Mechanisms of the Salutary Effects of Dehydroepiandrosterone After Trauma-Hemorrhage

Direct or Indirect Effects on Cardiac and Hepatocellular Functions?

Doraid Jarrar, MD; Ping Wang, MD; William G. Cioffi, MD; Kirby I. Bland, MD; Irshad H. Chaudry, PhD

Background: Dehydroepiandrosterone (DHEA) is the most abundant adrenal hormone in man and has been shown to improve immune functions after trauma-hemorrhage. However, it remains unknown whether this agent has any salutary effects on the depressed organ functions under such conditions.

Hypothesis: Administration of DHEA after trauma-hemorrhage attenuates depressed cardiac and hepatocellular functions, and beneficial effects are mediated via the estrogen receptors.

Design, Interventions, and Main Outcome Measures: Male rats underwent laparotomy and were then bled to and maintained at a mean arterial pressure of 40 mm Hg until 40% of the maximal bleed-out volume was returned in the form of Ringer lactate (RL) solution. The animals were then resuscitated with 4 times the maximum bleed-out volume with RL for 60 minutes. Subcutaneous administration of DHEA (30 mg/kg of body weight) or vehicle occurred after resuscitation. At 24 hours after resuscitation, cardiac output was measured by a dye-dilution technique. Hepatocellular function, ie, the maximum velocity of indocyanine green clearance (V\text{max}) and the efficiency of the active transport (K\text{m}), was determined using an in vivo hemoreflectometer. Plasma levels of DHEA, sex hormone binding globulin, 17\beta-estradiol, and testosterone were also determined. Moreover, additional groups of animals received a high-affinity estrogen receptor antagonist (ICI 182,780) with or without DHEA treatment.

Results: Cardiac output decreased by 12.9% at 24 hours after trauma-hemorrhage; however, it was similar to shams in DHEA-treated animals. Moreover, hepatocellular function was significantly depressed after hemorrhage (V\text{max}, −74.4%; K\text{m}, −62.3%), whereas DHEA treatment restored those values to sham levels. Plasma levels of 17\beta-estradiol and testosterone were not significantly altered in animals receiving DHEA. The hemorrhage group treated with DHEA and ICI 182,780 showed markedly depressed cardiac and hepatocellular functions.

Conclusions: Since DHEA treatment after trauma-hemorrhage restored the depressed cardiac and hepatocellular functions, it appears that DHEA is a safe and inexpensive adjunct to fluid resuscitation for restoring the depressed cardiac and hepatocellular responses after severe hemorrhagic shock in male subjects. Furthermore, since ICI 182,780 administration with DHEA abolished the salutary effects of DHEA, it appears that these effects on cardiac and hepatocellular functions after trauma-hemorrhage are mediated via the estrogen receptors.


Recent studies have indicated that circulating male sex steroids may account for depressed organ functions after trauma-hemorrhage.\textsuperscript{1,2} Furthermore, a number of investigators have shown that sexual dimorphism exists during circulatory stress, and that androgens and estrogens play a pivotal role in regulating the stress responses.\textsuperscript{3-7} In this regard, studies by Wichmann et al\textsuperscript{8} and Zellweger et al\textsuperscript{9} have shown that female mice have enhanced immune responses as opposed to decreased responses in male mice after trauma-hemorrhage. Moreover, castration of male animals 14 days before hemorrhagic shock prevented the depression in myocardial functions and immune responses usually observed under those conditions.\textsuperscript{1,10,11} Furthermore, administration of the testosterone receptor antagonist flutamide improved the depressed immune responses and cardiac and hepatic functions in male animals after trauma and severe hemorrhage.\textsuperscript{2,12} Thus, male sex hormones appear to play a deleterious role in the development of cell and organ dysfunction after trauma and hemorrhage.

