THE EFFECT OF EPINEPHRINE ON THE PULMONARY CIRCULATION IN MAN [1]

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Extensive studies are available concerning the effect of epinephrine upon the lesser circulation of several species of animals and a variety of animal preparations. Until recently, this type of investigation has not been possible in man. The development of methods has now made such studies feasible, and much can be learned in a quantitative and semi-quantitative way. The intracardiac catheter, the dye dilution techniques for blood flow and volume, and a high frequency recording manometer are the corner-stones of the present study.

The purpose of this work was to discover what changes in pulmonary circulatory dynamics resulted from an intramuscular injection of epinephrine into a human. This aim was primarily clinical; therefore, dose, route of administration, and drug preparation were those commonly employed in therapy.

MATERIALS AND METHODS

The patients were chosen at random from the medical and surgical chest services at Lawson VA Hospital. In age they ranged from 20 to 55 years. The average age was 31 years. All were male. Diagnoses and a summary of data are listed in Table I. None had clinical evidence of cardiovascular disease. With the exception of Cases 1, 2, 12, and 13, the pulmonary lesions were so sharply localized or limited in degree that no significant disturbance in the pulmonary circulation was suspected. The experiments dealing with intravenous and intramuscular injection of epinephrine were performed on these 13 patients in the post absorptive state.

The epinephrine [2] was a U.S.P. preparation and is said by its manufacturer to be a synthetic material, to exist 100 per cent in the levo-rotatory form as a hydrochloride, and to contain no traces of nor-epinephrine.

Pulmonary artery catheterization was performed in the usual way with a 6-F or 8-F intracardiac catheter. All systemic arterial blood samples and pressure records were obtained from an indwelling, femoral arterial needle. An electromanometer (Sanborn), recording through a single channel, direct-writing electrocardiograph (Sanborn), was used for all pressure tracings. Arbitrary reference point was 5 cm. below the sternal *angle of Louis.* Mean pressures were obtained by electrical integration of the pulse contours. Pulmonary "capillary" pressures were obtained as described by Hellems, Haynes, and Dexter (1).

Cardiac outputs were derived by the dye dilution method of Hamilton (2, 3), using Evans Blue dye (T-1824), and the technique of Dow and Pickering for determination of dye concentration (4). Dye output determinations done in this way have been shown to correlate well with the Fick procedure (5). The lesser, mean, and total circulation times, as derived from the graphic representation of the dye concentration curve, may be defined as follows: *Lesser (fastest) circulation time* is the appearance time (extrapolated) of the first detectable dye arriving at the femoral artery by the most rapid pathway. *Mean circulation time* is the mean of the appearance times of dye particles arriving at the femoral artery from all pathways during the dye's first complete circulation, and *total circulation time* is the time required for the dye column to completely circulate one time after having first reached the femoral artery (time of recirculation minus the lesser circulation time). A figure ("Q") was also derived from the dye curve as an index of pulmonary blood volume, as described by Ebert and associates (6). "Q" not only represents blood in the pulmonary vascular bed but also that in the left side of the heart, the aorta, and certain large arteries.

Although both Ebert and we ourselves have noted considerable scatter of values for "Q" in a series, we have also noted a surprising reproducibility in the same patient (7), even when the patient was in an unstable state. Figure 1 indicates that in the present study unless the "Q" value decreased by a very large amount, which we have attributed to the epinephrine, the majority of the figures changed less than 10 per cent in spite of gross changes in both cardiac output and mean circulation. In no case in which we have checked the procedure without disturbing the circulation, has there been a discrepancy of over 15 per cent, and almost all were within 10 per cent.

Vascular resistance and cardiac work were calculated according to the formulae mentioned by Dexter and associates (8).

The basic experiments were done as follows: The fast-

[1] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or the policy of the Veterans Administration.

[2] Gold Leaf Pharmacal Company, New Rochelle, New York.

