CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205029Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA number	205029
Submission type	Standard 505(b)(2)
Submission date	12/04/2012
Applicant name	Belcher Pharmaceuticals, LLC
Proposed brand name	(b) (4)
Generic name	Epinephrine, USP
Dosage form	Sterile solution for injection (1 mL ampule)
Dosage strengths	1 mg/mL
Proposed indication	To increase systemic arterial blood pressure in acute hypotensive states associated with septic shock
OCP division	Division of Clinical Pharmacology 1
OND division	Division of Cardiovascular and Renal Products
Primary reviewer	Sudharshan Hariharan, Ph.D.
Team leader	Rajanikanth Madabushi, Ph.D.

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1. EXECUTIVE SUMMARY

Belcher Pharmaceuticals, LLC is seeking approval of Epinephrine, USP [1 mg/mL, 1 mL ampule] via the 505(b)(2) pathway for increasing systemic arterial blood pressure in acute hypotensive states associated with septic shock. The proposed dosing regimen in septic shock patients is 0.05 to 2.0 µg/kg/min administered as continuous *i.v.* infusion titrated closely to achieve a target mean arterial pressure (MAP). The sponsor is relying on the safety information from Twinject [NDA 020800, approved May 2003] as the listed drug, an auto-injector approved for use in the emergency treatment of severe Type I allergic reactions. The sponsor relies on the published literature to support the non-clinical, clinical pharmacology and clinical efficacy of the proposed drug product. A literature based 505(b)(2) submission for epinephrine in support of the proposed indication was agreed upon by the Division of Cardiovascular and Renal Products during the pre-IND and pre-NDA meetings held on 02/03/2012 and 07/25/2012, respectively.

The clinical pharmacology package for this application primarily consists of published literature addressing the following topics – (i) pharmacokinetics (PK), (ii) pharmacodynamics (PD), (iii) dose-response in healthy and target population, and (iv) impact of intrinsic and extrinsic factors on PK and PD of epinephrine.

1.1. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The key clinical pharmacology features of epinephrine are summarized below:

- When administered intravenously, epinephrine rapidly disappears from the plasma with an effective half-life of <5 min. Time to reach pharmacokinetic steady state following continuous *i.v.* infusion is approximately 10 min.

- Following *i.v.* infusion, epinephrine has a quick onset of blood pressure response (<5 min). The time to offset the drug effect is approximately 10-15 min.

- There is a trend for dose-dependent increase in blood pressure and heart rate with increasing doses of epinephrine [0.001 to 0.2 µg/kg/min] in healthy subjects.

- In septic shock patients, there is an increase in mean arterial pressure with *i.v.* infusions of epinephrine. However, a naïve-pooled analysis shows a similar change from baseline MAP response over a wide range of epinephrine infusion rates suggesting a high degree of inter-patient variability.

- Intrinsic factors such as age, body weight and disease severity may affect the pharmacokinetics of epinephrine. However, due to quick onset and offset of effect, dose-adjustment based on exposure changes is not necessary as epinephrine is to be administered in a controlled clinical setting titrated to a target response. Similarly, drug interactions affecting the PK or PD of epinephrine also does not warrant any dose adjustment.

1.2. Phase 4 Requirements / Commitments

No Phase 4 Requirements / Commitments are proposed at this point of time.

1.3. Recommendation

The Office of Clinical Pharmacology (OCP/DCP1) recommends approval of epinephrine based on its effect on MAP in septic shock patients.

2. QUESTION BASED REVIEW

An abridged version of the question based review is used to address specific clinical pharmacology issues of epinephrine related to this submission. Review of individual publications pertaining to the clinical pharmacology aspects of epinephrine can be found in the Appendix.

2.1. What are the disposition characteristics of epinephrine?

Epinephrine is rapidly cleared from the plasma following an *i.v.* administration with an effective half-life of <5 min. A pharmacokinetic steady state following continuous *i.v.* infusion is achieved within 10-15 min. Epinephrine is not effective after oral administration because it is rapidly conjugated and oxidized in the gastrointestinal mucosa and liver. Absorption from subcutaneous tissues occurs relatively slowly because of local vasoconstriction and the rate may be further decreased due to systemic hypotension in cases such as septic shock. Following an intramuscular injection, absorption is relatively rapid, however, in emergencies such as septic shock, it is necessary to administer epinephrine intravenously. Pharmacokinetics of epinephrine is dose proportional in the infusion dose range of 0.026 to 1.67 µg/kg/min in the target population i.e., septic shock [Fig. 1].

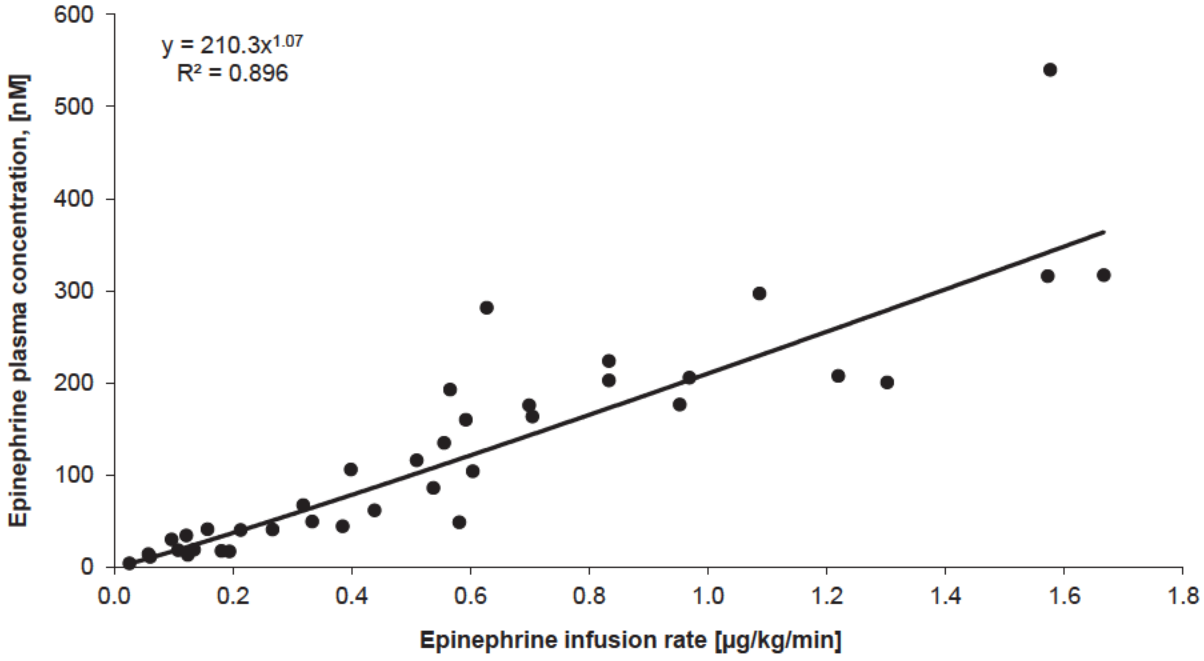


Figure 1: Epinephrine plasma concentration as a function of infusion rate at steady state showing dose linearity in the range 0.026 to 1.67 µg/kg/min.

Epinephrine is extensively metabolized with only a small amount being excreted unchanged. Both endogenous and exogenous epinephrine is preferentially metabolized by catechol-*O*-methyl transferase [COMT] in extraneuronal pathways, with less epinephrine being deaminated by monoamine oxidase [MAO]. COMT and MAO are abundantly expressed in the liver, kidneys

and other extraneuronal tissues. The relative contribution of organs/tissues in the removal of circulating exogenous epinephrine from plasma is liver (32%) > kidneys (25%) > skeletal muscle (20%) > mesenteric organs (12%). Metanephrine is the extraneuronal *O*-methylated metabolite of epinephrine which is further metabolized to vanillylmandelic acid (VMA), an inactive metabolite. Following *i.v.* administration, metabolites of epinephrine are primarily eliminated in the urine. Metabolic profile of epinephrine is shown in Figure 2.

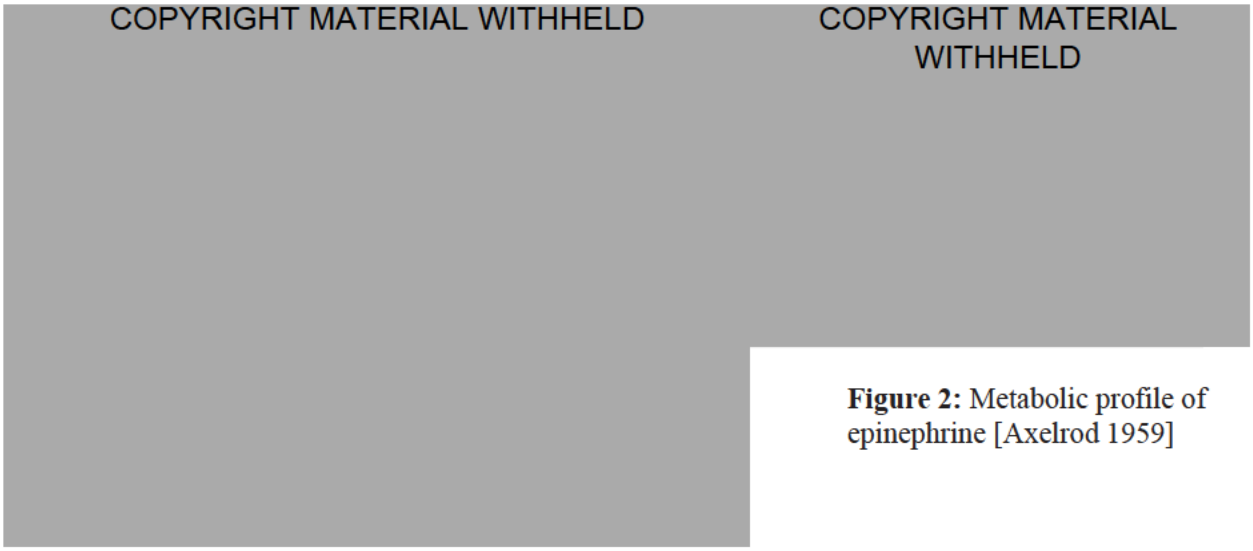


Figure 2: Metabolic profile of epinephrine [Axelrod 1959]

2.2. What is the proposed mechanism of action of epinephrine? How does it affect the important hemodynamic variables?

Epinephrine is a non-selective β- and α-adrenergic agonist. The affinity towards β- is greater than α-adrenergic receptors. Epinephrine increases blood pressure by 3 mechanisms: a direct myocardial stimulation that increases the strength of ventricular contraction (positive inotropic action); an increased heart rate (positive chronotropic action) – both these actions are mediated by β_1-adrenergic receptors; and vasoconstriction in many vascular beds – mediated by α_1-adrenergic receptors.

Table 1 briefly outlines the effect of epinephrine on cardiac function and blood pressure. Heart rate [HR], stroke volume [SV] and in turn cardiac output [CO=SV x HR] are increased due to the chronotropic and inotropic actions of epinephrine. An increase in CO leads to a corresponding increase in systolic arterial blood pressure [SBP]. However, the magnitude of effect on diastolic and mean arterial pressure may depend on the doses of epinephrine used. At relatively small doses of 0.1 µg/kg, systemic vascular resistance [SVR] and diastolic blood pressure [DBP] are shown to decrease due to the action of epinephrine on β_2-adrenergic receptors causing peripheral vasodilation. But, at higher doses, peripheral vasoconstriction mediated by action on the α1-adrenergic receptors takes over thus leading to a modest increase in DBP. Mean arterial pressure [MAP] which is a function of both diastolic and systolic arterial blood pressure [MAP=2/3 x DBP + 1/3 x SBP] shows a marginal change at lower epinephrine doses with the increase becoming evident as with the increase in epinephrine dose.

Table 1: Qualitative changes in cardiac function and blood pressure following epinephrine infusion. Symbols denote: '+' increase, '0' no change, '-' decrease

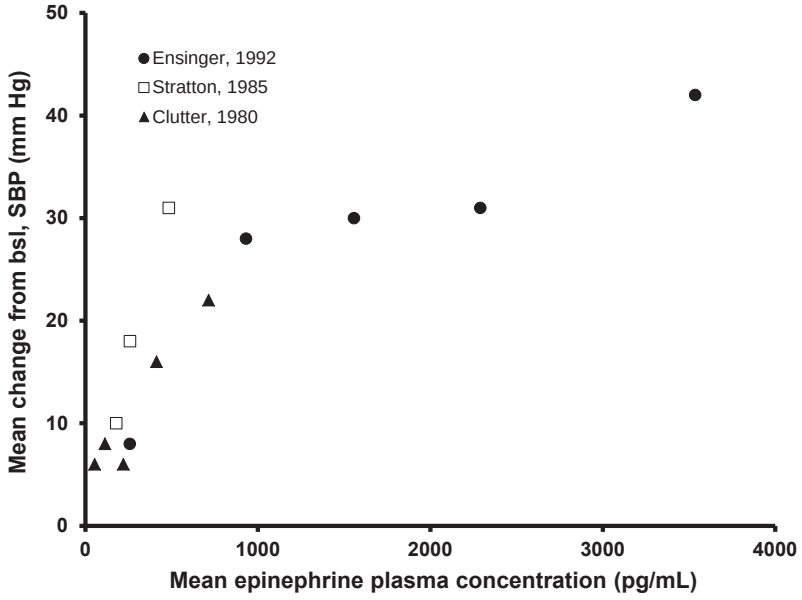
Effect on cardiac function	
Heart beat	+
Stroke volume	++
Cardiac output	+++
Arrhythmias	++++

Effect on blood pressure	
Systolic BP	+++
Diastolic BP	-,0,+
SVR	-,0,+
Mean BP	+

2.3. What is the effect of epinephrine on hemodynamic variables in healthy subjects?

Dose-blood pressure effect of epinephrine in healthy volunteers was evaluated in 3 published studies. In these studies, epinephrine was administered as a continuous intravenous infusion in a step-wise manner in the dose range: 0.01-0.2 µg/kg/min [Ensinger *et al*], 0.025-0.1 µg/kg/min [Stratton *et al*], and 0.001-0.064 µg/kg/min [Clutter *et al*]. Infusion times at a dose level were generally short, in the range of 10 to 60 min, as the PK steady state is achieved quickly [approx. 10 min]. Plasma concentration of epinephrine and hemodynamic variables were also measured at steady state following each infusion step. Figure 3 shows a scatter of mean change from baseline SBP and HR as a function of mean epinephrine plasma concentration across the 3 studies.

