The Inflammatory response in myocarditis and acute myocardial infarction

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Chapter 3

Ventricular myocarditis coincides with atrial myocarditis in patients

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SUMMARY

Background. Atrial fibrillation (AF) is a common complication in myocarditis. Atrial inflammation has been suggested to play an important role in the pathophysiology of AF. However, little is known about the occurrence of atrial inflammation in myocarditis patients. Here, we analysed inflammatory cell numbers in the atria of myocarditis patients without symptomatic AF.

Methods. Cardiac tissue was obtained post-mortem from lymphocytic myocarditis patients (n=6), catecholamine-induced myocarditis patients (n=5) and control patients without pathological evidence of heart disease (n=5). Tissue sections of left and right ventricle and left and right atrium were stained for myeloperoxidase (neutrophilic granulocytes), CD45 (lymphocytes) and CD68 (macrophages). These cells were subsequently quantified in atrial and ventricular myocardium and atrial adipose tissue.

Results. In lymphocytic myocarditis patients a significant increase was observed for lymphocytes in the left atrial adipose tissue. In catecholamine-induced myocarditis patients, significant increases were found in the atria for all three inflammatory cell types. Infiltrating inflammatory cell numbers in the atrial myocardium correlated positively with those in the ventricles, especially in catecholamine-induced myocarditis patients.

Conclusion. To a varying extent, atrial myocarditis occurs concurrently with ventricular myocarditis in patients diagnosed with myocarditis of different aetiology. This provides a substrate that potentially predisposes myocarditis patients to the development of AF and subsequent complications such as sudden cardiac death and heart failure.
INTRODUCTION

Myocarditis is a cardiac disease which is heterogeneous in aetiology and pathophysiology. Most commonly myocarditis is caused by viral infection, resulting in a distinct lymphocytic infiltration of the myocardium (lymphocytic myocarditis).\(^1\)\(^-\)\(^3\) A non-infectious form of myocarditis, which over the past 20 years has become a clinical topic of increasing interest is catecholamine-induced myocarditis, which is found in 62% of patients diagnosed with stress-induced cardiomyopathy.\(^4\),\(^5\) Although the mechanisms underlying catecholamine-induced myocarditis are still not well understood, an increased infiltration of different inflammatory cells was described in human ventricular heart tissue. Indeed, Yoshida \textit{et al.} observed mononuclear cell infiltration in endomyocardial biopsy samples taken from the left ventricle of three stress-induced cardiomyopathy patients,\(^6\) while Nef \textit{et al.} described increased macrophages and lymphocytes in the right ventricle in stress-induced cardiomyopathy.\(^7\) However, both the diagnosis as well as research into myocarditis are focused almost entirely on the ventricles of the heart (ventricular myocarditis), whereas very little is known about how myocarditis affects the atria.

Nonetheless, myocarditis is a known precursor of atrial fibrillation (AF),\(^8\) and AF is found in 14% of patients with suspected myocarditis.\(^9\) AF can result in sudden cardiac death, and indeed myocarditis is a commonly found underlying cause of sudden cardiac death, especially in younger patients.\(^10\),\(^11\) In addition, AF can result in the development and enhancement of heart failure.\(^12\) There is strong evidence linking both systemic and local inflammation to the initiation and perpetuation of AF in general.\(^13\),\(^14\) For instance, increased infiltration of macrophages\(^15\) and lymphocytes\(^16\) has been described in the left and right atria of patients with symptomatic atrial fibrillation, compared to control patients. These studies suggest that (cardiac) inflammation may predispose patients into developing AF. However, it is not known whether ventricular myocarditis coincides with infiltration of inflammatory cells in the atria (referred to as atrial myocarditis) in myocarditis patients. The presence of atrial myocarditis in myocarditis patients may predispose these patients to the development of AF.

In this study we quantitatively analysed neutrophilic granulocytes, lymphocytes and macrophages in the atria and ventricles of lymphocytic and catecholamine-induced myocarditis patients.
MATERIAL AND METHODS

Patients
The use of patient material as described in this article is approved by the medical ethics committee of the VU Medical Center (VUmc), Amsterdam, the Netherlands, in concordance with the guidelines established by the World Medical Association (Declaration of Helsinki). Human heart tissue was obtained at autopsy at the Pathology department of the VUmc and used in this study retrospectively. In the VUmc, as part of the patient contract, or in case relatives have given explicit prior written consent, tissue taken at autopsy can be used for research after completion of the diagnostic process. From each patient tissue from the left ventricular anterior wall, the right ventricular lateral wall and the left and right atrial appendages (auricles) of the heart was obtained for analysis.

