The Effects of Morphine on the Mechanical Properties of the Systemic Circulation in the Dog

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With the technical assistance of Jack Goldstein

Summary

We studied the effects of morphine on the mechanical properties of the systemic circulation in nine mongrel dogs. A right heart bypass preparation allowed the separation of venous return into splanchnic and extrasplanchnic (peripheral) flows. Each channel was drained by gravity into an external reservoir. Blood then was pumped into the pulmonary artery at a constant but adjustable rate. Venous resistances and compliances of both channels were calculated from transient and steady state volume shifts which occurred after rapid drops in splanchnic and peripheral venous pressures. Arterial pressure and changes in reservoir volume were measured. The following data, (mean ± SE) were obtained with the pump flow set at 80 ml·min⁻¹·kg⁻¹. The administration of morphine did not produce a significant change from control splanchnic compliance (0.0177 ± 0.0023 liter/mm Hg), peripheral compliance (0.0259 ± 0.0017 liter/mm Hg), or peripheral venous resistance (5.6 ± 0.6 mm Hg liter⁻¹·min⁻¹). Morphine increased splanchnic venous resistance from 13.2 ± 1.4 to 20.6 ± 2.4 mm Hg liter⁻¹·min⁻¹ (P < 0.05); it decreased the percentage of cardiac output perfusing the splanchnic channel from 33 ± 2 to 24 ± 2 (P < 0.01) and increased the percentage perfusing the peripheral channel from 67 ± 2 to 76 ± 2 (P < 0.001). Arterial pressure fell from 92 ± 7 to 59 ± 5 mm Hg (P < 0.001). Splanchnic arterial resistance decreased from 140 ± 19 to 111 ± 17 mm Hg liter⁻¹·min⁻¹ (P < 0.01) and peripheral arterial resistance fell from 68 ± 8 to 36 ± 6 mm Hg liter⁻¹·min⁻¹ (P < 0.001). Total peripheral resistance similarly declined from 51 ± 5 to 33 ± 4 mm Hg liter⁻¹·min⁻¹ (P < 0.001). Following the administration of morphine, the volume in the extracorporeal reservoir decreased by 0.508 ± 0.108 liter (P < 0.001). In four dogs before morphine and in all dogs after morphine, volume-flow relationships were determined by setting the pump to deliver five different flows (48, 64, 80, 96, and 112 ml·min⁻¹·kg⁻¹) and observing the steady state change in reservoir volume. On the average, morphine shifted the volume-flow curve by 0.423 liter to the right along the volume axis (P < 0.02) and produced a slight statistically not significant increase in the slope.

Methods

Nine mongrel dogs with a mean weight of 23.2 ± 0.4 (SE) kg were anesthetized with sodium thiamylal, 18 mg/kg, iv. During the control experiments, anesthesia was maintained with 70% nitrous oxide in oxygen and halothane at an end-expiratory concentration of 0.83%. The experimental preparation used for this study, which has been described previously, permitted separation of splanchnic and extrasplanchnic venous returns. In brief, the right atrial appendage, femoral veins, and inferior vena cava above the diaphragm were cannulated. Blood draining from the right atrium and femoral veins passed through two separate Starling resistors, joined, and then drained by gravity through an electromagnetic flowmeter (Carolina Medical) into an extracorporeal reservoir. Flow through this channel was the extrasplanchnic or peripheral flow (Qₚ). Blood draining from the isolated inferior vena cava was the splanchnic blood flow (Qₛ). After this flow passed through a separate Starling resistor and another flowmeter, it drained by gravity into the extracorporeal reservoir. The total venous return then was pumped at a constant but adjustable rate into the pulmonary artery. The extracorporeal circuit was primed with a mixture of three parts heparinized whole blood to two parts 3% Dextran 70. Splanchnic and peripheral venous flows, arterial, right atrial, inferior vena cava, hepatic venous, and portal venous pressures, and changes in reservoir volume were measured and recorded continuously. Body
temperature was measured with a rectal thermometer and maintained at 39°C by a heat exchange unit. Arterial \( P_{O_2} \), \( P_{CO_2} \), and \( pH \) were measured at half-hour intervals from the time the dog was connected to the bypass circuit. When acid-balance was abnormal, appropriate corrections were made by adjusting the frequency of ventilation and/or by infusing NaHCO₃ solution.

