# The Cardiovascular Effects of Morphine

## THE PERIPHERAL CAPACITANCE AND RESISTANCE VESSELS IN HUMAN SUBJECTS

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ABSTRACT To evaluate the effects of morphine on the peripheral venous and arterial beds, 69 normal subjects were evaluated before and after the intravenous administration of 15 mg morphine. Venous tone was determined by three independent techniques in 22 subjects. The venous pressure measured in a hand vein during temporary circulatory arrest (isolated hand vein technique) fell from 20.2±1.4 to 13.4±0.9 mm Hg ($P < 0.01$) 10 min after morphine, indicating that a significant venodilation had occurred. With the acute occlusion technique, morphine induced a reduction in forearm venous tone from 12.8±1.1 to 7.9±2.3 mm Hg/ml/100 ml ($P < 0.01$). Although forearm venous volume at a pressure of 30 mm Hg (VV[30]) was increased from 2.26±0.17 to 2.55±0.26 ml/100 ml, measured by the equilibration technique, the change was not significant ($P > 0.1$). Of note is that the initial reaction to morphine was a pronounced venoconstriction, demonstrated during the first 1–2 min after the drug. (Isolated hand vein pressure increased to 37.2±5.4 mm Hg, $P < 0.01$). This rapidly subsided, and by 5 min a venodilation was evident. Morphine did not attenuate the venoconstrictor response to a single deep breath, mental arithmetic, or the application of ice to the forehead when measured by either the isolated hand vein technique or the equilibration technique.

To evaluate the effects of morphine on the peripheral resistance vessels in 47 normal subjects, forearm blood flow was measured plethysmographically before and 10–15 min after the intravenous administration of 15 mg of morphine. Although mean systemic arterial pressure was unchanged, forearm blood flow increased from 2.92± 0.28 to 3.96±0.46 ml/min/100 ml ($P < 0.01$), and calculated vascular resistance fell from 42.4±5.2 to 31.6±3.2 mm Hg/ml/min/100 ml ($P < 0.01$). When subjects were tilted to the 45° head-up position, morphine did not block the increase in total peripheral vascular resistance that occurs; however, it did significantly attenuate the forearm arteriolar constrictor response (before morphine, + 25.7±5.4; after morphine, + 13.7±5.3 mm Hg/ml/min/100 ml, $P < 0.05$). However, morphine did not block the post-Valsalva overshoot of blood pressure, nor did it block the increase in forearm vascular resistance produced by the application of ice to the forehead. Similarly, morphine did not block the arteriolar or venoconstrictor effects of intra-arterially administered norepinephrine.

Morphine infused into the brachial artery in doses up to 200 μg/min produced no changes in ipsilateral forearm VV[30], forearm blood flow, or calculated forearm resistance. Intra-arterial promethazine, atropine, and propranolol did not block the forearm arteriolar dilator response to intravenous morphine; however, intra-arterial phentolamine abolished the response. These data suggest that in human subjects, morphine induces a peripheral venous and arteriolar dilation by a reflex reduction in sympathetic alpha adrenergic tone. Morphine does not appear to act as a peripheral alpha adrenergic blocking agent but seems to attenuate the sympathetic efferent discharge at a central nervous system level.

## INTRODUCTION

Morphine is one of the most useful drugs available for treating patients with acute pulmonary edema (1–4) and

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relieving the pain of acute myocardial infarction (5–9). Although respiratory depression is acknowledged as an important side effect of the drug, the unstressed human cardiovascular system appears to be little affected by the usual clinical doses of morphine (5–18). While much research has been done on the circulatory effects of morphine, there still exists considerable uncertainty regarding its precise mechanism of action. Some of the difficulty in interpretation of results may involve differential species responsiveness and the use of large pharmacologic doses. Despite certain limitations of previous studies, it is likely that the stressed cardiovascular system in man compensates less well after the administration of morphine (12, 13). Thus, orthostatic hypotension has been cited as a prominent side effect (12). A number of possibilities might explain this phenomenon. Morphine might alter any portion of the reflex arc from peripheral mechanoreceptor perception of hypotension through central nervous system integration to the usual effector responses of tachycardia, peripheral arteriolar constriction, and possibly venoconstriction. It has been suggested by animal studies that morphine does produce a venodilation that leads to a peripheral pooling of blood, and that this is the mechanism by which morphine improves pulmonary edema (2, 16, 18). Further, numerous studies have been done on the effects of morphine on the peripheral resistance vessels; however, considerable conflict still exists regarding the direction, magnitude, and mechanism of the response (2–19). Therefore, the purpose of the studies to be presented in this report was to evaluate the indirect and direct effects of morphine on the peripheral venous and arterial systems in human subjects. Preliminary reports of these studies have been previously presented (20–22).

## METHODS

Studies were performed on 69 normal subjects, inmate volunteers of the California Medical Facility and patients admitted to the Sacramento Medical Center, who were found on complete cardiovascular evaluation to have minimal or no cardiovascular disease. All studies were reviewed and approved by the Chancellor's Advisory Committee on Physiologic Studies Involving Human Subjects, an institutional review board of the California Medical Facility, and by a separate noninstitutional peer review committee of the Solano Institute for Medical and Psychiatric Research, a group that administers all inmate research. To minimize any possible acute or chronic psychological effects that might be produced by intravenous narcotic administration, the subjects were told they would receive a placebo and/or one of five drugs commonly given to patients with heart disease: aminophylline, digoxin, furosemide, morphine, or phenobarbital. However, informed consent was obtained in all circumstances for the administration of all five possible drugs. The subjects received only morphine and/or a placebo but were not informed as to whether morphine or another agent was given. The subjects ranged in age from 21 to 49 yr and were studied on one occasion, recumbent with the arms elevated above heart level.

Room temperature for these studies was maintained between 66 and 68°F. The subjects were studied without outer clothing but were covered to mid chest with a cotton sheet. This was to insure that the subjects were comfortable but cool. We specifically did not want to induce venodilation or arteriolar dilation by having the subjects in a warm environment (23). A single strand mercury-in-rubber strain gauge (24) was utilized for measurements of forearm venous tone and blood flow as described below. It was balanced with a Wheatstone's bridge (Parks Electronics Laboratory, Beaverton, Ore.) and was calibrated by stretching to known percents of resting lengths at 10 g of tension. The gauge was applied to mid forearm at a tension of 10 g. Venous and arterial pressures were measured with Statham P23Db pressure transducers (Statham Instruments, Inc., Oxnard, Calif.), and recordings were made with a Hewlett-Packard Model 4560 optical recorder with a rapid developer (Hewlett-Packard Co., Palo Alto, Calif.). Respirations were measured with a pneumograph. The changes in the variables recorded were analyzed statistically with the paired Student *t* test.