A



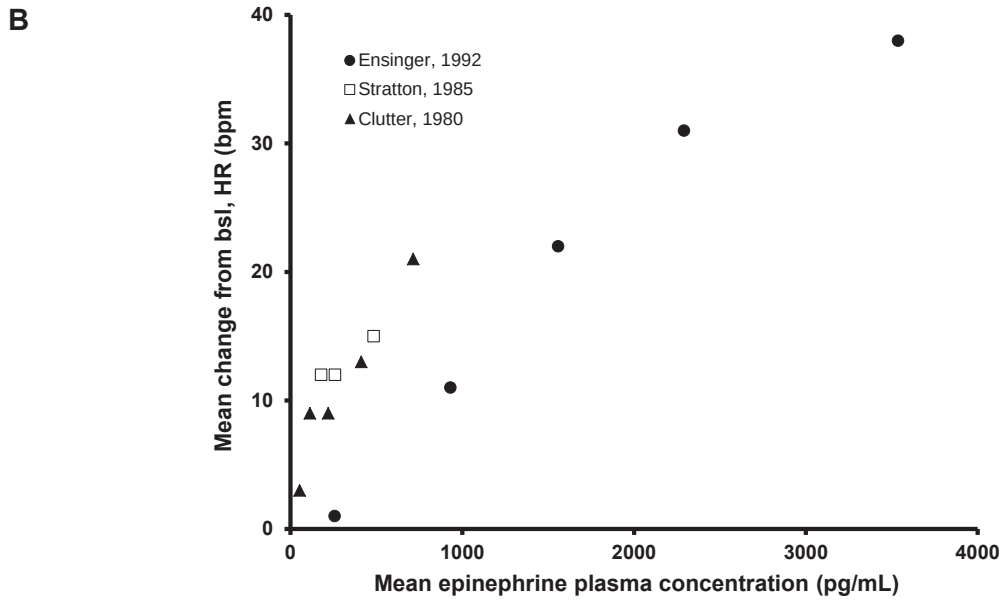


Figure 3: Plot of mean change from baseline (A) SBP or (B) HR *vs* epinephrine plasma concentration.

Based on a naïve-pooled data of the study and dose level means, there is a trend for concentration dependent increase in cumulative response for SBP as well as HR. With increase in epinephrine concentration there was an increase in cumulative response to a maximum of 40 mmHg and 30 bpm mean change from baseline SBP and HR, respectively for 0.2 µg/kg/min dose. The term 'cumulative response' is used as the drug effect for any given dose was not washed out before the administration of the next incremental dose. As for DBP, there was a decrease in mean change from baseline at lower epinephrine doses with a trend for approaching baseline at higher epinephrine doses [data not shown]. This is typical for epinephrine due to β_2-adrenergic peripheral vasodilatory effect at lower epinephrine doses which is reversed by α_1-adrenergic peripheral vasoconstriction at higher doses. There is one limitation that the exposure-response experience in healthy subjects is at relatively lower dose range than what is currently proposed for septic shock patients: 0.05 to 2.0 µg/kg/min.

2.4. Does epinephrine increase MAP in septic shock patients? Is the proposed dosing regimen justified?

Dose-blood pressure effect of epinephrine in septic shock patients was evaluated in a study published by Moran *et al*. In this study, epinephrine was administered as the lone vasopressor by continuous intravenous infusion in a step-wise manner in the dose range: 3.0 to 18 µg/min [0.04 to 0.26 µg/kg/min, assuming a 70 kg human]. Hemodynamics was measured at steady state [20 min] for each infusion rate. Epinephrine dose was titrated by increments of 3 µg/min until the endpoints of inotropic therapy were achieved [target MAP was one of the components]. In addition to Moran *et al*, there were other publications which reported the use of epinephrine in case of septic shock. However, these publications only report the mean baseline MAP, mean target MAP achieved and the individual or mean maximum stabilized dose that was required to bring patients to the desired MAP range.

Figure 4 shows a scatter of mean change from baseline MAP as a function of mean epinephrine infusion rate across studies. It is evident that epinephrine infusions increase MAP in septic shock patients. A trend for a dose-dependent increase in MAP was observed within the Moran *et al* study at lower epinephrine infusion rates. However, when mean study level data from all other publications were pooled in, there is no trend for a relationship between epinephrine dose and mean change from baseline MAP. The lack of a trend may in part due to the naïve pooled analysis without adjusting for the study level difference. However, it may also be due to the fact that the response to epinephrine is highly variable in septic shock patients. Figure 5 shows the maximal epinephrine infusion rates that were required for each individual patient to achieve a target MAP of 65 to 75 mmHg across 5 different studies. It is observed that there is a high degree of variability in response as seen by epinephrine infusion rates ranging as wide as 0.026 to 1.67 µg/kg/min to achieve target MAP [Abboud *et al*]. Therefore, based on the high inter-patient variability in epinephrine response, the proposed dosing regimen of 0.05 to 2.0 µg/kg/min in septic shock patients is acceptable.

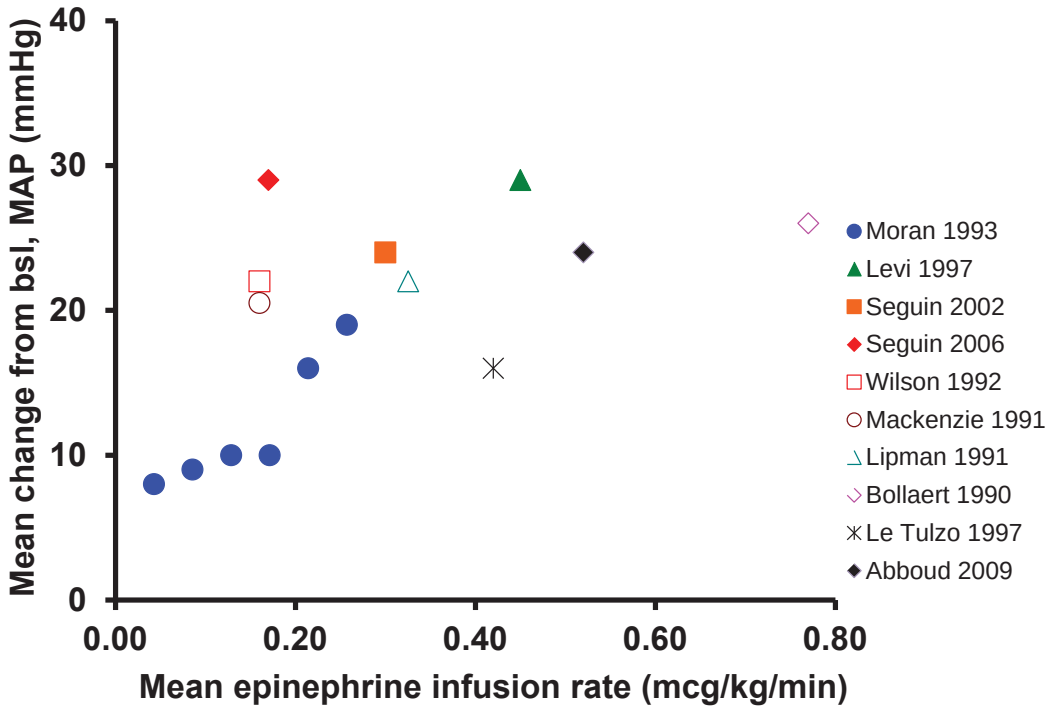


Figure 4: Plot of mean change from baseline MAP *vs* mean epinephrine infusion rate across studies.

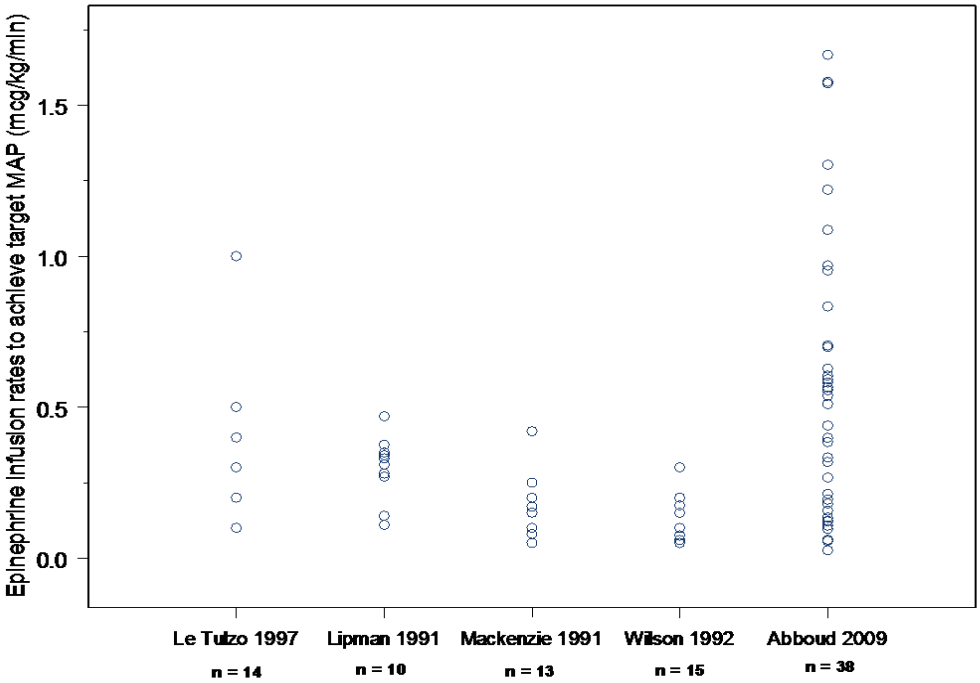


Figure 5: Maximal epinephrine infusion rate required per individual patient to achieve a target MAP of 65-75 mmHg across 5 studies in septic shock patients.

2.5. What is effect of important intrinsic factors on the PK and PD of epinephrine?

Age

Wilkie *et al* evaluated the age-related changes to plasma catecholamines and their hemodynamic response, basally and during epinephrine infusion. Plasma epinephrine levels were lower in relatively healthy old men when compared to young adults, as reflected by a 1.5- to 2.0-fold higher metabolic clearance (MCR) in the former [Fig. 6]. There was a diminished response in systolic blood pressure and heart rate to epinephrine infusion in elder subjects compared to baseline, though, hemodynamic variables at baseline were elevated compared to that of healthy young adults. The diminished hemodynamic response in elder subjects may be because of lower epinephrine plasma levels, or diminished end-organ responsivity i.e., β-adrenoceptors, or to decreased parasympathetic tone, or a combination of all. As epinephrine is titrated to a target response in MAP, no dosing adjustments are necessary in the elderly. Please see Appendix for individual publication review.

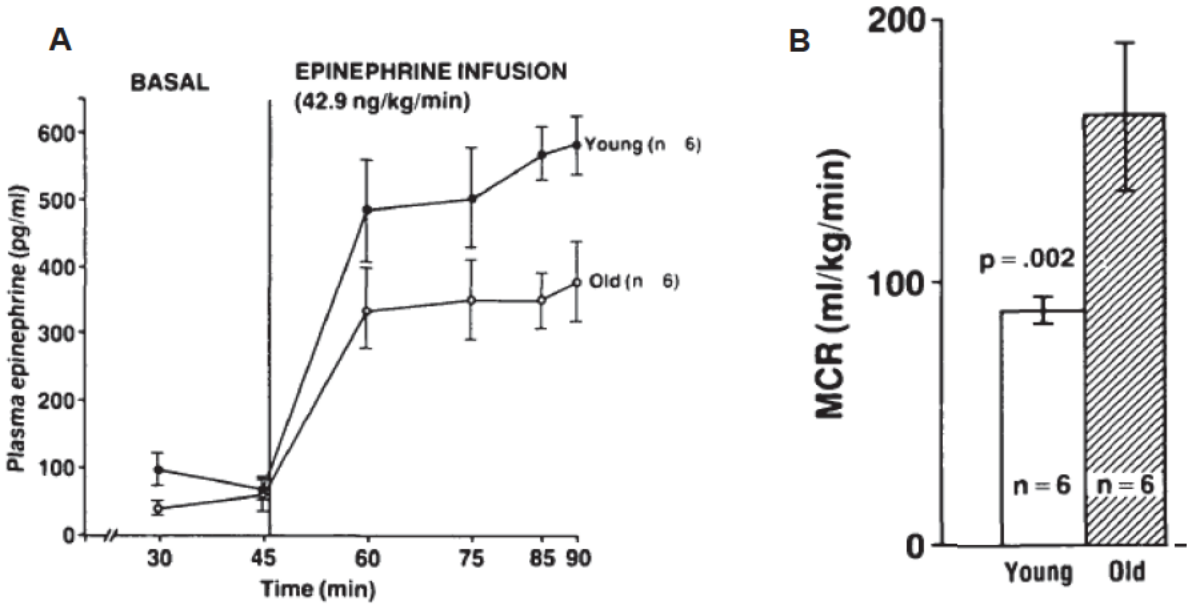


Figure 6: (A) Mean epinephrine plasma-time course and (B) metabolic clearance rate in healthy old *vs* young adults following epinephrine infusion of 0.043 µg/kg/min. Data expressed as mean ± S.D.