The compliance and venous resistance for both compartments were measured as follows. All venous pressures were initially set at 2.5 mm Hg by adjusting the level of the Starling resistor relative to the right atrium. The venous pressure of one compartment then was raised to 10 mm Hg and the other venous pressure was maintained at 2.5 mm Hg. As venous pressures were held at these values, blood volume in the extracorporeal reservoir decreased. Flow from the channel with the lower venous pressure did not change during this maneuver; therefore, it was assumed that all blood went into the compartment in which venous pressure was elevated. When transfer of blood from reservoir to dog stopped, the Starling resistor was lowered rapidly, returning the venous pressure to 2.5 mm Hg. Immediately following the decrease in venous pressure, the increase in blood volume diminished with time in the manner of a monoexponential decay curve. The time constant for venous drainage \( (R_VC) \) is the time, required for the blood volume in the external reservoir to increase by 0.63 \((V_m - V_i)\); where \( V_i \) = the initial reservoir volume (the volume when one venous pressure was elevated) and \( V_m \) = the new steady state reservoir volume when both pressures equaled 2.5 mm Hg. Since \( V_m - V_i \) is the inverse volume change to that occurring in the dog, the steady state change in reservoir volume \( (V_m - V_i) \) also could be used to calculate the compartmental compliances \( (V_m - V_i)/\Delta P_v \). Time constants and compliances \( (C) \) of both splanchnic and peripheral compartments were measured in this manner. With the time constant and compliance known, the venous resistance \( (R_v) \) of each compartment could be calculated by dividing the time constant by the compliance. The value obtained was corrected by subtracting the known hydrodynamic resistance of the extracorporeal tubing.

The effective splanchnic back pressure was measured by the method previously described. The hepatic venous pressure was elevated slowly by raising the Starling resistor until portal pressure rose. The level of the hepatic venous pressure when portal pressure began to rise was taken as the effective splanchnic back pressure \( (P'_h) \).

The upstream venous pressures for both compartments were calculated as: \( P_v = (Q_s + R_{vs}) \) \( P_{h_v} \) and \( P_p = (Q_p + R_{vp}) \) \( P_{h_p} \). \( P_v \) being the effective downstream venous pressure of the peripheral compartment. Arterial resistances for both compartments were then calculated as: \( R_{as} = (P_a - P_v)/Q_a \) and \( R_{ap} = (P_a - P_p)/Q_p \). The above variables and parameters were obtained at a constant pump flow of 80 ml·min⁻¹·kg⁻¹ before and after the administration of morphine.

In four dogs before morphine and in all dogs after morphine, volume-flow relationships were determined by setting the extracorporeal pump to deliver five different flows (48, 64, 80, 96, and 112 ml·min⁻¹·kg⁻¹) and observing the steady state changes in reservoir volume. Because of slight volume-flow hysteresis, only ascending curves will be reported.

Control 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, 4mg/kg·h⁻¹ was administered directly into the pulmonary artery. Statistical significance was determined by the \( t \)-test for paired variants unless otherwise specified.

### Results

#### General Results

Arterial pressure usually began to fall, splanchnic blood flow decreased precipitously, and the dog began to take up blood from the reservoir within 2 minutes following the administration of morphine. The decreasing splanchnic blood flow reached its nadir by about 4 minutes and then began to rise back toward control, reaching a steady state value somewhat less than control. In several dogs the extracorporeal reservoir blood volume rose slightly when splanchnic blood flow began to return toward control; however, this reversal was absent from most preparations. In some dogs portal pressure rose precipitously during the first few minutes, then returned to steady state at near initial values, suggesting a transient constriction of the hepatic outflow vessels. A new steady state usually was achieved within 10-15 minutes after the administration of morphine.

#### Arterial Parameters

Mean values of the arterial parameters are presented in Table 1. On the average, morphine reduced splanchnic arterial resistance \( (R_{sa}) \) from 140 to 111 mm Hg·l⁻¹·min and peripheral arterial resistance \( (R_{pa}) \) from 68 to 36 mm Hg·l⁻¹·min. The fall in splanchnic arterial resistance amounted to 21%, whereas peripheral arterial resistance fell 47%. Total peripheral resistance \( (TPR) \) fell by 36%, from 51 to 33 mm Hg·l⁻¹·min. Arterial pressure fell from 92 to 59 mm Hg.

#### Distribution of Cardiac Output

The average total circuit flow (cardiac output) was maintained constant by the extracorporeal pump at 1.85 liters/min. During the control period (Table 1), 33% of this flow passed into the splanchnic compartment and 67% perfused the peripheral compartment. Morphine (Table 1) produced a significant steady state decrease in splanchnic flow to 24% and a corresponding increase in peripheral flow to 76%.

