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Venoconstrictor Agents Mobilize Blood from Different Sources and Increase Intrathoracic Filling during Epidural Anesthesia in Supine Humans

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The authors studied the effects of dihydroergotamine (DHE) and etilefrine hydrochloride (E) on the regional distribution of ^{99m}Tc-marked erythrocytes during epidural anesthesia in eight supine men to determine if vasoactive agents with venoconstrictor action would enhance cardiac filling during epidural anesthesia. Radioactivity was recorded with a gamma camera, and its distribution determined in the thorax, abdomen, and limbs. Arterial and central venous pressure, heart rate, and calf volume by plethysmography were measured. During epidural anesthesia with a sensory block up to T4/5, DHE (7.5 μg/kg) reduced the radioactivity, *i.e.*, blood volume, in both the innervated (−5.9 ± 3.5%) and denervated muscle/skin (−16.9 ± 7%) regions, and increased it in both the intrathoracic (+7.0 ± 2.3%), and splanchnic vasculature (+4.2 ± 3.2). In contrast, E (6 $\mu g \cdot kg^{-1} \cdot min^{-1}$) decreased the blood volume most markedly in the splanchnic region (−5.4 ± 0.7%) and increased it in the thorax (+2 ± 0.6%). All these changes were statistically significant. The combined effects were estimated to be equivalent to a transfusion of nearly 1.0 l of blood. Both drugs reversed the hypotensive action of epidural anesthesia. During epidural anesthesia, DHE preferentially constricted the capacitance vessels in skeletal muscle and skin irrespective of the state of innervation, whereas E preferentially constricted the splanchnic vasculature. In the doses used, the two agents replenished in an additive fashion the central circulation during epidural anesthesia. (Key words: Anesthetic techniques: epidural. Pharmacology: dihydroergotamine; etilefrine hydrochloride. Veins: capacitance vessels; venoconstrictors.)

THE PRESENT EXPERIMENTS were designed to determine whether vasoactive agents with venoconstrictor action would enhance filling of the intrathoracic or central circulation and, thereby, that of the heart during epidural anesthesia. Epidural anesthesia reduces cardiac filling due to blood pooling in the denervated muscle/skin regions, an effect counteracted in part by constriction of capacitance vessels in the remaining innervated muscle/skin regions and, surprisingly, also by a constriction of the denervated splanchnic vasculature.[1] Circumstantial evidence also suggests that circulatory collapse may occur when the splanchnic constrictor mechanism fails.[1] Consequently, agents capable of constricting the capacitance vessels of the striated musculature and/or of the splanchnic region might be of use in the prevention and treatment of epidural anesthesia-induced cardiac filling disturbances.

Dihydroergotamine, an ergot alkaloid, which, as an alpha antagonist, preferentially constricts smooth muscle to the capacitance vessels,[2,3] and etilefrine hydrochloride, a catecholamine with α- and β_1-agonist properties but with little chronotropic action,[4] appeared to be useful candidates for such an attempt. The former mobilizes blood selectivity from muscle/skin regions, but the latter selectively from the splanchnic vasculature in favor of the pulmonary circulation in humans with an intact cardiovascular innervation.[5] It seemed reasonable to test if the two substances would act in a similar manner during epidural anesthesia, *i.e.*, when vasomotor tone is absent in some, but enhanced in other, vascular regions. We, therefore, studied the effects of dihydroergotamine and etilefrine hydrochloride on the distribution of the blood during epidural anesthesia by means of whole body scintigraphy in combination with leg plethysmography. It will be shown that the two agents mobilize blood from different sources and, thereby, in an additive fashion, replenish the pulmonary circulation during epidural anesthesia.

Methods

Eight healthy male volunteers between the ages of 22 and 42 years (average 33 years) with a body weight of 77 kg (range 60–92 kg) gave informed consent and received institutional approval to participate in the study. They had fasted overnight, but fluid intake was not restricted until 2 h before the start of the experiments. The subjects were studied in the supine position at a thermoneutral room temperature of 27° C between 9:00 A.M. and 12:00 A.M. (six experiments) and between 1:00 P.M. and 5:00 P.M. (two experiments). No fluids were given intra-

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venously, except a few milliliters to keep the catheters open.