TABLE I

Pulmonary circulation data before and after epinephrine

Case	Body surface area, *sq. m.*	Minutes after epinephrine	Cardiac output, *L/min.*	Cardiac index, *L/sq. m./min.*	Pulse, *rate/min.*	Stroke volume, *cc.*	Circulation time, *in sec.*			"Q", *in cc.* (pulm. blood vol. index)	Pulmonary artery pressure, *mm. Hg*			Mean pulm. "cap." press., *mm. Hg*	PA-"PC" gradient, *mm. Hg*	Pulmonary vascular resistance, *dynes sec. cm.$^{-5}$*	"Work" against pressure, *Kg. m./sq. m./min.*		Diagnosis
							Lesser	Mean	Total		Systolic	Diastolic	Mean				Rt. ventricle	L. ventricle	
1	1.62		3.8	2.3	100	38	2.5	7.5	9	470	26	10	19	7	12	266	.6	2.8	Extensive bronchiectasis
		7	8.1	5.0	112	72	1.5	3.8	4	511	34	12	24	7	17	169	1.7	5.9	
2	1.91		7.3	3.8	68	107	5.5	11.0	12	1333	33	8	18	4	14	154	.9	4.6	Tuberculosis, rt. pneumothorax
		10.5	10.3	5.4	75	138	3.5	8.4	10	1447	34	11	21	5	16	124	1.6	5.7	
3	2.06		7.4	3.6	76	97	5.5	10.5	10	1288	12	1	7	—	—	—	.4	4.0	Normal
		11	10.3	5.1	100	105	3.5	8.0	8	1277	17	4	9	—	—	—	.7	5.7	
4	1.58		3.9	2.5	90	45	4.0	10.5	12	685	17	6	9	5	4	81	.2	2.1	Bronchiectasis
		8	5.8	3.7	96	61	3.3	7.5	10	725	19	6	12	5	7	96	.6	4.2	
5	1.72		4.8	2.8	80	60	4.5	12.3	15	980	15	4	8	3	5	83	.3	3.1	Tuberculosis, rt. upper lobe
		6	7.6	4.4	96	79	1.5	7.2	12	910	19	4	13	3	10	105	.8	—	
		19.5	6.6	3.8	90	73	2.0	7.5	11	830	16	4	11	3	8	91	.5	3.6	
6	1.86		5.2	2.8	70	52	5.5	16.6	16	1430	23	10	14	—	—	—	.6	3.6	Bronchiectasis, rt. lower lobe
		3	5.9	3.1	100	85	7.5	13.5	12	1340	27	12	21	—	—	—	.9	4.8	
7	1.89		4.8	2.6	60	81	3.5	11.0	14	807	15	7	11	—	—	—	.4	2.9	Tuberculosis, rt. upper lobe
		6	8.1	4.3	80	102	3.5	7.7	8	1040	23	7	14	—	—	—	.9	4.9	
8	2.16		5.5	2.6	84	66	5.5	12.8	14	1180	14	3	9	—	—	—	.3	3.1	Bronchiectasis
		3	8.4	3.9	100	84	4.5	9.2	11	1280	17	5	11	—	—	—	.6	5.1	
9	1.62		5.8	3.6	108	51	7.5	12.4	11	1200	10	5	7	2	5	73	.4	3.7	Emphysema, bronchiectasis, and asthma
		8.5	7.8	4.8	120	65	1.5	5.9	10	770	17	5	11	2	9	92	.8	5.5	
10	1.70		4.7	2.7	80	52	3.5	9.3	14	825	17	5	11	—	—	—	.4	3.1	Normal
		5	4.5	2.6	110	41	1.5	6.0	10	447	25	7	15	—	—	—	.6	2.8	
11	2.06		7.2	3.5	70	103	8.0	14.5	14.4	1730	19	5	10	—	—	—	.5	5.5	Normal
		4	7.8	3.8	90	86	2.0	8.7	11.5	1130	25	7	17	—	—	—	.9	5.7	
12	1.78		7.7	4.3	80	97	5.5	10.5	12	1350	16	6	12	—	—	—	.7	5.7	Asthma, emphysema
		7	6.4	3.6	85	76	2.5	8.0	8.2	877	30	12	20	—	—	—	1.1	4.0	
13	1.53		3.8	2.6	96	40	5.5	13.5	14	858	21	6	13	—	—	—	.5	3.1	Chronic lung abscess—pulmonary fibrosis
		2.5	6.5	3.9	120	54	1.5	6.5	8	722	30	12	17	—	—	—	.9	6.2	

ing patients were sedated with .1 or .2 gm. of sodium phenobarbital intramuscularly, the catheter placed in the pulmonary artery, and the indwelling, femoral arterial needle inserted. A preliminary dye injection was made and several pressure tracings taken. Then 0.5 to 0.7 cc. of 1:1000 dilution of epinephrine was injected intramuscularly, and pressures were closely followed. From two and one-half to 10 minutes later, a second dye injection was made. In most instances, the pressures were followed until their return to normal. In one case, a third dye injection was done. In addition, 0.025 mg. of epinephrine was given intravenously on six occasions, and continuous tracings of either the femoral, pulmonary arterial, or pulmonary "capillary" pressures were recorded.

RESULTS

Pressure Changes in the Pulmonary Circulation

Under basal conditions at the beginning of the studies, the average pulmonary artery pressure for our 13 patients was 18.6 with a mean value of 11 mm. Hg. Mean "capillary" pressures in five patients averaged 4 mm. Hg with a range of from 2 to 7 mm. Hg. These pressures are generally lower than those found in some normal series (8). The reason for this difference probably lies in the arbitrarily chosen reference points. Our average pulmonary artery-pulmonary "capillary" gradient was 8.6 mm. Hg with a range of from 4 to 14 mm. Hg.

