Pulmonary embolism causes endomyocarditis in the human heart

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ABSTRACT

Objectives: Pulmonary embolism (PE) is a significant cause of morbidity and mortality. In a recent study in patients with PE, an increased amount of macrophages was found in the right ventricle. In the present study the presence of inflammatory cells, myocytolysis and intracavitary thrombi in the left and right ventricle of patients who died because of PE was evaluated as a putative new source of heart failure.

Design: 22 patients with PE were studied. For comparison, 8 controls and 11 patients who died of chronic pulmonary hypertension (PHT) were studied. Slides of the left and right ventricle were stained with antibodies, identifying neutrophilic granulocytes, lymphocytes and macrophages, which were subsequently quantified. Myocytolysis was visualised using complement staining. Thrombi were identified by conventional staining.

Results: Compared to controls, in patients with PE a significant increase in extravascular localisation of all three inflammatory cells was found both in the right and left ventricle, coinciding with myocytolysis, indicative for myocarditis. No increase in inflammatory cells was found in patients with PHT. Endocardial cellular infiltration was also found, partly coinciding with the presence of ventricular thrombi.

Conclusions: In patients with PE, endomyocarditis and intracavitary thrombi in the left and right ventricle were found. These abnormalities may be an additional new explanation for the observed cardiac enzyme release and functional abnormalities of the heart in these patients and may contribute to the morbidity and mortality of the disease.
INTRODUCTION

Pulmonary embolism (PE) is a potentially life-threatening condition, which is most commonly seen in patients with other diseases. The acute sequelae of PE can vary from no symptomatology to sudden death. Despite advances in diagnosis and treatment, PE remains a significant cause of morbidity and mortality. Its pathophysiology, including its effect on the heart, has been studied intensively over the past 50 years. Echocardiographic studies have shown that PE causes right ventricular dilatation and dysfunction. In some patients with PE, an increase in troponin I and T levels has been demonstrated, which is related to an increased risk in mortality. It has been suggested that the increased troponin levels as well as the observed heart failure are caused by an isolated right ventricular infarction. In an experimental model Vlahakes et al. showed that PE causes a selective decrease in blood flow of the right ventricular subendocardium, resulting in ischemia and infarction.

Interestingly, Iwadate et al. reported an increase in the level of CD68 positive macrophages in the right ventricle of patients with PE. They concluded that the influx of macrophages in the heart was caused by ischemia that occurred subsequent to PE, although they in fact did not prove these ischemic changes. They did not relate the inflammatory infiltrate in the heart to a putative myocarditis. In this study we therefore have evaluated the presence of inflammatory cells in more detail by analysing macrophages, lymphocytes and neutrophilic granulocytes in the hearts of patients who died subsequently to PE (acute pulmonary stress). For comparison, patients who died of the idiopathic form of pulmonary hypertension (PHT) -as a model of chronic increased right ventricular afterload and thus chronic pulmonary stress-, and control patients who died of other non-pulmonary causes were also studied.

MATERIALS AND METHODS

Human Heart Tissue

Human hearts were obtained by autopsy (n = 41). Table 1 presents the patient details. From each patient a tissue slide of the left ventricular anterior wall and the right lateral ventricular wall of the heart was analysed. On each heart slide, lactate dehydrogenase (LDH) staining was performed to detect putative infarction of at least 4 hours old. In total six patients had acute myocardial infarction of the left ventricle between 4-6 hours old (3 in the pulmonary embolism group, patient nr. 8, 9, 23), 3 in the pulmonary hypertension group. In these cases, heart tissue was derived from the remote, non-infarction area. Thrombi were analysed according to Stehbens and Lie. All patients with PE were checked for any systemic diseases which are known to cause myocarditis or endocarditis, or both, in the heart. In two patients we found a systemic disease (one patient had Cushing’s disease and one patient had Kahler’s
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disease). However, according to published reports neither diseases is associated with (endo) myocarditis. Other systemic diseases which are associated with (endo)myocarditis (e.g., rheumatic disease, systemic lupus erythematosus and sepsis) were not present in these patients. Eight control patients were included, 4 women and 4 men. Age varied between 49 and 86 years. They died of a cause not related to pulmonary disease, pheochromacytoma or brain injury. Twenty-two patients who died subsequent to PE were studied, 13 women and 9 men. Age varied between 27 and 93 years. Finally, we analysed eleven patients, 8 woman and 3 men, age varied between 23 and 85 years, who died owing to the consequences of idiopathic pulmonary arterial hypertension. The diagnosis of idiopathic pulmonary arterial hypertension was made at least 3 months before the patient died. None of these patients had evidence for an underlying autoimmune or liver disease, none had left ventricular dysfunction by echocardiography. All had a normal wedge pressure during right heart catheterisation, had no underlying pulmonary disease or sleep disorder and had a normal perfusion scintigram in the absence of a history of acute PE. Table 1 shows the treatment of the patients at the time of death.

