EFFECTS OF POSTURE AND ATROPINE ON THE CARDIAC OUTPUT[1]

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The factors determining cardiac output in man are incompletely understood. In this light, recent studies on vasodepressor syncope in this laboratory have suggested the presence in the upright subject of factors limiting the cardiac output response (1). In an attempt to investigate the nature of such factors, the present study on the effects of drug induced tachycardia in recumbent and upright subjects was undertaken. Atropine was selected as the experimental drug because of its well known cardio-accelerator effects, which in recumbent subjects is associated with little or no alteration in stroke volume. Additional observations have been made on modifications of the response to atropine during the peripheral pooling of blood with venous occlusive tourniquets and during anti-gravity suit inflation.

METHOD

The subjects were normal male university students, with ages from 18 to 25 years. The cardiac output was determined by the dye dilution method of Hamilton, Moore, Kinsman, and Spurling (2), as modified by Doyle, Wilson, Lépine, and Warren (3). In all studies a steady state, as determined by constancy of arterial pressure and pulse rate on monitored records, was achieved before the time of cardiac output determinations. Stroke volume was calculated from the pulse rate during the interval of the cardiac output determinations. Arterial and central venous pressures were obtained by strain gauge and recorded on a photographic multichannel recording system. The fourth intercostal space 5 cm. below the angle of the sternum was the reference point for all pressure determinations. Mean pressures were obtained electronically. A single balloon, half-body anti-gravity suit of the type reported by Beckman, Slaughter, and Wood (4) was employed in the studies of the effect of body compression. Inflation was maintained at 70 mm. Hg body pressure for five minutes before cardiac output determinations were performed in the control and postatropine states.

Mean circulation time and "central" blood volume was calculated by the Hamilton method from the dye dilution curves. Statistical analysis of the data was performed according to the methods described by Snedecor (5).

RESULTS

Effects of atropine in recumbent and passive erect postures

Two groups of six subjects each were studied, one in the recumbent and the other in the passive posture tilted head-up at 60 degrees. In all studies, control cardiac output determinations in the appropriate posture were made. Ten to fifteen minutes following the control determination, two milligrams of atropine sulfate were administered intravenously (catheter) over a one minute period, and cardiac output again determined one to three minutes after completion of the injection. In all subjects, tachycardia was in evidence at the time of this determination. In the studies performed with subjects tilted head-up at 60 degrees, the control and postatropine cardiac output determinations were performed during the same time intervals following assumption of the tilted position (usually three to six minutes). Arterial and central venous pressures were recorded continuously, except for interruptions during injection and collection periods.

The data are summarized in Tables I and II. In the recumbent position, striking increases in cardiac index and pulse rate were noted. The mean stroke volume was not altered significantly from control values. A fall in central venous pressure was noted in the four subjects in whom it was studied. Mean arterial pressure tended to rise slightly. The reductions in calculated total peripheral resistance can be attributed predominantly to the cardiac output changes.

In contrast to the changes noted with the subject in the recumbent position, the absolute and relative cardiac output elevations following atro-

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TABLE I

Effect of atropine on the cardiac index in recumbency and tilted head-up at 60 degrees

Recumbent				60° head-up tilt			
Subject		Cardiac index *L./min./M.²*	% change	Subject		Cardiac index *L./min./M.²*	% change
J. M.	B*	2.81		J. M.	B	2.55	
	A	5.19	+ 85		A	2.88	+13
J. G.	B	2.90		C. H.	B	2.32	
	A	4.53	+ 56		A	2.72	+17
D. M.	B	3.00		D. M.	B	2.86	
	A	6.71	+124		A	3.14	+10
A. Q.	B	2.94		R. K.	B	3.21	
	A	5.17	+ 76		A	3.21	0
P. B.	B	2.83		H. S.	B	2.01	
	A	5.31	+ 88		A	1.95	− 3
P. O.	B	2.91		J. C.	B	2.39	
	A	3.72	+ 28		A	2.96	+24
Average	B	2.90			B	2.56	
	A	5.06	+ 76		A	2.79	+10
p		<0.01				>0.05	

* B = Before atropine administration.
A = One to three minutes after atropine administration.

