Medial Hypertrophy in Patients with Pulmonary Embolism: Anatomopathological Study

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Summary
Objective: To compare the arterial response of cases of acute and chronic embolism, seeking to associate ischemic pulmonary remodeling with progression to chronicity.

Methods: Retrospective analysis of 61 necropsies of patients who died in the Instituto do Coração (31 cases of pulmonary embolism and 30 cases of acute myocardial infarction). Slides of pulmonary tissue were obtained from all cases and analyzed qualitative and quantitatively (medial thickness measurement).

Results: Qualitative analysis enabled the differentiation between cases of embolism and the control group, thus characterizing the two groups and defining the adequate choice of the control group. The alterations predominated in patients with embolism (alveolar inflammation and edema, infarction, vasoconstriction, concentric intimal proliferation, presence of thrombus). Quantitative analysis demonstrated higher percent medial thickness in the cases of embolism than in the control group; among the cases of embolism, no differences in intra (acute – 19.74 and chronic – 20.04) and pre-acinar (acute – 18.85 and chronic – 18.68) arteries were observed.

Conclusion: The lack of difference among the groups with embolism and the higher values of percent medial thickness in the peripheral arteries allow the conclusion that the vascular response is more intense and starts in these arteries. (Arq Bras Cardiol 2007;88(6):584-589)

Key words: Arterial occlusive diseases; pulmonary embolism/physiopathology; thromboembolism.

Introduction
The incidence of pulmonary thromboembolism caused by obstruction of pulmonary artery branches by emboli originating in other parts of the body is high, and is estimated at 600,000 cases/year in the United States\(^1\). Mortality of this condition is high, with 60,000 deaths, the majority of which within the first hour. Pulmonary embolism accounts for 0.27 to 0.40% of hospital admissions\(^2\). Because of increased blood coagulation and other effects of gestation and birth, pulmonary embolism is the major cause of maternal death in developed countries\(^3\).

Acute embolism may result in a transient pressure increase in the pulmonary territory, which tends to resolve in the absence of the obstructive factor. However, some factors may predispose to a sustained pressure elevation: previous massive embolism, multiple previous embolic episodes, significant perfusion defect, young age, and embolism of undetermined cause. The incidence of pulmonary hypertension after acute embolism is 1%, 3.1%, and 3.8% at six months, one year, and two years, respectively\(^4\).

Several studies have been recently conducted with the purpose of explaining progression to chronic embolism. Two hypotheses have been studied with greater enthusiasm: the first considers the maintenance of the occlusive factor as fundamental for the development of a pulmonary vascular response characterized by medial hypertrophy; the second relates pulmonary hypertension to a previous initial arteriopathy in patients who had an unfavorable outcome\(^5,6\).

The histological diagnosis of embolism itself is not simple; resorption of emboli by endogenous thrombolysis, variation in embolus size, and impossibility of morphological differentiation between thrombi embolized to the lungs and those formed in situ make this diagnosis difficult. Large thrombi in major pulmonary arteries tend to be embolic as long as no disease is observed within the arterial wall. Primary thrombi are more common in the upper lobes, whereas thromboembolic events are more common in the lower lobes\(^6,7\).

The alterations in the pulmonary vascular bed are characteristic of vascular remodeling, which consists in alterations resulting from pressure elevation both in the venous and the arterial bed, or from increased blood flow. Microscopic analysis allows the verification of endothelial injury, presence of muscle in non-muscular arteries, intimal proliferation, and medial hypertrophy\(^8\).

Arteriopathy secondary to thrombosis is therefore characterized by intimal fibrosis resulting from myofibroblast migration to the internal elastic layer that can lead, over time, to occlusion of the artery affected, presence of thrombus...
were prepared and stained with hematoxylin-eosin. For the case to be included in the study, at least two respective lung slides adequate for analysis were required. The histological lung sections were then also stained with Miller’s stain, thus facilitating the observation of elastic fibers. Therefore, each case resulted in four lung sections (two stained with hematoxylin-eosin and two with Miller’s stain).

All slides were blinded so that the observer did not know whether it was an embolism case or not.

With the 61 cases selected (16 acute embolism, 15 chronic embolism, and 30 control cases), an analysis could be performed with an optical microscope (Q500YW – Leica – UK) coupled to an image analyzer (Quantimet Q500YW – Leica – UK), using magnification ranging from 2.5 to 40 times.

The slides obtained were analyzed both qualitative and quantitatively (Figure 1).

The hematoxylin-eosin-stained histological sections were used for the qualitative analysis, which was based on the identification of pulmonary tissue alterations. The presence or absence of alterations was observed. The qualitative parameters of the pulmonary circulation analyzed were: permeability alterations: alveolar inflammation and edema; cell injury: infarction; vascular alterations: vasoconstriction, concentric intimal proliferation, presence of thrombus.

