Circulatory Shock 28:321–332 (1989)

Hemodynamic Response to Abdominal Aortotomy in the Anesthetized Swine

William H. Bickell, Stephen P. Bruttig, and Charles E. Wade

Division of Military Trauma Research, Letterman Army Institute of Research, Presidio of San Francisco, California

This study was conducted to determine the hemodynamic response to uncontrolled hemorrhage following aortotomy in anesthetized swine. Eight Yorkshire swine underwent splenectomy and stainless steel wire placement in the anterior infrarenal aorta and were instrumented with Swan-Ganz and carotid artery catheters. Following an equilibration period, the wire was pulled. This produced a 5 mm aortotomy and spontaneous intraperitoneal hemorrhage. Serial measurements of mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), and cardiac output (CO) were obtained. From baseline to 5 min after aortotomy, there was a profound decrease in MAP in conjunction with a significant decrease in CO and MPAP. After the initial 5 min period, there was a progressive elevation in MAP, CO, and MPAP. Peripheral vascular resistance (PVR) was significantly decreased after aortotomy and returned to baseline after 60 min. From these data, we conclude that aortotomy produces a rapid depression and spontaneous recovery in MAP, CO, and MPAP. Aortotomy also produces a significant decrease in PVR, which is not generally associated with hemorrhagic hypotension.

Key words: cardiac output, hypotension, hemorrhage, vascular injury, total peripheral resistance

INTRODUCTION

In an effort to gain a scientific understanding of the hemodynamic consequences of blood loss, Carl Wiggers developed a laboratory model of hemorrhagic shock [1]. Experimentally, blood was withdrawn through a catheter until an arbitrarily predetermined blood pressure reduction was achieved. The hypotensive state was maintained over time by the addition or further withdrawal of blood. This ex-

Submitted for publication September 12, 1988; revised February 21, 1989.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Address reprint requests to Dr. Charles E. Wade, Division of Military Trauma Research, Letterman Army Institute of Research, Presidio of San Francisco, CA 94219-6800.

perimental method results in a highly reproducible cardiodynamic state and hence gained considerable popularity in laboratory study of hemorrhagic shock. However, Wiggers' model is of questionable relevance to the clinical setting, in which fixed hypotensive states over prolonged periods are rarely if ever encountered. Hemorrhage to a predetermined volume has been suggested to simulate more closely the course of events that might occur in response to vascular injury [2]. However, this too is a controlled hemorrhage. That is, blood is atraumatically withdrawn through a surgically implanted catheter. It is unlikely that the experimental conditions of controlled blood withdrawal accurately reflect the hemodynamic sequelae of acute vascular injury and subsequent hemorrhage.

In an uncontrolled hemorrhage model, blood loss occurs as a direct result of injury to the vascular circuit. The rate and ultimate volume of hemorrhage are dependent on the area of the vascular injury and the dynamic factors of vascular contraction, transmural pressure, flow, and thrombus formation [3,4]. An uncontrolled hemorrhage model has been utilized by numerous investigators in an attempt to produce a more clinically relevant experimental condition [3,5–7]. The previous studies of uncontrolled hemorrhage have focused on therapeutic interventions or the hydrodynamics of vascular bleeding. Our knowledge of the systemic cardiovascular response to this condition is therefore limited. To address this issue, we developed an aortotomy hemorrhage model in the swine that would allow a more complete assessment of cardiovascular function. This model was utilized to determine the effects of uncontrolled arterial hemorrhage on systemic and pulmonary hemodynamic functions and oxygen transport following truncal vascular injury.

MATERIALS AND METHODS

Eight Yorkshire gilts were obtained from a commercial breeder (J.G. Boswell, Corcoran, CA) and were maintained in a common indoor holding area at the Letterman Army Institute of Research until they were utilized for the study 4–8 weeks after arrival. They were fed a commercial ration (Purina Pig Chow; Purina, St. Louis, MO) and allowed water ad libitum. The pigs were 4–5 months old and weighed 30–41 kg when the studies were conducted. After an overnight fast, each pig received a preanesthetic intramuscular injection of 2.2 mg/kg ketamine HCl, 0.09 mg/kg atropine, and 2.2 mg/kg xylazine. Halothane was given by facemask, and endotracheal intubation was performed. The animal was then placed on oxygen (FIO_2 0.6), nitrous oxide, and 1% halothane, i.e., a standard surgical anesthetic regimen at our institution. A celiotomy was performed, and the spleen was removed according to standard techniques, with double ligation of all vascular pedicles. The retroperitoneal fascia was incised, and the anterior surface of the aorta was exposed. On the coronal plane of the aorta, two points were placed with a surgical marker 10 and 10.5 cm proximal to the aortic bifurcation. A 27-gauge, 3.75 cm hypodermic needle, which had been previously formed to a semicircle with a radius of 5 mm, was precisely placed through the proximal point into the aortic lumen and exited out the distal point. A size 4-0 monofilament stainless steel surgical wire was passed through the lumen of the needle. The needle was withdrawn over the stainless steel wire, thereby leaving the wire through and through on the ventral wall of the aorta. The extraluminal exit sites of the wire were 5 mm apart. The free ends of the aortic stainless steel suture were exteriorized on the ventral abdominal wall. The abdominal surgical incision was