Gender and body weight
Abboud *et al* evaluated the PK of epinephrine and its covariates in septic shock patients. Body weight but not gender was shown to influence PK, with higher body weight associated with higher plasma clearance of epinephrine. Dose adjustments for epinephrine are not required as 'mg/kg' dosing is employed.

Renal and hepatic impairment
The PK and PD of epinephrine have not been evaluated in patients with renal or hepatic impairment. However, as shown by Eisenhofer *et al*, kidneys and liver contribute 25% and 32%, respectively to the extraneuronal removal of circulating exogenous epinephrine from plasma. High levels of COMT are reported to be found in the kidneys, liver and other extraneuronal tissues. Hence, it may be expected that kidney or liver dysfunction may lower epinephrine clearance. But, dose-adjustments based on PK changes may not be critical, as (i) the clearance of epinephrine is not dependent solely on one organ, and (ii) epinephrine is titrated to effect.

2.6. What is the impact of drug interactions on the pharmacokinetics and pharmacodynamics of epinephrine?

Drug interactions between epinephrine and (a) entacapone [a selective COMT inhibitor], (b) carvedilol [non-selective β-adrenergic blocker] and (c) propranolol [selective β-adrenergic

blocker] and phentolamine [α-adrenergic blocker] were assessed in 3 studies. Please see Appendix for individual publication review.

- When co-administered with entacapone, there was modest potentiation of the chronotropic effects of epinephrine in turn augmenting the hemodynamic response [HR, SBP]. However, this was not accompanied by changes in epinephrine plasma concentrations [Illi *et al*].

- Upon pre-treatment with carvedilol, a non-selective β-adrenergic antagonist, hemodynamic responses to epinephrine infusion was significantly attenuated [Hansen *et al*].

- There was a significant decrease in the metabolic clearance of epinephrine when co-administered with propranolol and not phentolamine which suggests epinephrine is predominantly cleared by β-adrenergic mechanisms in humans [Cryer *et al*].

In addition, Table 2 lists the class of compounds that is expected to affect the pharmacodynamic response to epinephrine based on their mechanisms of action. In the absence of dedicated studies, providing the direction of the change in epinephrine response is how best these interactions can be addressed. However, any dose-adjustments for interacting co-medications may not be required as epinephrine infusion rates are titrated to effect in a controlled medical setting with continuous monitoring of hemodynamic variables.

Table 2: Class of drugs that may augment or attenuate epinephrine's pharmacodynamic response

Drugs potentiating epinephrine's effect	Drugs antagonizing epinephrine's effect
• α-agonists: e.g. phenylephrine • Sympathomimetics: e.g. isoproterenol • Antidepressants • MAO/COMT inhibitors • K+ depleting drugs may potentiate hypokalemia • Cardiac glycosides: Potentiates arrhythmia	• β-blockers: Cardiopulmonary effects are antagonized, however, systemic vascular resistance may be potentiated due to unopposed α-vasoconstriction at high epinephrine concentrations • Vasodilators: e.g. nitrates • Diuretics • Antihypertensives

3. APPENDIX: Individual publication reviews

3.1 Epinephrine disposition:

3.1.1 Eisenhofer *et al*: J Clin Endocrinol Metab. 1995 Oct;80(10):3009-17

Title: Regional release and removal of catecholamines and extraneuronal metabolism to metanephrines

The objective of this publication was to examine the regional release (spillover) and removal of norepinephrine (NE), epinephrine (E) and normetanephrine (NMN) and metanephrine* (MN) upon infusion of radiolabeled catecholamines. Of relevance, this publication provides information on bio-distribution, metabolism and key organs responsible for clearance of both norepinephrine and epinephrine.

Briefly, [^{3}H]norepinephrine was administered as intravenous infusion alone [n=29] or in combination with [^{3}H]epinephrine [n=65] at 1.0-1.5 μCi/min to 94 subjects of whom, 14 were healthy volunteers and the remaining 80, were patients with angina pectoris, heart failure, hypertension, heart transplantations, renal artery stenosis, or carcinoma. Concentrations of catecholamines and their metabolites were measured in plasma flowing into and out of various organs/tissues such as heart, liver, lungs, kidneys, adrenals, mesenteric organs and forearm to examine the regional production of metanephrines from circulating and locally released catecholamines. Blood samples were generally collected 15 min after the start of radiolabeled infusion of the catecholamine(s). It should be noted that not all blood samples leading into or out of the various organs were collected from all subjects.

Unlabeled NE, E, NMN and MN were quantified by liquid chromatography with electrochemical detection. The eluents leaving the electrochemical cell were timed and collected for subsequent quantification of radiolabeled catecholamines and their metabolites using liquid scintillation spectroscopy. Inter- and intra-assay precision as defined by %CV were 12.2%, 11.2%, 6.5%, 11.4% and 4.2%, 3.3%, 1.9%, 3.0% for NMN, MN, NE and E, respectively. These results are within the ±15% limit for precision as per FDA guidance for bioanalytical method validation to industry.

Key results:

- Organs/tissues responsible for the removal of circulating exogenous epinephrine are liver (32%) > kidneys (25%) > skeletal muscle (20%) and mesenteric organs (12%) [Table 3]. Other organs such as heart and lungs have minimal contribution (4% and 7%, respectively).

- Epinephrine is predominantly produced in the adrenals (91%). Extra-adrenal tissues contribute small but detectable levels of epinephrine [Table 3].

* Metanephrines (NMN and MN) are the metabolic products of epinephrine and norepinephrine catalyzed extraneuronally by catechol-*O*-methyl transferase

- A small portion (6%) of plasma metanephrine was derived from metabolism of circulating epinephrine. Most plasma metanephrine (91%) was produced within the adrenals from regionally released epinephrine [Table 3]. Liver made the largest contribution (38%) to the production of metanephrine from circulating catecholamines [Table 3].

- Liver makes the largest contribution to the removal of circulating metanephrine (37.4%) [Table 4].

Table 3: Regional spillover [production] and removal rates of epinephrine; spillovers of metanephrine derived from epinephrine released locally or removed from plasma. Values represent mean ± S.E.

	E		MN spillover		
	Spillover	Removal	Released E	Removed E	Total
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Table 4: Regional fractional extraction of metanephrines. Values represent mean ± S.E.

	Fractional extraction (%):
	MN
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Reviewer's comment: This publication provides an overview of the organs/tissues involved in the extraneuronal production of epinephrine and contribution towards the clearance from plasma. It also provides information about the regional source of metanephrine formation and its subsequent removal from plasma.

3.2 Epinephrine MoA/Pharmacodynamics

3.2.1 Floras *et al*: Hypertension. 1990 Feb;15(2):132-9

Title: Desipramine blocks augmented neurogenic vasoconstrictor responses to epinephrine

The objective of this publication was to examine if systemic epinephrine augments fore arm vasoconstriction and heart rate in response to lower body negative pressure (LBNP), even following stoppage of short-term epinephrine infusion. Further, inhibition of the augmented response to epinephrine was examined following prior uptake with desipramine. LBNP procedure stimulates forearm vasoconstriction and tachycardia by triggering norepinephrine release.

The study design was randomized, crossover, double-blind, and placebo-controlled with two treatment arms – (a) placebo or (b) desipramine [125 mg p.o.], followed by epinephrine infusion. Both treatments were separated by at least 1 week apart. Eight healthy male adults [mean age=30 y] were enrolled in this study. Epinephrine was intravenously infused at 1.5 µg/min [0.021 µg/kg/min, assuming a 70 kg adult], 2.5 h following ingestion of desipramine or placebo tablets. Responses to LBNP were compared before and 30 min after epinephrine infusion which lasted 1 h. Blood pressure and heart rate were monitored at 1-min interval during LBNP procedure and at 3-min interval epinephrine infusion. Forearm blood flow was measured at 1-min interval by venous occlusion plethysmography in the non-dominant arm. Forearm vascular resistance was calculated by dividing mean arterial pressure by the average forearm blood flow. Venous blood samples were collected for assay of catecholamines before and at the last minute of LBNP procedure. Plasma catecholamines were analyzed by high-performance liquid chromatography with electrochemical detection and reported an inter- and intra-assay CV% of 7.5%. These results are within the ±15% limit for precision as per FDA guidance for bioanalytical method validation to industry.

Key results:

- Plasma levels of norepinephrine increased to LBNP stimuli which was further numerically augmented following epinephrine infusion [Table 5].

- Increase in norepinephrine plasma levels translated to augmented forearm vascular resistance and heart rate following epinephrine infusion [Table 5].

- There was no significant augmentation of other hemodynamic variables [SBP, DBP, MAP, and FBF] in response to epinephrine infusion [Table 5].

- Following prior administration of desipramine, augmented forearm vascular resistance response to epinephrine infusion was inhibited [Table 5]. However, norepinephrine plasma levels were still numerically augmented following epinephrine infusion [Table 5]. Heart rate also numerically increased following epinephrine infusion in the desipramine pre-treatment arm [Table 5].

Table 5: Hemodynamic variables before and 30 min after 1.5 μg/min intravenous infusion of epinephrine for 1 h in healthy male adults. Values are expressed as mean ± SE.

	Placebo day					
	Before epinephrine			After epinephrine		
Variable	Rest	LBNP	Change with LBNP	Rest	LBNP	Change with LBNP
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	Desipramine day					
	Before epinephrine			After epinephrine		
Variable	Rest	LBNP	Change with LBNP	Rest	LBNP	Change with LBNP
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Reviewer's comments: Exogenous epinephrine seems to increase norepinephrine plasma concentrations by possibly acting on prejunctional β-adrenoceptors triggering the release of norepinephrine. Functionally, this is translated to augmented response to forearm vasoconstriction and heart rate following LBNP stimuli, but not SBP, DBP and MAP. Moreover, pre-treatment with desipramine, a neuronal uptake inhibitor, seem to diminish the augmented response to epinephrine, however, without significantly inhibiting endogenous norepinephrine release.

3.2.2 Jern *et al*: Hypertension. 1991 Oct;18(4):467-74

Title: Infusion of epinephrine augments pressor responses to mental stress

The objective of the publication was to examine the possible effects and after effects of epinephrine on the hemodynamic reactivity to mental stress. The hypothesis tested was that the exogenous or circulating epinephrine may augment the simultaneous release of endogenous norepinephrine both during and after periods of sympathoadrenal activation and thereby contribute to development of stress-linked hypertension.

The study design was randomized, crossover, double-blind, and placebo-controlled with two treatment arms – intravenous infusion for 35 min of (a) 0.05 µg/kg/min epinephrine or (b) placebo, separated by at least 1 week apart. Mental stress tests, which lasted 15 min, were carried out both during the infusion of epinephrine/placebo and 1 h after the end of infusion. Fourteen young, normotensive male adults [mean age=27 y, mean weight=77 kg] without a history of smoking and cardiovascular disorders were enrolled in this study. Systolic and diastolic blood pressure was measured at 1-min intervals non-invasively in the non-dominant arm. Heart rate was continuously monitored. Venous blood samples were collected for assay of catecholamines at 10, 25, 35, 45, 55, 105, 115 and 125 min following start of infusion. Plasma catecholamines were analyzed by high-performance liquid chromatography with electrochemical detection.

Key results:

- Following epinephrine infusion, stress-induced heart rate and systolic blood pressure were augmented when compared to the placebo arm [Table 6].

- As observed in other studies, there was an immediate drop in diastolic blood pressure upon infusion with epinephrine during pre-stress period [Table 6]. This drop prevents any augmentation of stress-induced diastolic blood pressure response following epinephrine infusion.

- There was no change in the epinephrine plasma levels when compared to baseline following placebo infusion during periods of stress [Table 6]. Therefore, the increase in stress-induced hemodynamic response in the placebo arm cannot be attributed to circulating epinephrine.

- In addition, there was only a slight numeric increase in the norepinephrine plasma levels when compared to baseline following placebo infusion during periods of stress [Table 6]. Therefore, the increase in stress-induced hemodynamic response in the placebo arm cannot be convincingly attributed to circulating norepinephrine. However, the authors make a case that venous sampling as used in this study does not fully reflect the sympathetic norepinephrine outflow and observed plasma norepinephrine levels could have been underestimated.

- Comparison of stress-induced hemodynamic response during- and post-infusion period suggest that short periods of elevated physiological levels of epinephrine does not cause prolonged significant amplification of stress-induced hemodynamic response when plasma epinephrine levels has returned to baseline [Table 6].

Table 6: Changes in hemodynamics and plasma catecholamines in response to psychological stress during and 1 h after infusion with 0.05 µg/kg/min epinephrine. Values are reported as mean (SE).

