THE EFFECT OF EXPERIMENTALLY INDUCED HYPERVOLEMIA ON CARDIAC FUNCTION IN NORMAL SUBJECTS AND PATIENTS WITH MITRAL STENOSIS *

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The physiologic differences between various types of laboratory preparations and unanesthetized man have been in part responsible for a wide diversion of opinion concerning the control of cardiac function in man (1). While numerous studies of the regulation of cardiac performance have been carried out in animals, relatively few studies have been done in man (2). The present work was undertaken in an attempt to clarify some of the mechanisms concerned with the control of cardiac function in man and has included studies in normal subjects and patients with mitral stenosis.

During a study of the relation existing between renal and cardiac function, rapid intravenous infusions were given to normal individuals and patients with various types of cardiac disorders (3). When the infusions consisted of isotonic solutions of dextran¹ it was possible to analyze the relation of right heart filling pressure to cardiac output or right ventricular work, in a manner which closely simulated that used by Sarnoff and Berglund in the anesthetized dog (4), or Warren, Brannon, Weens and Stead in man (5). The present report is concerned with the effects on cardiac performance of varied degrees of expansion of the blood volume during 32 studies in 31 normal subjects and 16 studies in 15 patients with mitral stenosis.

MATERIAL

Normal Subjects. Twenty-seven normal volunteers who were either policemen, medical students, or nurses

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were studied on an ambulatory basis, each resting for an hour before and after the study. On the basis of a history and physical examination none of these subjects showed evidence of cardiac or renal disease. In addition, four patients hospitalized because of cardiac symptoms but lacking objective findings of heart disease were studied. One of these subjects (No. 864) had high control values for oxygen consumption (339 and 358 ml. per minute), pulse rate (109 and 118 beats per minute) and cardiac index (7.06 and 6.68 ml. per minute per M.² body surface area [B.S.A.]). The oxygen consumption, pulse rate and cardiac index remained high throughout the study. This subject did not give a history suggestive of hyperthyroidism and the renal excretion and thyroid uptake of I¹³¹ as well as the protein bound iodine were within normal limits.

One subject (No. 948 and 976) was studied on two occasions three and one-half months apart.

The age of the subjects ranged between 16 and 49 years. Nineteen subjects were male and 12 were female.

Patients. Seventeen patients with rheumatic heart disease and mitral stenosis were studied. The data in two patients have been excluded from the results. One of these patients developed an allergic reaction to dextran manifested by urticaria and a marked fall in blood pressure, while the other patient was unable to tolerate the procedure due to the severity of her cardiac disease. All of the patients had the classic signs of mitral stenosis. Most of the patients were only moderately limited by their heart disease and were classified functionally in group I or II according to the criteria of the American Heart Association. Two of the patients (Nos. 873 and 990) were more severely affected and were classified in group III. One of the patients was studied both before and after commissurotomy (No. 994 and 1009). This patient and one other (No. 979) had atrial fibrillation. All other patients had sinus rhythm. None of the patients were receiving cardiac medications at the time of the study except for three patients (Nos. 873, 994 and 1009) who were fully digitalized. The patients ranged in age from 26 to 49 years. Eleven patients were female and four were male.

Figure 1 shows the age and heart size of the patients as well as the physiologic data prior to the start of the intravenous infusions. The patients receiving infusions of dextran in isotonic saline solution had somewhat larger hearts, slightly lower cardiac indices and higher pulmonary arterial pressures than those receiving infusions of dextran in 5 per cent glucose and water.

FIG. 1. CONTROL DATA OBTAINED ON ALL PATIENTS RECEIVING INFUSIONS OF DEXTRAN IN 5 PER CENT GLUCOSE AND WATER (BLACK DOTS) AND DEXTRAN IN ISOTONIC SALINE SOLUTION (X)

Heart volume is given in ml. according to Liljestrand's method. RAM designates right atrial mean pressure in mm. Hg; PAM, pulmonary arterial mean pressure in mm. Hg; PR, pulse rate per minute; O₂ cons., oxygen consumption in ml. per minute; CI, cardiac index in L. per minute per M.² B.S.A.

METHODS

The pulmonary artery was catheterized according to the method of Cournaud and Ranges (6-8). In four normal individuals (Nos. 855, 864, 907 and 926) and in three patients (Nos. 858, 863 and 925) a double lumen catheter was used. In two normal individuals (Nos. 867 and 986) and in five patients with mitral stenosis (Nos. 897, 967, 969, 979 and 994) two catheters were introduced, the tip of one catheter being placed in the pulmonary artery and the tip of the other in the right atrium. In all other studies the right atrial pressure was measured during passage of the catheter into the pulmonary artery, and again on withdrawal of the catheter just before the intravenous infusion was ended.

An indwelling arterial needle was placed in the brachial artery. Cardiac output was determined according to the direct Fick principle with simultaneous sampling of expired air and blood from the pulmonary and brachial arteries during a two minute period (9). The blood gases were determined in duplicate according to the technique of Van Slyke and Neill (10). Duplicate analyses of the expired air were carried out in a Haldane apparatus.

Blood samples for hemoglobin determinations were obtained periodically from the indwelling arterial needle. Hemoglobin content was measured from the amounts of oxyhemoglobin read in a Beckman spectrophotometer. The percentage decrease in hemoglobin was used as an indication of the increase in blood volume. Pressures were measured by Elema strain-gage manometers, the zero point of reference being 5 cm. below the sternum at the level of the fourth costochondral junction.

The right ventricular work was calculated using the following formulae: Right ventricular work index (RVWI) in Kg. per minute per M.² B.S.A. = cardiac index $\times$ (mean pulmonary arterial pressure - mean right atrial pressure) $\times$ 13.6/1,000.

Right ventricular stroke work index (RVSWI) in Gm.-M. per beat per M.² B.S.A. = stroke index $\times$ (mean pulmonary arterial pressure - mean right atrial pressure) $\times$ 13.6.

Procedure. All studies were performed in the morning with the subject recumbent and in the postabsorptive state. Since the study included an evaluation of renal function and renal hemodynamics the patient was initially given a priming dose of inulin and para-aminohippurate intravenously. During the remainder of the study these substances were given at a constant rate with a motor driven syringe. As part of the renal study, collections of urine were begun 30 minutes following the priming dose of inulin and para-aminohippurate and were repeated every 10 to 15 minutes during the remainder of the procedure. Blood samples for the clearance determinations were obtained from the brachial artery at the time of each collection of urine.

Approximately one hour after the priming doses of inulin and para-aminohippurate had been given and 30 minutes after the catheter or catheters had been positioned, peripheral and pulmonary arterial blood samples were obtained with the collection of expired air and the measurement of right heart and peripheral arterial pressures. In most individuals two control determinations of the cardiac output were obtained one to two minutes apart. The mean of these two values was used for com-

parison with the data obtained as the study progressed (9). Similar duplicate determinations of cardiac output were not made during the remainder of the study.

The infusion was begun immediately following the determination of the control values for oxygen consumption, arteriovenous oxygen difference, pulse rate and right heart and peripheral pressures.

Initial studies carried out with infusions of dextran alone proved unsatisfactory due to the occurrence of hemolysis. In two normal subjects (Nos. 851 and 855) and one patient (No. 858), a 10 per cent solution of dextran in water was used. In all subsequent studies dextran was infused as a 6 or 8 per cent solution with either 5 per cent glucose and water or isotonic saline solution. No evidence of hemolysis occurred with infusions of dextran solutions of this type. Thus, in 18 normal subjects and 15 patients with mitral stenosis, 6 per cent dextran was given either in 3 per cent glucose and water (13 normal subjects and nine patients with mitral stenosis) or in isotonic saline solution (five normal individuals and seven patients with mitral stenosis). In 12 normal subjects infusions of 5 per cent glucose and water (three subjects), isotonic saline solution (five subjects) and distilled water (four subjects) were given.

