

Constant infusion of epinephrine, but not bolus treatment, improves haemodynamic recovery in anaphylactic shock in dogs

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Summary

Objective Epinephrine (Epi) is the treatment of choice for reversing cardiovascular collapse in anaphylactic shock (AS). In this condition, most treatment guidelines have been anecdotally derived and no randomized clinical trials have been conducted. In the present study, we examined the time course of haemodynamic recovery in a canine model of AS when Epi was administered at the initiation of allergen challenge before fully developed shock had occurred.

Methods Randomized, controlled, crossover studies were performed approximately 3–5 weeks apart in ragweed-sensitized dogs while the animals were ventilated and anaesthetized. Epi was administered by bolus intravenous (i.v.), subcutaneous (s.c.), intramuscular (i.m.) routes and by continuous i.v. infusion (CI). The findings obtained in the Epi treatment (T) studies were compared with those found in a no treatment (NT) study. In the bolus studies, Epi was administered at 0.01 mg/kg, while in the CI study, the dose of Epi was titrated to maintain mean arterial pressure (MAP) at 70% of preshock levels. MAP, cardiac output (CO), stroke volume (SV), and pulmonary wedge pressure (Pwp) were determined over a 3 h period.

Results In the CI study, haemodynamics (CO, MAP, and SV) were significantly higher than those measured in the NT study and the bolus studies over approximately the first hour of the study. In the CI study, the amount of Epi infused was significantly less than in the bolus studies.

Conclusion When administered at the initiation of allergen challenge, bolus treatment of Epi by i.m., i.v., or s.c. routes caused limited haemodynamic improvement in AS. In contrast, constant infusion of Epi at a lower total dose produced significant haemodynamic improvement. Within the limits of this anaesthetized canine model, the results suggest that CI should be the preferred route in the treatment of AS when this treatment option is available.

Keywords adrenaline, allergy, anaphylaxis, distributive shock, epinephrine, pharmacokinetics, vasoactive agents

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Introduction

In anaphylactic shock (AS), rapid release of potent vasoactive mediators, such as histamine and leukotrienes, from tissue mast cells or peripheral blood basophils leads to vascular permeability, vasodilation, and hypovolaemia and eventual shock. Mediators of anaphylaxis may also directly impair heart function and produce bronchoconstriction and laryngeal oedema [1–3]. The overall population at risk for anaphylaxis is estimated to be 1% or higher in the United States [4, 5]. Food allergy, insect stings and bites, latex rubber allergy, and medication allergy are the major provoking factors [2].

Epinephrine (Epi) is the treatment of choice in AS based on anecdotal experience [6–8]. Currently 0.95% of the general population in some areas carries Epi as first-line treatment [9].

Supportive evidence of efficacy comes from *in vitro* studies that showed that when administered prior to allergen challenge, Epi inhibited mediator release from mast cells [10]. This occurred through the β -adrenergic receptor, enhanced production of adenylyl cyclase, and subsequent conversion of adenosine triphosphate to cyclic 3'/5'-adenosine monophosphate (cyclic AMP). Based on the latter studies and Epi's favourable α_1 - and β -adrenergic systemic effects, Epi has assumed an important role in the treatment of AS in clinical medicine [3, 6].

Nevertheless, although *in vitro* studies have indicated that Epi may be useful when given before allergen challenge, the extent to which Epi may be beneficial in attenuating circulatory collapse when given after allergen challenge in the *in vivo* condition has not been adequately investigated. The few *in vivo* studies performed so far have not demonstrated a positive effect [11–13]. When Epi was administered by subcutaneous (s.c.) and intravenous (i.v.) routes to patients undergoing desensitization to Hymenoptera venom allergen, who developed shock during allergen rechallenge,

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Smith et al. [11] found no beneficial effect of Epi on reversing cardiovascular collapse. In ragweed-sensitized dogs, Mink et al. [13] showed that when an i.v. bolus of Epi was given during maximal hypotension, no positive effect on haemodynamic recovery was observed and negative effects on cardiac mechanics and mediator release were found when a relatively high bolus dose of Epi was used. In a subsequent study, Bautista et al. [14] compared the effects of bolus i.v., intramuscular (i.m.), and s.c. Epi on haemodynamic recovery given during fully developed shock in this ragweed model and found no difference among the treatments as compared with a non-treatment study.