Dehydroepiandrosterone (DHEA) is the most abundant adrenal hormone in men and has been shown to improve immune functions in mice after burn injury, sepsis, and trauma-hemorrhage.\textsuperscript{13-15}
MATERIALS AND METHODS

EXPERIMENTAL PROCEDURES

We used our previously described nonheparinized model of trauma-hemorrhage in the rat, with minor modifications. Briefly, food was withheld overnight from male Sprague-Dawley rats (275-325 g; Charles River Laboratories, Wilmington, Mass) before the experiment, but water was allowed ad libitum. The rats were anesthetized using methoxyflurane (Mallinckrodt Veterinary Inc, Mundelein, Ill) inhalation before the induction of trauma (ie, 5-cm midline laparotomy). The abdomen was then closed in layers, and catheters were placed in both femoral arteries and the right femoral vein (polyethylene [PE-50] tubing; Becton Dickinson and Co, Sparks, Md). The wounds were bathed with 1% lidocaine hydrochloride (Elkins-Sinn Inc, Cherry Hill, NJ) throughout the surgical procedure to reduce postoperative pain. The rats were then allowed to awaken, and bled to and maintained at a mean arterial pressure of 40 mm Hg. This level of hypotension was continued until the animals could not maintain a mean arterial pressure of 40 mm Hg unless given extra fluid in the form of Ringer lactate. This time was defined as maximum bleed out, and the amount of withdrawn blood was noted. After this, the rats were maintained at mean arterial pressure of 40 mm Hg until 40% of the maximum bleed-out volume was returned in the form of Ringer lactate. The animals were then resuscitated with 4 times the volume of the withdrawn blood for 60 minutes (approximately 45 mL/rat) with Ringer lactate. The shed blood was not used for resuscitation. At the end of the resuscitation period, the rats received DHEA, 30 mg/kg of body weight (Sigma-Aldrich Corp, St Louis, Mo) subcutaneously or an equal volume (approximately 0.5 mL) of the vehicle consisting of ethanol and propylene glycol. In additional groups of animals, the high-affinity estrogen receptor antagonist ICI 182,780 (3 mg/kg of body weight, Sigma-Aldrich) was given intraperitoneally with and without simultaneous subcutaneous injection of DHEA.

The catheters were then removed, the vessels were ligated, and the skin incisions were closed with sutures. Sham group animals underwent the same groin dissection, which included the ligation of the femoral artery and vein; however, neither hemorrhage nor resuscitation was performed.

After returning the rats to their cages, they were allowed food and water ad libitum. At 24 hours after the completion of fluid resuscitation or sham operation, the animals were anesthetized with methoxyflurane and then catheterized via the right jugular vein. Under continued general anesthesia with pentobarbital sodium (25-30 mg/kg of body weight), cardiac output and hepatocellular function were measured in each animal.

All animal experiments were performed according to the guidelines of the Animal Welfare Act and the Guide for Care and Use of Laboratory Animals from the National Institutes of Health, Bethesda, Md. This project was approved by the Institutional Animal Care and Use Committee of Rhode Island Hospital, Providence.

MEASUREMENT OF CARDIAC OUTPUT

A 2.4F fiberoptic catheter was placed into the right carotid artery, which was connected to an in vivo hemoflectometer (Hospex Fiberoptics, Chestnut Hill, Mass) as described previously. Indocyanine green (ICG) (Cardio Green; Becton Dickinson) solution was injected via the catheter in the jugular vein (1 mg/mL aqueous solution as a 50-µL bolus). Twenty ICG concentrations per second were recorded for approximately 30 seconds with the aid of a data acquisition program (Assyst; Asyst Software, Rochester, NY). The area under the ICG dilution curve was determined according to a previous publication from our laboratory to calculate cardiac output. Cardiac output was then divided by the body weight to determine cardiac index.

MEASUREMENT OF HEPATOCELLULAR FUNCTION

Hepatocellular function was measured by the in vivo ICG clearance technique. Indocyanine green was administered by bolus injection (50 µL) of 1-, 2-, and 5-mg/mL ICG in aqueous solvent. The arterial concentration of ICG was recorded each second for 5 minutes. After this, the initial velocity of ICG clearance for each dose was calculated after performing a nonlinear regression of the ICG clearance curves according to an e-raised second-order polynomial function. The initial velocities of ICG clearance were then plotted against the ICG doses according to the method described by Hauptman et al. This results in a straight line, allowing the determination of a maximum of ICG clearance ($V_{max}$) and the Michaelis-Menten constant ($K_m$). In this active hepatocellular membrane transport system, $V_{max}$ represents the functional hepatocyte ICG receptors, whereas $K_m$ represents the efficiency of the active transport process.