### Evaluation of venous tone

In 14 subjects, morphine sulfate (15 mg diluted in 10 ml of saline) was given slowly intravenously over 2 min, and changes in venous tone were determined by three methods.

*Isolated hand technique.* In 11 subjects, the isolated hand technique was utilized to evaluate directional changes in venous tone (25–27). A 21-gauge scalp vein needle was inserted into a vein on the dorsum of the hand, after which pressure was continuously monitored. The circulation to the hand was arrested for periods up to 15 min by inflation of a wrist cuff to suprasystolic pressure. Care was taken to place the hand at a level that would insure that the venous pressure in the isolated hand would plateau near 20 mm Hg after the initial transient changes in hand vein pressure after inflation of the wrist cuff had subsided. Since the venous volume of the hand is held constant with this technique, any subsequent changes in venous pressure reflect changes in venous tone. After injection of morphine, the changes in hand vein pressure were followed for 10 min, after which the subjects were asked to take a single deep breath to evaluate venous reactivity.

Before the injection of morphine, the changes in hand vein pressure were evaluated similarly for a similar period of time after an injection of 10 ml of saline. All intravenous injections were performed through a catheter placed in the contralateral antecubital vein.

*Acute occlusion technique.* In six subjects, venous tone was evaluated by the acute occlusion technique (28). With this technique, a 13-cm-wide blood pressure cuff on the upper arm was rapidly inflated to 30 mm Hg for 10–15 s. The rate of increase in volume of the elevated forearm, as measured with the mercury-in-rubber strain gauge plethysmograph, was related to the rate of increase in venous pressure, as determined through a 19-gauge catheter placed percutaneously into a large superficial vein at mid forearm. The rate of change of pressure divided by the rate of change of volume was used as an index of venous tone. In all instances, a wrist cuff was also inflated to suprasystolic pressures for 1 min before any determinations (29). 6–10 readings of venous tone were averaged before and 12–15 min after the administration of morphine.

*Equilibration technique.* The equilibration technique was the third procedure by which venous tone was measured

(23, 27, 30). This technique consists of rapidly inflating the upper arm cuff to 30 mm Hg for 3 min to allow the pressure in the veins to equilibrate with cuff pressure. The venous volume of the forearm after equilibration at 30 mm Hg (VV[30]) [1] is an index of venous tone. It is important with this technique to isolate the hand from the circulation similarly by the application of a wrist cuff to suprasystolic pressure (29) as well as to have the forearm significantly elevated above heart level to insure that the veins in the forearm are collapsed and are at a pressure of less than 1 mm Hg (27). Two measurements of venous tone by this technique were averaged before the administration of morphine and 12–15 min after the drug was given.

*Venous responses to reflexogenic stimuli and intra-arterial norepinephrine.* Venous reactivity was evaluated by the isolated hand and equilibration techniques by the utilization of three venoconstrictor interventions before and 15–20 min after the administration of morphine. The interventions utilized were the sudden voluntary inflation of the lungs by a single deep breath, the performance of mental arithmetic for 1 min, and the application of ice to the forehead for 1 min, as previously described (27).

In four subjects, a PE 10 catheter was passed retrograde to the midbrachial artery through a 20-gauge Cournand needle inserted in the antecubital area, and then the needle was removed (27). Heparinized saline (3,000 U/liter) was infused at 0.247 $cm^3$/min with a Harvard infusion pump (Harvard Apparatus Co., Inc., Millis, Mass.) during the control period before the infusion of drugs. The venous volume of the forearm was determined by the equilibration technique during the ipsilateral intra-arterial infusion of norepinephrine at 0.05, 0.1, and 0.2 μg/min for 5-min periods before and after intravenous morphine.

*Venous responses to intra-arterial morphine.* In four separate individuals, the VV[30] of the forearm was similarly determined before and during the intra-arterial administration of morphine at rates of 50, 100, and 200 μg/min for 5-min periods.

## Evaluation of arteriolar tone

Forearm blood flow was measured by the venous occlusion technique with a single-strand mecury-in-rubber strain gauge plethysmograph as previously described (24, 31–33). A 20-gauge Teflon intra-arterial needle was inserted in the contralateral radial artery for the measurement of systemic blood pressure, and forearm vascular resistance was calculated. Measurements of forearm blood flow and calculated vascular resistance were averaged from 10 to 12 readings before and 10–15 min after the intravenous administration of 15 mg of morphine in 10 ml, given slowly over 2 min through a catheter in the contralateral antecubital vein to 33 subjects. In six subjects, before morphine injection, 10 ml of saline was infused intravenously and forearm dynamics were measured 10 min later. In all instances, the hand was excluded from the circulation, as described above (29).

*Arteriolar responses to reflexogenic stimuli and intra-arterial norepinephrine.* In five subjects, the morphine was administered through a catheter passed percutaneously from the antecubital vein to the superior vena cava, which was also used for the determination of central venous pressure. In these subjects, forearm blood flow, central venous pressure, and cardiac output, determined in duplicate by the dye dilution technique, were measured before and during 45° head-up tilt. Measurements were made between the 3rd and 6th min of head-up tilt. Similar studies were performed 15–20 min after the intravenous administration of morphine.

In eight subjects, phasic arterial pressure was measured before, during, and after the forced expiration against a resistance of 40 mm Hg for a period of 10 s, the Valsalva maneuver. The increase in systolic blood pressure above control after release of the Valsalva maneuver was compared before and 12–15 min after the administration of morphine. In eight subjects, the changes in forearm blood flow, mean systemic arterial pressure, and calculated forearm vascular resistance were evaluated during application of ice to the forehead for a period of 1 min before and 12–15 min after the intravenous administration of morphine.

In four additional subjects, norepinephrine was infused intra-arterially as described above, at a rate of 0.05, 0.1, and 0.2 μg/min before and 15 min after the intravenous administration of 15 mg of morphine. The maximum rate of volume infused was no greater than 0.494 ml/min.

*Arteriolar response to intra-arterial morphine.* In five subjects, morphine was infused intra-arterially as described above at a rate of 50, 100, and 200 μg/min, and forearm blood flow was measured from the 3rd to 5th min of infusion.

