CLINICAL STUDIES ON MORPHINE. II. THE EFFECT OF MORPHINE UPON THE CIRCULATION OF MAN AND UPON THE CIRCULATORY AND RESPIRATORY RESPONSES TO TILTING *

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DESPITE the fact that morphine administered intravenously to dogs produces a marked fall in blood pressure (1), it is generally believed that in man "therapeutic amounts of morphine . . . have little if any effect upon the blood pressure, heart rate or rhythm" (2).

During a study of the effect upon human respiration of intravenously administered morphine (3) certain reactions suggestive of a circulatory origin were reported by our subjects. These included fullness in the head, a sensation of warmth spreading throughout the body, a feeling of faintness, palpitation, vertigo, nausea, and vomiting. Some of these symptoms became evident only when the subject stood up at the end of the study.

Consequently, we decided to investigate the circulatory effects produced in man by the intravenous and intramuscular injection of morphine together with the effect of morphine upon the normal circulatory adjustments to change of position.

Methods.—Each subject lay supine on an operating table, ballistocardiograph or tilt table for twenty to thirty minutes before the control observations were begun. Blood pressure was measured by the Riva-Rocci method with the stethoscope placed over the brachial artery, the arm being maintained at the level of the heart. Pulse rate was counted at the radial artery. Respiratory minute volume was measured by attaching Sadd valves to a full face mask and conducting the expired air through a Bohr gas meter or a delicately balanced spirometer. Respiratory rate was recorded by a pneumograph placed around the chest or abdomen. Cardiac output was calculated by the area method (4) from tracings obtained on the horizontal (5) ballistocardiograph. Morphine sulfate was administered in doses of 10 to 30 mg. When given intravenously, the drug was dissolved in 2 cc. of physiologic saline solution and injected during a fifteen second to two minute period. Intramuscular injections were made into a deltoid muscle.

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The responses to changes in position were observed by placing the subject on a tilt table. This was equipped with a footboard rather than the hip suspension device of Mayerson (6). After a control period, each subject was tilted abruptly to an angle of 75 degrees (head up) for a ten or fifteen minute period (or less if consciousness was lost). The subject was then tilted back abruptly to the horizontal position and after about five minutes morphine was injected intramuscularly. Thirty minutes later, a second tilt was performed. After return to the horizontal position, some subjects were wrapped with elastic bandages from toe to groin and a third tilt was performed.

The subjects ranged in age from 19 to 89 years. All had essentially normal cardiovascular and respiratory systems. They were either normal medical students or patients being studied preoperatively for elective operations. None had been confined to bed for any unusual period of time before the experiment.

RESULTS

I. Circulatory Effects of Morphine Administered Intravenously to Subjects in the Supine Position.

During the intravenous injection of morphine, the pulse was counted frequently in 19 subjects. In 18, the rate increased by 8 to 42 beats per minute; in one (an 89 year old man) there was no change. The average maximal immediate increase for the 19 subjects was 19 beats per minute. Blood pressure was measured in 11 of these subjects during the injection. The systolic pressure increased in 6 (2 to 12 mm. of mercury), decreased in 2 (4 mm. of mercury) and was unchanged in 3; the average change was an increase of 3 mm. of mercury. The diastolic pressure increased in 4 (2 to 4 mm. of mercury) and was unchanged in 7; the average change was an increase of 1 mm. of mercury.*

Cardiac output was measured on the ballistocardiograph during the intravenous injection of morphine in 7 subjects (table 1). It was increased in 6 and essentially unchanged in one. The increase in cardiac output per minute was effected chiefly by the increase in heart rate, for there was no consistent change in stroke volume.

The immediate circulatory changes described were brief. The time required for the pulse rate to return to approximately normal levels was ten minutes or less in 16 subjects, ten to twenty minutes in 2, twenty to thirty minutes in 2 and forty minutes in 1. The cardiac output per minute had returned to control values by the end of the two minute injection period in 2 subjects; when the next reading was taken (at forty minutes after injection) 6 of the 7 had deturned to approximately normal figures.

* Control injections of saline solution intravenously produce no measurable circulatory changes.