TABLE II

Hemodynamic effects of atropine administration in recumbency and tilted head-up at 60 degrees

Recumbent									
Subject		Cardiac output (*L./min.*)	Heart rate (*beats/min.*)	Stroke volume (*ml.*)	Mean arterial pressure (*mm. Hg*)	Total peripheral resistance (*units*)*	Central venous pressure (*cm. H_2O*)	Mean circulation time (*seconds*)	"Central" blood volume (*ml.*)
J. M.	B†	5.93	60	99	82	1,189	5	18.8	1,856
	A	10.96	120	91	90	656	−2	11.0	2,006
J. G.	B	6.20	64	98	76	980		22.6	2,337
	A	9.69	98	99	80	826		15.7	2,539
D. M.	B	5.70	68	84	87	1,220		25.7	2,440
	A	12.74	120	106	83	520		16.9	3,593
A. Q.	B	5.24	56	94	80	1,220	8	20.7	1,808
	A	9.20	94	98	93	808	4	14.1	2,162
P. B.	B	6.25	64	98	85	1,087	−1	20.8	2,169
	A	11.72	94	125	101	689	−4	15.5	3,024
P. O.	B	5.86	72	81	81	1,104	0	18.1	1,770
	A	7.48	120	62	89	951	−4	16.4	2,042
Average	B	5.86	64	92	79	1,133	3.0	21.1	2,063
	A	10.30	108	97	86	742	−1.5	14.9	2,561
S.D.‡		0.76	4.7	7.1	2.8	87		1.0	167
p		<0.01	<0.01	>0.5	<0.05	<0.01		<0.01	<0.05

* Dyne seconds times $cm.^{-5}$.
† B = Before atropine administration.
A = One to three minutes after atropine administration.
‡ Refers to standard error of the difference between means.

TABLE II—*Continued*

Subject		Cardiac output (*L./min.*)	Heart rate (*beats/min.*)	Stroke volume (*ml.*)	Mean arterial pressure (*mm. Hg*)	Total peripheral resistance (*units*)*	Central venous pressure (*cm. H_2O*)	Mean circulation time (*seconds*)	"Central" blood volume (*ml.*)
		60° head-up tilt							
J. M.	B	5.36	74	72	92	1,371	0	23.8	2,128
	A	5.84	136	43	95	1,300	0	23.1	2,248
C. H.	B	4.70	78	50	90	1,530		18.0	1,410
	A	5.52	148	37	85	1,231		16.8	1,546
D. M.	B	5.43	70	77	80	1,177		18.9	1,710
	A	5.96	138	43	80	1,073		16.5	1,639
R. K.	B	6.45	104	62	71	879		14.5	1,561
	A	6.45	168	36	69	854		20.2	2,174
H. S.	B	3.68	94	39	81	1,759	0	20.1	1,233
	A	3.58	152	24	85	1,846	−1	22.8	1,360
J. C.	B	4.37	60	73	87	1,591		21.2	1,543
	A	5.41	132	41	88	1,299		16.0	1,444
Average	B	5.00	80	64	84	1,385		19.4	1,598
	A	5.46	145	38	84	1,267		19.2	1,735
S.D.‡		0.18	2.2	4.2	1.7	62		1.6	104
p		>0.05	<0.01	<0.01	>0.9	>0.1		>0.9	>0.2

pine administration were significantly less in subjects in the passive erect posture ($p < 0.01$). The cardiac acceleration following atropine in this group was of greater relative and absolute magnitude, and the mean stroke volume fell significantly. Central venous pressure fell slightly in one of two subjects in whom it was studied. Mean arterial pressure and calculated peripheral resistance were not significantly altered.

