The Chronically Instrumented Ewe

A MODEL FOR STUDYING VASCULAR REACTIVITY TO ANGIOTENSIN II IN PREGNANCY

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ABSTRACT Vascular refractoriness to the systemic pressor effects of angiotensin II (AII) develops normally during human pregnancy. To ascertain if the ewe might provide a suitable animal model to study the mechanisms responsible for this response (unique to pregnancy) we studied this phenomenon in unanesthetized, chronically instrumented nonpregnant and pregnant sheep, 68-143 d gestation. In these studies dose-response curves were established for changes in both mean arterial pressure and uterine blood flow. The pressor response to continuous infusions of AII increases as a function of the dose of AII in both nonpregnant and pregnant animals ($P < 0.001$), $R = 0.943$ and 0.879, respectively. However, the pregnant animals were refractory to the pressor effects of AII, requiring 0.016 μg of AII/min per kg to elicit a 20 mm Hg rise in mean arterial pressure, in contrast to 0.009 for nonpregnant animals. The slope and intercept for the regression lines are different at $P < 0.001$. In pregnant animals the dose-response curve for uterine blood flow was also determined. Increases in uterine blood flow were observed at doses of AII < 0.016 μg/min per kg, while larger doses resulted in a progressively greater reduction in blood flow. It appears likely that the ewe may serve as an animal model suitable for the further study of the unique pregnancy-modified systemic and uteroplacental vascular responses elicited by AII.

INTRODUCTION

The cardiovascular system of the pregnant woman undergoes numerous changes throughout gestation. A change of particular interest, and one apparently unique to pregnancy, is the development of vascular refractoriness to the pressor effect of angiotensin II (AII).[1] This was first observed by Abdul-Karim and Assali (1) in normal pregnant women studied before and after delivery and was later confirmed by Chesley et al. (2), Talledo (3), and others (4–6) studying normal nonpregnant and pregnant women in the third trimester. In contrast, in pregnancies complicated by preeclampsia or pregnancy-induced hypertension (PIH) vascular reactivity is increased. In fact, women with PIH show an increased pressor response to infused AII when compared to normal nonpregnant women. Gant and coworkers (6) subsequently reported that the development of refractoriness to the pressor effects of AII occurs normally toward the end of the first trimester. They also reported that in those women destined to develop PIH, the increase in vascular reactivity characteristics of women with PIH developed as early as week 22 of gestation. While the changes in vascular responsiveness to AII have been studied extensively during human pregnancy by several investigators, the mechanism(s) responsible for these altered pressor responses remains poorly understood. Part of the explanation for this dilemma is the lack of a proper animal model in which to pursue such studies.

Although considerable information is available concerning the systemic vascular responses to AII in the human, almost nothing is known about the effects of AII on uteroplacental perfusion in the human. However, numerous animal studies have been reported in which AII appears to play a major role in the regulation and/or modification of uteroplacental perfusion. Unfortunately, the results of these studies have been conflicting, with reports of both increases (7–9) and decreases (10, 11) in uterine blood flow occurring during or after

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[1] *Abbreviations used in this paper*: AII, angiotensin II; PIH, pregnancy-induced hypertension.

infusions of AII. Furthermore, interpretation and comparison of these studies have been clouded by the use of anesthetized, surgically stressed animals and the administration of the AII by numerous different methods, i.e., systemic or local infusions, bolus or continuous infusions. Therefore, this study was designed to obviate such problems by measuring simultaneous systemic pressor responses and changes in uterine blood flow observed during continuous systemic infusions of AII in unanesthetized, chronically instrumented nonpregnant and pregnant ewes remote from surgery. From the results of this study, we confirm that the pregnant ewe is an excellent animal model that closely resembles the pregnant human in vascular responses to AII. Furthermore, the information obtained in the present study defines and helps to explain the previously conflicting reports of different uteroplacental blood flows measured during or after AII infusions.