TABLE 1

THE EFFECT OF 15 MG. OF MORPHINE SULFATE ADMINISTERED INTRAVENOUSLY ON THE CIRCULATION

		Control	During Injection, seconds			After Injection, minutes					
			60	90	120	5	10	20	30	40	60
H.M.	B.P.	112/64			120/80	120/80	118/80	108/76		110/62	
M—24	P.	62	85	78	72	68	66			60	
5'6"	S.V.	0.34	0.30		0.36						
135 lbs.	C.O.	21	26		26					22	
A.K.	B.P.	102/60		110/64	116/58	116/58	106/68	106/70	106/68	106/68	104/70
M—23	P.	74	102	104	98	86	86	86	82	80	76
5'11"	S.V.	0.27		0.27	0.35						
139 lbs.	C.O.	21		28	34					27	
S.M.	B.P.	98/74		102/72		116/90			108/78	108/78	
M—22	P.	78	108	124	108	96			90	76	
5'9"	S.V.	0.26		0.21	0.21						
177 lbs.	C.O.	20		26	23					18	
M.D.	B.P.	102/60			104/60	104/60	104/64	104/60	110/66	106/66	108/60
F—30	P.	76	88	92	86	88	84	88	88	78	84
5'8"	S.V.	0.36			0.36						
115 lbs.	C.O.	27			31					26	
P.R.	B.P.	98/60	110/64		100/60	98/58		98/60	96/60	96/60	100/66
M—19	P.	78	92	90	90	76		84	72	78	80
6'3"	S.V.	0.26	0.27		0.22						
195 lbs.	C.O.	20	25		20					21	
R.L.	B.P.	108/76			104/76				104/68	104/68	
M—26	P.	70	78	82	82				70	70	
6'2"	S.V.	0.31		0.27	0.28						
180 lbs.	C.O.	22		22	23					24	
M.N.	B.P.	112/70			116/74			112/80		104/74	
M—25	P.	92	108	112	104			80		76	
5'8"	S.V.	0.33		0.37	0.35						
148 lbs.	C.O.	30		42	36					28	

B.P.—blood pressure; P.—pulse rate; S.V.—stroke volume, expressed as cc./lb./min.; C.O.—cardiac output, expressed as cc./lb./min. Sex, age, height and weight of subjects are listed in the first column.

These data confirm the observations of Papper and Bradley (7), and indicate that after the intravenous administration of morphine the only circulatory changes which are significant are the immediate increase in pulse rate and in cardiac output.

II. Circulatory Effects of Morphine Administered Intramuscularly to Subjects in the Supine Position.

Morphine was also injected intramuscularly in 30 individuals; blood pressure and pulse were measured at thirty, sixty and ninety minutes after injection (table 2). There was no significant change in systolic pressure in 23 of these subjects; in 4 the systolic pressure increased

(12 to 20 mm. of mercury) and in 3 it decreased (10 to 20 mm. of mercury). There was no significant change in diastolic pressure in 16, an increase in 11 (8 to 25 mm. of mercury) and a decrease in 3 (8 to 12 mm. of mercury). Pulse increases were noted in only 9 of the 30 subjects. None of the above changes is statistically significant.

III. The Effect of Morphine upon the Circulatory Response to Subjects in the Upright Position.

It is evident from the preceding data that morphine given intravenously or intramuscularly, even in dosage of 20 mg., produced no

TABLE 2

THE EFFECT OF MORPHINE SULFATE ADMINISTERED INTRAMUSCULARLY ON THE BLOOD PRESSURE AND PULSE RATE OF 30 SUBJECTS. DOSE OF MORPHINE INDICATED IN FIRST COLUMN

	Control	After Injection, minutes				Control	After Injection, minutes		
		30	60	90			30	60	90
N.S. M—21 146 lbs. 30 mg.	100/58 60	98/64 72	104/58 60		A.B. F—58 187 lbs. 20 mg.	140/100 88	148/96 84	145/104 76	
J. T. M—23 140 lbs. 20 mg.	122/72 68	114/74 68	124/74 60		G.B. M—57 134 lbs. 20 mg.	120/78 94	128/86 90	114/80 80	
T.B. M—22 170 lbs. 20 mg.	128/66 60	122/64 68	126/68 68		B.R. F—56 163 lbs. 20 mg.	138/95 78	138/92 88	148/100 88	
B.G. F—20 121 lbs. 20 mg.	110/68 68	95/62 66	105/60 66		B.F. M—56 162 lbs. 20 mg.	120/80 98	140/95 88	140/95 84	
J.V. M—21 146 lbs. 20 mg.	118/72 64	118/82 64	124/76 56		I.T. M—23 130 lbs. 15 mg.	118/75 84	112/78 86	108/80 82	
W.F. M—22 170 lbs. 20 mg.	94/66 54	96/66 54	94/66 50		W.S. M—49 137 lbs. 15 mg.	120/70 80	118/72 78	128/78 78	
R.R. M—22 157 lbs. 20 mg.	116/78 60	112/72 72	108/80 60	116/76 64	M.P. F—63 128 lbs. 15 mg.	100/55 64	112/65 70	110/60 68	
R.C. M—22 150 lbs. 20 mg.	120/80 82	116/78 80	112/70 68		C.E. M—59 217 lbs. 15 mg.	148/100 64	148/100 64	145/105 62	

TABLE 2—*Continued*

	Control	After Injection, minutes				Control	After Injection, minutes		
		30	60	90			30	60	90
R.G. M—20 160 lbs. 20 mg.	116/66 66	110/70 70	108/76 76		W.M. F—57 130 lbs. 12 mg.	138/90 84	132/82 88	118/78 88	
I.Z. M—62 168 lbs. 20 mg.	128/80 78	128/90 82	140/95 80		E.B. F—60 115 lbs. 12 mg.	140/80 92	138/80 78	130/75 76	130/75 76
F.K. M—49 175 lbs. 20 mg.	120/90 76	134/100 68	135/98 80		W.D. M—72 160 lbs. 10 mg.	158/72 80	158/70 76	148/72 74	
W.P. M—61 110 lbs. 20 mg.	102/85 92	100/78 80	105/78 84	105/78 84	F.C. M—81 161 lbs. 10 mg.	148/74 72	130/68 70	136/75 60	
C.C. F—61 140 lbs. 20 mg.	145/90 104	140/85 104	138/88 100	135/85 98	L.C. M—68 116 lbs. 10 mg.	124/72 92	118/82 80	118/82 82	120/80 88
M.D. M—44 163 lbs. 20 mg.	110/76 78	105/76 78	115/86 72		L.R. M—68 118 lbs. 10 mg.	100/65 92	105/70 90	105/72 88	110/80 88
L.R. F—47 170 lbs. 20 mg.	108/65 86	106/60 82	110/65 64	112/65 76	H.H. M—80 123 lbs. 10 mg.	180/90 88	180/90 88	170/90 76	