The infusions were given with a syringe driven by a motor at a constant rate so that approximately 25 ml. of fluid were injected per minute (11). Infusions of distilled water were given through a catheter, the tip of which lay in the right atrium. All other types of infusions were given through a polyethylene catheter which was inserted for a short distance into one of the antecubital veins. In normal subjects, solutions containing dextran were ordinarily given for 60 minutes. All other infusions in the normal individuals were given for periods of up to 100 minutes. In patients with mitral stenosis the infusions of dextran were terminated 30 to 50 minutes after their onset due to the rapid rise in pulmonary arterial pressure that ordinarily occurred at this time.

Cardiac output ordinarily was measured twice during the period of the infusion and again, in some instances, 15 to 20 minutes following the termination of the infusion. Measurement of right heart and peripheral pressures were carried out at 10 to 15 minute intervals at the onset of the infusion and more often during its later phases. All of the physiologic measurements were made without interrupting the infusion once it was begun.

No complications were noticed except in the two patients mentioned previously. None of the other subjects manifested signs of apprehension, dyspnea, orthopnea or pulmonary edema despite increases in blood volume of approximately 25 per cent and marked elevation of pulmonary arterial and right atrial pressures.

RESULTS

The necessity for infusing large amounts of water, glucose or saline with the dextran lead to a study of the cardiovascular effects of these fluids when they were given in a manner similar

to that in which the dextran solutions were infused. Although infusions of distilled water produced hemolysis when given into a peripheral vein, no hemolysis developed when the infused water was given through a catheter, the tip of which lay in the right atrium.

In normal subjects infusions of isotonic saline solution, 3 per cent glucose in water and distilled water (Table I) produced a mean increase in blood volume of 5.3 per cent during the first 40 minutes of the infusion and 8.4 per cent when the infusion was continued for periods up to 80 minutes. Increases in blood volume of this magnitude produced no significant changes in heart rate, oxygen consumption, arteriovenous oxygen difference, cardiac index, stroke index, right atrial mean pressure and brachial arterial mean pressure (Table II). The mean value for pulmonary arterial mean pressure rose 2.5 mm. Hg or 27 per cent ($0.05 > p > 0.02$). Right ventricular stroke work index could be evaluated in only four studies rising less than 20 per cent in two subjects and 69 and 122 per cent in the other two individuals.

When dextran was given, with either 5 per cent glucose in water (Table III) or isotonic saline solution (Table IV), to normal subjects or patients without cardiovascular disease, the mean increase in blood volume was 12.9 per cent during the first 40 minutes of the infusion and 22.5 per cent when the infusion was continued for periods up to 60 minutes (Table V). A mean increase in blood volume of 12.9 per cent was not accompanied by significant changes in oxygen consumption, stroke index, brachial arterial mean pressure and the right ventricular stroke work index. Significant changes were found in the mean values for the arteriovenous oxygen difference (-4.6 ml. per L. or -12 per cent, $p < 0.001$), cardiac index ($+0.65$ L. per minute per $M.^2$ B.S.A. or $+17$ per cent, $0.01 > p > 0.001$), right atrial mean pressure ($+4.1$ mm. Hg or $+168$ per cent, $p < 0.001$). The pulse rate increased four beats per minute or $+5$ per cent ($0.05 > p > 0.02$).

During the latter period of the infusion when the mean increase in blood volume was 22.5 per cent, brachial arterial mean pressure was not significantly changed over control values. All other physiologic measurements were altered

TABLE I
Normal subjects

Case no.	Sex	Age	Body surface area M. ²	Time* min.	Heart rate beat/min.	O ₂ consumption ml./min.	A-V O ₂ difference ml./L.	Cardiac index L./min./M. ² B.S.A.	Stroke index ml./beat/M. ² B.S.A.	Blood pressure, † mm. Hg										Right ventricular stroke work index Kg. M./min./M. ² B.S.A.	Right ventricular stroke work index Gm. M./beat/M. ² B.S.A.	Decrease in hemoglobin %
										RA		RV		PA			BA					
										M	S	D	S	D	M	S	D	M	S			
A. 3 per cent glucose and water																						
744	F	18	1.52	C	84	281	34	5.49	65	2		16	8	11	119	79	96		0.67	8.0		
				18	84	243	43	3.72	44			19	9	14	116	70	88					
				60	87	250	37	4.42	51			21	8	15	131	83	102					
745	M	22	2.01	C	64	353	40	4.37	68	2	18	2			104	62	75		0.42	6.5		
				7	65	427	29	7.30	112						107	65	81					
				98	66	412	37	5.62	85						117	70	87					
				112	76	505	33	7.68	101	1					113	65	83		0.84	11.0		
746	F	21	1.61	C	74	269	36	4.68	63	3					115	62	92		0.57	7.7		
				11	87	291	35	5.24	60						128	67	91					
				48	81	273	33	5.16	64						126	67	89					
				80	91	275	31	5.60	62						130	67	91					
B. Distilled water																						
882	M	30	2.06	C	98	349	40	4.29	44			11			130	67	83			4		
				35	95	378	35	5.24	55			25	9	12	127	67	88			6		
				64	91	357	32	5.35	59			21	5	8	100	54	69					
886	F	22	1.56	CI	77	199	31	4.10	53						104	57	72			2		
				CI	77	187	31	3.87	50						104	57	72			4		
				25	69	173	31	3.59	52						104	57	72					
				50	80	186	31	3.81	48						104	58	73					
895	M	26	1.83	CI	56	246	50	2.70	48	2					98	59	69		0.22	3.9		
				CI	56	199	44	2.46	44						98	59	69		0.20	3.6		
				31	56	234	52	2.48	44						102	65	77					
				34	45	222	45	2.73	49						102	65	77					
				58	53	209	49	2.33	44						102	65	74					
				62	223	223	50	2.45	46	3					102	65	74		0.23	4.4		
944	M	32	1.97	CI	66	248	38	3.31	50						129	73	87					
				CI	71	258	39	3.39	48						127	69	92					
				22	63	232	41	2.90	46						127	69	92					
				53	71	236	39	3.05	43						120	64	84					
C. Physiologic saline solution																						
916	M	28	2.06	CI	67	282	41	3.32	50	-1					118	71	86		0.36	5.4		
				CI	67	292	41	3.44	51						118	71	86		0.37	5.5		
				31	69	282	34	4.01	58						120	72	88					
				56	66	296	39	3.73	57						128	79	89					
				80	66	265	38	3.40	52	0	16	1			125	76	93		0.42	6.4		
922	M	43	2.12	CI	63	293	49	2.84	45	3					138	83	102					
				CI	63	301	53	2.68	43	3					132	76	98					
				32.5	52	279	43	3.08	59	2					136	80	92					
				68	62	295	40	3.44	55													
1033	M	31	1.85	CI	203	203	30	3.64	44	1					132	72	95		0.30	3.6		
				CI	82	198	32	3.38	41						133	73	95		0.28	3.3		
				27	75	244	35	3.79	51						129	66	95					
				44.5	71	243	34	3.84	54													
1034	M	40	1.91	CI	237	237	38	3.30	54	3					137	88	107		0.31	5.1		
				CI	61	224	32	3.64	60						138	90	102		0.35	5.7		
				21	62	234	32	3.85	62						142	90	111					
				41.5	67	278	35	4.16	62													
				57.5	65	243	31	4.12	63	4	27	7							0.78	12.0		
BA-RA																						
1036	F	28	1.74	CI	208	208	40	3.01	44						132	71	88					
				CI	68	195	36	3.09	45	3					138	73	90					
				22.5	69	269	34	4.52	66	6					136	73	89					
				43.5	68	239	33	4.16	61	7					133	68	87					
				59.5	70	266	38	4.07	58	6												

* C designates control determination.

† Abbreviations are: R.A., right atrium; RV, right ventricle; PA, pulmonary artery; BA, brachial artery; M, mean; S, systolic; D, diastolic.

