High-Dose Atrial Natriuretic Factor Enhances Albumin Escape From the Systemic but Not the Pulmonary Circulation

Robert S. Zimmerman, Nick C. Trippodo, Allan A. MacPhee, Alberto J. Martinez, and R. Wayne Barbee

Atrial natriuretic factor (ANF) causes plasma fluid to shift out of the circulation and enhances the escape of radiolabeled albumin. Examination of the mechanisms by which ANF alters microcirculatory fluid and protein transfer will likely require studies in localized vascular regions. This study was aimed at determining the specific organs in which ANF increases the escape of albumin. Anesthetized, splenectomized rats that had both kidneys removed were infused with vehicle alone or rat ANF-(99-126) at 0.025, 0.05, 0.1, or 0.5 μg·min⁻¹·kg⁻¹ for 2 hours (n=8 per group). Total red cell and plasma volumes were measured with chromium-51-labeled erythrocytes and iodine-125-labeled albumin, respectively. At the end of 2 hours, the rats were frozen in liquid nitrogen, and organ blood volumes and tissue ¹²⁵I-albumin were determined. ANF decreased plasma volume at infusion rates of 0.1 and 0.5 μg·min⁻¹·kg⁻¹. ANF increased the rate at which ¹²⁵I-albumin escaped from the overall circulation at infusion rates of 0.1 and 0.5 μg·min⁻¹·kg⁻¹. At an ANF infusion rate of 0.1 μg·min⁻¹·kg⁻¹, the albumin escape rate increased in the gastrointestinal tract, skeletal muscle, heart, and lungs. At an infusion rate of 0.5 μg·min⁻¹·kg⁻¹, the albumin escape rate increased in the gastrointestinal tract, muscle, and skin, but not the lungs. These findings suggest that at pathophysiological levels, ANF shifts protein out of the circulation in peripheral vascular beds and the lungs and may contribute to pulmonary edema in states such as congestive heart failure. At pharmacological levels, ANF may be protective of the lungs by preventing increased pulmonary albumin escape. (Circulation Research 1990;67:461–468)

Atrial natriuretic factor (ANF) is elevated in certain disease states such as congestive heart failure, which is associated with both pulmonary and peripheral edema. Furthermore, some investigators have used ANF in treatment of patients with conditions such as congestive heart failure. Because short-term administration of pharmacological doses of ANF results in both enhanced net capillary filtration and attenuated net capillary absorption, it is important to determine whether ANF has a generalized effect on fluid exchange or if its action is confined to certain vascular regions. It is also important to determine whether the effects of ANF on fluid filtration in specific vascular compart-ments differ at pathophysiological and pharmacological infusion rates of ANF. Parkes et al. recently reported that the decreased plasma volume observed during the first day of long-term infusion of ANF in sheep was associated with an increased rate of escape of ¹²⁵I-albumin from the circulation. In this present study, we reasoned that an enhanced escape of ¹²⁵I-albumin from the circulation would be accompanied by increased fluid filtration and that if the escape rate of ¹²⁵I-albumin could be quantitated in specific organs, information with regard to the regional distribution of ANF's action on capillary fluid shift could be obtained. We hypothesized that ANF may contribute to edema formation at pathophysiological levels by enhancing albumin escape from the vasculature in both the pulmonary and peripheral vascular beds but may be protective of the lung at pharmacological levels by preventing increased pulmonary albumin escape by decreasing venous return. Therefore, the present study was performed in splenectomized, nephrectomized, anesthetized rats to determine the total-body and organ-specific albumin escape rates in rats infused...
with ANF at physiological, pathophysiological, and pharmacological doses.

