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# Different structural remodelling in atrial fibrillation with different types of mitral valvular diseases

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**Aims** The aim of this study was to determine the relationship between atrial structural remodelling and atrial fibrillation (AF) for different types of mitral valvular diseases (MVDs).

**Methods and results** Left atrial appendages tissue samples were obtained from 24 patients with MVDs undergoing mitral valve replacement surgery. Masson's trichrome staining and immunohistochemical staining were performed to assess the extent of the fibrosis. Ultrastructural changes in left atrial appendages were examined by electron microscope. The degree of fibrosis showed significant increases in patients with AF compared with patients with sinus rhythm (SR) ($P = 0.023$). The collagen volume fraction (CVF) of fibrosis significantly increased in mitral stenosis and atrial fibrillation (MS-AF) compared with the mitral regurgitation and atrial fibrillation (MR-AF) group ($P = 0.043$). Collagen Type I levels were significantly increased in AF patients with mitral stenosis compared with AF patients with mitral regurgitation ($P = 0.043$). Different CVF of Matrix metalloproteinases-2 was present between the MS-SR group and the MS-AF group ($P = 0.001$). Electron microscopy revealed normally structured sarcomeres with a predominance of loosely packed cardiomyocytes in samples from patients with SR. Fibrotic bands, which tended to separate individual cardiomyocytes, were apparent in samples from patients with AF.

**Conclusion** Atrial structural remodelling is associated with AF patients with MVDs. Different heart rhythm statuses with different types of MVDs are associated with variable atrial structural remodelling. Different atrial structural remodelling is a mechanism that may contribute to the increased risk of AF with MVDs.

**Keywords** Atrial fibrillation • Mitral valvular disease • Structural remodelling • Fibrosis

## Introduction

In recent years, atrial fibrillation (AF) has become the most common serious cardiac arrhythmia encountered in clinical practice, accounting for approximately one-third of all cardiac rhythm disturbance-associated hospitalizations.[1,2] Despite this, the detailed mechanism of AF is not fully elucidated. Recently, findings from several experimental studies and clinical investigations have indicated that atrial structural remodelling may play a role in the process of AF.[3–5]

Mitral valvular diseases (MVDs) are strongly related to AF, but the prevalence of AF in mitral stenosis (MS) and mitral regurgitation (MR) are not the same. The majority of patients with MS eventually develop AF; however, fewer patients with MR develop AF. Diker *et al.*[6] and Schwartz *et al.*[7] reported that AF occurred in 29% of patients with isolated MS and in 16% with isolated MR.

We hypothesized that the relationship between structural remodelling and AF may be associated with underlying heart disease. It is unclear whether atrial structural remodelling is associated with persistent AF in patients with MVDs, or whether AF

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patients with different types of MVDs are associated with variable atrial structural remodelling. The purpose of this study was to assess the relationship between atrial structural remodelling in AF patients with different types of MVDs.

# Methods

## Patients

The study group consisted of 24 MVDs patients scheduled for mitral valve replacement surgery. Twelve patients had a history of persistent AF (six each with MS and MR) and 12 with sinus rhythm (SR) (six each with MS and MR). Patients with persistent AF formed the AF group, while those with SR were designated as the SR group. Patients were further divided into subgroups according to the type of MVDs (i.e. MS-SR, MR-SR, MS-AF, and MR-AF).

Patients were excluded from the study on the basis of the following criteria: treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers within 1 month, existence of any other valvular stenosis or regurgitation other than mild, recent infection (within 1 month), previous cardiac surgery, hypertension, or any medical condition that, in the opinion of the investigators, could render the patient inappropriate for the study. Pregnant women and women who could become pregnant were also excluded from the study.

Before surgery all patients underwent echocardiographic evaluation for the determination of left and right atrial dimensions (LAD, RAD), left and right ventricular dimensions (LVD, RVD), left ventricular ejection fraction (LVEF), and left ventricular fractional shortening (LVFS).

The study was approved by the institutional Ethics committees for research and after getting informed consent from patients.

## Specimen preparation

Samples of the left atrial appendages were obtained from each patient during mitral valve replacement surgery before extracorporeal circulation. Tissue samples were prepared for pathological examination and electron microscopy.

## Masson's trichrome staining for fibrosis

Left atrial tissue samples were fixed in 10% formalin, then imbedded in paraffin according to the standard procedures, and were cut into slices of $\sim$5 $\mu$m thickness. The slices were deparaffinaged by dimethyl benzene and soaked into a series of gradient concentration from 100 to 75% of alcohol. Then the slices were put into haematine solution dyed for 5 min, then into acid water and ammonia water for 30 s separately. After being washed in distilled water for $\sim$1 h, they were dewatered in 70 and 90% alcohol for 10 min. After that, they were dyed in eosin liquid for 2–3 min, dewatered, and mounted with neutral gum.

