Meetings

Microcirculation and Shock

What happens to man's blood vessels when he encounters shock? How can one measure the blood flow through the microvasculature? These were but two of the many questions to which answers were sought at an international, interdisciplinary conference on Microcirculation as Related to Shock, held at Boston University, 29 March–1 April 1967. The conference chairman was G. P. Fulton (Boston University). Eighty-two participants and 275 invited guests came from 23 states and eight foreign nations. Two-thirds of the guests represented graduate centers; the rest were from research institutes associated with the armed services, government agencies, and private industry.

Robert H. Ebert (Harvard Medical School) as the keynote speaker stated that the focal point of shock is located in the microvasculature where the events that determine reversibility or irreversibility occur. He warned against the almost hypnotic preoccupation with the "esthetics" of blood flow as in classical microscopy, and praised the introduction of newer quantitative procedures and multidisciplinary efforts in the field of microvascular research.

P. C. Johnson (Indiana University Medical School) suggested that greater consideration should be given to the basic reasons for survival of individuals in shock instead of preoccupation with the lethal aspects. He showed that the oscillations of precapillary sphincters are dependent on pressure and not directly responsive to metabolic needs. It was pointed out that a decrease in blood flow through the spleen and liver apparently depresses reticuloendothelial system, affecting the endotoxin titers.

J. B. West (Hammersmith Hospital, London) discussed the consequences of pulmonary venous pressure, which frequently accompanies acute failure of the left ventricle. He demonstrated that the PCO_2 difference and the alveolar dead space increased with reduced pressure of the pulmonary artery. Because the dead space has a direct bearing on ventilation, the carbon dioxide titer was affected more than oxygen levels. Increased pulmonary venous pressure produced a concomitant increase in pulmonary edema and vascular resistance in the dependent region of the lung (as observed in left heart failure). The vascular resistance was due in part to changes to the extra-alveolar vessels.

W. N. Stainsby (University of Florida College of Medicine) spoke on autoregulation of blood flow in skeletal muscle during shock. He reported that microcirculatory functions in skeletal muscle were about the same in hemorrhaged animals as in controls; oxygen intake and autoregulation were adequate until irreversible shock and death. This suggested that the vascular bed in muscle during hypovolemia does not contribute significantly to the manifestations that occur in extreme hypotension and irreversible shock. The discussants could not concur with Stainsby that investigators should look elsewhere than muscle to study microcirculatory involvement in shock. Even the slightest vascular alteration in skeletal muscle becomes impressive when multiplied by the total amount of tissue, and skeletal muscle may be the site for microembolism during shock.

A direct, quantitative method for measuring intrarenal blood flow during hypotension was described by K. Aukland (University of Oslo). He found that hemorrhagic hypotension produced a proportionate and progressive increase in vascular resistance in the cortical and juxtamedullary circulation.

D. E. Gregg (Walter Reed Army Medical Center) presented data on the coronary circulation in the intact, unanesthetized dog implanted with electromagnetic flowmeters in the aorta and coronary arteries and with tubes for blood sampling and pressure recording. He found a relatively fixed flow pattern in response to natural stresses; dogs with blocked or paced hearts during excitement doubled and tripled their stroke coronary flow. In a state of reduced coronary flow, with normal aortic pressure, the compensatory mechanisms in the cardiac microvasculature reacted early and effectively. Myocardial failure could be explained on the basis of poor transmural blood distribution rather than by decrease of flow.

C. C. Hyman (University of Southern California Medical School) conceded that in spite of the limitations of this organ-system (heterogeneity of tissues, subservient role), the skin provides a valuable area for investigation because of quantity, sensitivity to change (for example, catecholamines), and accessibility. Data utilizing clearance techniques in the skin of six patients in shock did not provide a relationship between clearance rates of iodoantipyrine from the skin and systolic or diastolic mean pressures.

C. T. Dollery (Hammersmith Hospital, London), in his talk on the eye, presented quantitative data on capillary flow in swine during hemorrhagic shock and obstruction with glass microsphere-emboli. He measured the caliber of vessels at pressures as low as 10 mm-Hg, and determined critical closing pressures of the microvasculature. He demonstrated the reversibility of capillary closure after long periods of obstruction by an embolus, and showed that microplugging of the capillary bed did not occur as a consequence of extreme hypotension. He used cinephotomicrography of fluorescent angiograms. M. E. Knisley (University of South Carolina Medical School) noted that this was the first experiment to give some indication of volumetric flow, since both the flow rate of the axial stream and the vessel diameters were measured.

H. D. Green (Bowman Gray Medical School) discussed cerebral circulation and reviewed the various direct and indirect means of measuring flow. He presented data supporting the view that: (i) the cerebral vascular bed has the capacity to autoregulate; (ii) the cortical sinus and autonomic nerves appear to affect the micro- but not the macrocirculation; and (iii) increased CO_2 tension of arterial blood and the

*p*H were the most important vasodilating factors. He concluded with the observation that cerebral blood circulation does not seem to play a significant role in initiating the irreversibility of shock.