This study was approved by and performed according to the guidelines of the ethics committee of the VU University Medical Centre, Amsterdam. Use of material leftover after completion of a pathological examination is part of the patient contract in the hospital. This study was performed according to the Declaration of Helsinki.

**Immunohistochemistry**

Antibodies used were rabbit anti-human myeloperoxidase (MPO) (polyclonal), mouse anti-human CD68 (monoclonal), mouse anti-human CD45 (monoclonal), rabbit anti-human Complement C3d (polyclonal), rabbit anti-mouse biotin (monoclonal), swine anti-rabbit biotin (polyclonal), and streptavidin-biotin-complex, all from Dako Cytomation, Denmark. Heart tissue samples were prepared as described before. Sections were preincubated with normal serum for 10 minutes, followed by an incubation with an anti-MPO (1:50), anti-CD45 (1:50), anti-CD68 (1:400) or anti-complement C3d (1:1000) antibody for 1 hour. Sections were then incubated with rabbit-anti-mouse-biotin (1:500) and swine-anti-rabbit-biotin (1:300) for 30 minutes. Next, sections were incubated with streptavidin-biotin complex/HRP (sABC/HRP) (1:200) for 1 hour. Staining was visualized using 3,3'-diaminobenzidine (0.1 mg/ml, 0.02% H₂O₂). Sections were then counterstained with haematoxylin, dehydrated and covered. As a control, the same staining procedure was used, but instead of the primary monoclonal or polyclonal antibody, phosphate-buffered saline or an irrelevant antibody was used; these heart tissue slides were found to be negative (data not shown).
Table 1 Clinical data of patients included in the study.

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Controls (n= 8)</th>
<th>Pulmonary embolism (n=22)</th>
<th>Pulmonary hypertension (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (range)</td>
<td>70, 49-86</td>
<td>62, 27-93</td>
<td>51, 23-85</td>
</tr>
<tr>
<td>Male/female</td>
<td>4/4</td>
<td>9/13</td>
<td>3/8</td>
</tr>
<tr>
<td>Cause of death primary</td>
<td>Pneumonia (n=5) Drowned (n=1) Metastasis of carcinoma (n=1) Euthanasia (n=1)</td>
<td>AMI left ventricle 4-6 hours (n=3) Lung emboli (n=22) DIC (n=1) Euthanasia (n=1)</td>
<td>AMI left ventricle 4-6 hours (n=3) PHT (n=5) Euthanasia (n=2) Heart failure (n=3) Dissection pulmonary artery (n=2)</td>
</tr>
<tr>
<td>Cause of death secondary</td>
<td>-</td>
<td>Pneumonia (n=6) Metastasis of carcinoma (n=1)</td>
<td>PHT (n=5) Pneumonia (n=2) Heart failure (n=1)</td>
</tr>
<tr>
<td>Medical history</td>
<td>AV-block group I (n=1) DM-II (n=1) COPD (n=1) Lung carcinoma (n=1) Breast carcinoma (n=1) Tonsil carcinoma (n=1) Prostate carcinoma (n=1)</td>
<td>Accident (n=1) DM-II (n=1) Cervix carcinoma (n=1) Hip prosthesis (n=1) Lung carcinoma (n=2) Sarcoma (n=1) Ovary carcinoma (n=1) M. Cushing (n=1)</td>
<td>Endometrium carcinoma (n=1) M. Hodgkin (n=1)</td>
</tr>
<tr>
<td>Medication at time of death</td>
<td>Antibiotics (n=5) Heparin (n=1) Morphine (n=1)</td>
<td>Antibiotics (n=6) Acenocoumarol (n=2) Prednisolone (n=1) Heparin (n=4) Streptokinase (n=3) Omeprazole (n=1) Fentanyl (n=1)</td>
<td>Haloperidol (n=1) Hydroxyurea (n=1) Flecainide (n=1) Prostacyclins (n=3) Epoprostenol (n=5) Morphine (n=1) Prednisone (n=1) Antibiotics (n=1) Noradrenaline (n=1) Dopamine (n=1)</td>
</tr>
<tr>
<td>Other pathological findings</td>
<td>Pancreatitis (n=1) Squamous cell carcinoma (n=1) Metastasis of carcinoma (n=2)</td>
<td>Pancreas carcinoma (n=1) Infarction kidney (n=2) Thyroid gland carcinoma (n=1) Breast carcinoma (n=1) Metastasis of carcinoma (n=1) Pancreatitis (n=1)</td>
<td>Brain Infarction (n=1)</td>
</tr>
</tbody>
</table>