AVERAGE FOR ENTIRE GROUP

	Control	After Injection, minutes		
		30	60	90
Systolic	124.3	123.3	123.7	118.3
Diastolic	76.9	78.2	79.5	77
Pulse	78.2	77.5	73.5	82

important changes in blood pressure in normal supine subjects. So as not to overlook any tendency of morphine to affect the circulation, we decided to impose a strain upon the cardiovascular system by tilting each subject abruptly into the 75 degree head-up position. This produces a sudden displacement of blood from the upper to the lower parts of the body, with a consequent tendency toward cerebral anemia.

Lowering of the blood pressure in the aortic arch and carotid sinuses results and normally this initiates compensatory reflexes which accelerate and augment the heart beat and produce vasoconstriction to offset pooling of blood in the extremities. If morphine depresses the vasomotor center and produces direct vasodilatation in man (as found by Schmidt and Livingston (1) in dogs), these actions should interfere with the compensation to tilting after morphine, and thus reveal a circulatory action of the drug not apparent in the supine position.

Twenty-five subjects were tilted before and thirty minutes after the administration of morphine, each subject thus serving as his own control. All but four subjects were tilted for the same period before and after morphine; these four were tilted longer after morphine because of the presence of signs or symptoms suggesting imminent fainting.

A. Before Administration of Morphine.—The response of our group to tilting was essentially the same as that reported by others (8, 9, 10, 11). One minute after tilting to the head-up position, there was an average increase in pulse of 11.3 beats per minute, an average decrease in systolic blood pressure of 9.7 mm. and an average increase in diastolic pressure of 5.7 mm. of mercury. Two of the 25 (8 per cent) lost consciousness, one after nine minutes, the other after eleven minutes. Of the other 23, 14 were kept in the head-up position for ten minutes and 9 for fifteen minutes without any signs or symptoms suggestive of circulatory collapse.

B. After administration of Morphine.—When the same subjects were tilted thirty minutes after the intramuscular injection of morphine, 11 (44 per cent) either fainted or showed signs and symptoms indicative of imminent circulatory collapse. This occurred in 4, 4, 5, 5, 5, 6, 10, 12, 12, 14 and 14 minutes. It is obvious that morphine does produce circulatory changes in man, but as a rule these changes are revealed only when a strain is placed upon the cardiovascular system.

Certain data upon the 11 "fainters" and 14 "non-fainters" are presented in tables 3 and 4. Examination of data obtained during the pre-morphine tilts shows no important differences between the subsequent fainters and non-fainters that would enable one to predict susceptibility to fainting during the post-morphine tilt. The pre-morphine tilt in the group which subsequently fainted led to slightly less of an increase in pulse rate, a greater decrease in systolic pressure and less of an increase in diastolic pressure in the first minute of tilting, but these changes were not significant.

We were not able to determine from these experiments the predominant site of action of morphine upon the circulation. In 9 of the 11 fainters, the legs and thighs were bandaged from toes to groin with elastic bandages. These subjects were then tilted for a third time (within five minutes after the second tilt) and fainting occurred in

TABLE 3

BLOOD PRESSURE AND PULSE RATE DETERMINATIONS DURING TILT TO THE 75 DEGREE HEAD-UP POSITION BEFORE AND AFTER THE ADMINISTRATION OF MORPHINE SULFATE

Data presented are those obtained from the 14 "non-fainters."

Name, Sex, Age, Weight	Mg. M.S.	Systolic Blood Pressure									Diastolic Blood Pressure									Pulse Rate								
		0	1	3	5	7	9	11	13	15	0	1	3	5	7	9	11	13	15	0	1	3	5	7	9	11	13	15
J.T. M—23	0	116	102	104	98	104	104	108	108	104	70	72	78	80	84	86	88	90	86	76	88	88	92	92	92	92	88	88
140	20	114	104	106	108	106	104	105	102	102	74	80	80	84	84	84	85	84	85	68	88	84	84	84	84	80	80	84
T.B. M—22	0	124	124	122	112	116	110	120	112	116	66	88	90	80	80	88	86	85	80	64	80	76	68	76	72	80	72	88
170	20	122	120	120	128	116	116	114	124		64	82	84	84	78	76	84	84		68	76	76	80	92	92	92	92	
B.G. F—20	0	106	120	112	115	112	110	108			65	75	75	72	78	82	78			68	80	86	90	92	94	94		
121	20	95	105	105	108	108	106	105			62	75	75	80	80	76	75			66	92	96	94	94	96	96		
J.U. M—21	0	118	116	126	124	120	122	124	124	118	70	82	82	82	82	82	82	94	92	64	76	92	84	92	92	92	92	92
146	20	116	124	120	120	120	120	122			80	90	98	96	98	98	96			64	74	80	88	88	84	88		
I.T. M—23	0	112	118	120	120	120	122	122	112	118	75	90	95	86	78	80	82	78	84	82	104	88	88	90	86	92	94	100
130	16	112	110	122	124	120	122	118	115	112	78	75	90	88	85	85	88	88	88	88	126	100	98	100	106	108	86	92
N.S. M—21	0	98	94	98	96	92	94	94	92	86	60	80	70	72	76	70	70	76	76	68	88	100	96	100	96	100	100	96
146	30	98	90	94	98	88	100	100	100	100	64	78	78	82	78	78	74	74	78	72	88	96	92	92	88	100	96	92
W.F. M—22	0	86	76	90	88	90	92	92	90	90	60	62	72	78	68	76	72	76	74	58	82	90	94	90	90	96	96	96
170	20	96	90	92	94	98	98	98	98	98	66	70	72	74	76	82	80	80	80	54	80	90	90	88	86	90	90	88

