decrease as larger volumes are passed through the filter indicating some small variation in debris load or filter capacity even within the same brand of filter.

PLATELET SURVIVAL IN SHOCKED BABOONS





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 reliable 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 15±3 hours (n=5, $p < 0.01$), however, 50% of the platelets from 10 day old blood are still circulating 15 hours after transfusion.

Fig. 1

APPENDIX C

FILTER STUDY

CLINICAL TRIAL

1) Hypothesis: Massive transfusion of unfiltered stored blood will increase the risk of post traumatic pulmonary problems.

2) Background: As extensively outlined in Appendix B the precise clinical significance of stored blood microaggregate infusion remains in doubt. Few randomized clinical studies designed to address this problem have appeared. Virgilio, et al demonstrated no effect of filtration in altering pulmonary status after massive transfusion but utilized a less efficient microaggregate removing filter (Pall). We propose to use the above filters to perform a randomized study on the difference in pulmonary status with and without blood ultrafiltration in massively transfused patients and to compare the case of filter use and any impedence in resuscitation rate attendant on the filter use.

Parameters to be measured include (1) postoperative pulmonary status, (2) maximum infusion rate (when applicable), (3) number of units infused/filter, (4) time to initiate transfusion (when applicable), and (5) other noted problems with blood infusion.

3) Rationale and Relevance: The effect of massive microaggregate infusion on pulmonary function has not been thoroughly evaluated in humans nor compared with resuscitation with microaggregate free (filtered) blood. We believe a randomized clinical study will answer these problems.

4) Design: Two groups of patients will be studied:

a) A group of elective surgical patients in which massive transfusion (>3 units of whole blood) is anticipated (spinal fusion), total hip replacement, abdominal aortic resection, pelvic exenteration, cystectomy, total gastrectomy, esophagogastrectomy, G.I. bleeding requiring surgery).

b) Patients with multiple trauma, entering the emergency unit in which >3 units of blood is anticipated for resuscitation. Patients will be randomized from a previously prepared random numbers table assignment and either a Pall, Intersept, Bentley, Fenwal, Swank or standard transfusion filter is utilized.

Patients will have preoperative and postoperative pulmonary function studies as outlined. Each patient will have a multiple organ system summary data base prepared on entry and these parameters followed on a daily basis (attached).

Other parameters (items 2 to 5 under Background on previous page) will be determined by the study nurse present in the O.R.

5) Methods: Patients will be randomized as outlined above. Respiratory data and blood gases will be collected pre-transfusion and subsequently after surgery and at least twice daily for 4 days post injury and/or surgery. Specific respiratory blood gas data will be collected as outlined on the flow sheet in Appendix B. No attempt at stratification will be undertaken. Patients who recieve <3 units of blood will not be used in the study, although they will continue to be followed for 4 days.

After 150 patients (≈25/filter) have been studied the data will be analyzed by an independent investigator not connected with the study. If there is no statistical significance or if the variation is <5% in the incidence of pulmonary insufficiency, the study will be discontinued. Data will be compared on:

a) Mortality for PTPI.

b) Incidence of PTPI (defined as pO_2<60 mmHg, pCO_2>55 on room air or need for mechanical ventilation).

c) Lowest pO_2 on room air in first 72 hours after injury.

d) Comparison of parameters of respiratory function, shunt and ventilation will also be undertaken but will not constitute a portion of the definition of PTPI for purposes of this study.

e) Filter flow rates.

f) Number of transfusions/filter.

g) Primary volume and time.

h) General assessment by administering physician.

i) Cost per transfusion and per patient.

BLOOD FILTER STUDY

DIAGNOSIS:

SURGICAL PROCEDURE:

complications:

DATE									
	PRE-OP	O.R.	P.O.#1	P.O.#2	P.O.#3	P.O.#4	P.O.#5	P.O.#6	P.O.7
STATUS									
EKG									
Chest x-ray									
FLUID BALANCE — UNITS BLOOD									
FLUID BALANCE — I+O									
FLUID BALANCE — DAILY WEIGHT									
HEMODYNAMICS — PULSE									
HEMODYNAMICS — BP									
HEMODYNAMICS — MPP									
HEMODYNAMICS — CVP									
HEMODYNAMICS — PWP									
HEMODYNAMICS — CO									

DATE									
	PRE-OP	O.R.	P.O.#1	P.O.#2	P.O.#3	P.O.#4	P.O.#5	P.O.#6	P.O.#7
assessment HEART									
assessment LUNGS									
RESPIRATIONS									
arterial blood gas pH									
arterial blood gas pO_2									
arterial blood gas pCO_2									
arterial blood gas Sat									
arterial blood gas B.E.									
arterial blood gas HCO_3									
venous blood gas pH									
venous blood gas pO2									
venous blood gas pCO2									
venous blood gas Sat									
venous blood gas B.E.									
venous blood gas HCO3									
A-aDO_2									
%shunt									
Vd/Vt									
VO_2									
PVR									
FiO_2									
ventilator (MA-1, MON, BIRD)									
IMV/PEEP/C-PAP									
IPPB									

DATE										
		PRE-OP	O.R.	P.O.#1	P.O.#2	P.O.#3	P.O.#4	P.O.#5	P.O.#6	P.O.#7
COAGULATION	Hgb/Hct									
	Fibrinogen									
	PTT									
	Platelet Ct.									
	Bleeding time									
SEPSIS	Temp									
	WBC									
	Cultures									
'EDS										
:LINICAL										

'ISCHARGE SUMMARY:

DATE	UNIT BLOOD	Needle gauge	Urgent	Non setting	Set up time	Gravity flow	Pressure pump	Infusion time	Age of blood	Misc.

Filter #

Anesthesiologist:

APPENDIX D

Progress Report

The raw data for filter infusion rates is contained in Table I. This shows the number of filters randomized for each group to date. This includes only those infused under pressure. Data on infusion rates for gravity flow are meaningless. These patients all received blood under conditions of urgent need. Table II shows the average number of units infused per filter. Fig. 1 presents the data on first unit transfusions from Table I graphically. None of these differences are statistically significant at this point. Bar graphs (Fig. 2) illustrate infusion rates for subsequent units of blood when more than one is infused. Again, the numbers are too small for statistical comparison.

Infusion rates for packed cells infused under pressure are contained in Table III. Litwin has shown that most of the microaggregate material comes down with the cells. Again, the numbers are small but the data suggest no significant difference. Table IV shows mean infusion rates for each filter for each unit of packed cells.

Problems with using the filter are summarized in Table V-A. The only filter free of problems was the standard infusion filter. The most serious complaint, inability to plug the filter into the bag, was noted only with the Swank filter. Design complaints were frequent with the Johnson & Johnson and difficulty priming the filter and air in the line were noted with variable frequency in all other filters except the Swank and standard. Subjective evaluation by anesthesiologists (Fig. 3) including perceived ease of handling, setting up, priming and flow rates favor the Pall. Objective measurement of setup time (time from beginning to remove filter from the pack to actual blood leaving the end of the line) confirmed this impression (Fig. 4).

The data are too preliminary to draw conclusions at this point except to point out the necessity of evaluating all phases of filter utilization in considering filter efficiency than just flow rate and filtering capacity. The time to set up the filter and concomitant intercurrent difficulties can produce greater delay in blood delivery than the technical differences in pore size and filter capacity. From the present data, it appears that another year's study will provide us the information we need.

BLOOD FILTER STUDY

Clinical Study:

Evaluation of O.R. Flow Sheets

1) Total number of patients contacted = 86

2) Total number of patients meeting criteria for study = 64
(=i.e., >3 units of blood given or >2 units if under 100 lbs.)

Breakdown of Patients in Study

Description of Type of Flow	Unit of Blood	AGE OF BLOOD (in days) 1-11	12-21	No Date (≤21)	Total # of Patients
Pressure Flow	1st	14	8	7	29
Gravity Flow	1st	10	4	1	15
Gravity → Pressure	1st	5	7	0	12
Pressure → Gravity	1st	1	0	0	1
Incomplete Data	1st	-	-	-	7

Types of Filters	How Often Used
1) Fenwal	12
2) Swank	5
3) Johnson & Johnson	7
4) Bentley	12
5) Pall	10
6) Standard	11

Breakdown of When Filters Were Used

Types of Filters	PRESSURE FLOW - 1st UNIT 1-11 d	12-21 d	No Date	GRAVITY FLOW - 1st UNIT 1-11 d	12-21 d	No Date	GRAVITY→PRESSURE FLOW-1st 1-11 d	12-21 d	No Date
Fenwal	3	2	1	3	0	0	1	2	0
Swank	0	0	1	3	0	0	0	1	0
Johnson & Johnson	2	0	0	3	0	0	2	0	0
Bentley	4	1	2	1	2	0	1	1	0
Pall	4	1	1	0	0	0	1 (1)*	2	0
Standard	1	4		0	2	1	0	1	0

* Pressure → Gravity 1st Unit

Table

Infusion Rates - Pressure Flow, Whole Blood

Filter	Infusion Rates (in minutes) Unit 1	Unit 2	Unit 3	Unit 4	Unit 5	Total Units Infused	Overall Mean Infusion Rate
Fenwal	7	8	32	18		4	
"	18					2	
"	10	13	20			3	14.6 min/unit
"	10					4	
"	13	13				5	
"	13					1	
"	12	18				2	
Swank	15	15				2	
"	8					2	13.0 min/unit
"	15					2	
"	13	18	13			4	
"	7					2	
J & J	10	14				3	
"	20	50	33			3	23.4 min/unit
"	24					1	
"	24					2	
"	16	20				2	
Bentley	14	35				3	
"	30	21				3	
"	11	30				2	16.8 min/unit
"	10	10				2	
"	13					5	
"	8	10	16			3	
"	25	10	9			3	
Pall	36			20		6	
"	5	10		20		10	
"	7	8		7		4	
"	12	21	13			5	
"	25	28	14			3	15.9 min/unit
"	16					1	
"	25					4	
"	15	12	15	10		4	
"	26	9				2	
"	20	24				2	
"	14	12				2	
"	17	17	14	13		4	
"	11	15				2	
"	13					2	
Standard	24	20	25	26	21	5	
"	20	20	20			4	19.8 min/unit
"	6	14	11			3	
"	20	30				9	
	20					1	

