3.8. DYNAMICS OF SEQUENTIAL LARGE PULMONARY EMBOLI

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1. INTRODUCTION

The clinical importance of further clarifying the fundamental character of pulmonary embolism (PE) is amplified by recent statistics which estimate the total annual United States incidence of PE at 630,000 (1). Of the 89% of patients who survive the first hour, it is estimated that the diagnosis of PE is missed in 71% of the cases, and the total death rate sums to 200,000, almost 32% of the estimated incidence. Since early diagnosis and treatment can significantly reduce mortality (82% when diagnosed and 30% when undiagnosed), and in the light of newly available treatment modalities it is important not only to develop new and simpler methods of detecting the presence of PE, but also to provide information which will be helpful to the physician in selecting appropriate therapy (2). Since most emboli to the pulmonary vasculature originate in the leg and pelvic veins it is logical to view preventative therapy together with monitoring the development of venous thrombosis as a first line of defence in the prevention of PE in a selected class of high risk patients (3, 4, 5). Although noninvasive methods for detection of venous thrombosis are currently available, their sensitivity is limited to detecting hemodynamically significant thrombi while they are not feasible as a general screening technique (3, 6).

This state of affairs raises one of the questions which motivated the present study, namely: What is the relationship between the size of a clot and the effect it has when it embolizes to the pulmonary vasculature? Further, based on the recognition that venous thrombi may embolize, reform, and embolize again, thus producing a cardiovascular alteration attributable to multiple emboli, the second aspect of the present study was to determine the effect of sequential emboli of varying size on cardiovascular system dynamics.

2. METHODS

Eighteen unselected mongrel dogs (weight 11.4 to 20.5 kg) were embolized with autologous blood clots made radiopaque by mixing 6% Renographin with blood drawn 24 hours prior to each experiment. No quantitation of

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clot consistency was made. Three clot volumes (2.5, 5.0, and 10 ml) were formed in glass tubing having an inside diameter of 1.3 cm. The three clot volumes were equally divided between the total group in which, overall, 70 injections were made. In each animal the inferior vena cava (IVC) at the level of the renal vein confluence was exposed and the clots were injected via a Dacron graft sutured to the IVC. Only one clot size per animal was used. The clots were injected sequentially at times determined by stabilization of pulmonary artery pressure. Visualization of each clot was by fluoroscopy. Transit time of each clot from injection site to, and exit from the heart was observed and recorded on videotape. All animals were anesthetized using chloralose. Respiration was maintained constant and the following hemodynamic quantities were measured: pulmonary artery pressure (PAP), femoral artery pressure (FAP), left atrial pressure (LAP), right atrial pressure (RAP), and cardiac output (CO), using a thermodilution method. Arterial blood gases were measured and the electrocardiogram monitored via lead II. All data except as noted are reported as mean $\pm$ SEM; statistical significance of differences are based on students' t tests with $P < .05$ taken as statistically significant.

3. RESULTS

3.1. *Typical responses associated with clot embolization*

Typical changes following clot injection are illustrated in Figure 1. Following a transit time from injection site to heart entry of 1.9 ± 0.3 sec the clot enters the right atrium, proceeds into the right ventricle where it

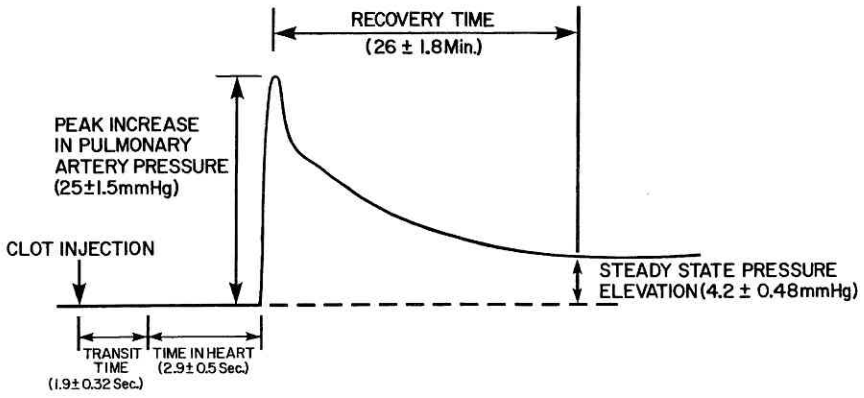

Figure 1. Typical response to clot injection. Data shown are mean $\pm$ SEM corresponding to all 70 clot injections. Note the rapid and gradual phase of recovery in pulmonary artery pressure.