Details of the included patients are listed in supplementary table 1. The patient groups did not differ between each other in gender or age. Patients were diagnosed post-mortem with lymphocytic myocarditis based on the presence of aggregates of lymphocytes adherent to cardiomyocytes, in combination with myocytolysis (objectified as complement factor 3d-positivity of cardiomyocytes) in the ventricular myocardium. Instead, patients were diagnosed with catecholamine-induced myocarditis when myocytolysis coincided with a diffuse infiltration of neutrophilic granulocytes, macrophages and lymphocytes in the ventricular myocardium rather than aggregates of lymphocytes. In addition, control patients were included without pathological evidence of heart disease. Of each patient a lactate dehydrogenase (LDH) staining was performed on a ventricular cross sectional heart slice to detect putative infarctions. As this study aims to investigate atrial myocarditis as a possible predisposing factor for AF, only patients were selected who did not have symptomatic AF. Patients with infarctions were also excluded from this study.

Immunohistochemistry
For immunohistochemical analysis, formalin-fixed paraffin-embedded tissue was cut into 4 μm sections, deparaffinised, rehydrated and incubated in methanol/H₂O₂ (0,3%) for 30 minutes to block endogenous peroxidases. Antigen retrieval was performed by heat inactivation in sodium-citrate buffer (10mM, pH 6.0) for slides to be stained for myeloperoxidase (MPO; neutrophilic granulocytes) and CD68 (macrophages). Slides stained for CD45 (lymphocytes) did not require antigen retrieval. The slides were incubated with either rabbit anti-human MPO (1:700, Dako, Eindhoven, The Netherlands), mouse anti-human CD68 (1:400, Dako) or mouse anti-human CD45 (1:50, Dako) for 1 hour at room temperature. The sections were then washed with phosphate-buffered saline and incubated with Real™ EnVision™ HRP α-mouse/rabbit (undiluted, Dako) for 30 minutes at room temperature. The staining was visualized using 3,3'-diaminobenzidine (DAB, 0,1 mg/ml, 0,02% H₂O₂). The sections were then
counterstained with haematoxylin, dehydrated and covered. With each staining a phosphate buffered saline control and an isotype control were included. All these controls yielded negative results (not shown).

**Quantitative immunohistochemical analysis**

The extravascular MPO-positive (neutrophilic granulocytes), CD68-positive (macrophages) and CD45-positive cells (lymphocytes) were quantified in the myocardium of the left and right ventricle and the left and right atria of the heart. CD45 (leukocyte common antigen) is also present on non-lymphocytic cells, but can be used as general lymphocyte marker based on morphology of positive-staining cells.\(^{17}\) Only compact cells with a high staining intensity were counted as lymphocytes. Recently, we observed in left atrial appendage tissue of AF patients that inflammatory cells also infiltrated the adipose tissue.\(^{18}\) Therefore, in this study we analysed the atrial adipose tissue separately. In the atria we identified areas of cardiomyocytes as ‘myocardium’ and areas of adipose tissue as ‘adipose tissue’, regardless of whether this adipose tissue was part of the epicardium or embedded in the myocardium. In one lymphocytic myocarditis patient the adipose tissue was not analysed as the atrial tissue slides contained an insufficient amount of adipose tissue (<0.3 mm\(^2\)). The total surface area of each sample was measured using QPRODIT and the numbers of cells were calculated as the total score for each specimen.

**Collagen staining and quantification**

Atrial collagen was visualized histochemically using a picrosirius red staining. Formalin-fixed paraffin-embedded tissue was cut into 4 µm sections, deparaffinised and rehydrated. The sections were incubated in a 0.2% Sirius Red solution (VWR International, Radnor, PA, solution made in 1.2% picric acid) for 60 min. Subsequently, the staining was differentiated in 0.01N HCl for 2 minutes. Following this, the sections were washed, dehydrated and covered. For quantitative analysis, six photos were taken randomly throughout the myocardium of each atrial tissue section, using a Leica DM/RB microscope equipped with a polarization filter. NIH Image software 1.63 was used to calculate the percentage of collagen on each photo, and the mean percentage was taken as data value of an individual patient. The quantitative analysis was performed blinded.

