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Research Article

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 dextran [1] 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 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 I^{131} 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.

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[1] Macrodex Rx® of constant molecular size was generously supplied by Pharmacia Inc., Upsala, Sweden.

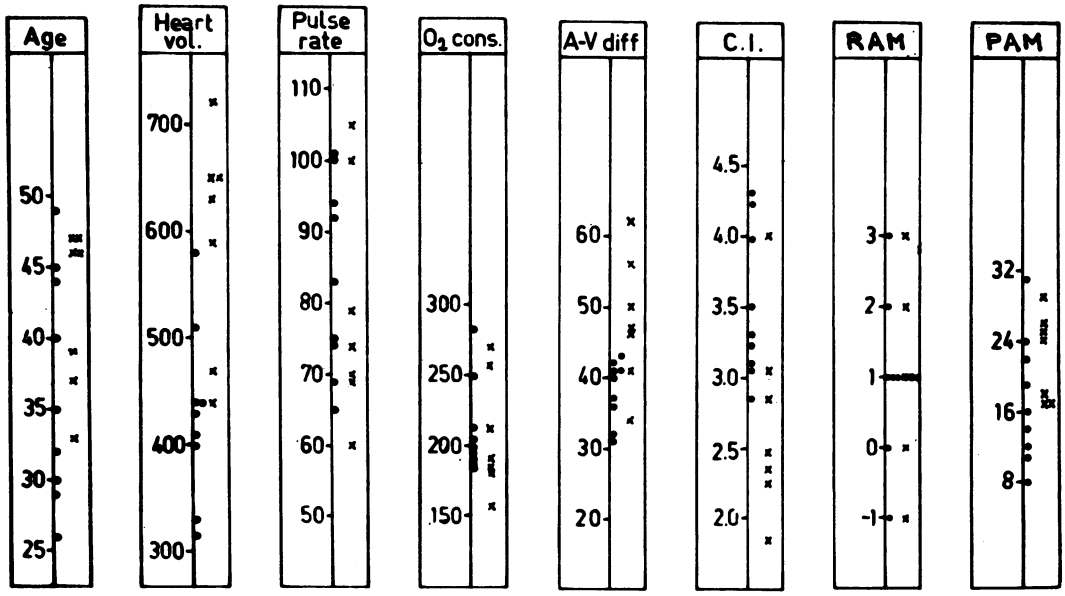

FIG. 1. CONTROL DATA OBTAINED ON ALL PATIENTS RECEIVING INFUSIONS OF DEXTRAN IN 5 PER CENT GLUCOSE AND WATER (BLACK DOTS) AND DEXTRAN IN ISOTONIC SALINE SOLUTION (X)

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; O_2 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 Cournand 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 × (mean pulmonary arterial pressure − mean right atrial pressure) × 13.6/1,000.