"Central" blood volume was significantly higher in the recumbent subjects ($p < 0.05$). Following atropine, the mean central blood volume rose in the recumbent group, but did not change significantly in the tilted subjects.

Effects of anti-gravity suit inflation

Four studies were performed in which cardiac output was determined successively tilted head-up at 60 degrees, in the same position during sustained anti-gravity suit inflation (70 mm. Hg body pressure for five minutes), and tilted head-up at 60 degrees during sustained anti-gravity suit inflation one to three minutes following the intravenous administration of two milligrams of atropine sulfate. The data are summarized in Table III.

Sustained anti-gravity suit inflation resulted in slight increases in cardiac output in three of the four subjects with significant increase in stroke volume and "central" blood volume ($p < 0.05$). The increases in cardiac output following atropine in the vertical posture during sustained compression of the lower abdomen and lower extremities were significantly greater than the changes in cardiac output following atropine in the vertical posture alone ($p < 0.01$). The magnitude of these increases fell midway between those in the vertical and recumbent postures.

The pulse rate, calculated stroke volume, and "central" blood volumes following atropine administration in the above subjects likewise fell midway between the results in the vertical and recumbent subjects.

Effects of peripheral blood pooling

In order to study a component part of the postural reaction, the effect of peripheral pooling of blood was studied in five subjects. Blood pooling was produced by placing pneumatic cuffs high on three extremities and inflating to diastolic pressure levels. Cardiac output determinations were performed in the following sequence: 1) con-

TABLE III

Response to atropine during head-up tilt as modified by anti-gravity suit inflation

Subject		Cardiac index L./min./M.²	% change*	Heart rate beats/min.	% change*	Stroke volume ml./beat	% change*	"Central" blood volume ml.	% change*
J. K.	T†	2.85		80		67		1,491	
	T+G	3.81		84		85		2,111	
	T+G+A	5.21	+37	136	+62	72	−15	2,360	+12
P. R.	T	2.08		80		47		963	
	T+G	2.66		62		78		1,460	
	T+G+A	4.15	+56	108	+74	70	−10	1,495	+ 2
D. M.	T	2.59		88		55		1,387	
	T+G	3.01		79		72		1,640	
	T+G+A	4.40	+46	136	+72	61	−15	1,803	+10
P. B.	T	2.31		75		68		1,615	
	T+G	2.19		63		77		1,750	
	T+G+A	2.84	+30	104	+65	60	−22	1,969	+13
Average	T	2.46		81		59		1,362	
	T+G	2.92		72		78		1,740	
	T+G+A	4.15	+42	121	+68	66	−16	1,907	+ 9
p*		<0.01		<0.01		<0.01		<0.05	

* Refers to change from T plus G following atropine administration.
† T = Tilted head-up at 60 degrees.
G = During anti-gravity suit inflation.
A = One to three minutes after atropine administration.

TABLE IV

The effects of peripheral pooling of blood on the response to atropine in recumbent subjects

Subject		Cardiac index L./min./M.² Cuffs off	Cardiac index L./min./M.² Cuffs on	Heart rate beats/min. Cuffs off	Heart rate beats/min. Cuffs on	Stroke volume ml./beat Cuffs off	Stroke volume ml./beat Cuffs on	Central venous pressure cm. H_2O Cuffs off	Central venous pressure cm. H_2O Cuffs on	"Central" blood volume ml. Cuffs off	"Central" blood volume ml. Cuffs on
E. W.	B*	2.35	2.10	64	66	73	64	4.0	−3.0	1,659	1,607
	A	4.14	2.85	124	130	67	44	−2.5	−3.5	2,169	2,027
C. H.	B	2.34	2.41	50	54	94	89	2.0	0.0	1,890	1,683
	A	5.17	3.46	112	106	92	65	−4.0	−4.5	2,565	2,197
E. F.	B	2.63	2.15	48	48	105	85	3.0	1.0	2,048	2,078
	A	4.94	3.13	106	106	89	57	1.5	−1.5	2,622	1,947
D. M.	B	3.00	2.36	68	66	85	69	1.0	−2.0	2,066	1,663
	A	4.51	3.29	112	126	77	50	−3.0	−5.0	2,120	2,030
D. C.	B	3.87	3.46	62	70	119	94	3.0	−2.5	2,208	2,169
	A	5.65	3.41	120	136	89	47	−2.0	−3.0	2,500	2,026
Average	B	2.84	2.50	58	61	95	80	2.6	−1.3	1,974	1,840
	A	4.88	3.23	115	121	83	53	−2.0	−3.5	2,395	2,045
S.D.†		0.24	0.20	3.2	2.5	5.0	5.5	0.9	0.8	111	142
p		<0.01	<0.05	<0.01	<0.01	<0.05	<0.01	<0.01	<0.05	<0.01	>0.2