DETERMINATION OF PLASMA SEX STEROIDS

At the end of all measurements (ie, 24 hours after the end of trauma-hemorrhage and resuscitation), unheparinized and heparinized whole blood was obtained and placed in microcentrifuge tubes. The tubes were then centrifuged at 16 000g for 15 minutes at 4°C. Plasma and serum were separated, placed in pyrogen-free microcentrifuge tubes, immediately frozen, and stored (−70°C) until assayed.

Plasma levels of DHEA and sex hormone binding globulin (SHBG) were determined using an enzyme immunoassay and a radioimmunoassay (RIA) kit, respectively, according to the manufacturer’s instructions (Diagnostic Systems Lab, Webster, Tex). Total plasma 17β-estradiol and testosterone concentrations were determined using a commercially available RIA kit specifically designed for rats and mice (ICN Biomedicals, Costa Mesa, Calif). The cross-reactivity of the RIA for 17β-estradiol was found to be 100% (estrone, 20%; estriol, 1.51%; 17α-estradiol, 0.68%; and all other tested steroids, <0.01%). The cross-reactivity of the RIA for testosterone was found to be 100% (5α-dihydrotestosterone, 3.4%; all other tested steroids, <0.01%). Plasma levels of protein were measured according to the method of Lowry et al.

STATISTICAL ANALYSIS

Results are presented as mean ± SEM. One-way analysis of variance and Tukey test were used, and the differences were considered significant at $P<.05$. 

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Depending on the prevailing hormonal milieu, DHEA has been shown to have androgenic and estrogenic effects. Evidence of the dual role of DHEA came from studies using orchiectomized and ovariectomized rats. Under both conditions, administration of DHEA restored seminal vesicle and uterine weight to values similar to those of intact animals. Moreover, studies by Nephew et al suggested that DHEA is an estrogen receptor agonist. In light of the above information, our aim was to determine whether administration of DHEA after trauma-hemorrhage and resuscitation has any salutary effects on the depressed cardiac and hepatocellular functions and, if so, whether this is mediated by an estrogen receptor–dependent process.

RESULTS

EFFECTS OF DHEA ON CARDIAC INDEX

The results in Figure 1 indicate that cardiac index was 40.1 ± 0.3 and 40.4 ± 0.5 mL/min per 100 g in the sham groups receiving vehicle and DHEA, respectively. Cardiac index decreased by 12.9% (P < .05) in the vehicle-treated hemorrhage group 24 hours after the completion of fluid resuscitation. Administration of DHEA after hemorrhage, however, restored the depressed cardiac index to sham levels.

EFFECTS OF DHEA ON HEPATOCELLULAR FUNCTION

The values of Vmax of ICG clearance were 1.3 ± 0.3 and 1.0 ± 0.3 mg/kg per minute in the sham groups receiving vehicle or DHEA, respectively (Figure 2, top). In the vehicle-treated hemorrhage group, Vmax decreased by 74.4% (P < .05) at 24 hours after trauma-hemorrhage. In contrast, the DHEA-treated hemorrhage group had Vmax values similar to those of the respective sham group. As indicated in Figure 2 (bottom), Km was 2.6 ± 0.4 and 3.2 ± 0.7 mg/kg in the sham groups receiving vehicle or DHEA, respectively, and it decreased by 62.3% (P < .05) after trauma-hemorrhage and resuscitation in vehicle-treated rats. Treatment with DHEA significantly improved Km at 24 hours after the completion of resuscitation compared with the vehicle-treated group, and the values were similar to those of the sham groups.