	Experiment I					Experiment II		
		Infusion						
Dependent variable	Rest (0–10 min)	Prestress (10–25 min)	Stress I (25–35 min)	Post-stress (35–45 min)	Rest (45–55 min)	Prestress (95–105 min)	Stress II (105–115 min)	Post-stress (115–125 min)

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Reviewer's comments: Conclusions from this publication are that epinephrine augments the stress-induced increase in heart rate and systolic blood pressure but not diastolic blood pressure at an infusion rate of 0.05 µg/kg/min. The augmentative effects to stress-induced hemodynamic response is lost after stoppage of epinephrine infusion i.e., when epinephrine plasma levels return to baseline. We also understand the release of endogenous epinephrine is not triggered during periods of psychological stress.

3.2.3 Stein *et al*: Hypertension. 1998 Dec;32(6):1016-21

Title: Basal and stimulated sympathetic responses after epinephrine: no evidence of augmented responses

The objective of this publication was to examine if short-term infusion of epinephrine augments hemodynamic response by delayed facilitation of norepinephrine release through action of epinephrine acting on prejunctional β-adrenoceptors.

The study design was randomized, crossover, single-blind, and placebo-controlled with two treatment arms – intravenous infusion of (a) placebo or (b) epinephrine at 0.02 µg/kg/min for 1 h. Both treatments were separated by 2 to 4 weeks. Nine healthy male adults [mean age=21 y] were enrolled in this study. Intravenous infusion of epinephrine was initiated at 0.067 µg/min and approximately doubled every 2 min to get to a target dose of 0.02 µg/kg/min which was maintained for a period of 1 h since the start of infusion. All subjects underwent mental stress test [Stroop test] and cold pressor test which were separated by a period of 10 min before the start of infusion [10 min pre-dose], during [40 min into the infusion], and after the end of infusion [1 h after the end of infusion]. Hemodynamic variables -- heart rate, blood pressure, fore-arm blood flow, catecholamine plasma concentration, and norepinephrine spillover were measured before, during and after infusion. Plasma catecholamines were analyzed by high-performance liquid chromatography with electrochemical detection. A radioisotope dilution method was used to measure norepinephrine spillover.

Table 7: Hemodynamics, epinephrine and norepinephrine plasma concentrations (i) before infusion and (ii) 1 h after the end of infusion. Values expressed as mean ± S.E.

	(i) before infusion			(ii) 1 h after end of infusion		
	Intervention			Intervention		
Measurement	Resting	Stroop Test	Cold Pressor	Resting	Stroop Test	Cold Pressor

Key results:

- Following pre-infusion stroop test, hemodynamic variables such as HR and MAP increased relative to control (resting). Interestingly, this increase was not accompanied by increase in epinephrine and norepinephrine plasma concentrations. However, following pre-infusion cold pressor test, there was a significant increase in epinephrine and norepinephrine plasma concentrations with an increment increase in hemodynamic variables [Table 7].

- To test the hypothesis of whether short-term epinephrine infusions augments hemodynamic response after stoppage of infusion, resting values pre-infusion and at 1 h after of infusion were compared [Table 7]. There was no change in HR, MAP or norepinephrine plasma concentrations between the 2 groups but slightly elevated levels of epinephrine. The changes in catecholamine plasma concentration and hemodynamic variables were similar at 1 h after the end of infusion compared to pre-infusion.

  Reviewer's comment: Results of this study do not support the hypothesis that short-term epinephrine infusion augments hemodynamic response by stimulating norepinephrine release. Hemodynamic variables were not different at 'resting' between pre-infusion and 1 h post-infusion termination groups. The changes in catecholamine concentrations, HR and MAP are similar following physiological interventions between the two groups.

3.2.4 Struthers *et al*: Br Heart J. 1983 Jan;49(1):90-3

Title: Effect of intravenous adrenaline on electrocardiogram, blood pressure, and serum potassium

The objective of this publication was to test whether transient hypokalaemia seen during acute myocardial infarction is a consequence of circulating catecholamines. To further examine the hypothesis, epinephrine was infused to the plasma levels observed in patients undergoing myocardial infarction and the effects on serum potassium and electrocardiogram were monitored.

Nine healthy male adult volunteers [mean age=26 y], whose serum electrolytes were normal and who did not have any signs or symptoms of cardiovascular disease were enrolled in the study. All subjects received epinephrine intravenous infusion at a dose of 0, 0.01 and 0.06 µg/kg/min in 5% dextrose containing 1 mg/mL ascorbic acid, with each infusion lasting 90 min. Blood pressure, heart rate and electrocardiogram were observed at 30 min intervals for 90 min before and up to 120 min after the infusion. During each infusion, recordings were made at 5 min intervals for the first 15 min and at 30 min intervals thereafter. The QT interval was calculated from the onset of the Q wave to the point where a tangent to the descending limb of the T wave crossed the baseline. QT_c was calculated according to the Bazett formula. Blood samples for serum electrolytes were taken at 30 min intervals before and after the infusion and at the 60^{th} and 90^{th} min during the infusion. Blood samples for plasma epinephrine were taken at the end of each infusion and analyzed by radioenzymatic assay.

Key results:

- Epinephrine at an infusion rate of 0.06 µg/kg/min produced a mean plasma concentration of ~ 1000 pg/mL which was comparable to the levels observed in patients after acute myocardial infarction.

- At steady state, following epinephrine infusion of 0.06 µg/kg/min, there was an increase in heart rate [+7 ± 9 bpm] and systolic blood pressure [+11 ± 6 mmHg], but a decrease in diastolic blood pressure [-14 ± 9 mmHg].

- At steady state, following epinephrine infusion of 0.06 µg/kg/min, there was a transient decrease in serum potassium [4.06 ± 0.14 to 3.22 ± 0.26 mM]. The levels returned back to baseline in about 2 h after the end of epinephrine infusion. A transient decrease in serum potassium as observed in this study could suggest that hypokalaemia during acute myocardial infarction may be due to circulating catecholamines.

- All subjects remained in stable sinus rhythm though out the infusion. At steady state, following epinephrine infusion of 0.06 µg/kg/min, T wave amplitude decreased [mean Δ = -2.5 ± 1.9 mm].

- At steady state, following epinephrine infusion of 0.06 µg/kg/min, the heart rate corrected QT interval [QT_c] increased from 0.36 ± 0.02 to 0.41 ± 0.06 s. Abnormalities of repolarization, as

reflected by T wave flattening and QT prolongation, may possibly suggest epinephrine's role in predisposing arrhythmias.

Reviewer's comments: As observed in other studies in healthy volunteers, there was an increase in heart rate and systolic blood pressure, but a decrease in diastolic blood pressure. The hypothesis of circulating catecholamines playing a causal role in the production of arrhythmias during acute myocardial infarction either via β-adrenoceptor stimulation and/or via epinephrine induced hypokalaemia remains suggestive but not conclusively proven.

3.2.5 Tulen *et al*: Psychosom Med. 1993 Jan-Feb;55(1):61-9

Title: Psychological, cardiovascular, and endocrine changes during 6 hours of continuous infusion of epinephrine or norepinephrine in healthy volunteers

The objective of this publication was to evaluate the psychological, cardiovascular, endocrine and metabolic responses to sustained intravenous infusions [6 h duration] of epinephrine and norepinephrine in healthy subjects.

The study design was randomized, crossover, double-blind and placebo-controlled with 3 treatment arms – continuous intravenous infusion of epinephrine [0.015 µg/kg/min], norepinephrine [0.03 µg/kg/min] and placebo for 6 h. Each treatment was separated by at least 10 days. Ten healthy male adults [mean age=23 y, mean weight=78 kg] were enrolled in this study. The infusion rates were selected so as to result in elevated, but physiologically relevant concentrations of catecholamines that are observed during real-life stresses or physical exercise. Cardiovascular variables measured were heart rate, intra-arterial BP [measured invasively by cannulation of the brachial artery in the non-dominant arm], systolic BP, diastolic BP and mean-arterial BP at baseline, at every hour during infusion and 30 min after end of infusion. Metrics for evaluating the psychological state such as changes in subjective mood were assessed using self-rating questionnaires such as Profile of Mood States (POMS) and the State-Trait Anxiety Inventory (STAI) at pre-dose, 3 h post-start of infusion and 1 h post-end of infusion. Plasma cortisol, prolactin and growth hormone were measured as response metrics to stress-induction. Since, catecholamines play a role in regulation of carbohydrate metabolism, plasma glucose, insulin and triglycerides were measured pre-dose, 1 and 5 h post-start of infusion. Venous and arterial blood samples for the assay of catecholamines were also collected at baseline, every hour during infusion and after end of infusion. Plasma catecholamines were analyzed by high-performance liquid chromatography with electrochemical detection.

Key results:

- Both, mean arterial and venous plasma epinephrine levels increased 10-fold when compared to baseline during infusion with epinephrine [arterial: 34 to 387 pg/mL; venous: 21 to 230 pg/mL]. Both baseline and post-infusion arterial and venous plasma epinephrine concentrations are in the range and comparable to levels reported commonly. The increase in plasma epinephrine levels were immediate upon start of infusion, remained constant throughout and returned to baseline within 5 min following stoppage of infusion.

- Upon infusion with epinephrine, there was a statistical significant increase in heart rate [6.8%] and decrease in mean arterial pressure [6.9%] when compared to placebo. Effect of epinephrine infusion on systolic arterial pressure was not significant.

- No significant effect of epinephrine or norepinephrine infusion was observed on plasma prolactin, growth hormone, cortisol and triglycerides when compared to placebo suggesting no direct role for circulating catecholamines in regulating markers of stress-induction.

- Plasma insulin and glucose levels increased following infusion with epinephrine suggesting induction of metabolic effects.

- Infusion with epinephrine or norepinephrine did not cause any changes in subjective mood suggesting healthy subjects without a history of anxiety reactions may not develop anxiety symptoms with increase in the circulating epinephrine in the physiological range.

  Reviewer's comments: Though there was a mild to moderate response in some cardiovascular variables and metabolic markers, the systolic arterial pressure did not change at the studied dose of 0.015 µg/kg/min. Based on available dose-response information in healthy subjects, an infusion rate of 0.015 µg/kg/min may not elicit a significant response in systolic arterial pressure. Assuming a similar exposure-response relationship between healthy subjects and septic shock patients, we may conclude that starting infusion rates should be higher than 0.015 µg/kg/min.

3.3 Dose-response: Healthy subjects

3.3.1 Clutter *et al*: J Clin Invest. 1980 Jul;66(1):94-101

Title: Epinephrine plasma metabolic clearance rates and physiologic thresholds for metabolic and hemodynamic actions in man

The objective of this publication was to determine the plasma epinephrine thresholds for producing measurable metabolic and hemodynamic actions in humans. Of relevance, this publication provides information on pharmacokinetics and dose-cumulative response i.e., blood pressure and heart rate, of epinephrine in healthy adults from 0.1 to 5.0 μg/min (0.001 to 0.064 μg/kg/min, assuming a 78 kg human, the mean weight of the subjects in this study).

The study was conducted in 6 healthy adults (5 males, 1 female: 25-38 y, 61-91 kg, mean weight=78 kg). Epinephrine was infused at nominal rates of 0.1, 0.5, 1.0, 2.5 and 5.0 μg/min for 60 min. In a given subject, infusions were separated by intervals of at least 1 week. Venous blood samples for plasma epinephrine levels were collected at pre-dose, every 5-10 min interval during each infusion and every 15 min interval for 30 min after each infusion. Hemodynamic measures i.e., heart rate and blood pressure was recorded at each time point when blood samples for measurement of plasma epinephrine was drawn. Plasma epinephrine concentrations were measured by a single-isotope derivative method. Plasma epinephrine thresholds for hemodynamic effects were estimated by regression through data points showing change from baseline and extending to the line of no change in the semi-logarithmic plots of steady state plasma epinephrine concentrations *vs* changes in each measured variable.

Key results:

- Steady state plasma epinephrine levels were achieved within 10 min of the start of infusion. Pharmacokinetics of epinephrine was not dose-proportional at the lower end of the infusion dose-regimen, however was reasonably proportional at the higher end [Fig. 7].

- There was a trend for dose- and concentration-dependent increase in HR and SBP, but decrease in DBP, from epinephrine infusion rate starting at 1.0 μg/min [Fig. 8].

- The plasma epinephrine threshold for increments in HR and SBP was 50-100 pg/mL and 75-125 pg/mL, respectively. The threshold of plasma epinephrine concentration to cause decrements in DBP was 150-200 pg/mL. The authors conclude that the plasma epinephrine thresholds for hemodynamic and metabolic actions lie within the physiologic range.

Reviewer's comments: Evidence of steady state epinephrine plasma levels achieved by 10 min following infusion. Evidence of a trend for dose- and concentration-dependent increase in SBP and HR in healthy subjects in the dose-range 1.0 to 5.0 μg/min. The studied dose-range falls at the lower end of the proposed dosing regimen.

3.3.2 Ensinger *et al*: Eur J Clin Pharmacol. 1992;43(3):245-9

Title: Relationship between arterial and peripheral venous catecholamine plasma catecholamine concentrations during infusion of noradrenaline and adrenaline in healthy volunteers

The objective of this publication was to describe the relationship between arterial and venous plasma catecholamine concentrations and to find out whether arterial and peripheral venous clearances of norepinephrine and epinephrine were dependent on their endogenous plasma concentrations. Of relevance, this publication provides information on pharmacokinetics and dose-cumulative response i.e., blood pressure and heart rate, of epinephrine in healthy male adults from 0.01 to 0.2 µg/kg/min.

