(Supplement—South African Journal of Laboratory and Clinical Medicine) LCM 55

EVIDENCE FOR A SLOW VASOMOTOR RESPONSE FOLLOWING UNILATERAL MILIARY EMBOLIZATION OF PULMONARY ARTERIES IN DOGS

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Although a great deal of experimental work has been reported on the effects of miliary pulmonary embolization on the pulmonary arterial resistance,[1-8] it has not been conclusively established whether pulmonary vasoconstriction occurs or not.

The literature on this subject has dealt largely with the response of the pulmonary arterial system as a whole. In reports favouring the occurrence of pulmonary vasomotion, embolization has been claimed to cause a *generalized* increase in pulmonary vascular resistance, which has been immediate and has occurred even after unilateral or lobar embolization. Not usually considered is the possibility that embolization of a *segment* of the pulmonary arterial tree may excite a response *localized to that segment,* independent of any generalized reaction, and occurring over an appreciable period.

Niden and Aviado[4] mention a localized vasoconstrictor response following injection of 60 μ glass beads into a lobar pulmonary artery, but, judging from the published tracing, this took only a few seconds to develop—a much more rapid reaction than we are reporting in this paper and, therefore, probably unrelated.

Bernthal *et al.*[8] demonstrate a slow (40 min.) increase in the vascular resistance of the (L) lower lobe of open-chested dogs following embolization. They used an auto-perfusion technique, as was used by Niden and Aviado[4] and McEvoy *et al.*[5] No particular emphasis, however, is given to this unusual finding.

Fouché and D'Silva,[9] assessing the size of vessels in cats angiographically, showed a slow ($\frac{1}{2}$-1 hour) diminution in calibre of pulmonary arteries on the affected side following unilateral embolization.

The purpose of the present experiments was to investigate this radiographic finding further and to determine by pressure measurements whether confirmatory evidence for slow vasomotion could be obtained.

Because of the known sensitivity of vascular systems to handling, the experiments were carried out on dogs rather than cats, as the size of the former animals enabled the whole procedure to be carried out via catheters in the pulmonary vessels, so that the thorax could remain closed.

The experimental concept was as follows: If the total cardiac output is deviated through one lung by transient occlusion of the contralateral pulmonary artery, a certain rise in the main pulmonary artery pressure will occur, and, each time this procedure is repeated, a rise to a similar level will follow. Miliary emboli are then injected into the pulmonary arteries of the non-occluded lung. If successive transient occlusions of the contralateral pulmonary artery produce a progressive rise of main pulmonary artery pressure, recorded at the time of these occlusions, then it can be assumed that the vascular resistance is increasing in the embolized lung, provided the cardiac output and the left atrial pressure do not rise.

If, however, successive transient occlusions do not raise the pressure in the main pulmonary artery above the immediate post-embolic level, then it can be assumed that vascular resistance is not increasing unless there is a proportionately greater fall in cardiac output or left atrial pressure.

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MATERIALS AND METHODS

Experiments were performed on 25 mongrel dogs whose bodyweight varied from 10 to 30 kg. The animals were deeply anaesthetized with pentobarbitone sodium (Sagital 0·4 ml./kg.), administered intravenously, and were also heparinized.

The following procedures were carried out on all animals: A cuffed endotracheal tube was inserted through the larynx; a No. 5 Rodriguez-Alvarez catheter was introduced by cut-down into the external jugular vein and advanced to the main pulmonary artery; balloon catheters were similarly introduced into both the right and left pulmonary arteries (Fig. 1); the carotid artery was cannulated and standard limb electrocardiographic leads were connected.

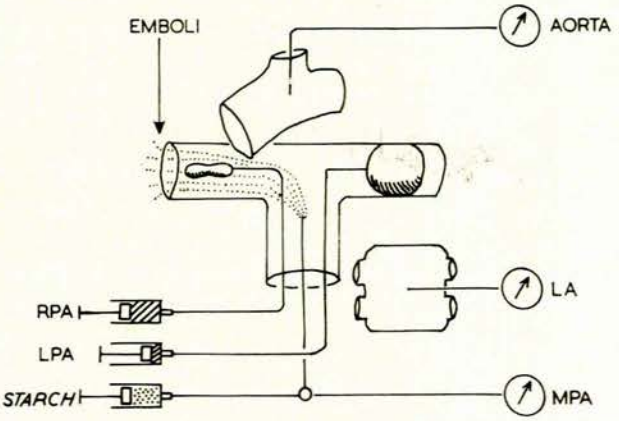

Fig. 1. Diagram illustrating the experimental method (see text). Two balloon catheters are shown in the right and left pulmonary arteries. The left balloon is distended with contrast medium during embolization of the right lung via the pulmonary artery catheter. Pressures were recorded at the sites indicated. Left atrial pressures (LA) were recorded via a transseptal catheter in 5 experiments.