**Statistical analysis**

Statistical analysis was performed using Prism 6.0 (GraphPad Software, La Jolla, CA). Differences in cell numbers per mm\(^2\) tissue and collagen deposition were calculated with the Mann-Whitney U-test, while correlations were determined using Spearman’s rank correlation coefficient. A correlation coefficient ranging from -0.29 to 0.29 constituted absence of correlation, from 0.30 to 0.49 or -0.30 to -0.49 constituted a medium correlation and from 0.50 to 1.00 or -0.50 to -1.00
constituted a strong correlation. Correlations were calculated separately for each myocarditis group. Age and gender differences between groups were determined using the Kruskal-Wallis test. P-values <0.05 were considered statistically significant.

RESULTS

Inflammatory cells infiltrating the atria
In general, a diffuse pattern of infiltrating neutrophilic granulocytes (figure 1A), lymphocytes (figure 1B) and macrophages (figure 1C) was observed in the atria of myocarditis patients. All these inflammatory cells were observed to infiltrate both the atrial myocardium and the atrial adipose tissue. In the atria of lymphocytic myocarditis patients focal aggregates of lymphocytes were present, similar to the ventricles. Other than that, there were no obvious differences in pattern or location of these infiltrating cells between lymphocytic and catecholamine-induced myocarditis patients.

Inflammatory cell quantification in lymphocytic myocarditis

Neutrophilic granulocytes
In lymphocytic myocarditis patients an increase in neutrophilic granulocytes was observed in the myocardium of the left and right ventricle and to a lesser extent also in the left and right atrium (figure 2A), although none of these increases were found to be statistically significant. In the adipose tissue of the left and right atrium, the numbers of neutrophilic granulocytes also did not differ significantly from controls, nor did the number of neutrophilic granulocytes compared between the ventricles and the atria. The number of neutrophilic granulocytes correlated strongly between left atrium and ventricle, and a medium correlation was found between the adipose tissue and myocardium of the left atrium. No correlations were found on the right side of the heart (table 1).

Lymphocytes
Similar to neutrophilic granulocytes, lymphocytic myocarditis patients showed an increase in lymphocytes in the myocardium of the left and right ventricle and the left and right atrium, which was significant only for the right ventricle (p=0.0043; figure 2B). In the adipose tissue of the left and right atrium lymphocytes were also increased, which was significant for the left atrium (p=0.0043). The number of lymphocytes did not differ significantly between the ventricles and the atria, but correlated strongly between the right ventricle and right atrium (table 1).
Figure 1. Immunohistochemical stainings of the atria

Representative images of: (A) diffuse infiltration of neutrophilic granulocytes (arrows) in the atrial myocardium (panel I) and atrial adipose tissue (panel II) of the left atrium of a catecholamine-induced myocarditis patient; (B) diffuse infiltration of lymphocytes (arrows) in the left (panel I) and right (panel II, 'm') atrial myocardium and the right atrial adipose tissue (Panel II, ‘a’) of a lymphocytic myocarditis patient; and (C) diffuse infiltration of macrophages (arrows) in the right (panel I) and left (panel II, ‘m’) atrial myocardium and the left atrial adipose tissue (panel II, ‘a’) of a catecholamine-induced myocarditis (panel I) and a lymphocytic myocarditis patient (panel II). Neutrophilic granulocytes, lymphocytes and macrophages were visualized immunohistochemically with antibodies binding MPO, CD45 and CD68 respectively. Scale bar = 80 μm.
Figure 2. Inflammatory cells in lymphocytic myocarditis patients
Box-and-whisker plot depiction of the number of (A) neutrophilic granulocytes (B) lymphocytes and (C) macrophages per mm², quantified in tissue obtained from the left and right ventricles (LV and RV; left graph) and the left and right atria (LA and RA; right graph) of control patients (n=5) and patients diagnosed with lymphocytic myocarditis (n=6). In the atria, the infiltrated inflammatory cells in the myocardium (Myo) and the adipose tissue (Adi) were quantified separately. The whiskers represent minimum and maximum values, the boxes the lower and upper quartiles. The black lines within the boxes represent the medians. **: p<0.01 compared to the corresponding cardiac compartment in controls.
Table 1. Correlations in lymphocytic myocarditis patients