The mean pulmonary artery pressure rose in every case following the injection of epinephrine. The average rise of the mean pulmonary artery pressure was 4.4 ± .54 [3] mm. Hg with a range of 2 to 8 mm. Hg. This rise was due chiefly to an elevation of systolic pressure which rose, on the average, 6 mm. Hg with a range of 2 to 14 mm. Hg. The average diastolic rise was only 2 mm. Hg with a range of 0 to 6 mm. Hg. The only two patients who had a striking diastolic rise (6 mm. Hg each) were among those four who were judged to have severe chronic lung disease but no pulmonary hypertension. The other two such patients had mild pulmonary hypertension but had diastolic rises of only 2 and 3 mm. Hg each.

The pulmonary pressure rise usually began in one to two minutes after the intramuscular injection, reached a peak in two to 16 minutes (average 7 mm. Hg), and gradually returned to basal levels in about 20 minutes. In three patients, however, the return to normal was not so prompt, and pressure was still elevated at 30, 32 and 46 minutes after injection. In these patients, no clinical or subjective signs of epinephrine effects were then present, with the exception of a slightly elevated pulse rate.

[3] All values are expressed as mean ± standard error of the mean.

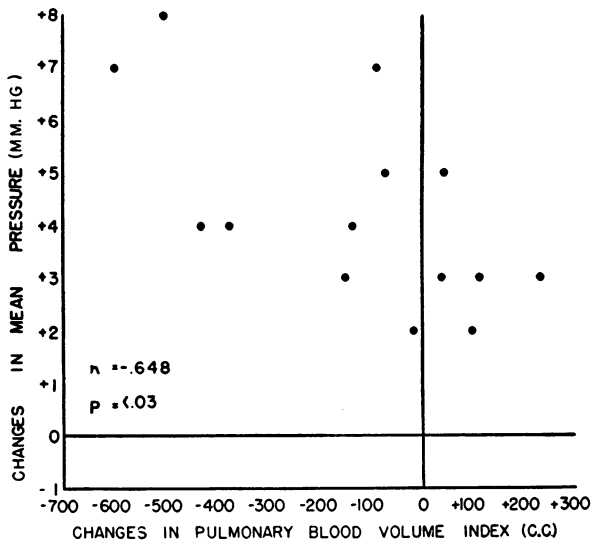

FIG. 1. RELATION BETWEEN CHANGES IN THE MEAN VALUES OF PULMONARY BLOOD VOLUME INDEX AND PULMONARY ARTERY PRESSURES AFTER ADMINISTRATION OF EPINEPHRINE

When the index of pulmonary blood volume ("Q") was determined at a time when the epinephrine-induced pulmonary hypertension was at its peak (in five cases), the pulmonary blood volume index had fallen considerably below its initial level. Also, in these five cases, the changes in cardiac output were much less than in the remaining eight cases.

The pulmonary "capillary" pressure measured in five cases rose very slightly if at all. The average pressure at the time of the second set of determinations was only 0.5 mm. Hg higher than the average before epinephrine. This average figure, derived from single readings, sometimes temporally distant from the peak effect, however, obscures the fact that there was a 2 to 3 mm. Hg rise in pulmonary "capillary" pressure in most cases coincident with the peak rise in mean pulmonary artery pressure. It was never of sufficient degree to account for the total elevation in mean pulmonary artery pressure and, as in Case 2 (Figure 2), had disappeared, while the pulmonary artery pressure was still high.

The pulmonary artery-pulmonary "capillary" gradient, however, had increased quite sharply in four cases and slightly in the fifth at the times at which it was measured. The average increase was 3 mm. Hg higher after epinephrine.

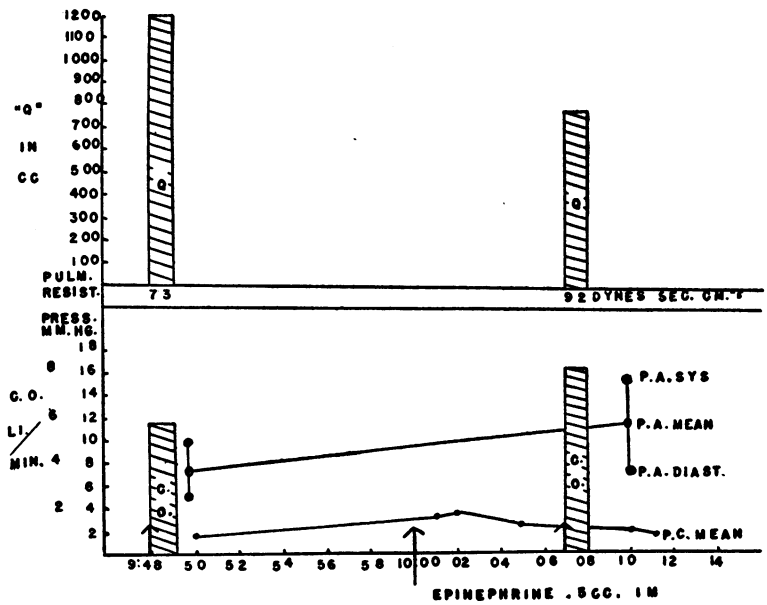

FIG. 2. HEMODYNAMIC CHANGES FOLLOWING EPINEPHRINE INJECTION AS OBSERVED IN CASE 9

C.O. = cardiac output
"Q" = index of pulmonary blood volume
P.A. Sys. = pulmonary artery systolic pressure
P.A. Mean = pulmonary artery mean pressure
P.A. Diast. = pulmonary artery diastolic pressure
P.C. Mean = pulmonary "capillary" mean pressure

