HÆMODYNAMIC EFFECTS OF MORPHINE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

BY

MICHAEL THOMAS, RAOUL MALMCRONA*, SIDNEY FILLMORE†, AND JOHN SHILLINGFORD

From the Medical Research Council Cardiovascular Research Group, Department of Medicine, Postgraduate Medical School of London W.12, and Medical Department 1, Sahlgrenska Sjukhuset, University of Gothenburg, Sweden

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The administration of analgesic drugs to patients with acute myocardial infarction is routine clinical practice for the alleviation of pain and anxiety or simply to ensure sleep. Because of the potent combination of analgesic and sedative properties, morphine is frequently given. Although the associated depressant effects on the circulatory and respiratory systems have been documented from animal experiments and work in normal man, the hæmodynamic consequences of the administration of the drug to patients with acute myocardial infarction have previously not been investigated.

The institution of a special unit for the intensive care and study of patients with acute myocardial infarction has enabled hæmodynamic measurements to be made throughout the acute illness and before and after the administration of drugs without disturbing the patients.

The object of this work has been to measure the changes in cardiac output, stroke volume, heart rate, and arterial blood pressure following the administration of morphine to a variety of patients with acute myocardial infarction and at the same time to observe the clinical effects.

SUBJECTS AND METHODS

Fifteen studies were made in 13 patients. All had clinical histories typical of acute myocardial infarction. In 12, the acute illness was accompanied by chest pain. Patient 3 presented following sudden loss of consciousness. All patients had electrocardiographic signs of myocardial infarction at some time during the acute illness: at the time of investigation S-T segment elevation was present in 11 and pathological Q waves in 3. Serum glutamic oxalo-acetic transaminase (SGOT) or lactic dehydrogenase (LDH) was raised in 9 of the 12 patients in whom it was measured.

Eight patients had previously had symptoms attributable to ischæmic heart disease. Patients 3 and 10 had had a myocardial infarction in the past. Patients 5, 11, and 12 were known to have been hypertensive before the acute illness. Patient 11 was receiving guanethidine until 24 hours before the investigation. Two patients (7 and 8) had chronic respiratory disease. The patient's body temperature was above 99° F. (37.2° C.) during seven investigations. Clinical details are given in Table I.

With one exception (Patient 8) the first investigation was undertaken within 24 hours of the onset of symptoms. Patients 2 and 5 were studied a second time within 48 hours of the onset of symptoms. Patient 8 was studied on the 2nd day only. All patients recovered and left hospital with the exception of Patient 10 who died in the 4th week of admission.