TABLE II
Normal subjects: H₂O, physiologic saline solution and 3 per cent glucose in H₂O

		Control	Difference from control values during infusion	
			20-39 min.	39 min.
Heart rate (beat/min.)	N*	12	9	12
	M	71.9	-3.4	0
	SE	3.39	1.57	1.49
	SD	11.76	4.72	5.15
	p		0.1 > p > 0.05	0
Oxygen consumption (ml./min.)	N	12	9	12
	M	261.6	17.9	14.7
	SE	15.75	8.76	7.66
	SD	54.57	26.27	26.55
	p		0.1 > p > 0.05	0.1 > p > 0.05
Arteriovenous oxygen difference (ml./L.)	N	12	9	12
	M	38.6	-2.1	-1.9
	SE	1.72	1.43	1.28
	SD	5.96	4.29	4.42
	p		0.2 > p > 0.1	0.2 > p > 0.1
Cardiac index (L./min./M. ² B.S.A.)	N	12	9	12
	M	3.74	0.36	0.35
	SE	0.245	0.204	0.197
	SD	0.847	0.613	0.684
	p		0.2 > p > 0.1	0.2 > p > 0.1
Stroke index (ml./beat/M. ² B.S.A.)	N	12	9	12
	M	52.3	7.2	4.6
	SE	2.57	2.54	2.75
	SD	8.92	7.63	9.51
	p		0.05 > p > 0.02	0.2 > p > 0.1
Right auricular mean pressure (mm. Hg)	N			
	M	9		6
	SE	2.0		0.6
	SD	0.44		0.601
	p	1.32		1.5 0.5 > p > 0.3
Pulmonary artery mean pressure (mm. Hg)	N	10	7	10
	M	9.2	2.3	2.5
	SE	0.55	0.47	0.95
	SD	1.75	1.25	2.99
	p		0.01 > p > 0.001	0.05 > p > 0.02
Brachial artery mean pressure (mm. Hg)	N	11	8	11
	M	87.8	1.4	1.7
	SE	3.79	1.53	1.74
	SD	12.58	4.34	5.76
	p		0.4 > p > 0.3	0.4 > p > 0.3
Right ventricular stroke work index (Gm. M./beat/M. ² B.S.A.)	N	7		4
	M	5.8		1.6
	SE	0.66		
	SD	1.75		
	p			
Decrease in hemoglobin (%)	N		9	9
	M		5.3	8.4
	SE			
	SD			
	p			

* Abbreviations are as follows: N, number of observations; M, mean; SE, standard error; SD, standard deviation; p, p value.

TABLE III
Dextran with 5 per cent glucose in water

Case no.	Sex	Age	Body surface area M. ²	Time* min.	Heart rate beat/min.	O ₂ consumption ml./min.	A-V O ₂ difference ml./L.	Cardiac index L./min./M. ² B.S.A.	Stroke index ml./beat/M. ² B.S.A.	Blood pressure, † mm. Hg										Right ventricular stroke work index Kg. M./min./M. ² B.S.A.	Right ventricular stroke work index % M. ² B.S.A.									
										RA		RV		PA				BA												
										M	S	D	S	D	M	S	D	M												
A. Normal subjects																														
851	M	19	1.93	CI	70	280	51	3.01	43	5	21	6	17	6	11	103	73	90	0.25	3.5										
				CII	70	267	46	2.99	43												20	10	15	110	69	86	0.24	3.5		
				50.5	66	291	34	4.48	68												28	15	19	117	77	95	0.55	8.3		
855	M	24	1.83	CI	74	234	32	4.01	54	10	19	3	16	4	9	103	71	82	0.33	4.4										
				CII	75	240	33	4.00	53												19	4	9	99	66	81	0.33	4.3		
				11.5	70	224	35	3.48	50												19	5	9	99	66	81	0.24	3.4		
				22	69	262	35	4.10	59												19	5	21	6	10	79	0.28	4.0		
				40.5	74	244	33	3.99	54												24	8	23	8	14	121	69	89	0.33	4.4
10 aft.	79	262	38	3.77	49	25	7	25	8	13	116	67	88	0.32	4.0															
867	F	21	1.63	CI	78	214	31	4.28	55	0	19	4	15	5	9	113	58	80	0.52	6.7										
				CII	80	189	33	3.52	44												7	22	11	15	111	61	77	0.43	5.4	
				23	75	221	19	7.10	95												10	22	13	18	113	67	80	0.77	10.3	
				41	73	219	30	4.55	62												12	26	16	22	110	62	77	0.50	6.7	
				58	80	224	31	4.45	56												19	7	13	112	67	76	0.61	7.6		
894	F	25	1.45	CI	70	216	41	3.61	56	3	19	7	19	7	13	112	67	76	0.53	7.1										
				CII	70	225	40	3.85	55												25	12	18	105	64	77	0.52	7.5		
				23	75	204	33	4.32	58												28	16	22	115	70	80	0.77	10.3		
				43.5	78	187	31	4.21	52												11	28	16	22	110	62	77	0.50	6.7	
				53.5	83	193	31	4.30	52												19	7	13	112	67	76	0.61	7.6		
926	M	42	2.04	CI	58	320	41	3.87	67	1	25	5	17	7	10	115	67	81	0.35	5.0										
				CII	55	283	38	3.70	67												3	29	1	112	68	86	0.29	4.4		
				19	59	294	36	4.00	68												5	36	10	119	71	87	0.35	5.0		
				41	69	307	39	3.90	57												3	17	7	10	115	67	81	0.29	4.4	
				CI	71	227	34	3.68	52												3	22	10	15	118	66	82	0.35	5.0	
902	F	26	1.82	CII	66	197	36	3.01	46	8	18	5	20	7	13	145	82	100	0.50	5.9										
				23.5	82	241	39	3.38	41												29	12	33	17	26	155	84	104	0.50	5.9
				50.5	79	244	29	4.62	58												32	13	33	19	27	150	83	101	0.94	8.8
				68	79	242	28	4.76	60												27	9	28	15	21	154	84	98	1.38	12.4
				CI	85	220	29	4.62	54												27	9	28	15	21	154	84	98	0.96	8.8
907	F	23	1.63	CI	85	220	29	4.62	54	18	5	20	7	13	145	82	100	0.50	5.9											
				CII	86	217	29	4.61	54											29	12	33	17	26	155	84	104	0.50	5.9	
				32.5	108	231	29	4.96	46											32	13	33	19	27	150	83	101	0.94	8.8	
				48	111	230	20	7.23	65											27	9	28	15	21	154	84	98	1.38	12.4	
				20 aft.	110	241	25	5.91	54											27	9	28	15	21	154	84	98	0.96	8.8	

* C designates control determination; aft., time after infusion terminated.

† Abbreviations are: RA, right atrium; RV, right ventricle; PA, pulmonary artery; BA, brachial artery; M, mean; S, systolic; D, diastolic.

TABLE IV
Normal subjects: Dextran with physiologic saline solution

Case no.	Sex	Age	Body surface area M. ²	Time*	Heart rate beats/min.	O ₂ consumption ml./min.	A-V O ₂ difference ml./L.	Cardiac index L./min./M. ² B.S.A.	Stroke index ml./beat/M. ² B.S.A.	Blood pressure,† mm. Hg										Right ventricular cardiac work index Kg. M./min./M. ² B.S.A.	Right ventricular stroke work index Gm. M./beat/M. ² B.S.A.	Decrease in hemoglobin %																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																								
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976	M	35	1.79	CI	69	232	44	2.95	43	1																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																				

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† Abbreviations are: RA, right atrium; RV, right ventricle; PA, pulmonary artery; BA, brachial artery; M, mean; S, systolic; D, diastolic.