Quantitative analysis was performed with the image analyzer (Quantimet), which enabled the performance of measurements in the vascular walls with the purpose of determining the presence of distal arteriopathy in the pulmonary bed. Acinar and pre-acinar arteries were analyzed, and the arteries not showing clear contours (internal and external elastic laminae) were excluded.

The following vascular structures were assessed: external diameter: smallest diameter delimited by the external elastic lamina of the pulmonary arteriole; medial thickness: distance between the external and internal elastic laminae of the pulmonary arteriole. Two measurements were taken for each arteriole, and the arithmetic mean was calculated.
Percent medial thickness (%MT): %MT = (2 x medial thickness / external diameter) x 100 (Figure 2).

Results

The analyses of the results obtained during the present study were divided into qualitative and quantitative analyses.

Qualitative analysis was performed using overall observation of the lung section with identification of histological alterations, without considering the degree of pulmonary involvement (edema, inflammation, and infarction). Vascular alterations, however, were assessed for each of the arteries found in the lung section studied, and presented as percent involvement, that is, percentage of arteries involved within the total studied (vasoconstriction, intimal proliferation, and thrombus).

Quantitative analysis included artery measurement, as previously described, using slides stained with Miller’s stain.

Qualitative analysis - Edema was more frequently observed in the cases of acute embolism (100%), followed by chronic cases (86.7%), and this difference was statistically significant. Inflammation was more frequent in the cases of both acute and chronic embolism, however a high incidence was also observed in the control group, with more than half of the cases presenting some degree of inflammation.

The incidence of pulmonary infarction was significantly higher in patients with acute embolism (recent infarction). Likewise, patients with chronic embolism presented alterations compatible with organized infarction in a greater number of cases. Control group patients with pulmonary infarction were those who developed some degree of associated pulmonary infarction as a result of the cardiac event, with the pulmonary infarction always being an acute event (Figure 3).

Vasoconstriction was not observed in the control group. The comparison between groups and artery types (intra-acinar and pre-acinar) showed a higher incidence of vasoconstriction in pre-acinar vessels (6.78 greater in pre-acinar vessels - p = 0.007), and in the group of patients with acute embolism in relation to chronic cases (11.26 greater - p = 0.011) (Table 1).

Intimal proliferation was assessed by comparing the artery types and then the groups with each other, since the estimation model used demonstrated that both factors had an influence...
on the incidence of this histological alteration (p = 0.006). In relation to the analysis of the type of artery affected: in patients with acute embolism and in the control group there was a higher frequency of cases of intimal proliferation in pre-acinar vessels than in intra-acinar vessels (p<0.0001). Although the incidence was higher among cases of chronic embolism, no difference was observed between the artery types.

The comparison between the different groups for intra-acinar arteries, in turn, demonstrated a significantly greater involvement in chronic cases in relation to the other two groups:

- 36.69 times in comparison to the acute embolism group, and 56.17 times in comparison to the control group.

The same was observed in the pre-acinar arteries, however with a slightly lower difference in comparison to intra-acinar arteries.

The acute embolism and control groups did not show differences as regards intimal proliferation in pre-acinar arteries; the alteration was identified only in smaller arteries (intra-acinar) (Table 2).

Quantitative analysis - Quantitative analysis was performed in 55 cases, with measurements of 2262 arteries. Control group cases with associated pulmonary infarction were excluded.

Arteries were characterized according to their location: a) pre-acinar; b) intra-acinar.

Further, patients of each group were compared in relation to the artery types and arteries within the same group (generalized estimation equation using Gamma distribution and multiple comparisons).

No difference was observed as regards artery diameter in the three groups (Table 3).

When percent wall thickness (%WT) of intra-acinar arteries is observed in the different groups, we can conclude that: values in the acute and chronic groups are higher than those of the control group, thus demonstrating medial hypertrophy in these two groups. However, no difference was observed between the groups with embolism.

In relation to %WT, the results were similar to those of the intra-acinar arteries, with values slightly lower than those of the arteries previously mentioned. Embolism groups presented greater wall thickness with higher %WT, consequently (Table 4).

Comparison of percent thickness between the groups and artery types - In the comparisons of patients of the different groups and artery types analyzed (pre and intra-acinar) in relation to their percent thickness, the model demonstrated that each of the parameters assessed individually presented statistical significance as for the presence of difference between patients. The joint analysis of factors established that the association of artery location and patient group did not show statistical significance.
Detailed analysis of this relation evidenced a constant increase of %WT in pre-acinar arteries when compared to intra-acinar arteries, always 1.09 times higher.

In the comparison between groups (acute, chronic and control) no difference was observed among patients with embolism (acute and chronic). When these two groups were individually compared with the control group, their percent thickness was shown to be approximately six times higher, with p < 0.0001 (Figure 4).