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TABLE
CLINICAL

Patient No.	Age (yr.)	Weight (kg.)	Day of infarct.	Body temperature* (°C.)	Past history	Present symptoms	General condition on admission†
1	67	63	1	36.7 (M)	Periph. isch. dis.	R. arm ache 2 wk. sudden sev. pain arms chest	In pain; moist warm skin; HR 90; JVP not raised; BP 170/90 mm. Hg; presyst. heart sound; few râles lung bases
2	64	72	1	37.3 (M)	Diab. mellit. 15 yr.	Sudden pain front chest; felt weak & faint; vomited	Pale & sweating; HR 100; JVP not raised; BP 115/70 mm. Hg; normal heart sounds
2'	—	—	2	37.8 (M)			
3	72	65	1	37.5 (M)	Myocard. infarct. 4 yr. prev.	Sudden loss of consciousness; recovered consc.; vomited; no pain	Pale; HR 88; JVP not raised; BP 145/75 mm. Hg; apex beat displaced laterally; normal heart sounds; râles at lung bases
4	73	64	1	36.9 (M)	Effort angina 6 mth.	Awoke morning with sev. chest pain & down both arms; weak and nauseated	Pale; in pain; HR 50; JVP +3 cm.; BP 140/80 mm. Hg; apex beat displ. lat.; presyst. heart sound
5	60	70	1	37.2 (M)	Hypertension 5 yr.; diab. mellit.; 6 mth. angina	Acute sev. chest pain extending to neck; weak feeling in arms	Sev. pain; HR 60; JVP +4 cm.; BP 200/120; presyst. heart sound
5'	—	—	2	36.9 (M)			
6	49	67	1	37 (R)	Nil relevant	Sudden chest pain while walking, arms felt heavy, slightly faint	Mod. sev. pain, HR 80; JVP not raised, BP 145/100 mm. Hg; presyst. heart sound
7	62	78	1	37 (M)	Cough + sputum many yr.; dyspn. on effort	Sudden sev. chest pain	Mod. sev. pain; HR 80; BP 150/90 mm. Hg; JVP not raised; presyst. heart sound; reduced breath sounds at both lung bases with coarse creps.
8	56	77	2	36.9 (M)	Winter bronchitis; effort angina 1½ yr.	Incr. frequency of angina 24 hr.; sudden sev. chest pain	In pain; HR 68; JVP not raised; BP 115/70 mm. Hg; heart sounds normal
9	58	62	1	37.3 (M)	Chest pain 6 yr. prev.	Sudden sev. chest pain	In pain; HR 90; JVP not raised; BP 134/90; presyst. heart sound
10	67	—	1	38.5 (R)	Effort angina 9 mth.; effort dyspn. 5 yr.	Sev. chest pain	Sev. pain; distressed; HR 118; JVP not raised; BP 125/90 mm. Hg; 3rd heart sound
11	55	82	1	36.7 (M)	Hypertension noted 1959; controlled by guanethidine	Sev. chest pain	In pain; HR 70; JVP not raised; BP 170/115 mm. Hg; presyst. heart sound
12	61	72	1	37.6 (R)	Renal tuberc.; L nephrectomy 1962; BP previously 190/110	Sev. chest & R. arm pain	Sev. pain; very pale; HR 90; JVP not raised; BP 150/100 mm. Hg; heart sounds normal
13	55	68	1	37.1 (R)	4 yr. occas. min. chest pain; 1 wk. incr. chest pain	Sev. chest pain	Pain-free; HR 80; BP 120/80; JVP not raised; heart sounds normal

* Body temperature at time of investigation, M, mouth; R, rectal.

† JVP, jugular venous pressure; HR, heart rate.

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DATA

Highest enzyme value	ECG†	X-ray appearances	Morphine sulphate (mg.)§	Severity of pain at time of morphine administration	Breathing air or oxygen	Response to morphine
Not measured	SR; S-T elevation V2-V4	Heart slightly enlarged; lung fields normal	5	Pain	O ₂	Loss of pain; remained awake
SGOT 102 I.U.	SR; S-T segm. elevation AVF, & III	Heart enlarged; lung fields normal	7.5	Pain	Air	Loss of pain; remained awake
			7.5	Discomfort	Air	Loss of pain
SGOT 6 I.U.	SR; S-T segm. elevation V2-V7	Heart enlarged; slight congestion; changes at bases	3	No pain	Air	Became sleepy
SGOT 22 I.U.	SR; S-T segm. elevation AVF & III	Heart enlarged; slightly full hilar shadows	5	Pain	Air	Loss of pain; asleep 1 hr. later
SGOT 56 I.U.	SR; path. Q with S-T segm. elevation & T inversion III, AVF	LV enlargement; lung fields normal	10	Sev. pain	O ₂	Pain diminished; less restless; remained awake
			10	Discomfort	O ₂	Less discomfort
LDH 410	SR; path. Q II, III, AVF; T inversion II, III, AVF	Heart normal; min. congestive changes at lung bases	5	Pain	O ₂	Loss of pain; returned 2 hr. later
LDH 100	SR with ventric. ectopic beats; S-T segm. elevation II, III, AVF, V4, V5, V6	Mod. cardiac enlargement; some collapse both lower zones with patchy consolidation	3	Pain	O ₂	Minor effect on pain but mod. sedation
LDH 150	SR; S-T segm. elevation III, AVF	Min. cardiac enlargement; segm. collapse at R. base	10	Pain	O ₂	Mod. sedation
LDH 1050	SR; S-T elevation I, AVL, V4-7	Heart slightly enlarged; lungs normal	3	Pain	O ₂	Vomited once after 3 mg. morphine sulphate; no other clinical change
LDH 1200	SR; S-T segm. elevation V2-V4	Mod. cardiac enlargement; subsequent LV aneurysm; very marked venous engorgement; pulmon. oedema	10	Sev. pain	O ₂	Sleep induced soon after morphine admin.; slept several hr.
LDH 775	SR; S-T segm. elevation V4R-V7	Mod. cardiac enlargement; lung fields normal	10	Sev. pain	O ₂	Rapid induction of sleep; slept 30 min.; pain relieved; looked pale after waking
SGOT 385 I.U.	S-T segm. elevation CR2, CR4	LV enlargement; lung fields normal	5	Sev. pain	O ₂	Pain subsided during investig.; patient remained awake
SGOT 74 I.U.	Path. Q in AVF, II, III	Normal	5	Pain	Air	Sleep almost induced; patient felt improved

† SR, sinus rhythm.

