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Effects of Controlled Acute Hemorrhage on Myocardial Contractile Force. (26778)

LAZAR GREENFIELD, PAUL A. EBERT, AND W. GERALD AUSTEN
(Introduced by Robert W. Berliner)
Clinic of Surgery, National Heart Institute, Bethesda, Md.

The concept that cardiogenic factors are contributory to death from shock has been well documented since the early observations of Werle, Cosby and Wiggers(1). These investigators showed that pulsus alternans, progressive bradycardia, and an elevated right atrial pressure are terminal features of hemorrhagic shock. Pathologic study of dog hearts following hemorrhagic shock(2) has suggested that myocardial ischemia is the underlying cause of the cardiac depression. Further support is lent to this view by studies of coronary blood flow and myocardial oxygen consumption(3,4,5,6) which demonstrated that flow is decreased in spite of coronary vasodilatation and that myocardial oxygen consumption is reduced even though the extraction of oxygen from coronary arterial blood is increased. That a net decrease in cardiac efficiency is associated with shock has been generally agreed upon, but some investigators feel that the observed reduction in coronary flow is insufficient evidence that cardiac failure contributes to the progression of hemorrhagic shock and have suggested that other properties of the myocardium be evaluated to elucidate further the mechanics of adjustment to the shock state(7). In the present study myocardial contractile force was measured during acute hemorrhage and onset and extent of myocardial depression assessed by this means.

Methods. Adult mongrel dogs weighing 9-14 kg and apparently in good health were anesthetized with thiopental (30 mg/kg) and respiration was maintained through a cuffed endotracheal tube attached to a piston-type respirator. Central aortic pressure was obtained by cannulation of one femoral artery and the opposite femoral artery was cannulated and connected to an elevated calibrated reservoir. A Walton-Brodie strain gauge arch(8) was sutured to the anterior surface of the right ventricle after the right chest had been opened. The segment of myocardium between the points of attachment of the arch was stretched by at least 50% of its initial length so that any change in fiber length would not affect the measurement of contractile force(9). Pressures measured by means of Statham transducers were recorded continuously, along with myocardial contractile force, on a direct-writing polygraph. The animals were given heparin intravenously (2 mg/kg) and after a control observation had been made they were allowed to bleed into the reservoir at a steady rate. Eight dogs were bled at a rate which lowered mean aortic pressure to 50 mm Hg within 2 minutes; 4 dogs were bled to this level of pressure in 5 minutes and another 4 dogs were bled to this pressure in 10 minutes. Blood pressure was maintained at or below 50 mm Hg by continued withdrawal of blood as necessary during the period of observation and the animals were then sacrificed.

An additional group of 4 dogs was studied utilizing total right heart bypass. Cannulae were inserted into the superior and inferior vena cavae and a third cannula was inserted into the right ventricle to return coronary blood and provide total ventricular decompression. The venous return from these cannulae was collected in a reservoir and re-

turned to a branch of the pulmonary artery by a Sigmamotor pump. Systemic pressure was acutely reduced by decreasing rate of flow into the pulmonary artery, simulating acute bleeding. Arterial pressure was reduced to 40-50 mm Hg within 2 minutes and changes in right ventricular contractile force were recorded.