Table II

Mean Values (in Minutes) of Whole Blood
Infused by Pressure Flow

	Unit 1		Unit 2		Unit 3		Unit 4		Unit 5		Average No. of Units Per Filter	
Fenwal	11.857	n= 7	13.0	n= 4	26.0	n=2	18.0	n=1			3.0	n= 7
Swank	11.6	n= 5	16.5	n= 2	13.0	n=1					2.4	n= 5
J & J	18.8	n= 5	28.0	n= 3	33.0	n=1					2.2	n= 5
Bentley	15.857	n= 7	19.333	n= 6	12.5	n=2					3.0	n= 7
Pall	17.826	n=14	15.6	n=10	14	n=4	14.0	n=5			3.643	n=14
Standard	18.0	n= 5	21.0	n= 4	18.667	n=3	26.0	n=1	21	n=1	4.4	n= 5

TABLE III

Infusion Rates (Pressure Flow, Packed Cells)

	Filter	Infusion Rates (In Minutes) Unit 1	Unit 2	Unit 3	Unit 4	Unit 5	Total Units Infused
1.	Fenwal	15	18				3
2.	Fenwal	35	30				2
3.	Fenwal	10	18	8	17	25	6
4.	Fenwal	45	17				3
1.	Swank	15					1
2.	Swank	20					2
3.	Swank	50					3
1.	J & J	15	13				2
2.	J & J	18	50				2
3.	J & J	7	10	11	10		4
4.	J & J	7	10				2
5.	J & J	5					1
6.	J & J	20					3
1.	Bentley	5	7	12			4
2.	Bentley	12	13	10	13		4
3.	Bentley	9	11				3
4.	Bentley	25		30			6
5.	Bentley	14	25				3
1.	Pall	23	20				2
2.	Pall	13	17				2
3.	Pall	10	25	17			4
1.	Standard	19	17				3
2.	Standard	15	10				4
3.	Standard	15	19	25			3
4.	Standard	30	30				3
5.	Standard	13	15				5

TABLE IV

Mean Values (in Minutes) of Packed Cells
Infused by Pressure Flow

	Unit 1		Unit 2		Unit 3		Unit 4		Unit 5		Average No. of Units Per Filter	
Fenwal	26.25	n=4	20.75	n=4	8.0	n=1	17.0	n=1	25.0	n=1	3.5	n=4
Swank	28.333	n=3									2.0	n=3
J & J	12.0	n=6	20.75	n=4	11.0	n=1	10.0	n=1			2.333	n=6
Bentley	13.0	n=5	14.0	n=4		n=3	13.0	n=1			4.0	n=5
Pall	15.333	n=3	20.667	n=3	17.0	n=1					2.667	n=3
Standard	18.4	n=5	18.2	n=5	25.0	n=1					3.6	n=5

TABLE V-A

Comments of Anesthesiologist Plus Observed Problems

	Filter	Refused to Use	Difficult to Prime	Air in Lines	Complaints About Design	Could Not Plug Into Bag
1.	Fenwal	1	4	8	4	0
2.	Swank	0	1	0	0	5
3.	J & J	0	4	8	1	0
4.	Bentley	0	1	1	0	0
5.	Pall	0	3	3	0	0
6.	Standard	0	0	0	0	0

TABLE V-B

Anesthesiologist Evaluation of Flow Rate

	Filter	Poor	Adequate	Excellent
1.	Fenwal	2	13	4
2.	Swank	2	3	8
3.	J & J	1	7	6
4.	Bentley	3	7	11
5.	Pall	1	7	13
6.	Standard	1	8	5