TABLE V

Normal subjects: Dextran in physiologic saline solution and dextran in 5 per cent glucose in H₂O

		Control	Difference from control values during infusion	
			20-39 min.	39 min.
Heart rate (beat/min.)	N*	20	17	16
	M	76.1	+4.0	+7.3
	SE	2.87	1.87	2.61
	SD	12.85	7.73	10.46
	p		0.05 > p > 0.02	0.02 > p > 0.01
Oxygen consumption (ml./min.)	N	20	17	16
	M	253.8	+7.1	+18.7
	SE	9.68	6.57	6.15
	SD	43.31	27.08	24.62
	p		0.3 > p > 0.2	0.01 > p > 0.001
Arteriovenous oxygen difference (ml./L.)	N	20	17	16
	M	38.0	-4.6	-7.0
	SE	1.73	1.10	1.38
	SD	7.73	4.54	5.54
	p		p < 0.001	p < 0.001
Cardiac index (L./min./M. ² B.S.A.)	N	20	17	16
	M	3.77	+0.65	+1.17
	SE	0.207	0.212	0.192
	SD	0.925	0.875	0.769
	p		0.01 > p > 0.001	p < 0.001
Stroke index (ml./beat/M. ² B.S.A.)	N	20	17	16
	M	49.3	+6.6	+10.0
	SE	1.90	3.17	2.58
	SD	8.51	13.08	10.30
	p		0.1 > p > 0.05	0.01 > p > 0.001
Right atrial mean or right ventricular indistolic pressure (mm. Hg)	N	20	7	14
	M	2.3	+4.1	+5.5
	SE	0.32	0.86	0.73
	SD	1.45	2.27	2.74
	p		0.01 > p > 0.001	p < 0.001
Pulmonary artery mean pressure (mm. Hg)	N	17	15	14
	M	10.4	+6.3	+9.9
	SE	0.52	0.85	1.06
	SD	2.15	3.28	3.97
	p		p < 0.001	p < 0.001
Brachial artery mean pressure (mm. Hg)	N	20	17	16
	M	89.1	+0.4	+2.1
	SE	3.27	1.04	1.56
	SD	14.62	4.30	6.26
	p		0.8 > p > 0.7	0.2 > p > 0.1
Right ventricular stroke work index (Gm. M./beat/M. ² B.S.A.)	N	16	5	10
	M	5.6	+2.0	+4.4
	SE	0.42	0.91	0.89
	SD	1.69	2.04	2.82
	p		0.1 > p > 0.05	p < 0.001
Decrease in hemoglobin (%)	N		17	16
	M		+12.9	+22.5
	SE		1.30	1.65
	SD		5.35	6.61
	p		p < 0.001	p < 0.001

* Abbreviations are as follows: N, number of observations; M, mean; SE, standard error; SD, standard deviation; p, p value.

TABLE VI
Patients with mitral stenosis

Infused solution		Control			15-39 min. after the onset of infusions		
		Dextran in physiologic saline solution	Dextran in 5% glucose and water	Combined values	Dextran in physiologic saline solution	Dextran in 5% glucose and water	Combined values
Heart rate (beat/min.)	N*	7	9	16	7	9	16
	M	79.5	83.6	81.8	3.9	.6	1.72
	SE	6.32	4.52	3.66	2.224	2.16	1.31
	SD	16.75	13.57	14.63	5.9	6.51	6.25
	p				0.2 > p > 0.1	0.8 > p > 0.7	0.3 > p > 0.2
Oxygen consumption (ml./min.)	N	7	9	16	7	9	16
	M	208	211	209.8	16.4	2.6	8.7
	SE	18.6	10.96	8.4	10.12	6.77	6.295
	SD	45.58	32.87	33.6	26.82	20.21	25.18
	p				0.2 > p > 0.1	0.8 > p > 0.7	0.2 > p > 0.1
Arteriovenous oxygen difference (ml./L.)	N	7	9	16	7	9	16
	M	48	38.11	42.44	-2.86	-2.77	-2.81
	SE	3.497	1.453	2.094	2.26	.686	1.04
	SD	9.266	4.36	8.376	5.99	2.059	4.81
	p				0.3 > p > 0.2	0.01 > p > 0.001	0.02 > p > 0.01
Cardiac index (L./min./M. ² B.S.A.)	N	7	9	16	7	9	16
	M	2.707	3.489	3.147	.443	.3844	.410
	SE	.256	.183	.1548	.1767	.142	.1118
	SD	.678	.549	.619	.468	.427	.4475
	p				0.05 > p > 0.02	0.05 > p > 0.02	0.01 > p > 0.001
Stroke index (ml./beat/M. ² B.S.A.)	N	7	9	16	7	9	16
	M	34.86	42.11	38.94	2.71	3	2.875
	SE	2.99	1.148	1.68	1.491	1.365	.976
	SD	7.91	3.446	6.72	3.949	4.096	3.903
	p				0.2 > p > 0.1	0.1 > p > 0.05	0.02 > p > 0.01
Right atrial mean or right ventricular indistolic pressure (mm. Hg)	N	7	9	16	6	7	13
	M	1	2	1.56	3.83	4.7	4.31
	SE	.184	.842	.5	.749	1.267	.745
	SD	.4873	2.528	2.00	1.834	3.356	2.69
	p				0.01 > p > 0.001	0.01 > p > 0.001	p < 0.001
Pulmonary artery mean pressure (mm. Hg)	N	7	9	16	7	9	16
	M	22.29	17.44	19.56	18.285	9.888	13.56
	SE	1.73	2.43	1.658	1.267	1.173	1.658
	SD	4.59	7.29	6.634	3.355	3.519	5.442
	p				p < 0.001	p < 0.001	p < 0.001
Brachial artery mean pressure (mm. Hg)	N	7	9	16	7	9	16
	M	100.5	75.33	86.37	7.71	1.89	4.437
	SE	6.179	3.1175	4.75	2.356	2.419	1.821
	SD	16.368	12.49	18.91	6.242	7.258	7.284
	p				0.02 > p > 0.01	0.5 > p > 0.3	0.05 > p > 0.02
Right ventricular stroke work index (Gm. M./beat/M. ² B.S.A.)	N	7	9	16	6	7	13
	M	9.73	8.9	9.26	7.45	4.086	5.638
	SE	.6995	1.624	.960	.818	.7837	.770
	SD	1.853	4.872	3.841	2.005	2.076	2.778
	p				p < 0.001	0.01 > p > 0.001	p < 0.001
Decrease in hemoglobin (%)	N				7	8	15
	M				14.57	18	16.28
	SE				1.97	1.32	1.207
	SD				5.219	3.742	4.671
	p				p < 0.001	p < 0.001	p < 0.001

* Abbreviations are as follows: N, number of observations; M, mean; SE, standard error; SD, standard deviation; p, p value.

significantly over the control values; pulse rate (+7.3 beats per minute or +9.6 per cent, $0.02 > p > 0.01$), oxygen consumption (+18.7 ml. per minute or +7 per cent, $0.01 > p > 0.001$), arteriovenous oxygen difference (-7 ml. per L. or -18 per cent, $p < 0.001$), cardiac index (+1.17 L. per minute per M.² B.S.A. or +31 per cent, $p < 0.001$), stroke index (+10 ml. per beat per M.² B.S.A. or +20 per cent, $0.01 > p > 0.001$), right atrial mean pressure (+5.5 mm. Hg or +242 per cent, $p < 0.001$), and right ventricular stroke work index (+4.4 Gm.M per

beat per M.² B.S.A. or +78.6 per cent, $p < 0.001$).

During the control period, patients with mitral stenosis (Table VI) differed from normal subjects in having higher pulmonary arterial mean pressures (normals, 10.4 mm. Hg; patients, 19.5 mm. Hg) and greater right ventricular stroke work indices (normals, 5.6 Gm.M. per beat per M.² B.S.A.; patients, 9.26 Gm.M. per beat per M.² B.S.A.).