#### Venous Parameters

The mean values for steady state venous parameters from all nine dogs before (control) and after morphine are presented in Table 1. On the average, morphine produced increases in splanchnic venous resistance \( (R_{sv}) \) of from 13.2 to 20.6 mm Hg·l⁻¹·min and in effective splanchnic back pressure \( (P'_h) \) of from 3.8 to 4.6 mm Hg. There was a slight decrease in splanchnic venous compliance \( (C_v) \) which was not statistically significant. Similarly, morphine
TABLE 1  The Effects of Morphine on the Mechanical Properties of the Systemic Circulation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output, Qₜ (liters/min)</td>
<td>1.85 ± 0.09</td>
<td>1.85 ± 0.09</td>
</tr>
<tr>
<td>Percent cardiac output to splanchnic compartment, Fₛ (% Qₜ)</td>
<td>32.9 ± 1.8</td>
<td>23.9 ± 2.3*</td>
</tr>
<tr>
<td>Arterial pressure, Pₐ (mm Hg)</td>
<td>92 ± 7</td>
<td>59 ± 5*</td>
</tr>
<tr>
<td>Splanchnic arterial resistance, Rₐₛ (mm Hg • liter⁻¹ • min)</td>
<td>140 ± 19</td>
<td>111 ± 17†</td>
</tr>
<tr>
<td>Peripheral arterial resistance, Rₐₚ (mm Hg • liter⁻¹ • min)</td>
<td>68 ± 8</td>
<td>36 ± 6*</td>
</tr>
<tr>
<td>Total peripheral resistance, TPR (mm Hg • liter⁻¹ • min)</td>
<td>51 ± 5</td>
<td>33 ± 4*</td>
</tr>
<tr>
<td>Splanchnic compliance, Cₛ (liter/mm Hg)</td>
<td>0.0177 ± 0.0023</td>
<td>0.0141 ± 0.0020</td>
</tr>
<tr>
<td>Peripheral compliance, Cₚ (liter/mm Hg)</td>
<td>0.0259 ± 0.0017</td>
<td>0.0259 ± 0.0010</td>
</tr>
<tr>
<td>Splanchnic venous resistance, Rᵥₛ (mm Hg • liter⁻¹ • min)</td>
<td>13.2 ± 1.4</td>
<td>20.6 ± 2.4‡</td>
</tr>
<tr>
<td>Peripheral venous resistance, Rᵥₚ (mm Hg • liter⁻¹ • min)</td>
<td>5.6 ± 0.6</td>
<td>5.8 ± 0.8</td>
</tr>
<tr>
<td>Effective splanchnic pressure, Pᵥₛ (mm Hg)</td>
<td>3.8 ± 0.4</td>
<td>4.6 ± 0.5</td>
</tr>
<tr>
<td>Portal venous pressure, Pᵥₚ (mm Hg)</td>
<td>9.9 ± 1.0</td>
<td>13.8 ± 2.1‡</td>
</tr>
<tr>
<td>Change in extracorporeal reservoir volume, ΔVₑ (liter)</td>
<td>0.508 ± 0.108*</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as means ± SEM.
* P < 0.001 compared to control.
† P < 0.01 compared to control.
‡ P < 0.05 compared to control.

produced no substantial change in the compliance or venous resistance of the peripheral compartment. Morphine, however, produced an average reduction in the extracorporeal reservoir blood volume (ΔVₑ) of 0.508 liter. Also presented in Table 1 are the values for portal venous pressure (Pᵥₑ).

Volume-Flow Relationships

Figure 1 illustrates steady state volume-flow curves from dog no. 1 obtained before and after morphine administration. In the example presented in Figure 1, morphine shifted the volume-flow curve to the right along the volume axis and slightly increased its slope. The lines are the relationships predicted by least squares linear regression. The regression equations for all volume-flow relationships are presented in Table 2. After morphine administration, volume-flow curves were obtained for all nine dogs; however, pre-morphine curves were obtained only for dogs 1–4. The regression equations obtained after morphine administration from dogs 1–4 were lumped with those obtained for dogs 5–9 when the coefficients of the regression equations from these two groups were shown not to be statistically different. On the average, morphine shifted the volume-flow curves by 0.423 liter to the right (P < 0.02, t-test for unpaired variants) and produced a slight, although not statistically significant, increase in the slope (Table 2).