Figure 1

Infusion Rates of P[illegible]ssure Flow,
Whole Blood (Uni #1) SEM

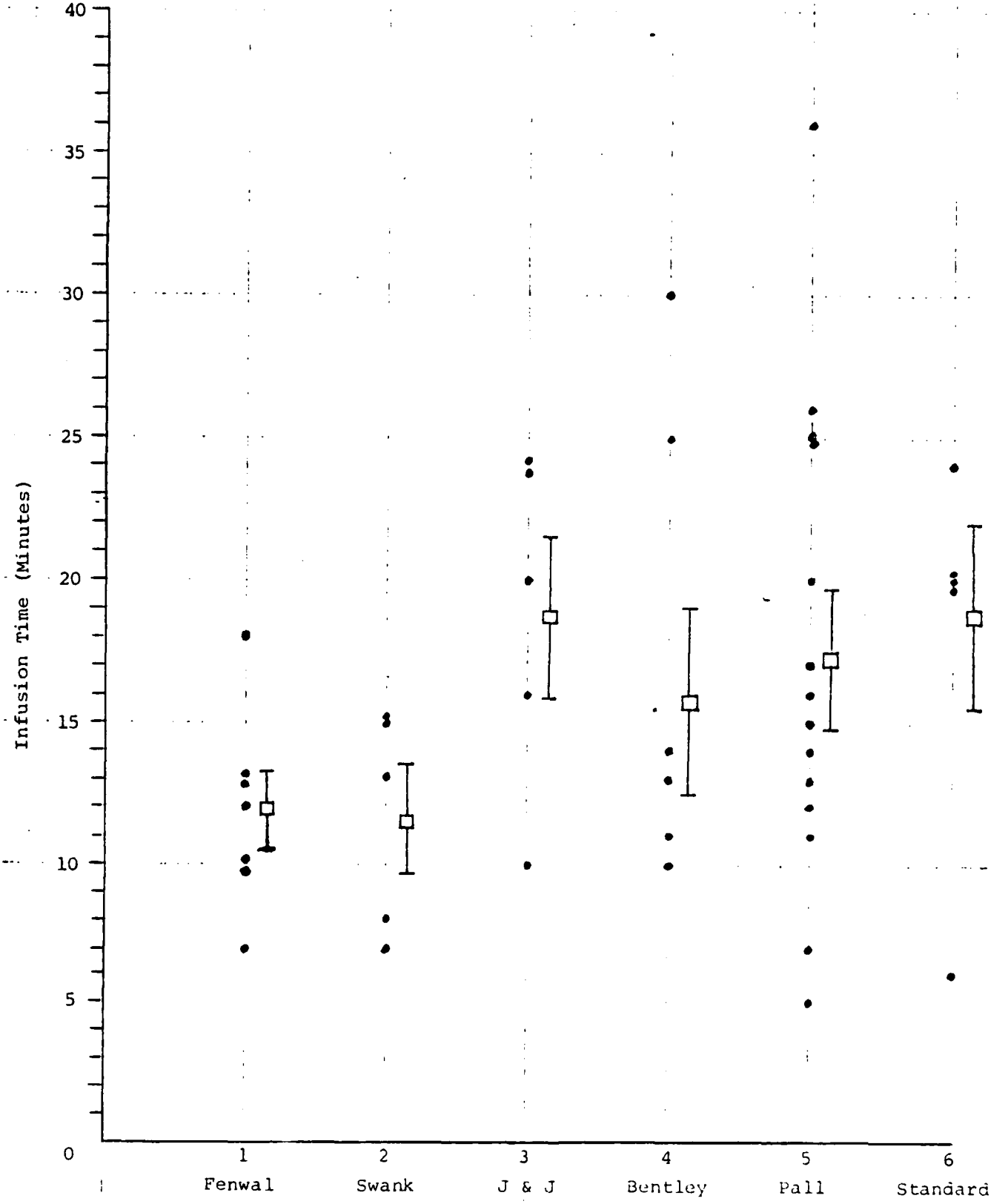


Figure 2

Mean Values in Minutes of Whole Blood Infused By Pressure Flow

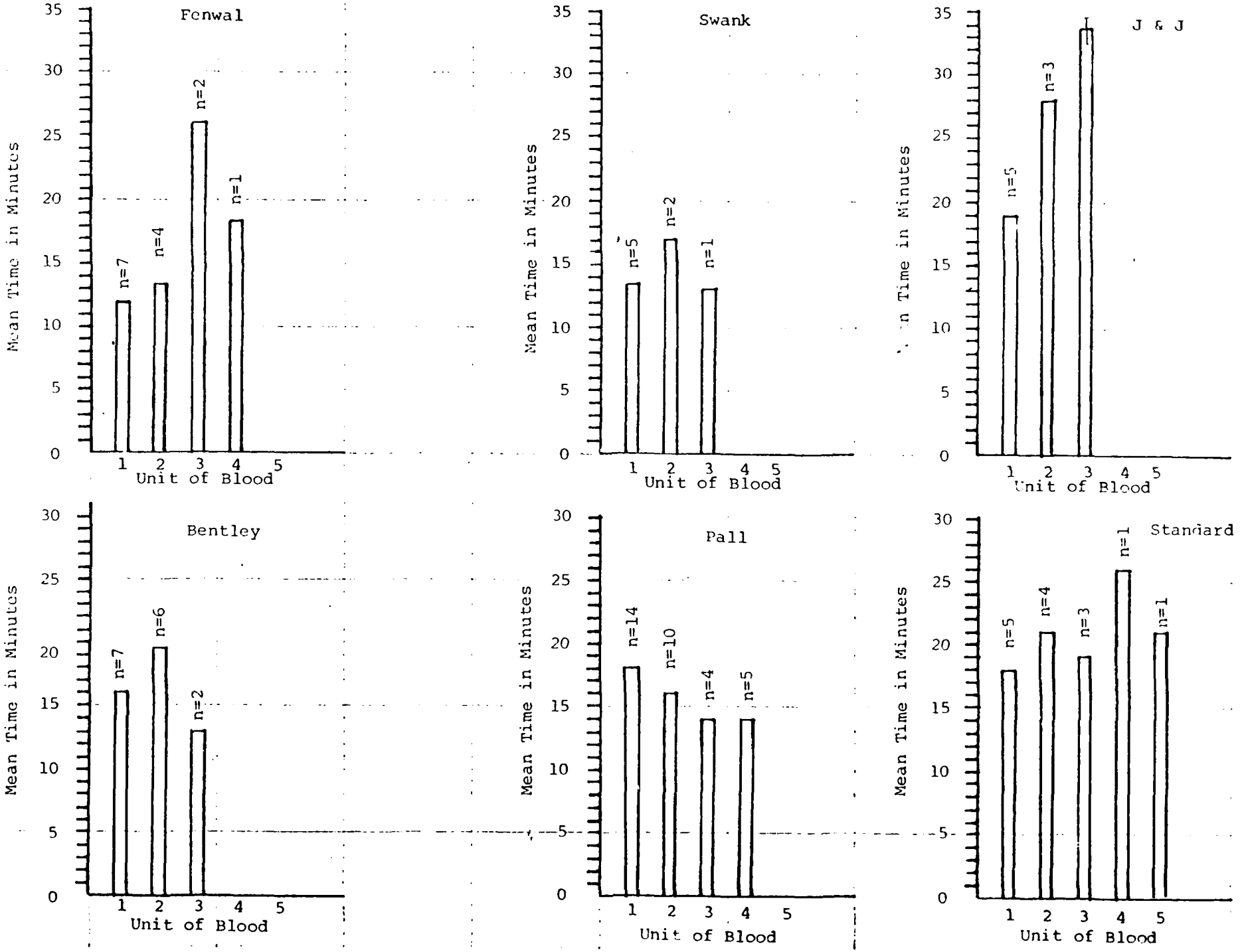


Figure 3 SUBJECTIVE EVALUATION OF FLOW RATE BY ANESTHESIOLOGIST

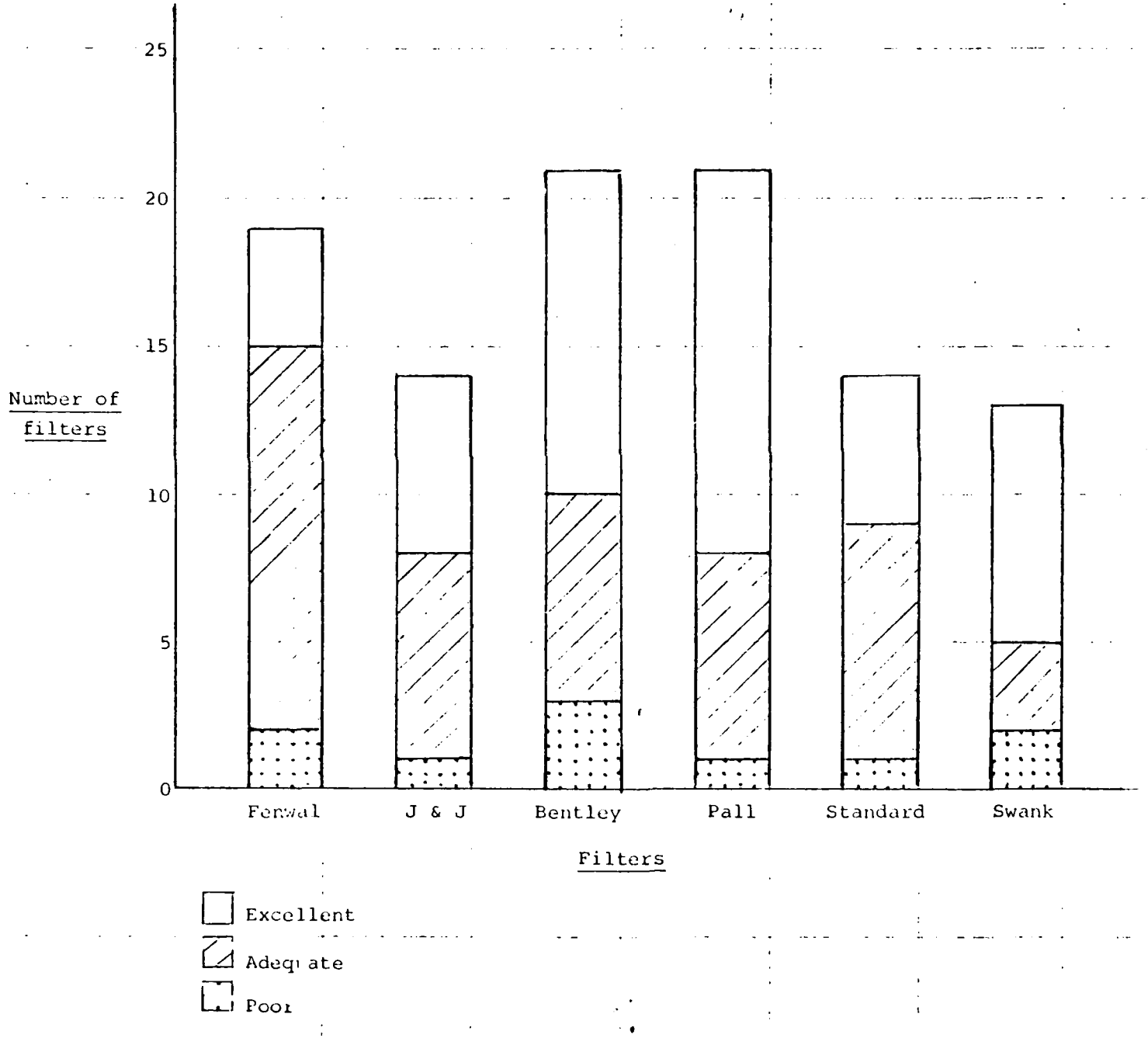
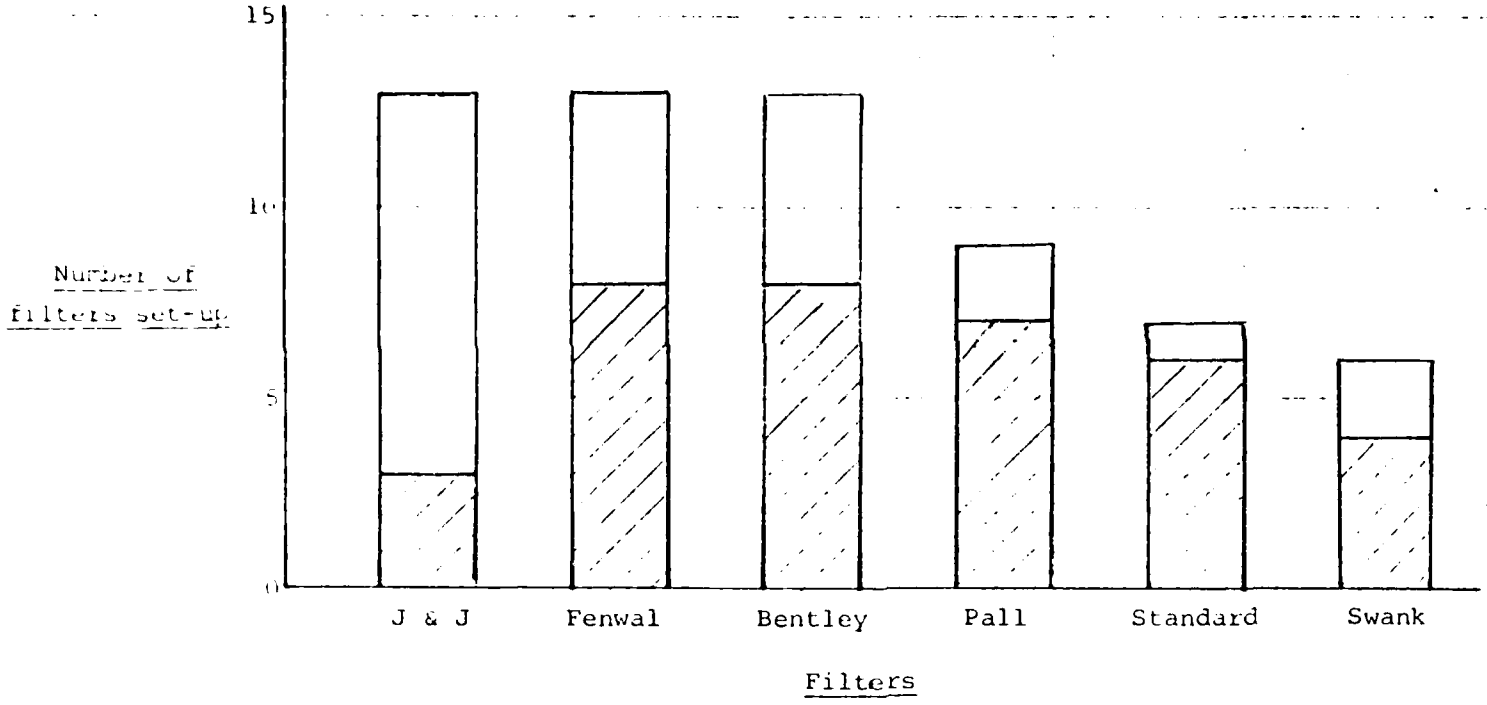


Figure 4

SET-UP TIME



APPENDIX E

PULMONARY PLATELET TRAPPING AFTER SEVERE THORACIC TRAUMA AND SHOCK

By

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Pulmonary insufficiency after shock and trauma was first described in World War II as traumatic wet lung.[6] It occurred in patients with thoracic injury, appeared within 24 to 48 hours and usually progressed rapidly to death or cleared in less than a week. This has subsequently been recognized as due to pulmonary contusion.

During the Korean War, and subsequently in civilian experience and through the War in Vietnam, pulmonary insufficiency was noted to occur in seriously injured patients without thoracic trauma and the term "shock lung" was coined.[27] Onset was usually beyond 2 to 3 days and frequently was progressive to death at a week to 10 days. It is likely that the problem had not been recognized previously because such critically injured patients would frequently not survive long enough to develop the problem. The advent of improved evacuation systems and more rapid access to expert treatment allowed the problem to surface in the Korean War. This proved to be a multifactorial problem and with understanding of the multiple etiologies as well as the development of improved methods of pulmonary care the problem, though still occurring is rarely fatal.

Now, with longer survival of these critically ill patients a third phase of pulmonary insufficiency has emerged usually beginning beyond a week after injury and frequently persisting until death, although pulmonary insufficiency per se is usually not the primary cause of death. Pulmonary insufficiency in this setting is nearly always associated with severe septic complications of injury or surgery.[8,22,29,30]

The microscopic pathology of pulmonary insufficiency is nearly the same for all three phases. Histology shows focal or diffuse microatelectasis, congestion and dilatation of lung capillaries, alveolar hemorrhage, peribronchial and peri-capillary interstitial edema, alveolar edema and hypertrophy of the alveolar lining cells with widening of the interalveolar septa, platelet and red cell thrombi.[2,4,11,16,24,31] The physiological and hemodynamic changes in shocked

animals have been investigated.

After moderate to severe blunt chest trauma, often early and progressive signs of respiratory failure are present.[1,7] Blood gas determinations reveal marked decrease in PaO_2 (<50 mmHg) while the patient is breathing 100% oxygen, a decrease in pH and an increase in $PaCO_2$ (>55 mmHg). The clear increase in the alveolar - arterial oxygen gradient (>450 mmHg) reflects the serious degree of injury.[10,26] Though trauma impact may have been unilateral, roentgenographic alterations in patients who subsequently die are present in both lungs.[24]

Material and Method

Thirty rabbits with a body weight of 3-5 kg were initially anesthetized with a mixture of ketamine/hydrochloride (10 mg/kg) and topical xylocaine in the chest wall (<2 cc). Anesthesia was maintained with sodium barbital intravenously as necessary. The animals were breathed room air spontaneously.

