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Effect of morphine on splanchnic blood flow[1]

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SUMMARY Splanchnic blood flow was measured by the constant infusion of indocyanine green given before and after morphine 0·2 mg/kg (maximum 15 mg) intravenously in 13 patients. Splanchnic blood flow increased from 1012 ± 98 ml/min to 1200 ± 118 ml/min after the administration of morphine, a 19 per cent increase ($P < 0·025$). Splanchnic vascular resistance decreased from 0·094 ± 0·010 to 0·081 ± 0·010 mmHg min/ml, a 16 per cent decrease ($P < 0·001$). There was no significant change between baseline and post-morphine values in systemic arterial pressure (92·2 ± 3·8 and 89·0 ± 2·9 mmHg), hepatic vein wedge pressure (7·1 ± 1·0 and 7·8 ± 0·6 mmHg), or right atrial mean pressure (4·5 ± 0·6 and 4·3 ± 0·7 mmHg). This study shows that morphine induced significant splanchnic arteriolar dilatation.

Morphine sulphate is frequently used for the relief of acute pulmonary oedema. Though extremely useful, and sometimes regarded as the 'drug of choice', the exact mechanism by which it acts is unknown (Robin *et al.*, 1973; Staub, 1974). Some believe it relieves the patient's anxiety; others that it causes peripheral pooling of blood in the systemic circulation (Henney *et al.*, 1966; Vasko *et al.*, 1966). Certainly, previous studies have shown that morphine produces venodilatation in normal subjects and in patients with significant pulmonary venous congestion, but the amount of blood which would be pooled peripherally in the limbs is relatively small, about 70 and 116 ml being the figures calculated respectively by Zelis *et al.* (1974) and Vismara *et al.* (1976), and this alone would not explain the beneficial effect in pulmonary oedema. To evaluate the effects of morphine elsewhere in the circulation, therefore, a study on splanchnic blood flow and vascular resistance was undertaken.

Subjects and methods

Thirteen patients about to undergo diagnostic cardiac catheterisation were studied. Four had mitral stenosis, 5 coronary artery disease, and 1 each, mitral regurgitation, aortic stenosis, pulmonary stenosis, and primary myocardial disease. The approval of the appropriate institutional ethical committee was given, and informed consent obtained in all instances. Patients fasted for 8 or more hours beforehand and received no premedication. An arterial needle was placed in the left brachial or radial artery for the measurement of systemic arterial pressure, using a Statham P 23 db strain gauge transducer and a Honeywell multichannel optical recorder with direct writer.

An end-hole catheter was used to obtain right atrial pressure and wedge pressure in the main right hepatic vein, after which it was replaced by a No. 8 French NIH catheter. As suggested by Rowell (1974) this catheter was advanced gently as far as possible into the main right hepatic vein until no blood could be withdrawn and was then withdrawn approximately 2 cm, when blood could be easily obtained. It was left in this position until the completion of the study for the measurement of splanchnic blood flow. For this, the Fick technique (Bradley, 1963) based on hepatic clearance of indocyanine green dye (Rowell, 1974) was used. An initial bolus of 12·5 mg of green dye was given over 1 minute, followed by a constant infusion of 0·5 mg per minute. Systemic arterial and hepatic vein blood samples were obtained at 13, 15, and 17 minutes after the start of the constant infusion. Then, a slow intravenous infusion of diluted morphine sulphate was given over 2 minutes (0·2 mg/kg, maximum 15 mg) and sampling was repeated 13, 15, and 17 minutes later. After sampling was com-

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plete, the NIH catheter was withdrawn to the right atrium, and simultaneous right atrial and systemic arterial pressures were obtained. The end-hole catheter was then substituted and the hepatic vein wedge pressure remeasured.