Materials and Methods

Protocol

Male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis) weighing 280–391 g were anesthetized with Inactin (100 mg/kg i.p.) (BYK Gulden, Konstanz, FRG). A 240-gauge polyethylene tube was placed in the trachea to facilitate breathing. To eliminate renal fluid and albumin loss and to ensure that changes in hematocrit were not the result of splenic contraction, both kidneys and the spleen were surgically removed through a midline incision. To facilitate later separation of frozen organs, a thin plastic sheet was positioned between the liver and other viscera before suturing the abdominal incision. By using a femoral approach, catheters were placed in the abdominal aorta for measuring mean arterial pressure and collecting blood samples, in the thoracic inferior vena cava for measuring central venous pressure, and in the abdominal inferior vena cava for injections and infusions. At 15 minutes after surgery, $^{51}$Cr-tagged erythrocytes ($-1 \mu$Ci) were injected intravenously. Five minutes later, $^{125}$I–human serum albumin ($-1.5 \mu$Ci) was injected. In four groups of eight rats, an intravenous infusion of rat ANF (99-126; Peninsula, Belmont, Calif.) at 0.025 $\mu$g · min$^{-1}$ · kg$^{-1}$, 0.05 $\mu$g · min$^{-1}$ · kg$^{-1}$, 0.1 $\mu$g · min$^{-1}$ · kg$^{-1}$, and 0.5 $\mu$g · min$^{-1}$ · kg$^{-1}$ in 0.9% NaCl (vehicle) was commenced at a flow rate of 5 $\mu$l/min. The vehicle alone was infused in a separate group of eight rats. Blood samples for measuring hematocrit and $^{51}$Cr and $^{125}$I radioactivities were collected at 10, 60, and 120 minutes after the start of ANF or vehicle infusion. Mean arterial and central venous pressures were monitored continuously with Gould-Statham transducers (Gould, Cleveland) and a Grass recorder (Quincy, Mass.). Immediately after the last blood sample was taken, the rat was quickly frozen by immersing it in liquid nitrogen for 90 seconds. The thoracic and abdominal viscera and samples of skin and skeletal muscle were dissected and separated from one another while they remained frozen. They were weighed and, together with washings from thawed blood for each organ, were placed in separate vials for determination of $^{51}$Cr and $^{125}$I radioactivities.

Red Cell, Plasma, and Blood Volumes

Erythrocytes were labeled with sodium 51-chromate in saline (DuPont Medical Products, Wilmington, Del.) as previously described and mixed in 0.9% NaCl solution to a hematocrit of 40–55%; approximately 1.5 $\mu$Ci of $^{125}$I–human serum albumin (Mallinckrodt, St. Louis) was injected intravenously in a volume of 0.15 ml. At 15 minutes after injection of $^{51}$Cr-erythrocytes (10 minutes after injection of $^{125}$I-albumin and 10 minutes after the start of ANF or vehicle infusion), triplicate blood samples were taken from the catheter in the abdominal aorta into glass capillary tubes calibrated to 24 $\mu$l. Duplicate blood samples were taken at 60 and 120 minutes. “Large-vessel” hematocrit (LVHct) was determined with a manual hematocrit reader (Damon/IEC Division, Needham Heights, Mass.). By using a Minaxi Auto-Gamma 5000 series gamma counter (Packard Instrument Co., Downers Grove, Ill.) the $^{51}$Cr and $^{125}$I radioactivities were determined for the blood samples, as well as for triplicate glass capillary tubes containing 24-$\mu$l samples of the mixture of $^{51}$Cr-erythrocytes and 10-$\mu$l samples of the solution of $^{125}$I-albumin used for injections. The counting rates were corrected for background activity and spillover across channels with the COMPUSPHERE software package (Packard).

For the first blood sample, red cell volume (RCV), plasma volume (PV), and blood volume (BV) were determined according to the following formulas:

$$\text{RCV} = \frac{\text{PV} \times \text{51Cr activity injected (counts per minute)}}{	ext{blood } 51\text{Cr activity concentration (counts per minute per milliliter)}}$$

$$\text{PV} = \frac{\text{RCV} \times \text{xLVHct/blood } 51\text{Cr activity concentration}}{1}$$

$$\text{51Cr activity measured during the first sample} - \text{RCV} \text{lost through sampling, } \text{RCV lost through sampling} = \frac{\text{PV} \times \text{51Cr activity per milliliter RCV}}{\text{51Cr activity per milliliter RCV}}$$

$$\text{RCV} = \frac{\text{RCV} \times \text{51Cr activity injected/RCV measured during first sample}}{\text{PV}}$$