The left and right pulmonary arteries were alternately occluded for periods of about 30 seconds by distending the appropriate balloon with radio-opaque dye under fluoroscopic control using a Phillips 5″ Image Intensifier. Systolic, diastolic and mean main pulmonary arterial and carotid arterial pressures were synchronously recorded before, during and after each occlusion.

After an initial control period comprising 4 - 6 occlusions on each side, one pulmonary artery, usually the left, was occluded as previously, but before the balloon was deflated a suspension of about 10% potato starch w/v in saline (particle size 2 - 80 μ) was injected via the catheter in the main pulmonary artery, thus embolizing the opposite pulmonary vessels (Fig. 1). The dose, which averaged 0·05 G/kg., was selected according to the response of the pulmonary artery pressure. An initial dose of about 8 ml. was followed by aliquots of 2 ml. until a rise of about 10 mm. mean pressure was obtained.

After release of the distended balloon, pressures were measured during alternate occlusions, as in the control period, for up to a further hour or longer, after which the dog was killed by injection of a large dose of Sagital.

Angiograms were performed immediately before the injection of starch suspension in 10 cases, to check that the distended balloon was correctly placed. With increasing experience however this practice was discontinued, as the injection of radio-opaque dye and the more prolonged occlusion necessary introduced additional factors possibly capable of influencing vasomotor tone.

In 5 animals pressures were also recorded in the left atrium via a transseptal catheter using a modified Ross[10,11] technique. This procedure was carried out on this small, limited number of animals as it was our experience that successful punctures could only be achieved in animals weighing 40 lb. or over, and only a limited number of dogs of this size were available. Furthermore, we could find no report in the literature of significant changes of left atrial pressure following miliary embolization. Our few results confirmed that left atrial pressure remained either constant or tended to drop slightly.

Pressures were recorded by Elema-Schonander inductance transducers and electromanometers in conjunction with a Siemens 6-channel Cardirex Mingograf recorder.

Serial cardiac output estimations were performed in 8 experiments by the dye dilution method using indocyanine green and a Waters densitometer, recording on the above recorder. Cardiac output was measured during separate occlusion of each pulmonary artery and with the circulation passing normally through both lungs, though the main object was to measure the flow through the embolized lung.

Here, again, this procedure was not carried out in all experiments, as it was considered to throw an added strain on the animal during the prolonged balloon occlusion necessary to obtain the dilution curve during occlusion of the non-embolized lung and had, on occasion, led to cyanosis and profound drop in blood pressure.

Postmortem examination was performed in 14 animals and in 9, sections of each lung and of kidney were stained with haematoxylin and eosin, with elastic and Van Gieson's stains, and examined histologically under normal and polarized light.

RESULTS

In the control period before embolization, all pressures measured remained fairly constant. Occlusion of the right pulmonary artery (total deviation of cardiac output through the left lung) usually produced a considerably greater rise in main pulmonary artery pressure than occlusion of the left pulmonary artery. Examples of this are demonstrated in Figs. 2, 3 and 4. This presumably repre-