then closed in two layers with size O Dexon. Through a midline neck incision, the right common carotid artery was exposed, and a polyvinyl catheter was inserted to the level of the aorta and secured by ligatures around the vessel. A 7.5 French Gould flow-directed thermodilution Swan-Ganz catheter was inserted through the right internal jugular vein and positioned with the distal port in the pulmonary artery. The surgical preparation required 30 to 45 min. The lumen of all catheters was filled with normal saline. The arterial and Swan-Ganz catheters were connected to Statham 23 Db pressure transducers, a Gould ES1000 multichannel polygraph, and a Gould cardiac output (CO) computer. The nitrous oxide was discontinued, and the animal continued to ventilate spontaneously oxygen (FIO_2 0.4) and 1% halothane. Thirty minutes after the completion of the surgical preparation and catheter placement, baseline hematocrit, arterial blood gases, and cardiodynamics (phasic aortic and pulmonary artery pressures and CO) were recorded. The stainless steel wire was then pulled to remove it from the abdominal cavity. The withdrawal of the wire suture resulted in a 5 mm aortotomy and spontaneous intraabdominal hemorrhage. Following aortotomy, the systemic arterial blood pressure was measured every 10 sec for the first minute, every 15 sec from 1 to 3 min, and every 30 sec from 3 to 4.5 min after aortotomy. Thereafter, measurements of arterial blood gases, hematocrit, and cardiodynamics were recorded 5, 15, 30, 60, 90, and 120 min after aortotomy. In pilot experiments, increasing the length of the aortic laceration to 6 mm generally resulted in a fatal outcome within 15 min of the vascular injury. An aortotomy of less than 3 mm produced only minor reductions in CO and mean arterial pressure (MAP). A 5 mm aortotomy was therefore utilized in the present study as a severe, yet survivable, injury.

To ensure the acquisition of fresh, circulating blood, removal of the sample was immediately preceded by withdrawal of 4 ml of fluid from the carotid arterial catheter and 2 ml of fluid from the pulmonary artery catheter. Following the removal of a 2 ml sample of blood, the catheters were flushed with 5 cc of normal saline. The blood samples were collected in a heparinized syringe and placed on ice. Blood gas measurements were made within 5 min of sample removal with an Instrumentation Laboratories Model 1303 blood gas analyzer and Instrumentation Laboratories Model 282 Cooximeter. Hematocrits of all samples were determined immediately using a Lourdes Model MH microhematocrit centrifuge (Venitron, Carlstadt, NJ). CO was estimated by a thermodilution technique. The injectate was 5 ml of normal saline at room temperature (20–20.5°C). Successive CO measurements were obtained until two consecutive recordings differed by no more than 0.2 liter/min and produced satisfactory logarithmic washout curves (usually two to four determinations). After the final blood samples and cardiodynamic measurements were obtained, the animals were euthanized with an intravenous injection of barbiturate (Euthanol-6; 10 ml). A gross necropsy was performed to examine the aortotomy site and surrounding thrombus. A section of the aorta 2 cm proximal and distal to the aortotomy was removed and examined.

Mean pressures were determined from the Gould recorder. Heart rate was determined from the pulse pressure tracing. Peripheral vascular resistance (PVR) was calculated from a standard formula [i.e., (MAP−CVP)/CO]. Arterial oxygen content (C_aO_2) and mixed venous oxygen content (C_vO_2) were determined from the aortic and pulmonary artery blood gases using the formula Hb × 1.39 × $\%O_2$, where Hb refers to the hemoglobin concentration in g/dl and $\%O_2$ is the oxygen saturation. Oxygen

delivery was the product of C_aO_2 and CO/body weight. Oxygen consumption (VO_2) was calculated from the formula $VO_2 = CO \times (C_aO_2 - C_vO_2)$/body weight.

The data were evaluated by an analysis of variance adjusted for repeated measures. When a significant F ratio was found, the Newman-Keuls test was used to identify the variant times. Differences were considered significant at $P < 0.05$. Values given in the text are expressed as mean ± SEM.

RESULTS

Cardiodynamics

Aortotomy produced a significant decrease in CO, stroke volume (SV), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), MAP, and mean pulmonary artery pressure (MPAP) (Figs. 1, 2). The lowest measured levels of these variables occurred 5 min after aortotomy. Following this sample time, there was a significant recovery toward control values. PVR decreased after aortotomy; however, the gradual decrease was not statistically significant until 15 min postaortotomy (Fig. 1). PVR and MPAP were no longer significantly different from control values 60 and 90 min after aortotomy, respectively (Figs. 1, 2). The heart rate was significantly increased over control values throughout the study (Fig. 2). The changes in systemic arterial blood pressure that occurred over the first 5 min are shown in Figure 3. Systolic pressure, diastolic pressure, and MAP were decreased significantly 10 sec after aortotomy. There was no further significant fall in systemic blood pressure beyond 90 sec after aortotomy.

