Membrane Oxygenation and Blood Compatibility

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Extracorporeal membrane oxygenation (ECMO) may be preferable in extended open-heart surgical cases and is attaining clinical prominence as a long term supportive/therapeutic procedure for potentially reversible neonatal, pediatric, and adult acute respiratory failure.[1] Despite a few optimistic claims from investigators using the inappropriate canine model,[2-4] successful performance of prolonged (several hours to days) cardiopulmonary bypass still requires some degree of systemic anticoagulation. Since potential bleeding complications obviate its use in patients that may otherwise benefit, the search for an ideal, or at least relatively, nonthrombogenic artificial surface continues to be a large part of biomaterials research. This research has been frustrated by a lack of detailed information regarding the thrombogenic mechanism (especially under conditions of high blood flow) and the dispersive effects of a plethora of new, sophisticated thrombogenic tests and indices.

Assuming the need for systemic heparinization, ECMO perfusion is clearly more blood compatible than systems requiring blood-gas interface oxygenators.[5] In "nonpulastile" membrane lung perfusion systems, clinical hemolysis as well as changes in erythrocyte and leukocyte count are either inconsequential, even after several days, or unrelated to the membrane surface. Thrombocytopenia, however, remains the predominant hematological (and perhaps physiological) change occurring during bypass.

Our ECMO team has undertaken at least 15% of the clinical trials reported worldwide with more newborn survivors[8] and total survivors[11] than any other group. We have extensive experience both clinically and in the laboratory with gas exchange devices and have done considerable biomaterials research from the standpoint of evaluating blood compatibility. The following intends to review, report, and integrate clinical and experimental information with regard to current perspectives and prospects in the blood compatibility of membrane oxygenation.

PLATELET CONSUMPTION DURING ECMO

The gas exchange membrane represents over 95% of the total ECMO circuit surface area and is therefore most influential in platelet-surface interaction. Platelet destruction, with the attendant potential of bleeding, is often a more important consideration in membrane lung design today than gas exchange. The majority of membrane lungs used clinically in 1977 utilize silicone rubber in various geometric configurations as the basic gas exchange surface. Others utilize microporous teflon,[6] and a high efficiency, vortex-shedding oxygenator with an ultra-thin, nonporous

polyalkylsulfone membrane has been developed[7] which promises improved blood compatibility.[8,9]

Since thromboctopenia and platelet dysfunction often accompany acute respiratory failure, membrane-related platelet consumption is best studied under controlled conditions on a healthy animal population.[10] The sheep is a suitable, if rigorous, model because of fibrinolytic activity less than man (that of the dog is much more active leading to risky clinical extrapolations regarding coagulation) and a high blood count of small, very adhesive platelets.[4,11]

Employing partial veno (jugular)-arterial (carotid) bypass on a population of normal lambs, we were able to compare decreases in blood platelet count (by phase microscopy) during 24 hr. of perfusing either the Travenol Teflo® microporous membrane oxygenator (1975) (TTMMO), The Lande-Edwards membrane oxygenator (1976) (LEMO), or the Sci-Med Kolobow membrane lung (1976) (SMKML). Whole blood priming procedures, anesthesia, anticoagulation, and management during ECMO have been previously reported for both clinical[1] and experimental[12] trials and were comparable for all three systems. Both LEMO and SMKML utilize silicone rubber membrane, the former in sandwich configuration and the latter in a spiral coil. The TTMMO system pumps require reservoirs, thereby imposing a blood-gas interface not physically associated with the oxygenator. The recommended vacuum priming of SMKML was eschewed. No on-line blood filters were used.

Individual animal trials are shown in Table I arranged in order of increasing platelet consumption measured at the end of bypass and including those ECMO parameters thought to be most relevant to platelet destruction. In general, higher extracorporeal flow relative to cardiac output (estimated from body weight) and rated flow of the oxygenator resulted in greater platelet consumption (percentage of baseline platelet count). Figure 1 suggests that the LEMO best preserves platelets, but in some instances LEMO trials were necessarily conducted at only a fraction of the rated flow, resulting in poor oxygenation of arterial blood. Since the animal was usually healthy and awake without ventilator support during bypass, metabolic requirements were not seriously compromised. Extremely plately-dilute primes also resulted in sharp decreases in blood platelet count (Table I, Figure 1), especially during the first hour of bypass. In contrast to the SKMKL, the LEMO has a wide-channel, low-pressure drop blood path. Interestingly, 51 Cr-platelet adherence per unit of LEMO surface area was more than an order of magnitude greater than on SMKML. We feel that under high-pressure, high-flow conditions, the number of surface adhering platelets are not necessarily indicative of platelet destruction in that adhesion represents only one phase of platelet activity.[9] Probably because of water accumulation in the gas phase, carbon dioxide transfer efficiency deteriorates in the TTMMO within 24 hours, making the device unsuitable for prolonged respiratory support cases.[12] Because of the constrained blood-gas interface, platelet destruction in the TTMMO is moderate; thus Teflon and silicone rubber surface thrombogenicity may be regarded as comparable.