Right ventricular stroke work index (RVSWI) in Gm.-M. per beat per M.^{2} B.S.A. = stroke index × (mean pulmonary arterial pressure − mean right atrial pressure) × 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	Time*	Heart rate	O_2 consumption	A-V O_2 difference	Cardiac index	Stroke index	Blood pressure,† *mm. Hg* RA M	RV S	RV D	PA S	PA D	PA M	BA S	BA D	BA M	Right ventricular work index	Right ventricular stroke work index	Decrease in hemoglobin
			M.²	*min.*	*beat/min.*	*ml./min.*	*ml./L.*	*L./min./ M.² B.S.A.*	*ml./beat/ M.² B.S.A.*										*Kg. M./ min./M.²*	*Gm. M./beat/ M.² B.S.A.*	%
								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	15	5	9	104	62	75	0.42	6.5	
				7	65	427	29	7.30	112				16	6	10	107	65	81			
				98	66	412	37	5.62	85				18	7	12	117	70	87			
				112	76	505	33	7.68	101	1			15	5	9	113	65	83	0.84	11.0	
746	F	21	1.61	C	74	269	36	4.68	63	3			17	7	12	115	62	92	0.57	7.7	
				11	87	291	35	5.24	60				17	6	12	128	67	91			
				48	81	273	33	5.16	64				15	7	10	126	67	89			
				80	91	275	31	5.60	62				16	7	11	130	67	91			
								B. Distilled water													
882	M	30	2.06	C	98	349	40	4.29	44						11						
				35	95	378	35	5.24	55				25	9	12	130	67	83			4
				64	91	357	32	5.35	59				21	7	12	127	67	88			6
886	F	22	1.56	CI	77	199	31	4.10	53				15	5	8	100	54	69			
				CII	77	187	31	3.87	50												
				25	69	173	31	3.59	52				18	7	12	104	57	72			2
				50	80	186	31	3.81	48				18	7	11	104	58	73			4
895	M	26	1.83	CI	56	246	50	2.70	48	2									0.22	3.9	
				CII		199	44	2.46	44				13	5	8	98	59	69	0.20	3.6	
				31	56	234	52	2.48	44												5
				34		222	45	2.73	49				15	7	10	102	65	77			5
				58	53	209	49	2.33	44												6
				62		223	50	2.45	46	3			15	7	10	102	65	74	0.23	4.4	6
944	M	32	1.97	CI	66	248	38	3.31	50												
				CII	71	258	39	3.39	48				13	5	9	129	73	87			
				22	63	232	41	2.90	46				16	7	11	127	69	92			2
				53	71	236	39	3.05	43				16	6	10	120	64	84			6
								C. Physiologic saline solution													
916	M	28	2.06	CI	67	282	41	3.32	50	−1									0.36	5.4	
				CII	67	292	41	3.44	51				13	3	7	118	71	86	0.37	5.5	
				31	69	282	34	4.01	58				13	4	8	120	72	88			3
				56	66	296	39	3.73	57				16	6	10	128	79	89			5
				80	66	265	38	3.40	52	0	16	1	14	4	9	125	76	93	0.42	6.4	5
922	M	43	2.12	CI	63	293	49	2.84	45	3											
				CII	63	301	53	2.68	43	3						138	83	102			
				32.5	52	279	43	3.08	59	3						132	76	98			6
				68	62	295	40	3.44	55	2						136	80	92			8
1033	M	31	1.85	CI		203	30	3.64	44	1									0.30	3.6	
				CII	82	198	32	3.38	41				15	3	7	132	72	95	0.28	3.3	
				27	75	244	35	3.79	51				19	7	11	133	73	95			10
				44.5	71	243	34	3.84	54				20	7	12	129	66	95			14
1034	M	40	1.91	CI		237	38	3.30	54	3									0.31	5.1	
				CII	61	224	32	3.64	60				17	5	10	137	88	107	0.35	5.7	
				21	62	234	32	3.85	62				20	7	12	138	90	102			9
				41.5	67	278	35	4.16	62				23	9	15	142	90	111			11
				57.5	65	243	31	4.12	63	4	27	7	27	7	18			104	0.78	12.0	13
							BA–RA														
1036	F	28	1.74	CI		208	40	3.01	44												
				CII	68	195	36	3.09	45	3						132	71	88			
				22.5	69	269	34	4.52	66	6						138	73	90			7
				43.5	68	239	33	4.16	61	7						136	73	89			12
				59.5	70	266	38	4.07	58	6						133	68	87			14

* C designates control determination.

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

TABLE II

Normal subjects: H_2O, physiologic saline solution and 3 per cent glucose in H_2O

			Difference from control values during infusion	
		Control	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	Time*	Heart rate	O_2 consumption	A-V O_2 difference	Cardiac index	Stroke index	Blood pressure,† *mm. Hg*									Right ventricular work index	Right ventricular stroke work index	Decrease in hemoglobin
										RA	RV		PA			BA					
										M	S	D	S	D	M	S	D	M			
			M.²	*min.*	*beat/min.*	*ml./min.*	*ml./L.*	*L./min./ M.² B.S.A.*	*ml./beat/ M.² B.S.A.*										*Kg. M./min./ M.² B.S.A.*	*Gm. M./beat/ M.² B.S.A.*	%
									A. Normal subjects												
851	M	19	1.93	CI	70	280	51	3.01	43										0.25	3.5	
				CII	70	267	46	2.99	43	5	21	6	17	6	11	103	73	90	0.24	3.5	
				17.5	62	274	47	3.02	49				20	10	15	110	69	86			8
				50.5	66	291	34	4.48	68	10			28	15	19	117	77	95	0.55	8.3	18
855	M	24	1.83	CI	74	234	32	4.01	54										0.33	4.4	
				CII	75	240	33	4.00	53		19	3	16	4	9	103	71	82	0.33	4.3	
				11.5	70	224	35	3.48	50		19	4	19	5	9	99	66	81	0.24	3.4	2
				22	69	262	35	4.10	59		19	5	21	6	10			79	0.28	4.0	5
				40.5	74	244	33	3.99	54		24	8	23	8	14	121	69	89	0.33	4.4	11
				10 aft.	79	262	38	3.77	49		25	7	25	8	13	116	67	88	0.32	4.0	13
867	F	21	1.63	CI	78	214	31	4.28	55										0.52	6.7	
				CII	80	189	33	3.52	44	0			15	5	9	113	58	80	0.43	5.4	
				23	75	221	19	7.10	95	7			22	11	15	111	61	77	0.77	10.3	18
				41	73	219	30	4.55	62	10			22	13	18	113	67	80	0.50	6.7	26
				58	80	224	31	4.45	56	12			26	16	22	110	62	77	0.61	7.6	31
894	F	25	1.45	CI	70	216	41	3.61	56										0.53	7.1	
				CII	70	225	40	3.85	55	3			19	7	13	112	67	76	0.52	7.5	
				23	75	204	33	4.32	58				25	12	18	105	64	77			16
				43.5	78	187	31	4.21	52				28	16	22	115	70	80			25
				53.5	83	193	31	4.30	52	11			28	16	25	107	64	77	0.82	9.9	28
926	M	42	2.04	CI	58	320	41	3.87	67												
				CII	55	283	38	3.70	67	1	25	5				97	67	84			
				19	59	294	36	4.00	68	3	29	1				112	68	86			13
				41	69	307	39	3.90	57	5	36	10				119	71	87			23
902	F	26	1.82	CI	71	227	34	3.68	52										0.35	5.0	
				CII	66	197	36	3.01	46	3			17	7	10	115	67	81	0.29	4.4	
				23.5	82	241	39	3.38	41				22	10	15	118	66	82			11
				50.5	79	244	29	4.62	58						19	128	74	87			18
				68	79	242	28	4.76	60	8			29	14	21	123	68	86	0.84	10.6	27
907	F	23	1.63	CI	85	220	29	4.62	54										0.50	5.9	
				CII	86	217	29	4.61	54		18	5	20	7	13	145	82	100	0.50	5.9	
				32.5	108	231	29	4.96	46		29	12	33	17	26	155	84	104	0.94	8.8	13
				48	111	230	20	7.23	65		32	13	33	19	27	150	83	101	1.38	12.4	15
				20 aft.	110	241	25	5.91	54		27	9	28	15	21	154	84	98	0.96	8.8	11