TABLE 3—*Continued*

Name, Sex, Age, Weight	Mg. M.S.	Systolic Blood Pressure									Diastolic Blood Pressure									Pulse Rate								
		0	1	3	5	7	9	11	13	15	0	1	3	5	7	9	11	13	15	0	1	3	5	7	9	11	13	15
R.R. M—22	0	116	122	110	110	118	120	114	110	110	70	78	82	84	92	96	92	90	92	64	80	76	84	92	88	84	96	94
157	20	112	108	120	120	112	114	120	120	116	70	78	90	88	88	90	88	98	92	72	88	80	84	92	88	92	88	88
W.S. M—49	0	124	100	100	118	112	112				68	75	74	78	75	80				80	88	90	90	90	92			
137	16	118	105	112	118	120	122				72	76	78	80	78	80				78	84	86	88	88	88			
I.Z. M—62	0	130	104	100	110	110	100				80	78	76	76	74	76				88	90	80	76	78	88			
168	20	118	92	104	104	100	100				76	76	76	80	78	80				82	88	88	90	92	86			
F.K. M—49	0	120	115	116	120	115	118	122			80	90	90	90	96	104	110			78	84	84	82	82	78	80		
175	20	120	128	120	118	118	124				88	95	98	102	102	105				72	84	80	80	84	80			
M.P. F—63	0	104	70	95	98	95	86				50	50	55	62	60	55				64	76	82	86	86	86			
128	16	112	90	100	95	90	92				65	60	65	62	60	60				70	72	80	82	80	82			
C.E. M—59	0	146	138	148	150	148	150				102	100	108	105	104	105				66	72	84	70	72	78			
217	16	148	145	145	148	145	138				100	105	105	104	105	105				66	84	78	84	84	88			
W.P. M—61	0	108	105	95	88	92	100				85	90	86	78	80	88				92	100	96	100	100	96			
109	20	105	84	74	84	90	88				78	70	68	74	78	78				84	88	88	92	88	88			
Average		115	107	110							72	79	81							72	85	87						
		113	107	110							74	79	83							72	87	86						

TABLE 4—SAME AS TABLE 3

Data presented are those obtained from the 11 "fainters."

Name, Sex, Age, Weight	Mg. M.S.	Systolic Blood Pressure									Diastolic Blood Pressure									Pulse Rate								
		0	1	3	5	7	9	11	13	15	0	1	3	5	7	9	11	13	15	0	1	3	5	7	9	11	13	15
C.C. F—61	0	145	110	112	106	76	90	?			88	86	82	80	58	80	?			110	118	124	124	124	116	110		
140	20	140	88	95	98	86	70	80	84	68	85	72	80	86	68	60	72	65	62	104	118	118	120	120	116	116	114	114
W.M. F—57	0	138	140	150	152	140	150				90	90	98	100	90	105				82	96	120	104	104	118			
130	12	132	125	138	?						82	102	98	?						88	116	110	62					
M.D. M—44	0	110	110	110	112	112	112				76	80	85	88	88	90				78	86	102	94	90	90			
163	20	105	105	98	102	105	98	70	50		76	80	84	84	88	80	58	?		78	76	88	90	88	84	70	54	
L.R. F—47	0	108	100	100	112	112	112	110	110		65	70	68	70	72	70	74	75		86	90	88	92	90	90	90	90	
170	20	106	90	98	98	95	90	90			60	70	66	70	70	70	70			82	88	90	94	90	90	88		
E.B. F—60	0	146	128	120	130	120					80	90	80	85	84					80	96	96	100	102				
115	12	140	115	100	?						80	85	75	?						70	96	108	?					
A.B. F—58	0	155	125	130	140	136	132				105	100	118	120	118	116				92	100	120	112	114	104			
187	20	148	124	122	114	102	94	80	74		96	94	100	100	94	78	68	64		80	92	96	88	96	92	88	88	
G.B. M—57	0	120	100	100	104	106	100	100			78	80	76	78	82	80	80			94	106	104	106	110	108	110		
134	20	128	108	100	?						86	80	78	?						90	98	104	?					
B.R. F—56	0	138	120	124	128	116	116				95	90	94	90	85	85				78	80	90	88	84	86			
163	20	135	122	116	112	110	110	98	92	92	92	92	88	88	85	85	80	78	78	88	94	94	92	90	90	92	92	90
B.F. M—56	0	125	115	104	106	110	110	110			80	90	84	86	86	88	88			98	96	100	100	120	124	108		
162	20	140	132	108	92	80					95	100	90	78	65					88	92	92	96	64				
R.C. M—22	0	120	110	110	112	118	118	120	114	118	80	85	84	80	84	88	86	86	88	82	106	98	98	98	100	98	98	100
150	20	116	102	102	66						78	90	78	?						76	100	100	50					
R.G. M—20	0	112	120	114	106	103	96	98	80		68	76	70	80	80	76	74	?		66	78	94	96	92	100	92	68	
160	20	108	110	82	74						72	92	64	?						68	80	80	60					
Average		129	116	116							82	85	85							86	96	103						
		127	111	105							82	87	82							83	95	98						