Having studies those ECMO parameters influencing platelet consumption, and having a large patient population from which to draw (about 40 ECMO cases), 14 clinical trials were selected for comparing platelet consumption resulting from either LEMO or SMKML with or without vacuum priming. Individual patients are matched horizontally in Table II after retrospectively considering initial platelet count with respect to normal values and the extracorporeal prime, size and age, etiology, and

TABLE I

BLOOD PLATELET CHANGES DURING EXPERIMENTAL ECMO.
IN ORDER OF INCREASING PLATELET DESTRUCTION.
BASELINE COUNTS RANGE FROM 302,000 to 895,000
DISTRIBUTED RANDOMLY AMONG THE THREE LUNG TYPES.

SHEEP TRIAL	MEMBRANE LUNG	MEMBRANE SURFACE AREA (M^2)	RATED FLOW (L/MIN)	BODY WEIGHT (KG)	MEAN EC FLOW (L/MIN)	% BASELINE PLATELET COUNT AT 24 HR.
EC-105	LEMO	3	2.0	30	0.3	58.7
EC-99	LEMO	6	4.0	32	0.6	51.1
EC-82	TTMMO	2.25	6.0	22	1.5	47.5
EC-106	LEMO	*6	4.0	28	1.1	44.8
EC-96	LEMO	3	2.0	34	1.1	37.6
EC-107	SMKML	4.5	5.4	25	1.4	31.3
EC-83	TTMMO	2.25	6.0	25	1.4	27.7
EC-104	SMKML	4.5	5.4	24	1.0	24.7
EC-88	TTMMO	2.25	6.0	24	1.1	24.7
EC-101	SMKML	4.5	5.4	24	1.6	23.2
EC-100	SMKML	2.5	3.0	36	1.9	18.3
EC-87	TTMMO	2.25	6.0	36	1.7	16.6
EC-108	LEMO	3	2.0	33	0.9	†11.7

*Significant number of envelopes not perfused.

†Prime platelet count 2,000; other prime platelet counts range from 33,000 to 327,000 distributed randomly among the three lung types.

outcome of ECMO. Blood platelet count was assessed at 24 hr. of bypass for several reasons: (1) flows are generally high during this period (about 80% of the cardiac output) and optimal for the size oxygenator chosen, (2) few if any platelet transfusions have been given, and (3) hemodynamic equilibration has been completed.[11] A number of recent ECMO trials have been instituted on neonates using an extracorporeal prime (volume large compared to patient) of freshly drawn heparinized blood rich in platelets and utilizing a vacuum-primed Kolobow lung (SMKML-VAC). It was therefore difficult to find older LEMO trials on babies with rich primes; however, a statistical comparison of prime/baseline platelet count ratios in selected LEMO versus SMKML-VAC trials indicated no significant difference ($P > .1$). Thus the only uncontrolled variable other than membrane surface nature is the fact that slightly more LEMO surface is required to equal the rated flow of SMKML (*cf.* Table I).

Only two perfusions were initiated utilizing non-vacuum primed SMKML units, and while they generally fit the criteria of Table II, they cannot be included in a statistical comparison. It is doubtful that the non-vacuum primed SMKML is less platelet destructive than the LEMO, and probable that it is more destructive, as indicated in sheep trials. Despite low baseline platelet counts and platelet-rich primes, multiple platelet transfusions were required early the first day of bypass in both SMKML patients, and platelet count at 24 hr. was still extremely low. Clearly evident in Table II is that platelet consumption in a vacuum-primed SMKML circuit is much (significantly) less than in either SMKML or LEMO primed at 1 atm. When gas-permeable biomaterials are subjected to a partial vacuum on one side and to a liquid at 1 atm on the other, stabilized gas nuclei are removed from microscopic surface

Figure 1.