Organ and Tissue Blood Volume

Corrected $^{51}$Cr and $^{125}$I radioactivities for organs and tissues were determined as described above. Organ blood volume (OBV) was calculated according to

$$\text{OBV} = \frac{\text{(organ } 51\text{Cr activity/blood } 51\text{Cr activity concentration)} \text{F cells, } \text{RCV} \times \text{RCV measured during the first sample} - \text{RCV} \text{lost through sampling, } \text{RCV lost through sampling} = \frac{\text{PV} \times \text{51Cr activity per milliliter RCV}}{\text{51Cr activity per milliliter RCV}}$$

The organ F cell ratios were determined in separate groups of rats as follows. Male Sprague-Dawley rats weighing 312–370 g were anesthetized and surgically prepared as described above. However, in this series, the infusion of vehicle ($n=3$) or ANF ($n=2$; 0.5 $\mu$g · min$^{-1}$ · kg$^{-1}$) at the same rates and duration described above) was commenced before labeled erythrocytes and albumin were injected. At 10 and 5 minutes before blood samples were drawn and the rats were frozen, $^{51}$Cr-erythrocytes and $^{125}$I-albumin were injected, respectively, as described above. Therefore, unlike the experiments described above, whereby $^{25}$I-albumin was allowed to escape from the circulation for 2 hours before the rats were frozen, the rats were frozen in liquid nitrogen at 5 minutes after injection of $^{125}$I-albumin. Based on the whole-body escape rate of $^{125}$I-albumin from the circulation as measured in the
experiments described above, it was estimated that approximately 1% of the injected 

\[ 125\text{I}-\text{albumin} \] would have crossed the capillaries into the tissues by 5

minutes after injection (see "Results"). Therefore, except for the liver, whose sinusoids are highly permeable to albumin, the level of 

\[ 125\text{I} \text{radioactivity} \] measured in each organ at 5 minutes after injection of 

\[ 125\text{I}-\text{albumin} \] provided an estimate of the organ plasma volume, while the organ \[ 51\text{Cr} \text{ activity} \] was a measure of organ erythrocyte volume. Each organ hematocrit was determined according to standard relations (see "Appendix"), which reduced algebraically to the following formula:

\[
\text{Organ hematocrit} = \frac{1}{1 + (1 - LVHct \cdot \text{ratio})} \]

where ratio is the ratio between \[ 51\text{Cr} \text{ activity/}\text{125I} \text{ activity} \] in each organ and \[ 51\text{Cr} \text{ activity/}\text{125I} \text{ activity} \] in blood, that is, \( (\text{Cr/I}) \text{ organ/}(\text{Cr/I}) \text{ blood} \). This formula, applied to an example of a set of data given by Jodal and Lundgren, yielded the same value for tissue hematocrit as reported by these authors, although they used a different method of calculation. Each organ F cell ratio was then determined, and the results were 1.02, 0.96, 0.83, 0.82, and 0.83 for heart, lung, gastrointestinal tract, skin, and skeletal muscle, respectively. The respective coefficients of variation were 1.8%, 1.6%, 6.8%, 3.1%, and 2.2%. This technique does not adequately reflect the F cell ratio for the liver because of very rapid albumin escape into the sinusoids. Hence, we assumed the liver hematocrit was equal to LVHct, which gives an F cell ratio of 1.

\[ 125\text{I}-\text{Albumin Escape Rate and Organ Mass} \]

The rate at which \[ 125\text{I}-\text{human serum albumin} \] escaped from the total circulation (\[ 125\text{I}-\text{AER} \]) was determined according to \[ 125\text{I}-\text{AER} = (\text{net } 125\text{I} \text{ activity injected total plasma } 125\text{I} \text{ activity at 120 minutes})/\text{net } 125\text{I} \text{ activity injected})/2 \text{ hours} \times 100 \text{, where net } 125\text{I} \text{ activity injected is the total } 125\text{I} \text{ activity injected minus the cumulative } 125\text{I} \text{ activity removed from the circulation by blood sampling. Total plasma } 125\text{I} \text{ activity is the product of plasma } 125\text{I} \text{ activity concentration and plasma volume at 120 minutes after the start of ANF or vehicle infusion and 120 minutes after injection of } 125\text{I}-\text{albumin.} \]