For the accurate determination of indocyanine green concentration and splanchnic blood flow, there are certain pitfalls which must be avoided (Rowell, 1974)—in particular, hepatic vein blood must be withdrawn slowly. After discarding an initial 2·5 ml blood, 5 ml were withdrawn over 2 minutes and halfway through this 5 ml systemic arterial blood were taken. All blood samples were centrifuged for 20 minutes. The supernatant plasma was then recentrifuged for a further 20 minutes to ensure the absence of red blood cells. Indocyanine green concentration was determined on this sample by measuring absorption at 805 Å using a Gilford model 250 spectrophotometer. Standard concentration-absorption calibration curves were prepared to bracket all readings with solutions of known dye concentration diluted with the subject's plasma obtained from blood drawn before any dye had been given. Splanchnic blood flow was calculated according to the formula of Bradley (1963):

$$SBF = SR/(A\text{-}V) \times (1 - Hct)$$

where SR = splanchnic removal rate of indocyanine green dye (removal rate = infusion rate), A = systemic arterial concentration, and V = hepatic venous concentration of the dye, and Hct = hepatic venous haematocrit. From pressure and flow recordings hepatic resistance was calculated by dividing the mean systemic arterial pressure minus mean right atrial pressure by the splanchnic blood flow.

Data are presented as mean ± SEM (standard error of the mean). Statistical analysis used the Student t test for paired data (Remington and Schork, 1970).

Results

During the control period, mean systemic arterial pressure was 92·2 ± 3·8 mmHg. After morphine administration this decreased insignificantly to 89·0 ± 2·9 mmHg (Table). Hepatic venous wedge pressure was also virtually unchanged by morphine (7·1 mmHg ± 1·0 to 7·8 ± 0·6 mmHg, NS) as was right atrial pressure (4·5 ± 0·6 to 4·3 ± 0·7, NS). Splanchnic blood flow before morphine was 1012 ± 98 ml/min (range 534 to 1559 ml/min), but after it flow increased significantly to 1200 ± 118 ml/min (range 577 to 1700 ml/min) ($P < 0·025$)—a 19 per cent increase. Baseline splanchnic vascular resistance was 0·094 ± 0·010 mmHg min/ml (range 0·053 to 0·176 mmHg min/ml). After morphine it decreased to 0·081 ± 0·010 mmHg min/ml (range 0·050 to 0·153 mmHg min/ml) ($P < 0·001$)—a 16 per cent decrease.

Discussion

In relieving acute pulmonary oedema secondary to left heart failure, morphine sulphate probably acts in several ways. One postulated mechanism is the relief of anxiety. The euphoric effect of the drug presumably blunts the recognition of dyspnoea; and there also appears to be a resetting of chemoreceptor-induced ventilatory drive (Weil *et al.*, 1975). A reduced respiratory rate, with its reduction in the work of breathing, may certainly be part of the

Table

Case No.	*SBF (ml/min) before morphine*	*SBF (ml/min) 15 min after morphine*	*SVR (mmHg/min per ml) before morphine*	*SVR (mmHg/min per ml) 15 min after morphine*	*RA (mmHg) before morphine*	*RA (mmHg) 15 min after morphine*	*BP (mmHg) before morphine*	*BP (mmHg) 15 min after morphine*	*Diagnosis*
1	1082	1388	0·091	0·067	4·0	2·0	103	96	CAD
2	1559	1690	0·067	0·056	6·0	6·0	114	100	MS
3	534	577	0·155	0·128	8·0	8·0	93	85	PS
4	643	656	0·115	0·102	6·0	8·0	79	76	MR
5	579	687	0·176	0·153	3·0	2·0	111	112	Primary myocardial disease
6	953	1070	0·065	0·059	1·0	2·0	66	70	MS
7	724	910	0·105	0·092	1·0	1·0	81	89	CAD
8	1058	1554	0·078	0·055	3·5	4·0	89	90	CAD
9	1021	831	0·097	0·103	5·5	4·0	105	92	CAD
10	939	1379	0·077	0·053	3·0	4·5	80	82	MS
11	1412	1700	0·063	0·050	6·0	4·5	95	90	AS
12	1633	1515	0·053	0·056	6·5	4·0	95	93	CAD
13	1025	1639	0·078	0·048	8·5	8·5	88	85	MS

SBF, splanchnic blood flow; SVR, splanchnic vascular resistance; RA, right atrial mean pressure; BP, systemic arterial mean pressure; CAD, coronary artery disease; MS, mitral stenosis; PS, pulmonary stenosis; AS ,aortic stenosis; MR, mitral regurgitation.

therapeutic effect which is seen, but it probably does not account for it in full.