remains on the average 2.9 ± 0.5 sec. Generally, the smaller the clot size, the shorter the transit time and the less time spent within the right heart. Since the mean control heart rate was 145 beats per minute the clot remained in the chamber for approximately 7 beats. Clot entry into the heart was as a single bolus in 84% of clots injected. In the remaining cases the clot was fragmented in transit and entered the heart usually in two pieces displaced in time by not more than a few seconds. Those 10 ml clots which entered the heart as a single bolus were fragmented in all but one case while in the heart. Twenty 10 ml clots entered as a single mass. Eleven were broken into two pieces, six into three pieces, and three into four pieces while in the heart. During a single injection the fragmented pieces tended to move into different pulmonary arterial vessels. The tendency for the clot to break into multiple pieces diminished as the size of the injected clot was reduced. In the case of 10 ml clots, 4% exited the heart intact, 36% in the case of 5 ml clots and 71% of the 2.5 ml clots.

Entrance of the clot into the pulmonary circulation was associated with a precipitous rise in pulmonary artery pressure (PAP). The average peak increase in pulmonary artery pressure produced by all clots was 25 ± 2 mmHg. In 49 of the 70 clots injected, the recovery phase of the PAP was characterized by a rapid abrupt drop, followed by a more gradual return towards the pre-injection level. The magnitude of this rapid pressure reduction was variable. The rapid phase of the recovery time never exceeded 120 sec. PAP reached a steady-state pressure level after an average time of 26 ± 2 min. This value was 4.2 ± 1.8 mmHg above control level.

In addition to the typical changes in PAP described above, several other hemodynamic changes attributable to the clot were observed. Two of these are illustrated in Figure 2. In this example the clot was seen to exit from the heart 12.8 sec after injection into the IVC. Associated with its exit was a precipitous rise in PAP and a concomitant reduction in FAP, which after a period of about 20 sec, returned to the pre-embolic value. Reductions in FAP following clot injection were noted in approximately 20% of cases and appeared to be more prevalent in larger clots. The increase in RAP concomitant with a rise in PAP may also be noted in this figure as well as the presence of two premature ventricular contractions (PVCs) denoted by the arrows in the lead II tracing of the ECG. The presence of cardiac arrythmias of this type have been quite prevalent and associated with embolus entrance into the pulmonary vasculature. The occurrence of PVCs depends on the size of the clot injected. They were observed in 80% of the 10 ml injections, 50% of the 5 ml injections and 25% of the 2.5 ml injections. In all but two experiments the effect of the emboli on cardiac output was to produce a slight transient increase (average increase 15%) followed by a return to control value; this measurement was taken approximately 2 min after the embolic event. The effect of pulmonary emboli on arterial blood