The rate at which \[ 125\text{I}-\text{albumin} \] escaped from the circulation in each organ (\[ 125\text{I}-\text{AER} \]) was determined according to the formula \[ 125\text{I}-\text{AER} = \text{tissue } 125\text{I} \text{ albumin activity/net } 125\text{I} \text{ activity injected/2 hours} \times 100/\text{corrected organ weight}. \]

Tissue \[ 125\text{I}-\text{albumin} \] activity was taken as the difference in total organ \[ 125\text{I} \text{ activity} \] and organ plasma \[ 125\text{I} \text{ activity} \], where the latter was the product of organ plasma volume and plasma \[ 125\text{I} \text{ activity concentration} \] at 120 minutes. Organ plasma volume was determined as organ blood volume \( \times [1 - (\text{organ F cells } \times \text{LVHct})] \). Organ weight was corrected by subtracting estimated organ blood weight, taken as organ blood volume \( \times \text{blood specific gravity} (1.06) \), from organ wet weight. The \[ 125\text{I}-\text{albumin} \] activity that accumulated in the tissues in whole organs was expressed as tissue \[ 125\text{I} \text{ activity/total } 125\text{I} \text{ activity} \] detected in all organs \( \times 100 \). Total \[ 125\text{I} \text{ activity} \] detected in all organs represented the activity in blood and tissue. Total skeletal muscle and skin masses were determined as 47% and 20% body weight, respectively. These latter values were determined by completely dissecting one rat weighing 350 g and boiling the muscle from the bones to determine skeletal weight; they compare reasonably well to values determined from previously reported data.

ANF levels were determined in a separate group of nephrectomized, splenectomized, anesthetized rats after saline infusion or ANF infusion at the same rates and concentrations used in the albumin escape studies. Approximately 2.5 ml blood was obtained after 2 hours of infusion. ANF concentrations were determined by radioimmunoassay after extraction on a C\textsubscript{18} Sep-Pak cartridge (Millipore Corp., Milford, Mass.) and elution with 1 ml of 60% acetonitrile in 0.2% ammonium acetate. The interassay and intra-assay coefficients of variation were 15% and 6%, respectively. Recovery was 75%.

Calculations were accomplished with a spreadsheet software package. Data were analyzed with a one-way analysis of variance. Subsequent comparisons between vehicle- and ANF-infused groups were analyzed by Dunnett's test for one-sided comparisons between treatment and control means. Values of \( p<0.05 \) were considered significant. Data are expressed as mean \( \pm \) SEM.

**Results**

Circulating ANF levels in control and ANF-infused animals are indicated in Table 1. Body weight and whole-body F cell ratios were similar in the groups and are listed in Table 1. After 2 hours of ANF infusion, mean arterial pressure was significantly lower than control levels of 107±4 mm Hg only at an ANF infusion dose of 0.5 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \), which decreased mean arterial pressure to 95±2 mm Hg (\( p<0.05 \)) as illustrated in Figure 1. ANF infusion for 2

<table>
<thead>
<tr>
<th>Rat group</th>
<th>Weight (g)</th>
<th>F cell ratio</th>
<th>ANF (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>317±6 (8)</td>
<td>0.85±0.01 (8)</td>
<td>57±5 (15)</td>
</tr>
<tr>
<td>2</td>
<td>322±5 (8)</td>
<td>0.86±0.01 (8)</td>
<td>146±62 (10)</td>
</tr>
<tr>
<td>3</td>
<td>317±6 (8)</td>
<td>0.83±0.02 (8)</td>
<td>336±78 (9)*</td>
</tr>
<tr>
<td>4</td>
<td>321±5 (8)</td>
<td>0.84±0.01 (8)</td>
<td>1,232±199 (6)*</td>
</tr>
<tr>
<td>5</td>
<td>325±6 (8)</td>
<td>0.81±0.01 (8)</td>
<td>7,734±675 (8)*</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Group 1 rats were infused with saline, group 2 was infused with ANF in saline at 0.025 \( \mu \text{g} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \), group 3 with ANF in saline at 0.05 \( \mu \text{g} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \), group 4 with ANF in saline at 0.1 \( \mu \text{g} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \), and group 5 with ANF in saline at 0.5 \( \mu \text{g} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \). ANF concentrations were determined in a separate group of rats. Number of rats in each group are shown in parentheses after the value. *\( p<0.05 \) vs. vehicle infusion.
Hemodynamic and Blood Volume Effects of ANF Infusion