Acid Base Status

Aortotomy produced a significant increase in mixed venous PCO_2 and a decrease in mixed venous pH that persisted throughout the study. Arterial pH and PCO_2 were significantly decreased only at 5 min and 1 hr postaortotomy, respectively. Mixed venous bicarbonate concentration was significantly decreased 30 min postaortotomy but otherwise remained at baseline levels throughout the study.

O_2 Transport

Hematocrit and arterial oxygen content were significantly decreased from control values throughout the study (Figs. 4, 5). The combined decrease in CO and arterial oxygen content produced a significant decrease in tissue O_2 delivery, with the lowest measured level occurring 5 min postaortotomy (Fig. 5). Thirty minutes after aortotomy, there was a significant recovery in O_2 delivery. Total body O_2 consumption was not significantly changed over the course of this study (Fig. 5). The O_2 extraction significantly increased, and hence the venous O_2 content was significantly decreased, from baseline levels after aortotomy (Fig. 5). Following the 5 min sample time, there was a significant change towards baseline values in these variables.

Thrombus Formation

At necropsy, the aortotomy was covered with a large thrombus, which was adherent to both the aorta and the surrounding tissue. No intraaortic thrombus formation was noted when the aorta at the laceration site was cross sectioned and examined.

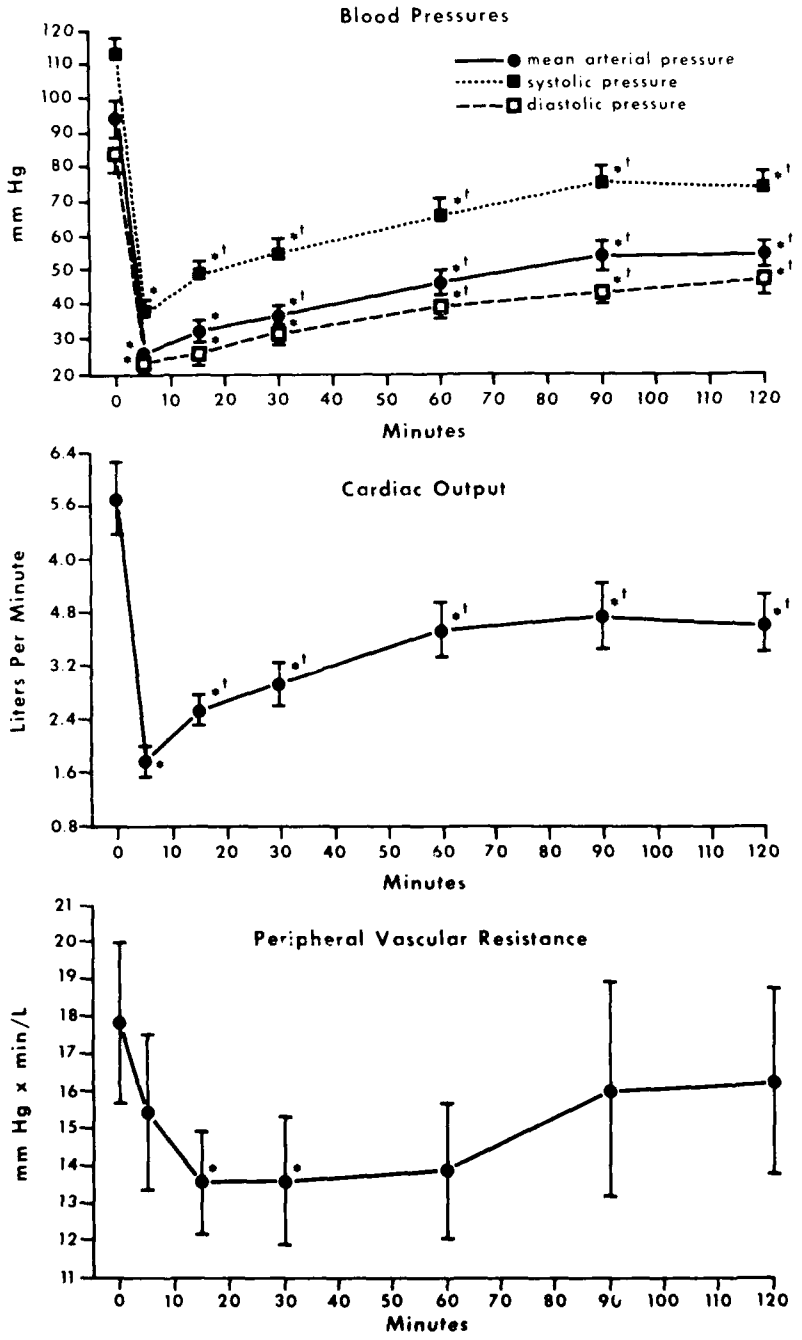

Fig. 1. Effects of aortotomy on systemic arterial blood pressures, cardiac output, and peripheral vascular resistance. Values represent the mean ± SEM. *Significantly different from baseline ($P < 0.05$). †Significantly different from the 5 min sample time ($P < 0.05$).