Mean changes in ovine blood platelet count during cardiopulmonary bypass for three different membrane lung systems. Lung abbreviations are explained in text and the number of animal trials per system are indicated in parenthesis. Individual trial parameters are presented in Table I. A fifth LEMO trial using a whole blood prime virtually without platelets dramatizes the dilution in count resulting on bypass.

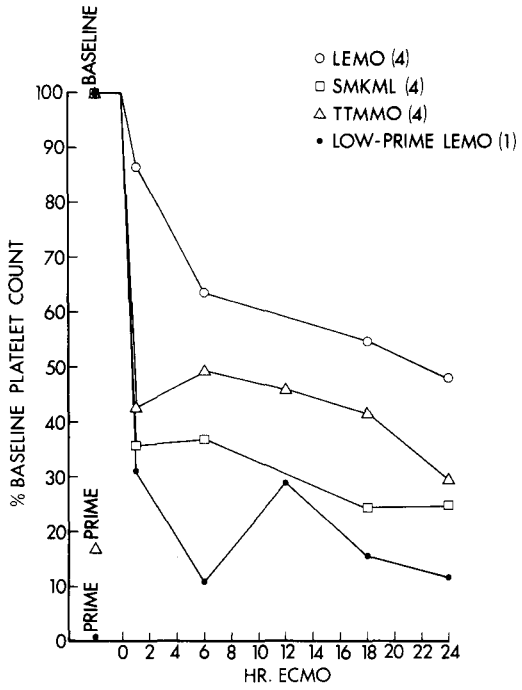

TABLE II
BLOOD PLATELET CHANGES DURING CLINICAL ECMO.
BASELINE COUNTS RANGE FROM 113,000 to 539,000
IN LEMO AND SMKML-VAC, 78,000 to 89,000 IN SMKML.

PATIENT BY SIZE/AGE LESION, OUTCOME	LEMO % BASELINE COUNT PRIME	LEMO % BASELINE COUNT 24 HR.	SMKML % BASELINE COUNT PRIME	SMKML % BASELINE COUNT 24 HR.	SMKML-VAC. % BASELINE COUNT PRIME	SMKML-VAC. % BASELINE COUNT 24 HR.
1.1-2.2 Kg, IRDS, Died	56.3	18.5	—	—	78.8	45.5
1.8-1.9 Kg, IRDS, Surv.	53.3	27.3	—	—	111.9	65.7
3.6-3.9 Kg, Mec. Asp. Surf.	65.5	9.7	123.1	*46.4	92.8	57.6
9.0-15.1 Kg, Pnm/Fbs, Died	5.2	19.7	—	—	2.6	44.9
Younger Adult, Emb., Died	4.0	10.2	—	—	10.6	36.2
Older Adult, Pnm., Died	14.4	*15.1	> 100	†*11.8	21.3	74.4
MEAN	33.1	18.4	> 100	29.1	53.0	54.0
S.D.	28.2	8.5	(Insufficient n)	—	47.0	14.4
P (LEMO vs. SMKML-VAC)	>.1	<.001	—	—	>.1	<.001

*Adjusted for platelet transfusions

†Goodpasture's Syndrome

Abbreviations: IRDS = Infant Respiratory Distress Syndrome; Mec. Asp. = Meconium Aspiration; Pnm. = Pneumonia; Fbs. = Fibrosis; Emb. = Embolism; Surv. = Survivor.

crevices. As shown by Ward and colleagues,[13 14] such microscopic nuclei may be the principal property giving rise to platelet adhesion on silicone rubber, either with or without protein–surface mediation.

ASSESSING SURFACE THROMBOGENIC POTENTIAL

Improvements in ultrathin silicone rubber membrane regarding gas transfer and blood compatibility have been regularly reported over the last few years[15–17] and reviewed by Kolobow.[18] But under what condition was blood compatibility evaluated, by what standards, how representative is the index, and how quantifiable? A simple, reliable test and universal index of blood compatibility does not exist. A thrombogenic predictor test and index that combine the economy, versatility, controllability, and quantifiability possible *in vitro* with the hard, overall information yielded *ex vivo* would be welcomed by polymer chemists, biomedical engineers, and clinicians.