Before each study, 5 ml of venous blood were withdrawn for erythrocyte labeling with technicium (^{99m}Tc, 5 mCi = 5 × 37 MBq) and reinjected intravenously.

An epidural catheter was inserted through an 18-gauge Crawford® needle at the L2-3 interspace for a distance of 2–3 cm. Both cephalic veins were cannulated, one for drug infusion, the other for recording the central venous pressure (CVP) via a catheter that was advanced into the superior vena cava as judged from the pressure contour. The ECG was obtained by standard leads using surface electrodes. For measuring calf volume and blood flow (occlusion plethysmography), mercury-in-rubber gauges[6] were fixed around both calves. Finally, two blood pressure cuffs (width 20 cm) were loosely fixed around the thighs. When pressurized to 100 mmHg, approximately 500–600 ml of blood could be pooled below the cuffs (leg congestion test).[1] The placement of the various catheters and transducers took about 30 min, an interval sufficient to allow for equilibration of the labeled erythrocytes.

Measurements

Radioactivity was recorded continuously by whole-body scintigraphy with the use of a gamma camera (Searle LFOV®, equipped with a parallel hole, high-resolution collimator) in the anterior-posterior direction. The subjects remained supine throughout the study, with their torso and extremities fixed by appropriate cushions. The counting sequence employed started on the left side from foot to head, and in the reverse order on the right side. Each counting cycle took 6 min (=1 scan), repeated without interruption over the duration of each study for a total of 96 min, *i.e.* 16 scans. The counts were acquired by a computer (DEC PDP 11/15), stored, processed, and whole-body images reconstructed for each scan.[7] Average counting rates (counts per scan = cps, corrected for the physical decay of ^{99m}Tc) were printed for the following regions: 1) skeletal muscle (arms and legs); 2) splanchnic region (abdomen and liver plus spleen); 3) thoracic region (heart and lung).

Additionally, the following variables were measured: central venous pressure (CVP) electromanometrically (Statham D23db®); heart rate with an ECG-triggered cardiotachometer, and calf circumference with a mercury-in-rubber strain gauge for following blood volume changes. The calf circumference was determined by tape, initially, and the mercury-in-rubber strain gauge was then calibrated at frequent intervals by an in-series micrometer. The arterial blood pressure was measured sphygmomanometrically by the same person at the end of each scan. The zero reference point for CVP was set at one-half the ventrodorsal thickness of the chest.

Drugs Used

Lidocaine (2% Xylocain® without epinephrine) was used for epidural anesthesia. The vasoconstrictor agents dihydroergotamine (Dihydergot® = DHE) and etilefrine hydrochloride (Effortil® = E) were administered intravenously. DHE, which in the therapeutic dose range selectively constricts capacitance vessels,[2] is a long-acting agent with a plasma half-life (β-phase) of 20 h,[2,3] was injected within 5 min. E, a sympathomimetic agent with α- and β_1-adrenergic properties,[4] selectively constricts capacitance vessels in the splanchnic circulation.[5] The half-life (β-phase) of E is approximately 2 h.[8] It was, therefore, infused continuously.

Experimental Protocol

All experiments commenced 1 h after the injection of the tracer, and the following protocol was used in each subject.

Control I. Control I for 18 min (= scans 1–3, 0–18 min) with a leg congestion test during scan 2.

Epidural anesthesia. Lidocaine 20 ml of a 2% solution was injected at the start of scan 4. The sensory block (tested by pin prick) reached T_5 in all of the subjects, and in the smaller subjects even T_4 within 24 min (= scan 4–7, 24–42 min, *i.e.* within 24 min of the epidural injection of local anesthetic).

