Mechanism of Morphine-Induced Shifts in Blood Volume between Extracorporeal Reservoir and the Systemic Circulation of the Dog under Conditions of Constant Blood Flow and Vena Cava Pressures

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SUMMARY The mechanism of a morphine-induced shift in blood volume between an extracorporeal reservoir and the systemic circulation of a dog under conditions of constant blood flow and vena cava pressures was investigated in 10 anesthetized dogs with the aid of right heart bypass. All blood returning to the heart was removed from the right atrial appendage and, after passing through a Starling resistor, drained by gravity into an extracorporeal reservoir. It then was pumped around a NaI(Tl) scintillation crystal, through a heat exchanger and a flowmeter, and returned directly into the pulmonary artery. The following data (mean ± SE) were obtained with the pump flow set at 80 ml/min kg−1. By the 5th minute following the administration of morphine, 4 mg/kg, arterial pressure fell from 99 ± 5 to 59 ± 6 mm Hg (P < 0.001). Reservoir volume fell by 578 ± 86 ml, and central hematocrit increased from 0.41 ± 0.02 to 0.47 ± 0.01 (P < 0.01) in 15 minutes. Plasma volume, determined by a 131I-tagged plasma tracer, decreased by 317 ± 32 ml in 15 minutes. Thus, following the administration of morphine, 58% of the decrease in reservoir volume was accounted for by fluid lost from the circulatory system. This filtration was preceded by an immediate 30% rise in the counts/min obtained from a scintillation probe positioned over the liver, suggesting a similar rise in liver volume. These counts remained elevated throughout the experiment. Ascites volume determined by an indicator dilution technique steadily increased from 78 ± 24 ml at the time of morphine administration to 276 ± 44 ml (P < 0.001) by the 60th minute following morphine. A mass balance calculated on the protein concentration of the ascites fluid suggested that the ascites produced by morphine resulted from the filtration of pure plasma. We conclude that morphine-induced decreases in extracorporeal reservoir volume at constant blood flow and vena cava pressure can be accounted for largely by blood trapped in the liver by constriction of the hepatic outflow vessels and plasma filtered at the liver sinusoids producing ascites.

Methods

Surgical Procedures

Ten mongrel dogs with a mean weight of 23.6 ± 1.2(±) kg were anesthetized with sodium thiamylal, 18 mg/kg. Anesthesia was maintained with 70% nitrous oxide in oxygen and halothane at an end-expiratory concentration of 0.83%. A tracheotomy was performed and the dog ventilated at a tidal volume and frequency appropriate for its size. A ventral laparotomy and splenectomy were then performed. The abdominal incision was not closed. A ventral thoracotomy was performed and sodium heparin (3 mg/kg) administered. The right atrium was cannulated through the atrial appendage with a wide-bore Tygon tube. Blood returning to the heart, Q, was withdrawn from the right atrium through the Tygon cannula and, after passing through a Starling resistor (Penrose tube),
was drained by gravity into an extracorporeal reservoir. A Sarns roller pump then pumped the blood around a NaI(Tl) scintillation crystal, through heat exchange unit, and a Carolina Medical square wave electromagnetic flowmeter. The blood returned to the circulation directly into the pulmonary artery via a stainless steel cannula placed in the pulmonary artery through the right ventricular outflow tract (Fig. 1). After the dog was placed on the extracorporeal circuit which had been primed with 1580–2780 ml of donor blood, an umbilical tape previously placed around the pulmonary artery was drawn tightly around the cannula, thereby preventing blood from entering the pulmonary artery except through the pulmonary arterial cannula. The Starling resistor was placed at an appropriate level, relative to the right atrium, to maintain right atrial pressure, P_{ra}, at atmospheric pressure. The pump was set to maintain a flow of 80 ml·min^{-1}·kg^{-1}.