### Table 4 - Mean percent thickness

<table>
<thead>
<tr>
<th>Group</th>
<th>Minimum</th>
<th>Median</th>
<th>Maximum</th>
<th>Mean</th>
<th>S.D.</th>
<th>S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute - intra-acinar</td>
<td>14.65</td>
<td>19.25</td>
<td>24.66</td>
<td>19.74</td>
<td>3.33</td>
<td>0.83</td>
</tr>
<tr>
<td>Chronic - intra-acinar</td>
<td>16.54</td>
<td>20.07</td>
<td>25.83</td>
<td>20.04</td>
<td>2.45</td>
<td>0.63</td>
</tr>
<tr>
<td>Control - intra-acinar</td>
<td>10.56</td>
<td>13.96</td>
<td>22.15</td>
<td>14.41</td>
<td>2.39</td>
<td>0.44</td>
</tr>
<tr>
<td>Acute - pre-acinar</td>
<td>12.33</td>
<td>18.38</td>
<td>24.22</td>
<td>18.85</td>
<td>3.09</td>
<td>0.77</td>
</tr>
<tr>
<td>Chronic - pre-acinar</td>
<td>13.29</td>
<td>18.55</td>
<td>24.65</td>
<td>18.68</td>
<td>3.45</td>
<td>0.89</td>
</tr>
<tr>
<td>Control - pre-acinar</td>
<td>9.32</td>
<td>12.85</td>
<td>19.08</td>
<td>13.16</td>
<td>2.49</td>
<td>0.45</td>
</tr>
</tbody>
</table>

SD – standard deviation; SE – standard error.

Fig. 4 - Percent thickness in the three groups related to the artery types. %WT – Percent medial thickness

### Discussion

Clot organization into fibrous tissue is associated with intimal disappearance and medial infiltration of arterial vessels. These lesions are partially repermeabilized at the great trunks, however they remain occluded at the ostia of the collateral branches.

Artery diameter reduction due to medial thickening (hypertrophy) starts at the intrapericardial segment of the pulmonary artery, and becomes progressively thicker toward segmental arteries, and occasionally become occluded. Progression to chronicity results in fibrotic or cellular intimal thickening accompanied by luminal obstruction of the small arteries that may coexist with recanalized thrombi or presence of plexiform lesion.

Acute embolism cases may progress in two ways: resolution or chronicity. The latter may be associated with pulmonary hypertension. Resolution results from local fibrinolytic action with clot resorption and total renewal of the pulmonary arterial vascular bed. Usually, the embolism resolves within weeks.

In some cases thrombus resorption does not occur and becomes an organized clot. This results from alterations in hemostasis and fibrinolysis, and from recurrent embolic events.

To date, we do not know for sure which cases will become chronic; those with pulmonary artery pressure higher than 40 mmHg at the moment of the acute event are known to have a higher probability of developing chronic pulmonary involvement. Remy-Jardin et al. demonstrated involvement of a larger pulmonary area in patients who did not present complete resolution of the acute episode.

Patients whose pulmonary condition progressed to chronicity had alterations characteristic of chronic arteriopathy at presentation of thromboembolism.

Chronic cases may progress without symptoms for some time, and recurrence of symptoms results from local thrombosis due to low local blood flow secondary to pulmonary artery obstruction or development of arteritis in the non-obstructed vascular bed. This sequence of events also explains the progressive worsening of pulmonary hypertension in those cases where the initial embolic condition does not resolve.

Some evidences suggest that other factors may be involved in the progression to chronic pulmonary embolism and worsening of pulmonary hypertension: recurrence of thromboembolism or in situ thrombosis, and small (distal) pulmonary artery remodeling in non-occluded areas, similar to what is observed in primary pulmonary hypertension cases.

These evidences are supported by the following theories: 1) low correlation between length of the central obstruction and degree of pulmonary hypertension; 2) progression of pulmonary hypertension in the absence of recurrence.
of recurrent thromboembolism; 3) evidence of pulmonary blood flow redistribution after thromboendarterectomy from non-occluded areas to endarterectomized areas as a consequence of the high resistance in the non-obstructed bed; 4) histopathological evidence of pulmonary vasculopathy with medial hypertrophy, intimal thickening and plexiform lesions; 5) persistence of pulmonary hypertension despite a satisfactory thromboendarterectomy.

In a previous study, Yi et al.9 presented a percent thickness value in cases of chronic embolism of approximately 10. This value did not vary in the different portions of the arteries analyzed. In this study, higher values were observed for percent medial thickness, of approximately 19 in smaller-diameter arteries and 18.5 in larger-diameter arteries. On average, values were 1.09 times greater for intra-acinar arteries.

The lack of difference between embolism groups and the higher percent thickness values in peripheral arteries allow the conclusion that the vascular response is more intense and starts in these arteries; these may be related not to blood flow obstruction, but to the ischemia resulting from this obstruction, since the response is similar in acute and chronic cases.

Potential Conflict of Interest
No potential conflict of interest relevant to this article was reported.

References