The Use of Hypertonic Saline/Dextran vs Lactated Ringer's Solution as a Resuscitation Fluid Following Uncontrolled Aortic Hemorrhage in Anesthetized Swine

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We tested the hypothesis that following aortotomy, the administration of hypertonic saline/dextran (HSD) will increase hemorrhage and mortality. In this study we also compared the effects of HSD to the standard therapy of attempting to replace three times the amount of lost blood with lactated Ringer's solution (LR). Twenty-four anesthetized Yorkshire swine underwent splenectomy and stainless steel wire placement in the infrarenal aorta and were instrumented with Swan-Ganz and carotid artery catheters. The wire was pulled, producing a 5 mm aortotomy and spontaneous intraperitoneal hemorrhage. From baseline to 5 min after aortotomy, there was a profound decrease in cardiac output, mean arterial pressure and mean pulmonary arterial pressure.
Following the administration of HSD there was a transient increase in cardiac output, but otherwise the hemodynamics were not significantly different from untreated control animals. The volume of hemorrhage and the mortality rate in the HSD-treated animals were significantly greater than in the non-resuscitated controls (1,340 ± 230 ml versus 783 ± 85 ml and 5/8 versus 0/8, respectively; p<0.05). The volume of hemorrhage in the LR group was significantly greater than that in both the HSD and control groups (2,142 ± 178 ml; p<0.05). Although the mortality rate in the LR group was not significantly different from the HSD group, the survival time was significantly less than in the HSD group. From these data, we conclude that, in this model of uncontrolled hemorrhage resulting from abdominal aortotomy, the IV administration of HSD significantly increased the volume of hemorrhage and mortality. However, the accentuation of hemorrhage and reduction in survival were not as great as that produced by the standard practice of attempting to replace three times the amount of lost blood with LR.
ABSTRACT

We tested the hypothesis that following aortotomy, the administration of hypertonic saline/dextran (HSD) will increase hemorrhage and mortality. In this study we also compared the effects of HSD to the standard therapy of attempting to replace three times the amount of lost blood with lactated Ringer's solution (LR). Twenty-four anesthetized Yorkshire swine underwent splenectomy and stainless steel wire placement in the infrarenal aorta and were instrumented with Swan-Ganz and carotid artery catheters. The wire was pulled, producing a 5 mm aortotomy and spontaneous intraperitoneal hemorrhage. The animals were randomly assigned to one of the three study groups: 1) Control group; 2) HSD group in which 6 min after aortotomy a 4 ml/kg mixture of 7.5% NaCl and 6% Dextran-70 was given intravenously (IV) over 1 min; 3) LR group in which 6 min after aortotomy 80 ml/kg LR was given IV over 9 min. From baseline to 5 min after aortotomy, there was a profound decrease in cardiac output, mean arterial pressure and mean pulmonary arterial pressure. Following the administration of HSD there was a transient increase in cardiac output, but otherwise the hemodynamics were not significantly different from untreated control animals. The volume of hemorrhage and the mortality rate in the HSD-treated animals were significantly greater than in the non-resuscitated controls (1,340 ± 230 ml versus 783 ± 85 ml and 5/8 versus 0/8, respectively; p<0.05). The volume of hemorrhage in the LR group was significantly greater than that in both the HSD and control groups (2,142 ± 178 ml; p<0.05). Although the mortality rate in the LR group was not significantly different from the HSD group, the survival time was significantly less than in the HSD group. From these data, we conclude that, in this model of uncontrolled hemorrhage resulting from abdominal aortotomy, the IV administration of HSD significantly increased the volume of hemorrhage and mortality. However, the accentuation of hemorrhage and reduction in survival were not as great as that produced by the standard practice of attempting to replace three times the amount of lost blood with LR.
INTRODUCTION