only 2 of these.* While this suggests that peripheral vasodilatation is an important factor, it does not indicate whether this dilatation is due to depression of the vasomotor center or to a nitrite-like action directly upon peripheral vessels. The fact that the immediate pulse increase in response to tilting was greater after morphine than before suggests that the cardio-accelerator centers were not depressed by the drug. It is unlikely that the slight respiratory depression noted following morphine is responsible for the greater incidence of fainting (by a decrease in the thoracic pump mechanism); the decreases in respiratory minute volume, rate and depth were not marked and were equal in the fainter and non-fainter groups.

It is interesting to note that there was a greater tendency to faint in the older age group; 9 of 15 subjects (60 per cent) in the 44 to 63 year group fainted after morphine while only 2 of 10 (20 per cent) of the 20 to 23 year old group fainted. This difference may be attributed to the better muscular tone and consequent better support of the leg veins in the younger group, or to arteriolar sclerosis and decreased efficiency of compensatory reflexes in elderly individuals.

Even in those individuals who did not faint there was a decided difference in the circulatory reaction to tilting between the young and the old. The older subjects showed less of a compensatory response, i.e., a greater drop in systolic pressure and less of a rise in diastolic pressure and pulse rate (table 5).

TABLE 5

MAXIMUM CHANGES IN SYSTOLIC AND DIASTOLIC PRESSURE AND PULSE RATE DURING CHANGE FROM HORIZONTAL TO 75 DEGREE, VERTICAL POSITION. CHANGES EXPRESSED IN PER CENT OF PRETILT CONTROL VALUES

Only those subjects in table 3 (non-fainters) are included.

		Before Morphine, per cent	After Morphine, per cent
Systolic pressure	Young	− 6.0	− 3.7
	Old	−14.4	−14.3
Diastolic pressure	Young	+28.7	+24.5
	Old	+12.4	+ 6.5
Pulse rate	Young	+36.5	+41.7
	Old	+18.4	+22.5

A final observation of interest was the finding that blood pressures readily heard with the subject supine would often be difficult to obtain when the erect posture was assumed. This change in auscultatory findings was not related to a change in level of blood pressure. Oliver commented on this curiosity in 1895, citing evidence to suggest that the difference was due to constriction of the artery (12). The possibility

* It has been shown in other experiments that repeated tilting within the course of 1–2 hours does not change the subject's reaction to tilting. Therefore the improvement brought about by bandaging should be regarded as significant.

of increased muscle tone in the arm with consequent displacement of the vessel should also be considered.

IV. Effect of Posture on Respiration.

In the course of these experiments, considerable data were obtained upon the effect of posture on respiration. This is a subject of considerable theoretical and practical importance, especially in view of the current interest in resuscitation by tilting methods. Respiratory measurements were made during 42 tilts upon 16 subjects. In table 6 are shown respiratory minute volumes and respiratory rates in the control period in the horizontal position, in the first minute after tilting to the head up position, in the last minute in this position and in the first minute after return to the horizontal position. (No figures have been included in the latter 2 columns "vertical to horizontal tilts" for subjects who had fainted or were about to faint just before the return to horizontal position; these will be referred to later.) Three significant trends are shown by these data. (1) Upon tilting from the horizontal to the 75 degree head-up position, the respiratory rate *immediately* decreased in 28 of 39 measurements (average decrease from eighteen to sixteen per minute in the entire group) and the minute volume decreased slightly. These changes were most consistent and marked in the 16 subjects tilted before administration of morphine; in these the average decrease in rate was from 20.1 to 17.1 and in minute volume from 8.9 to 7.6 liters per minute. (2) As the tilt continued the respiratory rate and depth gradually returned to the control (horizontal) figures. By the end of the ten or fifteen minutes in the tilted positions no further changes had occurred in respiration such as those in heart rate. (3) Upon termination of the tilt, respiratory minute volume increased *immediately* in each subject. The average increase before administration of morphine was from 9.2 to 11.8 liters per minute, an increase of 28 per cent (maximal increase was 4.8 liters or 87 per cent); quantitatively, similar changes occurred when the tilt was performed after morphine. This increase in respiration was accomplished chiefly by an increase in the depth of breathing.