Although the previous studies showed lack of effectiveness of Epi when given during fully developed shock, it is possible that a beneficial effect may have been observed if Epi were delivered earlier during challenge. The latter condition would mimic the clinical situation in which an individual who had access to an Epipen[®] (Allerex Lab. Ltd, Kanata, Ontario, Canada) administered treatment at the early onset of anaphylactic symptoms [9]. In the present study, we addressed this possibility in experiments in which bolus Epi was given at the onset of shock by i.v., i.m., and s.c. routes in a canine ragweed shock model. In addition, we examined the extent to which early administration of Epi by continuous infusion would produce a more beneficial haemodynamic response as compared with the bolus approaches, because a titratable infusion of Epi could be given. The overall aim of this study was to determine the best route by which Epi should be given in the treatment of AS.

Methods

Anaphylaxis model

This study was approved by the Central Animal Committee at the University of Manitoba. This investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (National Institutes of Health Publication No 85-23 [15]).

The ragweed model used in this randomized, controlled, crossover study has previously been described [13, 14, 16, 17]. Briefly, newborn mongrel dogs received 0.5 mg of ragweed mixed with 30 mg of Al(OH)₃ intraperitoneally within 24 h after birth. Injections were repeated weekly for 8 weeks, at biweekly intervals for approximately 30 weeks and then at monthly intervals. Sensitized animals develop bronchoconstriction in response to inhalation of the allergen, and cardiovascular collapse in response to i.v. administration [16]. The animals were studied at approximately 1 year of age.

Protocol

Ragweed-sensitized dogs ($n = 6$) were investigated on five different occasions approximately 3–5 weeks apart because challenges are reproducible when performed over this interval [13]. For each sensitized dog, the i.v. dose of ragweed to produce shock was previously determined, and this same dose was used in all five studies in that animal. In a non-treatment study, each animal was shocked and no Epi was administered. In the three bolus treatment studies, Epi was administered by

the i.v., i.m., and s.c. routes, respectively, immediately after allergen challenge in a dose of 0.01 mg/kg, which is the recommended dose described in the algorithm for the treatment of acute anaphylaxis in children and adults (to a maximum of 0.3 mg) [6]. By the i.v. route, Epi was administered through a central vein over 5–6 s as described by Smith et al. [11]; by the i.m. and s.c. routes, Epi was administered in the region of the left buttock [14].

In the continuous infusion study, the objective was to assess whether a constant infusion of Epi would provide sustained haemodynamic improvement and a reduction in the amount of Epi used as compared with the bolus approaches. As determined by Bautista et al. [14], the pharmacokinetics of Epi metabolism examined after shock can be described in terms of a monoexponential decay. The volume of distribution of Epi is approximately 2 L/kg and the average decay in Epi after peak levels are achieved averages approximately 30 pg/mL/min. Based on these variables and the body weight of the dogs, it was calculated that a constant infusion of Epi at a mean value of approximately 0.05 mcg/min/kg with a range between 0.005 and 0.5 mcg/min/kg would keep Epi concentrations at peak levels during the initiation of shock and would prevent the decline in mean arterial pressure (MAP) ordinarily observed. Based on the degree of hypotension that developed after allergen challenge in this model, the initial infusion dose was titrated within this range over the course of the experiment to maintain MAP at approximately 70% of baseline, the target MAP. The total amount of Epi required to achieve blood pressure control was calculated over the duration of experiment to see whether a more beneficial haemodynamic effect could be observed as compared with the bolus studies.

The measurement protocol for the five studies was as follows: after baseline measurements were obtained, allergen was given by the i.v. route. Either bolus Epi (i.v., i.m., s.c.), or constant infusion of Epi was then administered at first evidence of a fall in MAP as defined by a decrease of 15%, while in the non-treatment study no drug was administered. Because it was previously shown that the administration of a placebo (i.e. normal saline solution) by any of the routes had no effect in this model [14], no placebo was administered in the present study. Haemodynamics and blood samples were measured within 2–3 min after treatment (Tx), and at 5, 10, 15, 30, 45, 60, 90, 120, 150, and 180 min post-treatment.

Animal preparation and procedures

The animals were studied while anaesthetized with sodium pentobarbital (30 mg/kg, i.v.). Based on the previous studies in dogs [18] the half-life of pentobarbital anaesthesia is approximately 8 h. Preshock plasma pentobarbital concentrations average <25 mg/L at baseline [19], and although concentrations fall slightly, they remain fairly constant over the course of the study (17–20 mg/L). If additional anaesthesia was needed at the 120–180 min period, 60 mg of pentobarbital was administered over 1–2 min at least 10 min prior to obtaining the next measurement when concentrations would have plateaued.

The animals were studied in the supine position. The trachea was intubated with an endotracheal tube and the lungs were mechanically ventilated at a volume of 20 mL/kg

(Harvard Apparatus, Holliston, MA, USA). The ventilator rate was increased as needed to maintain the blood pH between 7.3 and 7.4, because slight metabolic acidosis develops during challenge [13, 20]. Oxygen, at a concentration of 40–50% was given to maintain arterial oxygen tension (PO_2) above 150 mmHg, as in previous studies [13, 20]. Haemodynamic measurements were obtained at end-expiration with the ventilator turned off for 3 s.