ALTERATIONS IN CIRCULATING LEVELS OF DHEA AND SHBG AFTER TRAUMA-HEMORRHAGE

Circulating levels of DHEA were found to be 7.0 ± 0.9 nmol/L in the vehicle-treated sham group and increased by 1971% after the administration of DHEA (Figure 3, top). In the vehicle-treated hemorrhaged group, DHEA levels increased by 170% at 24 hours after the end of resuscitation (P < .05), whereas the levels increased by 1767% in the DHEA-treated hemorrhaged group (P < .05). Serum levels of SHBG were 21.7 ± 0.2 and 21.3 ± 0.4 nmol/L in the sham groups treated with vehicle or DHEA, respectively (Figure 3, bottom). After trauma-hemorrhage and resuscitation, SHBG levels remained unchanged in both hemorrhaged groups.
ALTERATIONS IN CIRCULATING LEVELS OF 17β-ESTRADIOL AND TESTOSTERONE AFTER TRAUMA-HEMORRHAGE

Circulating levels of 17β-estradiol were found to be 115 ± 13 pmol/L (31.3 ± 3.5 pg/mL) in the vehicle-treated sham group, and were not significantly altered after DHEA administration or trauma-hemorrhage and resuscitation (Figure 4, top). Plasma levels of testosterone were 11.0 ± 2.0 and 8.8 ± 2.2 nmol/L (317 ± 58 and 254 ± 58 ng/dL) in the sham groups receiving vehicle or DHEA, respectively (Figure 4, bottom). At 24 hours after trauma-hemorrhage and resuscitation, circulating levels of testosterone decreased by 87.7% and 74.6% in vehicle- and DHEA-treated animals, respectively (Figure 4, bottom).

EFFECTS OF DHEA AND ICI 182,780 ON HEPATOCELLULAR FUNCTIONS

The values of the $V_{max}$ of ICG clearance were 0.8 ± 0.1 and 0.9 ± 0.2 mg/kg per minute in the sham groups receiving DHEA combined with ICI 182,780 or ICI 182,780 only, respectively (Figure 6, top), and decreased by 76.2% and 58.5% in the hemorrhage groups receiving DHEA combined with ICI 182,780 or ICI 182,780 only, respectively. As indicated in Figure 6 (bottom), $K_m$ was 2.5 ± 0.6 and 3.1 ± 0.6 mg/kg in the sham groups receiving DHEA combined with ICI 182,780 or ICI 182,780 only, respectively, and decreased by 65.9% and 59.6% ($P<.05$) in the hemorrhage groups receiving DHEA combined with ICI 182,780 or ICI 182,780 alone, respectively.

COMMENT

Recent studies using male animals have indicated that organ functions such as cardiac output, heart performance, adrenal responsiveness to exogenous corticotropin, and hepatocellular clearance of ICG are markedly depressed after trauma-hemorrhage and resuscitation.20,25,26 In contrast, female rats in the proestrus state, in which plasma estradiol levels were found to be the highest, showed normal organ functions at 24 hours after severe hemorrhagic...
Taken together, these studies suggest that significantly improved cardiac and hepatic functions after trauma-receptor antagonist flutamide in male animals significantly improved cardiac and hepatic functions after trauma-receptor antagonist flutamide.28 Furthermore, Angele et al15 showed that DHEA not only improved immune functions, but also decreased the susceptibility to sepsis after trauma-hemorrhage. In light of these findings, we hypothesized that DHEA administration after trauma-hemorrhage would improve the depressed heart and liver functions. Moreover, we hypothesized that the salutary properties of DHEA would be inhibited by the simultaneous administration of an estrogen receptor antagonist.

The results indicate that cardiac output and hepatocellular functions were significantly compromised at 24 hours after trauma-hemorrhage and crystalloid resuscitation. Subcutaneous injection of DHEA, however, significantly improved the depressed heart and liver functions. Moreover, the significantly increased circulating levels of DHEA in the DHEA-treated animals were not associated with changes in plasma level of 17β-estradiol or testosterone when compared with the respective vehicle-treated group. Simultaneous administration of the highly specific estrogen receptor antagonist ICI 182,780 prevented the salutary effects of DHEA, and such animals displayed significantly compromised organ functions comparable to those of untreated hemorrhage-group animals. Administration of ICI 182,780 with and without DHEA had no effect on heart and liver function in the sham group. Moreover, to avoid excessive numbers of groups, we have not included a comparison between vehicle-treated and untreated animals. However, recent studies in our laboratory have indicated that the vehicle ethanol combined with dimethyl sulfoxide administered intraperitoneally did not have any adverse or beneficial effects on cardiac and hepatocellular functions.29