Calculated figures for pulmonary vascular resistance are written beneath "Q" block graphs. Time of injection of epinephrine is represented by large arrow at time denoted as 10:00 o'clock. Note that "Q" decreased considerably in the presence of elevated pulmonary resistance, pulmonary artery pressure, and cardiac output.

An attempt was made to determine whether a direct effect of epinephrine on the pulmonary artery could be demonstrated by injecting 0.025 mg. of epinephrine directly into the antecubital vein and noting the time required for the expected rise in pulmonary artery pressure to occur. The procedure was then repeated in the same patient while a continuous tracing was made of the pulmonary artery, capillary, or femoral artery pressure. If the intravenously injected epinephrine had had a direct effect on the pulmonary vascular bed in its first passage through it, a rise in pulmonary artery pressure should be expected in eight to 10 seconds (9). Only one of three patients showed a detectable response at a time (11 seconds) approaching this, and that patient also had just as early a response in femoral artery pressure. Therefore, we were unable to demonstrate by this rough method and with this dosage, a direct effect of epinephrine on the pulmonary vascular tree. Doyle, Wilson, and Warren (10), using a similar technique, have shown that in four of a group of five patients there was a rise in pulmonary artery pressure within 10 to 12 seconds after the intravenous injection of epinephrine. Other studies with simultaneous ballistocardiograph and femoral and pulmonary artery pressure tracings, after a small intravenous dose of epinephrine, should be done.

Cardiac Output, Pulse Rate, Stroke Volume

Before epinephrine, our initial cardiac indices averaged 3.0 L/min./sq.m. with a range from 2.3 to 4.3, which compares favorably with basal patients studied by the Fick method (11). Two and one-half to 11 minutes after the intramuscular injection of epinephrine the mean rise of the cardiac index was 1.0 ± 0.1 L/min./sq.m. There was a

rise in 11 of the 13 patients, no change in one (Case 10), and a definite fall in another (Case 12). There was no apparent reason for the failure of the index to rise in Case 10. Case 12, however, was rather anxious and had a high initial cardiac output which probably masked any change that might have been caused by the epinephrine. There was, in addition, very little acceleration of the pulse in this patient after epinephrine in spite of a definite change in circulation time.

Pulse rate increased from five to 30 beats per minute following epinephrine. Averages before and after epinephrine were 82 and 98 respectively. A rise was noted in all 13 cases.

Stroke volume increased in 10 of 13 cases. Increases ranged from 8 to 90 per cent with an average rise of 26 per cent. In the other three cases, there was a moderate fall of from 16 to 22 per cent.

Circulation Times

Speed of circulation of the dye from pulmonary to femoral artery was increased in every instance following epinephrine. This was not so apparent in the "lesser" circulation time because sampling of femoral arterial blood was done only at two-second intervals, and the smaller absolute changes might have been partially missed. Average resting values for the lesser, mean, and total circulation times were 5, 11.7, and 12.8 seconds respectively. After epinephrine, these values dropped to 2.9, 8, and 9.4 seconds. There was an impressive acceleration of blood flow in every case when measured by the mean circulation time.

Pulmonary Blood Volume Index or "Q"

The average "Q" for our 13 patients under basal conditions was 1087 cc. ranging from 470 to 1730 cc. These figures are slightly lower than the figure given by Ebert and colleagues (6). One explanation may be that Ebert's group was a more nearly normal group. Moreover, the cardiac outputs and mean circulation times used in the formula for "Q" by Ebert were not simultaneous, since the outputs were done by the Fick procedure and the circulation time derived from a dye curve obtained afterwards. There may have been changes in the circulation time or cardiac output between the two procedures.

The average "Q" after epinephrine was 959 cc., an average decrease of 128 ± 72 cc., which is not significant. It must be remembered that usually only one dye dilution curve, covering a period of about 20 seconds, was done on each patient after the epinephrine injection. Transient changes might or might not have coincided with the dye procedure. This, indeed, seems quite probable when individual protocols are studied. Figure 1 illustrates a significant correlation between the height of the pulmonary artery pressure rise and the change in "Q." If the procedure was done when the mean pulmonary artery pressure was quite high, "Q" was apt to have fallen; if the determination was done before or after the peak rise in pressure, the "Q" value remained nearly the same. Figure 1 reveals five cases (Cases 9–13) in which "Q" fell from 16 to 46 per cent (150 to 600 cc.), well outside the usual variation of 10 per cent.