<table>
<thead>
<tr>
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<th>LA myocardium vs. LV</th>
<th>RA myocardium vs. RV</th>
<th>LA adipose tissue vs. LA myocardium</th>
<th>RA adipose tissue vs. RA myocardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophilic granulocytes</td>
<td>r=0.771 p=0.103</td>
<td>r=0.086 p=0.919</td>
<td>r=0.314 p=0.564</td>
<td>r=0.100 p=0.950</td>
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<td>Lymphocytes</td>
<td>r=0.200 p=0.714</td>
<td>r=0.886 p=0.033</td>
<td>r=0.200 p=0.714</td>
<td>r=0.200 p=0.783</td>
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<tr>
<td>Macrophages</td>
<td>r=0.771 p=0.103</td>
<td>r=0.943 p=0.017</td>
<td>r=0.600 p=0.350</td>
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Macrophages
Macrophages most abundantly infiltrated the hearts of lymphocytic myocarditis patients. Increased macrophages were found in the myocardium of the left and right ventricle and the left and right atria, although the increased cell numbers were not found to be statistically significant (figure 2C). Similarly, in the adipose tissue of the left atrium, a non-significant increase in macrophages was found. No increased macrophage numbers were observed in the right atrial adipose tissue. Macrophage numbers did not differ significantly between ventricles and atria, but correlated strongly between the left ventricle and atrium and the right ventricle and atrium, as well as between the adipose tissue and myocardium of both atria (table 1).

Inflammatory cell quantification in catecholamine-induced myocarditis

Neutrophilic granulocytes
Catecholamine-induced myocarditis patients showed an increase in neutrophilic granulocytes in the myocardium of the left and right ventricle and the left and right atrium, which was significant only for the right atrium (p=0.016; figure 3A). In the right atrial adipose tissue, neutrophilic granulocytes were also significantly increased (p=0.032). Neutrophilic granulocyte numbers did not differ between ventricles and atria, though correlated strongly between the right ventricle and atrium as well as the adipose tissue and myocardium of the left atrium, and correlated moderately (medium) between left ventricle and atrium (table 2).

Lymphocytes
In catecholamine-induced myocarditis patients lymphocyte numbers were increased in the myocardium of the left and right ventricle and the left and right atrium, which was significant for the left ventricle only (p=0.0079; figure 3B). Also in the adipose tissue of both atria an increase in lymphocytes was found, which
Figure 3. Inflammatory cells in catecholamine-induced myocarditis patients
Box-and-whisker plot depiction of the number of (A) neutrophilic granulocytes, (B) lymphocytes and (C) macrophages per mm², quantified in tissue obtained from the left and right ventricles (LV and RV; left graph) and the left and right atria (LA and RA; right graph) of control patients (n=5) and patients diagnosed with catecholamine-induced myocarditis (n=5). In the atria, the infiltrated inflammatory cells in the myocardium (Myo) and the adipose tissue (Adi) were quantified separately. The whiskers represent minimum and maximum values, the boxes the lower and upper quartiles. The black lines within the boxes represent the medians. *: p<0.05 compared to the corresponding cardiac compartment in controls. **: p<0.01 compared to the corresponding cardiac compartment in controls.
Table 2. Correlations in catecholamine myocarditis patients

<table>
<thead>
<tr>
<th></th>
<th>LA myocardium vs. LV</th>
<th>RA myocardium vs. RV</th>
<th>LA adipose tissue vs. LA myocardium</th>
<th>RA adipose tissue vs. RA myocardium</th>
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</thead>
<tbody>
<tr>
<td>Neutrophilic granulocytes</td>
<td>r=0.300 p=0.683</td>
<td>r=0.900 p=0.08</td>
<td>r=0.500 p=0.450</td>
<td>r=-0.100 p=0.950</td>
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<tr>
<td>Lymphocytes</td>
<td>r=-0.200 p=0.783</td>
<td>r=-0.100 p=0.950</td>
<td>r=0.000 p=1.000</td>
<td>r=0.000 p=1.000</td>
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<tr>
<td>Macrophages</td>
<td>r=0.800 p=0.133</td>
<td>r=0.600 p=0.350</td>
<td>r=0.500 p=0.450</td>
<td>r=0.500 p=0.450</td>
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was significant for the left atrium (p=0.016). Lymphocyte numbers were significantly higher in the left ventricle compared to the left atrium (p=0.032), although no correlations were found between the ventricles and atria, nor between adipose tissue and myocardium of the atria (table 2).