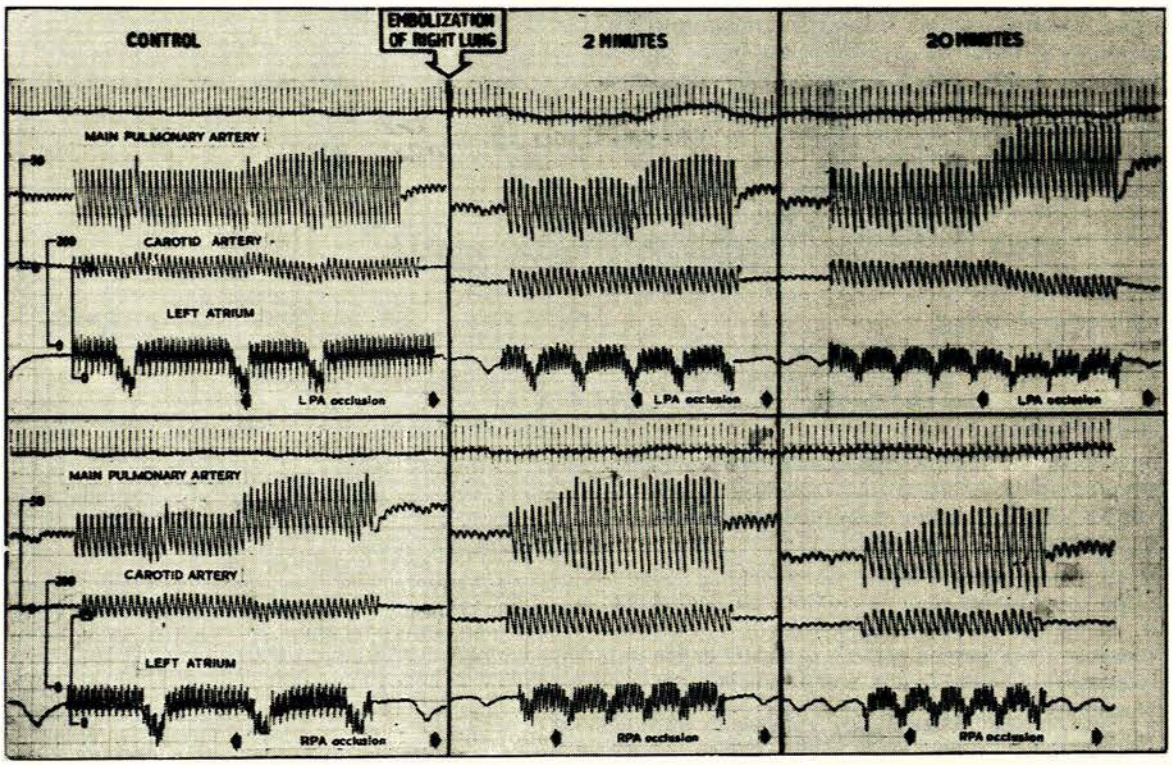

Fig. 2. Mean, systolic and diastolic pressure tracings recorded from main pulmonary artery, carotid artery and left atrium in 1 experiment of this series. The upper (left) panel shows the effect of left pulmonary artery occlusion before starch embolization of the right lung and the 2 panels to the right are the tracings recorded before and after similar occlusions of the left pulmonary artery 2 minutes and 20 minutes after embolization.

Before embolization there is a slight rise in main pulmonary artery pressure during occlusion of the left pulmonary artery with no change in left atrial or carotid pressure. Two minutes after embolization of the right lung the rise in main pulmonary artery pressure following left pulmonary artery occlusion is slightly greater and there is no change in left atrial or carotid pressures.

Twenty minutes later there is a marked rise in main pulmonary artery pressure and a significant fall in carotid pressure following left pulmonary artery occlusion, indicating an increased resistance to flow in the right lung over and above that produced by embolization and requiring time to develop.

The lower panels show the pressure changes before, 2 minutes and 20 minutes after embolization of the right lung, before and during transient occlusion of the right pulmonary artery. Before embolization the main pulmonary pressure rises to a higher level following right pulmonary artery occlusion than following left occlusion, presumably due to the larger capacity of the right lung.

After embolization of the right lung, right pulmonary artery occlusion produces progressively smaller rises in mean main pulmonary artery pressure, and no change in the left atrial and carotid pressures, suggesting a decreased resistance to flow through the left lung following embolization. Other changes noted are the increased respiratory rate and slightly slower heart rate following embolization. These have not been discussed.