METHODS

Eight oophorectomized, parous, nonpregnant ewes and eleven pregnant ewes 68-143 d gestation were used in this study. There were seven singletons, one twin, and two triplet pregnancies. Oophorectomized sheep were used to control for variables that might be associated with the changes in the hormonal milieu that occur with the estrous. The animal preparations were the same as those described for nonpregnant (12) and pregnant ewes (13). Briefly, electromagnetic flow probes (Micron Instruments, Inc., Los Angeles, Calif.) were chronically implanted around both major uterine arteries (3.0 or 3.5-mm i.d. probes for nonpregnant animals and 4.0, 5.0, or 6.0-mm i.d. probes for pregnant animals) and indwelling polyvinyl catheters (0.75-mm i.d. × 1.2-mm o.d.) were implanted in a maternal femoral vein to a level just below the diaphragm and both femoral arteries to the level of the trifucation of the abdominal aorta, two catheters on the left and one on the right. The flow probes and catheters were brought out to the flank through a subcutaneous tunnel and maintained in a canvas pouch attached to the skin with steel pins. Catheters were flushed daily with heparinized saline (250 U/ml) and closed with sterile pins.The oophorectomized, nonpregnant ewes received 1 μg/kg of intravenous 17β-estradiol every other day, but never before the evaluation of responses to infused AII. Penicillin (600,000 U) and streptomycin (0.5 g) were given on the day of operation and the two subsequent days.

The ewes were maintained after operation in stalls kept in the laboratory and studied after they were considered to have recovered from surgical trauma, as evidenced by a normal response of uterine blood flow to 1 μg/kg of intravenous 17β-estradiol (12, 14). Mean arterial pressure and heart rate were monitored by pressure transducers, (type 4-327-1019, Bell & Howell Co., Pasadena, Calif.) connected to an amplifier (model N-4307-04, Gould Inc., Instruments Div., Cleveland, Ohio) and two-channel recorder (model 220, Brush Instruments Div., Clevite Corp., Cleveland, Ohio). Uterine blood flow was monitored with electromagnetic flowmeters (model RC-1000, Micron Instruments, Inc.) and recorded on a second two-channel recorder. The flow probes have a linear response to flows in the range studied and are provided with a flow signal and zero-flow calibration.

The responses of systemic arterial pressure in pregnant and nonpregnant ewes and uterine blood flow in pregnant ewes were investigated as described below.

A stock solution of angiotensin amide or AII (Hypertensin-CIBA, CIBA Pharmaceutical Co., Summit, N. J.) was prepared by dissolving 2.5 mg of base in 5 ml of sterile distilled water, providing a concentration of 0.5 mg/ml. This solution is stable for 30 d when kept refrigerated at 38°F. Solutions suitable for systemic intravenous infusion were prepared by adding 0.9 ml (0.45 mg) of the stock solution to 149.1 ml of sterile isotonic saline (0.9% sodium chloride) in a sealed container (Travenol Laboratories, Inc., Morton Grove, Ill.), resulting in a concentration of 3 μg/ml of AII. This solution was kept refrigerated when not in use and was depleted every 5-7 d. The AII solution was infused with a single-channel Harvard infusion pump (Harvard Apparatus Co., S. Natick, Mass.) and sterile, lubricated, 50-ml glass syringe at various rates through the inferior vena cava catheter. The period of infusion for each rate examined was a minimum of 5 min or until there was stabilization of mean arterial blood pressure and, in the case of pregnant ewes, uterine blood flow. This was followed by a rest period of 10-15 min, permitting blood pressure and uterine blood flow to return to preinfusion levels. An example of typical blood pressure and uterine blood flow responses is illustrated in Fig. 1. No more than eight infusions were performed per day, and the rates of infusion were chosen randomly. Simultaneous measurements of mean arterial pressure, heart rate, and, in pregnant ewes, uterine arterial blood flows were recorded and electronically integrated. Dose-response curves were constructed for mean arterial pressure and uterine blood flow.

RESULTS

Blood pressure. 12 dose-response curves, expressing the absolute change in mean arterial pressure (Δ mm Hg) as a function of the dose of AII in micrograms per minute per kilogram, were determined in the nonpregnant sheep. Each curve represents an average of seven different rates of infusion of AII, a total of 86 data points (Fig. 2). The points obtained from the 12 dose-response curves were analyzed using simple linear regression. The correlation coefficient R is 0.943, $P < 0.001$, and the regression equation is $y = 77.31 + (28.11)$ Log X, where y is the change in mean arterial pressure in millimeters of mercury and Log X is the dose of AII in micrograms per minute per kilogram expressed as the common logarithm to the base 10. Using this equation one could predict a 20-mm Hg rise in mean arterial pressure in nonpregnant sheep during a constant infusion of 0.009 μg of AII/min per kg and a 40-mm Hg rise with a rate of infusion of 0.047 μg/min per kg.