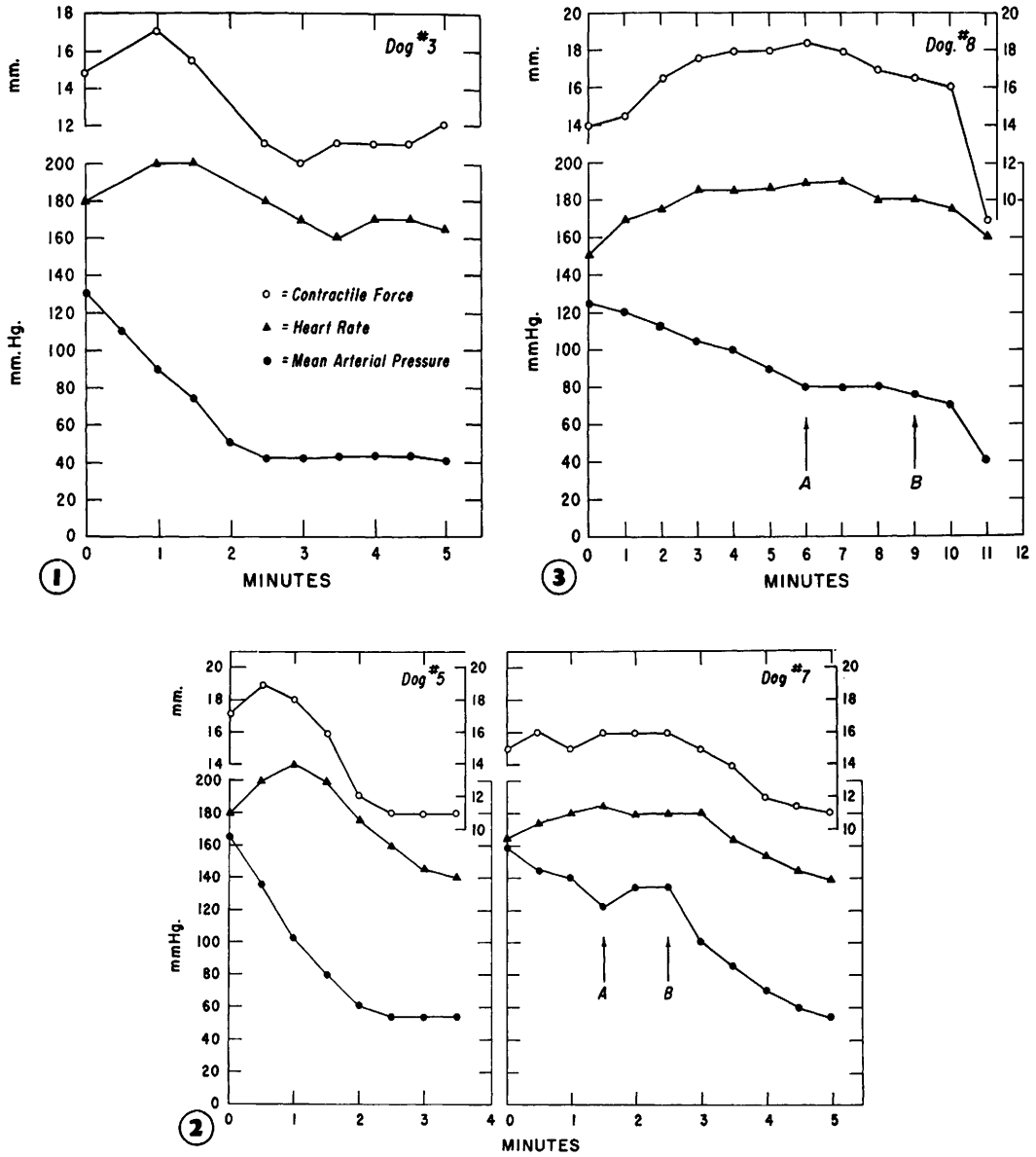

FIG. 1. Effects of acute hemorrhage on heart rate, myocardial contractile force and mean arterial pressure of a normal dog. Mean arterial pressure was lowered to 40 mm Hg within 2 min. of onset of bleeding.

FIG. 2. Effects of controlled acute hemorrhage on heart rate (▲—▲), myocardial contractile force (○—○) and mean arterial pressure (●—●) in 2 normal dogs. A mean arterial pressure of 50 mm Hg was attained within 2 min. in Dog #5 and within 5 min. in Dog #7. At point A in Dog #7 bleeding was stopped for 1 min., and bleeding was resumed at point B.

FIG. 3. Effects of acute hemorrhage on myocardial contractile force (○—○), heart rate (▲—▲) and mean arterial pressures (●—●). The dog was bled over a 6-min. period to a pressure of 80 mm Hg (point A). Bleeding was discontinued for 3 min. and then resumed (point B).

Results. The cardiovascular responses of a normal dog to sudden acute hemorrhage are shown in Fig. 1. With onset of bleeding there was an increase in heart rate and contractile force, but depression of both occurred when mean aortic pressure fell below 90 mm Hg. The decrease in contractile force preceded the fall in rate. Fig. 2 (dog #5) illustrates the findings in another experiment in which hemorrhage at approximately the same rate was induced; a decrease in contractile force occurred while heart rate was still increasing. Subseqeunt depression in both heart rate and contractile force were again noted when mean arterial pressure was lowered to 100 mm Hg. In the second experiment in Fig. 2 (dog #7) bleeding was stopped when arterial pressure reached 120 mm Hg (point A) and both rate and contractile force stabilized. When bleeding was resumed one minute later (point B) decreases in contractile force and rate were observed as arterial pressure fell to 100 mm Hg. In all animals bled to a mean arterial pressure of 50 mm Hg within 2 or 5 minutes an average initial increase in contractile force of 13.7% was noted. Contractile force and heart rate began to decrease at an average mean pressure of 95 mm Hg and when the pressure had fallen to 50 mm Hg, contractile force averaged 28.3% less than control levels. Measurements of right ventricular end-diastolic pressures in 4 of the dogs bled acutely showed no significant change during the period of observation.