Sixteen healthy male adults (21-28 y) were enrolled in this study. A 20-gauge radial artery cannula was inserted under local anesthesia. Two intravenous cannulae were inserted into forearm veins, on one side for administration of norepinephrine or epinephrine and Ringer's lactate and on the opposite side for venous blood sampling. For the purpose of constructing dose-cumulative response curves, both norepinephrine and epinephrine was administered in a stepwise incremental *i.v.* infusion rates of 0.01, 0.06, 0.1, 0.14, and 0.2 µg/kg/min each for 30 min. Arterial blood pressure and heart rate were continuously monitored. Arterial and venous blood samples were taken simultaneously pre-dose and every 28th min of each infusion period to determine plasma concentrations of norepinephrine and epinephrine. The catecholamine plasma concentrations were measured by HPLC with electrochemical detection. Blood pressure and heart rate was measured during the last 5 min of each infusion period.

Key results:

- There was a dose-proportional increase in steady state epinephrine venous plasma concentration with increasing infusion rates [Fig. 7].
- The arterial and venous clearances of epinephrine did not change with increasing infusion rates suggesting linear pharmacokinetics in the dose-range studied.
- There was a linear relationship between arterial and venous plasma concentration of epinephrine.
- There was a trend for dose- and concentration-dependent increase in mean change from baseline systolic blood pressure (SBP) and heart rate (HR) with increasing infusion rates of epinephrine from 0.01 to 0.2 µg/kg/min [Fig. 8]. On the contrary, diastolic blood pressure (DBP) decreased from baseline in this dose-range.

Reviewer's comments: Evidence of linear pharmacokinetics and trend for dose- and concentration-dependent increase in SBP and HR in healthy subjects. However, the studied dose-range falls at the lower end of the proposed dosing regimen.

3.3.3 Stratton *et al*: J Appl Physiol. 1985 Apr;58(4):1199-206

Title: Hemodynamic effects of epinephrine: concentration-effect study in humans

The objective of this publication was to define the overall hemodynamic effects of epinephrine mimicking the physiological range observed in humans and to compare it with the hemodynamic changes induced by symptom-limited supine bicycle exercise in the same patients. Of relevance, this publication provides information on plasma concentration and dose-cumulative response i.e., blood pressure and heart rate, of epinephrine in healthy male adults from 0.025 to 0.1 μg/kg/min.

The dose-ranging study was conducted in 10 healthy male adults (24-33 y). Epinephrine was infused at 0.025, 0.05, or 0.1 μg/kg/min for 14 min. Five subjects received a 14 min epinephrine infusion of 0.025 μg/kg/min followed immediately by a 14 min infusion of 0.05 μg/kg/min. The other 5 subjects received 14 min infusions of 0.05 μg/kg/min and then 0.1 μg/kg/min. Steady state plasma levels of epinephrine were reported to reach steady state by 10 min. Plasma epinephrine levels and hemodynamic measures were collected at baseline and at 7, 14, 21 and 28 min. However, the results shown are at the end of each infusion period. Plasma epinephrine concentrations were measured by a single-isotope radioenzymatic assay. The data on the 2 groups receiving 0.05 μg/kg/min were pooled as there was no significant difference in either plasma epinephrine levels or hemodynamic measures at baseline or end of study between these 2 groups. The 0.1 μg/kg/min infusion rate was designed to produce plasma epinephrine levels similar to those resulting from symptom-limited supine bicycle exercise. At the end of infusion, subjects rested for 45 min to allow the plasma epinephrine levels and hemodynamics to return to baseline before performing the fatigue-limited bicycle exercise.

Key results:

- There was a reasonable dose-proportional increase in steady state epinephrine plasma concentration with increasing infusion rates [Fig. 7]. However, the mean absolute plasma concentration for a given infusion rate does not fall in the range observed in other healthy volunteer studies.

- There was a trend for dose- and concentration-dependent increase in mean change from baseline SBP and HR with increasing infusion rates from 0.025 to 0.1 μg/kg/min [Fig. 8]. However, a decrease in mean blood pressure was noted in the same dose-range.

- There was also a dose-dependent increase in ejection fraction, stoke volume and cardiac output and a decrease in systemic vascular resistance with increasing infusion rates of epinephrine.

- Though the fatigue-limited bicycle exercise caused similar plasma levels of epinephrine, the increase in hemodynamic measures such as SBP and HR were significantly higher. This could suggest that circulating epinephrine might have a marginal role in regulating the cardiovascular response to exercise.

Reviewer's comments: Evidence of dose-proportional pharmacokinetics and a trend for dose- and concentration-dependent increase in mean change from baseline SBP and HR in healthy subjects

in the dose-range studied i.e., 0.025 to 0.1 µg/kg/min. The studied dose-range falls at the lower end of the proposed dosing regimen.

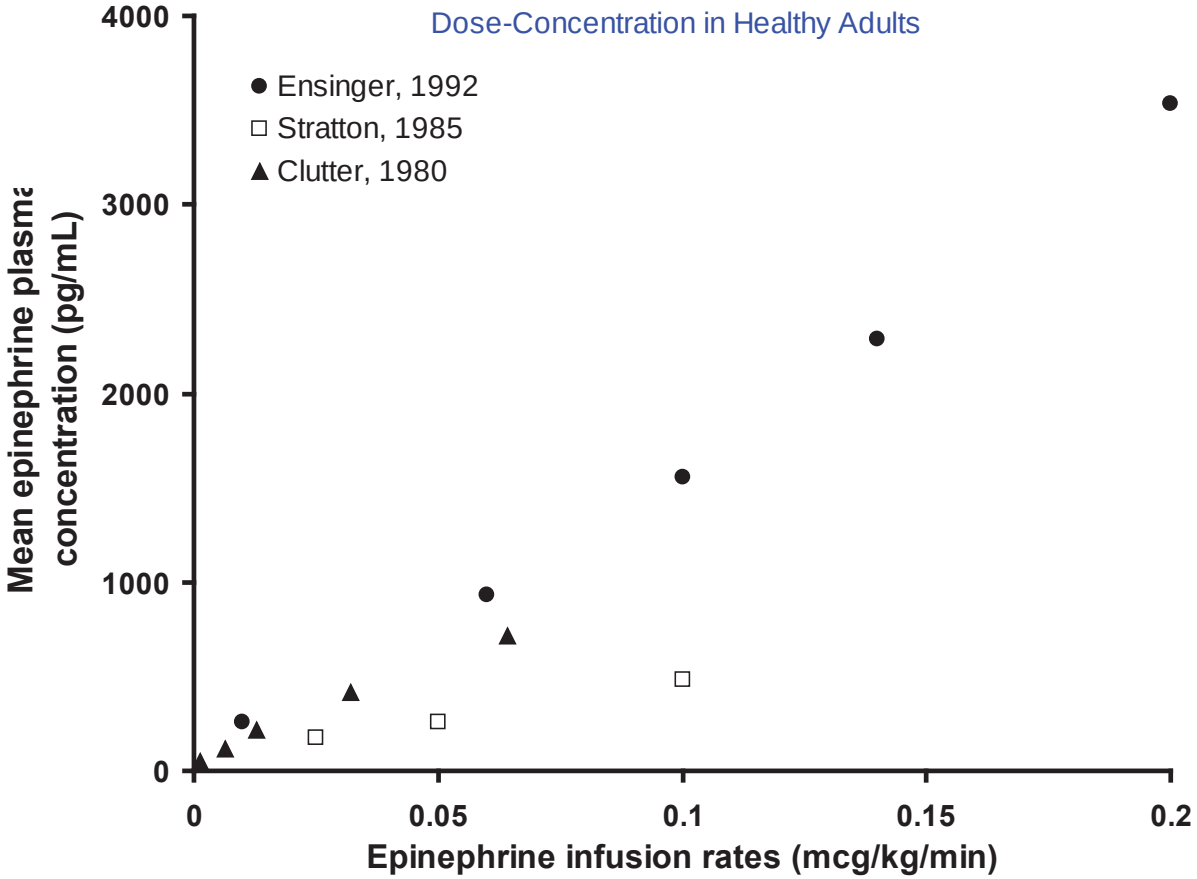

Figure 7: Mean epinephrine plasma concentration as a function of epinephrine infusion rates across studies in healthy adults.

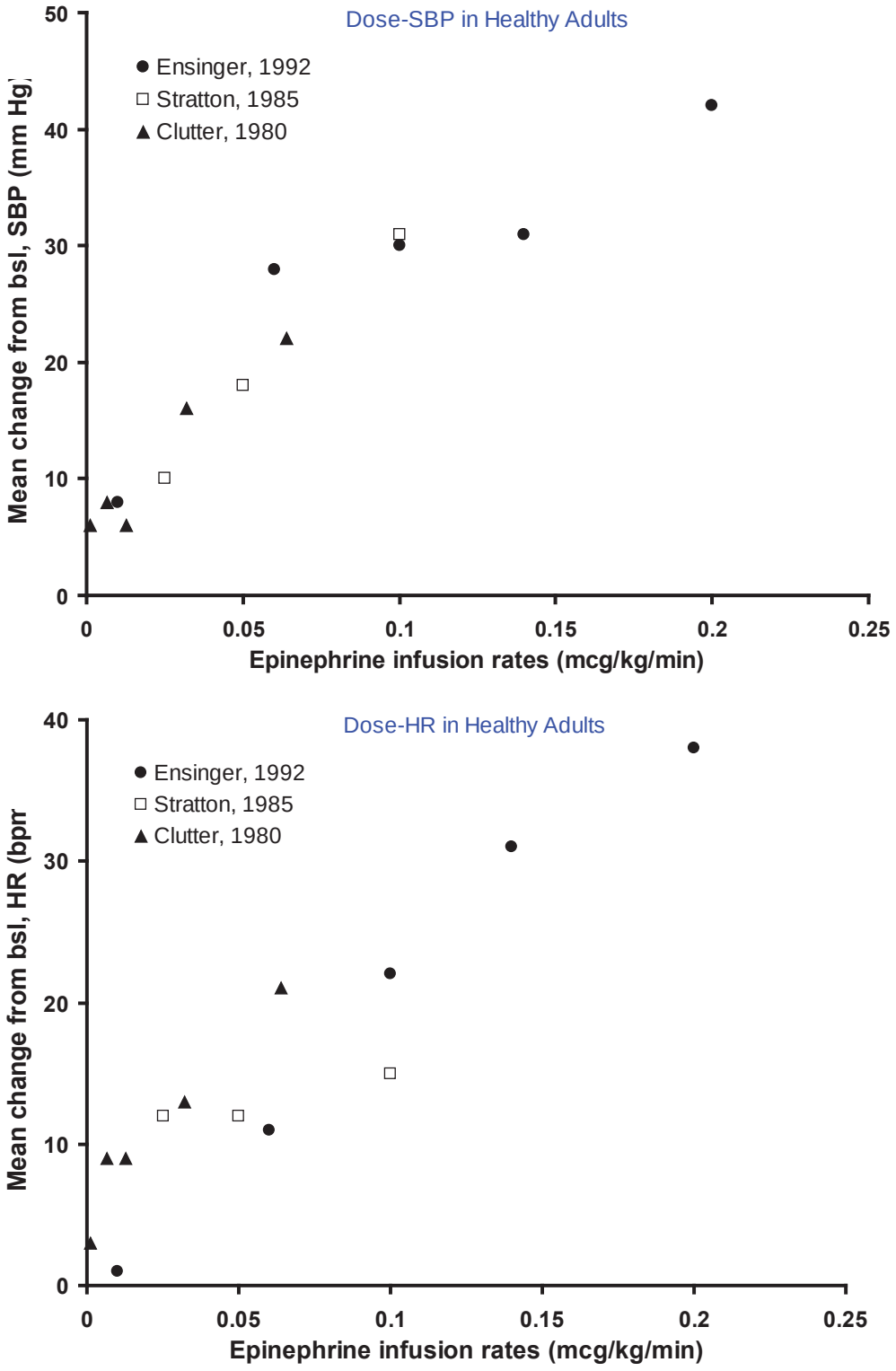

Figure 8: Mean change from baseline (A) SBP and (B) HR as a function of epinephrine infusion rates across studies in healthy subjects.

3.4 Dose-response: Septic shock patients

3.4.1 Abboud *et al*: Crit Care. 2009;13(4):R120 Epub 2009 Jul 21

Title: Pharmacokinetics of epinephrine in patients with septic shock: modelization and interaction with endogenous neurohormonal status

The objective of this publication was to evaluate the PK of epinephrine, the covariates influencing PK and to investigate whether differences in PK is a reason for the unpredictable pharmacodynamic response of epinephrine (e.g., mean arterial pressure) as seen across septic shock patients.

This was a prospective study in 38 adult septic shock patients [mean age=64 y; mean body weight=68 kg; male=66%] receiving epinephrine infusion as the first-line and exclusive vasopressor. Neither *i.v.* hydrocortisone nor recombinant human activated protein C was used. Septic shock was defined by the presence of infection, dysfunction in at least 1 organ, and fluid refractory hypotension [MAP <65 mmHg] requiring the administration of a vasopressor. Epinephrine was started intravenously at 0.15 μg/kg/min and subsequently adjusted to obtain a MAP between 65 and 75 mmHg. Blood sample at baseline was withdrawn at 15 min (C_0) prior to infusion, to assess endogenous epinephrine, norepinephrine, renin, aldosterone, and plasma cortisol levels. A second blood sample (C_1) was collected when cumulative epinephrine dose adjusted to body weight reached an arbitrarily threshold fixed at 0.15 mg/kg, provided the epinephrine infusion rate remained steady and fluid loading was not used in the preceding 15 min. Plasma concentrations of catecholamines were quantified using HPLC with coulometric detection. The limit of quantification (defined by a variability between measurements of <10%) for HPLC was 0.10 nM. This is within the ±15% limit for precision as per FDA guidance for bioanalytical method validation to industry. PK data were analyzed using the nonlinear mixed effect modeling program, NONMEM.