All procedures were performed under sterile conditions. A thermodilution balloon-tipped catheter was used to measure mean pulmonary arterial pressure, mean pulmonary capillary wedge pressure (Pwp), and to determine thermodilution cardiac output (CO) (Columbus Instruments, Columbus, OH, USA). The average of three CO determinations was reported. A polyethylene catheter was placed into the femoral artery and advanced to the mid-descending aorta to measure MAP and to withdraw samples of blood for arterial blood gases. All catheters were connected to transducers (Cobe Laboratories, Athens, TX, USA) and were referenced relative to the left atrium. All transducers were connected to a chart recorder (Astro Med, West Warwick, RI, USA). Stroke volume (SV) was calculated from: $SV = CO/HR$ (heart rate). Systemic vascular resistance (SVR) was estimated from $MAP/CO \times 80$ (dynes/cm⁵), because it was previously shown that including right atrial pressure in the calculation of SVR offered no additional information in this ragweed model [14]. Baseline measurements were made after 30 min of stabilization when Pwp was usually around 5–10 mmHg. No fluids were administered throughout the study.

At each measurement interval, 3 mL of mixed venous blood was also withdrawn from the distal port of the pulmonary artery catheter for determinations of plasma Epi concentrations. Samples were placed into a test tube that contained EDTA and centrifuged at 4 °C. Then plasma was transferred into a labelled polypropylene tube with a screw cap, frozen promptly in an upright position and stored at –20 °C. Following completion of the experiment, the arterial and venous catheters were removed, and haemostasis was obtained. The animals were given prophylactic i.v. antibiotics (cloxacillin, 10 mg/kg and gentamicin, 2 mg/kg) and returned to their cages.

Epi plasma levels were analysed in the non-treatment, i.v. bolus, and constant infusion studies, because major haemodynamic differences were found to occur only among these studies (see Results and Discussion). Epi concentrations were measured with a high-performance liquid chromatograph [21, 22] reverse-phase system (Waters Corp., Milford, MA, USA) with electrochemical detection. After thawing the plasma, solid phase extraction was performed, with an efficiency of 75–80%. It was possible to detect as little as 5 pg/mL (0.025 nmol/mL) of Epi. Calibration curves were linear over the range 25 to 1000 pg/mL with a coefficient of variation of 3% at 1000 pg and 10% at 25 pg. Epi concentrations were analysed as area under the curve as previously described [14].

Statistical analyses

Statistical analyses included a one-way ANOVA when one repeated measurement was obtained and a two-way ANOVA when two repeated measures were examined [i.e. factor A (treatments) and factor B (time periods)]. A Student–Newman–Keuls' (SNK) Multiple-Range Test was used to

determine where significance occurred in the different analyses when multiple comparisons were obtained. Results are reported as mean $\pm$ 1 SE.

Results

For each dog, the same dose of ragweed (range, 1 to 8 mg; mean ($\pm$ SE), 3.7 ± 0.3 mg) was used in each study. The major haemodynamic results found in the five studies are shown in Fig. 1. Although Epi was administered at the onset of the fall in MAP, measurements determined within 2–3 min of treatment showed a severe decrease in MAP in all studies as compared with baseline (see left upper panel in Fig. 1). In the i.v. bolus study, Epi caused an increase in MAP at the 5 min interval, but this effect was short-lived. For the most part, the haemodynamic recovery in the Epi bolus studies was not different from that observed in the non-treatment study. However, in the constant infusion study, after the initial decrease from baseline, MAP gradually increased and reached the baseline value within 10 min post-Tx. The results obtained in the constant infusion study were significantly higher over much of the recovery period as compared with the non-treatment and bolus studies.

The changes observed in CO are shown in Fig. 1 (left lower panel). As compared with baseline, CO decreased at Tx, and this decline occurred to a similar extent in all studies. In the bolus Epi studies, the time course of recovery of CO was not different as compared with the non-treatment study. In contrast, the time course of CO recovery in the constant infusion study was much faster than the other studies, and CO was higher as compared with the other studies for over much of the recovery period.

The changes observed in Pwp in the five studies are shown in Fig. 1 (right upper panel). Pwp were not different at baseline in the studies. Following allergen challenge, Pwp decreased to a similar extent in all studies. The recovery of Pwp to the baseline value was slower in the i.m. study in which Pwp was lower than the measurements obtained in the i.v. bolus study for 45 min post-Tx. In the constant infusion study, Pwp was not different from values measured in non-treatment study, despite the finding of a higher CO in the constant infusion study. After allergen challenge, HR (see Fig. 1, right lower panel) and SVR (see Table 1) were not different among the five studies and showed little change over the course of the post-treatment period.

