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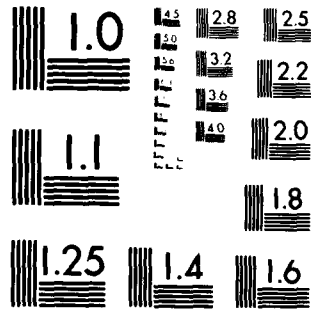
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CONTRACTILE STATE OF THE HEART DURING
HYPOVDEMIC SHOCK AND ENTOTOXEMIA

FINAL REPORT

Charles Urschel
and
Edmund W. Sonnenblick

April 1980
(For the period 1 July 1967-30 June 1973)

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) It was demonstrated that myocardial depression was not needed for the lethal progression of hemorrhagic shock. Furthermore, assays of fresh serum from animals in hemorrhagic shock resulted in an increase in the developed force of the muscles tested. A minimal degree of depression was demonstrated only if the serum were frozen prior to assay. Utilizing an isolated supported heart preparation, it was demonstrated that short periods of graded hypotension led to complete recovery following →		

20. Abstract (continued)

→ reperfusion as indicated by peak isovolemic pressure drops, peak dP/dT and v_{max}. Ventricular performance declined "roughly" in proportion to the perfusion pressure down to a level of 30-35 mm Hg. ←
Endotoxemia could not be demonstrated to have any depressant effect on the myocardium in an isolated heart lung preparation and in the intact animal. The use of positive inotropic agents in the presence of ischemia appeared to be deleterious as manifested by an increase incidence of serious arrhythmias with some drugs, delayed recovery time in others, and an attenuated inotropic response.

Loss of normal coronary tone was demonstrated to occur at pressures of 25 mm Hg as manifested by the loss of hyperemic response to nitroglycerin. This was thought to represent ischemia of the total ventricular as opposed to regional ischemia which occurs at pressures between 25 to 40 mm Hg. Myocardial ischemia was demonstrated to occur in a rather narrow range of systemic pressures and was thought to limit the degree of hypovolemia which can be tolerated.

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Review of Studies performed under this contract. - (Contractile State of the Heart During Hypovolemic Shock and Endotoxemia)

Studies during this period evaluated several basic areas.

1. They had evaluated the degree to which myocardial depression may appear during fatal standardized hemorrhagic shock in both cats and dogs. The data demonstrated that myocardial depression need not be present despite the lethal progression of hemorrhagic shock. Further it would appear that the maintenance of contractility depends at least in part on catecholamine support of the myocardium.
2. They had evaluated the effects of short periods of graded hypotensive perfusion on the time course of the mechanical events of the myocardium utilizing an isolated supported heart preparation. One effect of acute hemorrhagic hypotension will be the presence of ischemic perfusion of the heart. This model has allowed an evaluation of the changes brought about by this component of the hemorrhagic shock syndrome. Short periods of severe hypotensive perfusion are consistent with complete myocardial recovery following reperfusion, and the decrement in peak force development is roughly proportional to the decrement in perfusion pressure below 50 to 60mm mercury. Peak isovolumic pressure drops more rapidly with the onset of ischemia than does peak dP/dT and V_{max} but all three parameters of contractility fall within approximately four minutes of the ischemia of severe degree.
3. They had designed studies to evaluate the relation between the level of coronary perfusion pressure and the appearance of ischemia. Ischemia had been defined as a limitation in myocardial contractility reversed by hyperperfusion; Utilizing this model they had demonstrated that ischemia can just be detected at perfusion pressures of about 45mm. Hg., that subendocardium is affected first and that at arterial pressures of 25mm. Hg. that ischemia is present.

4. In view of the studies of other workers who have demonstrated a myocardial depressant factor in the blood during hemorrhagic shock, they assayed the blood from a large number of dogs in standardized hemorrhagic shock for such a depressant factor. Assay using fresh serum from animals in hemorrhagic shock resulted in a universal increase in the developed force of the assayed muscle. They could only demonstrate some degree of depression if the serums were frozen prior to assay of the serum from shocked dogs and even then such depression was minimal.