Key results:

- There was an increase in mean epinephrine plasma concentration upon exogenous epinephrine infusion in septic shock patients. This was accompanied by a corresponding mean increase in hemodynamic variables such as HR, SBP and MAP [Table 8]. In contrast, there was a decrease in the norepinephrine plasma levels upon exogenous epinephrine infusion, a finding not reported previously. Usually, it is the exogenous epinephrine triggering the release of norepinephrine from the sympathetic neuronal endings that is commonly observed.

- Pharmacokinetics of epinephrine was linear in the infusion dose range 0.026 to 1.67 μg/kg/min as shown in Figure 9.

- Body weight and disease severity [as defined by New Simplified Acute Physiologic Score: SAPSII] significantly influenced the pharmacokinetics of epinephrine. The clearance of epinephrine decreased with worsening disease severity [SAPSII score] and increased with higher body weight. A decrease in clearance with worsening disease severity could possibly be

explained due to worsening kidney/liver function, organs involved in the extraneuronal clearance of epinephrine.

- A scatter plot of change from baseline mean or systolic blood pressure as a function of epinephrine plasma concentration at steady state shows no trend for a relationship suggesting high inter-patient variability [Fig. 10].

Table 8: Changes in hemodynamic variables and plasma catecholamine concentrations in response to epinephrine infusion in septic shock patients. Values represent mean ± S.D. or median (range).

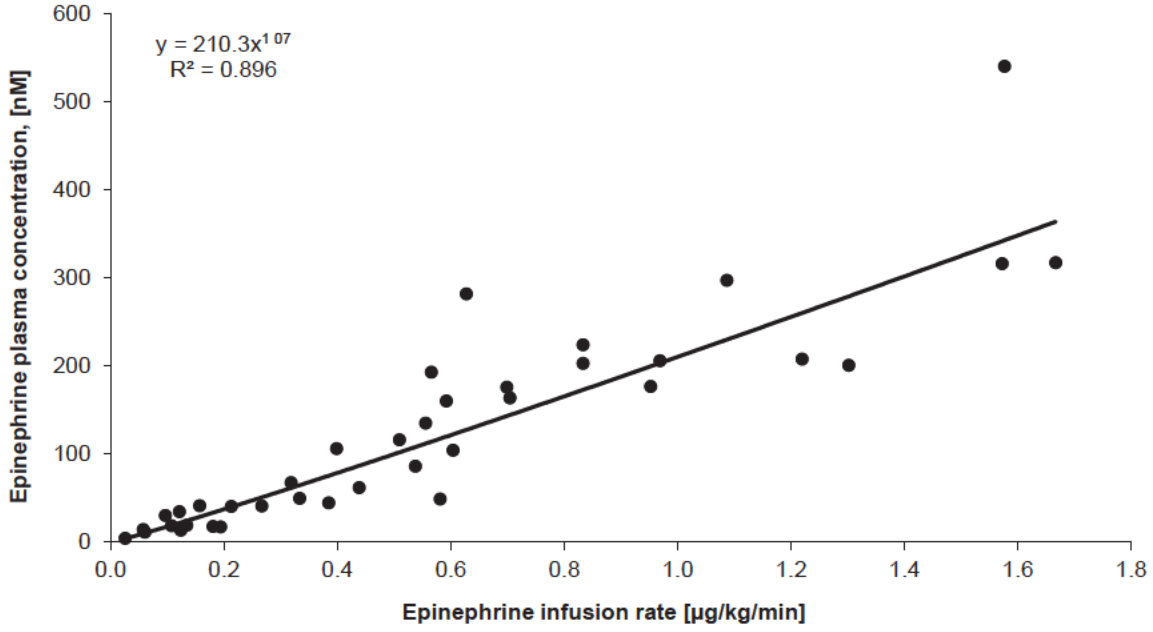

Figure 9: Epinephrine plasma concentration as a function of infusion rate at steady state showing dose linearity in the range 0.026 to 1.67 µg/kg/min.

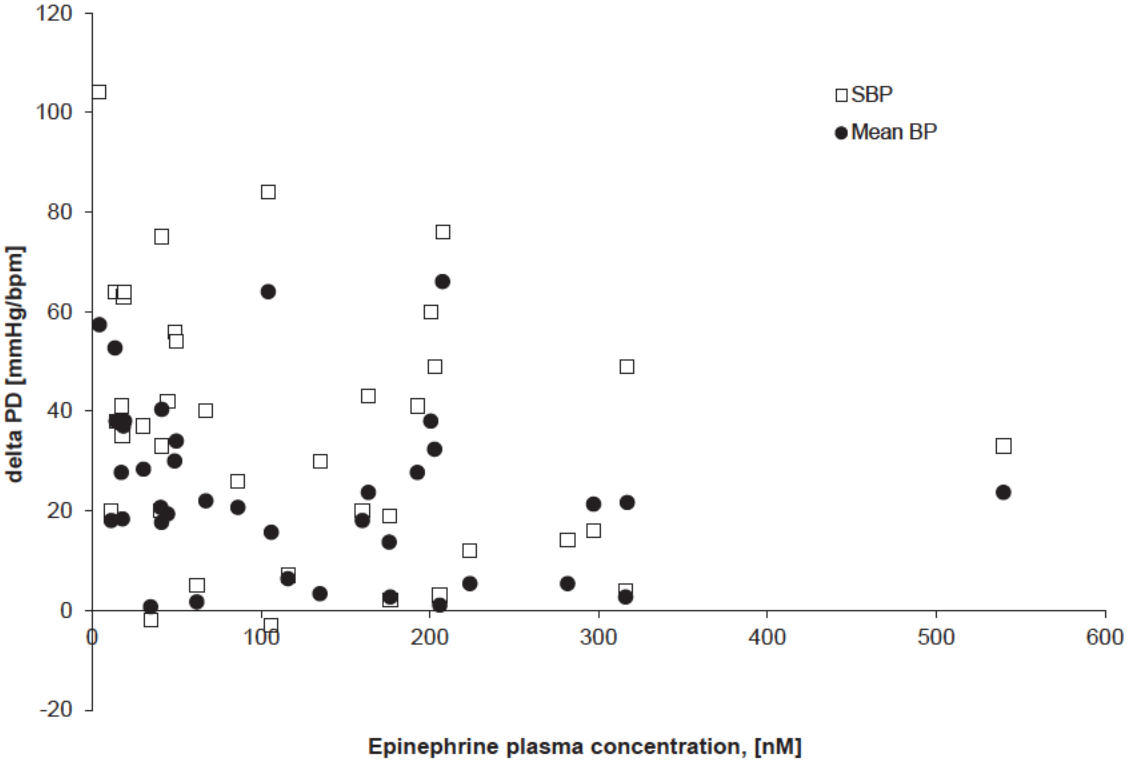

Figure 10: A scatter plot of change from baseline mean or systolic blood pressure as a function of epinephrine plasma concentration at steady state in 38 individual septic shock patients.

Reviewer's comments: Pharmacokinetics of epinephrine is linear in the dose infusion range 0.026 to 1.67 µg/kg/min. A high inter-patient variability in pharmacodynamic response was observed in septic shock patients. Body weight and disease severity, covariates of epinephrine PK may partly explain this variability in response.

3.4.2 Moran *et al*: Crit Care Med. 1993 Jan;21(1):70-7

Title: Epinephrine as an inotropic agent in septic shock: a dose-profile analysis

The objective of this publication was to prospectively determine the acute effects on cardio-respiratory variables and the physiologic dose profile of epinephrine in septic shock patients. Of relevance, this publication provides information on dose-cumulative response i.e., blood pressure and heart rate, of epinephrine as the lone vasoconstrictor in septic shock patients from 3.0 to 18 µg/min (0.04 to 0.26 µg/kg/min, assuming a 70 kg human).

Eighteen septic shock patients were enrolled into the study. Septic shock was defined as a clinical syndrome of inadequate tissue perfusion, along with systolic arterial blood pressure ≤90 mm Hg, oliguria <20 mL/h, evidence of a septic focus or positive blood cultures, fever or hypothermia (T >37.5°C or <36.5°C and leukocytosis or leukopenia (WBC count >$10x10^9$/L or <$4x10^9$/L). Cardio-respiratory variables being measured were - mean arterial pressure (MAP), right atrial pressure, pulmonary artery occlusion pressure (PAOP), mean pulmonary arterial pressure, heart rate and cardiac output. The derived variables calculated using standard formulas were - cardiac index, stroke volume index, systemic vascular resistance index, left ventricular stroke work index, oxygen delivery (Do_2), oxygen consumption (Vo_2), pulmonary shunt fraction and oxygen extraction ratio. Patients who did not sustain a systolic arterial blood pressure ≥90 mm Hg with volume therapy were begun on epinephrine. No other inotrope such as dopamine or digoxin was prescribed during the study.

Epinephrine was infused at a rate of 3 µg/min intravenously. Hemodynamics was measured at steady state [20 min] following which the infusion rate was increased by increments of 3 µg/min with hemodynamic profile measured at steady state for each infusion rate. Escalation of infusion rates followed until the endpoints of inotropic therapy were achieved - improvement in tissue perfusion (Do_2 >600 mL/min, Vo_2 >170 mL/min/m^2); return of urine output to >0.5 mL/kg/h, cardiac index >4.5 L/min/m^2 and restoration of systolic arterial blood pressure to a minimum of pre-morbid levels.

Key results:

- Mortality rate following this study was 33% (6 non-survivors). Primary reason for death was due to a combination of multiple system organ failure and recalcitrant hypotension.

- Following is the distribution of patients for each epinephrine infusion rate - 3 (n=18), 6 (n=15), 9 (n=13), 12 (n=10), 15 (n=6) and 18 µg/min (n=3).

- Trend for dose-dependent increase in HR, MAP, cardiac index, stroke volume index, left ventricular stroke work index, Vo_2 and Do_2 was observed with increasing epinephrine infusion rates from 3.0 to 18 µg/min [Fig. 11].

- Over the whole dose-range, no significant change in PAOP, mean pulmonary arterial pressure, shunt fraction or systemic vascular resistance index were observed.

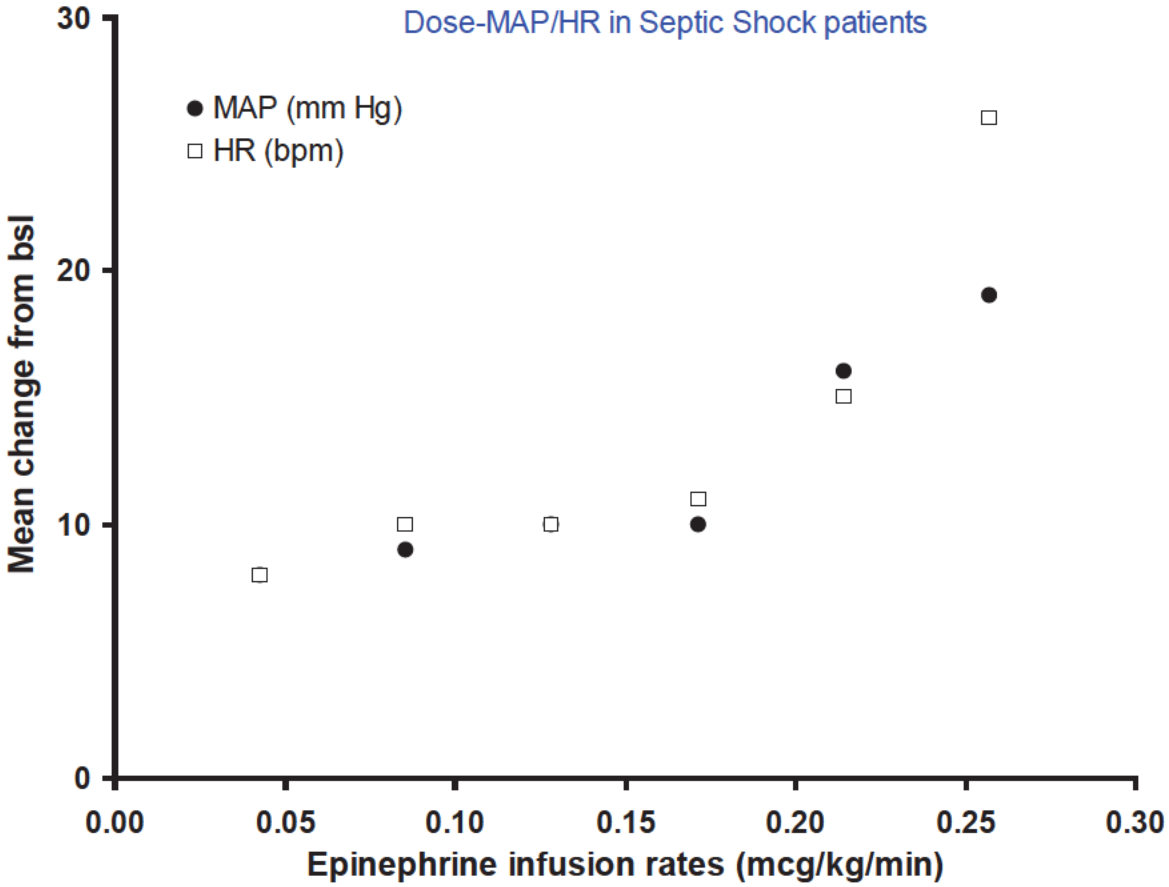

Figure 11: Mean change from baseline SBP and HR vs epinephrine infusion rates in patients with septic shock.