Dihydroergotamine. 7.5 μg/kg were injected intravenously over 5 min during scan 8, and its effects were monitored subsequently (= scans 8–10, 48–60 min, *i.e.* within 24–42 min after evidence of epidural block).

Etilefrine hydrochloride. 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ were infused for 18 min (scans 11–13, 66–78 min, *i.e.* 42–60 min after evidence of epidural block).

Control II. After discontinuation of the infusion of E recovery was followed for 18 min (= scan 14–16, 84–96 min, *i.e.* 60–78 min after evidence of epidural block), the leg congestion test was repeated during scan 14.

Total recording time was 96 min. Sensory block had reached its maximum height by the end of scan 7, remained at this level until the end of scan 16 in five subjects, but had regressed by two segments in two subjects, and by five segments in one subject. Calf blood flow as an indicator of sympathetic block was still elevated until the end of the recording period, and all subjects were able to walk at about 100 min after the start of epidural anesthesia.

Data Analysis

Data are expressed as averages (±SE). Wilcoxon rank test was employed for testing differences. P values less than 0.025 were considered significant.

Results

Blood Distribution

DHE and E mobilized blood from different sources and, thereby, in an additive fashion improved cardiac filling during epidural anesthesia which, in the present experiments, had produced a sensory block (pin-prick test) up until the end of the recording period in most subjects. The time course of the drug actions are shown in figure 1. The effects of epidural anesthesia have previously been described in detail.[1] To recapitulate, epidural anesthesia elicited an increase in regional blood content in the denervated legs at the expense of intrathoracic filling, in spite of a reflex decrease in blood content in both the innervated arms and the denervated splanchnic region. The opposite happened in response to DHE and E. Following the injection of DHE, the counting rates as a measure of blood content decrease in the muscle/skin regions, *i.e.* in both the denervated legs and in the innervated arms. In fact, in the legs, DHE reversed not only the pooling effects of epidural anesthesia, but, in addition, reduced the blood content further below the pre-block measurements. At the same time, the blood volume increased significantly in the thorax and abdomen. Thus, DHE elicited a decrease in blood content in the muscle/skin region, irrespective of whether they were innervated or not, and, as a consequence, redistributed blood into both the pulmonary and splanchnic circulation.

During the subsequent infusion of E, the blood volume in the abdomen fell significantly, but little change occurred in either the innervated arms or denervated legs. The only increase in regional blood volume took place in the central (pulmonary) circulation, where counting activity almost returned to control values. After discontinuation of the E infusion, the thoracic and abdominal blood volumes promptly reversed, with little change being reflected in either the arms or legs.

Scintigraphy provides only relative information on the distribution of blood between different regions. To obtain an estimate of the actual volume shifts, the leg congestion test was applied during scan 2, and also during scan 14. This approximated the same changes in thoracic and abdominal blood volumes that were measured either under the influence of epidural anesthesia or during the combined action of DHE and E. Because about 500–600 ml of blood were sequestered in both legs during the pooling period,[1] similar shifts of blood volume must have occurred with our experimental interventions.

To illustrate the response of special organs, like the heart, liver, and spleen, to the various experimental maneuvers, figure 2 contrasts the maximum changes in counting rates which occurred in each of the regions investigated. During epidural anesthesia, the counting rates