13 dose-response curves describing the absolute change in mean arterial pressure as a function of the dose of AII were determined as above in eight pregnant sheep studied between 99 and 143 d gestation. Each curve represents an average of six different rates of infusion of AII, a total of 83 data points (Fig. 3). The points obtained from the 13 individual dose-response curves were analyzed using simple linear regression. The correlation coefficient R is 0.879, $P < 0.001$, and the regression equation is $y = 57.88 + (20.96)$ Log X, where y is the change in mean arterial pressure in millimeters

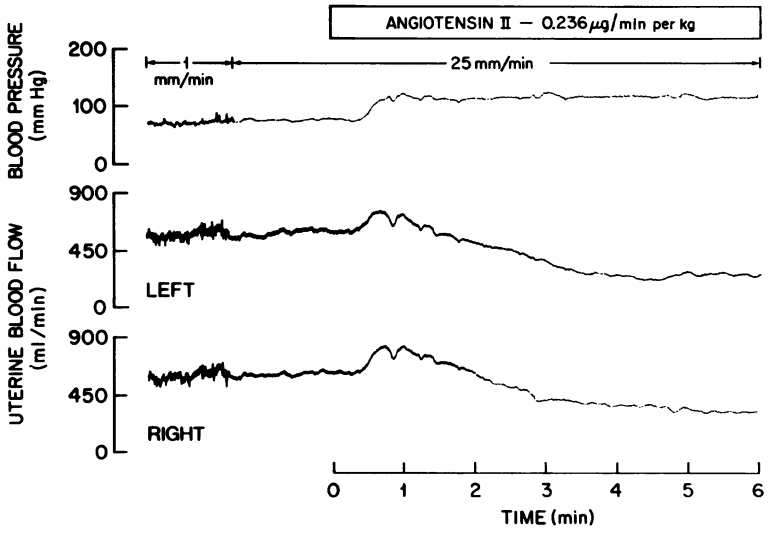

FIGURE 1 A continuous recording of mean arterial pressure and uterine blood flow in a pregnant ewe at 111 d gestation.

of mercury and Log X is the dose of AII expressed as the common logarithm to the base 10. With this equation, one could predict that a 20-mm Hg increase in mean arterial pressure in pregnant sheep would require a constant infusion of 0.016 μg of AII/min per kg and a 40-mm Hg rise, a rate of infusion of 0.140 μg/min per kg. When the regression equations expressing the responses of mean arterial pressure in the nonpregnant and pregnant ewes are compared, their slopes and intercepts are significantly different, $P < 0.001$, i.e., the nonpregnant animals are more sensitive to the pressor effects of AII.

To characterize the pattern of the change in the pressor response to AII during ovine pregnancy, we divided the pregnant animals into groups according to their stage of gestation at the time of study, and compared the dose of AII required to elicit a 20-mm Hg rise in mean arterial pressure. In this analysis we added three additional animals studied between 68 and 99 d gestation, thus providing groups at 68–99 d, 101–120 d, 121–130 d, and 131–140 d. The mean dose of AII required at each stage of pregnancy is greater than that needed in the nonpregnant animals (unpaired t, $P < 0.05$). However, there is no significant difference in the mean dose of AII required by any of the pregnant groups. Thus, the increase in the dose of AII required