Among the bolus studies and non-treatment study, there were no differences in SV-detected post-challenge at any measurement interval (Fig. 2, upper panel). In the continuous infusion study, SV was significantly higher as compared with most of the bolus studies for up to 45 min post-Tx. In the five studies, stroke work (SW) (Fig. 2, lower panel) was used as an index of myocardial function, because this parameter incorporates components of both after load (i.e. MAP) and preload (i.e. Pwp). In the continuous infusion, SW were higher as compared with all of the other studies over most of the recovery period.

Total plasma Epi concentrations were slightly higher in the i.v. bolus and constant infusion studies than in the non-treatment study, but there were no significant differences

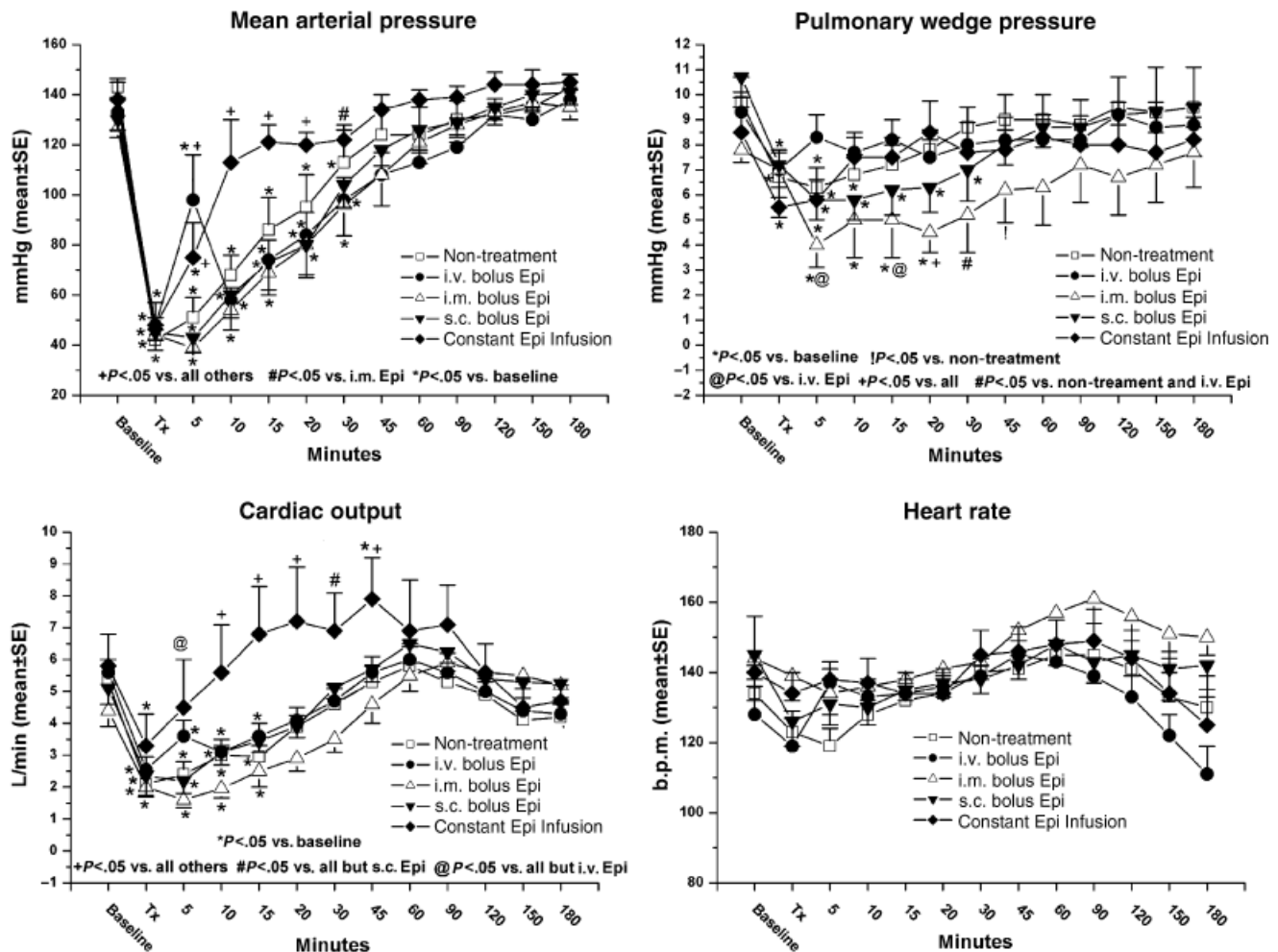


Fig. 1. Haemodynamic parameters are plotted over the course of the study (mean $\pm$ SE). Measurements were obtained at baseline, treatment (Tx), and until 3 h post-treatment. $N = 6$ for all parameters at all intervals. Epi, epinephrine; i.v., intravenous; i.m., intramuscular, and s.c., subcutaneous. Statistics by two-way ANOVA and Student–Newman–Keuls' multiple comparison test.

