The Effects of Morphine on Venous Tone in Patients with Acute Pulmonary Edema

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SUMMARY In order to compare the venodilation effect of morphine in normal individuals (22) with that in patients (13) with heart failure morphine sulfate (0.1 mg/kg) was administered to 13 patients with mild pulmonary edema. After morphine congestive symptoms improved and venodilation was induced as determined by two independent techniques: venous pressure fell 10.2 mm Hg by the isolated hand technique and the venous volume of the forearm increased by 0.48 cc/100 ml, measured by the equilibration technique. Neither finding differed from those in normal individuals. Reflex venoconstriction noted on the taking of a single deep breath was unaffected by morphine administration and was similar to that observed in normal subjects. Since the drug morphine sulfate does not cause a major pooling of blood in the limbs, the favorable effect of narcotics in patients with pulmonary edema must be caused by other mechanisms such as splanchic pooling, afterload reduction or reduced breathing effort.

ALTHOUGH MORPHINE has been used for years in the treatment of pulmonary edema, the mechanism by which it exerts its favorable effect is not completely understood. Animal studies suggest that morphine produces a significant venodilation and moves significant quantities of blood from the central to the peripheral circulation.1,2 The term “medical phlebotomy” has been coined to describe this phenomenon. In studies on normal human volunteers, however, the magnitude of the venodilation induced by morphine has been shown to be quite minimal, and the amount of blood that could be pooled in the limbs has been calculated to be quite small.3 The effects of morphine on the peripheral venous system in patients with pulmonary edema might be quite different. These patients have an increased venous tone,4,5 which is at least in part related to increased activity of the sympathetic nervous system.6 Since the vasodilation induced by morphine in normal subjects has been shown to be secondary to a reduction in sympathetic nervous system activity, perhaps at the central nervous system level,7 it is reasonable to postulate that morphine might induce greater venodilation in patients with pulmonary edema. Our study shows that even though morphine does induce a greater reflex relaxation of the limb capacitance vessels than that demonstrated in normal volunteers, the effect is still too minor to explain the clinically beneficial results of morphine administration.

Methods

Patients participating in this study were a highly selected group with acute pulmonary congestion who had been stabilized at least partially with the simple therapeutic measures of oxygen and bed rest. If a patient did not stabilize within 10 min, the patient was then given standard clinical treatment and the study was not performed. All 13 patients chosen for study still had rales over at least one-half of the posterior chest and were dyspneic in the seated position with oxygen. The etiology of their left heart failure was valvular (4), cardiomyopathic (3), and coronary (6) heart disease. No patient had acute myocardial infarction with pain at the time of study. Their average age was 51.8 ± 2.6 (SEM) years (range 35 to 64 years).

Since the equipment necessary to complete the study was strategically placed in locations where patients with acute pulmonary edema are normally seen, the total time between selecting a patient for study and instrumentation was no more than 10 min and morphine was administered within 30 min of admission to the study. All studies were reviewed and approved by an appropriate institutional committee for the evaluation of research on human subjects and informed consent was obtained.

Measurement of Venous Tone

Venous tone was determined by two procedures: the isolated hand technique and the equilibration technique.7,9 In the former procedure, a 21 gauge scalp vein needle was inserted into a vein on the dorsum of the hand and the pressure was continuously monitored using a Statham P23Db pressure transducer, recorded on a Hewlett Packard Model 4560 optical recorder with a rapid developer. Following inflation of a wrist cuff to suprasystolic pressure for periods up to 15 min, the hand becomes isovolumic and any changes in venous pressure reflect changes in venous tone.10,11

In five subjects, venous tone was also evaluated by the equilibration technique.9,12 The arm was elevated above heart level to insure that the forearm veins were collapsed and at a pressure of less than 1 mm Hg. Forearm volume was measured with a mercury-in-rubber strain gauge plethysmograph10 after rapidly inflating an upper arm cuff to 30 mm Hg above cuff zero and holding for three minutes to allow the pressure in the veins to equilibrate with the cuff pressure. The venous volume at a pressure of 30 mm Hg (VV [30]) is an index of venous tone.12

Experimental Protocol

Venous volume was measured by the equilibration technique and then venous tone, by the isolated hand technique, before and 10 min after the intravenous administration of 10 cc of normal saline. At the end of a 10 min period, the reactivity of the veins to the venoconstrictor stimulus of taking a deep breath was evaluated. Venous tone was then redeter-
minded by the equilibration technique. The wrist cuff was released and the subjects allowed to rest for five minutes. The wrist cuff was again inflated to evaluate the changes in the isolated hand vein before and after the administration of morphine sulfate (0.1 mg/kg) diluted to 10 cc, given slowly over 2 min. The venous reflex response to deep breath inspiration was again determined after 10 min, and the venous volume was redetermined by the equilibration technique.

All data are expressed as the mean values ± the standard error of the mean (SEM). Statistical analyses were performed using the Student's t-test for paired data. To compare the responses of these patients with pulmonary edema with those previously reported for 22 normal subjects, the Student's t-test for group data was utilized.

Results

Following saline, no change occurred in clinical status or respiratory rate; however following morphine, their dyspnea improved, and the respiratory rate fell from 24.3 ± 2.5 to 17.2 ± 2.0 per min ($P < 0.01$). Venous pressure measured in the isolated hand remained stable (31.1 ± 4.0 to 31.0 ± 3.8 mm Hg). Deep inspiration led to an increase in venous pressure from 31.8 ± 5.0 to 45.7 ± 6.0 mm Hg ($P < 0.02$).