Circulating levels of testosterone were significantly decreased at 24 hours after completion of fluid resuscitation when compared with the respective sham group. However, preliminary data indicated that at 4 hours after resuscitation, plasma levels of testosterone were not yet decreased. Thus, it could be argued that the high baseline levels of testosterone compared with female rodents are the culprit for producing organ dysfunction in male animals, despite a decrease at a later time. Plasma levels of SHBG were comparable in all 4 groups after sham operation or trauma-hemorrhage and resuscitation as measured by the indocyanine green (ICG) clearance technique. Vmax indicates the maximal velocity of ICG clearance (top); Km, the overall efficiency of the ICG transport (bottom). There were 3 to 5 animals in each group. Data are presented as mean ± SEM, and compared using 1-way analysis of variance and Tukey test. Groups are described in the legend to Figure 5. Asterisk indicates P < .05 compared with the respective sham group.

Dehydroepiandrosterone is the most abundant steroid secreted by the adrenal gland, and has been shown to have androgenic and estrogenic effects. In male patients who typically have low estrogen and high androgen levels, DHEA appears to have estrogenic properties, whereas in premenopausal women with high estrogen and low androgen levels, androgenic effects have been reported with DHEA.10 Studies by Catania et al14 demonstrated that DHEA administration after trauma-hemorrhage is immunoprotective in male mice. Moreover, they reported that the immunoenhancing effects of DHEA on splenocyte proliferation were ablated by the addition of the estrogen antagonist tamoxifen citrate, but not by the testosterone receptor antagonist.28 Furthermore, Angele et al15 showed that DHEA not only improved immune functions, but also decreased the susceptibility to sepsis after trauma-hemorrhage. In light of these findings, we hypothesized that administration of DHEA after trauma-hemorrhage would improve the depressed cardiac and hepatocellular functions. Moreover, we hypothesized that the salutary properties of DHEA would be inhibited by the simultaneous administration of an estrogen receptor antagonist.

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tion or trauma-hemorrhage. Sex hormone binding globulin is a glycoprotein that binds sex hormones with high specificity, and is synthesized primarily in the liver. Although stress and estrogens have been shown to induce SHBG production, the exact role of SHBG after trauma-hemorrhage and resuscitation with concomitantly decreased total testosterone concentration remains to be determined. Because the measured plasma levels of 17β-estradiol and testosterone represent total (ie, bound and unbound) portions of the sex steroids, it remains unknown whether the ratios of bound and free 17β-estradiol and testosterone are altered after trauma-hemorrhage.

Although several studies have shown beneficial effects of DHEA treatment on immune functions after injury such as burn, sepsis, and hemorrhagic shock, the precise mechanism for the salutary effects of DHEA remains unknown. Studies of Okabe et al suggested the existence of a high-affinity binding site for DHEA; however, a specific receptor has not been characterized yet. Furthermore, Nephew et al suggested that DHEA interacts with the estrogen receptor and modulates estrogen-signaling mechanisms. Using orchietomized and ovariectomized rats, Labrie et al showed that administration of DHEA increased prostate and uterine weight to levels of intact animals, respectively. Thus, DHEA can exert androgenic and estrogenic activity depending on the hormonal milieu and target tissue. Our data indicate that administration of DHEA had salutary effects on organ functions in male animals after trauma-hemorrhage. Sex hormone binding globulin and organ dysfunction after trauma-hemorrhage, whereas female sex steroids may have protective effects. The inexpensive steroid hormone dehydroepiandrosterone (DHEA) has been shown to exert androgenic and estrogenic effects, depending on the hormonal milieu. Moreover, DHEA has been used clinically to restore age-associated decline in bone density without any adverse effects. Our data indicate that DHEA administration after trauma-hemorrhage restored the depressed cardiac and hepatocellular functions usually observed in males under those conditions. Thus, it appears that DHEA could be a safe and inexpensive adjunct to fluid resuscitation for restoring the depressed cardiac and hepatocellular functions after trauma in male victims.