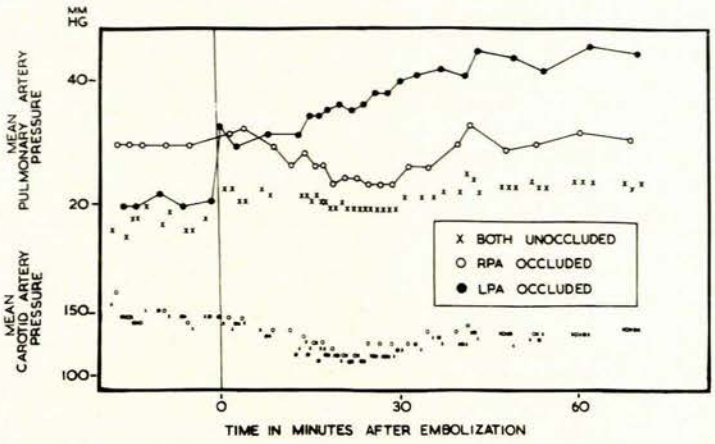

Fig. 3

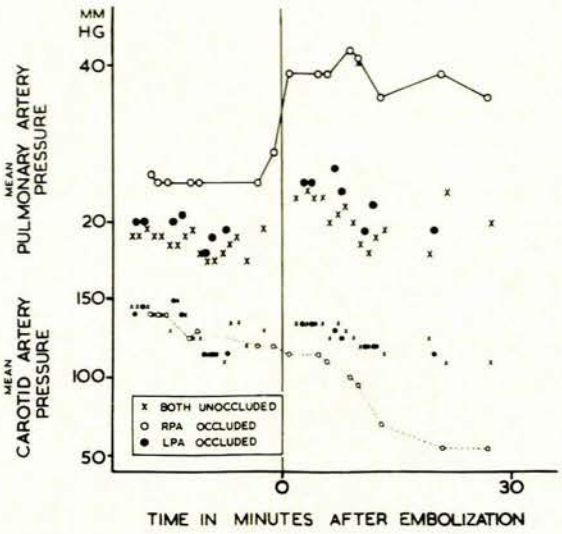

Fig. 4

Fig. 3. Mean pulmonary artery and carotid artery pressures during 1 experiment: the results are interpreted as showing evidence of a slow unilateral resistance change on the right. The right pulmonary artery was embolized in the period immediately preceding O on the time scale. The interval before this represents the control period. On successive occlusions of the left pulmonary artery (total deviation of cardiac output through the right lung), there is a rise in the main pulmonary artery pressure indicative of increasing resistance in the right pulmonary arteries since left atrial pressure and cardiac output did not increase. Carotid artery pressure is seen to fall initially at the same time that the resistance increase in the right lung occurs. In the control period it is seen that occlusion of the left pulmonary artery causes less rise in mean main pulmonary artery pressure than occlusion of the right pulmonary artery. After embolization the reverse gradually occurs.

Fig. 4. Mean pulmonary artery and carotid artery pressures during 1 experiment, illustrating the second type of pattern (see text). In this experiment the left pulmonary artery has been embolized in the short period before O on the time scale. It can be seen that a progressive rise in the mean main pulmonary artery pressure does not occur after embolization, but that total deviation of blood through the embolized lung (right pulmonary artery occlusion) produces falls of increasing magnitude in systemic artery pressure. It should be noted that post-embolic unoccluded mean pulmonary artery pressure rises above the level reached by occlusion of the left pulmonary artery in the pre-embolized period. This suggests that an immediate generalized resistance increase has occurred in this experiment in addition to any possible slow localized change which may have occurred.

sents the greater size of the right lung compared with the left. During the same period the carotid artery pressure and the main pulmonary artery pressure did not vary significantly. In those experiments in which left atrial pressure and cardiac output were measured there was little variation. Following the introduction of emboli into the pulmonary arteries of one lung, the main pulmonary artery pressure always showed an immediate rise while the collateral pulmonary artery was occluded (Figs. 3 and 4). In 21 of the 25 experiments this rise varied from 8 to 18 mm.Hg. In 3 experiments it rose from between 24 - 34 mm.Hg, while in 1 the rise was only 7 mm.Hg.

Subsequent transient occlusions of the non-embolized pulmonary artery produced 3 types of change in the main pulmonary artery pressure.

Type 1

In 13 of the 25 dogs successive occlusions of the non-embolized side resulted clearly in increasingly higher mean pressures in the main pulmonary artery during the period of the occlusion (Figs. 2, 3 and 5). This change usually developed over the period between 5 and 20 minutes after embolization, being preceded by a slight fall in 10 of the 11 cases in which pressures were recorded within 5 minutes of embolization.

Type 2

In 3 animals the main pulmonary arterial pressure changed little with successive occlusions of the non-embolized side, but the systemic arterial pressure fell markedly and to *progressively* lower levels during the occlusions (Fig. 4).