* 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 III—*Continued*

Case no.	Sex	Age	Body surface area	Time*	Heart rate	O_2 consumption	A-V O_2 difference	Cardiac index	Stroke index	Blood pressure,† *mm. Hg*									Right ventricular work index	Right ventricular stroke work index	Decrease in hemoglobin
										RA	RV		PA			BA					
										M	S	D	S	D	M	S	D	M			
			M.²	*min.*	*beat/min.*	*ml./min.*	*ml./L.*	*L./min./ M.² B.S.A.*	*ml./beat/ M.² B.S.A.*										*Kg. M./min./ M.² B.S.A.*	*Gm. M./beat/ M.² B.S.A.*	%
									A. Normal subjects												
948	M	34	1.78	CI	69	236	52	2.53			21	4									
				CII	68	254	53	2.69	40				12	4	8	132	86	105			
				28	68	285	44	3.66	54				19	7	12	139	87	101			10
				44	71	287	43	3.75	53	3	21	6	21	10	13	140	87	103	0.51	7.2	16
964	M	24	1.94	CI	77	290	31	4.86	63	0	13	3	14	8	11	113	59	76	0.73	9.4	
				CII	74	282	34	4.24	57				12	6	10	110	56	75	0.58	7.8	
				34	78	285	30	4.95	63				19	12	16	105	56	75			13
966	M	34	2.17	CI	63	289	42	3.21	51	3									0.26	4.2	
				CII	63	270	44	2.83	45				13	4	9	80	53	61	0.23	3.7	
				32	71	274	36	3.52	50				23	12	17	82	51	62			11
972	F	40	1.76	CI	81	221	34	3.69	46	1									0.30	3.8	
				CII	79	235	36	3.72	47				12	3	7	121	68	89	0.30	3.8	
				26.5	78	225	31	4.07	52				16	5	13	122	67	89			15
									B. Patients without cardiac disease												
899	F	31	1.79	CI	94	220	33	3.69	39	1	22	4							0.35	3.7	
				CII	94	209	29	4.01	43				13	4	8	103	59	70	0.38	4.1	
				40	93	248	30	4.62	50												15
				44	93	227	33	3.84	41				22	10	17						17
				61	88	241	31	4.33	49				25	14	18				0.82	9.3	23
				65	88	232	31	4.21	48	4			25	14	20	107	57	70	0.92	10.4	24
864	M	18	1.90	CI	109	358	27	7.06	65										0.77	7.1	
				CII	118	339	27	6.68	57	1	21	3			11	142	75	90	0.73	6.2	
				23	109	370	25	7.67	70		27	5	23	8	12	133	70	86	0.73	6.7	10
				40	107	350	21	8.90	83		25	5	26	8	14	136	73	91	1.09	10.2	16
896	F	16	1.56	CI	74	184	36	3.24	44	2									0.48	6.6	
				CII	75	198	37	3.46	46				20	8	13	104	55	75	0.52	6.9	
				32	79	200	30	4.33	55				31	16	23	115	66	81			22
				35	78	219	29	4.78	61				34	19	26	118	64	82			24
				47	83	199	30	4.33	52	9			36	21	28	113	73	94	1.12	13.4	27
903	F	49	1.68	CI	90	221	32	4.10	46	2									0.72	8.1	
				CII	88	200	32	3.71	42				26	6	15	140	74	109	0.66	7.4	
				18	91	208	31	4.04	44				31	10	20	135	70	98			14
				38	95	186	27	4.07	43				29	13	23	137	74	98			
				50	99	236	25	5.68	57	7			33	14	22	130	67	100	1.16	11.6	27