If these five experiments in which there was a considerable fall in "Q" are separated and compared with the remaining eight cases in which "Q" showed little change, it will be found that there is no great difference between the two groups in regard to the change in pulse rate and circulation time; also, the temporal relation between the determinations and the epinephrine injection was the same. In addition to the relationship illustrated in Figure 1, there is a great difference between this group of five cases and the remaining eight patients in regard to change in cardiac index and stroke volume. Among these five cases in which "Q" fell, only one had a large increase in cardiac index; the average rise in cardiac index was only 8 per cent. Average stroke volume rise was equally insignificant (0.6 per cent). In the remaining eight cases, however, the average rise in cardiac index was over 50 per cent and in stroke volume, over 30 per cent. The relationship of the changes of the cardiac index to the changes of the pulmonary blood volume index is graphically expressed in Figure 3. A positive correlation of stroke volume with pulmonary blood volume has been noted previously under physiological conditions in man (3).

In summary, five of 13 patients had a fall in "Q" following epinephrine administration, which was concomitant with the peak rise in pulmonary artery pressure. Four of these five cases had negligible changes in cardiac output, whereas most of the

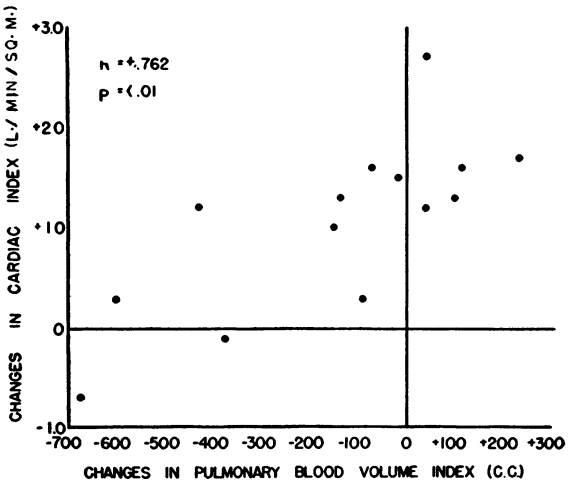

FIG. 3. RELATION BETWEEN CHANGES IN THE MEAN VALUES OF THE CARDIAC INDEX AND THE VOLUME OF BLOOD WITHIN THE LUNG ("Q"), FOLLOWING EPINEPHRINE ADMINISTRATION

When the output has changed little, the pulmonary blood volume index tends to fall; when the output increases, the index of pulmonary blood volume tends to remain the same or increase.

remaining eight cases had marked increases in cardiac output with relatively little change in "Q."

Pulmonary Vascular Resistance and Right Ventricular Work

In five cases (Cases 1, 2, 4, 5, 9), the pressure gradient between pulmonary artery and pulmonary "capillary" was determined before and after epinephrine and pulmonary vascular resistance calculated. This figure rose 26, 19, and 27 per cent in three cases (Cases 4, 5, 9) and fell 40 and 26 per cent in the other two cases (Cases 1, 2).

Looking at these cases individually, we see that all of the first mentioned patients had relatively mild disease and had little change in diastolic pressure after the drug. Calculated basal vascular resistances were within Dexter's normal range (8). The other two patients had severe lung disease, had mild pulmonary hypertension at rest (the two highest of all the 13 patients), and definitely had a rise in diastolic pressure after epinephrine. One of the two also had the very low "Q" value of 470 cc. (the lowest in the entire series). The resulting values for pulmonary vascular resistance in these two were markedly elevated at rest when compared with the other three or with Dexter's normal values.

To summarize this information, the three patients with relatively normal pulmonary vascular beds showed evidence of an increase in pulmonary vascular resistance following epinephrine. In two patients with considerable evidence of chronic lung disease and probable pulmonary vascular disease, there was a considerable fall in pulmonary vascular resistance.

The work of the right ventricle against pressure increased sharply in every case, from 30 to 174 per cent, with an average of 99 per cent. This result was not surprising since in almost every instance there was a rise in both pulmonary artery pressure and in cardiac output.

Left Ventricular Work, Systemic Arterial Pressure, and Peripheral Resistance

Since we were almost constantly recording pressure in the pulmonary circuit with our single manometer, it was impossible to study the pressure responses in the femoral artery adequately. A special point, however, was made of taking such a recording immediately following the dye injection so that peripheral resistance and left ventricular work could be calculated. Otherwise, our information was not adequate to draw conclusions about the systemic pressure response in these experiments. Such studies have been done (12), and our impression is that our cases would have shown nothing unexpected. In every case, the pulse contour suggested a decrease in peripheral resistance, and this was corroborated by calculation. There was a slight rise of 5 to 15 mm. Hg in the systolic pressure in a few cases, and the mean pressure rose slightly in six patients. Diastolic pressure fell slightly or did not change. Mean pressures fell slightly in six cases. No recording was made in one.