among the studies at any of the intervals measured (Table 2). In the continuous infusion study, the mean total amount of Epi required to produce the beneficial haemodynamic effect was approximately one half of that used in the Epi bolus studies (individual experiments shown in Fig. 3). The mean ($\pm$ SE) initial infusion rate was 0.33 ± 0.15 mcg/kg/min with a range of 0.19–0.45 mcg/kg/min. In three of the animals, the infusion rate was turned off by 20 mins post-Tx, while in all dogs, the infusion rate was turned off by 60 min post-Tx.

Discussion

In this canine model, when Epi was administered by the continuous infusion route, there was a sustained improvement in haemodynamics as compared with the non-treatment and bolus Epi studies. The results show that MAP, CO, SV, and SW measured in the constant infusion study were significantly greater than values obtained in the bolus i.v., i.m., and s.c. studies. In the constant infusion study, CO remained higher than most of the other studies for 90 min

post-shock, while MAP remained higher for 20–30 min post-shock, SV for 20–40 min post-shock, and SW for up to 90 min post-shock. In contrast, when administered by either the i.v., i.m., or s.c. routes, there was no sustained effect of bolus Epi on haemodynamic recovery. By the i.v. route, Epi produced a transient increase in MAP at the 5 min interval, whereas for the remaining intervals there were no differences in haemodynamics observed among the bolus and non-treatment studies. This confirms the findings of Bautista et al. [14] during fully developed canine AS in which bolus i.v. Epi produced a transient immediate haemodynamic effect, while bolus Epi by the i.m. and s.c. routes caused no haemodynamic improvement as compared with a non-treatment study.

The improvement in MAP noted in the continuous infusion study appeared to be because of Epi's β -effect on the heart, and not to its α_1 -vasoconstrictive effect on the systemic vasculature. The measurement of contractility used in this study, SW, increased over much of the post-shock period as compared with the other studies. In addition, as shown in Fig. 1, in the continuous infusion study, after the initial fall in MAP from baseline, the rate of increase in MAP over the course of the study was approximately double that found in

Table 1. Systemic vascular resistance ($n = 6$; dynes/cm⁵; mean $\pm$ SE)

	Baseline	Tx	5 min	10 min	15 min	20 min	30 min	45 min	60 min	90 min	120 min	150 min	180 min
Non-treatment study	2300 $\pm$ 257	1706 $\pm$ 210	1882 $\pm$ 238	1844 $\pm$ 169	2397 $\pm$ 328	1975 $\pm$ 225	1983 $\pm$ 158	1910 $\pm$ 101	1761 $\pm$ 96	2029 $\pm$ 145	2239 $\pm$ 183	2717 $\pm$ 189	2962 $\pm$ 333
i.v. bolus study	1959 $\pm$ 150	1813 $\pm$ 458	2456 $\pm$ 616	1633 $\pm$ 193	1705 $\pm$ 148	1683 $\pm$ 109	1739 $\pm$ 96	1597 $\pm$ 81	1551 $\pm$ 87	1786 $\pm$ 157	2161 $\pm$ 108	2482 $\pm$ 163	2646 $\pm$ 129
i.m. study	2473 $\pm$ 317	1975 $\pm$ 303	2182 $\pm$ 255	2088 $\pm$ 448	2093 $\pm$ 439	2104 $\pm$ 533	1968 $\pm$ 447	1733 $\pm$ 256	1579 $\pm$ 191	1570 $\pm$ 178	1709 $\pm$ 178	2000 $\pm$ 214	2028 $\pm$ 441
s.c. study	2151 $\pm$ 209	1772 $\pm$ 246	1632 $\pm$ 171	1588 $\pm$ 150	1649 $\pm$ 153	1617 $\pm$ 216	1631 $\pm$ 110	1679 $\pm$ 89	1610 $\pm$ 134	1729 $\pm$ 181	2114 $\pm$ 268	2217 $\pm$ 251	2371 $\pm$ 371
Continuous infusion study	2355 $\pm$ 506	1538 $\pm$ 234	1676 $\pm$ 339	2059 $\pm$ 552	1919 $\pm$ 479	1770 $\pm$ 407	1696 $\pm$ 356	1684 $\pm$ 388	2177 $\pm$ 528	1938 $\pm$ 406	2352 $\pm$ 401	3068 $\pm$ 564	2704 $\pm$ 417

By statistical analyses, within- as well as between-group analysis led to non-significant differences among studies and conditions.
Tx, treatment; i.v., intravenous; i.m., intramuscular; s.c., subcutaneous.