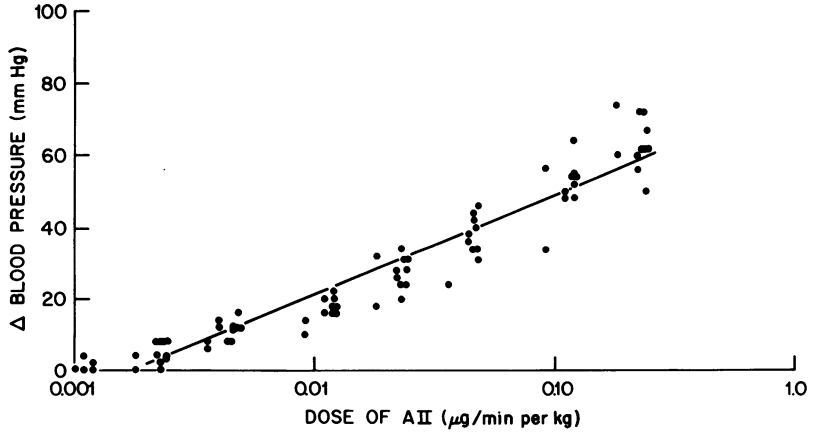

FIGURE 2 The change in mean arterial pressure in nonpregnant, oophorectomized ewes during the constant infusion of random doses of AII. The line expressing the linear regression is shown. $R = 0.94$, $y = 77.3 + (28.1)$ Log X, $P < 0.001$, and $n = 86$.

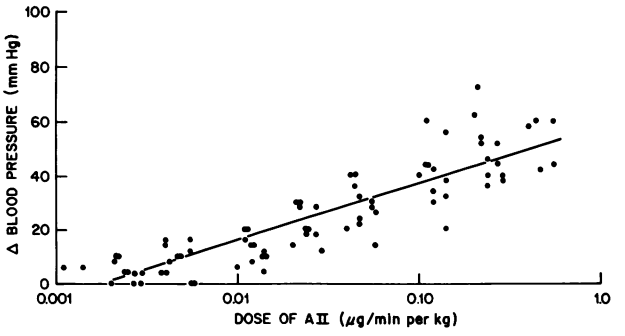

FIGURE 3 The change in mean arterial pressure in pregnant sheep 99-143 d gestation during the constant infusion of random doses of AII. The line representing the linear regression is shown. $R = 0.88$, $y = 57.9 + (21.0)$ Log X, $P < 0.001$, and $n = 83$.

during pregnancy to elicit a pressor response of 20-mm-Hg occurs early in gestation, <68 d, and remains constant thereafter.

Uterine blood flow. Changes in uterine blood flow in the nonpregnent animals could not be evauated because of very low control values. However, this was not a problem in the pregnant animals, and uterine blood flow was monitored continuously in each animal during the evaluation of the blood pressure responses. From these measurements, individual dose-response curves were constructed for each animal depicting the change in uterine blood flow in milliliters per minute as a function of the dose of AII in micrograms per minute per kilogram. The 80 data points thus obtained were analyzed, and the curve best describing these data was obtained using a polynomial regression (Fig. 4). The correlation coefficient is 0.70 and equation is $y = 40.0 - 2420\ (x) + 3046(x^2)$, where y is the change in uterine blood flow in milliliters per minute and x is the rate of infusion of AII in micrograms per minute per kilogram. The P value is <0.0001. It should be noted that with a rate of infusion of AII <0.016 μg/min per kg there was an increase in uterine blood flow, while doses of AII greater than that resulted in increasingly larger reductions in blood flow despite greater increases in mean arterial pressure.

Another observation of interest was the prompt rise in uterine blood flow that was simultaneous with the pressor response and occurred immediately after the initiation of high rates of infusions of AII (Fig. 1). This rise in uterine blood flow was transient, remaining evident for only 2–3 min, then gradually fell to stabilize at lower values within 5–7 min after the initiation of an infusion. This was observed to occur only with doses >0.016 μg/min per kg.

DISCUSSION

The development of vascular refractoriness to the pressor effects of infused doses of AII is a phenomenon apparently unique to normal pregnancy and has been clearly described in the human by a number of investigators (1–6). It is apparent that vascular refractoriness to AII develops in normal primigravid women as early as week 14 of gestation and persists until term (6). However, refractoriness to AII is lost in pregnancies complicated by PIH (3–6), and this loss of vascular refractoriness may preceed the development of hypertension by 18 wk (6). Moreover, women destined to develop PIH become even more sensitive to the pressor effects of AII as pregnancy progresses, subsequently requiring at term only half the dose of AII usually required to elicit a 20-mm Hg rise in diastolic pressure in normal nonpregnant subjects (3, 6). Similarly, nor-