### Statement of Clinical Relevance
Despite advances in the management of severely injured patients, a large number of trauma victims subsequently succumb to sepsis and ensuing multiple organ failure. Recent studies have indicated that male sex hormones appear to play a deleterious role in the development of cell and organ dysfunction after trauma-hemorrhage, whereas female sex steroids may have protective effects. The inexpensive steroid hormone dehydroepiandrosterone (DHEA) has been shown to exert androgenic and estrogenic effects, depending on the hormonal milieu. Moreover, DHEA has been used clinically to restore age-associated decline in bone density without any adverse effects. Our data indicate that DHEA administration after trauma-hemorrhage restored the depressed cardiac and hepatocellular functions usually observed in males under those conditions. Thus, it appears that DHEA could be a safe and inexpensive adjunct to fluid resuscitation for restoring the depressed cardiac and hepatocellular functions after trauma in male victims.

cific estrogen receptor antagonist ablated the salutary effects of DHEA on organ functions. Moreover, the significance of estrogens in maintaining organ functions after adverse circulatory conditions has been further established using proestrus, ie, high levels of 17β-estradiol, and in ovariectomized females with and without 17β-estradiol replacement therapy. Third, DHEA might be converted in target tissues to estradiol derivatives via dehydrogenase and aromatase enzyme activity. This might occur without leakage of DHEA-derived estrogens into the circulation. Since circulating levels of 17β-estradiol were not altered at 24 hours after subcutaneous injection of DHEA, it is possible that tissue-specific conversion of DHEA to estrogenic derivatives might account for the observed beneficial effects. This suggestion is in line with the results of Labrie et al, who showed that physiological changes in DHEA are not reflected by alterations in serum levels of active androgens and estrogens, but of their metabolites.

In contrast to our observations of the salutary effects of DHEA after trauma-hemorrhage, Schurr et al found no beneficial effects of DHEA in a 2-hit pig model of hemorrhage and subsequent lipopolysaccharide (LPS) infusion. This discrepancy might be explained by the difference of the models used, ie, hemorrhage and subsequent LPS challenge compared with our model of laparotomy and hemorrhage alone. Nevertheless, additional studies are required to determine the precise mechanism leading to improved cardiac and hepatocellular functions after trauma-hemorrhage and DHEA administration.

Our data indicate that administration of DHEA after trauma-hemorrhage and crystalloid resuscitation significantly improved cardiac output and hepatocellular functions. Moreover, it appears that the salutary effects of DHEA treatment are mediated via an estrogen receptor–dependent process. We therefore conclude that DHEA administration appears to be a useful adjunct for improving cardiac and hepatocellular responses after trauma and hemorrhagic shock in male subjects.
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Reprints: Irshad H. Chaudry, PhD, Center for Surgical Research, Rhode Island Hospital, Middle House II, 593 Eddy St, Providence, RI 02903 (e-mail: ichaudry@lifespan.org).

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DISCUSSION

Kenneth Burchard, MD, Lebanon, NH: Intriguing informa-

tion has been emerging for several years linking the male gen-

der with evidence of more severe organ dysfunction following trauma and hemorrhage, and this study along with the next study to be presented at this meeting are consistent with these find-

ings. I have several questions.

I presume the authors would contend that the 255% increase in endogenous DHEA blood levels is insufficient to protect cardiac and hepatic tissue and that clearly a pharma-

cologic dose of DHEA is needed for cellular protection. Why is the endogenous response insufficient? Has there been a dose-

response curve generated for DHEA that demonstrates that more

than 10 times the endogenous blood level is needed to cause organ improvement? Also, why did the blood level of DHEA given after trauma-hemorrhage increase more than after the admin-

istration of DHEA alone?