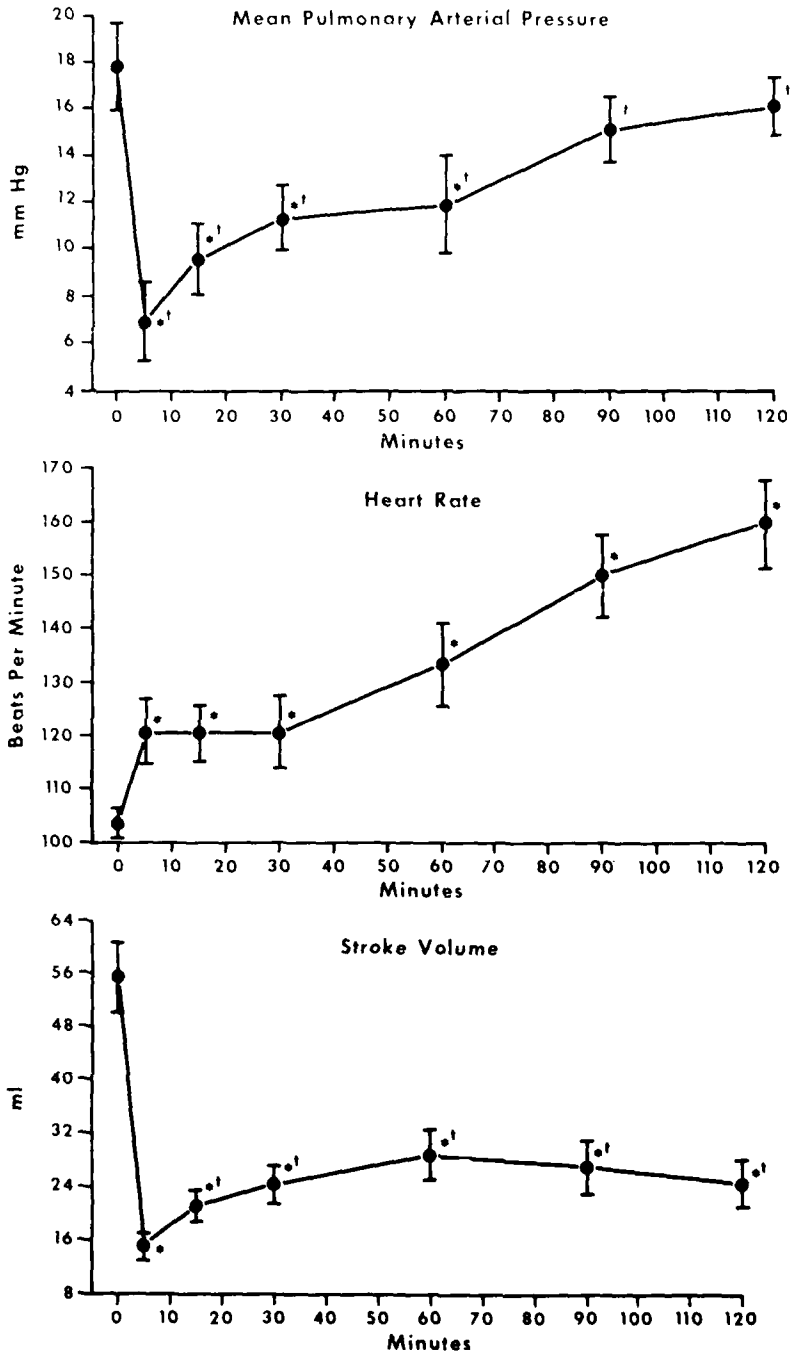

Fig. 2. Effects of aortotomy on pulmonary artery pressure, heart rate, and stroke volume. See Figure 1 for details.