Both femoral arteries were cannulated for pressure monitoring and blood withdrawal. One venous line in a femoral vein served for drug and intravenous fluid administration. Prior to the experiment 80 cc of blood were withdrawn from a donor rabbit. After centrifugation, the platelets were separated and tagged with 0.2 mCi ^{51}Cr as previously described.[23] The results were expressed as percent of the radioactivity of the platelet rich suspension injected.

[illegible] groups of animals were studied. Group I: Eight control animals. After cannulation, arterial blood was withdrawn for measuring blood gases. Then the suspension with radioactive labeled platelets was injected. Blood samples for measuring radioactivity were withdrawn initially every 5 minutes post injection and subsequently every hour.

After sacrifice with hypertonic potassium chloride, the lungs were flushed with saline via a catheter in the pulmonary artery, quickly excised and each half divided into three specimens of about equal size. These specimens were placed

into glass test tubes, weighed and put into a shielded well-type scintillation counter with a sodium crystal for measuring radioactivity. The results were expressed as percent of the radioactivity injected with 1 ml of platelet rich suspension (approximately 14 ml). The spleen and liver were also excised and radioactivity in these organs determined in a similar manner.

Group II: Five animals received severe blunt chest trauma from a 2 kg brick dropped on the right chest from a height of 1.5 m. Arterial pressure always initially fell to approximately 70% of baseline value. It recovered spontaneously within about 10 minutes at which time blood gases were determined and the radioactive platelet rich suspension injected. After 4 hours the animals were sacrificed and radioactivity in the lungs measured as described above.

Group III: Six rabbits were subjected to hemorrhagic shock. Blood was withdrawn from an arterial line until a blood pressure of 40 mmHg was reached. This pressure was maintained for 90 minutes by adding or withdrawing blood. Blood gases were determined every 30 minutes and metabolic acidosis was treated with sodium bicarbonate. After 90 minutes the animals were resuscitated by reinfusing shed blood. Care was taken to reinfuse the blood over a 30 to 45 minute interval. After resuscitation, radioactive tagged platelets were injected and the animals followed for 4 hours as described above.

Group IV: Eleven animals were first traumatized by dropping the 2 kg weight on the right chest and, after recovery, were subjected to additional shock as described above under Group III. After resuscitation homologous radioactive platelet rich suspension was injected and the animals followed up 4 hours as aforementioned.

In all experiments arterial blood gases were determined every 30 minutes. After injection of the platelet rich suspension, hematocrit, blood radioactivity per gram and blood platelets were counted every hour.

By summating the cpm of the different lung specimens for each lung, radioactivity could be determined for each half of a lung separately as well as for the total lung. Student's t-test was used for calculating significant differences between the individual groups.

Results

Following the trauma a transient arterial pressure decrease in the range of 20 to 40 mmHg was observed. AP always returned to normal or near normal values within 5 to 10 minutes. Resuscitation after hemorrhage required only shed blood. Baseline arterail pressure in all shock animals was reached after approximately half of the volume initially withdrawn had been reinfused. In no animal were additional saline infusions necessary to maintain baseline hemodynamics.

The mean blood volume removed from the animals were:

Group I: 0

Group II: 2

Group III: 78 cc (24 cc/kg)

Group IV: 68 cc (21 cc/kg).

As can be seen from Table I, platelet trapping in control, trauma or shock group (Groups I-III) did not differ significantly for the right, left or total lung. However, in Group IV (trauma plus shock) a significantly higher platelet trapping was observed in the right lung (59 ± 13%), the left lung (44 ± 11%) and the total lung (103 ± 23%) compared to controls. Although in Groups I to III all animals survived the 4-hour study period, 7 out of 11 animals died in the shock and trauma group. Splitting this group into survivors (N=4) and non-survivors (N=7) (Table II) the survivors had a normal pulmonary platelet trapping, whereas the non-survivors had significant platelet trapping increase in both lungs ($p<0.05$).

The temporal course of pO_2 and pCO_2 depicted in Fig. 1 shows pCO_2 slowly increasing and pO_2 decreasing in Group IV animals. The decline in pO_2 is significantly less ($p<0.05$) than control values at 2.5 hours. Too few animals survived beyond 2.5 hours to allow statistical comparison.

Serial platelet counts in the four groups of animals are depicted in Fig. 2. Although a decline in platelet count is apparent in Groups II and III animals, these changes were not significant. Group IV animals showed a significant decrease in platelet count at 3 and 4 hours, however, to just over 50% of baseline values ($p<0.025$).

Platelet trapping in the spleen did not differ significantly between the four groups of animals (Table I). However, dividing the Group IV animals into survivors and non-survivors, the lowest radioactivity and therefore the least platelet trapping is noted in the latter animals (153 ± 20) and the difference from survivors (232 ± 54) is significant ($p<0.025$) (Table II).

Discussion

The combination of direct thoracic trauma and hemorrhagic shock in the present model was associated with significantly greater reduction in platelet count, more pulmonary platelet trapping and higher mortality than in animals subjected to either trauma or shock alone. This is at variation with a similar model described by Hopkinson, et. al.[15] which resulted in a 100% mortality after experimental thoracic trauma in dogs. These authors related a reduced mortality and lower incidence of pulmonary lesions in a second group of traumatized animals to an increased lung inflation pressure which they had applied during the blow. Based on the results of their studies we would have expected all our Group II animals to have died since they were not intubated and were breathing spontaneously during trauma impact. The mode of trauma in both studies is comparable, although the animals used are different and the actual forces delivered to the chest wall and

intrathoracic structures may have been quite different as well. The latter unquantified variables are probably responsible for the differences in survival in the two studies.

In all animals in the present study which died after both trauma and shock a significantly higher concentration of radioactive labeled platelets was noted to be symmetrically distributed in the lungs. Other authors have described a similar phenomenon of platelet aggregation and increased pulmonary trapping of ^{51}Cr labeled platelets after soft tissue trauma.[19,21] Although the mode of trauma was different from the direct chest injury applied in this study, the final result was similar, showing increased platelet trapping in both lungs. If one assumes that an element of hypovolemic shock results from the soft tissue trauma model as originally suggested by Blalock, then their results may be comparable to our Group IV animals.[3]

This again suggests that distant injury may produce pulmonary effects similar to that seen with direct thoracic trauma. Peer and Schwartz assumed that "injury to the hind limb presumably damages vascular endothelium, thereby exposing and disrupting collagen. Platelet aggregates are formed and embolize to be subsequently screened by the pulmonary vasculature."[21] They hypothesized that in the area of injury and consequent vascular stasis and hypoxemia, platelets adhere to newly exposed collagen and release vasoactive substances like Serotonin, Histamine and Thrombaxane A promoting further platelet aggregation. In the present study, since the injury is in the lung itself, embolization cannot be the source of the observed platelet trapping.

Certainly, the direct injury will produce a hematoma with capillary damage and bleeding into pulmonary tissue. Platelets, red cells and leucocytes adhere to the exposed collagen under the endothelium of damaged vessels, forming micro-thrombi. The release of vasoactive amines again induces platelet aggregation and this results in local enlargement of the pulmonary lesion.

However, the platelet trapping observed in the present study was symmetrically distributed in both lungs, whereas the site of direct injury was unilateral. It appears likely that the major source of platelet trapping in the present model is similar to that noted with distant injury and shock, that is that systemic intravascular platelet aggregation is induced by some consequence of shock and massive injury.

Circulating platelets may be altered by an increased level of vasoactive amines and ADP and then become trapped in the pulmonary microcirculation which itself may have been altered by systemically transported vasoactive substances and ischemic effects of shock. A number of recent studies dealing with the influence of hemorrhagic shock on pulmonary function appear to support this hypothesis. Following hemorrhagic shock in dogs electronmicroscopic studies showed pulmonary capillaries to be filled with degenerating platelets, leucocytes and erythrocytes.[5,9,12,14,17,18]

As further data has accumulated on pulmonary microemboli or microthrombi, it has become evident, just as in the present study, that the uniform production of this pathological event requires both shock and trauma. This suggests that shock alone may render circulating platelets susceptible to aggregation but initiation of widespread intravascular aggregation requires an inciting event such as might occur with a major focal injury. Although it has never beer clearly demonstrated that shock and trauma produce disseminated intravascular coagulation, local intravascular coagulation at the site of injury is the rule and occurs in proportion to the magnitude of injury.[13,28] Platelet aggregates and even microclots from sites of distant injury are filtered in the pulmonary circulation and vasoactive substances released further inducing platelet microthrombi. Cafferata and others have also demonstrated a decrease in coagulation factors in shock and trauma suggesting some consumption by intravascular coagulation.[2,7,25]

It appears that with shock alone such platelet aggregation and consequent intravascular coagulation as may occur is not of sufficient magnitude to damage the pulmonary bed. One can speculate that in animals exposed to shock alone, the fibrinolytic and reticuloendothelial clearing capacity of the organism may be sufficient to deal with resulting microthrombi as soon as normal circulation is reinstituted. However, if the reticuloendothelial system is blocked or "overloaded" by the sequelae of both trauma and shock, the stimulus to both platelet aggregation and intravascular coagulation may exceed the capacity of these clearing mechanisms to prevent serious pulmonary impairment.

It is so noteworthy that in the present study platelet counts do decrease substantially in the non-survivors of Group IV (Fig. 2) and that splenic radioactivity in these animals (153 ± 20) was lower than in the other groups (247 ± 34) (Tables I and II). These findings suggest that platelets are being consumed in large numbers including utilization of the marginal platelet pool of the spleen.

Summary

The influence of shock and/or thoracic trauma on pulmonary platelet trapping was assessed in four groups of rabbits (total N=30) by injection of ^{51}Cr tagged platelets. Group I: control, Group II: trauma, Group III: hemorrhagic shock and Group IV: trauma and shock. Platelet trapping in Groups I, II and III did not differ significantly for the right, left or total lung. In Group IV significantly higher platelet trapping was observed in the right lung (59 ± 13%), the left lung (44 ± 11%) and the total lung (103 ± 23%) compared to controls. All animals in Groups I to III survived the 4-hour period of observation, whereas 7 out of 11 animals died in Group IV. The 4 survivors of these 11 animals had normal pulmonary platelet trapping, whereas the dead animals had a highly significant platelet trapping increase in either part of their lungs.

It is concluded that neither direct thoracic trauma nor shock alone induces lethal pulmonary dysfunction, however, after trauma plus shock massive pulmonary platelet trapping occurs contributing to the animal's death. Since embolization to the lungs is very unlikely it is probable that both the pulmonary microcirculation and circulating platelets are altered by a substance or substances in the blood in such a way as to induce massive pulmonary trapping.