Although patients with mitral stenosis receiving infusions of dextran in 5 per cent glucose and

TABLE VII
Patients with mitral stenosis

Case no.	Sex	Age	Body surface area M^2	Heart volume $ml./M^2$ B.S.A.	Time*	Heart rate beat/min.	O_2 consumption $ml./min.$	A-V difference $ml./L.$	Cardiac index $L./min./M^2$ B.S.A.	Stroke index $ml./beat/M^2$ B.S.A.	Blood pressures, $\dagger$ mm. Hg								Right ventricular stroke work index	Decrease in hemoglobin %																																
											PCV	RA	RV		PA		BA																																			
													M	M	S	D	S	D			M	M																														
A. Dextran with 5 per cent glucose and water																																																				
858	F	30	1.45	315	C	94	184	36	3.52	37	20	4	18	7	12	72	4.0	12																																		
																			23	83	216	37	4.01	48	33	11	32	15	22	87	7.2																					
																																39	91	223	34	4.47	49	36	14	38	20	27	90	8.7								
																																													12.5 aft.	114	256	30	5.86	51	40	11
863	F	44	1.53	510	C	83	204	41	3.25	39	29	7	30	10	16	89	4.8	29																																		
																			17.5	88	203	39	3.52	40	36	11	22	90	49	58	6.0																					
																																35.5	93	208	35	3.88	42	42	15	63	62	6.9										
																																											7 aft.	94	215	37	3.80	40	40	13	44	18
873	M	35	1.77	440	C	101	282	37	4.31	43	7	-1	43	22	31	106	60	75	18.7																																	
																				20	97	276	44	3.55	37	59	30	35	103	59	70	72	25.6																			
																																		33	99	294	36	4.62	47	2	61	31	42	103	56	72						
897	F	29	1.65	400	C	69	212	40	3.21	47	0	0	17	4	8	107	57	74	5.1																																	
																				20.5	70	218	33	4.05	58	2	18	7	11	99	54	69	7.1																			
																																		25	65	217	40	3.30	51	2	18	7	11	97	54	70	6.2					
																																																46.5	65	239	37	3.89
925	F	32	1.42	330	C	100	190	32	4.18	42	5	1	26	1	20	5	111	59	88	5.7																																
																					19	91	191	32	4.23	46	2	35	6	31	13	20	123	68	81	11.3																
																																					33.5	94	167	27	4.36	46	4	38	8	34	16	23	115	64	82	11.9
958	M	49	1.89	440	C	74	248	42	3.12	42	11	1	22	8	14	141	75	98	7.4	22																																
																					32	79	237	41	3.09	39	39	53	6	34	17	23	135	71	101	14.4																
																																					44	82	279	34	4.37	53	2	38	20	26	156	78	101	26		
960	F	40	1.60	430	C	92	195	31	3.93	43	10	2	28	13	19	106	56	73	9.9	12																																
																					27	85	169	29	3.68	43	7	36	19	25	105	56	72	11.4	20																	
																																				48	107	173	34	3.17	30	24	44	26	35	106	56	75	20			
967	F	45	1.50	580	C	65	187	41	3.04	47	21	3	38	16	24	106	58	80	13.4	18																																
																					25	74	188	38	3.33	45	8	47	21	33	109	59	80	15.3	24																	
																																				38	78	197	35	3.74	48	9	48	23	35	108	58	79	17.0			
969	F	26	1.62	410	C	75	198	43	2.84	39	1	1	27	15	22	105	45	59	11.1	18																																
																					29	79	212	41	3.23	41	6	39	25	33	111	51	66	15.1	20																	
																																				47	89	243	40	3.72	42	7	40	29	34							

* C designates control determination; aft., time after infusion terminated.

† Abbreviations are: RA, right atrium; RV, right ventricle; PA, pulmonary artery; BA, brachial artery; M, mean; S, systolic; D, diastolic; PCV, pulmonary capillary venous pressure.

TABLE VII—Continued

Case no.	Sex	Age	Body surface area	Heart volume M^2 $ml./M^2$ B.S.A.	Time* $min.$	Heart rate $beat/min.$	O ₂ consumption $ml./min.$	A-V O ₂ difference $ml./L.$	Cardiac index $L./min./M^2$ B.S.A.	Stroke index $ml./beat/$ M^2 B.S.A.	Blood pressures, † $mm. Hg$										Right ventricular stroke work index	Decrease in hemo- globin		
											PCV		RA		RV		PA		BA					
											M	M	M	M	S	D	S	D	S	D			M	M
979	F	39	1.36	590	C	69	191	56	2.51	36	22	1	40	3	42	16	26	110	54	75	12.2			
						72	187	58	2.38	33		6			61	25	40	118	61	80	15.3			
						77	203	58	2.59	34		7			64	26	43	117	61	81	16.6			
981	F	37	1.58	440	C	100	213	34	3.96	40	12	-1			30	10	17	143	76	99	9.8			
					24	110	234	29	5.07	46					43	22	32	134	74	92				
					37	111	231	29	5.09	46					49	27	38	136	74	96				
990	F	46	1.69	630	C	105	157	50	1.86	18	11	0			42	20	29	173	101	130	7.1			
					19	111	229	47	2.88	26		5			73	31	50	173	97	134	15.9			
991	M	33	1.47	470	C	79	185	41	3.07	39	21	3			40	18	25	122	75	95	11.7			
					19	75	206	48	2.90	39		4	57	12	57	27	41	129	75	103	19.6			
994	M	47	1.95	650	C	60	271	62	2.24	37	10	2			32	12	18	146	83	98	8.1			
					18.5	52	256	60	2.18	42		5			40	15	24	151	87	105	10.9			
					35.5	61	268	52	2.63	43		7			51	20	32	164	96	113	14.6			
					aft. 19	53	257	51	2.57	48		6			47	18	31	154	88	112	16.3			
1004	F	46	1.62	720	C	74	183	46	2.46	33	18	1			34	18	24	143	84	107	10.3			
					18	86	184	39	2.91	34					55	29	39	153	88	114				
					29	88	186	37	3.09	35		4	66	8	64	36	47	162	95	120	20.5			
					aft. 21	86	181	37	3.03	35		4			163	93	123				20			
1009	M	47	1.92	650	C	70	257	47	2.85	41	10	1			32	11	17	146	86	101	8.9			
					17	73	251	49	2.69	37					49	18	27	157	91	107				
					245	71	245	45	2.83	40		4	50	7	53	20	33	165	95	111	15.8			
					aft. 19	77	269	45	3.09	40		3			154	86	109				12			

water (Table VII) showed only slight differences from the normal group in their mean control values for cardiac index, stroke index and arteriovenous oxygen difference, patients infused with dextran in isotonic saline solution (Table VII) had significantly lower cardiac and stroke indices and higher arteriovenous oxygen differences than the normal volunteers.

The results of infusions of dextran for periods of 40 minutes in patients with mitral stenosis and normal subjects were similar in producing slight but not significant changes in heart rate, oxygen consumption and brachial arterial pressure, while blood volume, cardiac and stroke indices and right heart filling pressure were increased by roughly comparable amounts.

The results differed in the greater increase in mean pulmonary arterial pressure (normals, + 6.3 mm. Hg; patients, + 13.6 mm. Hg) (Figure 2), and right ventricular stroke work index (normals, + 2 Gm.M. per beat per M.² B.S.A.; patients, + 5.6 Gm.M. per beat per M.² B.S.A.) found in the patients. The difference was most marked in patients receiving infusions of dextran in isotonic saline solution in whom the mean increases in pulmonary arterial mean pressure and right ventricular stroke work index were 18 mm. Hg and 7.45 Gm.M. per beat per M.² B.S.A., respectively, approximately three times that found in normal subjects.

While mean increases in right heart filling pressures of 5.5 mm. Hg in normal subjects and 4.3 mm. Hg in patients were associated with significant increases in the mean values for cardiac and stroke indices and right ventricular stroke work index, the coefficients of the regressions of right heart filling pressures to the change in these indices were not significant (Figures 3-5).

Examination of the data in individual studies shows instances in which significant changes in right heart filling pressures were associated with changes in cardiac output which could not be considered significant, as the standard error of a single determination of cardiac output in this laboratory has been demonstrated to be 7.2 per cent (9). A 10 per cent variability in duplicate determinations of cardiac output has been shown elsewhere (12, 13).