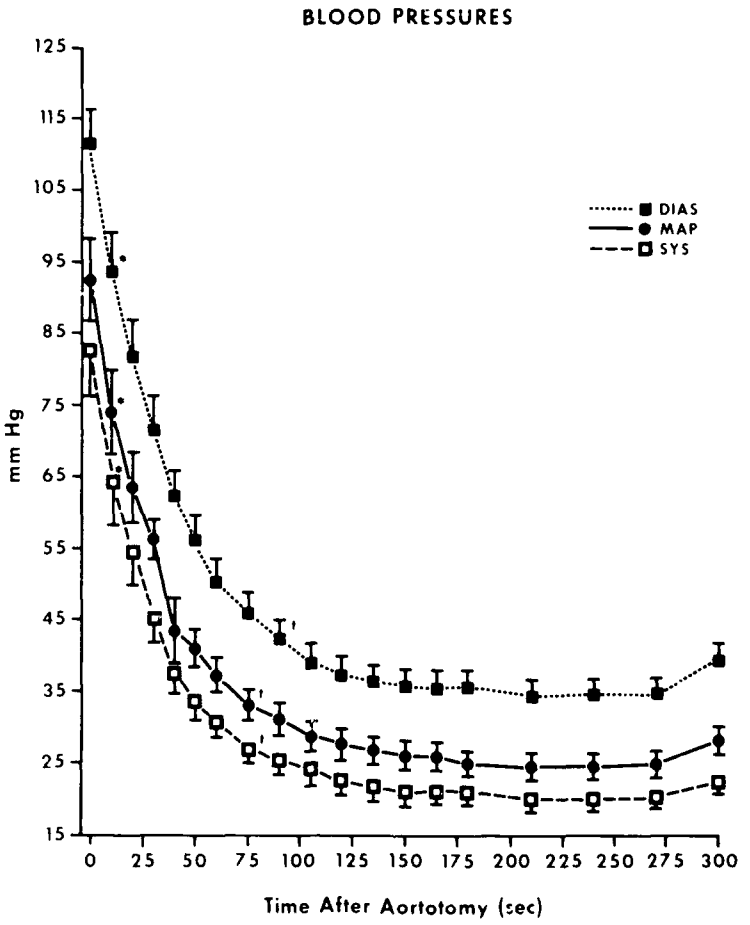

Fig. 3. Systemic arterial blood pressure changes over the first five minutes following aortotomy. *Significantly different from baseline ($P < 0.05$). #Succeeding blood pressure measurements not significantly different

DISCUSSION

The hemodynamic sequelae of controlled hemorrhage have been extensively studied in a variety of animal species, including the swine. The present study is unique in that hemorrhage resulted from an injury to the truncal vascular circuit and was therefore uncontrolled. The results of the present study are more than unique, however; they are clinically relevant as well, since most deaths from hemorrhage involve vascular injury to truncal vessels. Our results are considerably different from those noted when blood is atraumatically withdrawn through a surgically implanted catheter. The magnitude of the decrease in systemic arterial blood pressure following aortotomy is greater than what would be predicted from the apparent volume of blood loss. Although it was not possible to quantitate accurately the amount of hemorrhage,

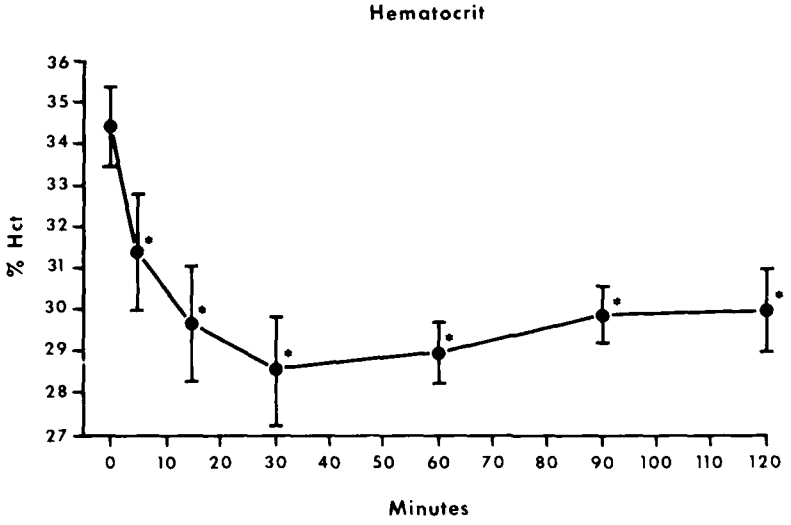

Fig. 4. Effects of aortotomy on the hematocrit. *Significant change from baseline ($P < 0.05$).

it was estimated by a combined volumetric and sponge weight technique that the animals lost 31–35% of their circulating volume (i.e., 21–24 ml/kg). When a similar decrease in blood volume is produced by an atraumatic withdrawal through a surgically implanted catheter, MAP is reduced by 31% [2]. A controlled withdrawal of 50% of the circulating blood volume reduces MAP by 56% [2]. Comparable fixed volume deficits in other species have demonstrated similar blood pressure reductions [8,9]. In contrast, MAP decreased 73% in the present study of uncontrolled aortotomy hemorrhage.

There are three possible explanations for the accentuated hypotensive response in this model of uncontrolled hemorrhage. First, it could be reasonably argued that the findings of this study resulted from the combined effects of the anesthetic and hemorrhage. For example, halothane decreases cardiac contractility and systemic arterial pressure [10]. It is possible that the combined effect of halothane coupled with hemorrhage yielded the profound hemodynamic depression seen in this study. However, preliminary results of aortotomy performed in conscious, chronically instrumented swine have demonstrated similar changes in systemic arterial pressure [11].