Left ventricular work rose in 10 of 12 cases where it could be calculated, but the average rise was only 25 per cent, about half the percentage rise of work in the right ventricle. In absolute terms, however, the changes in left ventricular work against pressure were considerably more than the changes occurring in the right ventricle.

DISCUSSION

Effect of Epinephrine on Pulmonary Blood Volume

Using dye injection methods, Hamilton has demonstrated that large doses (.1 to .5 mg.) of epi-

nephrine, injected intravenously into the intact dog under morphine anesthesia, result in a slowing of the pulse rate and circulation time, a fall in cardiac output, and an increase in the quantity of blood encompassed by the figure "Q" (13). This has been explained as the result of the inability of the left ventricle to increase its output against a suddenly increased pressure; as a consequence, blood dams back into the pulmonary reservoir and in the right side of the heart and in the veins. Wearn and associates have, by direct observation in animals, noted the opening up of new capillaries and engorgement of small pulmonary blood vessels after similar doses of epinephrine (14). It seems reasonable to believe that with these large doses in the dog, an increase in the volume of blood within the lung does occur.

With small doses of epinephrine, however, the evidence is to the contrary. By direct observations, Hall found a rapid pulse and alveolar capillaries which became thinner and contained less blood (15).

In the heart-lung preparation very small doses invariably increased heart rate and blood flow and decreased the pulmonary blood volume (16). Daly concluded that there was fairly good evidence from several sources that epinephrine caused a decrease in size in the large extrapulmonary portions of the pulmonary vascular system (17).

In a number of cases, we have demonstrated that the circulating pulmonary blood volume index probably drops precipitously for a short time after a small intramuscular dose of epinephrine. Since only about 60 cc. of blood are contained in the human pulmonary capillaries (18) and, of course, a very small amount in the precapillaries, the drop in "Q" of several hundred cubic centimeters probably cannot be explained on the basis of changes in the volume of these sections of the pulmonary vascular bed. Changes of this magnitude must reflect a decrease in the volume of the large pulmonary arteries and veins regardless of what is happening in the "arterioles" or "capillaries." If an increase in pulmonary vascular resistance reflects a decrease in size of the pulmonary "arterioles," our observations on a few cases indicate the lack of relations between total pulmonary blood volume and size of the "arteriolar" bed in these cases. In Figures 2 and 4, two cases are shown in which the vascular resistance definitely increased. In one, however, there was apparently a considerable decrease in pulmonary blood volume index, but in the other there was no change.

The question arises whether this change in "Q"

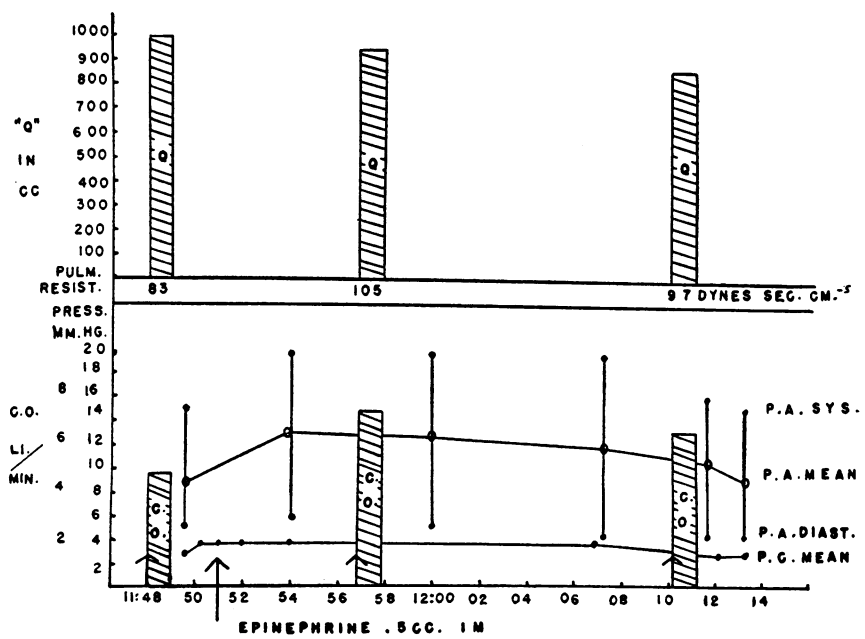

FIG. 4. HEMODYNAMIC CHANGES FOLLOWING EPINEPHRINE, AS OBSERVED IN CASE 5

Symbols are the same as in Figure 3. In this case, "Q" did not change appreciably, although all other values represented did increase.

might be due partially to changes in the extrapulmonary components that make up the total value. It is true that the size of the left heart might become smaller after epinephrine, but it seems unlikely that a normal heart would shrink enough to account for a drop of several hundred cubic centimeters. Little is known about the reaction of the living human aorta to epinephrine, but the evidence is that small doses probably dilate certain large arteries such as the femoral (19). This would actually tend to increase the "Q" value.