Alterations in respiration occurring during change in posture might be caused by several factors: (1) carotid sinus and aortic arch pressure reflexes, (2) changes in cerebral blood flow or (3) lung reflexes. The first may be discounted since tilting from the horizontal to the feet-down position would tend to decrease the pressure in the carotid sinus and aortic arch, decrease inhibitory reflexes to the respiratory center and so accelerate and augment respiration (13). The observed respiratory changes, both at the initiation and end of the tilt, are exactly the opposite of what would be expected on a pressure receptor reflex basis. The second possibility may also be dismissed since a decrease in cerebral blood flow should augment breathing, and vice versa (14); again the observed changes are exactly opposite. It is probable that the respiratory changes are the result of vagal Hering-Breuer re-

TABLE 6

RESPIRATORY RESPONSES TO TILTING. MINUTE VOLUMES OF EXPIRED AIR EXPRESSED AS LITER/MINUTE

Hor. = data obtained during control period in the horizontal position, and in the first minute after return to the horizontal.
Vert. = data obtained during first minute after tilting to the 75 degree head-up position, and during the last minute in this position.

Subject	Before Morphine								After Morphine								After Morphine and Bandages							
	Resp. Min. Vol.				Resp. Rate				Resp. Min. Vol.				Resp. Rate				Resp. Min. Vol.				Resp. Rate			
	Hor.	Vert.	Vert.	Hor.	Hor.	Vert.	Vert.	Hor.	Hor.	Vert.	Vert.	Hor.	Hor.	Vert.	Vert.	Hor.	Hor.	Vert.	Vert.	Hor.	Hor.	Vert.	Vert.	Hor.
B.G.	7.3	5.6	6.0	7.4	23	14	19	18	4.8	4.1	4.4	6.0	16	14	17	17	4.3	4.2	5.5	5.6	18	15	16	23
J.U.	8.9	8.9	9.5	12.5	16	15	14	15	5.7	5.8	8.0	10.8	11	9	16	16								
W.S.	8.1	6.2	8.1	11.7	15	13	16	17	7.9	7.4	7.8	11.6	17	14	15	17								
I.Z.	10.6	9.0	11.6	14.8	26	22	23	31	8.4	7.9	10.8	12.5	20	16	20	25	9.8	8.6	10.2	12.2	22	18	24	24
F.K.	7.2	5.8	9.6	12.4			20	21	6.7	5.6	8.5	13.1	20	13	16	17	8.4	7.1	6.8	10.8	17	17	15	19
M.P.	6.3	5.5	5.5	10.3	16	14	16	20	6.5	4.8	6.0	8.2	16	12	13	15								
C.E.	10.5	10.9	12.2	15.0	18	16	15	17	8.9	10.5	10.5	11.5	13	16	15	15								
W.P.	9.8	6.0	8.5	10.5	20	17	19	18	8.2	6.9	6.9	8.9	16	21	21	17								
C.C.	9.8	8.0	5.7	8.9	22	17	18	19	8.7	6.1			17	13			7.0	5.9	7.4	9.0	21	19	19	20
W.M.	7.0	5.4	7.1	8.2	25	18	24	23									5.2	7.0			21	23		
M.D.	11.0	10.7	13.6	14.8	17	14	19	20	10.1	8.5			16	14			8.4	7.2	9.8	12.2	17	18	18	18
L.R.			9.0	11.7			16	18	5.1	5.2			13	8			5.3	6.4			10	9		
A.B.	9.8	7.8	9.7	12.5	23	19	20	19	7.1	8.0			17	16			7.7	9.0	7.1	12.0			16	14
G.B.	10.0	10.2	12	14.1	16	19	19	19	8.3	9.7			14	15			8.9	8.3			15	17		
B.R.	7.4	7.6	8.5	10.5	24	24	24	24	6.0	5.9			16	18			7.3	5.0	5.4	8.3	18	16	17	16
B.F.	10.4	8.0	11.0	13.0	20	17	22	22	7.8	6.3			18	16			7.3	6.7	7.8	11.4	17	17	17	15
Average	8.9	7.6	9.2	11.8	20.1	17.1	18.8	20.1	7.3	6.9	7.8	10.3	16.1	14.4	16.7	17.4	7.3	6.9	7.5	10.2	17.6	16.9	17.8	18.6

flexes. In the feet-down position, the abdominal viscera slide down, pulling the diaphragm with them and thus causing the lungs to assume an inspiratory position. This leads to a slower respiratory rate. Upon return to the horizontal position the diaphragm moves upward and compresses the lungs, tending to augment respiration. However, the increase in minute volume at the termination of the tilt was much more marked and consistent than the decrease at the initiation of the tilt. Clearly, another factor must play a role at the termination; this is believed to be the result of sudden shift of a large volume of blood pooled in the lower parts of the body during the tilt (17, 29) to the lungs, with consequent pulmonary vascular congestion (15, 16, 30). The extent to which blood may be removed from the active circulation by tilting is indicated by the data of Asmussen (17) who measured leg volume with a plethysmograph and found that at a 60 degree head-up position, 550 cc. of blood could be immediately trapped in the legs alone.