Morphometrical analyses
In each tissue slide of the left and right ventricle of the heart, the number of extravascular neutrophilic granulocytes (MPO positive), lymphocytes (CD45 positive) and macrophages (CD68 positive) was counted perivascularly (area surrounding intramyocardial arteries) and in the interstitium (area in between cardiomyocytes). Myocytolysis was objectified as complement (C3d) positivity. Myocarditis was defined as aggregation of inflammatory cells in the myocardium coinciding with areas of myocytolysis, conforming to the Dallas criteria\(^{28,29}\). The presence of inflammatory cells in the endocardium of the heart was diagnosed as endocarditis. The total surface of each sample then was measured using QPRODIT\(^{30}\). The number of extravascular inflammatory cells per 100 mm\(^2\) was then calculated as the total score for each specimen. Two independent observers have scored the tissue slides (MPVB and HWMN). The interobserver variation was 10%.

Statistical analysis
Statistics were performed with the SPSS statistics program (windows version 11.5; SPSS Inc, Chicago, IL, USA). For each dependent variable (CD68, MPO and CD45) a repeated measure ANOVA was performed. Also post-hoc Bonferroni tests were conducted. Distribution data were compared by $\chi^2$ analysis. Values at the $p \leq 0.05$ level were considered significant.

RESULTS
Lactate dehydrogenase decolourisation was not found in any of the control hearts, indicating absence of infarction of more than 4 hours. In these control hearts, only focally neutrophilic granulocytes, lymphocytes, and macrophages were found perivascularly (area surrounding intramyocardial arteries) and in the interstitium (area in between cardiomyocytes), of both the right and left ventricle. However, no aggregation of these cells in the myocardium was found, and no localisation of inflammatory cells in the endocardium (excluding endocarditis), or myocytolysis (vacuolisation in cardiomyocytes, objectified as complement C3d positivity\(^{31}\)). These data therefore exclude myocarditis. In addition, no significant differences between the three different cell types were found (Figure 1).
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Figure 1: Number of myeloperoxidase (MPO), CD45 and CD68 positive cells in left and right ventricle of the heart when all patients combined.

The number of extravascular positive cells was scored per 100 mm² in respectively the right (RV) and left ventricle (LV) of the heart. Data were analysed for control patients (C; n = 8), patients with pulmonary embolism (PE; n = 22), patients with pulmonary hypertension (PHT; n = 11). A. Neutrophilic granulocytes (MPO positivity) (scores for LV are: C = 331 ± 35, PE = 680 ± 83, PHT = 138 ± 33 and for RV: C = 339 ± 75, PE = 964 ± 128, PHT = 100 ± 24*). B. Lymphocytes (CD45 positivity) (scores for LV are: C = 203 ± 32, PE = 397 ± 75, PHT = 212 ± 18 and for RV: C = 161 ± 33, PE = 657 ± 97, PHT = 221 ± 19*). C. Macrophages (CD68 positivity) (scores for LV: C = 164 ± 26, PE = 471 ± 65, PHT = 221 ± 30 and for RV: C = 184 ± 31, PE = 758 ± 137, PHT = 199 ± 30*). The error bars represent the standard error of the mean.