Afterload reduction is a second way by which morphine might act. The drug dilates systemic resistance vessels and has been shown to reduce limb vascular resistance by 25 per cent (Zelis *et al.*, 1974). This may be secondary to a centrally mediated reduction in alpha-adrenergic neurogenic vasomotor tone.

A third suggestion is that morphine pools blood in peripheral veins (Henney *et al.*, 1966; Zelis *et al.*, 1974). Though this undoubtedly occurs, as already pointed out, the amounts, even at a venous pressure of 30 mmHg or greater (Zelis *et al.*, 1974; Vismara *et al.*, 1976), are not enough to account totally for the beneficial effects which are seen.

However, one major region with the potential to pool blood is the splanchnic circulation. So far there is no readily available and accurate method of measuring splanchnic blood volume easily in human beings. From animal studies it has been suggested that up to 65 per cent of the reduction in splanchnic blood volume that occurs with sympathetic stimulation may be regulated by arterial rather than venous tone (Öberg, 1967; Brooksby and Donald, 1972). When blood flow to the gut is reduced, veins collapse passively; and the lower the portal vein pressure the greater is the proportion of splanchnic blood volume which is regulated by arterial inflow.

Our data show that there was a significant reduction in splanchnic vascular resistance (13 per cent) and increase in splanchnic blood flow (19 per cent) after the administration of morphine. This occurred with no significant change in mean systemic arterial, right atrial, or hepatic vein wedge pressures. Therefore, if the principles of control of splanchnic blood volume in animals can be extrapolated to human beings, an increase in splanchnic blood volume after morphine may be postulated. Unfortunately the magnitude of this change cannot be determined.

References

Bradley, S. E. (1963). The hepatic circulation. In *Handbook of Physiology, Section 2, Circulation*, Vol. 2, pp. 1387-1438. American Physiological Society, Washington, D.C.

Brooksby, G. A., and Donald, D. E. (1972). Release of blood from the splanchnic circulation in dogs. *Circulation Research*, **31**, 105-118.

Henney, R. P., Vasko, J. S., Brawley, R. K., Oldham, H. N., and Morrow, A. G. (1966). The effects of morphine on the resistance and capacitance vessels of the peripheral circulation. *American Heart Journal*, **72**, 242-250.

Öberg, B. (1967). The relationship between active constriction and passive recoil of the veins of various distending pressures. *Acta Physiologica Scandinavica*, **71**, 233-247.

Remington, R. D., and Schork, M. A. (1970). Estimation. In *Statistics with Applications to the Biological and Health Sciences*, pp. 148-191. Prentice-Hall, Englewood Cliffs, New Jersey.

Robin, E. D., Cross, C. E., and Zelis, R. (1973). Pulmonary edema. *New England Journal of Medicine*, **288**, 239-246 and 292-304.

Rowell, L. B. (1974). Measurement of hepatic-splanchnic blood flow in man by dye techniques. In *Dye Curves*, pp. 209-229. Ed. by D. A. Bloomfield. University Park Press, Baltimore.

Staub, W. C. (1974). Pulmonary edema. *Physiological Reviews*, **54**, 678-811.

Vasko, J. S., Henney, R. P., Oldham, H. N., Brawley, R. K., and Morrow, A. G. (1966). Mechanisms of action of morphine in the treatment of experimental pulmonary edema. *American Journal of Cardiology*, **18**, 876-883.

Vismara, L. A., Leaman, D. M., and Zelis, R. (1976). The effects of morphine on venous tone in patients with acute pulmonary edema. *Circulation*, **54**, 335-337.

Weil, J. V., McCullough, R. E., Kline, J. S., and Sodal, I. E. (1975). Diminished ventilatory response to hypoxia and hypercapnia after morphine in normal man. *New England Journal of Medicine*, **292**, 1103-1106.

Zelis, R., Mansour, E. J., Capone, R. J., and Mason, D. T. (1974). The cardiovascular effects of morphine: the peripheral capacitance and resistance vessels in human subjects. *Journal of Clinical Investigation*, **54**, 1247-1258.

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