It is hypothesized that the systemic fibrinolytic capacity and reticuloendothelial clearing mechanism are overloaded by the combination of shock and trauma with resulting overwhelming microembolization and microthrombosis of the pulmonary circulation.

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Legend

Figure 1 Temporal course of blood gases control and shock and trauma group. Blood gas curves for the shock and trauma groups are not shown since there is no significant difference to controls. No standard deviation for the last two points of the trauma and shock group since only two animals survived so far. Other points: mean values with standard deviation.

Figure 2 Temporal course of blood platelet count for the four groups (I=controls, II=trauma, III=shock, IV=trauma and shock). Control platelet count of blood before the experimental set to 100% and all other values related to this. Group IV only animals that died before the 4-hour period.

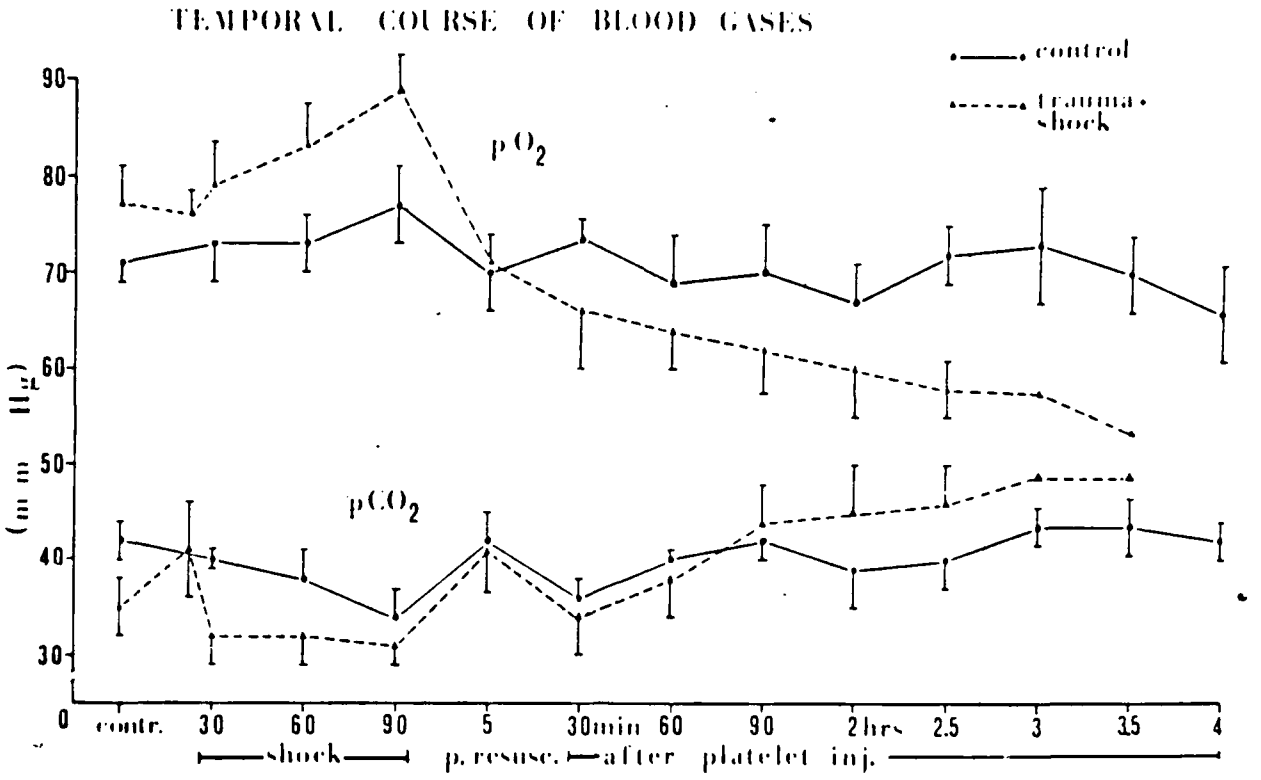
TEMPORAL COURSE OF BLOOD GASES
control
trauma-shock
pO_2
pCO_2
90
80
70
60
50
40
30
0
contr.
30
60
90
5
30min
60
90
2hrs
2.5
3
3.5
4
shock
p. resusc.
after platelet inj.

Fig. 1

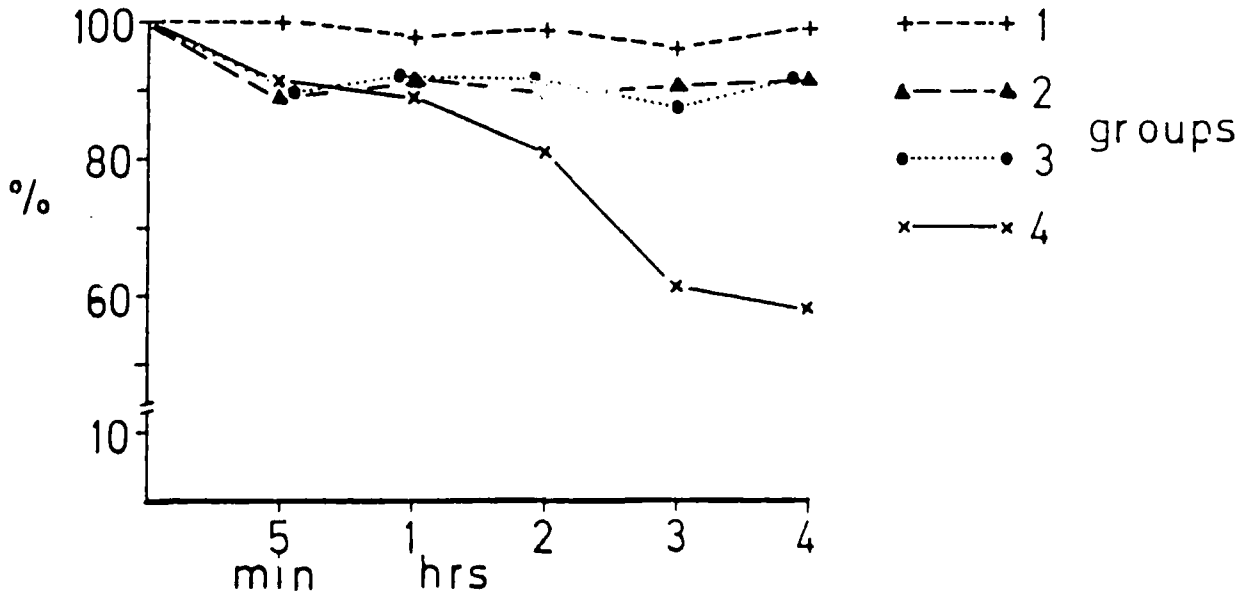
100
80
60
10
%
5
min
1
hrs
2
3
4
1
2
3
4
groups

Fig. 2

SPLENIC AND PULMONARY PLATELET TRAPPING
(% of injected platelet radioactivity)

	Control	Trauma	Shock	Trauma and Shock
Lung Total	37 ± 4	48 ± 12	42 ± 7	103 ± 23
Lung Right	17 ± 4	26 ± 8	23 ± 4	59 ± 13
Lung Left	18 ± 3	22 ± 5	18 ± 3	44 ± 11
Spleen	247 ± 34	191 ± 35	237 ± 81	184 ± 59

Table I Splenic and pulmonary platelet trapping. Values in percent of the radioactivity injected 1 ml of tagged platelet rich suspension. Mean values with standard deviation.

SPLENIC AND PULMONARY PLATELET TRAPPING
Trauma + Shock Group
(% of injected platelet radioacitivity)

	Combined (N=11)	Died (N=7)	Survivors (N=4)
Lung Tota	106 ± 23	129 ± 19	34 ± 8
Lung Right	59 ± 13	82 ± 15	20 ± 9
Lung Left	44 ± 11	68 ± 17	16 ± 7
Spleen	184 ± 59	153 ± 20	232 ± 54

Table II Splenic and pulmonary platelet trapping. Group IV: Trauma + Shock. Values in percent of radioactivity injected with 1 ml of tagged platelet rich suspension. Mean values with standard deviation. Group IV divided into animals which died before the 4-hour period and animals which survived the 4 hours.

APPENDIX F

Name	FAP (mmHg)				LAP (mmHg)			
	Pre-Shock	Shock	1 hour $\bar{p}$-resus.	6 hours $\bar{p}$-resus.	Pre-Shock	Shock	1 hour p-resus.	6 hours p-resus.
**Welsh Rabbit (Nipride)	64	44	60	--	3	7	2	--
Thumper (Nipride)	75	--	--	--	--	--	--	--
**Easter Bunny (Nipride)	66	47	68	95	3	1	2.5	3
**Fluff	88	40	65	--	2	1.2	2	--
**Mad Hatter	68	--	--	--	<0	--	--	--
**March Hare	79	45	73	--	7	1	5	--
Cottontail	74	42	88	65	1.5	0	0.5	1.5
**Flopsy	--	--	--	--	--	--	--	--
Benjamin Bunny	81	50	80	77	2	0	1	2.5
Hare Brain	80	50	67	60	4	2	3	4
Rabbit Punch	70	36	76	69	3.5	4.5	3.5	3
Fluffy	84	32	80	68	3	<0	2	2
**Brer Rabbit	87	48	78	--	3	<0	2	--
**Bongo the Bunny	--	--	--	--	--	--	--	--
**Snowfoot	--	--	--	--	--	--	--	--
**Dan-de-lion	72	37	--	--	3.5	0	--	--

** Death before end of experiment.

Name	Lactic Acid (mEq/L.)				Flow Probe	Complications
	Pre-Shock	Shock	1 hour $\bar{p}$-resus.	6 hours $\bar{p}$-resus.		
**Welsh Rabbit (Nipride)	18.0	18.9	13.2	--	Yes	Acidosis: dead space in respirator. Sensitivity to pentothal.
Thumper (Nipride)	4.4	8.3	6.5	8.9	No*	Mechanical failure.
**Easter Bunny (Nipride)	5.2	7.1	5.6	4.7	No*	Death during post-resuscitation: unknown cause.
**Fluff	--	16.8	14.8	--	No*	Sensitivity to pentothal 4 hr. into post-resuscitatic
**Mad Hatter	4.2	--	--	--	No*	Death during shock.
**March Hare	4.4	10.8	8.4	--	Yes	Death by misadventure.
Cottontail	10.1	12.7	11.5	9.8	No*	Sensitive to respirator.
**Flopsy	--	--	--	--	--	Would not tolerate mechanical respiration: death .
Benjamin Bunny	4.2	16.3	14.4	7.8	No*	
Hare Brain	12.1	12.3	12.2	9.3	No*	
Rabbit Punch	5.7	6.6	6.6	7.3	No*	
Fluffy	4.0	15.2	16.5	8.4	No*	
**Brer Rabbit	6.2	14.0	12.3	--	Yes	Death after resuscitation with donor blood.
**Bongo the Bunny	---	--	--	--	--	Death: respiratory failure.
**Snowfoot	--	--	--	--	--	Death from excessive blood loss.
**Dan-de-lion	4.3	7.8	--	--	Yes	Death after resuscitation with donor blood.