In contrast, in patients with acute PE, extravascular foci of aggregates of lymphocytes, neutrophilic granulocytes and macrophages were found dispersed in the right and left ventricle, coinciding with areas of myocytolysis (objectified as C3d positivity), indicating myocarditis (Figure 2A-C).
Figure 2: Microscopy of inflammatory cells in patients with pulmonary embolism (PE).

A. Microscopic picture of aggregates of inflammatory cells (arrow) in the heart of a patient with acute PE (#: localisation of inflammatory cells in the endocardium; objective x10). B. In more detail different inflammatory cells can be seen (lymphocytes, macrophages and neutrophilic granulocytes), with myocytolysis (*) (objective x40). C. Microscopic picture of complement C3d positive cardiomyocytes (*) (objective x40). D. Microscopic picture of a thrombus with endocarditis (arrow) in the right ventricle of the heart (objective x20).

Subsequently, we quantified these inflammatory cells in both the right and left ventricle of the heart of each patient. The mean plus 2 SD of all control patients was used as a cut-off point and thus as the upper limit of normal (Figure 3A-F). This enabled us to identify a putative positive score for the individual markers in each patient. In the right ventricle we found a significant increase of all three inflammatory cell types in 10 out of 22 patients. In six patients there was an increase of two inflammatory cell types, and in three patients one inflammatory cell type was increased compared to the controls. In all these 19 patients at least one area of myocytolysis (equivalent to complement positivity) was found, with aggregation of inflammatory cells in that area. Notably, in three patients no significant increase of inflammatory cells and complement positivity was found compared to the controls, excluding myocarditis.
In the left ventricle a different pattern was found. In seven out of 22 patients an increase of all three inflammatory cell types was found, in seven patients an increase of two different inflammatory cell types was found, in three patients only one inflammatory cell type was increased. Also here, the increase of inflammatory cells coincided with myocytolysis and aggregation of the particular inflammatory cells around cardiomyocytes. In five patients, no increase in the number of inflammatory cells was found and one patient was without complement positivity, excluding myocarditis in total six patients.

Figure 1A-C summarizes the data: compared with controls, patients with PE showed a significant increase in the number of neutrophilic granulocytes, lymphocytes and macrophages in the right ventricle (p=0.012, p=0.020 and p=0.027, respectively) and a significant increase in the number of neutrophilic granulocytes and macrophages in the left ventricle (p=0.034, p=0.018, respectively). No significant difference was found between the number of neutrophilic granulocytes in the left and right ventricle (p=0.352). However, the accumulation of lymphocytes and macrophages was significant lower in the left ventricle than in the right ventricle in patients with PE (p<0.0001 and p<0.0001, respectively).

To determine a putative relation between the age of the lung thrombo-emboli and the accumulation of inflammatory cells in the heart, patients were divided into two groups: thrombo-emboli < 4 days old and thrombo-emboli > 4 days old25. In 18 patients, thrombi in the lung were < 4 days old, whereas in 4 patients thrombi were 4-12 days old. No significant relation was found between the age of thrombi in the lung and the number of inflammatory cells in the heart (data not shown).

The data of controls and patients with PE were also compared with those for patients who died of chronic PHT. No aggregation of inflammatory cells, or myocytolysis was found in these patients. Furthermore, there was no significant difference between the level of inflammatory cells of controls and patients with chronic PHT both in left and right ventricle (Figure 1). The difference between patients with PE and patients with chronic PHT was highly significant for neutrophilic granulocytes and macrophages in the left ventricle and for all inflammatory cells in the right ventricle.
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Figure 3: Number of myeloperoxidase (MPO), CD45 and CD68 positive cells in the left and right ventricle of the heart in the individual patient.