In seven normal volunteers cardiac indices were altered by less than 15 per cent while right

FIG. 2. REGRESSIONS FOR THE INCREASE IN PULMONARY ARTERIAL MEAN PRESSURE ON THE PERCENTAGE DECREASE IN HEMOGLOBIN

On the lower half of the figure separate regression lines are plotted for infusions of dextran in isotonic saline solution (dotted line) and dextran in 5 per cent glucose and water (solid line). The coefficients of the regression equations, $E = 0.357x + 1.653$ (normal subjects) and $E = 0.576x - 0.855$ (patients receiving infusions of dextran in 5 per cent glucose and water), are significant ($p < 0.001$ in each instance). The coefficient of the equation $E = 0.485x + 9.035$ in patients infused with dextran in isotonic saline solution is not significant ($0.2 > p > 0.1$).

heart filling pressures rose 4 to 12 mm. Hg. Stroke indices were unaltered or fell in five subjects in association with increases in right filling pressures of 5 to 10 mm. Hg.

In six patients cardiac indices showed changes of less than 10 per cent while right heart filling pressures rose 2 to 6 mm. Hg. Stroke indices were unaltered or increased 1 to 2 ml. in three patients with increases in right heart filling pressures of 1 to 6 mm. Hg, while in three other patients stroke indices fell 1 to 10 ml. in association with increases in right heart filling pressures of 1 to 6 mm. Hg.

In all patients and in all normal subjects, save one, the right ventricular stroke work index rose in association with increases in right heart

FIG. 3. REGRESSIONS FOR THE PERCENTAGE CHANGE IN CARDIAC INDEX ON THE INCREASE IN RIGHT HEART FILLING PRESSURE

RAM designates right atrial mean pressure; RVD, right ventricular end-diastolic pressure. The coefficients of the regression equations, $E = 2.53x + 9.974$ (normal subjects) and $E = 1.182x + 6.406$ (patients with mitral stenosis), are not significant ($p > 0.1$ and $p > 0.3$, respectively).

filling pressures (Figure 6) and elevation of blood volume (Figure 7). The rise in right ventricular stroke work index was sometimes small in relation to the increase in right heart filling pres-

ures being less than 40 per cent in five patients and two normal subjects with increases in right filling pressures of 2 to 8 mm. Hg and 8 to 12 mm. Hg, respectively.

FIG. 4. REGRESSIONS FOR THE PERCENTAGE CHANGE IN STROKE INDEX ON THE INCREASE IN RIGHT HEART FILLING PRESSURES

RAM designates right atrial mean pressure; RVD, right ventricular end-diastolic pressure. The coefficients of the regression equations, $E = 1.76x + 6.896$ (normal subjects) and $E = 1.66x + 2.095$ (patients with mitral stenosis), are not significant ($p > 0.3$ and $p > 0.1$, respectively).

A significant linear relation was found between the percentage decrease in hemoglobin in normal subjects and the percentage change in cardiac index ($0.02 > p > 0.01$) (Figure 8), the percentage change in stroke index ($0.005 > p > 0.001$) (Figure 9), and the change in right ventricular stroke work index ($0.05 > p > 0.02$) (Figure 10). The correlation coefficients of 0.41, 0.36 and 0.47 relating the percentage decrease in hemoglobin in the normal subjects to these indices were also significant. In patients with mitral stenosis a significant linear relation was found between the percentage decrease in hemoglobin and the percentage change in cardiac index ($0.05 > p > 0.02$). The correlation coefficient of 0.37 was also significant. No significant linear relation was found between the percentage decrease in hemoglobin in the patients with mitral stenosis and the percentage change in stroke index or the change in right ventricular stroke work index.

DISCUSSION

The effect of rapid infusions of albumin (5), dextran (14) or saline (15, 16) on the cardiac output and pressures in the right atrium and

FIG. 5. REGRESSIONS FOR THE CHANGE IN RIGHT VENTRICULAR (RV) STROKE WORK INDEX ON THE INCREASE IN RIGHT HEART FILLING PRESSURE

RAM, right atrial mean pressure; RVD, right ventricular end-diastolic pressure. The coefficients of the regression equations, $E = 0.1754x + 2.46$ (normal subjects) and $E = 5.403 - 0.174x$ are not significant ($p > 0.3$ in each instance).

FIG. 6. THE RELATION BETWEEN RIGHT HEART FILLING PRESSURE AND RIGHT VENTRICULAR STROKE WORK INDEX IN EACH SUBJECT

The initial plots on the left hand side of the figure represent control values. All other plots occurred during the period of the infusions. Right atrial mean pressure was considered representative of right heart filling pressure except in those instances marked RVD, when right ventricular end-diastolic pressure was used.

pulmonary artery has been studied previously in man. While it has been found consistently that right atrial pressure rises as blood volume increases, the effect on cardiac output has varied, cardiac output remaining unchanged in one study (5) and rising in the others (14-16). This divergence in results may be due to variations in the magnitude of the blood volume increase, to physiologic differences among the subjects or to differences in the experimental procedures. In an effort to limit the effect of these variables, comparable studies were first carried out in normal volunteers and subsequently in patients with mitral stenosis.

In normal subjects infusions of 3 per cent glucose and water or isotonic saline solution increased blood volume 5 to 8 per cent with no significant change in right heart pressures and stroke or cardiac indices. Infusions of dextran in 5 per cent glucose and water or isotonic saline solution given in a similar manner to normal sub-

FIG. 7. THE RELATION BETWEEN THE PERCENTAGE DECREASE IN HEMOGLOBIN AND RIGHT VENTRICULAR STROKE WORK INDEX IN EACH SUBJECT

The plots on the left of the graph are control values; subsequent plots were obtained during the period of the infusion. Right atrial mean pressure was used in calculating right ventricular stroke work index except in those instances marked RVD, when right ventricular end-diastolic pressure was used.

jects and patients with mitral stenosis increased blood volume 22 and 16 per cent, respectively, and were associated with significant increases in right heart and pulmonary arterial pressures, the increase in pressures being related to the degree of blood volume expansion, a relation that had been found previously in anesthetized dogs (17, 18).

Right heart filling pressure increased to a mean value of 6 to 7 mm. Hg, a level commonly found in patients with right heart failure, yet the absence of a fall in cardiac output either in the normal subjects or the patients with mitral stenosis suggests that the heart was not in a failing state.

The rise in pulmonary arterial pressure was significantly greater in patients with mitral stenosis, a finding which might be due either to alterations known to occur in the pulmonary vascular bed of these patients or perhaps to the presence of right ventricular hypertrophy.

In these studies the correct evaluation of the effects of alterations in right heart filling pres-

ures on cardiac output and cardiac work is dependent on the relation existing between measured and effective pressure as well as the significance of right atrial mean pressure as an indicator of the filling pressure in the right ventricle.

Changes in intrathoracic and intrapericardial pressures were not measured during these studies making it impossible to determine the effective right heart pressures. Although the change in effective right atrial pressure was probably less than the measured pressure change, the difference was felt to be no greater than 1 to 2 mm. Hg.

In those instances in which right atrial mean and right ventricular end-diastolic pressures were measured simultaneously the latter was 1 to 4 mm. Hg higher than the former during the control period. During the period of the infusion, right atrial mean pressure and right ventricular end-diastolic pressures rose in a comparable manner (Figure 11) as had been noted previously during exercise studies in patients with mitral stenosis (19).

Besides increasing blood volume and elevating right heart filling pressure, an infusion of dextran causes other physiologic changes which in themselves may play some role in the regulation of cardiac output. Increased cardiac outputs found in dogs during dextran infusions were shown to be the result of a marked anemia and the associated decrease in the oxygen carrying capacity of the blood (18, 20). In the present studies the magnitude of the anemia was less than in the animal studies cited above, hematocrits being altered less than 30 per cent and hemoglobin levels never falling below 10 Gm., a level which has not been found to be associated with elevation of cardiac output in studies of patients with chronic anemia (21).