The second explanation is that rate of hemorrhage was the responsible factor. Increasing the rate at which a given volume of blood is removed decreases the time in which baroreceptor/mechanoreceptor activity, hormonal responses, and transcapillary refill can compensate for the volume deficit during hemorrhage. We compared our data with data collected on hemorrhage conducted over 1 hr. We were unable to determine accurately the time course of hemorrhage in our study; however, the finding that the blood pressure nadir and recovery occur within 5 min of aortotomy raises the possibility that hemorrhage transpires over this same time frame (Fig. 5).

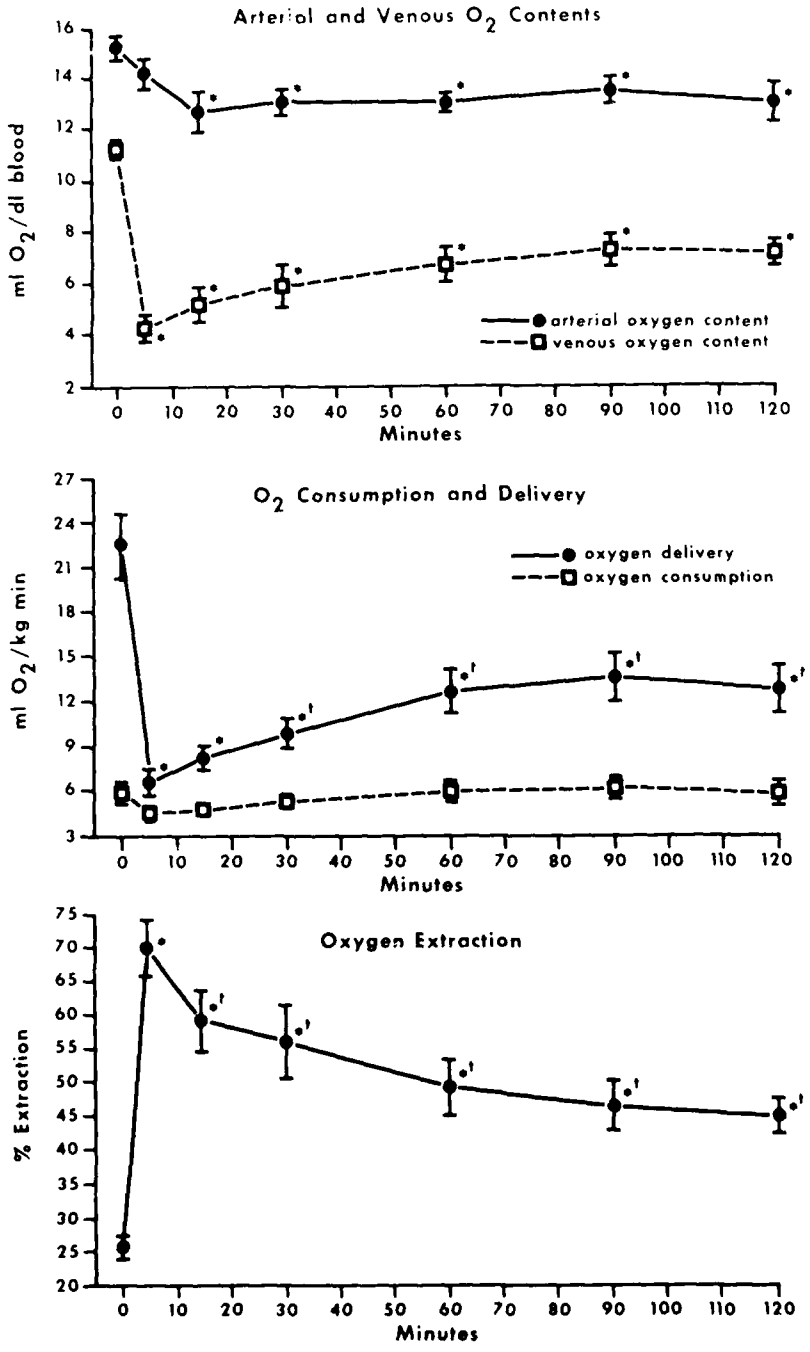

Fig. 5. Effects of aortotomy on O_2 transport. See Figure 1 for details.

Hence the marked decrease in arterial pressures may have resulted from a hemorrhage over this relatively brief time course.