Right atrial pressure was measured with a catheter advanced into the right atrium through the jugular vein. Aortic pressure was measured through a catheter advanced into the aorta through the femoral artery. Volume shifts between the dog and the extracorporeal reservoir were determined by measuring the pressure exerted by the column of blood in the reservoir. Body temperature was measured with a rectal thermometer and maintained at 39°C by the heat exchange unit. Arterial P_{O_{2}}, P_{CO_{2}}, and P_{O_{2}} greater than 100 mm Hg by appropriately fixing the frequency of ventilation and/or by infusing NaHCO_{3} solution. To avoid osmotic transients, no further adjustments were made once normal acid-base balance was established. That this procedure was satisfactory is attested to by the fact that pH never dropped below 7.38 for the remainder of the experiment which lasted for 60 minutes after the establishment of normal pH. During the initial period of the right heart bypass procedure, blood in a secondary reservoir (Fig. 1) was mixed continually with blood in the rest of the perfusion system (by maintaining clamps “a” and “c” open). Thus, osmotic and oncotic equilibrium was achieved between the blood of the donor and experimental animals. The secondary reservoir was necessary in the system to provide a site for the storage of nonradioactive blood during the experiment (see below).

Halothane anesthesia was terminated 10–15 minutes before the administration of morphine. When the end-expiratory concentration of halothane was reduced to 0.01–0.03%, morphine, 4 mg/kg, was administered directly into the pulmonary artery.

Arterial pressure, right atrial pressure, flow, and reservoir volume were recorded continually on an Electronics for Medicine multichannel recorder. Ten-ml samples of blood and 5-ml samples of abdominal fluid (see below) were obtained immediately before the administration of morphine and at 5, 10, 30, and 60 minutes after morphine was administered. The hematocrits were determined in triplicate immediately, read with a millimeter ruler, and averaged. After the hematocrit determinations, the blood was centrifuged at 5000 rpm for 5 minutes and the supernatant fluid was used for the determination of plasma protein concentration with an AO refractometer (model 10400) and osmolality measurements, using an Advanced Instruments osmometer. The osmolality measurements were made solely to establish the fact that no volume shifts were occurring due to osmotic pressure changes. The treatment of the abdominal fluid is described below.

Because one of the primary objectives of these experiments was to assess whether changes in plasma volume could account, in whole or in part, for the morphine-
induced translocation of blood volume between the extracorporeal reservoir and the systemic circulation under conditions of constant blood flow and vena caval pressures, we developed two independent methods to assess changes in plasma volume, one based on the dilution of a radioactive plasma tracer, the other based on changes in central hematomit. Since preliminary experiments suggested that ascites was being produced by the morphine, we also developed a nonradioactive dye dilution technique to quantify the formation of ascites. We also took advantage of the radioactive plasma tracer to assess qualitatively changes in the liver volume with an external scintillation probe.

$^{113}$In as a Plasma Tracer

A new England Nuclear generator containing 1 mCi of $^{113}$Sn on a zirconium oxide column was eluted with 0.05 N HCl and yielded about 700 $\mu$Ci of $^{113}$In in the first 4 ml of eluate. About 100 ml of venous blood were drawn from the experimental dog into 500 U of sodium heparin and centrifuged immediately at 5000 rpm for 10 minutes. Twelve to 15 ml of plasma were separated from the cells into a 20-ml plastic syringe to which sufficient $^{113}$InCl$_3$ was added with constant mixing to give about 350 $\mu$Ci of $^{113}$In-transferrin at the anticipated time of injection.

The chemical form of the injected tracer was tested in several ways. Electrophoresis on a 15-cm cellulose polyacrylate strip for 45 minutes, using 15 mA, 300 V, pH 8.6, NaBarbital (5,5'-diethylbarbituric acid) buffer showed that 100% of the activity migrated with a narrow band coincident with the $\beta$-lipoproteins, one of which is transferrin. No activity was found at the origin, where colloidal hydroxide at the time of injection. By our labeling method, all of the $^{113}$In was chelated to transferrin and that none of it existed as a soluble inorganic complex or colloidal hydroxide at the time of intravenous injection.

A citrate-phosphate-dextrose (CPD) anticoagulant which is the standard anticoagulant used for the preparation of radioisotopic plasma tracers was also tested for preparing $^{113}$In-transferrin. The CPD was mixed 15 vol/vol with whole blood but, otherwise, was treated exactly as described above for indium labeling of plasma collected in heparin. Under these conditions, we found that up to 40% of the indium formed a citrate coordination compound and was not available as a plasma protein tracer. The greater thermodynamic stability of $^{113}$In-transferrin relative to $^{113}$In-citrate means that, ultimately, all of the $^{113}$In would be bound to transferrin; however, the process is slow kinetically. Any injected $^{113}$In-citrate is rapidly excreted via the kidneys and hence lost to the experiment; therefore, CPD was not used for the plasma anticoagulant in the preparation of $^{113}$In-transferrin.