Type 3

In 9 animals successive transient occlusions of the non-embolized pulmonary artery produced no particular pattern in the main pulmonary artery pressure readings apart from an early fall in the 2 - 5 minute period after embolization. Subsequently the pressures either fell further, or, if they rose, the increase in pressure was too small to constitute clear-cut evidence of a gradual increase in resistance in the embolized arteries (Fig. 6). In these experiments a progressive change in carotid artery pressure during the occlusions did not occur. This group included the 3 dogs in whom embolization produced the greatest (24 - 34 mm.Hg) and the 1 dog with the least (7 mm.Hg) initial rise in main pulmonary artery pressure during occlusion of the non-embolized lung.

Other Observations

Left atrial pressure and cardiac output were measured in 5 instances and did not rise during this period. Systemic artery pressure remained static or fell moderately, sometimes beginning to rise again after about 30 minutes. The main pulmonary artery pressure during occlusion of the artery on the *embolized* side with 2 exceptions either fell or, less commonly, remained static (Fig. 7). The main pulmonary artery pressure measured when neither of the main branches was occluded always rose as soon as the emboli

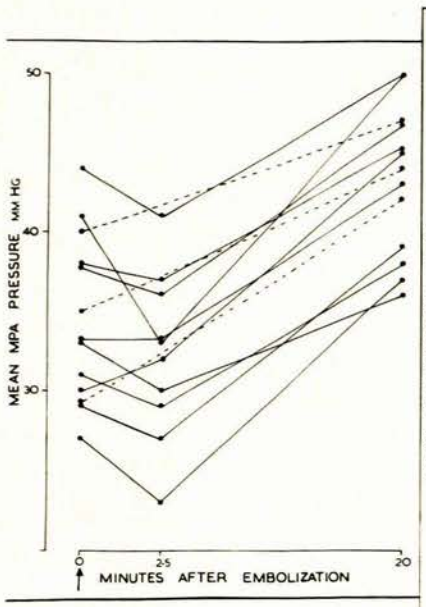

Fig. 5

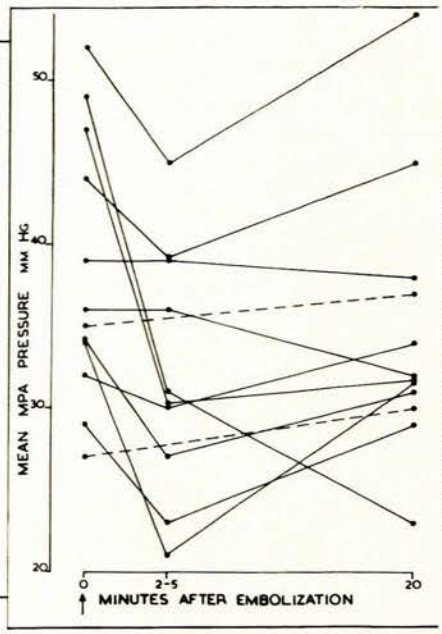

Fig. 6

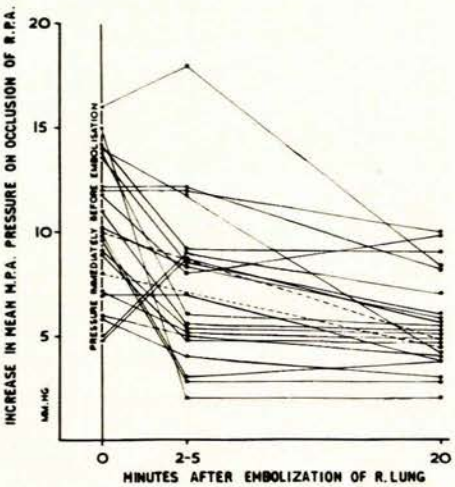

Fig. 7

Fig. 5. Results of 13 experiments in which a definite slow increase in vascular resistance is considered to have occurred in the embolized lung after about 5 minutes. The changes occurring in the first 20 minutes following embolization only have been recorded. The graphs represent mean main pulmonary artery pressures in mm.Hg on transient occlusion of the non-embolized pulmonary artery (total deviation of cardiac output through the embolized lung). Embolization occurred in the period immediately preceding O on the time scale. The first reading in each experiment thus indicates the mean main pulmonary artery pressure following embolization before the distended balloon in the contralateral pulmonary artery had been deflated. Measurements have also been recorded for the periods 2 - 5 and 20 minutes following embolization. The experiments in which records were not obtained in the first 5 minutes have been indicated by dashed lines. The early fall in pressure followed by the subsequent rise is demonstrated (see text).