5. They have evaluated the degree to which endotoxin in high dosages directly depress the myocardium. Both in an isolated heart lung preparation and in the intact animal, they have been unable to demonstrate that the endotoxemia per se has any depressant effect on the myocardium.

One major component of the shock syndrome is the potential appearance of myocardial hypoperfusion and ischemia. Their studies have been oriented toward an evaluation of three different aspects of the effects of ischemia on the heart.

First, they have evaluated the effects of short periods of ischemia on myocardial performance. Ventricular performance declines roughly in proportion to the perfusion pressure down to a level of 30-35mm mercury pressure. Below this level a steady state is not seen but there is a progressive decline in ventricular performance. With intermediated levels of ischemia a steady state lasted for at least 15 minutes followed by a relatively prompt return of all parameters of performance to control levels on reperfusion.

Second, the use of positive inotropic agents in the presence of ischemia appeared to be deleterious in several ways. Ischemia markedly attenuates the inotropic response to paired ventricular pacing, digitals and heart rate. The use of these agents prolongs the recovery from ischemia and then cessation in the presence of ischemia leads to a mortled degree of depression. Further the use of digitalis preparations during hypotensive perfusion increased the incidence of serious arrhythmias.

Third, they had investigated the relationship between the degree of myocardial ischemia and hemorrhage in the dog. This was approached by first operationally defining ischemia as a condition where cardiac function is compromised by an inadequate blood flow. Open chest dogs were progressively bled to hypotensive levels. The flow dependency of contraction was tested by periodically hyperperfusing the coronary arteries. Augmentation of the force recorded by an epicardial strain gauge arch with hyperperfusion indicated the heart had been inadequately perfused. At normal and moderately depressed aortic pressure, contractile force was not significantly changed by hyperperfusion. However force rose sharply with hyperperfusion as aortic pressure fell below 40mm Mg.

Normally coronary tone is adjusted to provide a blood flow which maintains the nutritional requirements of the heart regardless of the perfusion pressure. The range over which this control function is limited, however, and when the vessels reach their limit of dilation no further increase in flow can be achieved. Thus the onset of myocardial ischemia should be accompanied by loss of coronary tone. Coronary tone, indicated by the flow increase in response to intracoronary nitroglycerin. The hyperemia in response to nitroglycerin is lost at aortic pressures of 25mm Mg. indicating maximal state of vasodilation. Reinfusion of the shed blood returned tone to control levels. This indicated that coronary tone is lost at a somewhat lower pressure than that at which contraction becomes flow dependent. Explanation of this data is that tone is lost only when all of the tissue becomes ischemic. Functions however, will be depressed when just a fraction of the tissue is involved. This suggested that the amount of tissue experiencing ischemia is dependent on the level of hypotension in the range of 25-40mm Mg. This was confirmed by demonstrating that the distribution of the coronary blood flow at 25mm Mg. is grossly non-uniform with the epicardial layers receiving over twice the blood flow of the subendocardium.

Finally it was shown that the loss of tone does denote ischemia of the

of the total ventricle. To lose tone required an average bleed of about 700cc. At this level of loss the animals had a stable systemic pressure. Removal of an additional 50cc of blood however resulted in a steady decline in systemic pressure and cardiac function. Both were easily reversed by simply augmenting coronary flow. Failure to do so resulted in rapid death.

In conclusion, as systemic pressure falls below 40mm. Hg. regional ischemia appears in the subendocardium, at 25mm. Hg. all coronary tone is lost indicating that ischemia involves the entire ventricle. Any further hemorrhage can not be tolerated. Thus myocardial ischemia occurs in a rather narrow range of systemic pressures and places limit on the degree of hypovolemia which can be tolerated.

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