The number of extravascular positive cells was scored per 100 mm² in respectively the right and left ventricle of the heart. Numbers on the horizontal axis represent individual patients with PE (see also table 2). A, D. Neutrophilic granulocytes (MPO positivity) score in right (A) and left (D) ventricle. B, E. Lymphocytes (CD45 positivity) score in right (B) and left (E) ventricle. C, F. Macrophages (CD68 positivity) score in right (C) and left (F) ventricle.

The dotted line represents the mean value of control patients plus 2 SD value; a patient was scored positive for a cell marker when the score was above the dotted line.
We also analysed the distribution of inflammatory cells over the endocardium and myocardium in patients with PE. In patients without myocarditis of the right or left ventricle \((n=3 \text{ and } n=6, \text{ respectively})\), endocarditis was present in the right ventricle in one patient and in the left ventricle in two patients. In contrast, in patients with myocarditis of the right or left ventricle \((n=19 \text{ and } n=16, \text{ respectively})\), endocarditis was present in 10 patients with right-sided myocarditis and in seven patients with left-sided myocarditis.

Finally, thrombi in the ventricles were related to the presence of endocarditis. None of the patients without endocarditis of the right ventricle had ventricular thrombi, whereas only one patient without endocarditis of the left ventricle had a thrombus in the left ventricle. In contrast, in patients with endocarditis of the right or left ventricle irrespective of myocarditis \((n=11 \text{ and } n=9, \text{ respectively})\), thrombi were present in nine patients with right-sided endocarditis and in five patients with left-sided endocarditis (Figure 2D). The relation between endocarditis and thrombi was highly significant \((p<0.001)\).

As thrombi may embolise, specific embolisation features were looked for at autopsy. In two patients a kidney infarction was found, and in one out of seven brain autopsies performed in patients with endocarditis of the left ventricle, a recent brain infarction was detected.

**DISCUSSION**

To the best of our knowledge this is the first paper describing in detail the presence of inflammatory cells in the heart of patients who died of PE: aggregates of lymphocytes, macrophages and neutrophilic granulocytes were found, coinciding with areas of myocytolysis (figure 2). The results indicate the presence of myocarditis and endocarditis both of the right and left ventricle in these patients. Recently, Watts *et al* reported an increased level of neutrophils and monocytes/macrophages in the right ventricle of rats, but not in the left ventricle in a rat model of PE\(^3\)\(^2\). In this rat model PE was experimentally induced by infusing of microspheres for only a limited period of time, namely a maximum of 18 hours, which might explain why no inflammation was found in the left ventricle. Recently, Iwadate *et al* found an increase of the level of macrophages in the right ventricle in patients with PE\(^2\)\(^3\)\(^,\)\(^2\)\(^4\). They did not analyse neutrophilic granulocytes or lymphocytes, however, nor did they analyse the left ventricle in those patients. Notwithstanding the lack of findings indicative for ischaemia, they interpreted their results as an effect of ischaemia.

This observation of myocarditis/endocarditis is unexplained. From published reports it is known that a systemic disease, like rheumatic disease, systemic lupus erythematosus and sepsis, can contribute to a (non-infectious) (endo)myocarditis. However, a systemic disease, namely Cushing’s disease and Kahler’s disease, was present in only two out of 22 patients with PE. However, those disease are not associated with (endo)myocarditis. It has been suggested
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that pheochromocytoma or brain injury may result in catecholamine-induced myocarditis. The infiltrate we found, morphologically could fit with this catecholamine myocarditis. None of the patients in our study had a pheochromocytoma. An intriguing explanation therefore may be that local and/or systemic production of catecholamines, related to the stress of PE, secondarily results in catecholamine-induced myocarditis. Further studies are needed to substantiate this hypothesis. Besides catecholamines, chemokines could also induce the inflammation found in patients with PE. Watts et al recently showed in the above-mentioned rat model of PE that different chemokine mRNA levels (CINC-1, CINC-2, MIP-2, MCP-1 and MIP-1α) were increased in the right ventricle of the heart. Also MCP-1 protein was found to be increased in the right ventricle of these rats. Additionally, in left ventricular myocardial infarction it has also been shown that processes other than chemokine production, such as the production of reactive oxygen species, complement activation or cytokines within the heart, can attract neutrophils and monocytes. These mediators therefore might also be responsible for the inflammation we found in patients with PE, but this is now subject to further study.