Fig. 6. Results of 12 experiments in which a definite slow increase in vascular resistance in the embolized lung has not been demonstrated (group 2 and 3). Although several of the above experiments do show a slight rise in pulmonary artery pressures on total transient deviation of cardiac output through the embolized lung, this was not considered large enough to be significant. The diagram was derived in the same way as Fig. 4.

Fig. 7. Results of right pulmonary artery occlusion both before and after embolization in all those experiments in which the right lung was embolized. These show a progressive fall in pressure following embolization in the greater proportion of cases in contradistinction to the pressure increases demonstrated on total deviation of cardiac output through the embolized lung in the majority of cases.

All points on the diagram represent the *increase* in pressure measured in the main pulmonary artery on transient occlusion of the right pulmonary artery at the times stipulated. The first readings were obtained before embolization and the second and third after embolization.

These figures are taken to represent some decrease in vascular resistance in the left lung following embolization of the right lung. The dashed lines represent experiments in which pressure measurements were not made in the period 2 - 5 minutes after embolization.

had been injected, but this rise was usually relatively slight (Table I).

Postmortem Findings

Postmortem examination never revealed any macroscopic abnormality and pulmonary arterial thrombosis was not found. Histological examination always showed numerous starch granules in the embolized lung, these being readily identified under polarized light. The granules were predominantly in the pulmonary capillaries and only occasionally in the arteriole. Slight thickening of the alveolar wall with polymorph and round-cell infiltration was seen in relation to the emboli. This appearance was seen in all animals killed half an hour or more after the injection of emboli. Very occasional granules were seen in the opposite lung in 2 cases. None of the renal sections showed any emboli.

In an attempt to time the onset of the inflammatory response in the embolized lung, 4 additional animals were killed, 2 at 5 minutes and 2 at 15 minutes after embolization. At 5 minutes, there was no difference between the 2 lungs, while at 15 minutes, a slight reaction was apparent on the embolized side.

DISCUSSION

It can be seen from the above data that the main pulmonary artery pressure rises above the immediate post-embolic level in the majority of animals when successive transient occlusions of the non-embolized side are performed (type 1 reaction, Figs. 2, 3 and 5). These findings are identical to observations previously made on cats.[12] This slow rise can be attributed solely to increasing pulmonary arterial vasoconstriction, provided that the left atrial pressure and the cardiac output do not increase and that there is no progressive mechanical blockage or distortion of the pulmonary vessels. No significant change occurred in the left atrial pressure in all 5 instances where this pressure was recorded. Cardiac output did not rise during the experiment and indeed always showed a steady decrease, as might be expected in an animal subjected to repeated stressful manoeuvres over a prolonged interval. Cardiac output estimations were made in only 8 experiments. During these, however, numerous estimations were carried out, with the left, the right and neither pulmonary artery occluded. Three of these animals were among those showing the response exemplified by Fig. 3. An increasing cardiac output was not responsible for the rising pressure

readings in these animals at least, and, by inference, was unlikely to have been so in the others.

TABLE I. MEAN PRESSURES OF MAIN PULMONARY ARTERY IN MM. HG

Control period		*Period after embolization (minutes)*		
No occlusion	*Occlusion of artery to side to be embolized*	*0*	*2–5*	*20*
17	24	21	21	21
14	19	17	15	20
12	33	38	37	32
23	34	25	25	27
15	28	17	20	20
11	18	17	15	18
18	26	23	22	21
13	25	22	22	20
17	30	21	22	23
24	35	30	28	28
18	30	23	21	20
17	28	35	24	16
18	28	26	21	16
21	30	25	25	25
22	26	27	27	25
18	23	19	20	22
13	23	22	17	22
20	30	27	27	25
18	21	24	20	19
27	45	31	27	34
25	33	27	30	29
22	32	26	25	23
12	24	13	17	16
15	20	17	16	14
16	23	20	18	20

It seems unlikely that further mechanical obstruction in the pulmonary vessels occurred after the initial blockade due to the embolization. We found no change in the size of the starch granules on immersion in saline or plasma for several hours. Furthermore, if granules were slowly propelled peripherally by blood flow during the experiment this could only lead to a reduction in the number of blocked vessels. No evidence of thrombosis or infarction was detected in the lungs after the experiment.