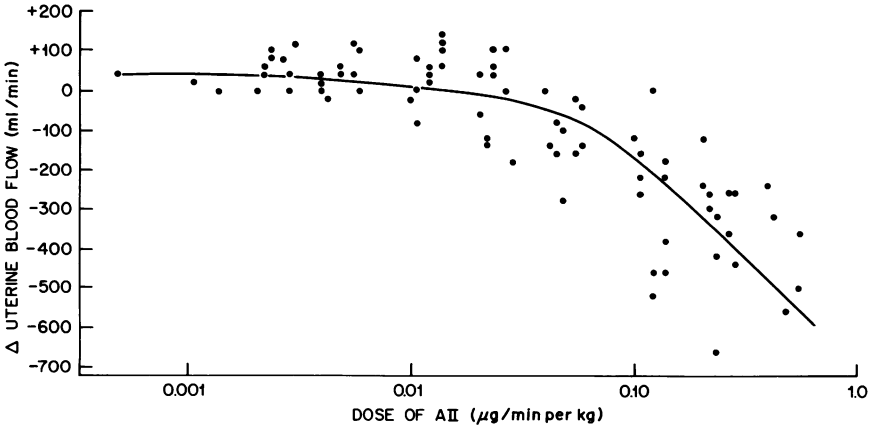

FIGURE 4 The change in uterine blood flow during the constant infusion of (AII) in pregnant sheep 99–143 d gestation. The line representing the polynomial regression is presented. $R^2 = 0.70$, $y = 40.0 - 2420\ (x) + 3046\ (x^2)$, $P < 0.0001$, and $n = 80$.

epinephrine infusions will elicit an increased pressor response in women with PIH (3). The mechanisms by which these changes in vascular reactivity occur are poorly understood. However, it appears likely that the principal determinant of the pressor response to AII in human pregnancy is the development of arteriole or vessel-mediated refractoriness (15). Although studies attempting to explain this phenomenon in women have been reported (16, 17), there is to date only a single report extending these observations to an animal model, which in this case was the rabbit (18). Therefore, it was our purpose to ascertain in the present investigation whether the chronically instrumented, unanesthetized ewe might serve as an animal model in which systemic and uterine vascular responses could be studied simultaneously.

We previously reported that the uteroplacental and other vascular responses to systemic infusions of 17β-estradiol in nonpregnant sheep are blunted significantly when the animal is under the influence of anesthesia or surgical stress, and that a normal response may not be seen for 4-5 d thereafter (12, 19). Assali et al. (20) have also reported that in anesthetized sheep the uterine response to bolus infusions of AII is quite different from that found in unanesthetized animals. Thus, it is preferable to use unanesthetized, unstressed animals remote from surgery to study the responses of the cardiovascular system (in particular the uteroplacental circulation) to vasoactive compounds. This has been addressed in the present investigation by the use of pregnant and nonpregnant ewes remote from surgery or anesthesia that were shown to be in an unstressed, normal physiologic state as determined by an adequate uterine-blood-flow response to an infusion of 17β-estradiol (12, 14, 19) and a mean arterial pressure within the normal range (21).

Although various investigators have reported rather complete dose-response curves describing the pressor response to infused doses of AII in women (3, 4), and have compared these responses in nonpregnant and pregnant women, similar work has not been reported in an animal model. Although Berssenbrugge et al. (18) recently compared the pressor responses to AII in nonpregnant and pregnant rabbits and observed vascular refractoriness to AII in the pregnent doe, they studied the pressor responses to only two doses of AII. Thus, to the best of our knowledge, the present study is the first to include complete dose-response curves describing the change in mean arterial pressure as a function of the dose of AII in both pregnant and nonpregnant animals. Of particular interest in the present study is the observation that the linear regression lines and equations obtained in both nonpregnant and pregnant animals are similar to those previously determined by Talledo et al. (4) in normal nonpregnant and near-term pregnant women. Although they used a bolus infusion of AII in contrast to our use of a continuous infusion, the calculated dose of AII necessary to elicit a 20-mm Hg rise in mean arterial pressure is similar to that determined for the sheep. Moreover, these doses of AII (0.009 and 0.016 μg/min per kg in nonpregnant sheep and pregnant animals, respectively) are virtually the same as those previously reported by us to be required to elicit a 20-mm Hg increase in diastolic pressure in normal nonpregnant and pregnant subjects, respectively (6). In addition to the similarity in the dose of AII necessary to elicit a 20-mm Hg rise in mean arterial pressure in normal women and sheep, we also observed that, as in the human (6), the mean dose of AII required beyond the first one-third of pregnancy remains relatively constant. Thus, it appears that during ovine pregnancy vascular refractoriness to AII develops in a pattern similar to that seen in the human, providing additional support for the conclusion that the pregnant ewe can serve as a useful model in studying the mechanisms responsible for this physiologic adaptation to pregnancy.