We have reported an *in vitro* test system using a roller pump that measures the adsorption of radioactive fibrinogen and/or adherence of radioactive platelets to tubular test surfaces.[9 19 20] Chromium–51–platelet adherence to polyvinyl chloride (PVC) was shown to be increased in plasma on surfaces pre–coated by circulating fibrinogen and retarded on albumin pre–coated surfaces. That silicone rubber (Silastic) pre–coated with a physiologic concentration of fibrinogen also increases platelet adherence and to about the same degree relative to uncoated controls was recently demonstrated in our laboratory. As shown in Figure 2, increased 51 Cr–platelet adherence to fibrinogen–coated Silastic occurred when either fresh or 4–day (outdated but functional) human platelets were compared in a compatible fresh plasma medium at 70 ml/min constant flow.

The importance of fibrinogen as the chief cofactor of platelet adherence to a surface has been demonstrated in other test systems.[21 22] Since plasma proteins also play roles in platelet secretion and aggregation, it's reasonable that ^{125}I–fibrinogen adsorption in plasma or saline may be representative of thrombogenic potential of a variety of surfaces.[9] Having previously demonstrated differences in ^{125}I–fibrinogen adsorption in saline to several tubular surfaces including Silastic,[19] we decided to compare LEMO salted (standard), unsalted, gum–coated, and the current homogenous, reinforced SMKML silicone rubber membrane envelopes (.1 M^2) in the LEMO sandwich configuration. Test modules of a given surface preparation were connected in parallel in a circuit composes of polycarbonate connectors and PVC tubing, and ^{125}I–fibrinogen in saline was recirculated by roller pump to and from a plastic reservoir. Fibrinogen adsorption to each of the four surfaces is compared in Figure 3 during 1 hr. recirculating at constant flow per membrane surface area. Other component materials in this test system can also be compared for radioactive fibrinogen adsorption. Although the LEMO has not been commercially available for one year, this method of blood compatibility testing could be of practical value to those who wish to re–introduce an improved version.

FUTURE IMPROVEMENTS IN BLOOD COMPATIBILITY

Of synthetic pretreatments that render (by at least some indices) commercial biopolymers—PVC, silicone rubber, polyurethane—less thrombogenic, heparin–bonded tridodecylmethylammonium chloride complex (TDMAC/hep) is attractive for several reasons: (1) it can be applied to a variety of biomaterials successfully and

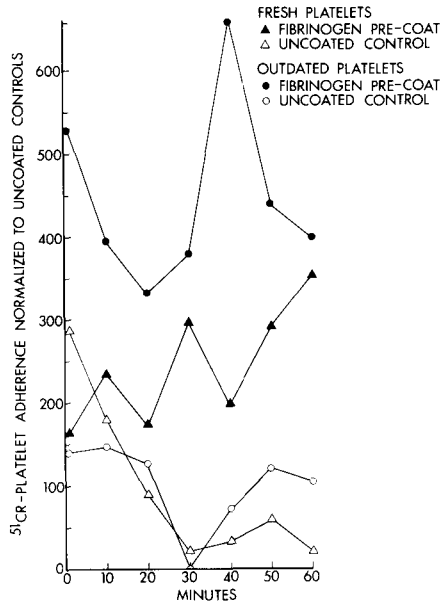

Figure 2.

Changes in platelet adherence relative to mean uncoated control values (100%) during one hour of *in vitro* recirculation in fresh-frozen plasma (FFP) at 70 ml/min. Concentration of human fibrinogen in pre-coating solution was 300 mg/dl. Fresh human platelets are compared to 4-day old human platelets in each experimental pairing. The *in vitro* test system has been previously described.[19]

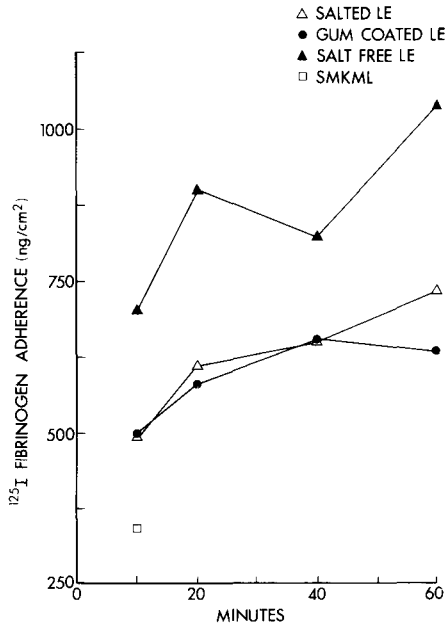

Figure 3.