In his experiments with epinephrine, using dogs, Hamilton (13) found a prolonged dye dilution curve which indicated a low output and slow circulation. Using comparatively much smaller doses in the human, we have found dye curves of short duration which indicate increased outputs and rapid circulation. In Hamilton's experiments, heart rates were slowed, but in ours they were accelerated. Our epinephrine dye curves very closely resembled those in Hamilton's dogs following amyl nitrite. Apparently, circulatory dynamics in such experiments also closely approached those in ours. After amyl nitrite there was an increase in cardiac output, rapid circulation, accelerated heart rate, a fall in systemic peripheral resistance, and a decreased intrathoracic blood volume.

There is ample evidence from many sources that in therapeutic doses in man, epinephrine is a general vasodilator drug. This is apparent from pulse contours, fall in peripheral resistance, and direct effect on large arteries (12, 20–22). There is a profound redistribution of blood flow, the best known examples of which are the blanching of the skin and the increased flow to skeletal muscle (19).

It seems possible that the mechanisms whereby amyl nitrite and small amounts of epinephrine cause the heart to pump blood from the lesser into the greater circulation may be similar. In both cases the lung is giving up blood to widely dilated vascular areas. There is, nevertheless, one great difference in the action of the two drugs. Although their peripheral actions are similar, epinephrine has a stimulating effect on the myocardium that amyl nitrite lacks. McMichael and Sharpey-Schafer have shown that with very small doses this effect may be evident in an increased stroke volume without change in pulse rate or blood pressure (23). This implies a separation of the central and peripheral actions of the drug and suggests why in our experiments the fall in pulmonary blood volume index is probably so inconstant. When cardiac output increase is substantial, as in most of our cases, the dilated areas can be served without calling on the pulmonary circulation, but when the peripheral action of the drug is the more pronounced, there is relatively little change in output, and the pulmonary vascular circuit is drained to supply the dilated peripheral arterial beds. This explanation fits in with the fact that in our experiments demonstrating a fall in pulmonary blood volume index, there was very little or no increase in cardiac output and in stroke volume, although a fall in peripheral resistance and circulation time, and an increase in pulse rate had taken place. In the other cases, however, there was a decided increase in stroke volume and minute output, and the pulmonary blood volume index did not change.

Effect on the Pressures in the Pulmonary Circuit

The most consistent effect of epinephrine on the lesser circulation has been a rise in pulmonary artery pressure. The pressure in this system is continually influenced by the output of the right ventricle, the effect of back pressure in the pulmonary veins, and peripheral resistance in the pulmonary circuit (9). To elevate the pulmonary artery pressure in the normal human by increasing the cardiac output is difficult. When this is done by exercise, a minimum cardiac index of 5.5 to 6.0 is necessary (8, 24). These values were not approached in our cases. In addition, the largest increases in pulmonary artery pressure, which were accompanied by a fall in "Q," had the smallest increases in cardiac output. Although an increase in blood flow might tend to increase the pressure, it is an insufficient reason to explain the rise in the present experiment.

Hamilton's experiments with dogs given large doses of epinephrine clearly indicated that the pulmonary artery pressure increases so recorded were simply a reflection of an increased pulmonary venous pressure and that no change in the pressure gradient between the pulmonary artery and vein occurred (25). This does not seem to be an adequate explanation in the present experiments, because in the cases in which it was measured, there was very little change in the pulmonary "capillary"