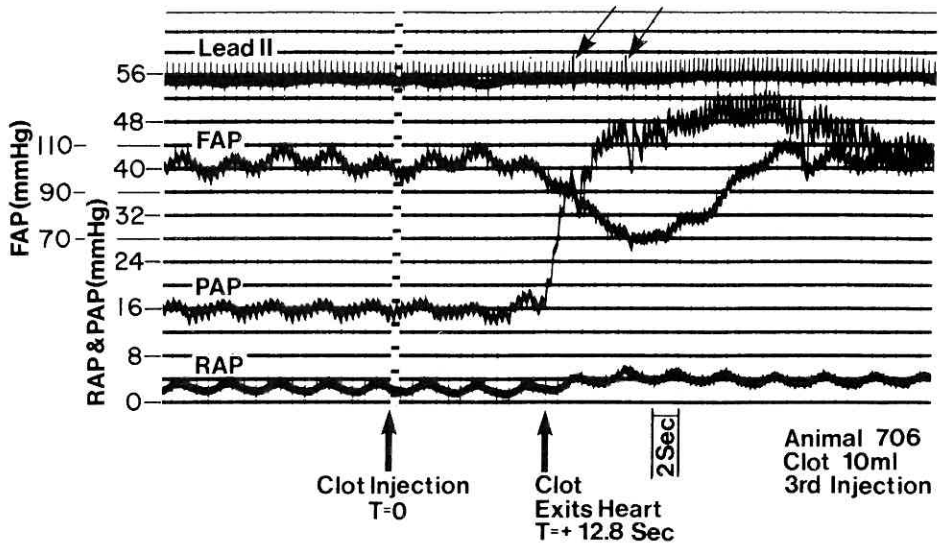

Figure 2. Example of response to 10 ml clot injection. Note the rapid rise in pulmonary artery pressure (PAP), transient fall in femoral arterial pressure (FAP) and occurrence of two premature ventricular contractions (denoted by arrows). RAP:right atrial pressure.

gases was rather consistent. Following each embolus there was a precipitous drop in arterial O_2 tension and an elevation in CO_2 tension. Oxygen tension tended to recover in a staircase fashion with successive injections. This staircasing effect was less evident in the smaller-sized clots.

3.2. *Effect of clot size and injection sequence on pulmonary pressure*

As seen in Figure 3, the transient peak increase in PAP appeared to be independent of the number of clots injected (1 to 4 injections). However, the peak increase in pressure was sensitive to the volume of clot injected. This difference showed up most dramatically between the 2.5 ml clot and the 5 or 10 ml clots. Although there was no statistically significant difference between the effect of the 5 ml as compared to the 10 ml clot, each produced a significantly greater effect than the 2.5 ml clot ($P<.05$). Comparing all data only by clot volume shows the 2.5 ml, 5 ml, and 10 ml clots produced peak PAP increases of 16, 33, and 28 mmHg ($P<.001$) respectively.

The steady-state PAP reached after each embolism was strongly dependent on the clot sequence (Figure 4). With each successive clot injection mean steady-state PAP was seen to increase with increasing clot size. This finding was statistically significant for the 5 and 10 ml clots ($P<.05$) for all injections as compared to the control PAP, but did not achieve statistical significance for the 2.5 ml clot until the third injection had been made. However, when the effects of the emboli are compared on the basis of the equivalent total blood clot volume injected (Figure 5) it is found that the