The combination of hypertonic saline and dextran has been shown to improve the survival of animals subjected to blood loss that would otherwise be fatal (1-3). Following a fixed volume hemorrhage, in which blood is atraumatically withdrawn through a surgically implanted catheter, hypertonic saline/dextran (HSD) has been shown to return cardiac output, arterial pressure, and tissue blood flow to normal or near normal levels in pigs, dogs and sheep (1-5). This hemodynamic response is believed to occur through a fluid mobilization from the extravascular compartment which in turn increases venous return and cardiac output (2,4,5). The encouraging results from the aforementioned laboratory studies have led to the use of a combined solution of hypertonic saline/dextran for the out-of-hospital resuscitation of patients with hemorrhagic hypotension (6,7,8). However, in this clinical setting, blood loss most often results from an interruption in the vascular circuit that is inaccessible to external control (9,10). Moreover, it is doubtful that fluid resuscitation in an experimental model of controlled blood withdrawal through a catheter will produce the same outcome as that clinically observed when the body is attempting to control hemorrhage through a variety of hemostatic mechanisms.

In an effort to create a clinically relevant study design, investigators have utilized uncontrolled hemorrhage models in which blood loss results from an injury to the vascular circuit (11-16). In these previous studies, the IV administration of isotonic (0.9%) saline or hypertonic (7.5%) saline was shown to increase hemorrhage and mortality. To our knowledge, there are no studies which have examined the effect of administering a combined hypertonic saline/dextran solution following vascular injury and subsequent hemorrhage. We recently developed a model of uncontrolled arterial hemorrhage in which blood loss results from an abdominal aortotomy (17). This model was utilized in the present study to test the hypothesis that, after aortotomy, the administration of hypertonic saline/dextran will increase hemorrhage and mortality. We also compared the effects of HSD to the standard therapy of replacing three times the amount of lost blood with lactated Ringer's solution (18).
MATERIALS AND METHODS

SURGICAL PREPARATION

Twenty-four immature Yorkshire gilt swine were obtained from a commercial breeder (J.G. Boswell, Corcoran, CA) and were maintained in a common indoor holding area until utilized for the study 2-4 weeks after arrival. They were fed a commercial ration (Purina Pig Chow, St. Louis, MO) and allowed water ad libitum. The pigs were 4-5 months old and weighed 23-40 kg when the studies were conducted. After an overnight fast, each pig received a preanesthetic intramuscular injection of 2.2 mg/kg ketamine HCl, 2.2 mg/kg xylazine HCl, and 1 mg/kg midazolam HCl. Halothane was given by face mask and endotracheal intubation was performed. The animals were then administered oxygen (FI O₂ = 0.6), nitrous oxide, and 1% halothane. 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 ventral surface of the aorta was exposed. Ten centimeters proximal to the aortic bifurcation, on the ventral median surface of the aorta, a 4-0 monofilament stainless steel wire was inserted through the aortic wall into the aortic lumen and then exteriorized through the same surface 5 mm cephalad. The details of the stainless steel wire placement have been described previously (17). 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 0 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 flow-directed thermodilution Swan-Ganz catheter (Gould Inc., Cleveland, OH) was inserted through the right internal jugular vein and positioned with the distal port in the pulmonary artery. An 8 French polyvinyl catheter was inserted into the right external jugular vein. The surgical preparation required 35 to 45 min. The lumina of all catheters were filled with normal saline. The arterial and Swan-Ganz catheters were connected to Statham 23 Db pressure transducers, a Gould ES1000 multi-channel polygraph, and a Gould cardiac output computer. The animals were then given 50 ml of 0.5% chloralose in 3% urethane solution. The halothane, nitrous oxide, and oxygen were discontinued and the animals were allowed to breath room air spontaneously through the
endotracheal tube. Twenty-five ml of the chloralose/urethane mixture was administered as needed whenever the animal demonstrated spontaneous extremity or truncal motion.

EXPERIMENTAL PROTOCOL

One hour after the halothane had been discontinued, baseline hematocrit, arterial blood gases and cardiodynamics (phasic aortic, pulmonary arterial, central venous, pulmonary capillary wedge pressures, and cardiac output) were recorded. The stainless steel wire was then removed from the abdominal cavity by simultaneously pulling the two ends of the wire. The withdrawal of the wire suture resulted in a 5 mm laceration in the long axis of the aorta and spontaneous intra-abdominal hemorrhage (17). Measurements of arterial blood gases, hematocrit, and cardiodynamics were recorded 5, 15, 30, 60, 90, and 120 min after aortotomy.