TABLE IV

Normal subjects: Dextran with physiologic saline solution

Case no.	Sex	Age	Body surface area	Time*	Heart rate	O_2 consumption	A-V O_2 difference	Cardiac index	Stroke index	Blood pressure,† *mm. Hg*							Right ventricular cardiac work index	Right ventricular stroke work index	Decrease in hemoglobin
										RA	PA			BA					
										M	S	D	M	S	D	M			
			M.²	*min.*	*beat/min.*	*ml./min.*	*ml./L.*	*L./min./ M.² B.S.A.*	*ml./beat/ M.² B.S.A.*								*Kg. M./min./ M.² B.S.A.*	*Gm. M./beat/ M.² B.S.A.*	%
976	M	35	1.79	CI	69	232	44	2.95	43	1							0.36	5.3	
				CII	69	219	45	2.69	39		17	5	10	121	75	90			
				28	78	235	41	3.20	41		27	11	17	126	74	90			12
				44	82	267	33	4.49	55		29	11	20	120	73	93			19
				57	94	290	34	4.79	51		29	14	21	115	64	85			24
986	M	27	2.14	CI	71	306	38	3.74	53	2	18	5	11	141	77	96	0.46	6.5	
				CII	71	325	40	3.78	53	1	19	4	11	141	77	94	0.51	7.2	
				22	79	313	32	4.58	58	4	26	10	18	142	77	100	0.87	11.0	7
				45	87	337	29	5.36	62	6	34	13	25	150	78	103	1.39	16.0	16
				21 aft.	90	343	27	5.92	66	4	30	11	20	146	76	99	1.29	14.4	18
							BA–RA												
996	M	45	2.22	CI	86	300	40	3.35	39	1									
				CII	84	304	39	3.50	42	0				157	99	116			
				31	86	361	30	5.44	63	5				157	92	120			13
				48	98	364	32	5.16	53	7				153	89	117			19
				18 aft.	99	366	32	5.22	53	4				143	85	107			20
1003	M	36	1.87	CI	68	240	54	2.37	35	3							0.19	2.9	
				CII	61	289	53	2.89	47		16	6	9	136	89	105	0.24	3.8	
				21	60	279	48	3.10	52		23	11	15	138	85	109			11
				40	57	301	45	3.58	63		27	13	19	137	81	110			25
				56	57	270	38	3.77	66	10	30	15	22	142	82	106	0.62	10.8	36
				20 aft.	61	260	38	3.65	60	7				145	87	105			34
							BA–RA												
1006	M	32	2.14	CI	68	272	31	4.14	61										
				CII	68	281	30	4.32	64	2				140	91	108			
				14	76	251	28	4.17	55	5				142	88	105			4
				31	79	263	32	3.89	49	7				143	88	107			6
				12 aft.	78	271	27	4.78	61	5				137	91	107			7

* 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 V

Normal subjects: Dextran in physiologic saline solution and dextran in 5 per cent glucose in H_2O

		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 indiastolic 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 indiastolic 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	Heart volume	Time*	Heart rate	O_2 consumption	A-V O_2 difference	Cardiac index	Stroke index	Blood pressures,† *mm. Hg* PCV	RA	RV		PA			BA			Right ventricular stroke work index	Decrease in hemoglobin
											M	M	S	D	S	D	M	S	D	M		
			M.²	*ml./M.² B.S.A.*	*min.*	*beat/min.*	*ml./min.*	*ml./L.*	*L./min./ M.² B.S.A.*	*ml./beat/ M.² B.S.A.*											*Gm. M./beat/ M.² B.S.A.*	%
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	
					23	83	216	37	4.01	48			33	11	32	15	22			87	7.2	12
					39	91	223	34	4.47	49			36	14	38	20	27			90	8.7	22
					12.5 aft.	114	256	30	5.86	51			40	11	35	20	27			85	11.1	29
863	F	44	1.53	510	C	83	204	41	3.25	39			29	7	30	10	16	89	43	59	4.8	
					17.5	88	203	39	3.52	40			36	11			22	90	49	58	6.0	10
					35.5	93	208	35	3.88	42			42	15	43	17	27	96	52	63	6.9	19
					7 aft.	94	215	37	3.80	40			40	13	44	18	27	92	49	62	7.6	21
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		13
					33	99	294	36	4.62	47		2			61	31	42	103	56	72	25.6	20
897	F	29	1.65	400	C	69	212	40	3.21	47		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	10
					25	65	217	40	3.30	51		2			18	7	11	97	54	70	6.2	13
					46.5	65	239	37	3.89	60		7			25	11	16	107	60	72	7.3	19
					2 aft.	78	222	35	3.85	49					20	8	14	100	55	73		20
925	F	32	1.42	330	C	100	190	32	4.18	42	5	1	26	1	20	5	11	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	
					32	79	237	41	3.09	39					34	17	23	135	71	101		22
					44	82	279	34	4.37	53		6			38	20	26	156	78	101	14.4	26
960	F	40	1.60	430	C	92	195	31	3.93	43	10	2			28	13	19	106	56	73	9.9	
					27	85	169	29	3.68	43					36	19	25	105	56	72		12
					48	107	173	34	3.17	30	24	7			44	26	35	106	56	75	11.4	20
967	F	45	1.50	580	C	65	187	41	3.04	47	21	3			38	16	24	106	58	80	13.4	
					25	74	188	38	3.33	45		8			47	21	33	109	59	80	15.3	18
					38	78	197	35	3.74	48		9			48	23	35	108	58	79	17.0	24
969	F	26	1.62	410	C	75	198	43	2.84	39		1			27	15	22	105	45	59	11.1	
					29	79	212	41	3.23	41		6			39	25	33	111	51	66	15.1	18
					47	89	243	40	3.72	42		7			40	29	34				15.4	20