* Implantation of the flow probe was unfeasible.
** Death before end of experiment.

APPENDIX G

The following preliminary data relates to experiments on hemorrhagic shock in two groups of animals:

Control Group: Five animals put into shock (60 mmHg for one hour and 40 mmHg for an hour) and resuscitated with shed blood to baseline pressures, then maintained with maintenance (50 cc/hr) fluid - all shed blood was replaced.

Treatment Group: Two animals, shocked and resuscitated as above and then began on nitroprusside for an hour, reducing MAP to 80% of baseline.

As can be seen, with time control animals MAP fell whereas nitroprusside treated animals maintained their blood pressure with slight increase (Fig. 1). Cardiac output did not differ significantly in either group (Fig. 2). Control animals required all their shed blood for resuscitation and slightly more saline than nipride treated animals. Control animals experienced the greater reduction blood volume than nipride treated animals (Fig. 3). Organ flow studies, completed in four animals, showed persistent significant reduction in visceral organ flow at 18 hours. No data is yet complete for the two nipride animals (Fig. 4).

These preliminary results suggest that maldistribution of organ blood flow persists after successful resuscitation. The blood volume and blood pressure data suggests that nipride restores this rapidly to normal.

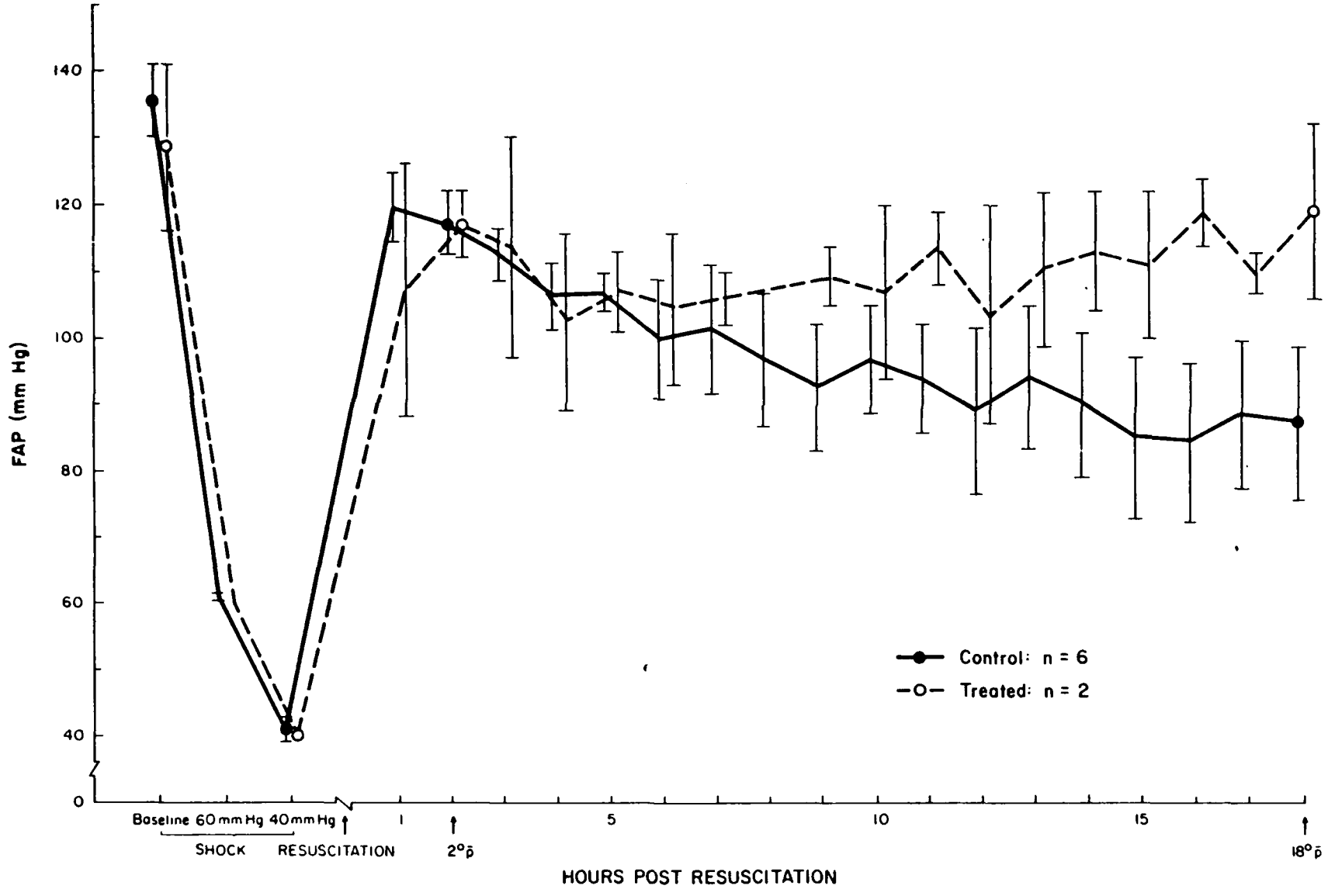

Fig. 1. Femoral Artery Pressure (mm Hg) ± S.E.M.

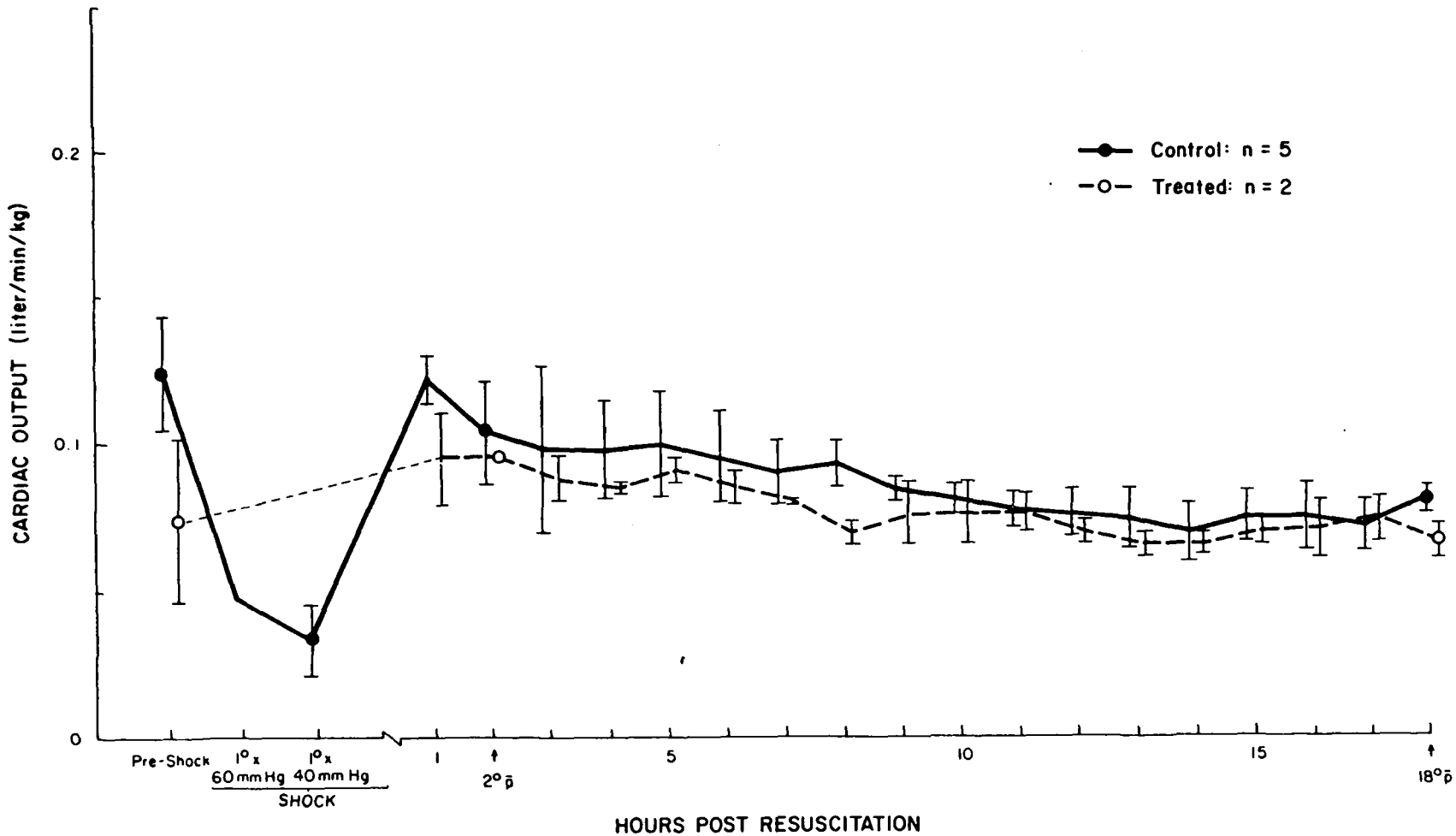

Fig. 2. Pulmonary Artery Flow (L./min./kg.) ± S.E.M.