* B = Before atropine administration.
A = After atropine administration.
† S.D. refers to standard error of the difference between mean values.

trol observations before cuff inflation, 2) during the tenth to twelfth minute of cuff inflation, 3) two to three minutes following atropine sulfate administration during a comparable period of cuff inflation, and 4) six to eight minutes after atropine administration, but following deflation of the cuffs. The atropine was administered intravenously in two milligram doses as in the previous studies. In this manner the effects of venous pooling on the hemodynamic alterations induced by atropine were ascertained.

The data are summarized in Table IV. Sustained cuff inflation resulted in slight falls in cardiac index in four of the five subjects, and a slight decrease in stroke volume in all the subjects. Heart rate remained virtually unchanged while central venous pressure fell consistently. The "central" blood volume tended to be diminished during cuff inflation.

The effects of atropine when the pneumatic cuffs were not inflated were similar to the changes in the previous group of recumbent subjects. A comparison of the atropine effects before and during cuff inflation reveals a significant diminution in the cardiac output and stroke volume response during the peripheral pooling of blood ($p < 0.01$), associated with only slight differences in the degree of tachycardia. Central venous pressure fell consistently following atropine administration, the magnitude of these falls being less during cuff inflation. The increases in "central" blood volume following atropine were of lesser degree during cuff inflation.

DISCUSSION

Employing a variety of techniques, numerous investigators have reported that the cardiac output falls when man assumes the passive upright posture (6–8). On analysis in theory, these observed decreases in cardiac output might occur as the result of either reduced demands on the circulation, or limited ability of the heart to respond in the vertical stance. Oxygen consumption in the upright posture has been found to increase in most instances (7, 9), suggesting increased rather than decreased metabolic demands. If the diminished cardiac minute volume during standing reflects a limitation on the cardiac output in this position, a study of the response to an agent which ordinarily elevates cardiac output might serve to illuminate this factor more clearly. Accordingly, the effect of atropine has been studied. Although there have been somewhat conflicting experimental data reported, it appeared clear that the effect of rather large doses of atropine given intravenously would significantly elevate the cardiac output of the human subject in the recumbent position (10–12). The control observations of the present study confirm this finding.

The most striking feature of the observations reported here is that with the subject in the tilted position, atropine no longer elicits an increase in cardiac output. Furthermore, the failure of atropine to increase cardiac output in this position can be in part reversed by the application of anti-gravity suit compression. Similar reductions in the cardio-stimulatory effects of atropine are observed during the peripheral pooling of blood with venous occlusive tourniquets. Explanations for these phenomena must be considered.