* 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	Time*	Heart rate	O_2 consumption	A-V O_2 difference	Cardiac index	Stroke index	Blood pressures,† *mm. Hg*										Right ventricular stroke work index	Decrease in hemoglobin
											PCV	RA	RV		PA			BA				
											M	M	S	D	S	D	M	S	D	M		
			M.²	*ml./M.² B.S.A.*	*min.*	*beat/min.*	*ml./min.*	*ml./L.*	*L./min./ M.² B.S.A.*	*ml./beat/ M.² B.S.A.*											*Gm. M./beat/ M.² B.S.A.*	%
									B. Dextran in isotonic saline solution													
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	
					21	72	187	58	2.38	33		6			61	25	40	118	61	80	15.3	13
					31	77	203	58	2.59	34		7			64	26	43	117	61	81	16.6	15
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		18
					37	111	231	29	5.09	46					49	27	38	136	74	96		24
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	10
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	10
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	10
					35.5	61	268	52	2.63	43		7			51	20	32	164	96	113	14.6	15
					aft. 19	53	257	51	2.57	48		6			47	18	31	154	88	112	16.3	20
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		10
					29	88	186	37	3.09	35		4	66	8	64	36	47	162	95	120	20.5	18
					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		5
					33	71	245	45	2.83	40		4	50	7	53	20	33	165	95	111	15.8	10
					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 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.

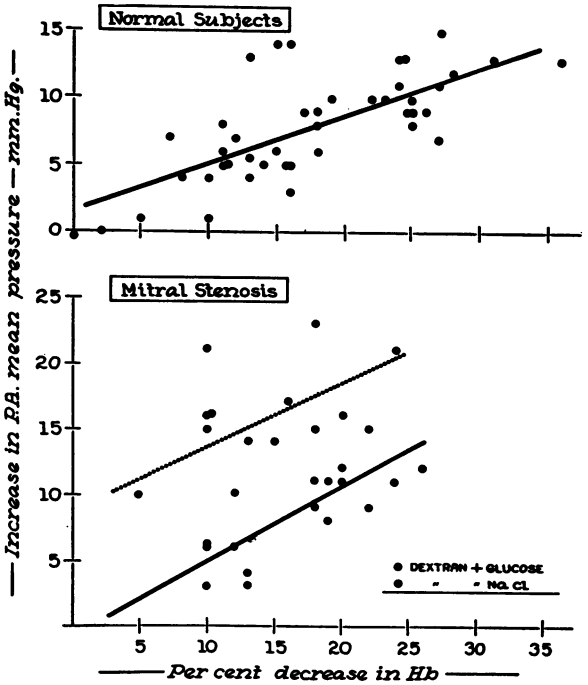

FIG. 2. REGRESSIONS FOR THE INCREASE IN PULMONARY ARTERIAL MEAN PRESSURE ON THE PERCENTAGE DECREASE IN HEMOGLOBIN

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 ($0.2 > p > 0.1$).