An interesting and, as far as we know, unreported finding is the slight inflammatory reaction in the alveolar walls adjacent to starch granules, seen in the histological sections. This was found in slight degree in animals killed 15 minutes after the injection of emboli and was well established in those sacrificed at half an hour. Despite the similarity in time relationships of the histological and haemodynamic reactions, it does not seem likely that they are causally related. From the site of the reaction the cellular infiltration does not appear capable of narrowing vessels not containing emboli. Moreover, the histological changes were only minimal at 15 minutes, by which time the described haemodynamic change is usually nearly complete. In similar experiments performed on cats, increasing vascular resistance occurred on the embolized side in the absence of inflammatory changes around the starch granules.[8,12] In these animals, however, the emboli were found in arterioles and arteries and not at the capillary level, which may account for the difference in histological appearance.

Balloon occlusion of one pulmonary artery has been reported to affect resistance changes on the contralateral side.[9] There is, however, no evidence that this mechanism operates more strongly with increasing time and it seems improbable that it was concerned in the reaction described in this paper.

During the first ½-hour after embolization, pulmonary arterial pressure readings during successive occlusions of the *embolized* pulmonary artery with 2 exceptions either remained unchanged or fell, suggesting a stable or diminishing resistance on the non-embolized side (Fig. 7). After this period there was often a rise in all pulmonary and carotid arterial pressure recordings, as shown in Fig. 3. It would seem, therefore, that the major resistance change in the embolized lung is probably complete within the 15 - 30 minutes of the injection of emboli.

In the 3 dogs showing the type 2 reaction (Fig. 4), the main pulmonary arterial pressure on occlusion of the non-embolized pulmonary artery remained fairly constant. These occlusions, however, produced an increasing fall in systemic artery pressure which tended to become so marked that inflation of the balloon could only be sustained for the minimum of time. Because of this, output measurements could not be carried out at these times. It seems reasonable to postulate, however, a profound drop of cardiac output during these manoeuvres. If that were the case, then this was probably due to increasing resistance in the embolized pulmonary arteries and an inability of the right ventricle to sustain normal output.

The mechanism underlying unilateral vasoconstriction is not clear and the present experiments were not designed to elucidate this. It is unlikely that a neurogenic reaction would take so long and a humoral one would not be expected to act in a localized manner. As previously suggested[8] a possible explanation is a localized response by the arterial musculature to an altered pressure gradient along the length of the vessels.

It would seem that some form of generalized rapid vasoconstriction, of the type reported by others, occurred in at least some of our animals. In these animals it was found that the main pulmonary artery pressure rose higher after unilateral embolization than during balloon occlusion of the same lung in the control period before embolization. As the embolization itself could not have led to the total mechanical obstruction produced by the balloon catheter, some generalized resistance increase must have occurred thoughout both lungs. To support this is the fact that the animals in which the greatest post-embolic rise in pulmonary artery pressure occurred often had surprisingly small doses of emboli relative to their weight. It is possible, too, that the frequent falls of pressure in the first 5 minutes after embolization, as demonstrated in Fig. 5, might be due to the relaxation of an initial mild generalized constrictive response rather than to variations in cardiac output.

SUMMARY

Experiments were carried out on intact, anaesthetized dogs to test the possibility of a slow unilateral vasoconstriction following embolization of one pulmonary artery, and the findings suggest that this has occurred over a 5 - 30 minute period after embolization.

An inflammatory reaction was seen around vessels containing emboli but was not thought to be causally related to the increasing resistance.

The mechanism of this resistance change is not clear, but may be localized arterial response to a change in pressure gradient.

Evidence suggestive of a rapid generalized resistance change of the type reported by others was also obtained in some of our experiments, but was found less commonly than the slow localized type of reaction, the documentation of which was the main object of this paper.

We wish to thank Prof. V. Schrire, Director of the Cardiac Clinic and the Council for Scientific and Industrial Research Cardiovascular-Pulmonary Group, for his support and encouragement; Dr. L. Anstey of the Pathology Department, Red Cross War Memorial Hospital, for the histological findings; Mr. L. W. Piller, Principal Technician of the Cardiac Clinic, for his technical assistance; and the Council for Scientific and Industrial Research and the City Council of Cape Town, for their financial support. Our thanks are also due to Prof. C. N. Barnard, Department of Surgical Research, for providing the facilities for the experimental work.

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