To assure the acquisition of fresh circulating blood, removal of the sample was immediately preceded by withdrawal of 4 ml of fluid from the carotid artery 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 ml of normal saline. The blood samples were collected in a heparinized syringe and placed on ice. The arterial blood gas measurements were taken within 5 min of sample removal. Hematocrits of all samples were determined immediately using a Lourdes Model MH microhematocrit centrifuge (Ventitron, Carlsbad, NJ). Cardiac output (CO) was estimated by a thermodilution technique. The injectate was 5 ml of room temperature (20°-20.5°C) normal saline. Successive cardiac output measurements were obtained until two consecutive recordings differed by no more than 0.2 l/min and produced satisfactory logarithmic washout curves (usually 2-4 determinations).

TREATMENT GROUPS

Animals were assigned to one of three study groups: 1) control group, in which no fluid was administered after aortotomy; 2) HSD group, which 6 min after aortotomy received a 4 ml/kg bolus of 7.5% NaCl and 6% Dextran-70 through the external jugular catheter over a 1 min time interval; 3) lactated Ringer's solution (LR) group, which 6 min after aortotomy received 80 ml/kg of LR through the external jugular catheter.
catheter over 9 min utilizing a roller pump (Model #610, Bio-Rad Laboratories, Richmond, CA). The 7.5% NaCl in 6% Dextran-70 solution was obtained from Pharmacia, Inc. (Piscataway, NJ, lot number NC 54845), while the lactated Ringer's solution was obtained from Travenol Labs, Inc. (Deerfield, IL). The solutions were administered at room temperature (20°-20.5° C).

At the termination of the study, the surviving animals were euthanatized with an intravenous injection of barbiturate (Euthanol 6; 10 ml). In all animals a 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 inspected. The combined volume of blood and thrombus in the intraperitoneal cavity was measured as an estimate of the hemorrhage volume.

DATA ANALYSIS

Mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), and central venous pressure (CVP) were determined from the pressure tracings of the Gould recorder. Heart rate (HR) was determined from the pulse pressure tracings. Stroke Volume (SV) was calculated as CO (ml/min) / HR (beats/min). Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated from standard formulae (i.e., $SVR = [(MAP - CVP) \times 79.98] / CO$; $PVR = [(MPAP - PCWP) \times 79.98] / CO$). Left and right ventricular stroke work (LVSW and RVSW) were calculated from the formulae $LVSW = (MAP - PCWP) \times SV \times 0.0136$ and $RVSW = (MPAP - CVP) \times SV \times 0.0136$, respectively. Arterial oxygen content ($C_{aO_2}$) and mixed venous oxygen content ($C_{vO_2}$) were determined from the respective aortic and pulmonary artery blood gas measurements: Hb x 1.39 x %O$_2$Sat, where Hb refers to the hemoglobin concentration in grams/dl blood and %O$_2$Sat refers to the percent saturation of hemoglobin with oxygen. Oxygen delivery (standardized for body weight) was calculated from the formula $CO \times C_{aO_2} \times 10) / body weight$. Oxygen consumption ($VO_2$) (standardized for body weight) was calculated from the formula $VO_2 = [CO \times (C_{aO_2} - C_{vO_2}) \times 10) / body weight$. Percent oxygen extraction was calculated as follows: $[(C_{aO_2} - C_{vO_2}) / C_{aO_2}] \times 100$.

The data were evaluated using an analysis of covariance adjusted for repeated measures, with the 5-min (pre-treatment) sample as the covariate (19,20). When the F ratio was significant, the Newman-Keuls test
was used to identify the specific group and time differences. Reported values are expressed as means ± standard error of the mean (SEM). Survival was analyzed utilizing Fisher's exact test and the generalized Wilcoxon test (19). Statistical differences were considered significant at p<0.05.

RESULTS

HEMORRHAGE

The administration of intravenous HSD resulted in a statistically significant increase in the volume of hemorrhage over control conditions (1,340 ± 230 ml versus 783 ± 85 ml, respectively). The total hemorrhage volume after resuscitation with LR (2,142 ± 178 ml) was significantly greater than that produced in either of the other two groups.