*The effects of alpha and beta adrenergic, cholinergic, and histaminergic blockade on morphine-induced changes in forearm arteriolar tone.* In 27 subjects, forearm blood flow was measured bilaterally, simultaneously with comparably balanced plethysmographs. In 11 of these subjects, phentolamine (2 mg) was injected intra-arterially in one brachial artery. After the initial direct phase of dilation and stabilization of the blood flow at a new higher alpha adrenergically blocked level, eight control readings of forearm blood flow were averaged, after which 15 mg morphine was administered intravenously. The changes in forearm blood flow were evaluated 10 min after the administration of morphine. At that time, it had been demonstrated that the forearm arteriolar constriction during application of ice to the forehead was significantly attenuated, and the response of lower limb resistance vessels to a 1-μg injection of norepinephrine was abolished (33).

Similarly, one forearm was treated intra-arterially with either 10 mg promethazine (six subjects), 0.5 mg atropine (seven subjects), or 2 mg propranolol (three subjects), after which morphine 15 mg was given intravenously; measurements were made bilaterally 10 min later. This dose of promethazine abolished the 19% decrease in forearm vascular resistance produced by intravenous histamine (0.004 mg/kg). Atropine attenuated the arteriolar dilation induced by intra-arterial edrophonium (1 mg) by 70%. The arteriolar dilation produced by isoproterenol (0.2 μg/min) was reduced by 95% by this dose of propranolol.

In one subject, amyl nitrite was administered after phentolamine blockade of one forearm, and in three subjects it was administered after morphine had been given intravenously after intra-arterial phentolamine.

## RESULTS

*Effects of morphine on venous tone.* With the intravenous administration of morphine, characteristic changes occurred in venous tone, as measured by the isolated hand vein technique. Hand vein pressure, which was 20.2±1.4 mm Hg (SEM) initially, rose to 37.2±5.4

[1] *Abbreviations used in this paper:* VV[30], venous volume of forearm after equilibration at 30 mm Mg.

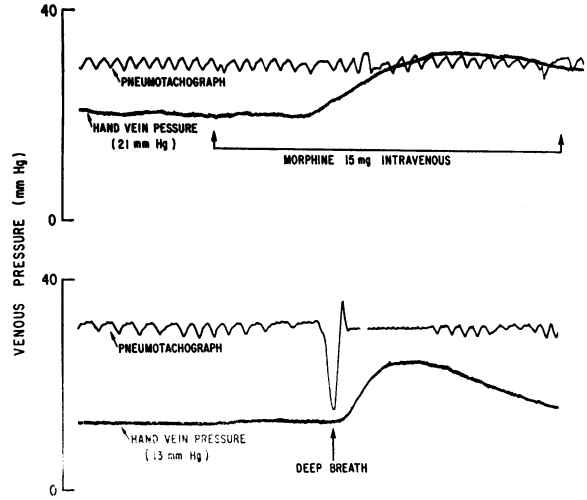


FIGURE 1 The effects of morphine on venous tone as determined by the isolated hand vein technique. The venous pressure tracing is that recorded from a superficial vein of the dorsum of the hand subjected to circulatory arrest by the inflation of a wrist cuff to suprasystolic pressure. The increase in venous pressure during the 2 min during which morphine was infused intravenously indicates that a venoconstriction has occurred. The reduction in hand vein pressure from 21 to 13 mm Hg recorded 10 min after the injection of morphine indicates that the drug induced a reflex venodilation. The increase in hand vein pressure with a single deep breath as recorded by a pneumotachograph reflects the fact that the hand vein is still capable of venoconstriction with an appropriate stimulus.

mm Hg during the 2 min of administration of the drug ($P < 0.01$). By 5 min, the venous pressure fell to 13.9± 0.8 mm Hg, a plateau that persisted until 10 min, when the pressure was 13.4±0.9 mm Hg ($P < 0.01$) (Figs. 1 and 2). At this time, ventilatory rate decreased by 3–4 breaths/min. With a taking of a single deep breath 10 min after the administration of morphine, the venous

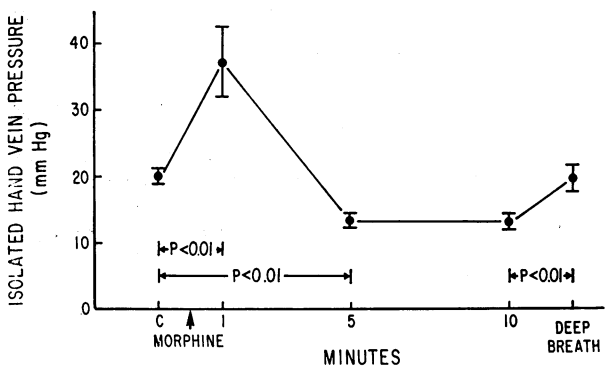


FIGURE 2 Sequential changes in pressure in an isolated hand vein (±SEM) at 1 min, 5 min, and 10 min after the intravenous infusion of morphine and after the taking of a single deep breath. Brackets and $P$ values indicate statistical comparison between pairs of data.

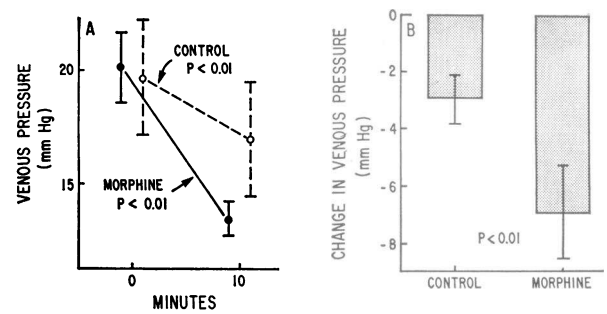


FIGURE 3 A: The fall in venous pressure (±SEM) in the isolated hand vein before and 10 min after the intravenous administration of saline (control, open circles, dash line) and after the administration of morphine (closed circle, solid line). B: Comparison between the change in pressure within an isolated hand vein after saline administration (control) and after the intravenous administration of morphine. $P$ values indicate the level of significance between paired comparisons.

pressure in the isolated hand rose to 19.9±1.9 mm Hg ($P < 0.01$) (Figs. 1 and 2). When 10 ml of saline was injected intravenously before the administration of morphine, an initial increase in venous pressure was not seen in the isolated hand; however, venous pressure did fall significantly from 19.7±2.5 mm Hg to 16.8±2.2 mm Hg ($P < 0.01$) at 10 min (Fig. 3A). Of importance is that the fall in venous pressure after the saline control (− 2.9±0.9 mm Hg) was significantly less than that after morphine (− 6.9±1.6 mm Hg, $P < 0.01$) (Fig. 3B).

Venous tone measured by the acute occlusion technique went from 12.8±1.1 mm Hg/ml/min/100 ml to 7.9±2.3 mm Hg/ml/min/100 ml 12–15 min after intravenous morphine in six subjects ($P < 0.01$) (Fig. 4A). When the venous volume of the forearm was studied by the equilibration technique, there was a slight but insignificant increase in the VV[30] from 2.26±0.17 to 2.55±0.26 ml/100 ml ($P > 0.1$) (Fig. 4C).