Macrophages
Catecholamine-induced myocarditis patients also showed an increase in macrophages in the myocardium of the left and right ventricle and the left and right atrium, which was significant for both the left and right ventricle (both p=0.0079) and the left and right atrium (p=0.0079 and p=0.0159 respectively; figure 3C). In the adipose tissue of the left atrium a large increase in macrophages was also observed, although this increase was not found to be statistically significant. Macrophage numbers did not differ significantly between ventricles and atria. However, macrophage numbers correlated strongly between atrium and ventricle for both sides of the heart, as well as between adipose tissue and myocardium of both atria (table 2).

Notably, the numbers of neutrophilic granulocytes, lymphocytes and macrophages in the atria did not differ significantly between lymphocytic myocarditis and catecholamine-induced myocarditis patients.

Atrial fibrosis
It is known that atrial inflammation can stimulate the formation of atrial fibrosis, which by itself increases the risk of AF development. Therefore we determined whether the increased inflammatory cell numbers in the atria of our included myocarditis patients is accompanied by an increased amount of collagen in the atrial myocardium. In the right atrium of lymphocytic myocarditis patients, the
observed a decreased amount of collagen compared to control patients and catecholamine-induced myocarditis patients (figure 4A). However, no significant differences were found in the percentage of collagen in the myocardium of control patients compared to lymphocytic or catecholamine-induced myocarditis patients for both atria. Interestingly, for all three patient groups we observed an increased amount of collagen in the right atria compared to the left atria of the same patient group (figure 4B), which was significant for control patients (p=0.032) and lymphocytic myocarditis patients (p=0.026, figure 4A).

**DISCUSSION**

The aim of this study was to quantify the infiltration of inflammatory cells in the atria of patients diagnosed with myocarditis based on the ventricles. In lymphocytic myocarditis patients we observed a significant increase for lymphocytes in the left atrial adipose tissue only. Next to these patients, the atrial myocarditis in catecholamine-induced myocarditis patients appeared more extensively. In the myocardium and adipose tissue of the right atrium, a significant increase was observed for neutrophilic granulocytes, for lymphocytes in the left atrial adipose tissue, and for macrophages in the myocardium of
both atria. The numbers of infiltrating inflammatory cells in the atrial myocardium correlated positively with those in the ventricles, especially in catecholamine-induced myocarditis patients.

Myocarditis is commonly diagnosed via (immuno)histological analysis of endomyocardial biopsies obtained from the ventricles. Atrial myocarditis has been observed before in atrial tissue obtained post mortem from young patients after sudden death\(^{20}\) and in atrial tissue obtained from living patients with idiopathic enlargement of bilateral atria,\(^{21}\) with transient sinoatrial disease\(^{22}\) and with atrial giant cell myocarditis.\(^{23}\) In all these cases however, atrial myocarditis occurred in the absence of ventricular myocarditis. Here, we demonstrate for the first time that atrial myocarditis also occurs in patients diagnosed with ventricular myocarditis.