Fibrinogen adsorption per unit area on four different silicone rubber surfaces during one hour of *in vitro* recirculation in saline. Four LEMO-like modules containing the same surface were connected in parallel and clamped off one by one for sampling. Flow as adjusted to maintain 1 ml/min.cm^2 of membrane surface. Modular leaking developed after 10 minutes in SMKML system.

thus could be used to coat an entire ECMO circuit, (2) it is transparent (unlike graphite), and (3) it has been shown to significantly reduce fibrinogen adsorption[19] and platelet adherence.[23]

TABLE III
RABBIT *EX VIVO* LOOP PATENCY.
VALUES ARE MEANS ± S.D. WITH NUMBER OF ANIMALS IN PARENTHESIS.
ARRANGED IN DECREASING ORDER OF PATENCY.

	PATENCY TIME (MIN.)	INITIAL FLOW (ML/MIN.)	PLATELET COUNT ($\times 10^{-3}$/ML)
1. Autoclaved TDMAC/Hep.	**57.4 ± 21.8 (5)	6.1 ± 2.6 (5)	324 ± 54 (5)
2. TDMAC/Hep. + Albumin	46.5 ± 9.2 (2)	6.6 ± 3.4 (2)	342 ± 200 (2)
3. TDMAC/Hep.	41.0 + 25.2 (10)	7.0 ± 4.4 (9)	247 ± 130 (10)
4. ETO TDMAC/Hep.	33.1 ± 32.8 (7)	6.3 ± 3.0 (7)	353 ± 130 (7)
5. Silastic	*†25.6 ± 13.6 (11)	6.6 ± 3.7 (10)	323 ± 124 (11)
6. Latex	*†11.2 ± 6.5 (5)	4.2 ± 3.2 (5)	270 ± 102 (4)

*$P < .01$
†$P < .05$
All other combinations $P > .1$

We have found the rabbit a good model of human hematology; blood platelet count, platelet size and morphology, post-splenectomy platelet dynamics, and some aspects of platelet function are comparable. Using a unilateral jugular *ex vivo* loop preparation described elsewhere,[9] we compared times-to-zero-flow for unheparinized rabbit blood through Silastic tubing either untreated (control) or pretreated with TDMAC/hep. Pretreatment with TDMAC/hep was followed by either autoclaving, gas (ethylene oxide) sterilization, 5 GM/dl human serum albumin soaking, or nothing, before surgical cannulation. As indicated in Table III, with a sufficient number of trials per treatment group, important variables such as initial flow and platelet count average out among groups, allowing comparison of patency times with respect to tubing surface. Autoclaving significantly increases patency time on TDMAC/hep when compared to untreated Silastic, but ethylene oxide (ETO) sterilization does not; in fact, gas sterilization appears in some way to negate some of the non-thrombogenic contribution of TDMAC/hep. One criticism of TDMAC/hep complex is its apparent lack of binding permanency, especially under high flow conditions (and in the raceway of a roller pump); autoclaving may be effective in "baking" it into the surface somewhat. Albumin in conjunction with TDMAC/hep probably augments patency time, which is in agreement with the original notion of Lande that priming extracorporeal circuits with concentrated albumin solution retards platelet consumption.[24] This has also been shown for ^{51}Cr-platelet adherence *in vitro* when Silastic is pre-coated with a physiologic concentration of albumin. Results on variations of Silastic are contrasted to the brief patency times on latex rubber, a material known to be thrombogenic.

In the last year, the Addonizio–Edmunds group at the University of Pennsylvania has reported minimal platelet destruction in both *in vitro* and *ex vivo* silicone rubber ECMO (SMKML) circuits to which the fatty acid derivative prostaglandin E_1 has been added in heparinized blood.[25,26] This group has recently found that a synthetic methylation of PGE_1 greatly prolongs its effectiveness as a platelet preservative in monkeys undergoing 4-hr. bypass by retarding its metabolism, and have reported that another species of prostaglandin found in vascular endothelium may be nature's way of preserving platelet function *in vivo*. Perhaps a combination of synthetic prostaglandion and an autoclaved TDMAC/hep-coated circuit primed with concentrated albumin will permit us to perform clinical ECMO without thrombocytopenia and systemic anticoagulation.

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