*Venomotor responses to reflexogenic stimuli, intra-arterial norepinephrine, and intra-arterial morphine.* Venomotor reactivity was evaluated by the use of three venoconstrictor stimuli; the taking of a single deep breath, the performance of mental arithmetic, and the application of ice to the forehead. The venomotor reflexes were not inhibited after the administration of morphine, but rather, the decrease in venous volume as measured with the equilibration technique (Fig. 5A) was actually enhanced ($P < 0.05$). Whereas venomotor activity appeared to be greater after morphine with the other stimuli, no significant change was noted with the equilibration technique (Fig. 5B and C). Venomotor reactivity was also evaluated by the isolated hand vein technique. The increase in venous pressure in the isovolumic hand to the three venoconstrictor stimuli was

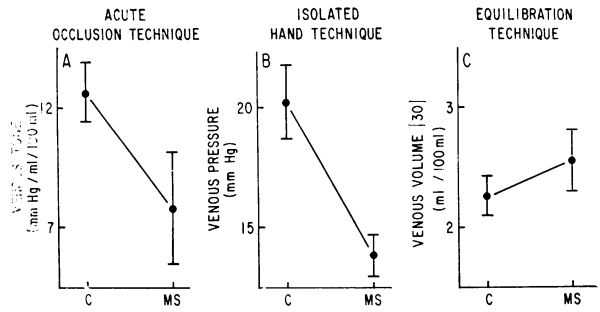


FIGURE 4 Morphine-induced changes in venous tone (±SEM) measured by three separate methods. C, control; MS, morphine. A: In the acute occlusion technique, the ratio of the rate of change in venous pressure to the rate of change of venous volume during temporary venous occlusion is taken as an index of venous tone. $n = 6$, $P < 0.01$. B: In the isolated hand technique, the changes in venous pressure in a vein on the dorsum of the isovolumic hand during circulatory arrest is an index of venous tone. $n = 11$, $P < 0.01$. C: With the equilibration technique, the change in venous volume at a constant venous pressure of 30 mm Hg is taken as an index of venous tone. $n = 14$, $P > 0.1$.

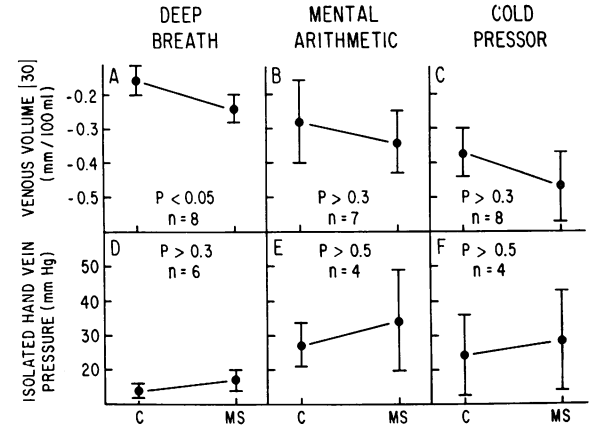


FIGURE 5 Change in venous tone (±SEM) as measured by the equilibration technique (A, B, and C) and the isolated hand vein technique (D, E, and F) with the introduction of three venoconstrictor stimuli: A and D, the taking of a single deep breath; B and E, the performance of mental arithmetic; and C and F, the application of ice to the forehead (cold pressor). $P$ values indicate the level of significance between paired comparisons and $n$ refers to the number of subjects studied.

not significantly different before or after the administration of morphine (Fig. 5D, E, and F).

When norepinephrine was infused into the brachial artery at doses of 0.05, 0.1, and 0.2 μg/min, the venous volume fell from a control of 2.17±0.22 to 1.94±0.17, 1.91±0.16, and 1.51±0.11 ml/100 ml ($P < 0.01$) before the administration of intravenous morphine. After morphine, VV[30] fell from 2.66±0.65 to 1.80±0.13, 1.73±0.17, and 1.43±0.12, respectively, with intra-arterial norepinephrine ($P < 0.01$); these responses were unaltered by morphine ($P > 0.5$). When morphine was infused intra-arterially, venous volume went from 1.98±0.21 to 1.93±0.31, 2.07±0.30, and 2.07±0.30 when the dose of morphine was 50, 100, and 200 μg/min. No significant changes in venous volume were seen at any dose of intra-arterial morphine ($P > 0.5$).

*Effects of morphine on arteriolar tone.* 10 min after the intravenous administration of morphine, mean systemic arterial pressure was unchanged. However, forearm blood flow increased from 2.92±0.28 to 3.96±0.46 ml/min/100 ml ($P < 0.01$), and forearm vascular resistance was reduced from 42.4±5.4 to 31.6±3.2 mm Hg/ml/min/100 ml ($P < 0.01$) (Fig. 6). When the placebo effect from the injection of saline was determined in six subjects before the administration of morphine, no significant change was seen in forearm vascular resistance (56.2±9.9 to 62.2±10.1 mm Hg/ml/min/100 ml, $P > 0.5$).

*Arteriolar reactivity to reflexogenic stimuli, intra-arterial norepinephrine, and intra-arterial morphine.* During 45° head-up tilt, mean systemic arterial pressure fell 1.4±2.5 mm Hg, central venous pressure fell 2.7±0.9 mm Hg, calculated forearm vascular resistance increased 25.7±5.4 mm Hg/ml/min/100 ml, and calculated total peripheral resistance increased 435±163 dyn

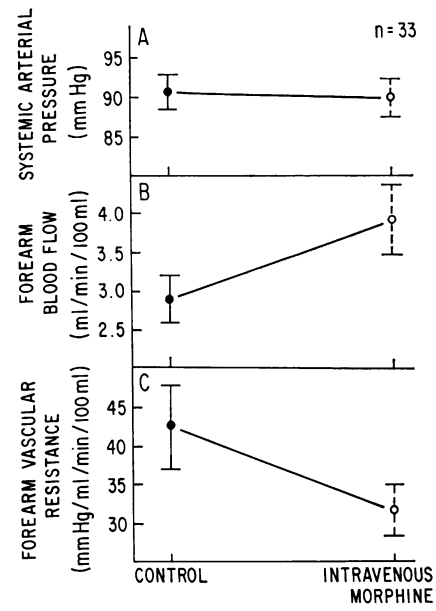


FIGURE 6 The effects (±SEM) of intravenous morphine on (A) systemic arterial pressure, $P > 0.3$. (B) forearm blood flow, $P < 0.01$. (C) forearm vascular resistance $P < 0.01$. $P$ values indicate the level of significance between comparisons and $n$ indicates the number of subjects studied.