The effects of a slower rate of bleeding are shown in Fig. 3. In this dog the gradual decline in arterial pressure was accompanied by a marked increase in heart rate and contractile force. When bleeding was stopped at a mean pressure of 80 mm Hg (point A) a gradual decrease in both contractile force and heart rate occurred. When bleeding was resumed 3 minutes later (point B) a more rapid decline in both modalities was observed. Observations in all 4 dogs bled to 50 mm Hg during a 10 minute period showed that average initial increase in contractile force was 27.6%. Decreases in contractile force and heart rate were noted at an average mean pressure of 86 mm Hg; at the end of the 10 minute observation period contractile force averaged 37.7% less than control levels.

In the dogs subjected to right heart bypass, the effects of acute hypotension on myocardial contractile force were identical to the effects of acute bleeding. Decreases in heart rate and contractile force occurred at an average mean pressure of 85 mm Hg and average depression in contractile force at the end of 5 minutes of hypotension was 47.8%. At the end of the hypotensive period, rate of perfusion was increased sufficiently to return arterial pressure to control levels; the contractile force showed a corresponding return to an average of 105% of control.

Discussion. The cardiovascular response to hemorrhagic shock in dogs has been studied in most cases after shock levels of arterial pressure had been induced. At this level of circulatory depression, it has been shown that there is coronary vasodilatation(6), decreased coronary flow(6), elevated atrial pressure(3), decreased stroke output(10), and increased oxygen extraction from coronary blood(5). From investigations made during induction of shock it has been shown that a metabolic conversion occurs from the aerobic phase of the Krebs cycle to an anaerobic phase with increased levels of pyruvate and lactate in coronary venous blood(4). It has also been demonstrated by electropolarographic technics that a decline in myocardial oxygen availability in the tissues occurs in proportion to the decline in arterial pressure induced by rapid hemorrhage(12). The changes in contractile force noted in the present study no doubt result from the metabolic and hemodynamic alterations above. In every animal, regardless of rate of bleeding, a decrease in contractile force occurred when mean arterial pressure fell to 85-95 mm Hg, and shortly thereafter was accompanied by a fall in heart rate.

In the animals subjected to right heart bypass, identical depression of heart rate and contractile force was noted during hypotension. As arterial pressure was increased to normal, heart rate and contractile force returned to control levels. This constant relationship of contractile force to arterial pressure, and the coincident decrease in heart

rate, support the assumption that the changes are due to myocardial depression. The most logical explanation for the depression of contractile force and heart rate below a mean arterial pressure of 90 mm Hg is that this represents a critical coronary perfusion pressure. With profound hypotension the role of coronary insufficiency in the depression of ventricular function has been previously shown(11), but the present results indicate that neither prolonged nor severe circulatory depression is necessary for the occurrence of myocardial depression in response to hemorrhage. In a study of dogs with totally denervated hearts* neither augmentation nor depression of heart rate and myocardial contractile force occurred in response to acute hemorrhage. These findings suggest that in addition neurogenic factors influence the myocardial response to rapid blood loss.

Summary. The changes in myocardial contractile force and heart rate which accompanied acute bleeding were studied in normal dogs. Increases in contractile force and heart rate were noted in response to hemorrhage until mean arterial pressure fell to less than 90 mm Hg. Below this level of pressure depression of both modalities began and continued as pressure was further lowered. These findings indicate that myocardial depression occurs at an early stage in acute bleeding and probably results from a critical diminution in coronary perfusion pressure.

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Partial Purification of Cattle Serum Transferrin Using Rivanol.* (26779)

BECCA PATRAS AND W. H. STONE (Introduced by M. R. Irwin)
Department of Genetics, University of Wisconsin, Madison

Chemical studies of genetic differences in proteins are invaluable in understanding the mechanism of gene action. Inherited variations in the serum proteins of many animal species can be used to study gene-controlled protein specificity(1). Transferrin, also known as siderophilin or β-metal combining globulin, appears to be a very promising subject for such a study, since inherited variations in this protein have been demonstrated in many animal species(2-5), and much is known about its chemical properties(6).

Transferrin of cattle serum can be resolved into at least 4 components by starch gel electrophoresis(7,8). The mobility of all of these are affected by a change in the transferrin locus. Five alleles have been described so far, designated β^A, β^B, β^D, β^F, β^E, in order of decreasing mobility of the corresponding transferrin(9). Different breeds of cat-

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