The radioactivity circulating in the dog was monitored by two 2 × 2-inch NaI(Tl) scintillation crystals. One was surrounded by 110 ml of blood in the extracorporeal circuit (Fig. 1) and the other was positioned over the liver in a right anterior oblique position normal to the midline and centered 3–5 cm below the costal margin. The blood probe was shielded with 4 inches of lead. It was impractical to shield the liver probe with more than a standard 2-inch parallel hole steel collimator with 1-cm walls; however, this probe was pointed away from any major volumes of activity, e.g., the heart or any extracorporeal reservoirs, to minimize its radiation background. The external probe was used to give a qualitative estimate of change in hepatic blood volume.

Both detectors were powered by an Ortec model 446 high-voltage supply operated at 900 V. Their output signals were collected by preamplifiers (Ortec model 276) and fed to linear amplifiers (Ortec model 490A) prior to pulse height analysis. A 60-keV window centered at the 393-keV emission of $^{113}$In was selected. The analyzer output was scaled by a home-constructed four-channel buffered scalar which drove a teletype (ASR 33). Data were printed at 1-minute intervals, and the teletype-punched paper tape output was analyzed by computer.

The $^{113}$In-transferrin complex was injected directly into the pulmonary artery at time $t = 0$. Immediately prior to the injection, clamp “c” (Fig. 1) was closed, and a sufficient quantity of untagged blood was pumped from the primary to the secondary reservoir. Clamp “a” then was closed and clamp “b” opened. The mixing pump then mixed, the blood in the primary reservoir for the rest of the experiment. A period of 15–30 minutes was allowed to elapse while control data were taken. Figure 2, which illustrates the $^{113}$In method of determining total blood volume and changes in plasma volume, is a plot of the natural logarithm of the decay-corrected counts per min-

![Figure 2](https://example.com/image2.png)
ute, $N$, obtained from the extracorporeal scintillation crystal vs. time. These counts have been corrected for radioactive decay of $^{113m}$In as follows: $\ln N = \ln N_0 + 0.00693t$, where $N_0$ is the observed counts/min, and $t$ is the minutes after injection of the $^{113m}$In-transferrin complex. The constant 0.00693 is $\ln 2/100$ min$^{-1}$, reflecting the 100-minute nuclear decay half-life of $^{113m}$In.

The total blood volume in the dog plus that in the extracorporeal circuit was determined prior to morphine injection by tracer dilution. A known volume, $\Delta V$, of untagged blood, equilibrated with the circulating blood volume prior to $^{113m}$In administration, was added to the extracorporeal system from the secondary reservoir (by opening clamp "c," Fig. 1). This diluted the concentration of radioactivity in the blood and thus caused a sharp drop in the concentration measured by the blood probe. The count rate prior to volume addition, $N_0$, and the count rate after volume addition, $N_f$, were determined by regression analysis of $\ln N$ vs. $t$ before and after the volume addition and extrapolated to the time of volume addition. The total circulating blood volume, $V$, before the addition of the untagged bolus was calculated as

$$V = \Delta V \cdot \frac{N_f}{N_f - N_i}.$$  

Equation 1 is derived in the Appendix.

In the example illustrated in Figure 2, an untagged bolus of 286 ml was added to the system at minutes 35; this caused the count rate to drop from 474,492 to 438,011 counts/min and yielded a calculated total volume of 4259 ml. This example compares very favorably with the average value of 4247 ± 125 (SEM) ml, obtained from all 10 dogs. When the known volume of the extracorporeal system was subtracted, we obtained a blood volume of 1811 ± 125 ml or 77.8 ± 5.9 ml/kg for the average dog.

To assess the accuracy of this procedure for determining total blood volumes, several successive boluses of untagged volumes were added in a number of dogs. The volume was calculated from the known total blood volume, prior to the addition, $V_i$, from the corrected count rates before and after the addition of $N_i$ and $N_f$ as follows:

$$\Delta V = V_i \cdot \frac{N_i}{N_i - N_f}.$$  

The calculated volume addition ($\Delta V$) was then compared with the known addition. Figure 3 is a plot of calculated volumes vs. known volumes. The points scatter tightly about the line of identity. Even with very small volume additions, the technique yielded excellent agreement because of the high count rates obtained from the extracorporeal scintillation crystal surrounded by 110 ml of blood. Typical count rates were about 500,000 counts/min, yielding a standard deviation for Poisson distribution of 707 counts/min or 0.14%. Since $N_i$ and $N_f$ were determined by linear regression of $\ln N$ vs. time, using a time interval of at least 10 minutes, the error was reduced even further. Thus the major source of error in this system stems not from our ability to observe changes in the concentration of the $^{113m}$In tracer but, rather, from our ability to resolve changes in reservoir volume (from which we determined the exact amount of untagged volume addition). This resolution, using Statham Db transducers, is about ±0.75% (error due to nonlinearity and hysteresis, combined). Thus, the resolution of our system is easily of the order of ±1% and could be improved further if $\Delta V$ were determined gravimetrically.

In every experiment, the slope of the plot of $\ln N$ vs. $t$ decreased after morphine administration (Fig. 2). This indicates a decrease in the total volumetric concentration of the $^{113m}$In-transferrin. If it is assumed that this decrease results from a loss of whole plasma from the intravascular space and that the total red cell volume remains constant, the total volume of plasma lost at any point in time, $\Delta V_{in}$, may be calculated as

$$\Delta V_{in} = \frac{(1 - H_o)V_o}{1 - H_o - H_o}.$$  

where $V_0$ is the corrected counting rate, $H_o$ is the hematocrit/100, $V_o$ the total volume immediately after the volume determination described above, and $N$ the corrected counting rate at the time for which $\Delta V_{in}$ is to be calculated. Justification for the major assumptions of this model will be deferred until the Discussion section. Equation 3 also is derived in the Appendix.

**Volume of Filtered Plasma, Calculated from Hematocrit Data**

If it is assumed that the total volume of red blood cells within the vascular space is constant during the course of any plasma change, it is possible to calculate any decrease in plasma volume, $\Delta V_{pl}$, from hematocrit values, as shown in the Appendix.

$$\Delta V_{pl} = V_o\left(1 - \frac{H_o}{H_i}\right).$$  

where $H_i$ is the observed hematocrit at the time of interest and $H_o$ is the hematocrit observed immediately before the administration of morphine. It is important to note that
Equations 3 and 4 present entirely independent observations of the filtered volume. Equation 3 is based on a mass balance for a tagged plasma tracer whereas Equation 4 is based on a red cell volume balance.

**Determination of Ascites Fluid**

To quantify the formation of ascites fluid, a dye dilution technique was employed. A solution of 500 mg of a fluorescent-tagged dextran of molecular weight 150,000 (Pharmacia FITC 150) was dissolved in 500 ml of Ringer’s solution. After the dog had become stabilized on bypass, a measured volume of this dye (225 ± 8 ml) was poured directly into the open abdominal cavity. The solution then was mixed by gentle external manipulation of the abdomen, and a 5-ml sample was collected via a catheter placed at the base of the cavity. Additional 5-ml samples were withdrawn at regular intervals during the experiment. Before each sample was collected, the abdomen was manipulated to mix the abdominal fluids. Immediately after collection, all samples were centrifuged at 5000 rpm for 10 minutes to remove any solids and then sealed in glass vials for later analysis of protein dye content. To detect bleeding, hematocrits were also determined on the abdominal fluids. In none of the dogs reported in this paper was an abdominal hematocrit value of greater than 3% observed.

On completion of the experiment, the abdominal samples were analyzed for protein concentration, using a refractometer (AO model 10400), and a portion was diluted 100-fold with saline solution and analyzed for dye concentration, using a Farrand Optical Mark I spectrofluorometer with the stimulation monochromator set at 494 nm and the emission monochromator at 520 nm. A sample of the original dye solution served as a reference. The response of the spectrofluorometer was found to be extremely linear at the dilutions employed here. We estimate total concentration errors to be less than 2%, mostly due to a slight electronic drift in the spectrofluorometer. Although we have no direct measure of the thoroughness of mixing in the abdominal cavity, the smooth trend of the data strongly indicates that mixing was nearly complete.

Total ascites production was calculated from the time the dye solution was poured into the abdomen. If the added dye solution had volume, \( V_o \), and concentration, \( C_o \), then the volume of ascites formed at any point in time, \( \Delta V_{as} \), is given by \( \Delta V_{as} = [(V_t C_t)/C] - V_o \), where \( C \) is the dye concentration at the time ascites volume is to be determined. Substituting the relationship \( C_t = M_d/V_o \), where \( M_d \) is the mass of dye yields,

\[
\Delta V_{as} = \frac{M_d}{C} - V_o. \tag{5}
\]

Because of sample withdrawal, \( M_d \) decreases with each sample. This loss is calculated by multiplying the sample concentration by the sample volume.