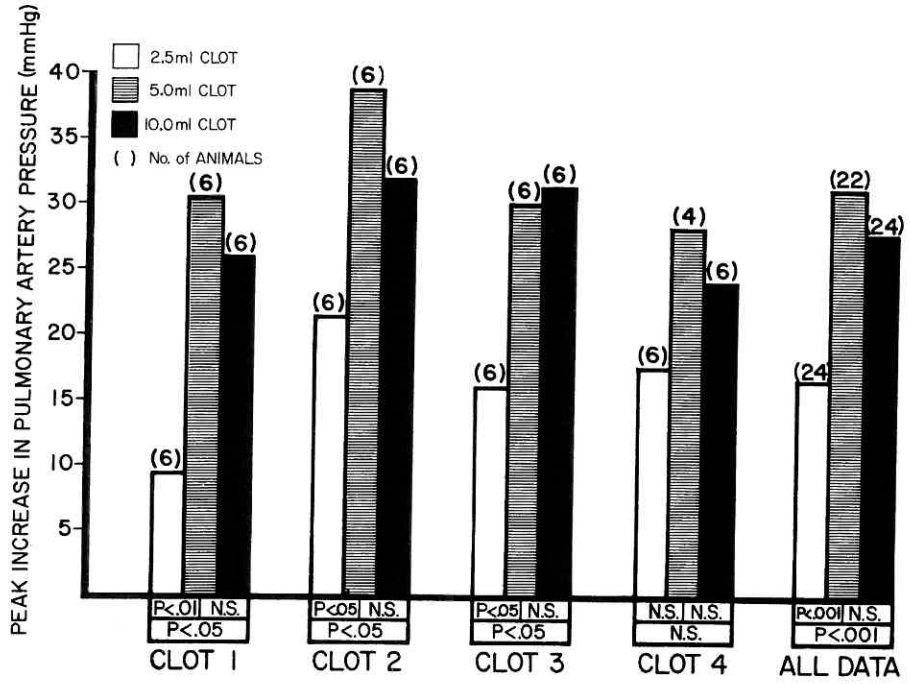

Figure 3. Peak increase in pulmonary artery pressure as a function of clot size and numbers of injection.

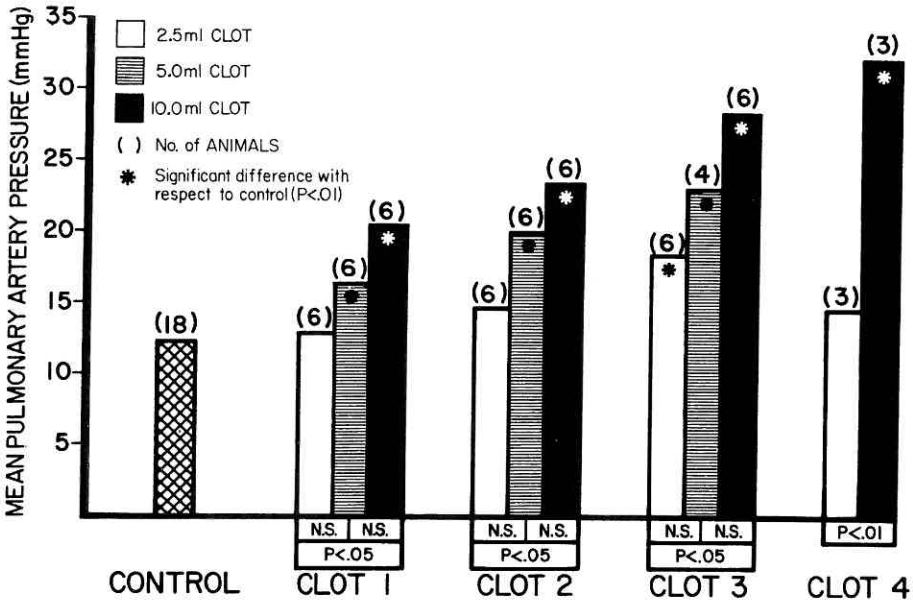

Figure 4. Steady-state pulmonary artery pressure after embolism (as a function of clot size and number of injection).

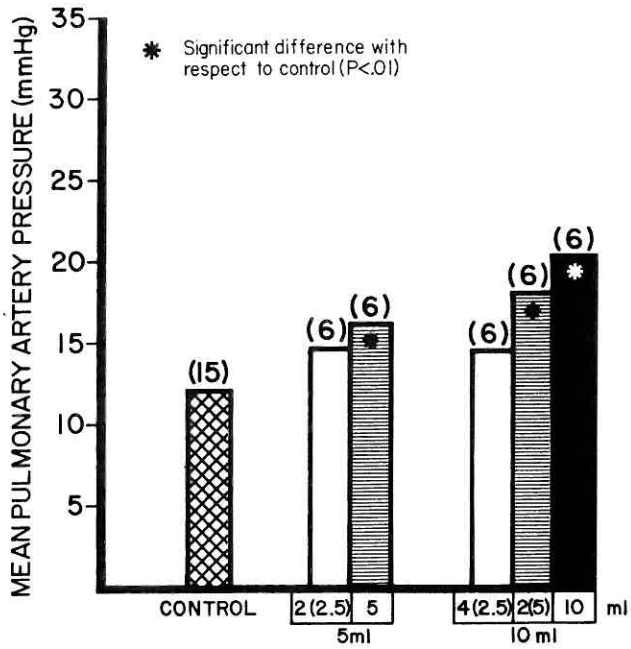

Figure 5. Steady-state pulmonary artery pressure after embolism with equivalent blood clot volume. Note that a single 10 ml injection results in a greater pressure than four 2.5 ml injections.