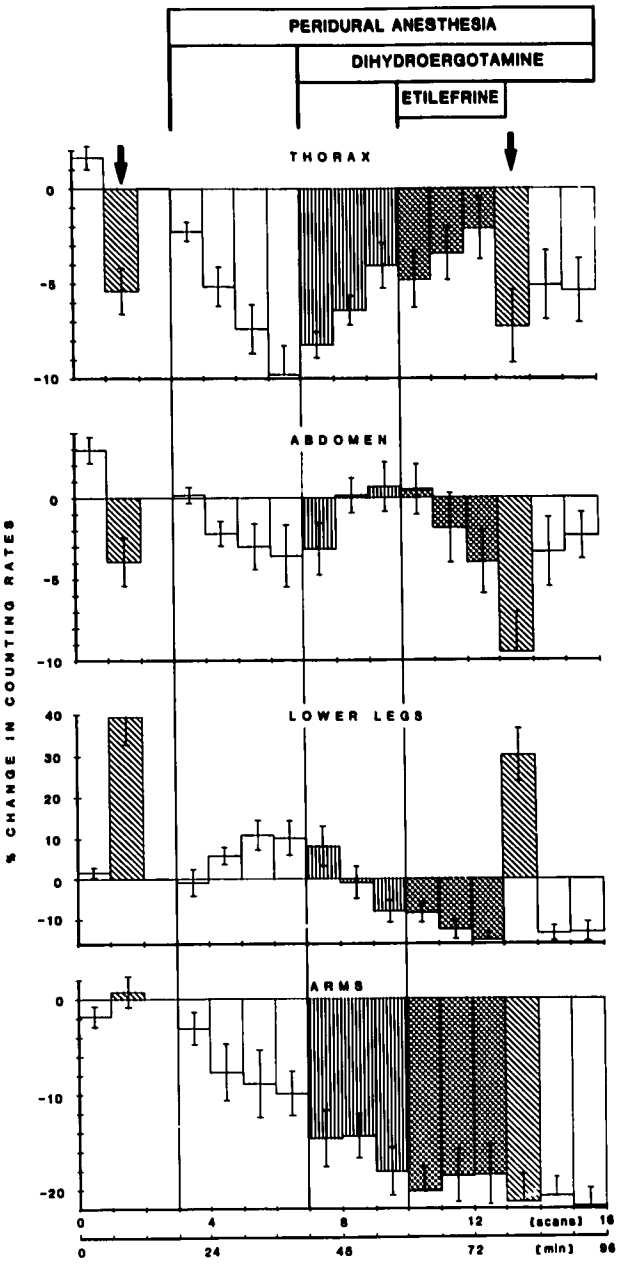

FIG. 1. Regional distribution of blood during epidural anesthesia and its response to dihydroergotamine (DHE) and etilefrine hydrochloride (E) in supine healthy humans. Percent changes (3rd scan = 100) in counting rates of ^{99m}Tc-labeled erythrocytes. Each sampling period, *i.e.* whole body scan = 6 min. Leg congestion test performed during scan 2 and 14, shown by arrows. Averages (±SE), n = 8. Shading has been used to highlight periods of drug treatment and the leg congestion tests. The reduction in counting rates in thorax and abdomen with epidural anesthesia is reversed by the combined actions of DHE and E. The drug effects are duplicated by the leg congestion test.

decreased reflecting reduced blood volumes in all regions, except in the legs, where significant increases were noted. In contrast, DHE decreased the blood volume in the skel-