Atrial myocarditis coincided with ventricular myocarditis of different aetiology, i.e. lymphocytic myocarditis, which in majority is caused by viral infection and/or resulting autoimmunity and catecholamine-induced myocarditis. In our study, atrial myocarditis appeared to be most pronounced in catecholamine-induced myocarditis patients, although the extent of the inflammatory infiltrate did not differ significantly between both myocarditis patient groups. As local catecholamine overload is considered an important cause of ventricular catecholamine-induced myocarditis,\(^{24}\) such catecholamine overload may underlie atrial myocarditis as well, all the more since adrenergic receptor-protein coupling in human atrial cardiomyocytes appears similar to ventricular cardiomyocytes.\(^{25}\) In addition, in catecholamine-induced myocarditis an elevated blood pressure is expected, as high levels of catecholamines can result in hypertension.\(^{26}\) This in turn could result in pressure overload and stretching of cardiomyocytes in the heart, including the atria. Stretching of atrial cardiomyocytes has been shown to promote inflammation.\(^{27}\) Interestingly, circulating catecholamine levels were also found to be increased in a mouse model of virus-induced myocarditis,\(^{28}\) suggesting the possibility that enhanced catecholamine release may also be an underlying cause of atrial involvement in lymphocytic myocarditis. Alternatively, viral infection of the atria could also directly cause atrial myocarditis in lymphocytic myocarditis patients. In a mouse model of coxsackievirus B3-induced myocarditis, atrial myocarditis was also induced and coincided with high virus titres in the atria.\(^{29}\) However, viral infection of the atria coinciding with viral infection of the ventricles in humans has not been reported yet. Unfortunately, in our lymphocytic myocarditis patients, no culprit virus was determined. Lastly, autoimmunity against cardiomyocytes, an important co-founder of cardiac damage and inflammation in myocarditis, may underlie atrial myocarditis. Indeed, in a rat model of experimental autoimmune myocarditis, inflammatory lesions were observed in the atria as well.\(^{30}\) The mechanisms underlying the concomitant atrial myocarditis in myocarditis of both aetiologies remain to be determined.

The clinical relevance of the atrial myocarditis we describe here also remains to be established. As mentioned above, myocarditis is listed as a cardiac precursor for AF\(^{8}\)
and AF is found in 14% of patients with suspected myocarditis. Furthermore, local and systemic inflammation have been implicated in the pathophysiology of AF, ranging from observed increased local and systemic production of pro-inflammatory cytokines to increased inflammatory cell infiltration in the atria in patients with lone AF. Therefore, although the myocarditis patients included in this study did not have symptomatic AF, the increase in atrial inflammatory cell infiltration may indicate a predisposition toward the development of AF. Our finding of increased inflammatory cell infiltration in the adipose tissue of the atria is also of interest, as a role for atrial adipose tissue in AF has been postulated. An association has been described between atrial epicardial adipose tissue volume and AF. In our study, we found no clear relation between adipose tissue volume and inflammatory cell numbers (not shown). Nonetheless, atrial adipose tissue may be an important source of pro-inflammatory cytokines such as IL-6, TNF-α and MCP-1, which may induce AF. Infiltrated inflammatory cells could in theory add to this paracrine effect. Moreover, a recent study showed that the inflammatory activity of epicardial adipose tissue is was significantly increased in patients with AF. Additionally, we observed in left atrial appendage tissue of AF patients that inflammatory cells also infiltrated the adipose tissue. This is similar to the present study, where we also observed an increase in atrial inflammation, especially in the adipose tissue. This similarity in observations in AF patients and myocarditis patients suggests, but does not prove, that adipose tissue inflammation may precede AF in myocarditis patients.

As mentioned above, inflammation can induce the formation of atrial fibrosis, which increases the risk of AF development. In our analysis however, atrial myocarditis did not coincide with an increase in atrial fibrosis. As no increase was observed between patient groups, this analysis provides no further insight into whether the observed atrial myocarditis precedes AF. However, the amount of collagen did differ between left and right atria of the same patient group. It is already known that left and right atrium differ in morphology and gene expression profile. To the best of our knowledge however, this difference in intramyocardial collagen deposition has never been described before and further indicates that left and right atrium may respond differently to myocarditis.

**Study Limitations**
The main limitation of this study is the limited amount of pre-death patient information. In the myocarditis patients, myocarditis was diagnosed post-mortem. For most patients therefore, no data was recorded of cardiac function or events that can be linked to the catecholamine exposure that triggered catecholamine-induced myocarditis. A second limitation is the small patient group sizes. Finally, in a post-mortem setting such as presented here, it is not possible to firmly prove that the observed atrial myocarditis indeed predisposes patients with ventricular myocarditis into developing AF. Prospective studies in living myocarditis patients are required for this.
Conclusion
In this study we demonstrated that ventricular myocarditis coincides with atrial myocarditis. The observed atrial myocarditis may predispose patients to the development of AF and subsequent complications such as sudden cardiac death and heart failure. However, although the link between inflammation and AF has been firmly established, the causal relation between the two remains a topic of controversy. Prospective studies in living patients will be necessary to determine whether the observed atrial myocarditis indeed predisposes towards AF.

References