Ferris and co-workers (22), while studying uterine renin production, observed that a reduction in uterine perfusion by hemorrhagic hypotension or partial ligation of the uterine arteries in pregnant rabbits resulted in the release of large amounts of renin into the uterine venous blood. Because this released renin might be associated with local angiotensin production, these investigators measured the effect of small pressor doses of AII administered to anesthetized pregnant rabbits and found that AII increased the uterine blood flow. Terragno and co-workers (8), studying anesthetized pregnant dogs, observed a similar uterine response to systemic infusions of AII. The increased uterine perfusion was accompanied in this case by a release of significant amounts of prostaglandin E or prostaglandin-like compounds into uterine venous blood. They concluded, as had Ferris et al. (22), that AII, a potent vasoconstrictor agent, acted to release uterine prostaglandins, that in turn caused uterine vasodilation, thus providing a means whereby uteroplacental perfusion could be maintained during periods of systemic vasoconstriction. Such a theory raises the possibility of autoregulation of uterine blood flow. Unfortunately, these measurements of uteroplacental blood flow were made in animals during surgical anesthesia, an experimental variable that, as pointed out earlier, will alter uterine responses to numerous vasoactive substances (12, 19, 20). Moreover, these observations conflict with the studies of Greiss and VanWilkes (10) who reported that in anesthetized pregnant ewes uterine conductance fell as a function of the dose of AII. Unfortunately, Greiss and VanWilkes (10) did not describe the changes in absolute uterine blood flow.

Because of the conflicting data concerning the effects of AII on uterine blood flow and because of the

capability of measuring directly and simultaneously uteroplacental perfusion and mean arterial pressure in the awake, unanesthetized pregnant animal recovered from surgery, we planned to ascertain whether systemic infusions of AII resulted in increases or decreases in uterine blood flow. As during the pressor experiments, we chose to study the steady-state responses. These responses were obtained with continuous intravenous infusions of AII (Fig. 1), and dose-response curves were constructed as previously reported (23, 24). We observed that under these circumstances the response of uterine blood flow to AII was dose dependent, with increases in blood flow occurring at low doses (<0.016 μg/min per kg) and decreases in flow occurring at higher doses of AII. This result obtained in unstressed, unanesthetized animals explains the divergent results reported by earlier investigators who infused different doses, and/or used anesthetized animals.

A further observation made with respect to the response of uterine blood flow during the constant systemic infusion of AII was the transient though significant increase in blood flow that was observed shortly after initiating the infusion (Fig. 1). This increase in uterine blood flow was intimately associated with the rapid rise in mean arterial pressure. However, in contrast to the rapid stabilization and persistent elevation seen in mean arterial pressure, this increase in uterine blood flow persisted for no more than 2-3 min and then fell gradually, stabilizing at 4–5 min. This biphasic response in uterine blood flow was not evident with doses of AII <0.016 μg/min per kg, in which case the rise in uterine blood flow was found to persist. From these observations it appears that if one were to study the response of uterine blood flow to systemic doses of AII only during the first 3 min of an infusion or immediately after a bolus injection, an increase in blood flow would be observed at all doses. Thus, the observed response would not necessarily reflect the true physiologic response to or pharmacologic effect of AII on uterine blood flow. This observation could provide another explanation for the suggestion in previous reports that uterine vasodilation occurs simultaneous with the profound systemic vasoconstriction observed with systemic doses of AII. We recently have completed additional studies of the mechanisms responsible for the uterine responses to infused AII, measuring cardiac output in addition to the variables reported in the present experiments (25).

We conclude from the results of these studies that the systemic pressor response of chronically instrumented, unstressed nonpregnant and pregnant sheep to infused doses of AII is similar to that previously observed in nonpregnant and pregnant women. Thus, this animal provides a means whereby this particular and unique aspect of pregnancy can be studied further. Moreover, it also provides a means for the detailed investigation of responses of uteroplacental blood flow, and with additional techniques, of the responses of cardiac output and blood flow to other organ beds.

ACKNOWLEDGMENTS

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