§ Quantity of morphine sulphate injected intravenously.

Eleven patients were investigated in a special intensive care and study unit with recording equipment permanently installed (Shillingford and Thomas, 1964). Two (12, 13) were studied in a general ward. After clinical assessment, electrocardiograph, and chest radiographs, fine polythene catheters (PE60 Intramedic U.S.A.) were introduced percutaneously into a brachial artery and an antecubital vein, using local anaesthesia. The tip of the arterial catheter was advanced 10 cm. from the point of insertion and the tip of the venous catheter was advanced until it lay in the region of the great veins.

Intravascular pressures were measured by use of P23Gb Statham transducers and were recorded on a direct writer (Devices Ltd). Measurements were made with respect to a point 5 cm. below the sternal angle. With one exception the patients lay horizontally with head and shoulders comfortably supported on one or two pillows. Patient 7 was supported from the waist at an angle of 45° to the horizontal. In 11 patients the cardiac output was measured by a dye dilution technique using the photoelectric earpiece (Cambridge Instrument Co. Ltd.) with Coomassie Blue dye (I.C.I.) as indicator. The first curve was calibrated by equating the height of the tail of the curve three minutes after injection of dye with the concentration of dye in a central venous blood sample taken at this time. Dye was extracted from the plasma and measured by spectrophotometry. Subsequent cardiac outputs were calculated according to the relative areas of the curves (Gabe, Tuckman, and Shillingford, 1962). In Patients 12 and 13, cardiac output was measured by intermittent arterial sampling using bromsulphthalein as indicator.

Heart rate was measured over 30-second intervals from an electrocardiographic tracing: in Fig. 5 and 6 heart rate was measured over shorter periods. Peripheral resistance was calculated as the mean pressure in the brachial artery, expressed in mm. Hg, divided by the cardiac output expressed in litres/min. In Fig. 8 values are given to the nearest whole number.

After insertion of catheters and preliminary preparations for the investigation, repeated measurements of arterial blood pressure were made for approximately 30 minutes or until a steady level of blood pressure was recorded. In one patient (5) this was not achieved. Two, or in some cases three, dye dilution curves were then drawn at five-minute intervals, the first one being calibrated. Intravascular pressure measurements were made immediately before and immediately after each cardiac output measurement. Morphine sulphate 10 mg. in 10 ml. of saline was then infused unknown to the patient into the central venous system via the venous catheter at a rate of approximately 1 mg./minute. Brachial arterial blood pressure was continuously recorded during injection. The infusion was terminated if a persistent fall in blood pressure was seen. If the blood pressure did not fall during injection, the maximum dose given was 10 mg. Measurements of heart rate and arterial blood pressure were then made at frequent intervals. Cardiac output was measured at intervals of 5–10 minutes over a period of 30–40 minutes.

Arterial blood samples were taken for measurement of Po_2 and Pco_2 before the administration of morphine and at 10 and 20 minutes after completion of injection. Arterial Po_2 was measured by means of a Beckman electrode and arterial Pco_2 by means of a Severinghaus electrode. pH was calculated from Pco_2 and serum bicarbonate values.

RESULTS

Results of the haemodynamic investigations are illustrated in Fig. 1–8. In the diagrams the left-hand circled number identifies patients; the right-hand circled number represents in addition an observed value, except in Fig. 4 and 7 in which it is only an identification. Control measurements shown are those obtained five minutes before and immediately before the injection of morphine. The times of subsequent measurements are given as the time after completion of the morphine injection.

Heart Rate (Fig. 1). In 7 instances (1, 2', 7, 8, 10, 11, 13) there was no change in heart rate after the injection of morphine. In 6 instances (2, 4, 5, 5', 6, 9) heart rate increased, and in 2 (3, 12) the heart slowed. In those cases in which a change occurred, it was apparent at the first measurement after the completion of injection.