![Graph](http://circres.ahajournals.org/)

**FIGURE 1.** Changes in mean arterial pressure (MAP), central venous pressure (CVP), red cell volume (RCV), and plasma volume (PV) in anesthetized, nephrectomized, splenectomized rats receiving intravenous infusion of 0.9% NaCl (vehicle) or rat atrial natriuretic factor (ANF)-(99-126). n=8 per group.

hours increased LVHct from 50.7±0.3% (control) to 54.6±1% at 0.1 μg·min⁻¹·kg⁻¹ ANF infusion (p<0.05) and to 56.3±0.5% at an ANF infusion rate of 0.5 μg·min⁻¹·kg⁻¹ (p<0.05); however, lower infusion rates did not significantly affect the LVHct. The increase in hematocrit resulted from a shift in plasma volume from the intravascular space with no change in red cell volume as illustrated in Figure 1. Plasma volume decreased from control levels of 24.9±1.0 to 22.4±1.0 ml·kg⁻¹ after 2 hours of ANF infusion at 0.1 μg·min⁻¹·kg⁻¹ (p<0.05). Plasma volume decreased from 27.0±0.7 to 23.0±0.6 ml·kg⁻¹ at an ANF infusion rate of 0.5 μg·min⁻¹·kg⁻¹ (p<0.05). No change in plasma volume was observed at lower infusion doses of ANF. Despite the change in plasma volume observed at an ANF infusion rate of 0.1 μg·min⁻¹·kg⁻¹, a significant change in central venous pressure was observed only at an ANF infusion rate of 0.5 μg·min⁻¹·kg⁻¹.

The total-body albumin escape rate did not change at the lowest levels of ANF infusion but increased by 56% at an ANF infusion rate of 0.1 μg·min⁻¹·kg⁻¹ and by 127% at an ANF infusion rate of 0.5 μg·min⁻¹·kg⁻¹ (Figure 2). ANF selectively enhanced the organ albumin escape rate only at the two highest infusion rates of ANF as shown in Figure 3. At an ANF infusion rate of 0.1 μg·min⁻¹·kg⁻¹, the albumin escape rate was increased in the heart, lung, gastrointestinal tract, and muscle. At an infusion rate of 0.5 μg·min⁻¹·kg⁻¹, the albumin escape rate increased in the gastrointestinal tract, muscle, and skin, but the lungs were protected. Although the albumin escape rate per gram of tissue suggests that muscle accounts for only a small fraction of the total-body albumin escape, when total organ...
accumulation is measured, as shown in Figure 4, muscle albumin escape accounts for the highest percentage of albumin escape. Organ plasma volume is illustrated in Figure 5. Plasma volume significantly decreased in heart and muscle at an ANF infusion rate of 0.1 μg · min⁻¹ · kg⁻¹ and decreased in heart and lung at an ANF infusion rate of 0.5 μg · min⁻¹ · kg⁻¹. Organ blood volume as a percentage of total blood volume is shown in Table 2. No change in blood volume distribution was observed at any dose of ANF infusion.