Discussion

The preparation used for this study permitted isolation of the splanchnic and extrasplanchnic vascular beds and, thus, allowed our findings to be analyzed in terms of a two-compartment lumped parameter model of the systemic circulation which conceptually divides the systemic circulation into parallel splanchnic and peripheral (extrasplanchnic) channels. Each compartment of this model consists of a single elastic locus which is perfused through a single equivalent arterial resistance, Rₐ, and drained through a single equivalent venous resistance, Rᵥ. The distinguishing characteristic of each compartment is its time constant, T, which is the product of the compartmental venous resistance and compliance (RᵥCᵥ). Flow through this model can be summarized mathematically by the following general expression:

\[ Qᵥ = \frac{1}{FₛFₛ + FᵥFᵥ} \left[ (V - V₀) - PᵥₚCᵥ - PᵥₚCᵥ \right], \]  

where \( Qᵥ \) is the total venous return, \( Fₛ \) and \( Fᵥ \) are the respective fractions of venous return from the splanchnic and peripheral channels, \( V \) is the total vascular volume, and \( V₀ \) is the total unstressed vascular volume. This equation for the venous return for the two-compartment
The volume-flow relationships presented in Figure 1 and Table 2 are actual experimental determinations of the general expression for flow in the two-compartment model except that the time constant is calculated by weighing the individual compartmental time constants with the respective flow fractions, and the volumes sequestered in each channel due to the elevated back pressures at the downstream venous ends of the channels are subtracted from the total stressed vascular volume, \( V \). This equation is required if the time constants of the two compartments are unequal; otherwise, the equation would reduce to that for a single channel model. The fact that the splanchic channel time constant \( R_{\text{SC}} \) was greater than the peripheral channel time constant \( R_{\text{P}} \) by a factor of nearly 2 supports the validity of the two-compartment model in interpreting the results obtained in this study.

The decrease in arterial blood pressure at constant blood flow that was produced by morphine can be accounted for by a dilatation of the systemic blood vessels between the aorta and compliant areas. This is supported by the decrease in both \( R_{\text{a}} \) and \( R_{\text{vp}} \). The mechanism by which morphine decreased reservoir volume at constant blood flow and vena caval pressure is, however, not as easily delineated.

The volume-flow relationships presented in Figure 1 and Table 2 are actual experimental determinations of the general expression for flow in the two-compartment model as presented in Equation 1. Morphine produced an increase in the slope of this volume-flow curve and shifted it to the right along the volume axis. The increase in the slope of the volume-flow relationship is explicable in terms of the redistribution of cardiac output away from the long time constant area, \( \tau_a \) (decreasing \( F_a \)), in favor of the short time constant area, \( \tau_p \) (increasing \( F_p \)). The shift in the curve, if interpreted purely on the basis of changes in mechanical properties (Equation 1), suggests an increase in the volume trapped by the back pressures \( P_{\text{hv}} \) and \( P_{\text{vp}} \) and/or an increase in the unstressed vascular volume. Based on our measured values, it would appear that neither the volume trapped by the effective splanchic nor the peripheral back pressures \( P_{\text{hv}} \) and \( P_{\text{vp}} \), respectively) was of any consequence. This, however, is probably misleading with respect to the trapped splanchic volume, since our method of assessing the effective splanchic back pressure can measure only the lowest back pressure. This is because we determined the effective splanchic back pressure by observing the level of the hepatic venous pressure at which portal pressure began to respond to gradually increased hepatic pressure. Since parallel channels undoubtedly exist, the pressure observed would correspond to the lowest back pressure in any channel. Thus there could have been and probably was an increase in the back pressure in parallel channels. This also could account for the 4 mm Hg rise in portal pressure we observed (Table 1).

We were only able to infer, on the basis of Equation 1, that possible causes for the shift to the right in the volume-flow curve and the decrease in reservoir volume include an increase in trapped volume and an increase in unstressed vascular volume. However, a mechanism unrelated to the direct mechanical effects of morphine (i.e., fluid filtration) also could affect the volume translocation produced by morphine. Different methods were, therefore, needed to gain insight into the detailed mechanism(s) responsible for the shift in the volume-flow curve and the decrease in extracorporeal reservoir volume produced by morphine. The results of another series of experiments using different techniques which supplied these details are presented in the following paper.

In summary, this study reaffirmed the observation of Henney et al. that, under conditions of constant blood flow and vena caval pressures, large doses of morphine decrease arterial blood pressure and produce a translocation of a significant volume of blood from an external reservoir to an experimental animal. We demonstrated for the first time a decrease in splanchic blood flow, an increase in splanchic venous resistance, an increase in
the splanchnic back pressure, and an increase in portal venous pressure following the administration of morphine. The exact mechanism for the volume shift, however, remained undefined.

References

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doi: 10.1161/01.RES.42.4.474

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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