s $cm^{-5}$. When head-up tilt was repeated after the intravenous administration of morphine, the changes which occurred in blood pressure, central venous pressure, and calculated peripheral vascular resistance were similar to those observed before the administration of morphine (Figs. 7A, B, and C). However, the increase in forearm vascular resistance with tilt was significantly less after morphine (+13.7±5.3 mm Hg/ml/min/100 ml) than before morphine ($P < 0.05$) (Fig. 7D). The increase in systolic blood pressure after the termination of forced expiration against increased airway resistance (the Valsalva blood pressure overshoot) was 16.8±4.1 mm Hg before morphine and was 15.1±2.4 mm Hg after the administration of morphine ($P > 0.4$). The increase in forearm vascular resistance after the application of ice to the forehead was 49.3±21.9 mm Hg/ml/min/100 ml before morphine and 33.5±10.2 mm Hg/ml/min/100 ml after morphine ($P > 0.5$).

Before morphine, intra-arterial norepinephrine in a dose of 0.05, 0.1 and 0.2 μg/min increased forearm vascular resistance from 33.6±9.8 to 44.5±14.2, 62.0±22.8, and 63.0±20.3 mm Hg/ml/min/100 ml ($P < 0.01$). After the intravenous administration of morphine, the changes in forearm vascular resistance induced by intra-arterial norepinephrine were similar (from 26.1±6.4 to 38.1±8.9, 49.8±13.7, and 61.7±17.5 mm Hg/ml/min/100 ml, $P < 0.01$); these responses were unaltered by morphine ($P > 0.2$).

In five subjects, the brachial intra-arterial administration of morphine at doses up to 200 μg/min produced no detectable change in ipsilateral forearm blood flow or calculated forearm vascular resistance (Fig. 8).

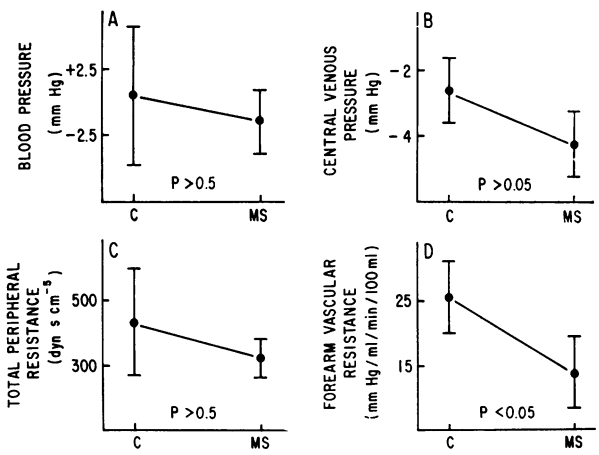


FIGURE 7 Hemodynamic changes with 45° head-up tilt. A: The change in blood pressure with tilt before morphine (C) compared to the change in blood pressure with tilt after morphine (MS) (±SEM). $P$ values indicate level of significance between comparisons. B, C, and D represent the changes in central venous pressure, total peripheral vascular resistance, and forearm vascular resistance during head-up tilt before and after the injection of morphine.

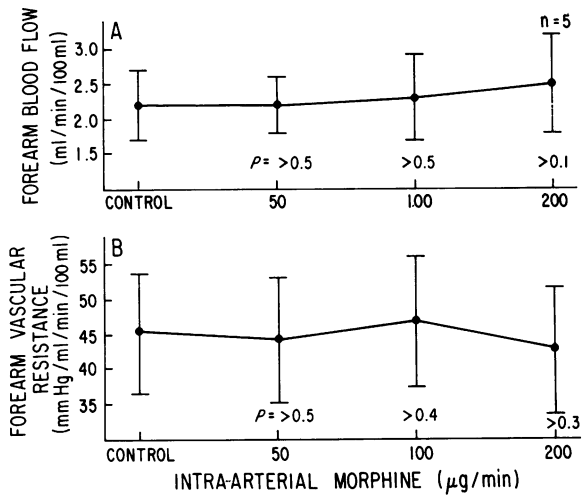


FIGURE 8 The changes in forearm blood flow (A) and forearm vascular resistance (B) (±SEM) at rest and during the intra-arterial infusion of morphine. $P$ values indicate the level of significance and $n$ indicates the number of subjects studied.

*Effects of morphine on arteriolar tone in the presence of alpha and beta adrenergic, cholinergic, and histominergic blockade.* When forearm vascular resistance was evaluated bilaterally after alpha adrenergic blockade of one forearm with intra-arterial phentolamine, intravenous morphine reduced forearm vascular resistance from 32.1±5.2 to 14.5±3.3 ($P > 0.01$) in the control forearm (Fig. 9A). However, in the phentolamine-treated forearm, forearm vascular resistance went from 13.7±2.6 to 12.6±3.0 mm Hg/ml/min/100 ml, a change that was not significant ($P > 0.1$) (Fig. 9B). When forearm vascular resistance was calculated bilaterally in subjects who received promethazine intra-arterially in one forearm, intravenous morphine produced a significant reduction in forearm vascular resistance in both the control forearm (Fig. 10A, $P < 0.01$) and the promethazine-treated forearms, (Fig. 10B, $P < 0.05$). When forearm vascular resistance was evaluated bilaterally in subjects who had received atropine intra-arterially in one forearm, morphine produced a significant reduction in forearm vascular resistance in the control forearm (Fig. 10C, $P < 0.01$) as well as a reduction in forearm vascular resistance in the atropine-treated forearm (Fig. 10D, $P < 0.01$). Similarly, morphine significantly reduced vascular resistance in both the propranolol-blocked forearm 26.5% ($P < 0.05$) and contralateral unblocked forearm 19.2% ($P < 0.05$).

Amyl nitrite reduced forearm vascular resistance, measured at the time of peak tachycardia response, from 18.0 to 9.9 mm Hg/ml/min/100 ml in the phentolamine-

blocked forearm on one individual and increased resistance in the control forearm (from 22.3 to 33.0 mm Hg/ml/min/100 ml). Similarly, after morphine had reduced forearm vascular resistance in the control forearm of three subjects by 23%, amyl nitrite produced an additional, significant 28% increase in forearm vascular resistance. In the alpha-adrenergically blocked forearm, intravenous morphine had little effect (from 15.5 to 14.8 mm Hg/ml/min/100 ml); whereas amyl nitrite induced a reduction in forearm vascular resistance to 8.8 mm Hg/ml/min/100 ml.