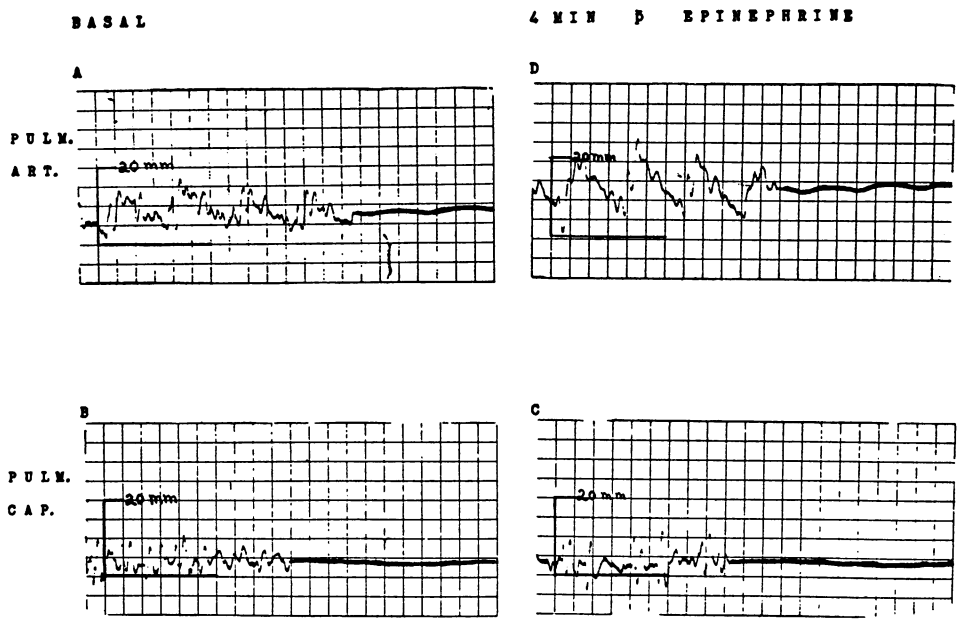

FIG. 5. SAMPLE TRACINGS FROM EXPERIMENT ON CASE 9 (Figure 3).

At the left are pulmonary artery and pulmonary "capillary" tracings taken shortly before the injection of epinephrine. Similar tracings 10 minutes after epinephrine are seen on the right. The dampened portions of the records are electrically integrated mean values. Standardizations and base lines have been copied into the left corner of each record. Time interval between C and D was less than 15 seconds.

pressure, and consequently an increased gradient resulted. In the cases in which the pulmonary "capillary" pressure was not measured, there was relatively little change in the diastolic pressures after epinephrine, and since a relation between pulmonary artery diastolic and pulmonary "capillary" pressure has been established (8), the pulmonary "capillary" pressure probably did not rise very much in this group either. The exceptions to the previous statement are the patients with widespread chronic lung disease.

Hamilton has pointed out that changes in the pressure gradient across the pulmonary circuit are considerably more important than the actual level of pressure in the pulmonary artery in determining whether peripheral resistance has changed or not (26). A sudden large increase in the cardiac output might conceivably widen the gradient, but cardiac output changes of the order of magnitude that we have found do not. The only explanation remaining, that there has been a decrease in the cross sectional areas of the terminal "arterioles," is likely (27). Hall's observations suggest the same conclusion (15). In three relatively normal cases (Figures 3 and 4), a moderate but definite increase in pulmonary vascular resistance has been demonstrated. Pressure records of one of these are seen in Figure 5. In the two cases with chronic lung disease and resting pulmonary hypertension, an entirely different result occurred. The elevated figures for pulmonary vascular resistance at rest fell considerably after epinephrine. This would be more difficult to understand were we to believe that the high pulmonary artery pressures and resistance were due to irreversible organic narrowing of the terminal "arterioles" and precapillaries. Cournand and his coworkers have recently shown quite definitely that the pulmonary hypertension of chronic lung disease is reversible to a large extent (28). This suggests that the high resistances in these cases might well have been due in part to vasoconstriction. In addition, Hickam (29) and Dexter and associates (8) have given evidence that the pulmonary hypertension of left ventricular failure may be partially due to an increased peripheral resistance within the circuit. The different response to epinephrine in normals and in two patients with mild pulmonary hyper-

tension suggests the possibility that the action of epinephrine upon the small arborizations of the pulmonary artery is dependent upon their state of contraction at the time the drug is given.

Finally, what is the mechanism by which epinephrine acts upon the small end branches of the pulmonary artery? We have failed to produce convincing evidence that it acts directly upon the blood vessels of the lung while on its first circulation in fairly high concentration. Our intravenous experiments are admittedly crude, however, and dosage small. The evidence for reflex vasomotor control of the human pulmonary circulation is "by and large" non-convincing (9), and we can add nothing to this argument. With the methods now available, such evidence should be forthcoming.

SUMMARY

1. Epinephrine, uncontaminated by nor-epinephrine, in intramuscular doses of from 0.5 to 0.7 cc. of a 1 : 1000 solution causes the following events to occur in the pulmonary circulation:

a. A decrease in the intrapulmonary circulation time.

b. A decrease in pulmonary blood volume index under certain circumstances when its action is suggestively that of a peripheral vasodilator and central effect is minimal.

c. A rise in the systolic and mean pulmonary artery pressures. The diastolic pressures are usually increased very little. Pulmonary "capillary" pressures are usually slightly elevated also, but the degree and duration is not sufficient to account for the rise in pulmonary artery pressure. The moderate increases in cardiac output are also insufficient to account for the rise.

2. In three cases, it was evident that an increase in pulmonary vascular resistance was the primary cause for this epinephrine-induced pulmonary hypertension.

3. In two patients with severe chronic lung disease, a greater increase in diastolic pressure occurred, and pulmonary vascular resistance was found to fall after epinephrine.

4. By the method used, it could not be demonstrated that the effects were due to a direct action of the drug on the pulmonary vascular tree, and the mechanism of this phenomenon remains obscure.

5. The work of the right ventricle against pressure increases proportionately much more than that of the left ventricle.

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