SURVIVAL

All eight of the control animals survived to the completion of the study, i.e., 2 hrs after aortotomy (Fig. 1a). In the HSD treatment group, mortality was observed following the 30-min sample time, and at the termination of the study (2 hrs after aortotomy), 5 of 8 animals in the HSD group had expired (a significant increase, p<0.05). In the LR treatment group, mortality was observed following the 30-min sample time and all animals had expired within 100 min of aortotomy. Although there was no statistically significant difference in the mortality rate between the LR and HSD treatment groups, the survival time was significantly greater in the HSD group (Fig. 1b). Beyond the 90-min sample time, too few animals remained alive in the HSD group to allow for valid statistical comparison of physiologic variables (i.e., cardiodynamics and arterial blood gases). Likewise, the LR treatment group experienced sufficient mortality following the 30-min sample time thereby limiting comparisons to 30 min post-aortotomy.
HEMODYNAMICS

PRE-TREATMENT (Baseline to 5 min after aortotomy)

Aortotomy produced significant decreases in CO, SV, MAP, MPAP, PCWP, and CVP (Fig. 2 & 3) in the immediate post-aortotomy period. There was no significant change in SVR; however, PVR increased significantly (Fig. 4). The fall in CO, MAP and MPAP contributed to a significant decrease in left and right ventricular stroke work (Fig. 5). There were no significant differences between the treatment groups with respect to the pre-treatment measures.

POST-TREATMENT

HSD versus CONTROL: The administration of HSD produced a significant increase in SV and a significant decrease in HR (Fig. 6) and SVR when compared with untreated control animals. Mean arterial pressure, MPAP, PCWP, CVP, and PVR were not significantly affected by the administration of HSD (Fig. 3). Cardiac output was significantly increased over untreated control animals at the 15-min sample times (Fig. 2). Beyond the 15-min sample time, there were no significant treatment differences observed for CO.

HSD versus LR: Following the administration of lactated Ringer's, CO, SV, MAP, MPAP, PCWP, and CVP were significantly increased over that of animals receiving HSD (Fig. 2,3). However, 30 min after aortotomy all these variables, with the exception of MAP, fell and were no longer significantly different from the HSD group. At this sample time, MAP was significantly decreased in the LR treatment group. With the rise and fall in cardiac output and arterial pressures, both left and right ventricular stroke work significantly increased and then subsequently returned to the level of the HSD treatment group. There was no significant effect of LR on HR when compared with the HSD group.

OXYGEN TRANSPORT

PRE-TREATMENT (Baseline to 5 min post aortotomy)

Aortotomy produced a significant decrease in hematocrit and arterial oxygen content (Fig. 7). The combined decrease in cardiac output and oxygen carrying capacity resulted in a significant decrease in total
body oxygen delivery (Fig. 7). Correspondingly, percent oxygen extraction increased (Fig. 8). However, this failed to sustain oxygen consumption, as there was a significant decrease in this variable (Fig. 8).

POST-TREATMENT

CONTROL versus HSD: The administration of HSD produced a significant decrease in hematocrit, arterial oxygen content, and arteriovenous O₂ content difference (Fig. 8). The percentage of oxygen extraction from the systemic arterial blood was not significantly affected. Total body oxygen delivery and oxygen consumption significantly increased at the 15-min sample time and then subsequently returned to the levels of the control group.

HSD versus LR: The hematocrit and oxygen carrying capacity in the LR group were significantly decreased below those observed in the HSD treatment group. There were no significant differences in oxygen delivery nor consumption 15 min after aortotomy. However at the 30-min sample time, both of these variables were significantly decreased in the LR treatment group. The percentage of arterial oxygen extraction was not significantly different.

DISCUSSION

In this model of uncontrolled arterial hemorrhage resulting from aortotomy, the administration of hypertonic saline/dextran significantly increased the volume of blood loss. Both the survival time and the survival rate were significantly decreased by HSD administration. The reason for the observed increase in mortality is not readily apparent. The increased volume of hemorrhage would appear to be offset by either a direct improvement in cardiodynamic performance or increase in venous return; that is, the hemodynamics and oxygen transport were either significantly above or at the same levels observed in the untreated control group. Despite this, 5 of 8 animals in the HSD treatment group expired prior to the termination of the study.