## DISCUSSION

*Morphine and venous tone.* In this study, three independent methods were used to evaluate changes in venous tone produced by intravenous morphine. With the isolated hand technique, the volume of the hand is held constant; therefore, if venous pressure increases, it suggests that the veins have constricted. Conversely, if venous pressure falls in the isovolumic hand, venodilation can be said to have occurred (26, 27). This technique is especially useful in evaluating venomotor reactivity. The technique is quite sensitive and can evaluate moment-to-moment changes in venous tone (34, 35). However, it does not give an absolute number for venous tone, since the volume of the hand, though constant, is unknown. Before inflation of the wrist cuff to suprasystolic pressure, the arm was placed in a position to insure that the venous pressure in the isolated hand would plateau in the range of 20 mm Hg for all subjects before intervention. This was done to insure that all subjects started at approximately similar places on the venous pressure volume curve. With this technique, an immediate rise of venous pressure in the isolated hand vein

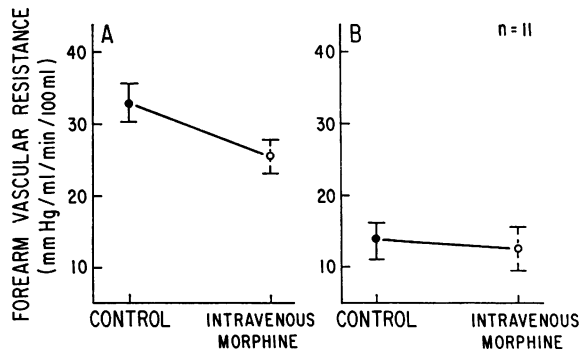


FIGURE 9 The changes in forearm vascular resistance induced by intravenous morphine measured in both forearms simultaneously. A represents the control, untreated forearm ($P < 0.01$.). B represents the changes in forearm vascular resistance which occurred in the arm in which intra-arterial phentolamine had been administered before the injection of morphine ($P > 0.1$). $P$ values indicate level of significance, and $n$ indicates the number of subjects studied.

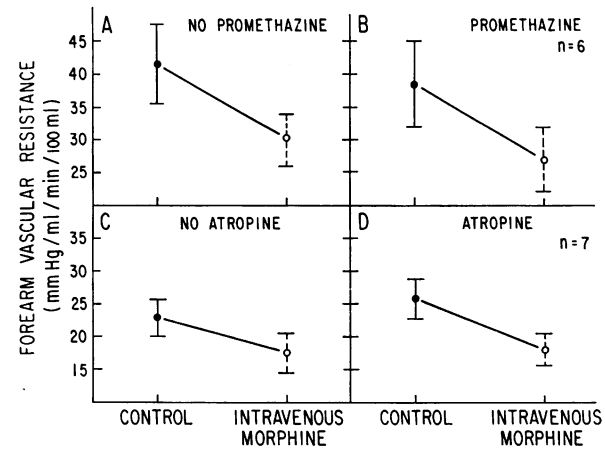


FIGURE 10 Changes in forearm vascular resistance induced by intravenous morphine when measured in both forearms simultaneously. A represents the simultaneously determined changes in forearm vascular resistance in the control forearm in six subjects ($P < 0.01$). B represents the changes in forearm vascular resistance seen in the forearm in which intra-arterial promethazine had been previously administered ($P < 0.05$.). In seven separate subjects intra-arterial atropine was administered to one forearm (D, $P < 0.01$) before intravenous morphine and the opposite forearm served as the control (C, $P < 0.01$). $P$ values indicate the level of significance and n indicates the number of subjects studied.

was demonstrated almost immediately during the intravenous injection of morphine. This indicates that a significant venoconstriction had occurred (Figs. 1 and 2). Although it has been suggested that morphine causes an adrenal release of catecholamines, this could not be responsible for the observed initial venoconstrictor effect of morphine (16, 36). Since the hand was isolated from the circulation, the venoconstriction could not have been from a direct effect of the drug on the veins or secondary to a humoral blood-borne mediator. On the contrary, it must have been secondary to a reflex increase in venous tone. It is quite likely that the initial euphoria from the drug played a role in this initial sympathetic adrenergic discharge.

The occurrence of an initial venoconstriction may partially explain some of the paradoxical effects of the drug that have been noted by others. In particular, it has been suggested that morphine may initially increase pulmonary arterial pressure (4). Although this effect has been ascribed to the decreased respiratory rate (13) and the resultant mild hypoxia and hypercapnia, a transient increase in venous return may also play a role. In these studies reported here, arterial blood gases were not measured, however, the reported changes that occur in these parameters are usually quite small and related to decreased ventilation (3, 13, 17). The reduced respiratory rate noted in these studies, though significant, was

quite minimal. It is most unlikely that changes in blood gases through a cerebral or peripheral chemoreceptor mechanism could have been responsible for the dramatic increase in the venous tone seen immediately during the administration of the drug, since the venoconstriction reached its peak within 1–2 min and was gone well before 5 min.

By 5–10 min, venous pressure in the isolated hand vein was significantly reduced, indicating that a reduction in venous tone had occurred (Figs. 1, 2, and 4B). When the isolated hand vein technique is used to evaluate venous tone, other possible causes for a reduction in hand vein pressure should be considered besides a reflex reduction in sympathetic adrenergic nerve traffic (26, 37). The venous system, unlike the arterial system, is quite resistant to the effects of local hypoxia and should maintain normal tone even though the circulation is arrested for periods up to 15 min. To insure that the veins were not paralyzed and were capable of responding to a venoconstrictor stimulus, a single deep breath was taken by all subjects at the end of the 10-min postmorphine period. It was demonstrated that in all subjects, a hypoxia-induced venodilation had not occurred, since in each subject the hand veins were capable of constricting to the stimulus of a deep breath (Figs. 1 and 2). A second reason for a fall in the venous pressure in the isovolumic hand is that fluid might leave the venous system and be taken up in the tissues or the dilated arterial compartment, or be extravasated around the site of venipuncture. Therefore, it was important to determine what changes would occur in venous pressure in the isolated hand over a comparable period after the injection of saline, before the injection of morphine. Although no initial venoconstriction was seen, it was noted that the hand vein pressure did fall significantly, but minimally, over a 10-min period of observation (Fig. 3A). This could have been secondary to fluid shifts, as suggested above, or it may be secondary to relaxation by the subjects (26, 37). Importantly, it was demonstrated that the fall in isolated hand vein pressure after morphine was considerably greater than that observed during the control period (Fig. 3B). This suggests that the dramatic reduction in isolated hand vein pressure after morphine is due to an effect of the drug to induce a reflex reduction in venous tone.