difference between the 2.5 ml, 5 ml, and 10 ml clots becomes smaller and non-significant although the trend suggests greater effects for larger-size individual clots as well as greater effects for the larger total volume.

The recovery time dependence on clot sequence and clot volume is shown in Figure 6. First injection recovery times for the 2.5 ml, 5 ml, and 10 ml clots were 9, 23, and 38 minutes respectively, demonstrating a strong dependence on clot volume. Similar results were obtained for the second injections, being 19, 25, and 40 minutes for the 2.5 ml, 5 ml, and 10 ml clots respectively. These data suggest a recovery time dependence both on the number of clots injected of the same volume as well as the total volume injected per clot. Expressed somewhat differently when clots are grouped together by volume independently of injection number, the recovery time with a 2.5 ml clots is 17.2 min, for the 5 ml clots it is 24 min, and for the 10 ml clots it is 31.5 min, all data being statistically significant.

4. DISCUSSION

The use of experimental emboli in the form of blood clots has yielded information which has helped elucidate the hemodynamics associated with pulmonary emboli. Just-Viera and Yeager, using barium-loaded blood clots,

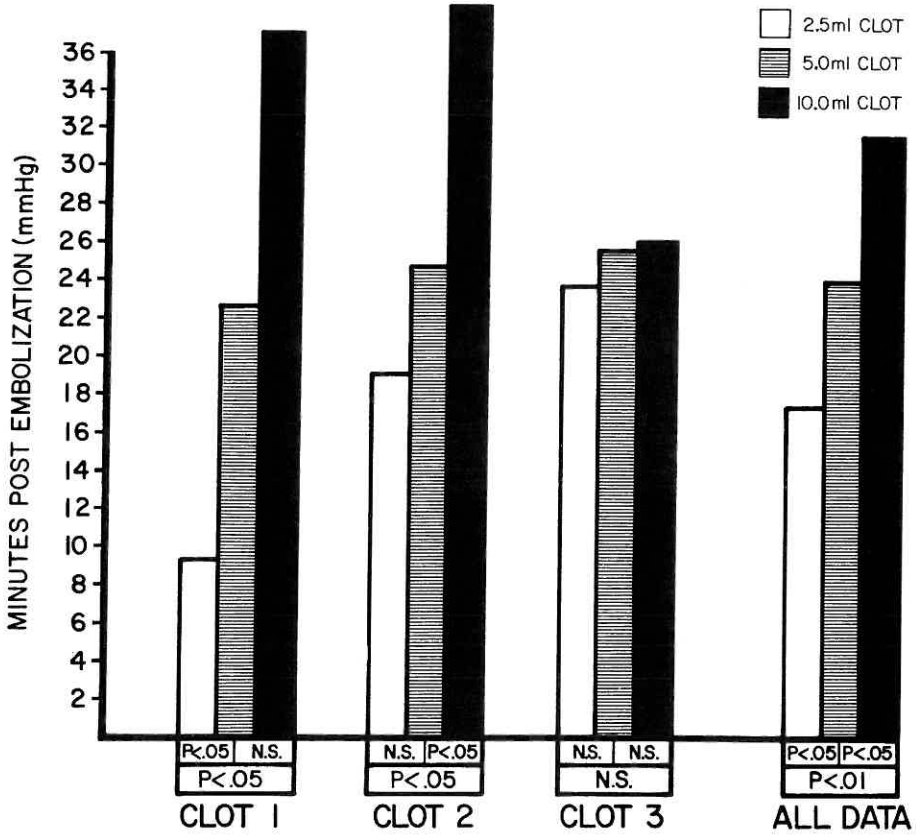

Figure 6. Recovery time required for pulmonary artery pressure to reach new steady state (as a function of clot size and number of injections).