The administration of HSD produced a wide variation in the volume of hemorrhage. The mean volume
of hemorrhage for those animals which survived was approximately 800 ml versus 1,550 ml for those animals who expired during the study. As expected, the initial hemodynamic response to the administration of HSD was inversely related to the volume of hemorrhage. Those animals with a lower volume of hemorrhage demonstrated a higher hemodynamic response than those animals which hemorrhaged twice as much and therefore had a lower intravascular volume but showed a blunted hemodynamic response (i.e., cardiac output, oxygen delivery, and mean arterial pressure).

The standard practice of replacing the estimated blood loss with three times as much lactated Ringer's solution (18) resulted in a volume of hemorrhage that was significantly greater than that observed in the HSD treatment group. Furthermore, the isotonic crystalloid administration produced a marked hemodilution, as evidenced by the observed fall in hematocrit and 70% decrease in oxygen carrying capacity. The physiologic consequences of the increased blood loss and hemodilution were clearly evident by the 30-min sample time, as cardiac output and oxygen delivery fell significantly below both the control and the HSD treatment group. Although the mortality rate of the LR treatment group and the HSD treatment group were not significantly different at the termination of the study, the survival time of the HSD-treated animals was significantly greater than that of the LR treatment group.

In previous studies comparing the effects of hypertonic saline (7.5%) to isotonic (0.9%) saline in uncontrolled hemorrhage, Gross and colleagues demonstrated that hypertonic saline significantly increased the volume of hemorrhage over that of untreated control animals or of animals given an equivalent volume of isotonic saline (14-16). In their model of uncontrolled intra-abdominal hemorrhage from ileocolic artery laceration and from partial resection of the tail in rats, the administered volume of both hypertonic and isotonic saline was 10% of the estimated blood loss. In the case of hypertonic saline, this small volume will produce a significant expansion of the intravascular volume and a significant increase in cardiac output and arterial pressure (2,3,5). However, the same small volume of isotonic saline will provide very little volume expansion and hence an insignificant hemodynamic effect (1,2). In clinical practice, however, much larger volumes of isotonic crystalloid are administered, as it is currently recommended that
the volume of blood loss be replaced with three times as much crystalloid solution (18).

In the present study, early, aggressive fluid volume resuscitation with isotonic crystalloid solution was an ineffective therapeutic measure. In fact, this therapy caused 100% mortality. Attempts to improve on current resuscitative therapy by the use of HSD were also largely ineffective. The results of the present study are consistent with those obtained by Gross and colleagues (14-16) and others (11-13) also using models of uncontrolled hemorrhage; i.e., the more aggressive the volume expansion in the face of uncontrolled vascular lesion, the worse the outcome (8-11).

The results of this study indicate that there is nothing inherently detrimental about the administration of a hypertonic-hyperoncotic resuscitation solution compared with that produced by isotonic crystalloid. The detrimental effect lies in the degree of volume expansion under the dynamic conditions of vascular injury, hemorrhage, and spontaneous hemostasis. The order in which treatments are applied to significant, uncontrolled hemorrhage may be the critical feature in determining a favorable outcome. During both World War I and II it was cautioned that fluid resuscitation, before surgical hemostasis, may have the deleterious effect of promoting hemorrhage and mortality (21,22). The results of our study support this philosophy and further indicate that early and aggressive volume resuscitation, from either isotonic or hypertonic/hyperoncotic solutions, may cause a significant and potentially fatal second hemorrhage.

CONCLUSIONS

In this model of uncontrolled arterial hemorrhage resulting from abdominal aortotomy, the IV administration of hypertonic saline/dextran significantly increased the volume of hemorrhage and decreased survival compared to spontaneous recovery. However, the accentuation of hemorrhage was not as great as that produced by the standard practice of attempting to replace the lost blood with three times as much lactated Ringer's solution. Although the mortality rate at the termination of the study was not significantly different from the lactated Ringer's
treatment group, the survival time was significantly improved in hypertonic saline/dextran treatment group relative to the lactated Ringer's group. These results support the previously established principle that attempting volume replacement in the face of uncontrolled vascular injury will further promote hemorrhage and hence adversely influence outcome.