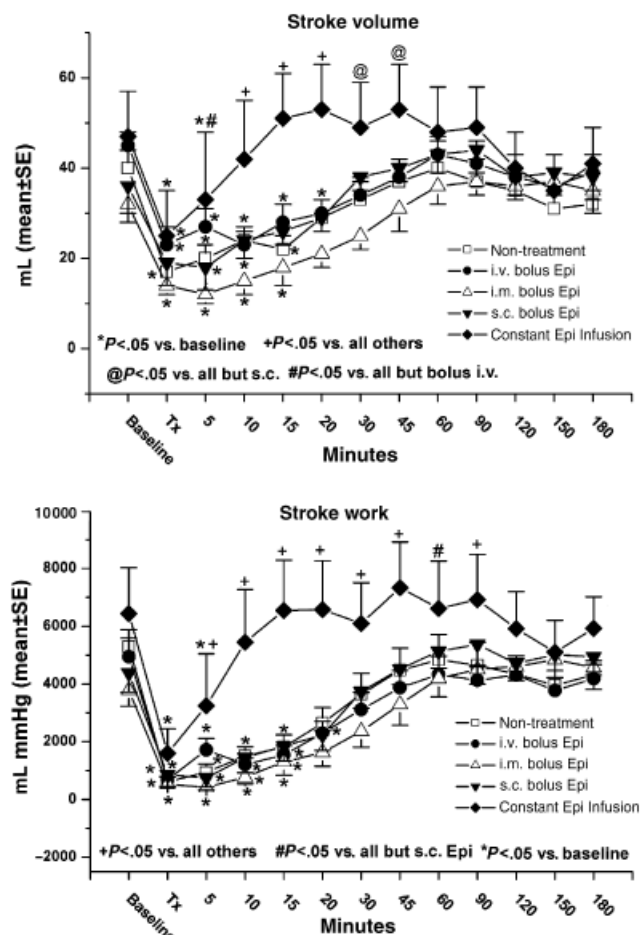


Fig. 2. Stroke volume and stroke work are plotted over the course of the study (mean $\pm$ SE). Measurements were obtained at baseline, treatment (Tx), and until 3 h post-treatment. $N = 6$ for all parameters at all intervals. Epi, epinephrine; i.v., intravenous; i.m., intramuscular; and s.c., subcutaneous. Statistics by two-way ANOVA and Student–Newman–Keuls' multiple comparison test.

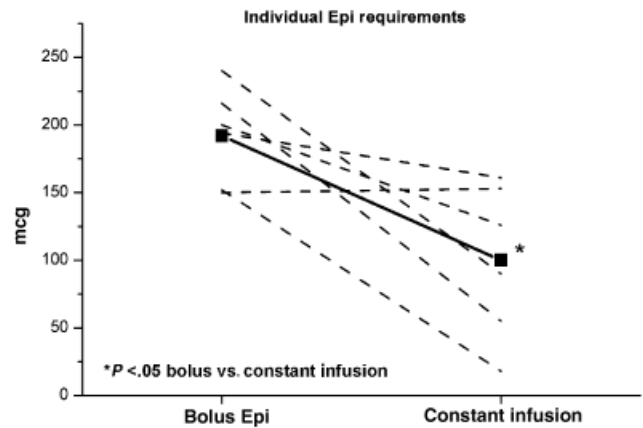
the other studies, and CO showed a similar proportional increase. Thus, the increase in MAP found in the continuous infusion study could be totally accounted for by an increase in CO and not by accompanying arterial vasoconstriction. The fact that SVR did not increase after Epi was administered in the continuous infusion study also supports this conclusion.

In addition, based on our measurement of left ventricular preload, Pwp, left ventricular filling volume was not different in the continuous infusion study as compared with the non-treatment study. Thus, the higher CO found in the continuous study was not because of an increase in left ventricular filling pressure as compared with the non-treatment study. Moreover, in all studies, after allergen challenge, Pwp fell to a similar degree between baseline and shock, from approximately 9–6 mmHg. This fall after allergen challenge reflects the venodilation and the subsequent reduction in preload that occurs during shock in this model [13]. Over the course of the study, Pwp rose to the baseline value by 45 min in all studies, except for the i.m. study, in which Pwp was lower than in the other studies. Although the explanation for this finding is not clear, it is known that Epi may have dose-dependent vasodilatory and vasoconstrictive effects on the vasculature