determined that the single dose of embolus injected through the external jugular vein required to cause death in 50% of canines studied, was 0.81 ml/kg (7). In unanesthetized dogs a value of 0.86 ml/kg was found (8). If blood clots without barium were used these values were 1.5 ml/kg in anesthetized dogs and 2.86 ml/kg in unanesthetized animals. In the present study no single dose exceeded 0.18 ml/kg. However, the toal cumulative dosage per animal varied from 0.58 to 2.94 ml/kg. Since only 2 of 18 animals used in our study succumbed to the effects of the emboli (cumulative doses for these anımals were 2.84 and 2.94 ml/kg) it may be that the use of Renographin as the radiopaque substance renders the consistency of the clot more physiological. Allison et al. used Dionicil to produce radiopaque clots approximately 5.5 ml in volume; these were injected into the left jugular vein and/or the inferior vena cava (9). Using cineradiography they reported that the time required for the clot to transmit from the systemic vein to the pulmonary artery was about 6 seconds. Distinction between

transit to the heart and time spent in the heart was not made. The results of the present study clarify this issue and confirm the vein-to-pulmonary-artery transit time to be less than 6 seconds but also show that a larger fraction of that time is spent within the heart chamber itself. Allison et al. also briefly described the action of the heart dynamics on the clot and indicate that most clots exit the heart as a single piece, which is in contrast to the results obtained in this study: we found most clots were fragmented into at least two pieces. Finally, these authors state that the passage of the clot into the pulmonary circulation caused no change in the electrocardiogram. This finding is also in direct opposition to the present results which confirm the presence of multiple arrythmias often in the form of premature ventricular contractions associated with the exit of the clot and subsequent rapid rise in pulmonary artery pressure. Although Just-Viera et al. reported on severe abnormalities of the electrocardiogram subsequent to lethal injected clots including ST segment depression and T wave inversion occurring as early as 5 seconds post embolus (10), it is evident from the present results that clots well below the lethal level can and do induce electrocardiographic irregularities. The consequences of these emboli-induced arrythmias and their relationship to sudden death remain speculative.

Several investigators, using either single bolus injections or injection of masticated clot through small-bore needles have observed immediate increases in PAP (11, 12, 13). In all of these cases PAP was reported to return to near-normal levels within hours. In one of the most careful hemodynamic studies related to the effects of emboli on PAP, Dalen et al. showed a correlation between the changes in PAP and the diameter change of the main pulmonary artery (11). In their study, as well as most other related studies, pulmonary hemodynamic data is not systematically reported for times less than three minutes after embolus injection. As a consequence, the initial instantaneous pressure transient discovered in the present study has not been previously included as a component in the PAP response to PE. For a complete characterization two separate aspects of the transient hypertension produced by pulmonary emboli must be dealt with. The first is to account for the initial rise and rapid fall of the pulmonary artery pressure and the second is to account for the more gradual reduction in pulmonary artery pressure toward pre-embolic levels.

To address the first aspect it is useful to examine two working hypotheses as to the cause of the initial elevation. Two possibilities are: mechanical blockage superimposed upon arteriolar vasoconstriction or mechanical blockage alone. The vasoactive aspect of pulmonary hypertension associated with pulmonary emboli is quite controversial, however, the temporal character of the rapid phase of PAP recovery is consistent with a neural or vasoactive component. On the other hand, if the vasoactive