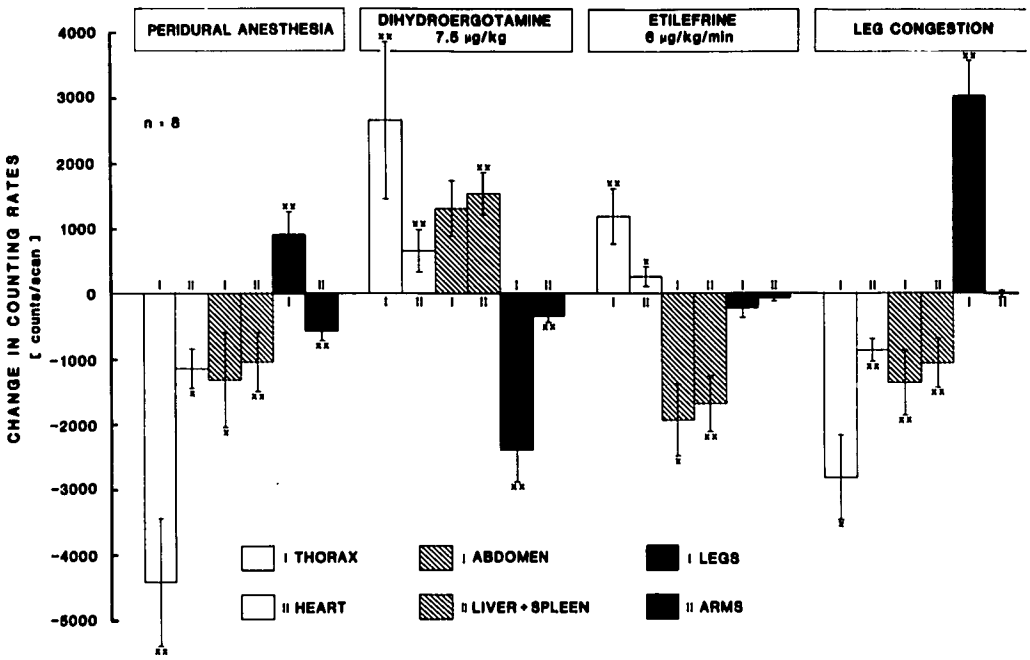

FIG. 2. Effects of dihydroergotamine (DHE) and etilefrine hydrochloride (E) on the regional distribution of ^{99m}Tc-marked erythrocytes in supine humans during epidural anesthesia. Differences in counting rates between the maximum values during drug action and the control values, *i.e.* before the injection DHE and E, respectively. Averages (±SE) from eight experiments. Asterisks designate significant differences × $P < 0.025$, ×× < 0.01 (Wilcoxon rank test). DHE reduces the counting rates in denervated muscle more than in innervated muscle regions, and increases them both in the thorax and abdomen. However, adding E reduces counting rates preferentially in the abdomen without much change in the muscle regions, whereas an increase is only noted in the thorax. The drug-induced increase of counting rates in the thoracic region almost entirely reverse the epidural anesthesia-induced decrease. Note also that the leg congestion test approximates the effects of epidural anesthesia.

etal musculature and increased it in the thorax (lung and heart) and abdominal region, particularly liver and spleen, whereas E lowered the blood volume in the splanchnic region, particularly the liver and spleen, and increased it in the thorax. Finally, the leg congestion test performed during scan 2, *i.e.* during the second control period, duplicated the effects of epidural anesthesia both qualitatively and quantitatively.

Cardiovascular Measurements

The time course of the cardiovascular measurements is illustrated in figure 3. The effects of epidural anesthesia and the leg congestion test have been described in our previous report,[1] and it should be noted only that the epidural anesthesia-induced fall in CVP is small (−1.3 cm of H_2O) compared to that which follows the leg congestion test (−3.5 cm of H_2O), even though the former event reduces intrathoracic blood volume more than the latter maneuver (fig. 1).

Concerning the drug effects, DHE and, likewise, E each increased CVP by 3 cm of water resulting in a total increase of 6 cm of water during the combined drug action. CVP rapidly decayed after the discontinuation of E, and approximately reached the level attained by the previous injection of DHE.

Calf volume, which had increased by 1 ml/100 ml tissue during epidural anesthesia, was decreased by 1.67 ml/100 ml tissue after the injection of DHE and, in addition, by 0.83 ml/100 ml tissue during the infusion of E. Thus, the combined action of both agents mobilized a total of about 2.5 ml/100 ml muscle tissue from the denervated muscle region.

Little change in heart rate occurred, and changes in arterial pressure paralleled CVP. During epidural anesthesia, systolic, diastolic, and pulse pressure decreased slightly, while pulse pressure increased during DHE and E. E, in particular, elevated systolic pressure, as is also shown by the disappearance of this effect in the post-infusion period.