Table 2. Area under the curve for plasma Epi concentrations ($n = 6$; pg/mL over interval measured, mean $\pm$ SE)

	Baseline to Tx	Tx to 5 min	5–10 min	10–15 min	15–20 min	20–30 min	30–45 min	45–60 min	60–90 min	90–120 min	120–150 min	150–180 min	Total Epi
Non-treatment study	1869 $\pm$ 474	2010 $\pm$ 701	1625 $\pm$ 423	2603 $\pm$ 997	2525 $\pm$ 1086	2800 $\pm$ 567	6475 $\pm$ 3078	5899 $\pm$ 2914	6455 $\pm$ 1786	20535 $\pm$ 8714	2245 $\pm$ 8091	22543 $\pm$ 8091	97883 $\pm$ 28340
i.v. bolus study	3646 $\pm$ 1675	3640 $\pm$ 1785	2031 $\pm$ 599	1994 $\pm$ 644	2153 $\pm$ 865	4708 $\pm$ 2084	5204 $\pm$ 2183	22771 $\pm$ 16862	50348 $\pm$ 37926	13560 $\pm$ 4541	8560 $\pm$ 3582	9568 $\pm$ 4208	128182 $\pm$ 55415
Continuous infusion study	2329 $\pm$ 760	1774 $\pm$ 481	3195 $\pm$ 1551	4886 $\pm$ 3149	4002 $\pm$ 2144	4508 $\pm$ 1468	5871 $\pm$ 1144	12539 $\pm$ 7414	26723 $\pm$ 15607	15033 $\pm$ 4217	15105 $\pm$ 4321	21905 $\pm$ 7878	117668 $\pm$ 34359

Tx, treatment; Epi, epinephrine; i.v., intravenous. By statistical analyses, within- as well as between-group analysis led to non-significant differences among studies and conditions.

**Fig. 3.** Individual (thin dashed lines) and mean (thick solid line) values of epinephrine (Epi) doses administered in the bolus and continuous infusion studies. Statistics by one-way ANOVA.

[23]. The lower Pwp found in the i.m. study may indicate that Epi's β -adrenergic effect on the vasculature caused more venodilation and reduced preload when given by this route as compared with the other routes.

Although a greater haemodynamic effect was observed in the continuous infusion study, there was little difference in plasma Epi concentrations as compared with the i.v. bolus route and the non-treatment study. Moreover, the plasma concentrations of Epi determined in the non-treatment study subsequent to all of the intervals after shock showed no clear increase as compared with the baseline value. There are some possible explanations for this finding. In terms of the Epi response, the variation in the magnitude of this response among the individual animals is quite large and the time course of endogenous Epi release is quite variable. Among the individual dogs, a peak Epi response may occur within seconds of shock or much later over the course of the study. This would prevent the finding of a clear peak at a specific interval after allergen challenge. In addition, the magnitude of the Epi response determined in the individual animals in the present study was less than that observed in the study by Bautista et al. [14], although some of the same dogs were used in both studies. This may reflect a decrement in the Epi response when repeated challenges are administered in an animal as was reported in a preliminary study [24].

In the bolus Epi i.v. study, there was a definite haemodynamic response observed, in that MAP increased from a mean of approximately 40 mmHg at baseline to 100 mmHg at 5 min post-treatment. Because the Epi haemodynamic response occurred so promptly, it is possible that the peak Epi response was missed within the time frame of the measurements obtained. In addition, the variability in the endogenous Epi response, insofar that it may occur at a delayed interval in a given animal, may have made it difficult to identify a clear peak in the Epi response in the bolus i.v. study. A final reason is that magnitude of the expected response may be relatively small. In the bolus studies, the dose of Epi administered was 0.01 mg/kg, a dose recommended for the treatment of acute anaphylaxis in children [6]. Based on the weight of the animals, the average amount of Epi given in the bolus studies was 200 mcg. The volume of distribution of Epi was previously calculated in AS as 2 L/kg or 40 L per 20 kg dog

[14]. If Epi were indeed distributed within this volume, then the expected increase in plasma Epi would be 200 000 pg/40 000 mL or 20 pg/mL. This increase in Epi might be difficult to detect, given the variation in the Epi measurements that occur in these animals.

In the continuous infusion study, the amount of Epi required was approximately half that used in the bolus studies and averaged 100 mcg. Most of this dose was given early during the course of shock, after which the infusion rate was steadily decreased as MAP increased. In approximately one-half of the animals, the Epi infusion was discontinued by 20 min post-shock, and in all dogs, the infusion was stopped by 60 min post-shock. Even though a haemodynamic effect was very apparent by this route, it was not possible to detect a significant increase in plasma Epi concentrations as compared with the other routes. Again, the magnitude of the increase in plasma Epi concentrations expected in the continuous infusion study would be less than that anticipated in the i.v. bolus study, so that it is not surprising that a significant increase in plasma Epi concentrations was not observed in the continuous infusion study. Thus, overall, our results point out that haemodynamic measurements may be more sensitive to Epi infusion than is the detection of an increase in Epi plasma concentrations.