V. Effect of Fainting upon Circulation and Respiration.

In these experiments, data were obtained upon 15 instances of fainting or imminent fainting (2 before morphine and 13 after morphine) in 11 subjects. The pulse at the moment of loss of consciousness was below 70 in 7 cases (68, 64, 62, 60, 58, 54 and 50), above 80 in 6 (82, 88, 88, 90, 110, 114): in 2 the pulse was imperceptible at the wrist at the moment of fainting but had been 108 and 104 a minute before syncope (table 7). The high incidence of pulse slowing at or near the moment of fainting has been described frequently (18, 19). Similar slowing occurs with the cerebral anemia attendant upon increase in intracranial pressure (20, 21) and upon hemorrhage in the supine position (22). The mechanism of this slowing is not known. One would expect that, as the blood pressure approaches shock levels, release of the inhibitory influences from the pressure receptors should lead to maximal pulse acceleration. Some new and more potent factors must supersede these reflexes in cases of cerebral anemia resulting from tilting, increased intracranial pressure and hemorrhage; why they do not slow the pulse in traumatic shock is unknown.

While fainting was often heralded by complaints of weakness, vertigo, anxiety and by pallor, sweating and coolness of the hands, in 6 instances the systolic blood pressure level fell very abruptly and there was little or no warning of imminent syncope. The diastolic blood pressure reading also fell abruptly in 8 subjects.

Respiration was measured in 11 tilts upon 8 subjects (1 before and 10 after morphine) at the moment of fainting or imminent syncope, with the subjects still in the feet-down position. The figures are shown in table 7 along with simultaneous arterial blood pressure measurements. The remarkable feature to be noted is the absence of marked hyperpnea. The maximal increase was from 10.1 to 15.1 liters and the average was from 7.7 to 9.2 liters per minute, an increase of only 20

per cent. At the same time the systolic pressure had decreased below 60 mm. of mercury in 4 instances and the average blood pressure fall was from 129 to 71 mm. systolic and 83 to 63 mm. diastolic. At least two mechanisms might be expected to augment respiration markedly in response to a falling blood pressure. Experiments on dogs indicate that the carotid sinus and aortic arch pressure receptors are capable of increasing respiration reflexly when arterial pressure decreases (13).

TABLE 7

BLOOD PRESSURE, RESPIRATORY MINUTE VOLUME AND PULSE RATE IMMEDIATELY BEFORE FAINTING

Subject	Blood Pressure		Pulse		Respiratory Min. Vol.	
	Control	Last Minute	Control	Last Minute	Control	Last Minute
CC*	145/88	82/70	110	110	9.7	7.3
CC	140/85	68/62	104	114	8.3	8.0
WM	132/82	<82/60	88	62	6.4	7.2
WM†	118/74	58/?	82	58	5.8	8.0
MD	105/76	50/?	78	54	10.1	15.1
LR	106/60	<90/70	82	88	5.1	11.0
AB	148/96	72/62	80	88	7.1	7.4
GB	128/86	<90/66	90	—	8.3	12.0
GB†	125/84	40/?	80	82	8.8	9.0
BR	138/92	92/78	88	90	6.0	8.1
BF	135/92	56/40	88	64	7.8	8.0
RG*	112/68	80/?	66	68	—	—
RG	108/72	74/?	68	60	—	—
EB	140/80	?/?	70	—	—	—
RC	116/78	66/?	76	50	—	—
Average	126/81	<71/63?	83	76	7.7	9.2

* Before morphine.

† After morphine and application of elastic bandages. All others—after morphine but before application of bandages.

Respiration has also been shown to increase under similar conditions even when the pressure receptors are completely denervated (23); this change was thought to be brought about by a decrease in cerebral blood flow which permits an accumulation locally of the metabolites constantly being formed within the respiratory center in the medulla (24). Regulation of respiration by alterations in cerebral blood flow is regarded by some (14, 24) to be of prime importance in the control of normal breathing. However, enough data are presented here to indicate that the peripheral pressure receptors and the central regulatory mechanism either do not respond well in unanesthetized man or are suppressed during cerebral anemia. It is significant that the anticipated increase in pulse rate is often lacking under these same conditions. It should be pointed out that the chemoreceptors of the carotid and aortic bodies are not concerned in this response to low blood pressure, since the arterial oxygen tension remains normal.

While we have insufficient information upon respiration during fainting in normal non-morphinized individuals, our 1 case suggests that the failure of respiration to respond more vigorously to cerebral anemia is not attributable to the action of morphine upon the respiratory center.

DISCUSSION

While it may be reassuring to clinicians to know that morphine given intravenously to normal supine patients does not produce the fall in blood pressure so characteristically seen in dogs, this does not mean that the drug has no effect upon the human circulation. During or immediately after an intravenous injection of morphine, both pulse rate and cardiac output per minute increased significantly. The cause of this circulatory effect is not clear. No drop in blood pressure could be detected at this time, using the Riva-Rocci technic.