Second, if DHEA can be metabolized to testosterone as well as estradiol, why did the DHEA-treated animals exhibit a de-

crease in testosterone similar to the trauma-hemorrhage ani-

m
mals without DHEA? Has DHEA been given to female animals to determine if protection can be achieved beyond that of the female gender alone?

And finally, are there any clinical data that support the concept that male gender is a disadvantage following inflammation and hypoperfusion? I performed a short review of burn mortality statistics to look for a model I thought would exhibit consistent injury across genders, and the data I found related to burn injuries suggest that females are at greater risk than males.

Richard J. Shemin, MD, Boston, Mass: I'd like to ask the authors a methodological question in that cardiac index is one of the crudest measurements of cardiac performance and whether or not any other technique, such as maybe echocardiography, would give more information about cardiac filling and myocardial contraction, which would be much more germane to the cellular function of the heart.

Erwin F. Hirsch, MD, Boston: Going back to the issue of burns, Basil Pruitt once said that the burn patient is the universal model of trauma, and along those lines, he once studied patients that were resuscitated with Ringer's lactate, and another group of burn patients that were resuscitated with early use of albumin. The net result of that study was that the albumin-treated group regained a hyperdynamic state much sooner than the Ringer's lactate group of patients, but ultimate survival was not different. My question to the authors is what is the carrot and what is the stick? If they would have elevated the cardiac index of these animals by means other than Ringer's lactate, like a colloid solution, would they have seen the same changes in liver function? Is this an issue or just better perfusion, or is this just a separate issue altogether?

Dr Jarra: With regard to Dr Burchard's first question as to why the 255% increase in endogenous DHEA following trauma-hemorrhage is not sufficient to protect organ functions, we speculate that this is part of the adrenal stress response. We have observed increased levels of corticosterone and aldosterone in this model of injury. In addition, we presented a paper last year at this meeting, showing that there was a 30% decrease in hepatic enzyme 11β-hydroxysteroid dehydrogenase, which is primarily responsible for the degradation of steroids. It could be argued that the elevated levels of DHEA following trauma-hemorrhage may also be due to the increased production of this agent. Although this may be the case, it is most likely that the elevated levels of DHEA are due to both increased production and depressed clearance following trauma-hemorrhage.

To address your second question, we have not carried out detailed dose-response studies, and we have chosen the present dose based on data by other investigators using a rat model.

Your third question dealt with whether DHEA can be metabolized to estradiol or testosterone and why their plasma levels were not altered. It has been shown that DHEA administration might not be reflected by changes in plasma levels of estradiol or testosterone in laboratory as well as clinical studies. However, DHEA may be metabolized to estradiol or testosterone in target tissues and exert its beneficial effects locally.

With regard to your fourth question, it has been shown that estrogen receptors are expressed in the male cardiovascular system. One would expect that this is even much greater abundance in females, so that administration of DHEA in females should also exert salutary effects on cell and organ functions following trauma-hemorrhage.

In regard to the burn data and mortality studies, Drs Henderson and Barrow published a paper in 1990 reporting 185 burn patients with injury greater than 30% of the total body surface area. They indeed observed a higher mortality in the males than in females. Moreover, the late Roger Bone actually analyzed several sepsis studies and reported that males were at greater risks for developing infections, multiple organ failure, and subsequently dying following severe injury. Thus, the above clinical data support our current observation.

With regard to cardiac index measurement, we have also performed measurements of heart performance, but data are not presented here. In this regard, measurements of tissue perfusion and oxygen delivery and consumption will also provide further insight of the beneficial effects of DHEA following trauma and hemorrhage. It should be noted that different organ systems relate to each other. The improvement of cardiac output will most likely result in better tissue perfusion and an improvement in hepatic function.

With regard to the resuscitation regimen, recent studies have indicated that autologous blood does not necessarily improve organ dysfunction, despite an increase in mean arterial pressure in comparison to Ringer's lactate group. In this regard, recent studies published in the American Journal of Physiology (Kerger et al; 1999:276[Heart Circ Physiol]:G2035-H2043) this year have shown that microcirculatory disturbance in perfusion still exists despite the use of blood products. This would suggest that simply elevating the blood pressure is not enough to affect distal organ function.