When man assumes the upright posture, there is a considerable shift of blood to the lower part of the body, and a depletion of the central venous reservoir (13, 14). The decline in cardiac output, observed under these conditions, is associated with a decreased pressure in the right atrium (15), and evidence indicative of a decreased rate of ventricular filling (16). It is under these circumstances that tachycardia fails to produce an increased cardiac output. This observation is of particular interest in light of the suggestion that the central venous volume plays a strategic role as an immediate source of blood to sustain any sudden increase in cardiac output (14). In the recumbent posture, it would appear that more than adequate blood is available to meet the demands of a sudden tachycardia. Atrial pressure is relatively high and cardiac filling occurs rapidly. On assuming the upright position, the thoracic venous reservoir is depleted, ventricular filling is slower, and now stroke volume falls as the heart rate is suddenly increased. The capacity of the heart to increase its output becomes more directly dependent upon the systemic venous inflow. Under these circumstances, factors which increase venous inflow by diminishing gravitational effects, such as body compression by the anti-gravity-suit, restore cardiac responsiveness.

It is interesting to note that a higher pulse rate appears folowing atropine in the tilted individual,

as compared with the recumbent one. It would appear possible that the diminished stroke volume following atropine in the upright subjects could be related to the greater degree of tachycardia, the heart rate now being beyond an optimum level for ventricular filling. The observations on the effects of blood pooling, however, demonstrate a similar response to atropine but without significant differences in heart rate.

Consideration has been given to actions of atropine other than its effect on heart rate. It is possible, for instance, that atropine enhances peripheral blood pooling in the upright subject and in this manner further depletes the central reservoir. Such a peripheral action of atropine has not been demonstrated to our knowledge. The observations on the central blood volume and central venous pressure in the tilted subjects do not support such a formulation. However, if additional pooling did occur in the upright subject it would fortuitously complement the design of these experiments and would not alter their interpretation.

The atropine induced increases in cardiac output are primarily the result of rate alterations with practically no change in stroke volume. Other substances such as isoproterenol (Isuprel®) appear to produce increases in cardiac output by a more direct action on the myocardium. Studies in this laboratory on the effects of isoproterenol have demonstrated only slight diminution in the cardiac output response to this agent with subjects in the upright position (17). These observations would indicate that the limitations imposed on cardiac responsiveness by a diminished central reservoir may in part be superseded by alterations in ventricular dynamics.

Although there has been considerable debate in the literature on the validity of the determinations of central blood volume from dye injection data, the changes in calculated central volume ("Q" value) in the upright posture, during anti-gravity suit inflation and with peripheral blood pooling, were generally consistent with those expected from knowledge of the blood volume shifts induced in these situations (3). It is of particular interest that under the experimental situations when the cardiac output increased significantly, an elevated calculated central volume also appeared. The exact location between catheter tip and sampling site (including all temporally equidistant points) where this increase occurs unfortunately cannot be ascertained by the present methods. It is of further interest that the measured pressure at the point of dye injection (superior vena cava) consistently fell when the cardiac output and central volume increased. The exact meaning of these observations remains obscure at this time and their interpretation with respect to the central venous reservoir thesis outlined above can only be speculative. It should be emphasized, however, that the central reservoir of blood immediately available to the heart is probably but one compartment in the so-called central blood volume calculated from dye injection data, and that each may change independently during hemodynamic alterations. Studies are presently in progress in an attempt to delineate better the nature of these pressure and volume phenomena.

SUMMARY AND CONCLUSIONS

1. The cardiac output response to tachycardia induced by the intravenous administration of atropine sulfate has been studied in twelve normal subjects in recumbency and tilted head-up at 60 degrees. In four instances the effects of anti-gravity suit compression on the response to atropine in tilted subjects were studied. In five subjects the effects of peripheral venous pooling of blood on the response to atropine were also observed.

2. Significant increases in cardiac output, primarily the result of increased heart rate with little change in mean stroke volume, occurred in recumbent subjects. Only slight elevation of cardiac index, despite even greater tachycardia associated with a fall in mean stroke volume, occurred in the tilted group. Similar results following atropine were observed during peripheral pooling of blood. Sustained anti-gravity suit inflation restored, in part, the cardiac responsiveness to atropine in tilted subjects.

3. These data support the thesis that the central venous reservoir is an important determinant of cardiac responsiveness.

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