Masson's trichrome staining was used to evaluate the extent of fibrosis in all sections. Collagen volume fraction (CVF) as the percentage of atrial cross-sectional area comprised of fibrous tissue was measured.

## Immunohistochemical staining for collagen Type I, collagen Type III, MMP-2, MMP-9, TIMP-1, and TIMP-2

Slices were incubated with primary antibodies: rabbit anti-human of collagen Type I, matrix metalloproteinases-2 (MMP-2), and tissue inhibitor of metalloproteinase-2 (TIMP-2) and rabbit anti-human of collagen Type III, MMP-9, and TIMP-1 (Bios, Beijing, China) overnight, after being washed in phosphate buffered solution three times, each for 5 min. Slices were incubated with peroxidase-labelled goat anti-rabbit immunoglobulin G (Bios). The streptavidin–biotin complex was added after the second washing and then washed again for the third time. The double antibody, substrate of peroxydase, was then added to produce yellow-brown substance that could be seen under the microscope. Images were viewed using an Olympus microscope with a DP70 digital camera, and assessed using image-Pro Plus 5.1 software.

## Electron microscope examination

Tissues samples were modified into 1 $mm^3$ and fixed in 3% glutaraldehyde for 3 h. After being washed in 0.1 mol/L cacodylic acid buffer solution five times for 4 h, the tissues were fixed with 1% osmic acid. They were then soaked into 50, 70, 80, 90% alcohol for 10 min separately to be dewatered, then into 90% acetone for 10 min, and 100% acetone three times for 10 min. The tissues were saturated in mixed liquor of acetone and extemporized epoxide resin embedding medium with the ratio of 1:1 for 1 h, then in the 1:3 mixtures for 3 h, and at last in pure embedding medium for 1 h. In the end, the tissues were embedded in capsules. Next, they were put in a thermostat oven at the temperature of 35°C overnight for the imbedding medium to polymerize. Then, 70-nm ultrathin sections were cut out from the tissues. The sections were soaked in a saturate uranyl acetate solution, heated by microwave for 30 s, and then washed in a buffer solution. Finally, the sections were air dried for observation.

## Statistical analysis

All the data in this study are presented as mean $\pm$ standard deviation (SD) for continuous variables; frequencies were measured for categorical variables. Baseline characteristics were examined for statistical significance of continuous variables by an unpaired Student's *t*-test, and the $\chi^2$ test was performed for categorical variables. Differences were considered statistically significant when $P < 0.05$. All statistical analyses were performed with SPSS 13.0 for Windows.

# Results

## Clinical characteristics

The clinical characteristics of the study population are summarized with respect to heart rhythm status in *Table 1*. There were significant differences in the echocardiographic findings pertaining to LAD, RAD, LVEF, or LVFS between the AF and the SR groups ($P < 0.05$). No significant differences between the AF and the SR group were apparent in RVD or LVD ($P > 0.05$).

The characteristics of the MS-AF and MR-AF subgroups are summarized in *Table 2*. There were no significant differences between these groups in the echocardiographic findings pertaining to LAD, RAD, LVEF, or LVFS ($P > 0.05$).

## Masson's trichrome staining results

Masson's trichrome staining was used to evaluate the degree of interstitial fibrosis in the left atrial appendage (*Figure 1*). In the left atrial appendages, an increased degree of interstitial fibrosis was seen both in MS and MR with AF patients; patients with MS-AF had even thicker fibrotic septa forming, which isolated islands of myocytes.

Bar graphs showed quantitative comparison of fibrosis by heart rhythm status with different types of MVDs (*Figure 2*). The degree

**Table 1 Characteristics of the study group patients by the heart rhythm status**

| | SR ($n = 12$) | AF ($n = 12$) | *P*-value |
|---|---|---|---|
| Age (years) | 37 ± 11 | 45 ± 9 | 0.11 |
| Gender (M/F) | 5/7 | 6/6 | 0.82 |
| NYHA (II/III) | 6/6 | 4/8 | 0.51 |
| LAD (mm) | 47 ± 7 | 57 ± 11 | 0.01 |
| LVD (mm) | 51 ± 13 | 53 ± 12 | 0.76 |
| RAD (mm) | 37 ± 6 | 52 ± 11 | 0.00 |
| RVD (mm) | 19 ± 2 | 22 ± 5 | 0.23 |
| LVEF (%) | 64 ± 7 | 56 ± 11 | 0.04 |
| LVFS (%) | 36 ± 5 | 30 ± 8 | 0.03 |

AF, atrial fibrillation; SR, sinus rhythm; F, female; M, male; NYHA, New York Heart Association; LAD, left atrial dimension; LVD, left ventricular dimension; RAD, right atrial dimension; RVD, right ventricular dimension; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening.