When morphine was administered to the subjects, the venous pressure in the isolated hand immediately rose from 34.2 ± 4.9 to 39.0 ± 4.6 mm Hg ($P < 0.01$), following which it fell to 24.4 ± 3.6 mm Hg ($P < 0.01$) (fig. 1 left). The taking of a deep breath ten minutes after the administration of morphine induced an increase in venous pressure to 33.4 ± 4.0 mm Hg ($P < 0.01$).

The venous volume at 30 mm Hg prior to morphine was 1.74 ± 0.08 cc/100 cc. After the administration of morphine VV [30] increased to 2.22 ± 0.13 cc/100 cc ($P < 0.01$) (fig. 1 right), reflecting an increase in venous capacitance.

When the venous responses of these patients with pulmonary edema to morphine were compared with those of normal subjects previously reported, no significant differences were noted (fig. 2). The fall in hand vein pressure was similar as was the venoconstriction seen following the taking of a single deep breath (fig. 2). The increase in venous volume, though 66% greater in the pulmonary edema subjects than in the normal subjects, was not significantly different. Following morphine the reduction in venous tone determined by the equilibration technique was significant in the pulmonary edema subjects; in contrast, in the normal subjects an increase in venous volume followed morphine, but the change was not significant.

Discussion

The patients evaluated in this study were not in severe pulmonary edema, for which treatment should not be delayed for even the short interval of our study protocol. The subjects did exhibit marked venoconstriction. Their VV [30] was one third of that seen in normal individuals.

Morphine administration markedly improved the clinical status of these patients and a significant venodilation was measured, using both the isolated hand technique and the equilibration technique (fig. 1, left). In the isovolumic hand, the reduction in venous pressure can only be explained by a reflex mechanism since circulation to the hand was arrested. Utilizing the equilibration technique where the venous pressure is held constant, the venous volume increase that was observed post-morphine also reflected a venodilation effect (fig. 1, right).

The magnitude of the venodilation demonstrated by the isolated hand technique was quite similar to that observed in normal subjects (fig. 2). Likewise, the venoconstrictor reflex elicited by taking a deep breath remained unchanged after the administration of morphine, a finding similar to that observed in normal subjects. Lastly, no significant difference was determined between the magnitude of the venodilation induced by morphine in normal subjects and patients with pulmonary edema using the equilibration technique. Although the magnitude of the increase in venous volume was somewhat larger in the pulmonary edema subjects, it was not a statistically significant difference.

The initial and transient venoconstriction observed in the isolated hand in both normal subjects and patients with pulmonary edema is reflex in nature, but of unknown etiology. Following this acute reaction, the veins relaxed and a minimal venodilation could be measured. Recent studies on venous tone may explain why morphine does not effect major venodilation. Whereas previously the marked venoconstriction and reduction in venous volume seen in heart failure patients was ascribed to an exaggerated sympathoadrenal activity, in a recent report it was demonstrated that

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Changes in venous tone induced by the intravenous administration of morphine as determined by the isolated hand technique (left panel), and the equilibration technique (right panel). Values presented are averaged data ± the standard error of the mean. P values refer to the level of significance between control and post-morphine values and n refers to the number of subjects studied.
at least 84% of the reduction in venous volume could be explained by local factors. An increase neurohumoral sympathetic system efferent discharge accounts for a small portion (16%) of the increase in venous tone and thus reduction of sympathetatic activity by a drug such as morphine has a limited effect.

Similarly, morphine exerts its effects only on the neurogenic and not the humoral component of the enhanced sympathoadrenal activation seen in heart failure. Based on calculations at 30 mm Hg and assumption of a flattened pressure-volume curve at levels above 30 mm Hg, morphine would be expected to produce a total peripheral pooling of blood in the limbs of only 70 ml of blood in normal subjects and 116 ml of blood in patients with acute pulmonary edema. This volume is hardly enough to explain the dramatic improvement in the pulmonary edema and left ventricular hemodynamics that this drug produces.

Other mechanisms may be implicated. One alternative mechanism might be increased pooling in the splanchnic circulation caused by arteriolar dilation and passive filling of previously unperfused venous segments. Recently morphine has been shown to increase splanchnic blood flow 19%. Whether this results in passive pooling of blood in the splanchnic circulation requires further study. Secondly, the drug's well-known ability to dilate resistance vessels leading to reduction in ventricular afterload may be more important than its ability to dilate veins. Lastly, morphine's other mechanisms of action such as the reduction in dysnea, the work of breathing, and induction of a central nervous system euphoria may be the primary factors in relieving pulmonary edema.

Acknowledgments
The authors gratefully acknowledge the technical assistance of Mrs. Mimi Winterhalter, Mr. Robert Kleckner, and the secretarial assistance of Ms. Judith Holzer, Mrs. Jane Shuey, and Miss Kimberly Cassey.

References
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*The volume of the four limbs of a 70 kg person was estimated to be 24,000 ml calculated from limb measurements using the formula for the volume of a truncated cone.

Figure 2. Comparison of venous tone and venoarterial reactivity between normal subjects (clear bars) and patients with acute pulmonary edema (stippled bars) after morphine. The changes in venous tone were determined by the isolated hand technique (left panel) and the equilibration technique (right panel). The venoconstrictor response noted on the taking of a single deep breath is presented in the center panel. ns = nonsignificant.
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Circulation. 1976;54:335-337
doi: 10.1161/01.CIR.54.2.335
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1976 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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