The rationale for the use of Epi in the treatment of AS is based on the understanding that β -adrenergic agents such as Epi increase cellular levels of cyclic AMP [10]. The cyclic AMP system has been shown to modulate the immunological release of histamine and other mediators in isolated tissue preparations. Studies with human lung and nasal-polyp fragments demonstrated a bidirectional effect of tissue levels of cyclic AMP, with elevations suppressing mediator release and diminutions enhancing release [25, 26]. β -adrenergic agents increase cellular levels of cyclic AMP and inhibit the antigen-induced release of histamine and other anaphylactic mediators. In contrast, α_1 -adrenergic stimulation causes a decrease in tissue levels of cyclic AMP enhancing the release of anaphylactic mediators during allergen challenge [10]. In addition to its favourable effect on mediator release, Epi has a beneficial haemodynamic profile that would be useful for the treatment of AS. Epi causes an increase in cardiac inotropy, as well as venous and systemic vasoconstriction [3]. All of these attributes might be life-saving in the treatment of AS.

Although Epi has assumed an important role in the care of AS in clinical medicine, results of bolus studies performed in humans [11] and in animals models [13, 14] have shown no beneficial effect on haemodynamics. Nevertheless, a marked improvement in haemodynamics was observed when Epi was given in the continuous infusion study in the present study. The property of Epi attributable to this improvement appeared to be related to its β -adrenergic effect on the heart that resulted in an increase in CO and SW. Because Epi was administered in a slow and sustained manner in the continuous study, it may have selectively targeted the β -adrenergic receptors to improve cardiac function, while by rapid i.v. bolus, any effect was short-lived, and SVR tended to increase as compared with the other studies, these results indicating that α -adrenergic receptors may have primarily been stimulated in the i.v. bolus study. By the i.m. and s.c. routes, absorption may be delayed and unpredictable [21, 27]. Indeed, in the bolus i.m. and s.c. studies performed by

Bautista et al. [14], plasma Epi concentrations were measured and did not increase after challenge, and thus there was little rationale for measuring Epi concentrations by the i.m. and s.c. routes in this study. Thus, it appears that continuous infusion of Epi because of its sustained infusion may be the most efficient and effective route to administer Epi in AS. Nevertheless, it is important to note that in the bolus studies, only a single dose of Epi was used, and the results might be different if other dosing regimens were employed.

In the present study, the major objectives were concerned with the haemodynamic consequences of anaphylaxis, because respiratory changes are minor when i.v. allergen is given in this model. PO_2 was maintained > 150 mmHg, and pH was kept within the normal range to prevent haemodynamic deterioration because of respiratory consequences. In human anaphylactic shock, bronchospasm and laryngeal oedema may benefit from bolus Epi treatment [3]. In addition, the present study was not designed to address other important outcomes, such as neurological and renal function, cutaneous and gastrointestinal symptoms and decreased release of mediators of inflammation. These aspects need to be examined in the context of other investigations and represent limitations of this study.

It also must be recognized that haemodynamics were examined while the animals were anaesthetized, because it would be impossible to study conscious animals. Of the anaesthetic agents available, all types would affect some aspect of the anaphylactic response in our model (i.e. histamine release and/or bradycardia by narcotic agents [28] and vasodilation by inhalational agents [29]). Pentobarbital may increase baseline heart rate and alter other haemodynamic responses as compared with the awake condition [19]. The lack of a further increase in heart rate after AS was produced may have reflected the effect of pentobarbital anaesthesia on our results, although we previously showed that at least in part, histamine H_3 receptor activation, which inhibits adrenergic norepinephrine release, may be responsible for this finding [30]. Because pentobarbital anaesthesia is often used for investigating haemodynamics in allergic models [31], this agent was administered in the present study. The dose of pentobarbital was identical in all studies, so that it is not clear why the effect of pentobarbital would behave differently in the constant infusion study vs. the other bolus studies. Because it is not possible to exclude an effect of anaesthesia on our results, we recognize that our findings must be interpreted in this context.

In summary, when Epi was administered at the initiation of allergen challenge in this ragweed shock model, bolus treatment by i.m., i.v., or s.c. routes caused limited haemodynamic improvement. In contrast, constant infusion of Epi produced significant haemodynamic improvement at a lower total dose of Epi. From the results obtained in this canine model, it appears as if Epi is best administered by the continuous route in order to provide cardiovascular support.

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