component is small or nonexistent and the response is due solely to mechanical blockage then there are three principal mechanisms whereby one could account for the rapid recovery phase (14). These are (1) passive recruitment of pulmonary arterial vessels, (2) passive dilation of already patent pulmonary vessels, and (3) movement of the clot. Both vessel recruitment and vessel dilation are known to be pressure-dependent. Therefore it could be argued that the observed initial peak pressure rise caused by emboli lodging in pulmonary vessels will be the stimulus to dilate or recruit additional vessels. This would cause the initially elevated vascular resistance to fall from its peak value until a quasi-steady state is achieved. Data from our present experiments do not support these possibilities for the following reasons. If either mechanism were at work one would predict that the rapid phase of recovery should diminish with increasing clot injection. This follows because with each injection, both distension and recruitment reserve should become diminished. However, the data show no reduction in the presence or magnitude of the rapid recovery phase. Therefore, the above passive methods are probably not responsible for rapid recovery. The third mentioned mechanism, slight movement of the clot, may account for this phenomena. If for example the clot is initially lodged in one or more labar arteries at a point near a first order branch the resultant elevated PAP would have the tendency to push the clot distally. If conditions were favourable it may be pushed into one or more of the first order branches. The hemodynamic effect would be to reduce abruptly the magnitude of the initially elevated vascular resistance and subsequently reduce PAP. The phenomena would not be dependent upon the number of clots injected in the same manner as would passive dilation or recruitment. Further, there is additional evidence to support this conclusion. Lockhead et al., using angiography, noted that many vessels initially occluded by emboli were only partially occluded seconds or minutes later (15); similar observations were made by Dalen et al (11). If this is the mechanism of PAP recovery from severe hypertensive states subsequent to PE, it implies that the propensity of clot deformation, as well as its size, can play an important role in the ability of the pulmonary vasculature to accommodate.

The slower phase of PAP recovery can be related to both clot movement and dissolution. As shown, steady-state pressure after embolization increases both with number of clots injected and with the volume of the clot injected. Further it was shown that the time to reach this new steady-state pressure increased with clot size. Data on the dissolution rate of pulmonary emboli in the form of blood clots over the small time spans measured in these experiments could not be found in the literature. However, other investigators using angiography have shown that after embolization gradual reduction in PAP was accompanied by a reduction in the number of first-order arteries that were initially occluded (11). Although the angio-

graphic data was inconclusive concerning mechanism it was noted that small changes in the position of radiopaque blood clots often resulted in a change from complete to partial obstruction of embolized pulmonary vessels. Further, Moser et al, showed that 3 hours after injection of 4 ml clots at autopsy only half the injected clot volume could be recovered (16). This suggests a rather high clot dissolution rate. These investigators felt fibrinolysis was primarily responsible. Based on observations of the present study it is clear that at least in part the slow phase of the recovery is due to a reduction in the embolic material in previously occluded vessels. We observed that, when a clot fragments within the heart, the fragments embolize to different pulmonary vessels. However, once pressure reaches its new equilibrium level and a second injection is made, clot fragments frequently are seen to propagate in the same vessel which had been previously embolized. Extrapolated to the clinical setting the present findings indicate that the ultimate effect of pulmonary embolism depends not just on the size of the embolus but on the time interval between successive emboli.

SUMMARY

Radiopaque autologous blood clots (2.5, 5.0, and 10 ml) have been used to study the dependence of cardiovascular dynamics on pulmonary emboli size and embolization sequence. Each embolus caused an initial peak increase in pulmonary artery pressure which after partial recovery resulted in a sustained pulmonary hypertension. The magnitude of the hypertension was greater for larger individual clots and increased with the number of clots injected. For equal total injected volumes the sustained hypertension was less when produced with multiple 2.5 ml clots as compared to the larger-size clots. The initial peak increase in PAP and subsequent recovery time increased by an amount dependent on the volume of each clot injected and not on the number. Further it was discovered that the recovery of PAP occurred in two phases characterized by an initial rapid reduction in PAP explainable on the basis of emboli movement, followed by a more gradual reduction attributable to additional effects. The data suggest that individual clots of larger volume produce greater functional derangements but that factors other than size, such as clot consistency, may be of fundamental as well as clinical importance.

ACKNOWLEDGEMENTS

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