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Figure 1a. Survival curves of animals during the experiment. Data points for the experimental groups indicate the actual times at which each loss occurred.
Figure 1b. Survival of animals during the experiment: treatment groups' respective mean and median survival times post aortotomy.
**Figure 2a.** Cardiac output (ml/min/kg) versus time (min) during the experiment. All points are means ± SEM. Fine dotted lines indicate the times at which the number of animals dropped below the valid sample size for the statistical analysis.
Figure 2b. Ventricular stroke volume (ml/beat) versus time (min) during the experiment. All points are means ± SEM. Fine dotted lines indicate the times at which the number of animals dropped below the valid sample size for the statistical analysis.
Figure 3a. Relationship between mean systemic arterial pressure (mm Hg) and time (min) during the experiment. All points represent means ± SEM. Fine dotted lines indicate the times at which the number of animals dropped below the valid sample size for the statistical analysis.
Figure 3b. Relationship between mean pulmonary arterial pressure (mm Hg) and time (min) during the experiment. All points represent means ± SEM. Fine dotted lines indicate the times at which the number of animals dropped below the valid sample size for the statistical analysis.
Figure 3c. Relationship between mean pulmonary capillary wedge pressure (mm Hg) and time (min) during the experiment. All points represent means ± SEM. Fine dotted lines indicate the times at which the number of animals dropped below the valid sample size for the statistical analysis.
Figure 3d. Relationship between mean central venous pressure (mm Hg) and time (min) during the experiment. All points represent means ± SEM. Fine dotted lines indicate the times at which the number of animals dropped below the valid sample size for the statistical analysis.
Figure 4a. Vascular resistance versus time (min) during the experiment: systemic vascular resistance (dyne x sec x cm$^{-5}$). All points are means ± SEM. Fine dotted lines indicate the times at which the number of animals dropped below the valid sample size for the statistical analysis.
Figure 4b. Vascular resistance versus time (min) during the experiment: pulmonary vascular resistance (dyne x sec x cm⁻²). All points are means ± SEM. Fine dotted lines indicate the times at which the number of animals dropped below the valid sample size for the statistical analysis.
Figure 5a. The relationship between the work done by the heart and time (min): left ventricular stroke work (gm x ml/beat) versus time (min). All points are means ± SEM. Fine dotted lines indicate the times at which the number of animals dropped below the valid sample size for the statistical analysis.
Figure 5b. The relationship between the work done by the heart and time (min): right ventricular stroke work (gm x ml/beat) versus time (min). All points are means ± SEM. Fine dotted lines indicate the times at which the number of animals dropped below the valid sample size for the statistical analysis.
Figure 6. Heart rate (beats/min) versus time (min) during the experiment. All points are means ± SEM. Fine dotted lines indicate the times at which the number of animals dropped below the valid sample size for the statistical analysis.
Figure 7a. Oxygen carrying capacity during the experiment: systemic hematocrit (%) versus time (min). All points are means ± SEM. Fine dotted lines indicate the times at which the number of animals dropped below the valid sample size for the statistical analysis.
Figure 7b. Oxygen carrying capacity during the experiment: arterial oxygen content (ml O$_2$/dl blood) versus time (min). All points are means ± SEM. Fine dotted lines indicate the times at which the number of animals dropped below the valid sample size for the statistical analysis.
Figure 7c. Oxygen carrying capacity during the experiment: oxygen delivery (ml O₂/min/kg) versus time (min). All points are means ± SEM. Fine dotted lines indicate the times at which the number of animals dropped below the valid sample size for the statistical analysis.
Figure 8a. Total body oxygen consumption (ml O₂/min/kg) versus time (min) during the experiment. All points are means ± SEM. Fine dotted lines indicate the times at which the number of animals dropped below the valid sample size for the statistical analysis.
Figure 8b. Percent oxygen extraction versus time (min) during the experiment. All points are means ± SEM. Fine dotted lines indicate the times at which the number of animals dropped below the valid sample size for the statistical analysis.
Figure 8c. Arteriovenous $O_2$ content difference (ml $O_2$/dl blood) versus time (min) during the experiment. All points are means ± SEM. Fine dotted lines indicate the times at which the number of animals dropped below the valid sample size for the statistical analysis.