A third explanation for the accentuated hypotensive response is that, in addition to blood loss, other mechanisms were responsible for the hemodynamic changes. This appears to be the case with the initial period after aortotomy. Our data demonstrate that aortotomy produces a significant reduction in systemic arterial blood pressure within seconds of the vascular laceration (Fig. 3). It seems unlikely that arterial hemorrhage alone could reduce left ventricular venous return and CO within this time frame. The initial changes in systemic arterial pressure therefore appear to have resulted from the creation of an additional circuit for blood flow (i.e., the tear in the aorta) which in turn reduced PVR and hence systemic arterial pressure. Although the PVR effect of free vascular hemorrhage may explain the immediate drop in blood pressure after aortotomy, it does not account for the progressive fall over the ensuing 90 sec (Fig. 3). Furthermore, we would expect this effect to decrease as tamponade and/or thrombus formation closes the vascular interruption. The hypotensive response could also be accentuated if the arterioles vasodilate or fail to vasoconstrict in response to aortotomy hemorrhage. It may seem improbable that this could occur during hemorrhagic hypotension, because this is contrary to the accepted mechanisms of blood pressure regulation. A fall in arterial pressure is reported to decrease and eventually eliminate baroreceptor-mediated inhibition of the vasomotor center [12,13]. As a result, efferent vasomotor sympathetic stimulation will increase heart rate, cardiac contractility, and vasomotor tone of both arteriolar and venous capacitance vessels [14–17]. Although there was a significant increase in heart rate postaortotomy, there was no evidence that the arterioles constricted in response to hypotension; PVR significantly decreased after aortotomy (Figs. 1, 2). This reduction in PVR may simply reflect the sudden appearance of an additional conduit for blood flow as discussed above. However, PVR was significantly reduced 15–30 min after aortotomy. At this time, there was no evidence of continued hemorrhage; blood pressure and CO had progressively increased since the 5 min sample time. The reduction in PVR could also have resulted from the rheological effects of the hemodilution that occurred after aortotomy (Fig. 4) [18]. With changes in intravascular volume and hematocrit, the relationship between PVR and vasomotor tone is by no means direct. Nonetheless, the observed fall in PVR raises the possibility that aortotomy decreases the vasomotor tone of the resistance vessels (arterioles). Moreover, the simultaneous occurrence of hypotension and a reduction in PVR raises the possibility that the baroreceptor/vasomotor reflexes may be altered by aortic hemorrhage. This concept is supported by the findings of Chen et al. [19] that, during hemorrhagic hypotension, vagal afferents can produce a vasodilatory effect, which becomes more pronounced as the degree of hemorrhage increases. This finding suggests that vagally mediated vasomotor inhibition can occur even when the inhibitory influence of the baroreceptors is minimal or absent. Such a phenomenon would also support the hypothesis first suggested by Pearce and Henry [20] that a small ventricle contracting against reduced afterload may stimulate ventricular mechanoreceptors and result in vasodilatation.

The aortotomy produced in this protocol is the maximum injury from which spontaneous hemodynamic recovery can be expected. Although the injury produced under the antecedent experimental conditions is a severe insult, it did appear to be within the limits of compensation. This is illustrated by the finding that the profound

changes in cardiodynamics did not significantly affect O_2 consumption. With the initial decrease and subsequent recovery in CO that occurred following aortotomy, there were corresponding changes in tissue O_2 delivery. The nadir in tissue O_2 delivery was further accentuated by the reduction in arterial O_2 content that resulted from hemodilution. Despite the immense changes in tissue O_2 delivery, O_2 consumption and presumably O_2 demand were not significantly affected because of an increase in tissue O_2 extraction (Fig. 5). The finding that the animals survived for 2 hr after their MAP had fallen to 25 mm Hg is also unique to this study. Controlled hemorrhage studies in both swine and dog have shown that posthemorrhage blood pressure reductions to 30 mm Hg or less are routinely fatal within 75 min [21–23].

We have demonstrated that aortotomy results in a uniform cardiodynamic response in the anesthetized swine. The hemodynamic results of this uncontrolled hemorrhage model are considerably different from those attributable to a decrease in blood volume alone. The rate and magnitude of the fall in blood pressure following aortotomy are considerably greater than what is seen with a controlled hemorrhage. Aortotomy also produces a significant decrease in PVR, which is not normally associated with a decrease in blood volume. It may seem paradoxical for the cardiovascular system to accentuate the fall in blood pressure and reduce PVR in the face of blood loss. However, the critical factors of vascular hemorrhage and thrombus formation reveal the value of these hemodynamic changes. Following aortotomy, the rate and ultimate volume of hemorrhage are primarily dependent on aortic blood pressure. An amplified fall in blood pressure will have the effect of reducing transmural pressure, which in turn will reduce the rate of hemorrhage [3,4,6]. Furthermore, with the recovery in CO, the hydrostatic stress on the thrombus is attenuated by a decrease in PVR. We therefore suggest the teleologically attractive concept that the cardiovascular system participates in the control of hemorrhage and the promotion of thrombus formation by actively reducing systemic arterial pressure and PVR.

ACKNOWLEDGMENTS

The authors thank Sgt. G. Kim, F.L. Tillman, and the Animal Care and Services Branch and Operating Room Staffs at Letterman Army Institute of Research for their technical assistance.