Heart rate increase was related to vomiting in 2 patients (5 and 9). In Patient 9 this occurred soon after beginning morphine injection. In 3 patients with an increased heart rate the increase was sustained over the period of observation. The other patients who showed a heart rate increase returned to control levels within 15 minutes.

Cardiac Output (Fig. 2). In 7 instances (1, 2, 2', 5, 6, 9, 11) there was no change in cardiac out-

FIG. 1.—Heart rates measured before and after the injection of morphine.

put after injection of morphine. In 8 instances (3, 4, 5, 7, 8, 10, 12, 13) cardiac output was increased for part or the whole of the period of observation. In no patient did a convincing fall of cardiac output occur, though in one (Patient 5) with a high cardiac output and tachycardia the measurement showed considerable fluctuation.

Stroke Volume (Fig. 3). In 7 instances (1, 2', 6, 9, 10, 11, 13) the stroke volume remained unchanged after injection of morphine. In 4 instances (3, 7, 8, 12) stroke volume rose after the injection: in 2 of these (7 and 8) the times of the measurements were such that it was possible to see that the rise in stroke volume occurred more than ten minutes after the injection was complete. In four instances (2, 4, 5, 5') there was a decrease in stroke volume. The decrease in one of these (4) was preceded by a slight rise, while in the others an early decrease was followed by a return to the control value.

Arterial Blood Pressure (Fig. 4). In 7 instances (2, 3, 4, 5, 6, 10, 13) arterial mean blood pressure decreased transiently, and in an eighth instance (12) there was a persistent fall.

The injection of morphine was stopped at an early stage (3 mg.) in one patient (3) on account of a fall in blood pressure which continued progressively to very low levels (Fig. 5). When the patient's legs were raised arterial blood pressure rapidly increased and returned in three minutes to the control level after an overshoot. Systolic blood pressure fell from 140 to 70 mm. Hg, while the heart rate remained constant. A further fall of 30 mm. Hg was then accompanied by a fall in heart rate from 85 to 20 a minute. When the patient's legs were raised, heart rate increased to 100 a minute before becoming stable at 70 a minute. A few minutes after this event, cardiac output exceeded control levels.

FIG. 2.—Cardiac output measurements made before and after the injection of morphine.

Patient 12 showed a sustained fall in blood pressure, which began during injection of morphine. Heart rate and blood pressure fell concomitantly to a lower level (Fig. 6), while cardiac output was maintained by an increase in stroke volume.

In 3 instances (1, 2', 11) blood pressure remained unchanged after morphine. In 4 (5', 7, 8, 9) blood pressure increased, but in only 2 (5', 8) was the increase large.

Pulse Pressure (Fig. 7). Pulse pressure fell after the injection of morphine in 9 instances (2, 2', 3, 4, 5, 5', 6, 9, 12). In 5 of these (4, 5, 6, 9, 12) the fall was present within 10 minutes of the end of the injection period. In all other instances, except Patient 8 who showed a rise, no clear change in pulse pressure occurred.

During the injection of morphine, small transient falls of arterial blood pressure and pulse pressure were frequently seen.

Peripheral Resistance (Fig. 8). In 6 instances (1, 2, 2', 7, 9, 11) peripheral resistance did not change after injection of morphine. In one (5) the peripheral resistance fluctuated widely. On the eight other occasions there was either a consistent (3, 4, 5', 8, 10, 12) or a transient (6, 13) fall.

Central Venous Pressure. Central venous pressures were measured. The changes in mean pressure were small and within the range to be expected from change in the patient's position in bed. The amplitude of the central venous pressure waves usually became progressively smaller after morphine.

FIG. 3.—Stroke volume calculated from cardiac output and heart rate measurements made before and after the injection of morphine.

TABLE II
HÆMODYNAMIC STUDIES BEFORE AND AFTER MORPHINE

Patient No.	Breathing oxygen or air	Before morphine			5–10 minutes after morphine			20–30 minutes after morphine		
		pH	Po ₂	Pco ₂	pH	Po ₂	Pco ₂	pH	Po ₂	Pco ₂
3	Air	7.34	60	35.5	7.31	58	38.5	—	—	—
4	Air	7.41	74	37	7.36	65	40	—	—	—
2	Air	—	68	38	—	69	42.5	—	—	—
2'	Air	—	63	44	—	—	—	—	65	47.5
8	Oxygen	—	204	46	—	255	51	—	245	50
9	Oxygen	—	272	44.5	—	260	39	—	281	41
10	Oxygen	—	157	41.5	—	164	45	—	149	45.5
11	Oxygen	—	212	40	—	220	43	—	—	—

FIG. 4.—Brachial arterial mean pressure measured before and after the injection of morphine.