Cardiac output and right heart filling pressures may be altered by the occurrence of tricuspid insufficiency during dextran infusions in animals with open pericardiums (22). Examina-

FIG. 8. REGRESSIONS FOR THE PERCENTAGE CHANGE IN CARDIAC INDEX ON THE PERCENTAGE DECREASE IN HEMOGLOBIN

The coefficient of the regression equations, $E = 1.058x + 4.18$ (normal subjects) and $E = 1.188x - 6.78$ (patients with mitral stenosis), are significant ($0.02 > p > 0.01$ and $0.05 > p > 0.02$, respectively).

FIG. 9. REGRESSIONS FOR THE PERCENTAGE CHANGE IN STROKE INDEX ON THE PERCENTAGE DECREASE IN HEMOGLOBIN

The coefficient of the regression equation, $E = 1.2x - 4.95$ in normal subjects, is significant ($p < 0.005$). The coefficient of the regression equation, $E = 0.9133x - 6.78$ in patients with mitral stenosis, is not significant ($p > 0.1$).

tions of the atrial pressure curves recorded at the end of the infusion periods failed to reveal evidence of tricuspid insufficiency in either normal volunteers or patients with mitral stenosis.

Data on renal blood flow obtained during the present studies show that infusions of dextran are often associated with changes in renal hemodynamics. In normal subjects renal blood flow was not significantly altered during infusions of isotonic saline solution or 5 per cent glucose and water. When normal volunteers received infusions of dextran with 5 per cent glucose and water or isotonic saline solution, renal blood flow increased, in some instances, to twice the control values. Increases in renal blood flow of this magnitude, although partially explicable on the basis of the measured change in cardiac output, would appear also to be indicative of vasodilatation in the renal vascular bed.

While the data in normal subjects and patients

FIG. 10. REGRESSIONS FOR THE CHANGE IN RIGHT VENTRICULAR STROKE WORK INDEX ON THE PERCENTAGE DECREASE IN HEMOGLOBIN

The coefficient of the regression equation, $E = 0.15x + 0.656$ in normal subjects, is significant ($0.05 > p > 0.02$). The coefficient of the regression equation, $E = 0.044x + 3.829$ in patients with mitral stenosis, is not significant ($p > 0.9$).

with mitral stenosis show a mean rise in cardiac and stroke output occurring in association with increases in right heart filling pressures, no uniform way of relating these variables was found; indeed in 13 instances, changes in cardiac output of questionable significance occurred in the presence of increases in right heart filling pressures of 4 to 12 mm. Hg. Previous studies in subjects with induced fluid retention have in some instances also failed to show a relation between right heart filling pressure and cardiac output (23).

Increases in right heart filling pressures of the magnitude produced in these studies are not usually encountered in the intact normal individual even under conditions of moderate to severe exertion (24) when the cardiac output is elevated to a far greater extent than was encountered in this work (25). The occurrence of only slight to moderate increases in cardiac output in association with abnormal increases in right heart filling pressures in healthy subjects implies the importance of other mechanisms by which cardiac output may be elevated from normal levels to the higher values associated with the physiologic stresses of daily life.

The significance of increases in right heart

filling pressure to the elevation of cardiac output in patients with mitral stenosis cannot be clearly assessed since it is well known that these patients may be unable to increase their cardiac outputs to the extent found in normal subjects. It appears, however, that the effect on cardiac output of increases in right heart filling pressures, within the range studied, was essentially the same in healthy subjects and in patients with mitral stenosis.

Changes in blood volume were also associated with significant increases in the mean values of cardiac and stroke indices in both patients and normal subjects. The relation between blood volume changes and these indices was significant in normal subjects. In patients with mitral stenosis the relationship was significant only as regards the cardiac index. There were again eight normal subjects and five patients in whom maximum increases in blood volume of 10 to 31 per cent were associated with changes in cardiac output of less than 15 per cent, a change which should be considered of questionable significance in view of the limitations of the methods utilized.

FIG. 11. DATA OBTAINED DURING AN INFUSION OF DEXTRAN IN 5 PER CENT GLUCOSE AND WATER IN A NORMAL SUBJECT (No. 926)

The vertical dotted lines represent the start and the finish of the dextran infusion. Syst. designates systolic; Diast., diastolic; M, mean.

The belief that right heart filling pressure is of dominant importance in the control of cardiac output in man has been based partly on studies conducted during pressure breathing (26), acute hemorrhage (27) and tilting (28, 29), experimental procedures which lead to a decreased venous return and a fall in the effective filling pressure of the right heart. Under these circumstances an ultimate fall in cardiac output would appear inevitable for the heart cannot pump out more blood than it receives. It does not necessarily follow that an increased venous return and an elevated cardiac filling pressure need be associated with an increased cardiac output.

The data in the present study suggest that the alterations in cardiac filling pressure and venous return cannot adequately explain the wide variations in cardiac output occurring in normal man; indeed the lack of a significant change in cardiac output in 13 subjects despite a steady increase in blood volume and right heart filling pressure suggests the presence of some mechanism by which cardiac output is maintained at a relatively constant level under these conditions.

In each subject, save one, increase in blood volume and elevation of right heart filling pressure were associated ultimately with an increase in right ventricular stroke work, a finding which is in accordance with Starling's law of the heart (30). However, no significant linear relation between these two variables and work was found except in the normal subjects where a significant linear relation existed between the percentage decrease in hemoglobin and the increase in right ventricular stroke work index. In individual subjects the increase in work for a given change in pressure was often far less than has been reported previously in animals. While this difference in the pressure volume relation (the ventricular function curve) of man and animal might be explained on the basis of the species studied, it might also be the result of the altered physiologic status of a laboratory preparation as compared to intact unanesthetized man. In a laboratory preparation, the normal state is sacrificed in varying degrees to reduce the number of variables under study to a minimum. In intact man these many variables operate simultaneously,

each altering to some degree the manner in which the others would function were they to be operating alone.

Other investigators (2, 4) have felt that the response of the heart to a given filling pressure may vary widely as a result of changes presumably in myocardial tone or contractility; functions of cardiac muscle which appear at least in part to be under neurohumoral control. The presence of these neurohumoral factors in intact man and their absence in many laboratory preparations would appear to be the most likely explanation of the disparity between the magnitude of the work increase found in this study and that found in the animal studies cited above.

The greatest increase in work for a given increase in blood volume or filling pressure was found in those patients with mitral stenosis whose hemodynamic findings showed the most marked deviations from normal. Whether this difference between patients and normal subjects was due to the presence of right ventricular hypertrophy, or the result of a change in myocardial contractility or tone initiated by some neurohumoral mechanism, cannot be determined from the present data.

The present study is an attempt to place in proper perspective the relation of increased blood volume and filling pressure to cardiac function in intact man. The data in no way deny to cardiac muscle its inherent ability of responding to increased tension with increased force (Starling's law of the heart), all other variables remaining constant. The data do, however, show that in normal man the response of cardiac muscle to an abnormal increase in filling pressure and blood volume is not of a sufficient degree to warrant the assumption that the filling pressure is necessarily the main determinant of the level of cardiac output or cardiac work. One explanation for the findings may lie in a continuous shift of cardiac function from one Starling curve to another as filling pressure rises. The implication is strong that a mechanism of this type or some other mechanism under neurohumoral control may be of more importance to the level of cardiac function than the small variations in filling pressure which occur in normal man or patients with mild to moderate forms of cardiac disease.

CONCLUSIONS

1. Intravenous infusions of distilled water, 3 per cent glucose in water, physiologic saline solution and 6 or 8 per cent dextran in either 5 per cent glucose and water or physiologic saline solution were given at a constant rate of 25 ml. per minute for periods of 30 to 100 minutes to 31 normal subjects and 15 patients with mitral stenosis.

2. During infusions of water, physiologic saline solution and 3 per cent glucose in water in normal subjects, blood volume increased 5 to 8 per cent. No other significant changes in cardiovascular hemodynamics occurred.