We also found that the myocarditis/endocarditis is related to acute pulmonary stress. In patients with chronic pulmonary stress (idiopathic pulmonary arterial hypertension), no myocarditis was found (figure 1). It has to be emphasised that none of the patients with PHT had recurrent thrombo-emboli in the lung, while the time point of diagnosis of their disease was at least 3 months and in most cases years before their death. This may indicate that the increase of inflammatory cells in the heart is dependent on an acute pulmonary stress event and not a chronic pulmonary stress event (idiopathic pulmonary arterial hypertension).

In some of the patients the infiltrate extended throughout the endocardium. In 70% (14/20) of these cases of endocarditis ventricular thrombi were found, whereas a thrombus without endocarditis was found in only 4% (1/24). This suggests that the inflammation of the endocardium results in cavitary thrombus formation. Right-sided thrombi may result in recurrence of lung emboli, whereas left-sided thrombi may lead to systemic embolisation. However, in only one patient a recent brain infarction was detected, and in two patients a kidney infarction was found.

One may question if PE is primary or secondary to the myocarditis. However, as the endocarditis extended from the myocarditis in most cases, as only part of the patients showed the combination of myocarditis plus thrombi in the right ventricle, and as no other local cardiac causes of ventricular thrombi were found, our findings are more in line with primary PE and secondary myocarditis.

In some of the patients with PE, an increase in troponin T and/or troponin I levels, but also in CK-MB levels was previously found. Our finding of myocarditis might provide a pathophysiological basis for this observation, since myocytolysis was clearly found in our study. The fact that the level of inflammatory cells in the myocardium varied considerably in
our study may explain the rise of troponins in part of the patients as described in literature. In some of the aforementioned studies, regional right ventricular dysfunction was detected by echocardiography. This has been related to right ventricular overload, ischaemia and infarction. The presence of myocarditis may be an additional explanation. Further studies are needed to relate the enzyme release and ventricular dysfunction to the extent of cellular inflammation.

The results in our study suggest, but as yet do not prove, the following hypothetical pathophysiological mechanism in patients with PE, as depicted in figure 4: not only the haemodynamic overload may result in left- and right-sided heart failure, but in addition the presence of myocarditis in the right and left ventricle and myocytolysis may cause or aggravate heart failure. Moreover, endocarditis may result in intracavitary thrombi, with pulmonary and systemic emboli as a consequence.

A few limitations need to be discussed. The present study describes patients who died of PE. The degree of inflammation in unselected patients is unknown and needs to be determined. Also, the effects of inflammation on enzyme release, right and left ventricular dysfunction and on prognosis need to be determined in unselected patients in prospective trials. In three patients with acute PE an acute myocardial infarction of the left ventricle was found. It is known that myocardial infarction also results in cellular infiltration. However, the infarcts were estimated to be between 4 and 6 hours old, and no increase of granulocytes was found in the extravascular space in the infarct area, which normally starts within days after the acute event. Also, we analysed remote areas, not the infarction areas themselves. And finally, three patients with chronic PHT also had an acute myocardial infarction. None of these patients showed cellular infiltration in the remote areas.

Most patients of the control group, of the PE group and PHT group had concomitant disease and were receiving drug treatment. The influence of the disease and therapy on the cellular infiltration is at present unknown and needs to be studied in a large group of patients. Also, the time-course (infiltration and disappearance) of the cellular infiltration is unknown. This may limit the quantification of the inflammation.

In conclusion, we found endomyocarditis and intracavitary thrombi in the left and right ventricle of patients with PE. These abnormalities give an additional and novel explanation for the observed cardiac enzyme release and function abnormalities of the heart and may contribute to the morbidity and mortality of the disease.
Figure 4: Hypothetical scheme of the pulmonary embolism (PE) cycle. The grey arrows show the putative mechanism of heart failure in patients with PE, as hypothesized until now. The black arrows show additional pathways in line with our findings as depicted in the present manuscript. LV = left ventricle of the heart, RV = right ventricle of the heart.
REFERENCES


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