Discussion

To obtain direct evidence regarding the mechanisms by which ANF shifts fluid and protein out of the vascular system will likely require studies of regional or local microcirculations. Therefore, this present study was aimed at determining the specific organs in which ANF enhances protein transfer. ANF was infused in anesthetized, anephric, and splenectomized rats for 2 hours at physiological, pathophysiological, and pharmacological doses. Plasma volume decreased, while the rate of escape of 125I-albumin from the circulation increased at ANF infusion rates of 0.1 and 0.5 μg · min⁻¹ · kg⁻¹. At a pathophysiological ANF infusion rate (0.1 μg · min⁻¹ · kg⁻¹), labeled albumin escaped mainly into the muscle and gastrointestinal tract but also significantly increased in the lung. At pharmacological levels of ANF infusion (0.5 μg · min⁻¹ · kg⁻¹), the greatest increase in escaped albumin accumulated in the tissues of the skeletal muscle, skin, and gastrointestinal tract, but not in the lungs. A similar increase in the 125I-albumin content of skeletal muscle after ANF infusion was previously reported by Winquist et al.¹⁶ in conscious rats. These findings suggest that the action of ANF to shift protein out of the circulation is not selective for various peripheral vascular beds. At high ANF infusion rates, it is likely that the lungs are protected by decreases in pulmonary pressures, as suggested by the decrease in central venous pressure.

Irrespective of the mechanism by which ANF increased the transmicrocirculatory movement of albumin, it is reasonable to assume that the increased tissue content of 125I-albumin was attended by some increase in tissue fluid as well. For instance, if ANF facilitated the transmicrocirculatory movement of 125I-albumin by diffusion or vesicular exchange, an enhancement of fluid filtration would likely occur because of the changes in microcirculatory oncotic forces. Another possibility is that ANF altered the microcirculatory hydrostatic forces in favor of filtration, and the increased transport of albumin reflected transmicrocirculatory albumin flux that was directly

**Figure 2.** Rate at which 125I-albumin escaped from the total circulation over a 2-hour period in the groups of rats featured in Figure 1. ANF, atrial natriuretic factor.

**Figure 3.** Rate at which escaped 125I-albumin (125I-ALB) accumulated in selected tissues over a 2-hour period in the groups of rats featured in Figure 1. GI, gastrointestinal tract; ANF, atrial natriuretic factor.
coupled to the outward volume flow. Finally, it is possible that ANF altered capillary hydraulic conductivity, as was observed by Huxley et al. in vessels isolated from the frog mesentery, but this was not addressed in this study. These observations do not exclude the possibility that there were markedly unequal regional differences in coupling of albumin and fluid transport; however, this is unlikely because in most tissues, convection appears to be the dominant mechanism for the transmicrocirculatory transport of macromolecules with dimensions similar to albumin.

To distinguish the $^{125}$I-albumin activity in the tissues from that in the plasma, we determined the plasma volume in each organ. The product of organ plasma volume and plasma concentration of $^{125}$I-albumin activity yielded the amount of $^{125}$I-albumin activity in the plasma; this subtracted from the total $^{125}$I-albumin activity in each organ gave the amount that accumulated in the tissues. A critical aspect of this approach is the measurement of organ plasma volume, which in turn depends on the determination of organ hematocrit. Partly because the hematocrit in the microcirculation is less than that in large vessels and partly because of albumin leakage from the vascular space, the whole-body hematocrit (measured RCV/measured PV) is less than LVHct. If the ratio of whole-body hematocrit to LVHct (F cell ratio) is known for a certain set of experimental conditions, this parameter can be used to convert LVHct to the whole-body value. This same approach can be used to convert LVHct to organ hematocrit, if the organ F cell ratio is known for each organ. To this end, the organ F cell ratios were determined in preliminary experiments, and these values were used to determine organ hematocrit in the rats included in the main study. The organ F cell ratios determined in the

**Figure 4.** $^{125}$I-Albumin activity that accumulated in tissue over a 2-hour period in selected whole organs in the rats featured in Figure 1. GI, gastrointestinal tract; ANF, atrial natriuretic factor.

**Figure 5.** Organ plasma volume during vehicle and atrial natriuretic factor (ANF) infusion at 0.1 and 0.5 $\mu$g/kg/min. Organ plasma volumes at 0.025 and 0.05 $\mu$g/kg/min were not significantly different from vehicle infusion.
preliminary studies for the three rats receiving vehicle were similar to those in the two rats receiving a pharmacological dose of ANF. In the main study, the average whole-body F cell ratio was similar in the vehicle and ANF groups (Table 1). These considerations support the assumption that ANF did not change the F cell ratio and that the data obtained in the preliminary experiments could be applied to all groups in the main study.