Although the isolated hand technique is a very sensitive indicator of instant-to-instant changes in venous tone, it cannot be used to determine an absolute numerical value for venous tone in an individual. For these measurements, either the acute occlusion technique of Sharpey-Schafer (28) or the equilibration technique of Litter and Wood (30) must be used. The acute occlusion technique is relatively sensitive and produces an absolute number for venous tone; however, it is somewhat dependent on flow and the vein chosen for venous pressure measurement, and should not be used in studies as the sole index of venous tone. Measurements can be taken repeatedly over a short period of time; however, in the studies described here, it was only evaluated before and 15 min after the administration of morphine. For the first 10 min after the administration of morphine or the saline control, the subject was not stimulated in any way by sight, sound, or smell, a procedure that was scrupulously observed because of the known sensitivity of the isolated hand vein technique to any extraneous stimulus, including periodic inflation of an arm blood pressure cuff (37). Despite the limitations of the acute occlusion technique, a significant late reduction in venous tone (the ratio of the rate of change in venous pressure to the rate of change of the venous volume) was observed (Fig. 4A). This change is directionally opposite to that expected to be produced secondary to the error inherent in this technique. The increased forearm blood flow produced by morphine (see below) would be expected to make the veins appear stiffer when evaluated by this method, and not more compliant, as was observed.

Although the equilibration technique of Litter and Wood (30) is the most reliable for determining the absolute value of venous tone, it is relatively insensitive to changes in venous tone and has limited usefulness in determining moment-to-moment changes in venomotor activity (35). With this technique, the effective pressure in the arm veins is held constant; therefore, any observed changes in venous volume reflected changes in venous tone. With this technique it was determined that VV[30] was slightly but insignificantly increased after morphine (Fig. 4C). This is similar to the report by Ward, McGrath, and Weil (18), who evaluated the venous volume in the dog hindlimb. On the other hand Kayan, Wheeler, and Wood have reported that venous volume determined by this technique did significantly increase after morphine (38). In the latter studies, the basal VV[30] was significantly higher than that which we determined, presumably because their subjects were not cool as ours were in the present studies. It is still surprising that a morphine-induced venodilation could be seen by this technique when the veins were nearly maximally dilated, but was not observed when the veins were partially constricted. Because the veins are very compliant in the lower ranges of venous pressure, it is most important to have the arm significantly elevated before the period of venous pressure equilibration. In our studies, we insured in all instances that the veins were collapsed and the measured venous pressure was less than 1 mm Hg. If the veins were not completely collapsed, the measured venous volume would be reduced and the magnitude of the error would not be predictable.

The mechanism of the venodilation was next evalu-

ated in this study. In four subjects, morphine infused intra-arterially in a dose up to 200 μg/min for a period of five min did not result in any measurable change in ipsilateral venous tone by the equilibration technique. Because of the insensitivity of this technique, it is possible that a direct effect of morphine on the veins might be missed, especially since a significant venodilation to intravenous morphine could not be demonstrated by this method. On the other hand, the dose infused regionally (approximately 1 mg/kg) was five times that given intravenously.

It has been demonstrated in dog studies that morphine appeared to inhibit the venoconstrictor effects of directly administered norepinephrine and sympathetic nerve stimulation (18). This was not seen in the present studies. The dose-response curve to continuously infused intra-arterial norepinephrine was unaffected after intravenous morphine administration. Therefore, it does not appear that morphine-induced venodilation is secondary to peripheral alpha-adrenergic blockade. When a reflex venoconstriction was induced by the taking of a deep breath, by the performance of mental arithmetic, or by the application of ice to the forehead, morphine did not attenuate the response when measured by the equilibration technique or the more sensitive isolated hand vein technique (Fig. 5). With taking a deep breath, there appeared to be a minmally but significantly enhanced venoconstrictor response demonstrated only with the equilibration technique (Fig. 5A). This was not seen with the other two stimuli. Therefore, in human subjects, unlike the experimental animal, no significant direct peripheral alpha-adrenergic blockade by morphine was demonstrated. On the other hand, intravenous morphine did produce a significant venodilation in the hand isolated from the circulation. Therefore, it seems likely that the mechanism of the observed venodilation is a reduction in neurogenically determined venous tone (Figs. 1, 2, 3, and 4B). We would have to explain this reflex reduction in venous tone and the preservation of venoconstrictor responsiveness to direct and reflex stimulation as being compatible with an inhibition of central nervous system determinants of venous tone, a process that we and others have termed "central sympatholysis" (19, 39). Although ganglionic blockade has been suggested as a possible mechanism of action of morphine, such an action should lead to reduction in reflex responsiveness, and this was not seen. Alternatively, the reduction in respiratory rate, by reducing afferent stimuli, could be another potential explanation for these results.

*Morphine and arteriolar tone.* In this study, morphine given intravenously resulted in a significant arteriolar dilation. This is manifest not only by a reduction in total systemic vascular resistance, but also as a reduction in forearm vascular resistance as well (Fig. 6). In our studies, forearm blood flow increased 36%, and forearm vascular resistance fell 25%. No significant changes were noted in mean systemic arterial pressure. To evaluate the mechanism by which morphine produced a dilation of forearm resistance vessels, morphine was infused intra-arterially in doses up to 200 μg/min. At no level of infusion was a significant change noticed in forearm blood flow or forearm vascular resistance (Fig. 8). The direct effect of morphine in most isolated smooth muscle preparations is to stimulate contraction (40, 41). However, some observers have noted that very large doses of the drug will cause a minimal nonspecific relaxation of rabbit vascular smooth muscle (42, 43). On the other hand, it has been recently demonstrated that canine isolated vascular smooth muscle neither contracts nor relaxes when morphine is added to the myograph in clinically significant concentrations (44). This lack of a direct effect of morphine on vascular smooth muscle is consistent with our inability to demonstrate a direct arteriolar dilation in the forearms of our subjects.

It is known that morphine, when given to a number of species, will release histamine from skeletal muscle (45–52). Humans seem to release less histamine than dogs. To evaluate whether direct histamine release or activation of sympathetic histaminergic fibers could account for the vasodilation seen after morphine, a potent antihistamine was administered regionally to one forearm before intravenous morphine. It was noted that the morphine-induced arteriolar dilation was similar in both forearms (Fig. 10A and B). This finding suggests that histamine release plays little role in the vasodilation produced by intravenous morphine in humans. The possibility of activation of sympathetic cholinergic fibers was also ruled out by the demonstration that intra-arterial atropine did not inhibit the effects of intravenous morphine to dilate the forearm resistance vessels (Fig 10C and D). This is consistent with the findings of Nadasdi and Zsotér, who showed that the forearm arteriolar dilation induced by meperidine is not attenuated by atropine (50). The lack of effect of propranolol blockade would also speak against a significant beta adrenergic effect from adrenal epinephrine.