Reviewer's comment: There is an increase in MAP with intravenous infusion of epinephrine. Moreover, there is evidence for a trend in dose-dependent increase in change from baseline MAP with increase in epinephrine infusion rates, more evident at doses greater than 0.15 mcg/kg/min. However, the experience is relatively at the lower dose range when compared to the proposed dosing regimen in septic shock patients.

3.5 Impact of intrinsic factors

3.5.1 Wilkie *et al*: J Gerontol. 1985 Mar;40(2):133-40

Title: Age-related changes in venous catecholamines basally and during epinephrine infusion in man

The objective of this publication was to evaluate the age-related changes to plasma catecholamines and their hemodynamic response, basally and during epinephrine infusion.

Seven young [mean age=23 y] and old [mean age=63 y] healthy male normotensive adults with comparable mean body weight were enrolled in the study. Epinephrine was infused intravenously at dose levels – 0.014 μg/kg/min and 0.043 μg/kg/min, each for a period of 45 min, separated by a week. Blood samples for catecholamine plasma concentrations were collected at 30 and 45 min pre-dose and at 15, 30, 40 and 45 min into the infusion period and analyzed by single isotope enzymatic assay. Intra- and inter-assay CV% was 10% and 12%, respective for plasma catecholamine concentration > 100 pg/mL. For concentrations, 20-100 pg/mL, the assay variability was 30%. Heart rate was monitored continuously and blood pressure was measured over a 2-min period at the time of each blood sample. The metabolic clearance rate [MCR] of epinephrine was calculated using = [infusion rate/steady state epinephrine concentration] – epinephrine basal concentration.

Key results:

- Following epinephrine infusion at both dose levels, elder subjects resulted in lower epinephrine plasma concentration at steady state when compared to young adults [Fig. 12].

- The metabolic clearance rate of epinephrine was significantly higher [1.5- to 2-fold] in elder subjects when compared to young adults at both epinephrine infusion rates [Fig. 13]. However, the authors state that the result should be interpreted with caution, as venous blood measurements may possibly over predict this difference.

- Norepinephrine plasma levels were significantly higher in elder subjects than young adults, both at rest and during epinephrine infusion. The incremental increase in plasma norepinephrine levels following infusion when compared to basal levels was higher in young adults than in elder subjects.

- Age affected the basal plasma levels of norepinephrine, but not epinephrine. This observation was consistent with similar findings from previous published studies.

- Heart rate increased with epinephrine infusion, more prominent with the high epinephrine infusion rate than low, but to a similar magnitude in both elder subjects and young adults.

- There was an increase in change from baseline systolic blood pressure in young adults following epinephrine infusion at both doses. However, there was no trend for a dose-response. In elder subjects, baseline systolic blood pressure was relatively higher and epinephrine infusion at both

doses did not cause any significant increase. On the other hand, diastolic blood pressure decreased with epinephrine infusion, the drop more prominent with young adults at the higher infusion rate.

- Mean arterial pressure, which was calculated as diastolic plus one-third pulse pressure, did not show any significant increase following epinephrine infusion at both doses. This may be driven by a decreasing trend for diastolic blood pressure following epinephrine infusion.

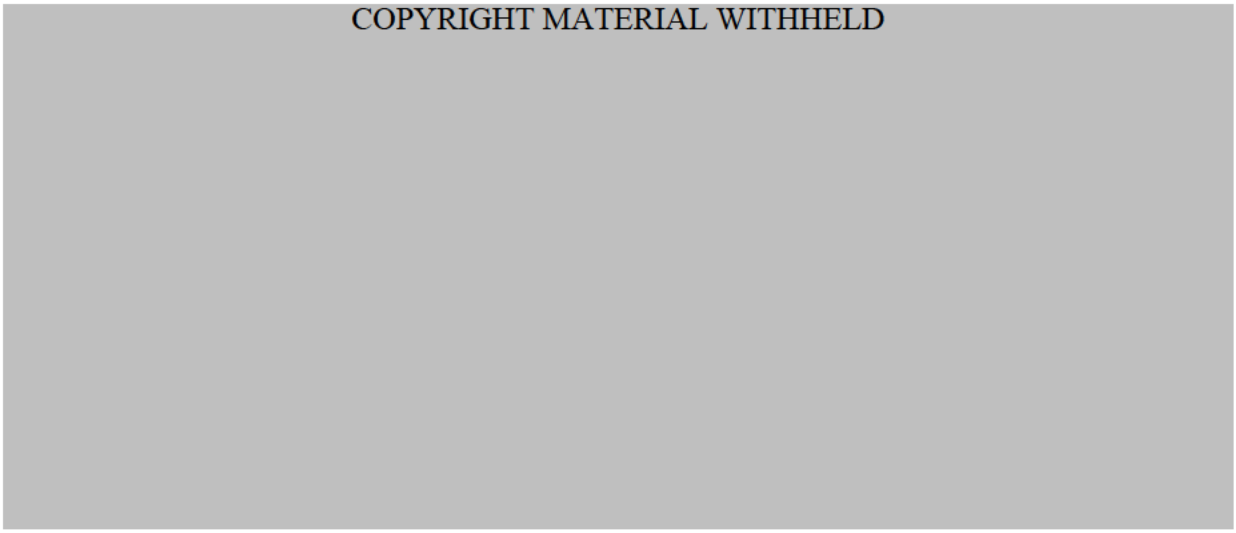

Figure 12: Mean plasma epinephrine levels in young and old healthy men, basally and during epinephrine infusion of 0.014 µg/kg/min and 0.043 µg/kg/min. Data expressed as mean ± S.D.

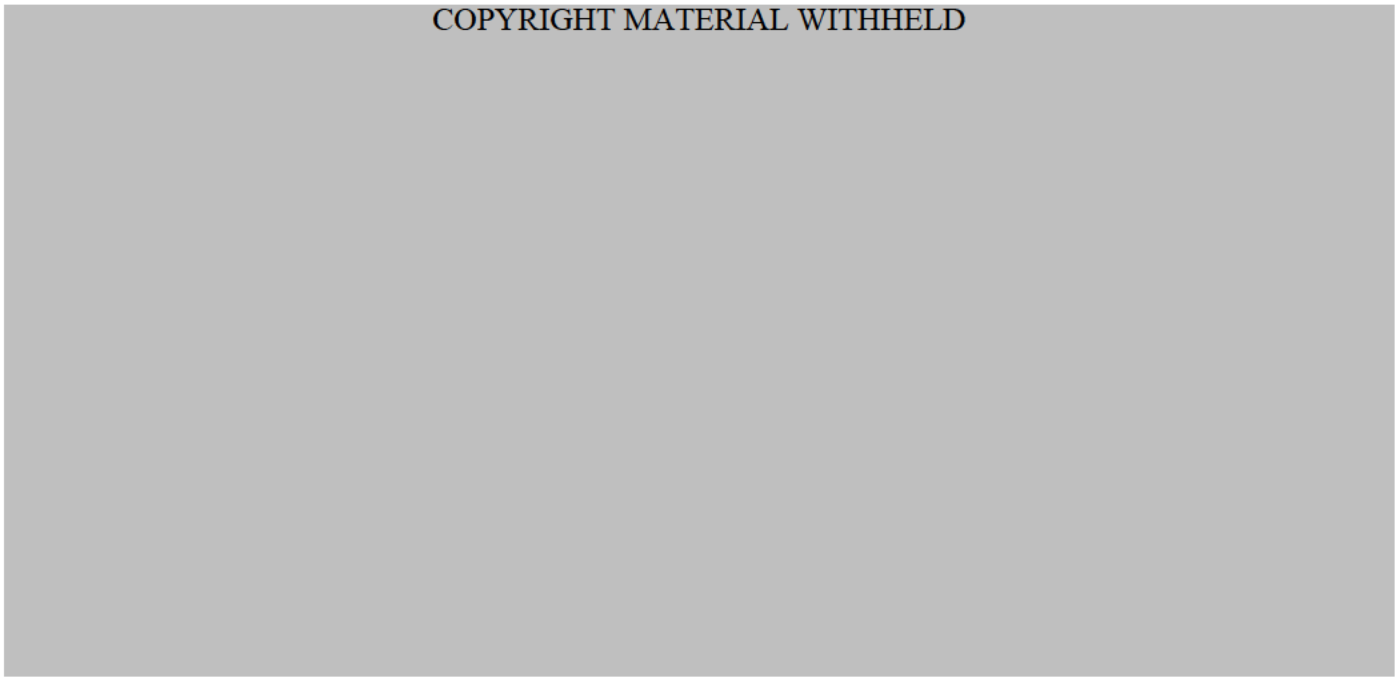

Figure 13: Metabolic clearance rate of epinephrine in young and old healthy men following epinephrine infusion of 0.014 µg/kg/min and 0.043 µg/kg/min. Data expressed as mean ± S.D.

Reviewer's comments: From this publication, we can conclude that plasma epinephrine levels are lower in relatively healthy old men when compared to young adults, probably due to higher metabolic clearance in the former. There was a diminished response in systolic blood pressure to epinephrine infusion in elder subjects. The diminished hemodynamic response in elder subjects could be interpreted due to lower epinephrine plasma levels, or diminished end-organ responsivity i.e., β-adrenoceptors, or to decreased parasympathetic tone, or a combination of all.

3.6 Impact of extrinsic factors

3.6.1 Cryer *et al*: Metabolism. 1980 Nov;29(11 Suppl 1):1114-8

Title: Epinephrine and norepinephrine are cleared through beta-adrenergic, but not alpha-adrenergic, mechanisms in man

The objective of this publication was to determine the effect of α- and β-adrenergic blockade on the metabolic clearance of epinephrine.

This study was done in 2 parts. Briefly, in part 1, 5 women [age=19-21 y; weight=55-74 kg] were administered 4 infusions on separate occasions: (a) saline, (b) epinephrine (50 ng/kg/min) for 180 min, (c) epinephrine + propranolol (80 μg/min after a 5.0 mg dose infused over 2 min, a β-adrenergic blocker) for 180 min, and (d) epinephrine + phentolamine (500 μg/min after a 5.0 mg dose infused over 2 min, an α-adrenergic blocker) for 180 min. In part 2, a separate group of 6 women and 1 man [age=19-36 y; weight=45-75 kg] were administered (a) epinephrine for 120 min, (b) epinephrine + propranolol for 120 min, and (c) epinephrine + propranolol + phentolamine for 120 min. Plasma concentrations of epinephrine and norepinephrine were measured with a single isotope derivative method. The plasma metabolic clearance rate of epinephrine was calculated as the epinephrine infusion rate divided by the difference between baseline and infusion steady state plasma epinephrine concentrations.

Key results:

- In part 1, mean steady state plasma concentration following epinephrine infusion was 834 pg/mL (*vs* 21 pg/mL with saline). Upon co-administration with phentolamine there was no change (853 pg/mL) in the steady state plasma concentration of epinephrine, however, upon co-administration with propranolol there was a 3-fold increase (2400 pg/mL) [Fig. 14]. Correspondingly, there was a 3-fold reduction in the metabolic clearance of epinephrine when administered with propranolol (64 *vs* 21 mL/min)

- In part 2, mean steady state plasma concentration following epinephrine infusion was 776 pg/mL. Upon co-administration with propranolol there was a 3.3-fold increase (2580 pg/mL) in the steady state plasma concentration of epinephrine, however, there was no incremental increase (2720 pg/mL) when co-administered with both propranolol and phentolamine [Fig. 14]. The decrease in the metabolic clearance of epinephrine was similar upon co-administration with propranolol or propranolol + phentolamine.

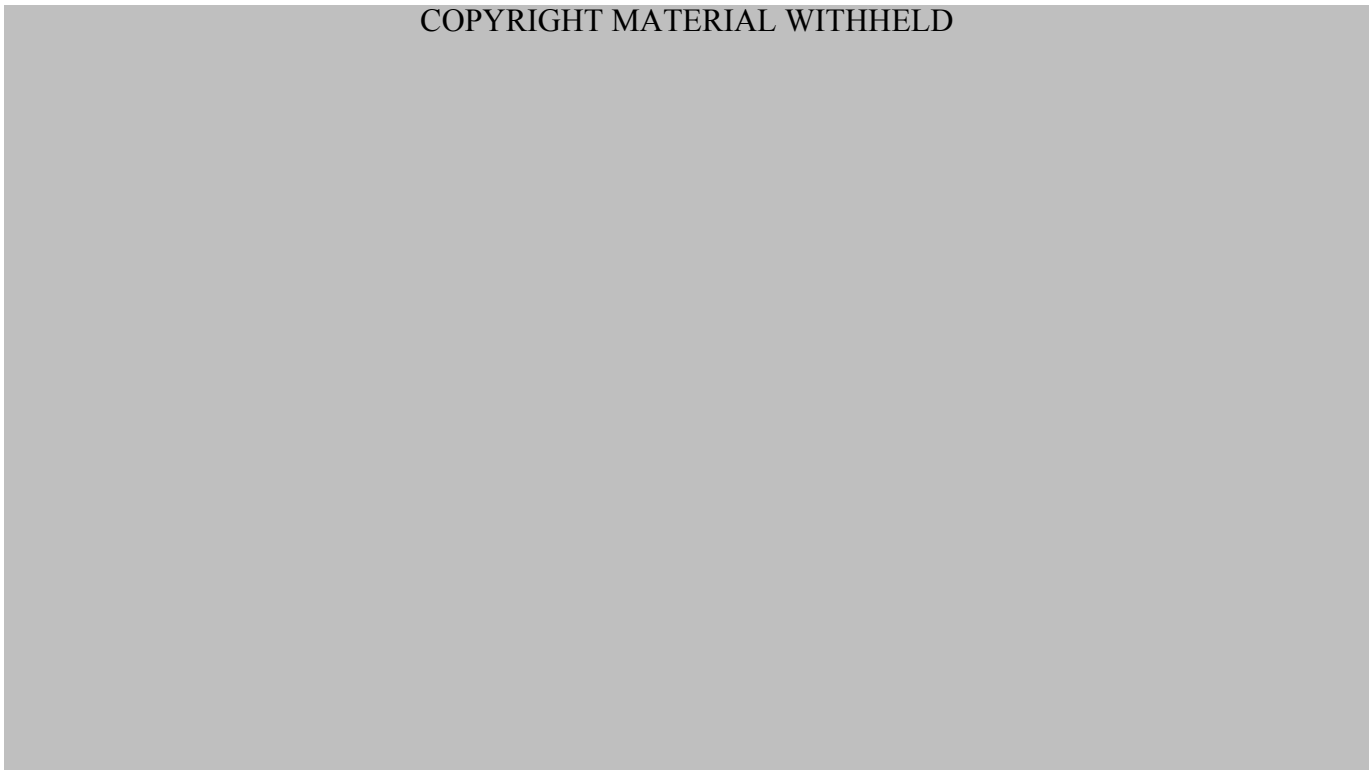

Figure 14: Epinephrine plasma concentration-time profile in 5 subjects from Part-1 and 7 subjects from Part-2 of the study. Values represent mean ± S.E.