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

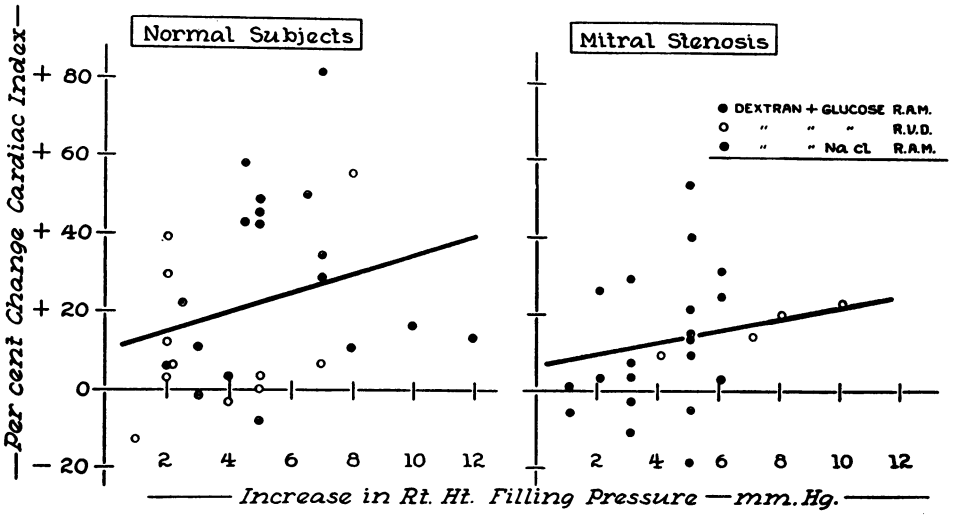

FIG. 3. REGRESSIONS FOR THE PERCENTAGE CHANGE IN CARDIAC INDEX ON THE INCREASE IN RIGHT HEART FILLING PRESSURE

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 pressures 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.

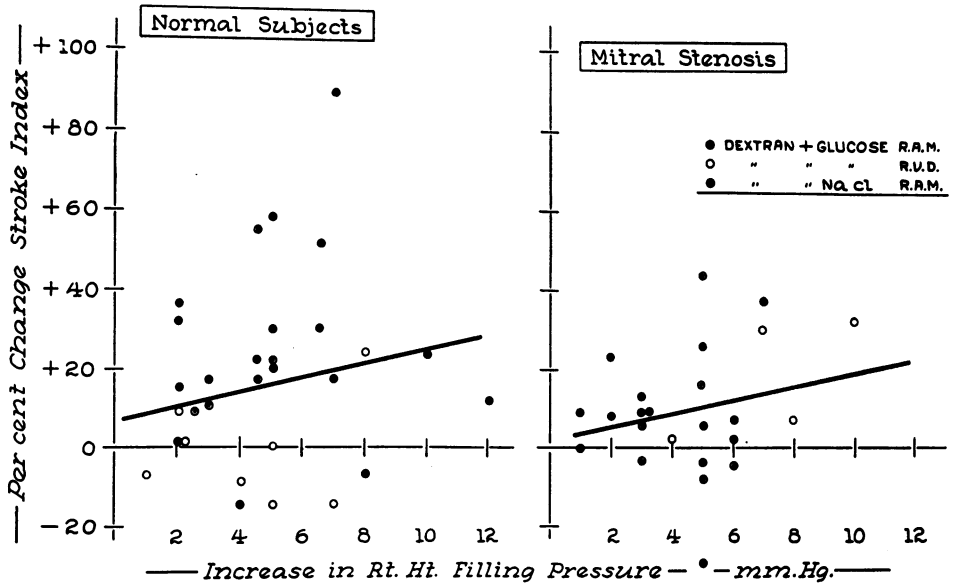

FIG. 4. REGRESSIONS FOR THE PERCENTAGE CHANGE IN STROKE INDEX ON THE INCREASE IN RIGHT HEART FILLING PRESSURES

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 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-

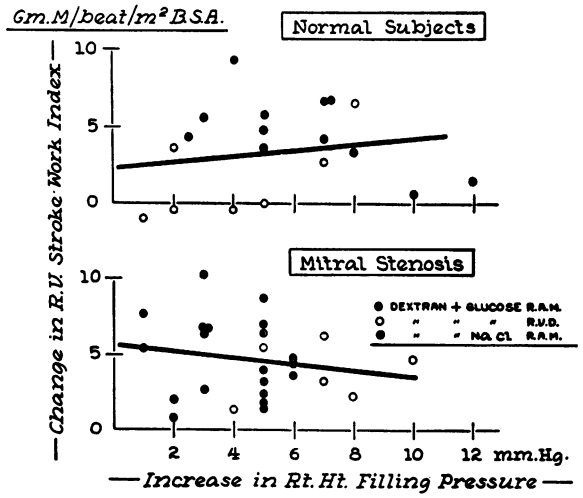

FIG. 5. REGRESSIONS FOR THE CHANGE IN RIGHT VENTRICULAR (RV) STROKE WORK INDEX ON THE INCREASE IN RIGHT HEART FILLING PRESSURE

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).