Circulating ANF levels in rats infused with 0.1 μg·min⁻¹·kg⁻¹ were 1,232±199 pg/ml. These levels are within the range of ANF levels previously reported from this laboratory for rats with experimental heart failure. It is interesting that at ANF levels seen in heart failure, albumin escape is enhanced in the lungs, whereas at pharmacological levels of ANF, the lung is protected from albumin escape. Although there may be differential effects of ANF on the peripheral and pulmonary vasculature, this is unlikely because no differences are seen at the lower infusion rates. It is most likely that the differential effect of ANF on the pulmonary vasculature and the peripheral circulation noted at pharmacological infusion rates of ANF are due to the overall hemodynamic effects of ANF. At the highest ANF infusion rate, central venous pressure significantly decreased, most likely reflecting a decrease in venous return. This decrease in venous return most likely resulted in a decrease in pulmonary artery pressure, as previously shown during similar infusion rates of ANF in the dog. Studies in isolated perfused guinea pig lung have suggested that ANF protects against chemically induced pulmonary edema. Whether this protective effect was partially mediated by a direct action of ANF to prevent capillary damage, as was suggested by Imamura et al., or by an action of ANF on the ratio of arterial to venous resistance, as was reported in a preliminary study in perfused dog lung lobe, remains to be investigated. From the results of our study, it might be speculated that this hormone could be a potential etiologic factor in the pulmonary edema associated with certain disease states, such as congestive heart failure. At pharmacological levels, however, ANF may be beneficial in heart failure by helping to distribute retained body fluid away from the lungs and into the innocuous areas of the interstitial spaces of skin and skeletal muscle. This last finding is in agreement with a recent study by Williamson et al., showing that ANF does not promote albumin escape in the lungs at pharmacological infusion doses. Unlike the previous study, however, we have also evaluated organ-specific albumin escape rates at pathophysiological ANF infusion doses and found that ANF does enhance albumin escape at these levels.

Finally, although not a primary aim in this study, the data confirmed earlier findings in rats with intact kidneys and spleens that ANF did not cause a major redistribution of blood volume to the splanchnic region, as shown in Table 2. The splanchnic circulation contains the greatest vascular capacitance of the circulation, and dilatation of the splanchnic capacitance vessels would be expected to cause a redistribution of blood volume into these organs, as was observed in ganglionic blocked rats. The lack of such an effect by ANF supports our contention that ANF is not a potent dilator of capacitance vessels and does not lower cardiac output via a redistribution of blood volume.

Appendix

Calculations used for deriving the equation in “Materials and Methods” for organ hematocrit are defined as follows.

Abbreviations

ORCV, organ red cell volume; OPV, organ plasma volume; OBV, organ blood volume; OHct, organ hematocrit.

Note: Volume is in milliliters. ¹²⁵I and ⁵¹Cr activities are in counts per minute; units of activity concentration are in counts per minute per milliliter.

Calculations

\[ ⁵¹\text{Cr activity per milliliter erythrocytes} = \frac{⁵¹\text{Cr activity in 0.024 ml blood sample}}{(\text{Hct blood sample} \times 0.024 \text{ ml})} \]  
\[ (A-1) \]

\[ ¹²⁵\text{I activity per milliliter plasma} = \frac{¹²⁵\text{I activity in 0.024 ml blood sample}}{(1 - \text{Hct blood sample}) \times 0.024 \text{ ml}} \]  
\[ (A-2) \]

\[ \text{ORCV} = \text{organ} ⁵¹\text{Cr activity}/⁵¹\text{Cr activity per milliliter erythrocytes} \]  
\[ (A-3) \]
OPV = organ $^{125}$I activity/$^{125}$I activity per milliliter plasma (A-4)

OBV = ORCV + OPV (A-5)

OHct = ORCV/OBV (A-6)

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References


KEY WORDS • hematocrit • serum albumin • plasma volume • congestive heart failure • rat
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