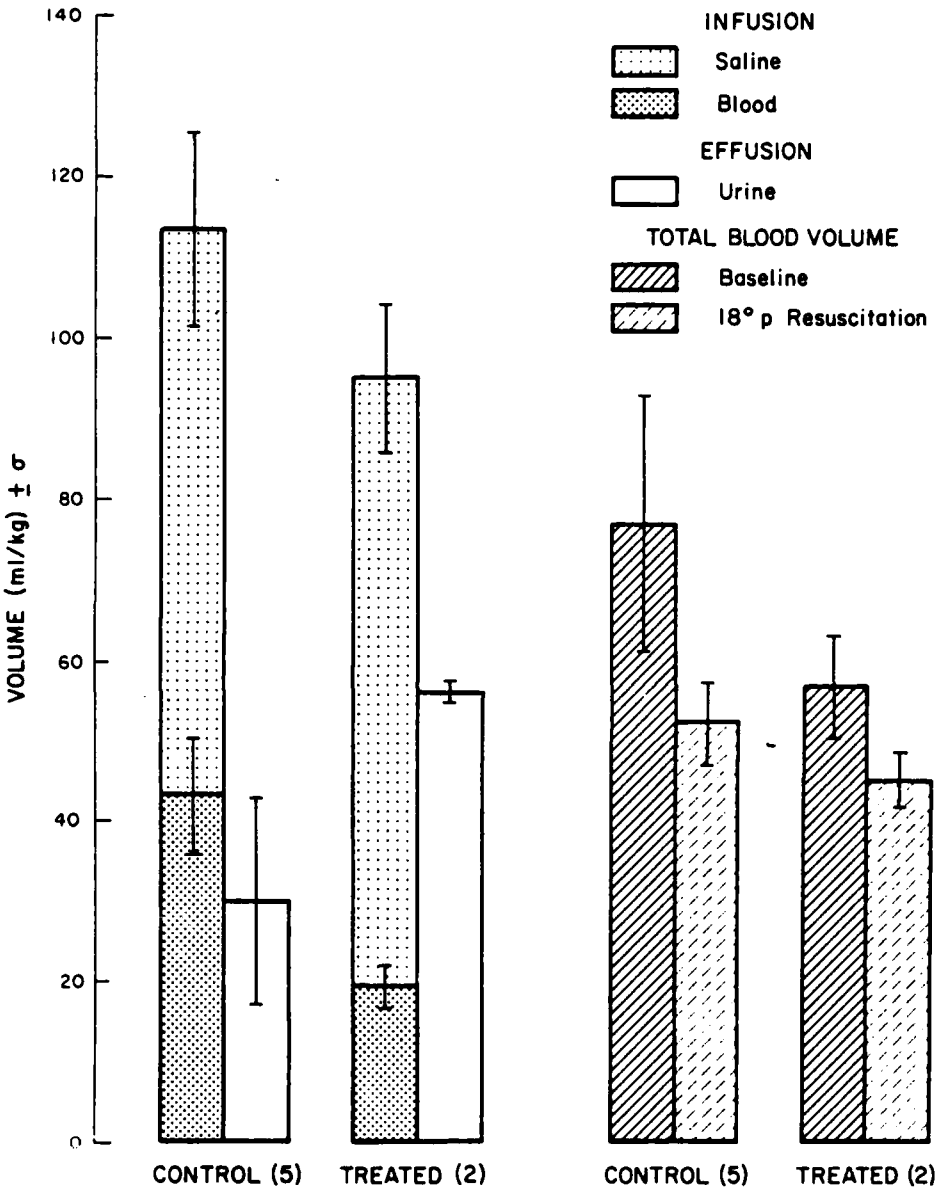

Fig. 3. Volume (ml/kg) ± σ

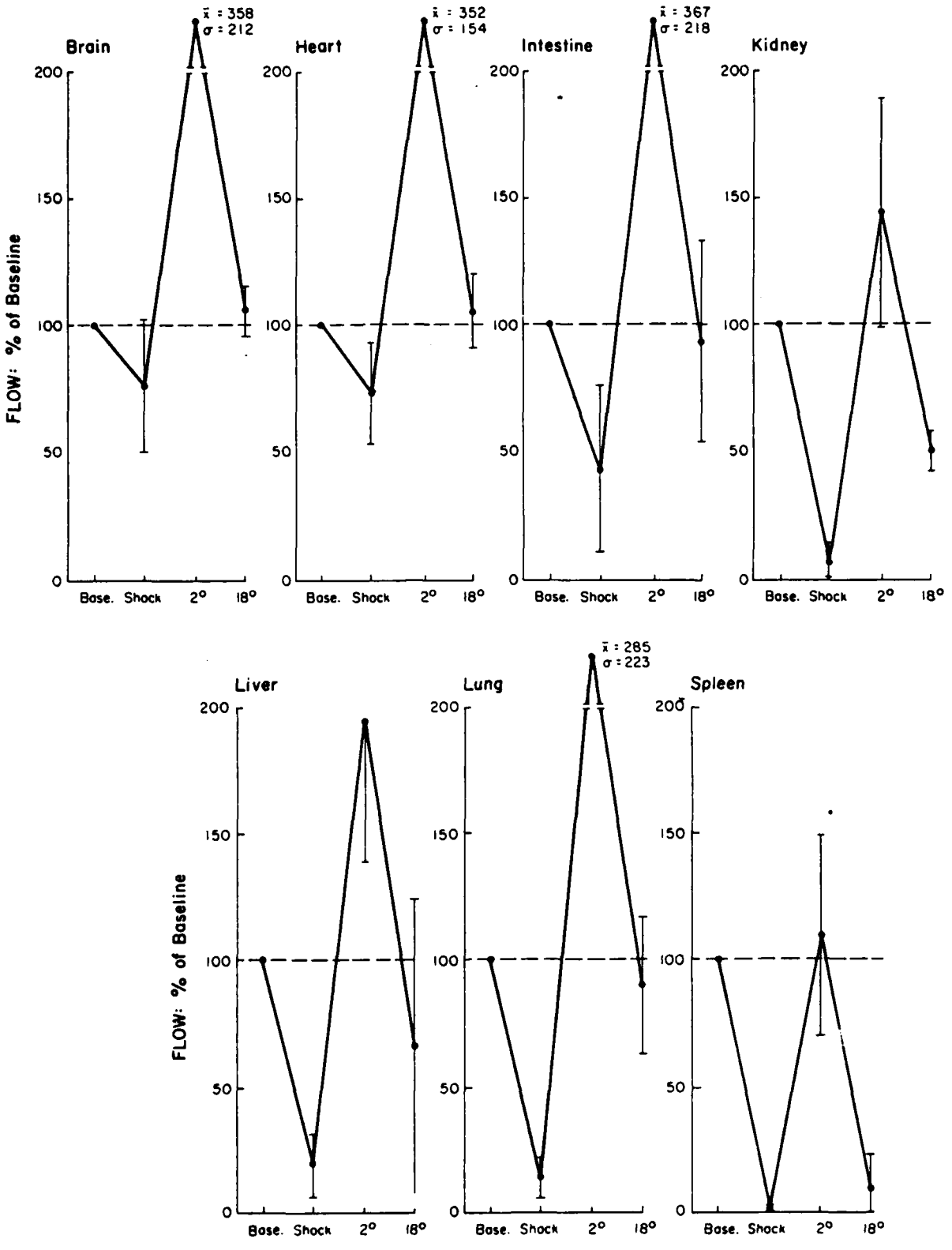

Fig. 4. Tissue Perfusion (Percent of Baseline)

CONTROL: FLOWS - PAIRED t TEST

Baseline vs. 18 hr. post.

d.f. = 4

Brain	$t = 1.35$	$p > 0.2$
Heart	$t = 0.59$	$p > 0.5$
Intestine	$t = 0.29$	$p > 0.5$
Kidney	$t = 7.19$	$p < 0.005$
Liver	$t = 1.51$	$p > 0.2$
Lung	$t = 0.92$	$p > 0.4$
Muscle	$t = 0.37$	$p > 0.5$
Spleen	$t = 4.83$	$p < 0.01$

APPENDIX H

PLATELET TRAPPING AND TISSUE ISCHEMIA IN SHOCK

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Platelet aggregation in vivo has been shown to further reduce already compromised tissue perfusion in animals with septic shock. An isolated hind limb perfusion model in a pig was used to study the effects of hypoperfusion and hemorrhagic shock on oxygen consumption ($\dot{V}O_2$), limb resistance (R), platelet count (PC) and platelet aggregation to ADP. Seven domestic pigs (20-40 kg) were studied. The femoral vessels were cannulated, the limb amputated and perfusion begun immediately using a membrane oxygenator and roller pump primed with autologous whole blood. The animal was then bled into shock (BP 60 mmHg for 30 minutes and 40 mmHg for 45-60 minutes). The limb was perfused at steady state maximal flows for 15 minutes, 50% reduced flows (hypoperfusion) for 15 minutes, returned to normal flows and then the perfusion switched to a parallel system primed with blood taken from the shocked animal and the protocol repeated. A significant increase in R occurred with shock blood, perfusion to the point that in 4 of 7 animals adequate perfusion could not be established with shock blood ($p<0.05$). In limbs hypoperfused with shock blood R increased from a normal of 0.94 to 1.89 ($p<0.005$). Reperfusion with normal blood returned R to normal. Oxygen consumption declined significantly ($p<0.05$) from a normal of mean 1.1 to 0.82 with hypoperfusion and 0.57 with hypoperfusion of shock blood. Platelet counts with shock and hypoperfusion fell from 347,000 to 260,000 within 15 minutes ($p<0.01$). The data show that hypoperfusion and shock decrease oxygen consumption, increase peripheral vascular resistance and decrease PC. Microvascular platelet trapping would explain these observations and contribute to reduced tissue perfusion and hypoxia in hemorrhagic shock.

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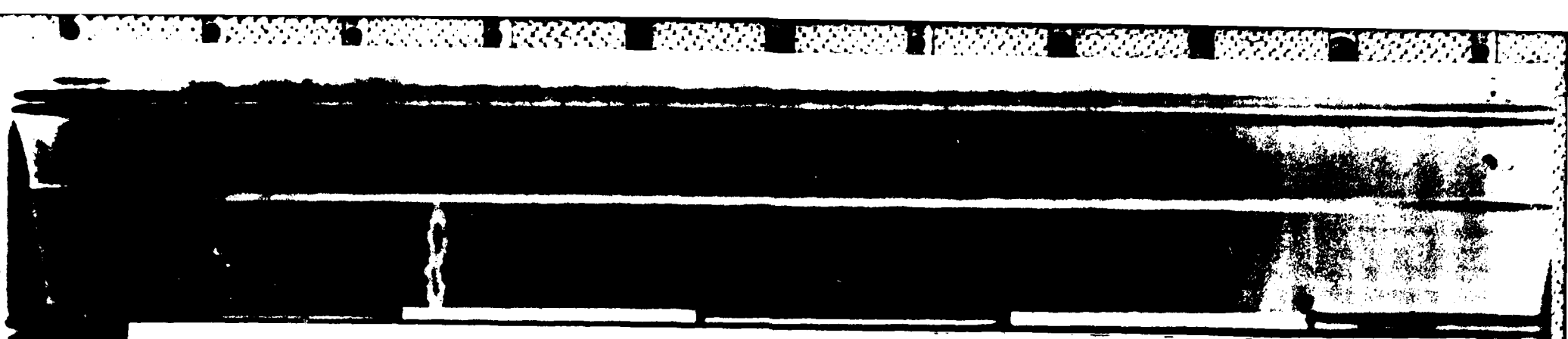
ISOLATED LIMB PERFUSION