**Results**

The means and standard errors of the means for the variables measured in these experiments are presented in Figure 4 as functions of time after administration of morphine. Statistical significance was determined by the one-tail \( t \)-test for unpaired variants unless otherwise specified (9 df).

**Blood Measurements**

Morphine produced a drop in arterial pressure from 99 ± 5 to 59 ± 6 mm Hg \((P < 0.001)\) by the 5th minute; pressure then rose slowly to 80% of control in 60 minutes. Reservoir volume fell by 578 ± 86 ml by the 15th minute and remained essentially unchanged until 45 minutes, at which time there was a gradual decrease that was associated with bleeding (see Discussion). Central hematocrit increased from 0.41 ± 0.02 to 0.47 ± 0.01 \((P < 0.01)\) by the 15th minute, then remained unchanged throughout the rest of the experiment. Filtered volume (decrease in plasma volume) calculated from the \(^{113}\text{In} \) tracer (\( \Delta V_{In} \)) was 317 ± 32 ml by the 15th minute and increased slightly.
to $378 \pm 59$ ml ($P < 0.3$) in 60 minutes. Filtered volume calculated by the hematocrit method ($\Delta V_H$) was $349 \pm 58$ ml by the 15th minute and rose to $415 \pm 61$ ml ($P < 0.4$) in 60 minutes. Both methods of calculating filtered volume gave values that were not statistically different from each other ($t$-test of paired variants). This conclusion was reinforced by a linear regression of $\Delta V_H$ against $\Delta V_H$, pairing values at the appropriate time interval after morphine, and yielding a regression equation of $\Delta V_H = 12.5 + 0.905 \Delta V_H$, $r = 0.893$. Thus by the 15th minute after morphine was administered, approximately 58% of the decreased in reservoir volume could be accounted for by fluid lost from the circulatory system. The protein concentration of the abdominal fluid remained essentially unchanged from its control value of $5.2 \pm 0.2$ g/100 ml until 30 minutes ($P < 0.7$). In 60 minutes, the protein concentration of the blood had increased slightly to $5.6 \pm 0.1$ g/100 ml ($P < 0.1$).

**Change in Liver Volume**

The change in the count rate (corrected for radioactive decay) recorded from the external collimated scintillation crystal placed over the liver was $22 \pm 7$% 5 minutes after the administration of morphine, increased to $28 \pm 9$% in 15 minutes, and remained essentially unchanged for the rest of the experiment (Fig. 4). This suggests that the filtered volume was preceded by an immediate and rapid increase in liver volume. This is illustrated further in Figure 5, which presents the time course of the change in liver counts and filtered volume as a percent of their 30-minute values.

**Ascites Measurement**

Ascites volume steadily increased from $78 \pm 24$ ml at the time of morphine administration to $276 \pm 44$ ml ($P < 0.001$) in 60 minutes for a total accumulation of $198 \pm 50$ ml. The protein concentration of the abdominal fluid (instilled dye plus ascites) increased rapidly during the first 5 minutes following morphine administration from $1.1 \pm 0.2$ to $2.0 \pm 0.2$ g/100 ml ($P < 0.01$), then slowly and steadily increased to $2.7 \pm 0.2$ g/100 ml in 60 minutes. Thus, during the course of the experiment, morphine increased the protein concentration of the abdominal fluid by $1.6 \pm 0.3$ g/100 ml.

**Ascites Protein Mass Balance**

To determine the nature of the fluid producing the ascites, a protein mass balance was calculated as follows. At the time of morphine injection, there was, on the average, $303$ ml of abdominal fluid consisting of $78$ ml of ascites and $225$ ml of instilled fluorescent dye. This abdominal fluid had a protein concentration of $1.1$ g/100 ml. In 60 minutes, an additional $198$ ml of ascites had been produced, and the protein concentration of the abdominal fluid was $2.7$ g/100 ml. Thus, $303 (1.1) + 198 X = 501 (2.7)$ where $X$ is the protein concentration of the produced ascites. Solution of this equation yielded a value of $5.15$ g/100 ml for the value of $X$. Since this is nearly identical to the observed control plasma protein concentration and since the 99% confidence interval for the blood protein concentration was 4.55 to 5.85 g/100 ml, we conclude that the 198 ml of ascites produced by the morphine resulted from the filtration of essentially pure plasma.