FIG. 5.—Brachial arterial mean blood pressure fall observed in Patient 3 after 3 mg. of morphine sulphate had been slowly injected into the central venous system. Measurements of heart rate are shown below the appropriate blood pressure record.

FIG. 6.—Diagrammatic representation of brachial arterial blood pressure and heart rate fall which occurred simultaneously in Patient 12 after the injection of morphine.

Respiration. A fall in respiration rate and depth was observed clinically in most cases after morphine injection. In 8 patients in whom arterial blood samples were taken before and after morphine (2, 2', 3, 4, 8, 9, 10, 11) arterial PO_2 did not show any consistent change (Table II), but all except one (9) showed a small rise in PCO_2 .

Clinical Response to Morphine. The severity of pain experienced by the patients at the time of morphine injection varied widely and is graded in Table I as discomfort, pain, and very severe pain. In all but one of the patients with symptoms, some improvement occurred during the course of the investigation. Five patients (3, 4, 10, 11, 13) became drowsy after morphine and in 2 (10, 11) sleep occurred for a period of 30 minutes and several hours respectively.

DISCUSSION

The use of opiates for the alleviation of pain has been practised for many years and the clinical consequences of their use have been recognized (Comroe and Dripps, 1948; Denton and Beecher, 1949). At an early stage in the study of acute myocardial infarction the powerful analgesic and hypnotic effect of morphine was reported as beneficial (Moor, 1930). Since then the use of the drug in this condition has become widespread.

Although much has been written (Eckenhoff and Oech, 1960) on the effects of the opiate group of drugs, there has been no attempt to measure the circulatory changes following morphine administration under the conditions in which it is used in the treatment of acute myocardial infarction. Without such information a critical evaluation of the use of the drug in these patients would be incomplete.

Previous work using ballistocardiography and sphygmomanometry, in normal subjects and in

FIG. 7.—Brachial arterial pulse pressure measurements made before and after the injection of morphine.

patients, has shown only small changes in heart rate, cardiac output, and blood pressure after doses of morphine within the therapeutic range (Starr *et al.*, 1937; Papper and Bradley, 1942; Wangerman and Hawk, 1942; Drew, Dripps, and Comroe, 1946; Denton and Beecher 1949; McCall and Taylor, 1952; Moyer, Morris, and Pontius, 1956; Malt, 1958). The extensive and well-controlled study by Drew *et al.* showed an increase in heart rate, with a proportional increase in cardiac output and an insignificant fall in blood pressure.

Our results show that in patients with acute myocardial infarction the circulatory response to an intravenous injection of morphine is very variable; the magnitude of the changes is sometimes more pronounced than that shown in normal subjects.

A fall in brachial arterial pressure during or soon after slow injection was seen in many patients. In 2 (3, 12) it was marked. Hypotension in Patient 12 was accompanied by a simultaneous fall in heart rate, but in Patient 3 the arterial systolic pressure fell from 140 to 70 mm. Hg before the heart slowed. The mechanisms of bradycardia in these patients are conjectural. In some ways the response in Patient 3, illustrated in Fig. 5, resembles the changes following hæmorrhage in blood donors lying in the horizontal position (Wallace and Sharpey-Schafer, 1941; Shenkin *et al.*, 1944). The heart rate increase which occurred in association with the rise in blood pressure after raising the patient's legs suggests that the bradycardia in this patient represents a physiological reaction rather than a direct effect of morphine. Changes in heart rate in experimental animals following alterations in perfusion of the medulla are documented (Anrep and Segall, 1926). In Patient 12 bradycardia and hypotension began synchronously, and this response is the only example in these studies

FIG. 8.—Peripheral resistance calculated from measurements of brachial arterial mean blood pressure and cardiac output made before and after the injection of morphine.

of a possible primary action of morphine on the vagus nucleus; bradycardia is a recognized feature of the drug's action in dogs (Powers, Reed, and Gregersen, 1947).