On the other hand, intra-arterial phentolamine completely abolished the arteriolar dilator effects of intravenous morphine (Fig. 9). In this and previous studies, the direct action of arteriolar dilating agents (sodium nitrite, amyl nitrite) could be demonstrated even in the presence of reduced vascular resistance produced by phentolamine blockade (33). This gives credence to the hypothesis that the arteriolar dilation produced by morphine is mediated by a reduction in sympathetic alpha-adrenergic tone. However, the precise site at which morphine alters sympathetic tone is unclear. In the isolated canine cutaneous resistance vessel preparation noted above, morphine was found to have no alpha-

adrenergic blocking properties when the vascular smooth muscle was exposed to norepinephrine (44). Similar findings were noted in our human volunteers. The forearm arteriolar constriction produced by the infusion of norepinephrine into the brachial artery was not attenuated by prior administration of morphine. A similar lack of alpha adrenergic blocking potential was also seen in the venous system, as reported above.

Where else might morphine act to reduce alpha adrenergic tone? In the nictitating membrane of the cat, morphine has been shown to block release of norepinephrine after postganglionic nerve stimulation (42). Although morphine does block acetylcholine release at the sinus node, it does not appear to alter norepinephrine release there (51, 52). Morphine also does not appear to be a catecholamine-depleting agents (53). Unfortunately, there is little evidence on whether or not the drug blocks norepinephrine release at the arteriolar level. On the other hand, there is considerable evidence to support the concept that morphine may act as a weak ganglionic blocking agent (54–56). The blockade of either pre- or postganglionic adrenergic transmission to resistance vessels could explain the orthostatic hypotension noted by Drew, Dripps, and Comroe (12). We did not find major changes in blood pressure with orthostatic stress after morphine. When our subjects were tilted to the 45° head-up position, the change in blood pressure with tilt was similar before and after the administration of morphine (Fig. 7A). This finding is not in conflict with the report of Drew et al. In their study, only certain volunteers classified as "fainters" demonstrated a significant fall in systolic blood pressure. Further, their orthostatic stress was 75° rather than the lesser 45° we utilized. Despite what appear to be differences between our study and theirs, in fact, their blood pressure changes with tilting were remarkably similar to ours. The averaged calculated mean blood pressure change that they observed during the last minute of head-up tilt before fainting was + 2.0 mm Hg before morphine (ours + 0.5 mm Hg) and − 1.3 mm Hg when head-up tilt was evaluated after morphine (ours − 1.4 mm Hg) (Fig. 7A).

One of the more interesting aspects of our study was the differential effect of morphine on reflex arteriolar constrictor responses. The cold pressor and Valsalva responses were unaffected by morphine; however, there was some attenuation of the response to orthostatic stress. Although blood pressure did not fall significantly with head-up tilt after morphine, the forearm resistance vessels did not react appropriately. The normal arteriolar constriction seen with head-up tilt was significantly attenuated to 53% of control (Fig. 7D). The reduced ability to constrict the limb resistance vessels could lead to a greater peripheral pooling of blood by the passive filling of limb veins and might explain the slightly but insignificantly greater fall in central venous pressure with tilting after morphine (Fig. 7B). Although it is possible that morphine could be blocking norepinephrine release or producing ganglionic blockade, a more complete attenuation of arteriolar and venous reflexes might have been expected. Although an effect on afferent mechanisms has not been excluded, it is likely that the morphine-induced vasodilation is centrally mediated.

*Clinical implications.* Although the venodilation induced by morphine is small, it is important to speculate about the possible clinical implications. It is unlikely that the minimal reduction in venous tone would contribute to morphine-induced orthostatic hypotension. In fact, the importance of peripheral venoconstrictor mechanisms in maintaining blood pressure upon assumption of the upright position has recently been challenged (34, 37). It has been suggested that baroreceptor-induced changes in venous tone play little role in maintaining blood pressure and preventing fainting (57). The peripheral arterial constrictor response to upright tilt, which we found to be only partially inhibited by morphine, seems to be a more important compensatory mechanism than venoconstriction (57). Likewise, it has been suggested that the contraction of lower leg muscles and the compression of the soleus plexus of veins plays a more important role in venous return from the extremities than peripheral venoconstriction. Limb venoconstriction is confined to cutaneous veins and appears to be more important in shunting blood from superficial to deep venous circuits and thus is an important mechanism in body temperature regulation (27). The fact that deep muscle veins have a limited capacity to constrict might explain why a significant venodilation with morphine could not be demonstrated with the equilibration technique, but could be seen with the isolated hand technique, which measures predominantly cutaneous venous tone.

On the other hand, there is preliminary evidence to suggest that there is a significantly increased VV[30] (+ 0.49 ml/100 ml) after morphine in patients with pulmonary edema (44). If one assumed that this venodilation occurred predominantly in skin veins and venous pressure was at the upper noncompliant end of the venous pressure volume curve, the increase in venous volume produced by morphine would be expected to shift only 59 ml of blood peripherally to the limbs. This is probably an overestimation. Circulatory findings of a similar magnitude were recently reported when the response of patients in pulmonary edema to furosemide were studied (58). In these patients, it was noted that the reduction in left ventricular filling pressure after the drug was earlier than the observed diuresis and correlated temporally with an arterial and venous dilation. Although the venodilation was half again as much as that noted in our preliminary report (44), it is difficult to explain the marked clinical improvement in pulmo-

nary edema after administration of these agents on their peripheral venodilator actions alone.

It is important to note that the effect of morphine on the important splanchnic circulation has not been studied. It is possible that a greater pooling of blood could occur there rather than in the limbs. The mechanisms for splanchnic pooling of blood, however, also may not be an active venodilation, since it has been demonstrated that of the fraction of the splanchnic blood volume capable of being translocated, 65% is moved by passive means and only 35% is transferred by active venoconstriction (59, 60). The portion of this blood volume under passive control appears to be regulated by arteriolar tone rather than by venous tone. With arteriolar constriction, there can occur a passive collapse of distal venous segments and a passive reduction in organ blood volume. Conversely, the failure of arteriolar constriction on assumption of the upright posture may be important in allowing previously unperfused vascular beds to be perfused. This could result in a passive filling of venous channels and a peripheral pooling of blood. A similar effect would be seen with the administration of ganglionic blocking agents, which at one time were used for the treatment of pulmonary edema. Whether or not the effects of morphine on the splanchnic circulation in humans are more pronounced than on the limb circulation is an important area for further study.

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