**Discussion**

The plasma tracer selected for these experiments was $^{113m}$In-transferrin prepared in vitro. It was selected over the more traditional plasma marker, $^{125}$I-albumin, because of the lower radiation exposure to the investigator per detectable gamma emission, the increased radiation safety associated with shorter-lived nuclides, the availability of a $^{113m}$Sn/$^{113m}$In generator for our use, and the simplicity with which $^{113m}$In-transferrin can be prepared. The safe radiation practice associated with the 100-minute half-life of this nuclide was particularly advantageous to us because of the complexity of our preparation, with its potential for serious contamination.

Indium binds to transferrin as well as iron; however, $^{113m}$In-transferrin remains in the circulation and is not removed rapidly for erythrocyte production as is tracer iron from $^{59}$Fe-transferrin. The clearance of $^{113m}$In-transferrin has been compared with $^{125}$I-albumin in dogs and rabbits. The plasma clearance curves of the two tracers were parallel; however, the zero-time intercept or initial volume of distribution was $32-35\%$ greater for $^{113m}$In-transferrin than for $^{125}$I-albumin. This probably reflected the presence of colloidal hydroxide in $^{113m}$In-transferrin labeled by direct intravenous injection of acidic $^{113m}$InCl$_3$. Evidence presented earlier demonstrated that all of our injected $^{113m}$In was bound to protein and is, therefore, a valid marker for plasma volume.

The major consumptions underlying both methods of measuring changes in plasma volume were (1) that all filtered volume was pure, unfractionated plasma and (2) that the total circulating volume of red blood cells remained constant. Justification for these assumptions rests mainly with the results of the experiments themselves. The decrease in indium concentration (counts/min) which occurred after morphine administration could have occurred by either plasma loss or water absorption. If water absorption were the cause, then the hematocrit value

![Figure 5](https://example.com/figure5.png)

**Figure 5** Time course of the change in liver and filtered volumes as a percent of their 30-minute values.
would fall rather than rise as it did. This alone is strong
evidence to support the assumption that the filtered vol-
ume was plasma. This assumption is strengthened con-
siderably by the protein mass balance calculated on
the protein concentration of the abdominal fluid. This
leaves no doubt that the ascites was produced from a fluid
of protein concentration equal to that of plasma, i.e.,
plasma itself. In addition, the constancy of the plasma
proteins suggests that it was plasma that was lost.

The assumption of a constant red cell volume is harder
to document, at least for the first 45 minutes of the
experiment. Measurements of osmotic pressure and
plasma protein concentration were constant throughout
this experimental period in all dogs. Thus, red cell volume
changes due to osmotic or oncotic pressure changes seem
unlikely. Further, there was no evidence of bleeding
during this period which would result in a loss of red cell
volume. During the last 15 minutes of the experiment,
there was slight bleeding. Thus, during this period, the
total circulating red cell mass inevitably decreased and this
resulted in a slight overestimation of the calculated filtered
volumes. However, the major conclusions drawn from this
study rest on data obtained during the first 30 minutes.

Although it may not be of any consequence as far as this
study is concerned, it is nevertheless of academic interest
why bleeding commenced 45 minutes after morphine
administration (or approximately 1 hour and 45 minutes
from the start of bypass). The bleeding that we observed
is not unlike the altered hemostasis observed in patients
following cardiopulmonary bypass. Although the patho-
physiology of the altered hemostasis created by cardiopul-
monary bypass is not fully understood, there appear to be
at least two primary causes: (1) a functional platelet defect
of unclear etiology and (2) a hyperfibrinogenolytic de-
fect. We suspect that the bleeding that we observed was
produced by the same or similar mechanisms induced by
the extracorporeal bypass circuit.