		Perfusion Time	PLATELET COUNT (000's) Normal A	Normal V	Hgb	Shock A	Shock V	Stored	% AGGREGATION TO ADP Normal A	Normal V	Shock A	Shock V	Stored	LIMB O_2 CONSUMPTION Time	Flow ml/min Kg	pH	LIMB RESISTANCE (PRU)
ILP 25 Amputated	(nn)	40 min	288	327	10.8			348	83	71			74	(nn) 15 min	72 2.2	7.46	.69
Shock:		75 "	257	271	10.0			337	70	82			76	(nn) 40 "	89 2.5	7.5	.57
15 min @ 60	(ni)	95 "	262	224	9.9			370	68	64			66	(nn) 75 "	89 2.0	7.5	.45
45 min @ 40	(nn)	110 "	292	393	9.0			288	73	72			60	(ni) 95 "	42 1.5	7.53	.43
	(si)	140 "			8.4	281	272	222			74	73	75	(nn) 115 "	89 1.7	7.55	.43
	(si)	155 "			8.6	299	293	502			73	66	79	(si) 140 "	41 .86	7.43	.97
	(nn)	175 "	295	246	8.9			549	72	62			79	(si) 155 "	41 .86	7.4	1.10
														(nn) 175 "	100 1.7	7.4	.48
ILP 26 Amputated	(nn)	25 min	329	346	9.0			328	77	83			70	(nn) 25 min	68 2.3	7.45	.74
Shock:		50 "	320	311	8.9			539	75	73			81	50 "	68 2.1	7.42	.66
20 min @ 60	(ni)	65 "	349	311	8.4			493	74	73			75	(ni) 65 "	32 1.1	7.44	.78
45 min @ 40	(nn)	100 "	360	405	8.2			528	70	70			63	(nn) 100 "	70 1.2	7.42	.57
	(sii)	115			8.4	341	246	437			66	70	86	(sii) 115 "	16 .5	7.38	3.38
		130 "			9.2	297	311	500			69	69	72	130 "	16 .5	7.34	2.88
	(nn)	145 "	317	326	8.6			424	64	69			68	(nn) 145 "	68 1.3	7.34	.66

nn = normal blood, normal flow
ni = normal blood, ischemic flow
sn = shock blood, normal flow
si = shock blood, ischemic flow @ ½ normal flow
sii = shock blood, ischemic flow @ ¼ normal flow

ISOLATED LIMB PERFUSION

		Perfusion Time	PLATELET COUNT (000's) Normal A	Normal V	Shock Hgb	Shock A	Shock V	Stored	% AGGREGATION TO ADP Normal A	Normal V	Shock A	Shock V	Stored	LIMB O_2 CONSUMPTION Time	Flow ml/min	Kg	LIMB RESISTANCE pH	(PRU)
ILP 10	Isolated with tourniquet	(nn) 30 min	428	451	10.0				81	74				(nn) 25 min	37	1.35	7.38	2.16
	Shock:	(nn) 60 "	582	504	10.0			484	84	80			78	55 "	37	1.50	7.36	1.89
	25 min<60mmHg	(nn) 80 "	444	556	10.0			565	82	84r			98	85 "	37	1.42	7.35	1.75
	45 min<40mmHg	(nn)120 "	565	449	9.6			703	76	71			87	120 "	45	1.23	7.32	1.44
		(sn)180 "			10.3	523	527	555			71r	76r	84	(sn)180 "	37	1.31	7.51	1.55
		(sn)215 "			10.2	453	410	528			73r	73r	74	240 "	37	1.27	7.3	1.44
		(sn)275 "			9.8	457	611	553			79r	76r	69	280 "	44	.90	7.48	1.47
ILP 11	Amputated	(nn) 60 min		518	9.8			475		66			76	(nn) 30 min	17	.63	7.2	3.47
	Shock:	90 "		552	9.7			446		72			77	80 "	36	.63	7.51	1.66
	60 min<60mmHg	140 "		578	9.8			556						140 "	50	.53	7.4	.98
	55 min<40mmHg	155 "	569	479				449	80	67				(sn)200 "	50	.27	7.49	.96
		(sn)175 "			7.5	410	418	406			87	81	91	220 "	50	.37	7.45	1.16
		205 "			8.2	559	564	426			82	73	72					
ILP 20	Amputated	(nn) 40 min	555	570	8.0			582	72	78			79	(nn) 40 "	38	.65	7.31	1.6
	Shock:	75 "	400	452	7.1			582	74	73			76	65 "	38	.50	7.6	1.3
	35 min<60mmHg	95 "	480	398	6.2			521	83	76			77	110 "	50	.80	7.33	1.1
	30 min<40mmHg	(sn)125 "			5.5	377	411	557			65	75	71	(sn)125 "	33	.80	7.13	1.8
		135 "			5.6	346	332	564			74	78	83	145 "	33	.77	7.47	1.3
		(si)165 "			5.6	286	327	515			67	73	86	(si)170 "	16	.38	7.28	1.9
		(nn)190 "	456	309	5.9			580	78	77			79	(nn)185 "	50	.71	7.37 (sn)	1.2
																	(nn)	1.2
ILP 21	Amputated	(ni) 25 min	555	557	10.6			481	78	63			71	(nn) 25 "	19	.58	7.59	2.6
	Shock:	(nn) 85 "	401	589	7.2			380	81	76			82	85 "	39	.50	7.38	1.3
	25 min<60mmHg	(ni) 95 "	401	528	7.7			358	61	70			73	(ni)105 "	20	.41	7.41	1.5
	45 min<40mmHg	(ni)135 "	595	408	7.2			586	74	75			81	(nn)135 "	60	.56	7.3	1.0
		(sn)165 "			7.5	398	368	573			75	73	83	(sn)165 "	50	.55	7.4	1.2
		(si)195 "			7.8	288	279	595			64	58	90	(si)195 "	20	.39	7.29	1.9
		(sn)210 "			7.4	367	369	571					85	(sn)210 "	57	.60	7.33	1.1
		(nn)225 "	349	328	7.3			602	78	79			77	(nn)225 "	53	.55	7.2	1.1
ILP 22	Amputated	(nn) 55 min	413	433	8.4			571	74	80			70	(nn) 25 min	53	1.4	7.7	.94
	Shock:	90 "	526	351	8.8			632	73	73			67	50 "	65	1.4	7.37	.92
	25 min<60mmHg	(ni)115 "	271	559	8.8			612	68	77			62	82	74	1.3	7.6	.76
	55 min<40mmHg	(nn)143 "	570	359	8.3			493	74				85	(ni)100	37	.9	7.7	.76
		(si)165 "			8.5	312	293	545			87	75	79	(nn)120	65	.6	7.6	.77
		195 "			8.6	260	313	583			76	74	94	(si)145	25	.6	7.4	2.3
														165	37	.4	7.36	1.6



ISOLATED LIMB PERFUSION

		Perfusion Time	PLATELET COUNT (000's) Normal A	Normal V	Normal Hgb	Shock A	Shock V	Shock Stored	% AGGREGATION TO ADP Normal A	Normal V	Shock A	Shock V	Shock Stored	LIMB O_2 CONSUMPTION Time	ml/min Flow	ml/min Kg	LIMB RESISTANCE pH	LIMB RESISTANCE (PRU)
ILP 24 Amputated	(nn)	45 min	263	250	9.6			262	72	75			78	" 18 min	36	.68	7.48	1.4
Shock:		70 "	347	284	10.5			385	70	92			73	n 50 "	36	1.0	7.45	1.5
45 min=60mmHg	(ni)	110 "	254	253	10.4			274	75	84			86	(nn) 70	50	.60	7.47	1.1
55 min=40mmHg	(nn)	125 "	267	255	10.5			293	83	72			74	(ni) 90 "	20	.50	7.51	1.5
	(si)	160 "			8.8	216	186	304			76	79	82	(nn) 115 "	47	.64	7.47	1.1
	(si)	185 "			7.8	179	178	276			76	76	78	(nn) 130 "	44	.66	7.47	1.1
	(ni)	205 "	206	224	10.6			307	72	80			86	(si) 150 "	21	.64	7.38	2.4
	(nn)	225 "	237	230	9.6				80	79				(si) 155 "	21	.66	7.38	2.4
	(si)	240 "			7.4	150	175				79	63		(si) 175 "	29	.68	7.28	1.9
														(ni) 200 "	26	.78	7.34	1.9
														(nn) 220 "	50	.76	7.52	1.3
														s 235 "	32	.66	7.48	1.9
ILP 25 Amputated	(nn)	40 min	288	327	10.8			348	83	71			74	(nn) 15 min	72	2.2	7.46	.69
Shock:		75 "	257	271	10.0			337	70	82			76	(nn) 40 "	89	2.5	7.5	.57
15 min@60mmHg	(ni)	95 "	262	224	9.9			370	68	64			66	(nn) 75 "	89	2.0	7.5	.45
45 min@40mmHg	(nn)	110 "	292	393	9.0			288	73	72			60	(ni) 95 "	42	1.5	7.53	.43
	(si)	140 "			8.4	281	272	222			74	73	75	(nn) 115 "	89	1.7	7.55	.43
	(si)	155 "			8.6	299	293	502			73	66	79	(si) 140 "	41	.86	7.43	.97
	(nn)	175 "	295	246	8.9			549	72	62			79	(si) 155 "	41	.86	7.4	1.10
														(nn) 175 "	100	1.7	7.4	.48

n =
nn = normal blood, normal flow
ni = normal blood, ischemic flow
sn = shock blood, normal flow
si = shock blood, ischemic flow @ ½ normal flow
s =

APPENDIX I

CONSENT FORM FOR STUDY OF
MICROAGGREGATES IN THE BLOOD
CONTRACT DADA 17-73-C-3040

Stored blood, used for transfusions, has small particles in it composed of some normal blood substances which have clumped together. Although it is not known that transfusion of these particles does any harm, it probably does not do any good and a number of different kinds of blood filters have been developed to remove these particles. The study you are being asked to participate in involves an attempt to see if any one kind of these filters is superior to another in preventing any change in lung function which might result from some of these particles reaching the lungs.

The filter to be used will be determined on a chance (random) basis. All three types of filters are standard types of blood filters, all used regularly in this hospital. There is no evidence that one filter provides superior treatment over another; that is the purpose of this study.

No laboratory tests will be performed which would not be performed in the course of normal care and the study will in no way interfere with your treatment and treatment methods for a patient with your injuries/ operation.

If you agree to participate in this study, then please sign below. Your signature indicates that you have had the study explained to you in full.

_____	_____
Name (Participant)	Name (Witness)
_____	_____
Address	Address
_____	_____
Date	Date

APPENDIX J

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