REFERENCES

1 Wiggers CJ. Experimental hemorrhagic shock. In Wiggers CJ (ed): "Physiology of Shock." New York: *Commonwealth Fund*, 1950, pp 121–146.

2 Hannon JP, Bossone CA. The conscious pig as a large animal model for studies of hemorrhagic hypotension. In Tubbleson ME (ed): "Swine in Biomedical Research, Vol. 3." New York: Plenum Press, 1986, pp 1413–1428.

3 Shattan GW, Chiu CJ, Dennis C, Harris B. Fundamentals of physiologic control of arterial hemorrhage. *Surgery* 58:851–856, 1965.

4 Wangensteen SL, Eddy DM, Ludewig RM. The hydrodynamics of arterial hemorrhage. *Surgery* 64:912–921, 1968.

5 Ludewig RM, Wangensteen SL. Aortic bleeding and the effect of external counterpressure. *Surg Gynecol Obstet* 128:252–258, 1969.

6 Milles G, Koucky CJ, Zachers HG. Experimental uncontrolled arterial hemorrhage. *Surgery* 60:434–442, 1966.

7. Shaftan GW, Chiu CJ, Grosz CS, Dennis C: The effect of transfusion and of certain hemodynamic factors on the spontaneous control of arterial hemorrhage. J Thoracic Cardiovasc Surg 5:251–256, 1964.
8. Larsson B, Olsson K, Fyhrquist F: Vasopressin release induced by hemorrhage in the goat. Acta Physiol Scand 104:309–317, 1978.
9. Weitzman RE, Reviczky A, Oddie TH, Fisher DA: Effect of osmolality on arginine vasopressin and renin release after hemorrhage. Am J Physiol 238:E62–E68, 1980.
10. Manohar M, Parks C: Hemodynamic effects of halothane-O_2 and halothane-nitrous oxide anesthesia in swine: Comparisons with equipotent isoflurane, enflurane and sevoflurane anesthesia. In Tumbleson ME (ed): "Swine in Biomedical Research, Vol. 3." New York: Plenum Press, 1986, pp 1353–1369.
11. Bickell WH, O'Benar J, Bruttig S, Wade CE, Hannon JP, Tillman F, Rodkey W: The hemodynamic response to aortotomy in the conscious chronically instrumented swine. Physiologist 30:228, 1987.
12. DiSalvo J, Parker PE, Scott JB, Haddy FJ: Carotid baroceptor influence on total and segmental resistances in skin and muscle vasculatures. Am J Physiol 220:1970–1978, 1971.
13. Donald DE, Edis AJ: Comparison of aortic and carotid baroreflexes in the dog. J Physiol 215:521–538, 1971.
14. Folkow B, Mellander S: Veins and venous tone. Am Heart J 68:397–408, 1964.
15. Heymans C, Neil E: "Reflexogenic Areas of the Cardiovascular System." Boston: Little, Brown, 1958.
16. Sarnoff SJ, Gilmore JP, Brockman KS, Mitchell JH, Linden RJ: Regulation of ventricular contraction by the carotid sinus: Its effect on atrial and ventricular dynamics. Circ Res 8:1123–1136, 1960.
17. Stegemann J, Geisen K: On standard theoretical analysis of the blood circulation. II: The persistence of the flow volume-pressure relation in the arterial system with and without regulation in dogs. Pflugers Arch Ges Physiol 287:257–264, 1966.
18. Sunder-Plassmann L, Kessler M, Jesch F, Dieterle R, Messmer K: Acute normovolemic hemodilution. Changes in tissue oxygen supply and hemoglobin-oxygen affinity. Bibliogr Haematol 41:44–53, 1975.
19. Chen HI, Stinnett HO, Peterson DF, Bishop VS: Enhancement of vagal restraint on systemic blood pressure during hemorrhage. Am J Physiol 234:H192–H198, 1978.
20. Pearce JW, Henry JP: Changes in cardiac afferent nerve-fiber discharges induced by hemorrhage and adrenalin. Am J Physiol 183:650, 1955.
21. Mamingas PA, DeGuzman LR, Tillman FJ, Hinson CS, Priegnitz KJ, Volk KA: Small-volume infusion of 7.5% NaCl in 6% Dextran 70 for the treatment of severe hemorrhagic shock in swine. Ann Emerg Med 15:1131–1137, 1986.
22. Rawson RA, Chien S, Peng T, Dellenback RJ: Determination of residual blood volume required for survival in rapidly hemorrhaged splenectomized dogs. Am J Physiol 196:179–183, 1959.
23. Traverso LW, Lee WP, Langford MJ: Fluid resuscitation after an otherwise fatal hemorrhage. I: Crystalloid solutions. J Trauma 26:168–175, 1986.

In conducting the experiments described in this report the investigators adhered to the NIH guidelines for the use of laboratory animals.