Discussion

Much like the results of our previous studies in humans with intact sympathetic innervation,[5,10] during epidural anesthesia, DHE and E mobilized blood from different sources. The level of sensory block and its duration (see Experimental Protocol section) correspond with previous observations in a similar group of healthy volunteers,[11,12] in which case it seemed justifiable to state that the drug effects described were studied under the influence of epidural anesthesia, *i.e.* with a nerve block to a pin-prick level of at least T5. In fact, the cardiovascular changes observed in the earlier studies were maintained for a minimum of 60 min.[11,12] Under these conditions, DHE pref-

erentially constricted the vasculature of the striated muscles, whether denervated or innervated, while E almost exclusively constricted splanchnic vessels. Given that the greater proportion of the blood is contained within the capacitance vessels, and that the radioactivity reflects the erythrocyte concentration in the regions looked at, the present experiments show that both agents are capable of shifting substantial blood volumes into the central vasculature.

The observation that DHE in the therapeutic dose range preferentially constricts the capacitance vessels of striated musculature and skin is supported by plethysmography[9,10] and scintigraphy.[5,13] The regional blood volume of the legs in supine healthy men with intact vascular innervation amounts to 5.5 ml/100 g tissue,[14] which, according to the present observations, increased by 1.0 to a total of 6.5 ml/100 g tissue. Assuming that these figures are applicable to all muscle regions, and assuming, furthermore, that the muscle mass amounts to 40% of the body weight, our subjects (average body weight of 77 kg) may have held between 1.7 liters (innervated) and, maximally, 2 liters of blood (denervated) in the striated musculature alone. DHE, at the dose used (7.5 μg/kg), reduced calf volume by 0.7 ml/100 g tissue, or by 13%,[10] with intact innervation, but by as much as 1.7 ml/100 g tissue, or by 25%, in the absence of efferent sympathetic drive. Thus, depending on the state of innervation, DHE is capable of mobilizing between 0.25 and 0.5 liters of blood from the capacitance vessels of the striated musculature alone.

This rough estimate is also supported by the accompanying increase in central venous pressure. In healthy adults, central venous pressure[15] increases by 7 cm of water in response to a blood transfusion of 1 l, of which one-half is accommodated in the intrathoracic circulation because the compliance ratio between the intra- and extrathoracic vascular beds is unity.[16] Thus, the central circulation actually accommodates only 0.5 liter of blood for a change of 7 cm H_2O. Since central venous pressure in our subjects increased by 3 cm of water in response to DHE, intrathoracic blood volume is equivalent to a transfusion of 0.5 liters of blood. A part of this volume must have been accommodated in the splanchnic circulation, where, in fact, the blood content had also increased.

Thus, DHE did mobilize roughly 0.5 l of blood, but it only partially reversed the epidural anesthesia-induced fall in intrathoracic filling, because half of the mobilized volume remained in the splanchnic circulation.

The splanchnic vasculature, which contains about 1.5 l of blood in adults,[17] is an important blood reservoir,[18] whose filling is believed to be regulated by the sympathetic nervous system.[17,19] E, a catecholamine with α- and β_1-adrenergic properties, conspicuously and preferentially reduced the splanchnic filling in supine healthy humans.[5]