3. Infusions of 6 or 8 per cent dextran solutions in normal subjects were associated with increases in blood volume of 20 to 35 per cent, rises in right heart filling pressures of 2 to 12 mm. Hg and elevations of pulmonary arterial mean pressure of 3 to 15 mm. Hg. With the greatest expansion in blood volume, cardiac and stroke output were increased 31 and 20 per cent, respectively. In seven subjects, however, increases in right heart filling pressure of 4 to 12 mm. Hg were associated with changes in cardiac output of less than 15 per cent.

4. In patients with mitral stenosis increases in blood volume of 10 to 29 per cent were associated with increases in right heart filling pressures of 1 to 10 mm. Hg and increases in pulmonary arterial mean pressures of 8 to 23 mm. Hg. The mean increase in pulmonary arterial mean pressure of 13.56 mm. Hg was twice that found in normal subjects. The increase in pulmonary arterial mean pressure was most marked in patients receiving infusions of 6 per cent dextran in physiologic saline solution, being on the average three times greater than the increase found in normal subjects. Mean values for cardiac and stroke output increased 13 and 7 per cent, respectively. In six patients cardiac output changed less than 10 per cent while right heart filling pressure increased 2 to 6 mm. Hg.

5. In all patients and in all normal subjects save one, maximum increases in blood volume and right heart filling pressure were associated with increases in right ventricular stroke work. In seven instances the increase in right ventricular work was relatively small compared to the increase in right heart filling pressure, the in-

crease in right ventricular work being less than 40 per cent while right heart filling pressures rose 2 to 12 mm. Hg.

6. No significant relation appeared to exist in normal subjects or patients between the magnitude of the increase in right heart filling pressure and the percentage change in cardiac and stroke output or the change in right ventricular stroke work.

7. In normal subjects a significant linear relation was found between the degree of blood volume expansion and the percentage change in cardiac output, stroke output and the change in right ventricular stroke work. In patients with mitral stenosis a significant linear relation was found only between the degree of blood volume expansion and the percentage change in cardiac output.

8. The relatively small alterations in cardiac function occurring with the moderate to marked elevations of right heart filling pressure suggest the importance of factors other than filling pressure in the control of cardiac function in man.

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REFERENCES

1. Symposium on the regulation of the performance of the heart. *Physiol. Rev.* 1955, 35, 90.
2. Rushmer, R. F. Applicability of Starling's law of the heart to intact, unanesthetized animals. *Physiol. Rev.* 1955, 35, 138.
3. Ek, J., Bucht, H., and Werkö, L. The influence of a rapid infusion of glucose on renal dynamics and sodium excretion in patients with arterial hypertension; preliminary report. *Amer. Heart J.* 1954, 48, 102.
4. Sarnoff, S. J., and Berglund E. Ventricular function. I. Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog. *Circulation* 1954, 9, 706.
5. Warren, J. V., Brannon, E. S., Weens, H. S., and Stead, E. A., Jr. Effect of increasing the blood volume and right atrial pressure on the circulation of normal subjects by intravenous infusions. *Amer. J. Med.* 1948, 4, 193.
6. Cournand, A., and Ranges, H. A. Catheterization of the right auricle in man. *Proc. Soc. exp. Biol. (N. Y.)* 1941, 46, 462.
7. Lagerlof, H., and Werkö, L. Studies on the circulation in man. A technique of venous catheterization with determination of cardiac output and simul-

- taneous recordings of the blood pressures, the electrocardiogram, phonocardiogram, and respiration. *Acta med. scand.* 1949, 132, 495.
8. Lagerlof, H., and Werkö, L. Studies on the circulation of blood in man. VI. The pulmonary capillary venous pressure pulse in man. *Scand. J. clin. Lab. Invest.* 1949, 7, 147.
 9. Thomasson, B. Cardiac output in normal subjects under standard basal conditions. The repeatability of measurements by the Fick method. *Scand. J. clin. Lab. Invest.* 1957, 9, 365.
 10. Van Slyke, D. D., and Neill, J. M. The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. I. *J. biol. Chem.* 1924, 61, 523.
 11. Ek, J. The influence of heavy hydration on the renal function in normal and hypertensive man. *Scand. J. clin. Lab. Invest.* 1955, 7, Suppl. 19.
 12. Werkö, L. The influence of positive pressure breathing on the circulation in man. *Acta med. scand.* 1947, Suppl. 193.
 13. Harvey, R. M., Ferrer, M. I., Cathcart, R. T., Richards, D. W., Jr., and Cournand, A. Some effects of digoxin upon the heart and circulation in man. *Amer. J. Med.* 1949, 7, 439.
 14. Witham, A. C., Fleming, J. W., and Bloom, W. L. The effect of the intravenous administration of dextran on cardiac output and other circulatory dynamics. *J. clin. Invest.* 1951, 30, 897.
 15. Doyle, J. T., Wilson, J. S., Estes, E. H., and Warren, J. V. The effect of intravenous infusions of physiologic saline solution on the pulmonary arterial and pulmonary capillary pressure in man. *J. clin. Invest.* 1951, 30, 345.
 16. McMichael, J. Circulatory failure studied by means of venous catheterization. *Advanc. intern. Med.* 1947, 2, 64.
 17. Henry, J. P., Gauer, O. H., and Sieker, H. O. The effect of moderate changes in blood volume on left and right atrial pressures. *Circulat. Res.* 1956, 4, 91.
 18. Fowler, N. O., Franch, R. H., and Bloom, W. L. Hemodynamic effects of anemia with and without plasma volume expansion. *Circulat. Res.* 1956, 4, 319.
 19. Eliasch, H. Pulmonary circulation at rest and on effort in mitral stenosis. *Scand. J. clin. Lab. Invest.* 1952, 4, Suppl. 4.
 20. Sunahara, F. A., and Beck, L. Cardiovascular effects of acutely produced anemia in the normal dog. *Amer. J. Physiol.* 1954, 176, 139.
 21. Brannon, E. S., Merrill, A. J., Warren, J. V., and Stead, E. A., Jr. The cardiac output in patients with chronic anemia as measured by the technique of right atrial catheterization. *J. clin. Invest.* 1945, 24, 332.
 22. Berglund, E., Sarnoff, S. J., and Isaacs, J. P. Ventricular function: Role of the pericardium in regulation of cardiovascular hemodynamics. *Circulat. Res.* 1955, 3, 133.
 23. Albert, R. E., Smith, W. W., and Eichna, L. W. Hemodynamic changes associated with fluid retention induced in noncardiac subjects by corticotropin (ACTH) and cortisone; comparison with the hemodynamic changes of congestive heart failure. *Circulation* 1955, 12, 1047.
 24. Holmgren, A. Circulatory changes during muscular work in man. with special reference to arterial and central venous pressures in the systemic circulation. *Scand. J. clin. Lab. Invest.* 1956, 8, Suppl. 24.
 25. Asmussen, E., and Nielsen, M. Cardiac output during muscular work and its regulation. *Physiol. Rev.* 1955, 35, 778.
 26. Cournand, A., Motley, H. L., Werkö, L., and Richards, D. W., Jr. Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. *Amer. J. Physiol.* 1948, 152, 162.
 27. McMichael, J., and Sharpey-Schafer, E. P. Cardiac output in man by direct Fick method. Effects of posture, venous pressure change, atropine, and adrenaline. *Brit. Heart J.* 1944, 6, 33.
 28. Stead, E. A., Jr., Warren, J. V., Merrill, A. J., and Brannon, E. S. Cardiac output in male subjects as measured by the technique of right atrial catheterization. Normal values with observations on the effect of anxiety and tilting. *J. clin. Invest.* 1945, 24, 326.
 29. Hickam, J. B., and Pryor, W. W. Cardiac output in postural hypotension. *J. clin. Invest.* 1951, 30, 401.
 30. Starling, E. H. *The Linacre Lecture on the Law of the Heart.* (Cambridge, 1915.) London, Longmans, Green and Co., 1918.