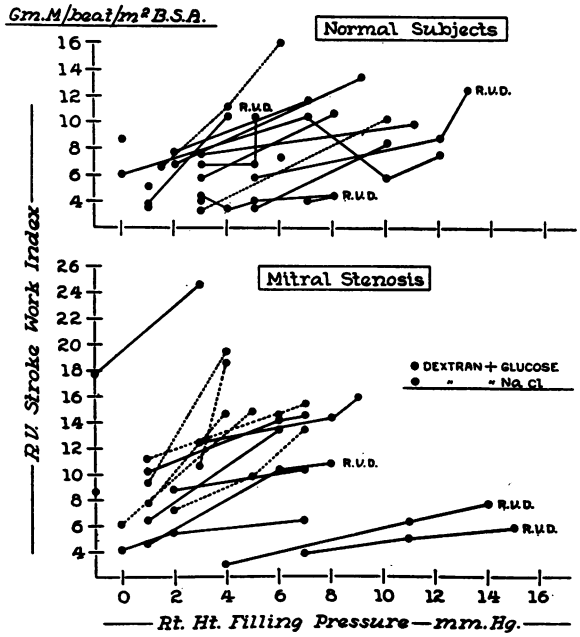

FIG. 6. THE RELATION BETWEEN RIGHT HEART FILLING PRESSURE AND RIGHT VENTRICULAR STROKE WORK INDEX IN EACH SUBJECT

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.

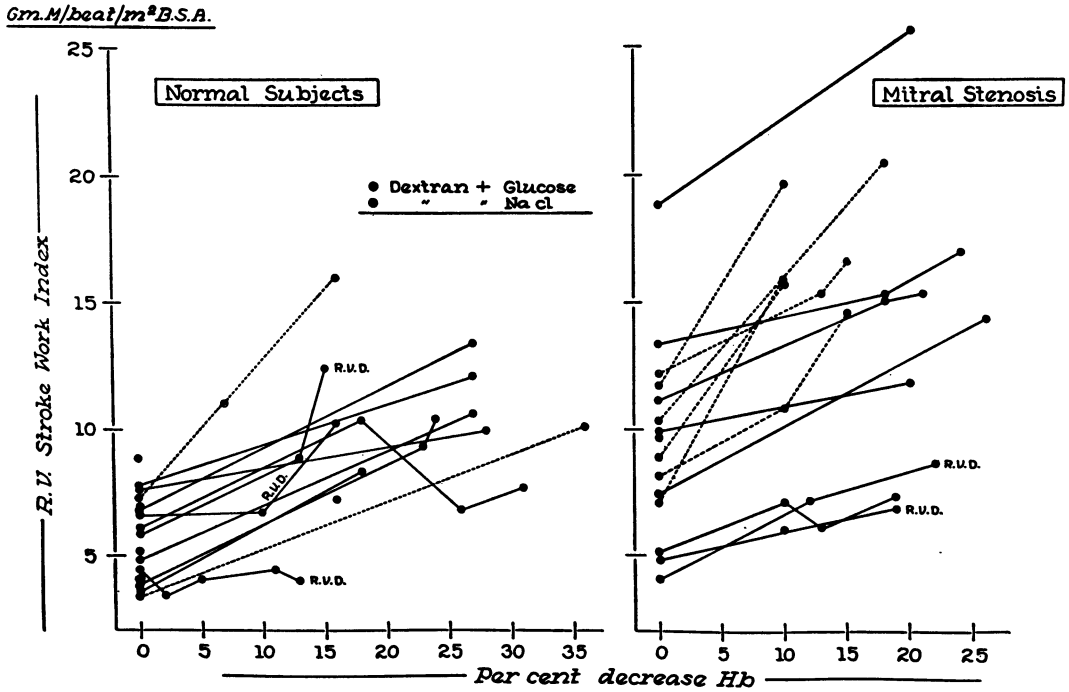

FIG. 7. THE RELATION BETWEEN THE PERCENTAGE DECREASE IN HEMOGLOBIN AND RIGHT VENTRICULAR STROKE WORK INDEX IN EACH SUBJECT

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 pressures 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). Examinations 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.

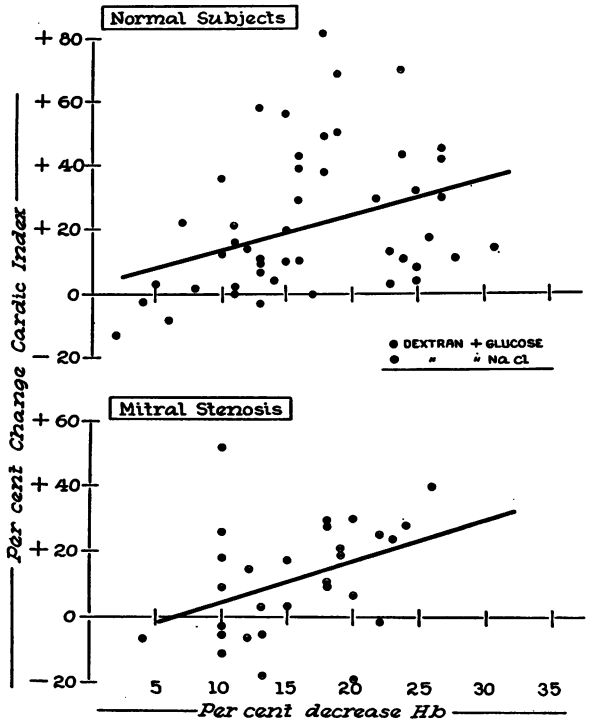

FIG. 8. REGRESSIONS FOR THE PERCENTAGE CHANGE IN CARDIAC INDEX ON THE PERCENTAGE DECREASE IN HEMOGLOBIN

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).