F. T. Moore (Harvard Medical School) summarized the sessions on the first day with a discussion of the microcirculation and its relevance to man. In his laboratories, the most useful single measurement of total body perfusion is lactate ion concentration. Lactate titer more than 10 mmole/liter is a harbinger of death; its accumulation is more sensitive to low flow state than to anoxia. From 30 to 50 percent of patients who die following shock have pulmonary insufficiency, with pulmonary embolism as a major aspect of the pathogenesis. In closing, Moore emphasized that "peripheral reflections of flow should replace other clinical indices in the monitoring of patients with shock."

E. M. Renkin (Duke University Medical Center) discussed neurogenic factors in shock, pointing out that regulator substances other than the sympathetic adrenergic vasoconstrictors, are still in the "unsolved" category. The failure of adrenergic vasoconstrictors to maintain the normal control of the microcirculation contributes to the irreversibility of shock. One avenue under investigation is the relationship between the β-receptors of the vascular bed and vasodilation. H. Viveros, in Renkin's laboratory, has been able to produce dilation after α-adrenergic blockade; the status of this mechanism as a normal physiological variable has not been clarified.

P-I Brånemark (University of Gothenburg, Sweden) discussed the microvasculature at a resolution level of 1 micron. High resolution microscopic analysis in vivo disclosed that blood cells (singly or in clumps) maintain their shape and function in shock. These findings are in contradiction with some early assumptions on cell integrity to low flow states based upon theoretical models, in vitro experiments, and low-resolution microscopy. The most important conclusion from Brånemark's experiments was that the microcirculatory system of man will return to almost normal function after several hours of reduced blood flow.

E. D. Frank (Harvard Medical School) spoke on traumatic and toxic factors in shock, emphasizing the significant role of toxic substances in the lethal aspect. He stressed the importance of monitoring a wide range of parameters while a patient is in a critical hypotensive state. For example, compensatory mechanisms such as heart rate or hematocrit do not always provide an accurate index of the vitality of the patient. Frank and co-workers were able to prevent shock in many cases as a result of direct measurement of blood volume.

The Workshop of Tracer Techniques, chaired by B. A. Burrows (Boston University School of Medicine), served the purpose of characterizing and evaluating the techniques now in use. Transport of tracers did not necessarily correlate with blood flow. Even xenon-132 clearance, once thought to approximate blood flow, is less valid at high flow rates. Rubidium can be used to measure a fraction of cardiac output if the blood is sampled within 2 minutes after injection. Permeability surface product ratios are flow dependent, and the exchange rate and the site of exchange in the capillary bed varies with the solute.

E. Selkurt (Indiana University School of Medicine) summarized the Workshop on Thermal Conductivity with the opinion that these measurements gave direct insight into metabolic derangements that occur in shock.

The Video Scanning Procedure Workshop, chaired by E. H. Bloch (Western Reserve University School of Medicine), clearly demonstrated how optical images could be enhanced by their conversion into electronic images. The latter procedures can record changes in cellular inclusions, and wavelengths which the eye cannot perceive, all in relation to time.

In E. M. Landis' (Harvard Medical School) workshop on Micro Blood Pressure Measurements, A. C. Guyton (University of Mississippi) reported that by using implanted, perforated capsules he was able to indirectly measure tissue pressure at 6 to 7 mm-Hg.

E. M. Merrill (Massachusetts Institute of Technology), reporting on the Rheology Workshop, presented data that whole blood has a higher viscosity as measured by conventional in vitro systems than in the rat-tail artery techniques. In vessels less than 80 microns in diameter, blood viscosity is irrelevant and different fluid mechanics must be applied. Furthermore, we know very little about blood rheology during low flow states. Merrill reasserted his view that the viscous property of blood is ascribable to the hematocrit and fibrinogen concentration.

B. Zweifach (University of California, San Diego) summarized the conference as follows: (i) Microvasculature is a functional but not homogeneous unit since the structure of the vessels may vary and the filtration coefficient is not constant; (ii) there is no single shock organ with a supersensitive microcirculation; (iii) the question of control (intrinsic and extrinsic) is not resolved; (iv) restoration of central pressure does not necessarily mean a concomitant return of normal transcapillary exchange and other functions of the terminal bed; (v) more attention should be given to the rheological aspects of microcirculation, and to the mechanisms resulting in peripheral shunting; and (vi) the effect of endotoxins in producing severe low flow states requires a great deal more clarification.

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Ribonuclease: Recent Advances

Pancreatic ribonuclease is one of the most intensively studied proteins in nature and probably the most completely characterized enzyme. The primary structure of this enzyme has been known for about 7 years, and it seemed possible to deduce the catalytic mechanism using the amino acid sequence, chemical modification work, and kinetic studies. Unfortunately, juxtaposition of various parts of the polypeptide chain in a catalytically active center could not be inferred from these facts; even recent attempts to do so have failed. Clearly, the three-dimensional structure of the enzyme molecule was needed for characterization of the active center and the mechanism of action. Since December 1966, the three-dimensional structure of ribonuclease A, determined by x-ray diffraction analysis, has been reported from two laboratories and that of subtilisin-treated enzyme (ribonuclease S-protein + S-peptide) reported from a third laboratory. A symposium was held at the State University of New