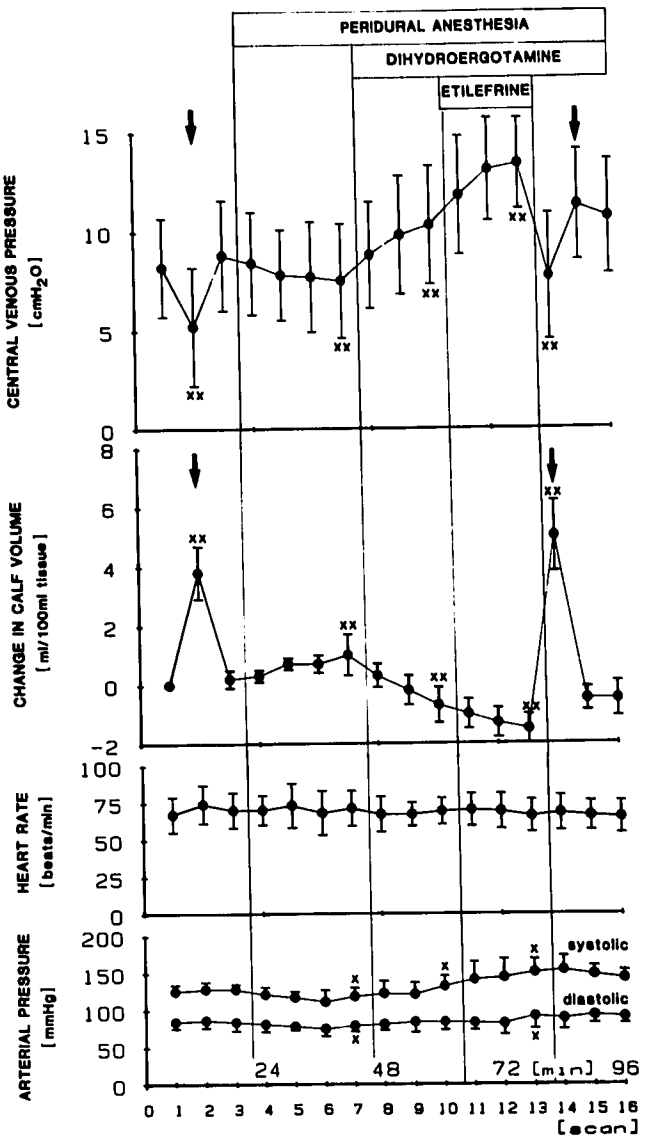

FIG. 3. The effects of dihydroergotamine (DHE) and etilefrine hydrochloride (E) on central venous pressure (CVP), calf volume, heart rate, and arterial pressure during peridural anesthesia in supine humans. For comparison, blood was sequestered in both legs (leg congestion test) during the scans indicated by arrows. Averages (±SE), n = 8. Asterisks designate significant differences for X = $P < 0.025$, XX < 0.01 (Wilcoxon rank test). DHE and E increase CVP by 3 cm to a total of 6 cm of water. This is paralleled by a decrease in calf volume, particularly in response to DHE. Pulse pressure increases with DHE and particularly with E without changes in heart rate.

The present experiments now show that this is still so when sympathetic efferent drive had been eliminated and when blood volume in the splanchnic circulation was increased by DHE. Under these conditions, E also reduced the splanchnic blood content in favor of the pulmonary circulation. In fact, the intrathoracic blood volume and, likewise, the central venous pressure increased in an ad-

ditive fashion when the effect of E was superimposed on that of DHE.

By the combined drug action, the intrathoracic blood volume was nearly returned to the control values before epidural anesthesia was induced, and the increase in CVP by a total of 6 cm of water suggests that this effect is equivalent to a transfusion of nearly 1 l of blood. The effectiveness of this treatment in stabilizing the arterial side of the circulation is also reflected by the significant increase in pulse pressure in response to DHE and E.

Because of their different sites of action, DHE and E compliment each other by effectively replenishing the central circulation during epidural anesthesia. DHE, by preferentially constricting the capacitance vessels in the striated musculature and in the skin,[9] expels venous blood without altering flow, so that the increase in limb blood flow during epidural anesthesia is maintained.[20] DHE, through its long duration of action, appears to be a useful agent for the prevention of hypotension that can occur during epidural anesthesia, particularly in view of recent observations showing that volume loading does not necessarily prevent hypotension.[21] For its selective vasoconstrictor effect on the splanchnic circulation, E, as a drug with a specific site of action, not only merits attention as a rational supplement to DHE, but also for the treatment and prophylaxis of circulatory collapse. Our previous observation[1] suggests that the pooling effect of epidural anesthesia is, to a large extent, counteracted by a vasoconstriction, possibly reflex in nature, in the splanchnic circulation. Circulatory collapse seems to ensue when, for whatever reasons, this vasoconstrictor response by the splanchnic circulation fails, so that it appears reasonable to consider drugs such as E for the treatment of such mishaps.

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