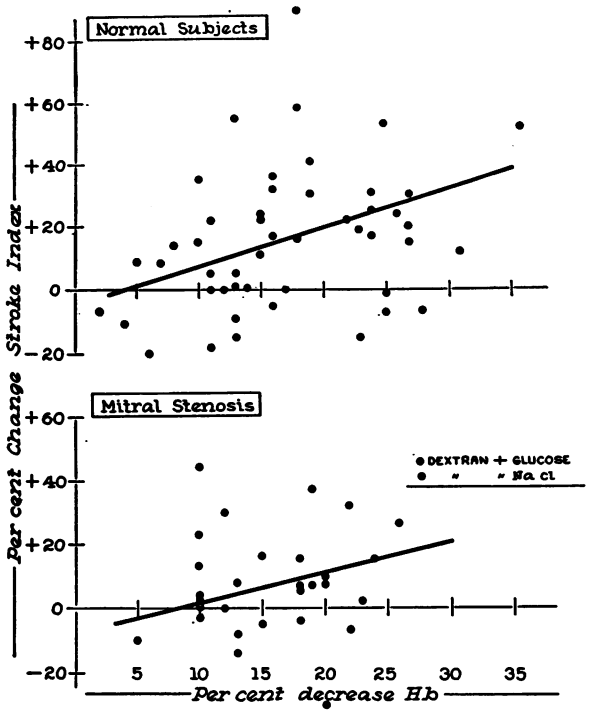

FIG. 9. REGRESSIONS FOR THE PERCENTAGE CHANGE IN STROKE INDEX ON THE PERCENTAGE DECREASE IN HEMOGLOBIN

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 ($p > 0.1$).

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

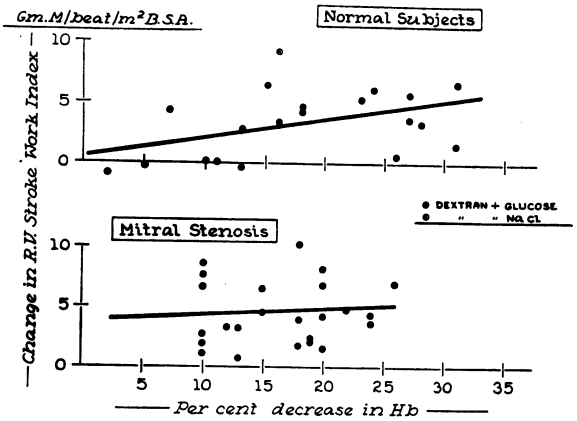

FIG. 10. REGRESSIONS FOR THE CHANGE IN RIGHT VENTRICULAR STROKE WORK INDEX ON THE PERCENTAGE DECREASE IN HEMOGLOBIN

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.

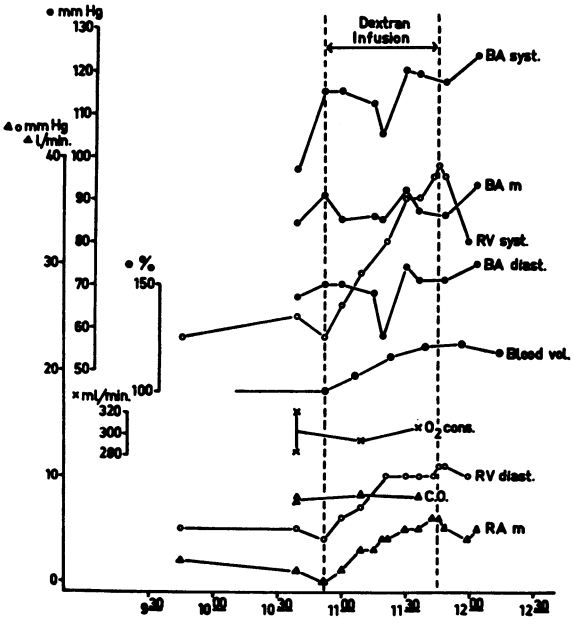

FIG. 11. DATA OBTAINED DURING AN INFUSION OF DEXTRAN IN 5 PER CENT GLUCOSE AND WATER IN A NORMAL SUBJECT (No. 926)

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 increase 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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