It is possible that the compensatory mechanisms of unanesthetized man are more sensitive than the methods ordinarily used to measure blood pressure. Thus, reflexes from the pressure receptors of the carotid sinus and aortic arch areas may initiate reflexes for the stabilization of blood pressure even though little change in arterial pressure is noted by clinical measurements. On the other hand the increase in pulse rate and cardiac output which immediately followed the injection may have been caused by a cerebral action of morphine similar to that produced by other narcotics or anesthetics, i.e., the response being a reaction to the feeling of vertigo or imminent syncope. That it was not a result of anxiety about venipuncture is evident from the absence of changes in the pulse rate following the intravenous injection of physiologic saline solution.

Although the circulatory effects of morphine are unimportant in the normal supine individual, they assume much more significance when the circulation is put under a strain. A great increase in the incidence of fainting or circulatory collapse resulted from tilting head-up after the injection of morphine. This may be caused by a number of factors, such as decreased skeletal muscle tone, diminished respiration (3), depression of carotid sinus and aortic arch reflexes, depression of the vasomotor center, increased capillary permeability with loss of circulating fluid, or peripheral vasodilatation. Of all these factors, the last named is in our opinion the most important. The immediate response of pulse, systolic and diastolic blood pressure to tilting was not greatly different after morphine; this excludes marked depression of the pressure receptor zones and of the vasomotor center. While increased capillary permeability in the dependent areas may be an important factor when tilting is carried out for long periods (17), its effect cannot be great in a subject who fainted four minutes after tilting. If direct peripheral vasodilatation is the predominant factor, morphine consequently has a circulatory action similar to that of histamine (1) and the nitrites (25).

The influence of drugs upon the circulatory compensation in response to the erect position has not been studied extensively. The ability of various sympathetic amines to prevent orthostatic hypotension is well known (26). Weiss (25) has reported upon the action of sodium nitrite in inducing orthostatic collapse. Hill in 1895 (27) reported that chloroform rapidly paralyzed compensatory vasomotor mechanisms in dogs (the animals dying when the head was raised) and Gordh (28) has noted the effects of ether and short-acting barbiturates upon the response to tilting. It is particularly important that the effects of sedatives, analgesics and anesthetics upon the circulation be studied since these substances are often employed in individuals suffering from shock and hemorrhage.

Our results indicate that movement of a "morphinized" patient from the supine to the sitting or semi-erect position may be followed by vascular collapse. During operations performed with the patient in the sitting position, the surgeon or anesthetist must bear in mind the possibility of sudden vascular collapse if large amounts of morphine (and presumably other narcotics) have been used, particularly in elderly patients. In our clinical experience, vascular collapse occurs less often in such operations (such as section of the fifth cranial nerve for trigeminal neuralgia) if ether is used than if morphine and regional block are employed; this may be the result in part of the stimulating effect of ether upon the sympathetic nervous system (31, 32). Hill (27) also noted that ether paralyzed compensatory mechanisms very slowly and only when given in large amounts.

Our results also indicate that injured individuals given large doses of morphine should be transported by litter and not by "passive walking" between attendants. It is probable, in addition, that shock and hemorrhage impose strains upon the circulation analogous to those produced by our tilting experiments and if our interpretation is correct, morphine given in large amounts to patients with surgical shock or hemorrhage would be expected to aggravate the circulatory inadequacy. The same may be true of other conditions in which impairment of vascular regulatory mechanisms has been shown to occur, such as in certain types of heart disease, hypertension, thyrotoxicosis, neurocirculatory asthenia and following dorsolumbar sympathectomy (26). Finally, when a patient must be operated upon in the sitting position it might be of value to test preoperatively his response to tilting after morphine.

The data likewise demonstrate that prevention of pooling of blood in the extremities by bandaging of the legs (8, 33) is of real therapeutic value; 9 of 11 subjects (who fainted when tilted after morphine) did not faint when retilted after application of elastic bandages. Others have suggested that resistance to orthostatic circulatory collapse may be increased by "training," either by graduated periods in the head-up position (33) or by improvement of muscle tone through exercise (8,

11). Bandaging is obviously a more practical emergency or preoperative measure than these others.

Since warm environments predispose to circulatory collapse on tilting (16), it is likely that the hot humid environment of many operating rooms may be a factor in vasomotor collapse.

It appears, then, that bandaging of the legs, a temperate environment, and a supine or slight Trendelenburg position may prevent vascular collapse following strains upon the circulation imposed by morphine, hemorrhage, shock, the erect position or combinations of these. Sympathomimetic drugs may also be employed.

The respiratory responses to tilting from the vertical to the horizontal are of interest chiefly in that they supply an indication of the magnitude of the reflex respiratory response to sudden pulmonary congestion. In addition, it is noteworthy that the respiratory centers do not respond more vigorously to a marked fall in blood pressure level and presumably in cerebral blood flow.

CONCLUSIONS

1. The effect of morphine upon the circulation of man in the supine and erect position has been studied.

2. Morphine injected intravenously produces an immediate but transient increase in pulse rate and cardiac output.

3. Morphine administered intramuscularly or intravenously has no significant effect on blood pressure level while the subject remains supine. When the 75 degree head-up position is assumed, a circulatory action of the drug becomes apparent. This is manifest by an increased incidence of fainting in response to this postural change.

4. The clinical implications of these findings are discussed.

5. Data are presented on the circulatory and respiratory responses at the time of fainting.

6. The respiratory response to change in position has been measured.

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