Reviewer's comment: Epinephrine is predominantly cleared by β-adrenergic mechanisms in humans as the metabolic clearance of epinephrine sharply decreased in the presence of propranolol [β-blockade] but not phentolamine [α-blockade].

3.6.2. Hansen *et al*: J Cardiovasc Pharmacol. 1994 Dec;24(6):853-9

Title: Effects of carvedilol on the metabolic, hemodynamic, and electrocardiographic responses to increased plasma epinephrine in normal subjects

The objective of this publication was to investigate the effect of carvedilol pre-treatment on metabolic, hemodynamic and electrocardiogram responses to epinephrine intravenous infusion in patients undergoing acute myocardial infarction.

Twelve healthy male volunteers [mean age=28 y] were enrolled in this study. Epinephrine, at 0.05 μg/kg/min for 2 h, was intravenously infused on two separate occasions – following randomized pre-treatment to placebo or carvedilol 25 mg QD for 14 days. Blood samples were collected pre-infusion, every 15 min during infusion and at 15 and 30 min after the end of infusion to measure serum potassium *K*, magnesium *Mg*, calcium *Ca*, phosphate *P*, glucose, insulin, C-peptide, free fatty acids, and glycerol. Systolic and diastolic blood pressure was recorded following the collection of each blood sample. Total cholesterol, triglycerides, HDL- and LDL-cholesterol was measured pre-infusion and 30 min after end of infusion. Electrocardiogram was monitored continuously to analyze heart rate, QT, and QT_c duration.

Key results:

- Following epinephrine infusion, there was a trend for decrease in serum *K*, *Mg*, and *Ca*. Upon pre-treatment with carvedilol, the effect was maintained [*Mg*], attenuated [*Ca* and *P*] and blunted [*K*], respectively for these electrolytes.

- Epinephrine infusion caused a significant increase in blood glucose. Upon pre-treatment with carvedilol, the response was attenuated but did not affect baseline blood glucose values.

- Epinephrine infusion caused an immediate decline in serum insulin values [t<60 min] which started to increase later with the increase being sharp after the end of epinephrine infusion.

- Carvedilol pre-treatment did not have a significant effect on lipid variables.

- Epinephrine infusion caused an increase in heart rate from baseline, as expected. However, upon pre-treatment with carvedilol, the baseline heart rate was significantly lower [due to β-blockade] which further decreased following epinephrine infusion [Table 9]. The values progressed towards baseline after stoppage of epinephrine infusion.

- Epinephrine infusion caused an increase in SBP when compared to baseline, as observed in other publications. However, there was no change in SBP at baseline and following epinephrine infusion when pre-treated with carvedilol [Table 9].

- Epinephrine infusion caused a decrease in DBP when compared to baseline, as observed in other publications. However, upon pre-treatment with carvedilol, the baseline DBP was relatively lower when compared to the placebo arm and showed a trend for increase following epinephrine infusion [Table 9].

- Epinephrine infusion alone caused a significant increase in QT [Δ=0.02 s at 60 min] and QT_c [0.03 s at 60 min]. Carvedilol pre-treatment significantly altered the response in QT_c and prevented epinephrine induced QT_c prolongation, however, it did not affect QT [Table 9].

Table 9: Effects on hemodynamic and ECG variables following epinephrine infusion pre-treated with placebo or carvedilol for 14 days. Values represent mean ± S.D.

Variable	0 min	60 min	120 min	150 min
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Reviewer's comment: Pre-treatment with carvedilol, a non-selective β- and α-adrenergic antagonist, attenuates hemodynamic responses of epinephrine.

3.6.3 Illi *et al*: Clin Pharmacol Ther. 1995 Aug;58(2):221-7

Title: The effect of entacapone on the disposition and hemodynamic effects of intravenous isoproterenol and epinephrine

The objective of this publication was to evaluate whether entacapone, a potent and selective catechol-*O*-methyltransferase [COMT] inhibitor, potentiates the hemodynamic responses and increases the plasma concentrations of epinephrine, following an exogenous administration of intravenous epinephrine infusion. Epinephrine is metabolized by COMT and mono-amino oxidase [MAO].

Twelve healthy male volunteers [mean age=26 y, mean weight=76 kg] were enrolled in this randomized, placebo-controlled, double-blind, parallel arm study where intravenous epinephrine infusion was administered while taking entacapone [n=5] and placebo [n=6]. During the study day, 400 mg entacapone or placebo was administered followed by blood pressure and heart rate measurements 15, 20, and 25 min post-dose, the average of these values constituting the baseline. At 30 min post entacapone or placebo administration, epinephrine was intravenously infused at 1.5, 3, 6, and 12 µg/min, each dose-step for 5 min for a total duration of 20 min. Blood samples for measurement of plasma epinephrine concentration was collected pre-epinephrine infusion, and at 5, 10, 15, 20, 22, 25, 30, 40, and 60 min post-infusion. Epinephrine was analyzed by HPLC coupled with electrochemical detection with an intra- and inter-assay CV% of 7% and 13%, respectively. These results are within the ±15% limit for precision as per FDA guidance for bioanalytical method validation to industry.

Key results:

- Hemodynamic measures such as systolic blood pressure and heart rate showed a trend towards an augmented response with entacapone than placebo both during infusion and following stoppage of the infusion [Fig. 15]. Absence of achieving statistical significance may be an issue of small sample size.

- As observed in other publications, diastolic blood pressure decreased with epinephrine infusion, however, a maximum decrease observed in the background of placebo than entacapone.

- Change from baseline epinephrine plasma concentration was not significantly different following epinephrine infusion with entacapone or placebo [Fig. 15]. Increase in epinephrine levels locally at the receptor site may not be ruled out.

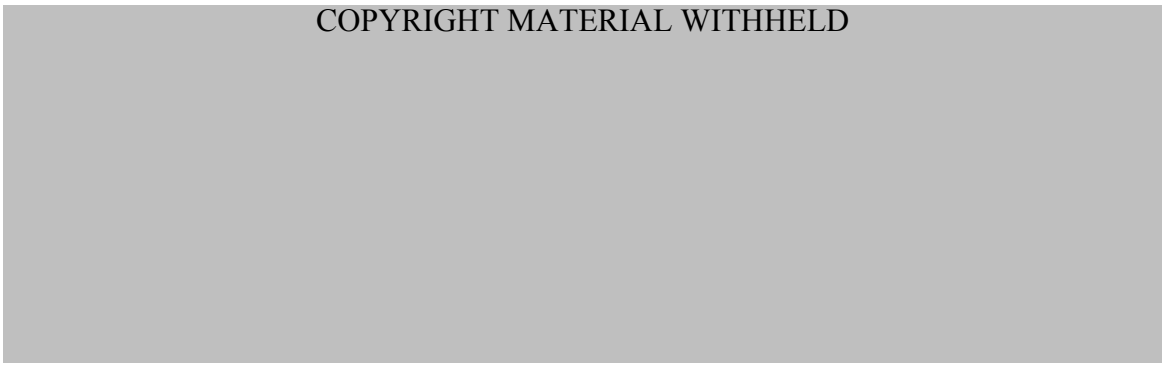

Figure 15: Mean change from baseline [± SD] in epinephrine plasma concentration [A], systolic blood pressure [B], and heart rate [C] following epinephrine infusion in the background of entacapone 400 mg or placebo.

Reviewer's comment: Though, a single dose of 400 mg entacapone did not result in any changes in plasma epinephrine levels, a modest potentiation of the chronotropic effects of epinephrine in turn augmenting the hemodynamic response was observed.

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/s/

SUDHARSHAN HARIHARAN
09/06/2013

RAJANIKANTH MADABUSHI
09/09/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**205029**	**Brand Name**	**(b) (4)**
OCP Division (I, II, III, IV, V)	**I**	**Generic Name**	**Epinephrine**
Medical Division	**DCRP**	**Drug Class**	**α- and β- adrenergic agonist (+chronotropic, +inotropic, vasopressor)**
OCP Reviewer(s)	**Sudharshan Hariharan**	**Indication(s)**	**To increase systemic arterial blood pressure in acute hypotensive states associated with septic shock.**
OCP Team Leader	**Raj Madabushi**	**Dosage Form**	**Sterile solution for injection**
Pharmacometrics Reviewer	**--**	**Dosing Regimen**	**Intravenous infusion 0.05 to 2.0 mcg/kg/min, and is titrated to achieve a desired MAP**
Date of Submission	**12/04/2012**	**Route of Administration**	**Intravenous**
Estimated Due Date of OCP Review	**08/04/2013**	**Sponsor**	**Belcher Pharmaceuticals, LLC**
PDUFA Goal Date	**10/04/2013**	**Priority Classification**	**Standard; 505(b)(2)**

Summary

The mechanism of the rise in blood pressure due to epinephrine is because of a direct myocardial stimulation that increases the strength of ventricular contraction (positive inotropic action); an increased heart rate (positive chronotropic action); and vasoconstriction in many vascular beds. The proposed indication is for use in increasing systemic arterial blood pressure in acute hypotensive states associated with septic shock. The proposed drug product is a sterile solution for intravenous injection containing epinephrine as the active ingredient (USP 1 mg/mL).

Belcher, LLC is relying on published literature and safety information from Twinject (NDA 20800, approved May 2003) as the listed drug. Twinject is an approved epinephrine (1 mg/mL) product for use in the emergency treatment of severe allergic reactions (Type I). There are several unapproved and at least 39 approved drug formulations containing epinephrine currently marketed. Epinephrine injection is available in 1 mg/mL, 0.1 mg/mL, and 0.5 mg/mL solutions.

Fifteen studies from the published literature are summarized in the summary of clinical pharmacology studies. The literature primarily addresses the following:

- Mass balance and metabolism (n=1)
- PK/PD in patients with septic shock (n=1)
- Dose-response in septic shock patients (n=1) and healthy subjects (n=3)
- PD -- mechanism of action (n=5)
- PD -- effects of age, gender, body weight and organ impairment (n=1)
- Drug interactions -- pharmacodynamic effects -- with catechol-O-methyltransferase (COMT) inhibitors, carvedilol and α- & β-adrenergic blockers (n=3)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	Relies on published literature
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			An attempt has been made
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately			X	Sponsor is seeking waiver

	designed to demonstrate effectiveness, if the drug is indeed effective?				
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			Information request will be sent to acquire individual patient level PK/PD data from Abboud *et al* 2009 publication (see below)
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

Sudharshan Hariharan 01/23/2013
Reviewing Clinical Pharmacologist Date

Raj Madabushi 01/23/2013
Team Leader/Supervisor Date

Information Request (01/23/2013):

Please provide patient level data from the following publication,

Abboud I, Lerolle N, Urien S, *et al*. Pharmacokinetics of epinephrine in patients with septic shock: modelization and interaction with endogenous neurohormonal status. Crit Care. 2009 Jul 21;13(4):R120.

Data requested:

- PK: Epinephrine and norepinephrine plasma concentrations at C_0 and C_1. Include data [if any] for any measurements made between C_0 and C_1.
- PD: Systolic BP, diastolic BP, mean BP and heart rate at C_0, C_1 and at time points when infusion rate was adjusted.
- Dose: Epinephrine infusion rates at C_0, C_1 and at time points when infusion rate was adjusted.
- Patient characteristics: Age, gender, body weight, SAPS II score and disease etiology.

The data from this publication is useful that it is derived from septic shock patients and reflects the most recent available information including the bioanalytical method used. A concentration-blood pressure relationship constructed using this data can help evaluate effectiveness and provide dosing instructions in the product label. Further, the literature available on dose-blood pressure relationship from healthy subjects (n=3) and septic shock patients (n=1) are not recent and the doses studied fall on the lower end of

your proposed dosing regimen. Therefore, we recommend you to request the authors of the publication and acquire the patient level PK/PD data as described.

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/s/

SUDHARSHAN HARIHARAN
01/23/2013

RAJANIKANTH MADABUSHI
01/24/2013