The results reported herein are consistent with those
reported in the preceding paper and more accurately
define the mechanism responsible for the morphine-in-
duced translocation of blood volume which occurs be-
tween the extracorporeal reservoir and the systemic cir-
culation of a dog under conditions of constant blood flow
and vena caval pressures. When analyzed purely on the
basis of the two-compartment model of the systemic
circulation, which considers only mechanical parameters,
the mechanism for the translocated blood volume pro-
duced by morphine appeared to be an increase in volume
trapped by the effective splanchnic back pressure and/or
an increase in the unstressed vascular volume. The current
study demonstrates that at least 58% of the translocated
volume could be accounted for by plasma being filtered
from the circulatory system at the liver and eventually
finding its way into the abdominal cavity as ascites. The
rapid change in the liver volume, which increased 30% by
the 15th minute following morphine administration, sug-
gests that the remaining volume may be accounted for by
volume trapped in the liver by a constriction of the hepatic
outflow vessels.

Our conclusion that the ascites resulted from the hepatic
filtration of essentially pure plasma is in keeping with
similar conclusions of others. Greenway and Launth pre-

Appendix

In the following, all count rates are assumed to be
controlled for radioactive decay.

I. Determination of total vascular volume by dilution of a
radioactive tracer.

Since the total number of radioactive particles per unit
of blood volume at any instant of time is directly propor-
tional to the count rate per unit volume, a radioactive
particle mass balance may be determined with the substi-
tution of count rates per unit volume for particle concen-
tration. Thus, the total count rate for blood can be
calculated as the product of the total blood volume, \( V \),
and the count rate per unit volume seen by the
scintillation crystal, \( \lambda \). The total count rate is then \( \lambda \),
where \( V \) is the initial count rate. After the addition of
a given volume of untagged blood, \( \Delta V \), the count rate
will decrease from \( N_0 \) to \( N_f \), the final count rate. Since the
total count rate (reflecting the number of radioactive
particles) remains unchanged, we can equate the initial and final rates as follows: \( V(N_N/V_s) = (V + \Delta V)(N_f/V_s) \). Solving for \( V \) yields,
\[
V = \Delta V \cdot \frac{N_f}{N_i - N_f} .
\] (1)

II. Determination of plasma filtration from decrease in \(^{113m}\text{In} \) count rates.

The assumptions involved in this calculation are (1) that all filtered volume is pure, unfractionated plasma and (2) that the total circulating volume of red blood cells remains constant at the value obtained immediately prior to morphine administration. Justification for these assumptions may be found in the Discussion. The count rate prior to morphine, \( N_0 \), is proportional to the plasma fraction, \( V_{p,0}/V_0 \), where \( V_{p,0} \) and \( V_0 \) represent the plasma and total blood volumes prior to morphine. Thus,
\[
N_0 \approx \frac{V_{p,0}}{V_0} = 1 - H_0 ,
\]
where \( H_0 \) is the hematocrit prior to morphine. Similarly, the count rate at some point during the morphine-induced filtration, \( N \), is proportional to the then existing plasma fraction \( V_{p,\text{in}}/V_0 \). Therefore,
\[
\frac{N}{N_0} = \frac{V_{p,\text{in}}/V_0}{V_{p,0}/V_0} .
\]

Since both the plasma and total volumes are diminished by the amount of plasma filtered, \( \Delta V_{\text{in}} \), this may be written as
\[
\frac{N}{N_0} = \frac{(V_{p,0} - \Delta V_{\text{in}})/(V_0 - \Delta V_{\text{in}})}{V_{p,0}/V_0} .
\]

Solving for \( \Delta V_{\text{in}} \) yields
\[
\Delta V_{\text{in}} = \frac{(1 - N/N_0) V_0}{V_{p,0} - N} .
\]

Since \( V_{p,0}/V_0 = 1 - H_0 \), the above equation becomes
\[
\Delta V_{\text{in}} = \frac{(1 - N/N_0) V_0}{1 - H_0 - N/N_0} .
\] (3)

III. Determination of plasma filtration from increase in hematocrit.

Using the same assumptions described above, the volume of red cells present before morphine is given by \( V_0H_0 \), and that after morphine, by \( VH \). Equating these two volumes since red cell volume is conserved, yields \( V_0H_0 = VH \). \( V \) may be replaced by \( V_0 - \Delta V_{\text{H}} \), where \( \Delta V_{\text{H}} \) is the volume filtered (as determined from hematocrit data). Therefore, \( V_0H_0 = (V_0 - \Delta V_{\text{H}})H \), and solving for \( \Delta V_{\text{H}} \) yields
\[
\Delta V_{\text{H}} = V_0 \left( 1 - \frac{H_0}{H} \right) .
\] (4)

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