The factors concerned in hypotensive responses are of importance both from the point of view of practical therapy and also for understanding the circulatory failure in acute myocardial infarction. It is probable that many homeostatic mechanisms are deranged, and defects of the myocardium, regulation of heart rate, and control of peripheral vascular tone can all be responsible for inadequate maintenance of blood pressure (Thomas, Malmcrona, and Shillingford, 1965a). In some patients hypotension after morphine persisted without a rise in cardiac output. In other patients cardiac output increased in association with an increase in heart rate or of stroke volume. None of the patients showed a fall in cardiac output, though it was probably reduced during the profound hypotension in Patient 3.

The analysis of the circulatory adaptation to morphine will require further work, but some comment on these data may be useful. In certain cases cardiac output rose in association with a fall in blood pressure; it is probable that peripheral arterial dilatation occurred to an important extent in some regions. Calculated peripheral resistance fell after morphine in many instances. The measured change that was most common was a fall in pulse pressure; systolic blood pressure fell while diastolic pressure usually remained more constant. As stroke volume remained the same or increased, the fall in pulse pressure could represent increased distensibility of the arterial wall, possibly due to a direct effect of the drug on smooth muscle. Experiments in animals (Schmidt and Livingston, 1933) have suggested regional differences in vascular response to morphine but possible species differences discourage acceptance of this in man.

The action of morphine on veins is not easily assessed from our results. Little confidence can be placed in measurements of small changes in central venous pressure on account of frequent movements of seriously ill patients. The dramatic increase in arterial blood pressure after raising the legs in Patient 3 suggests that pooling of the blood in the venous system may be an important consequence of morphine administration, but the evaluation of this will require special techniques.

Respiratory depression may contribute to the net circulatory changes after morphine. Arterial PCO_2 rose in nearly all cases in which it was measured. Arterial PO_2 did not change consistently. Interpretation is made difficult by the fact that some patients were breathing air and some were breathing oxygen. The pressor effect of oxygen (Thomas, Malmcrona, and Shillingford, 1965b) could be of benefit in minimizing hypotension after morphine, but the data are insufficient to establish this.

It would be of practical assistance in the management of the individual patients to be able to predict the type of cardiovascular response to an injection of morphine. The haemodynamic pattern found in patients with acute myocardial infarction is very variable and the efficacy of homeostatic mechanisms is probably dependent on many factors. Frequently there was a fall in systolic pressure when morphine first entered the circulation but this did not always indicate the eventual response to the drug. The degree of analgesia for a given dose was not related to the severity of the pain and the type and extent of circulatory change did not appear to be related to the existing haemodynamic state. Individual sensitivity seems to be important.

The route of administration of morphine most suitable for patients with myocardial infarction is open to discussion, the important difference between the intravenous and intramuscular or subcutaneous routes being the time course of the action of the drug. Previous studies (Drew *et al.*, 1946; Dripps and Comroe, 1945) on respiratory depression following morphine have shown that maximal effect occurs within a few minutes after intravenous injection and much later after intramuscular or subcutaneous injection. Our observations suggest that hypotension after morphine in patients with acute myocardial infarction also occurs soon after intravenous injection. A serious unpredictable blood pressure fall would occur while the patient was under direct medical supervision, and appropriate measures, such as raising the legs or the foot of the bed, would be immediately undertaken. The slower and unpredictable rate of absorption after intramuscular injection might result in a delayed respiratory and cardiovascular depression, especially if repeated injections are given.

Exaggerated hypotensive response to morphine in the upright posture has been pointed out in the past (Drew *et al.*, 1946). This may be important in patients with acute myocardial infarction who are liable to a fall in blood pressure. On this account patients who have received morphine should not be carried with the legs dependant.

SUMMARY

Haemodynamic changes following intravenous administration of morphine to patients with acute myocardial infarction have been studied. Heart rate, cardiac output, stroke volume, and arterial blood pressure were measured before and after morphine. Blood pressure changes ranged from a small fall in pulse pressure to a large fall in mean arterial pressure. In some patients who

showed a fall in blood pressure, the cardiac output rose due to an increase in heart rate with or without an increase in stroke volume. The significance of these changes with respect to the treatment of patients with acute myocardial infarction is discussed.

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