**Table 2 Characteristics of the atrial fibrillation patients by mitral valvular disease type (MS and MR)**

| | MS-AF ($n = 6$) | MR-AF ($n = 6$) | *P*-value |
|---|---|---|---|
| Age (years) | 49 ± 13 | 44 ± 4 | 0.74 |
| Gender (M/F) | 2/4 | 4/2 | 0.72 |
| Duration of AF (months) | 48 ± 39 | 38 ± 9 | 0.62 |
| NYHA (II/III) | 2/4 | 2/4 | 0.51 |
| LAD (mm) | 59 ± 9 | 54 ± 11 | 0.21 |
| LVD (mm) | 48 ± 11 | 57 ± 14 | 0.14 |
| RAD (mm) | 52 ± 9 | 52 ± 15 | 0.79 |
| RVD (mm) | 24 ± 5 | 20 ± 3 | 0.71 |
| LVEF (%) | 57 ± 11 | 55 ± 13 | 0.53 |
| LVFS (%) | 31 ± 6 | 30 ± 8 | 0.88 |

MS, mitral stenosis; MR, mitral regurgitation; AF, atrial fibrillation; F, female; M, male; NYHA, New York Heart Association; LAD, left atrial dimension; LVD, left ventricular dimension; RAD, right atrial dimension; RVD, right ventricular dimension; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening.

of fibrosis showed significant increases of the collagen in patients with AF compared with patients with SR (5 ± 2% and 8 ± 1%, $P = 0.023$). The CVF of fibrosis significantly increased in the MS-AF compared with the MS-SR group (5 ± 1% and 10 ± 1%, $P = 0.008$). Likewise, the CVF of fibrosis significantly increased in patients with MR-AF in comparison with patients in MR-SR (4 ± 1% and 8 ± 1%, $P = 0.037$).

Subsequently, we focused on the influence of different types of MVDs (MS and MR) on fibrosis production in the AF group patients. Subgroups of AF patients with different types of MVDs exhibited different extent of increase in fibrosis; the results are shown in *Figure 2*. We found fibrosis expressed a significant increase in MS-AF patients compared with that in patients with MR-AF (10% ± 2% and 8% ± 1%, $P = 0.043$).

## Immunohistochemical staining results for collagen Type I and collagen Type III

Significant increases in Type I and Type III collagen were found in samples from patients with AF compared with samples from patients with SR [Type I (4 ± 1% and 6 ± 2%, $P = 0.021$) and Type III (3 ± 3% and 6 ± 2%, $P = 0.001$)]. The content of both collagen Type I and III was significantly increased in the MS-AF compared with the MS-SR group [Type I (4 ± 1% and 7 ± 2%, $P = 0.006$) and Type III (4 ± 1% and 7 ± 1%, $P = 0.017$)]. Likewise, collagen Type I and III levels were significantly higher in patients with MR-AF compared with those with MR-SR [Type I (3 ± 1% and 5 ± 2%, $P = 0.012$) and Type III (2 ± 2% and 5 ± 2%, $P = 0.023$)].

The subgroups of AF patients with different types of MVDs exhibited differing degrees of increase in collagen Type I and III. Collagen Type I content was significantly increased in MS-AF patients compared with MR-AF patients (7 ± 2% and 5 ± 2%, $P = 0.043$). Collagen Type III content was slightly increased in the MR-AF group compared with the MS-AF group, but did not reach significant difference (7 ± 1% and 5 ± 2%, $P = 0.210$).

## Immunohistochemical staining results for MMP-2, MMP-9, TIMP-1, and TIMP-2

Left atrial appendage biopsies of total AF patients with mitral valve disease had a significantly higher CVF of MMP-2 compared with SR patients with MVDs (6 ± 1% and 9 ± 2%,$P = 0.021$). Different CVF of MMP-2 was present between the MS-SR group and the MS-AF group (6 ± 1% and 10 ± 3%, $P$=0.001). Interestingly, the CVF of MMP-2 showed a tendency to rise in the MS-AF group as compared with that in the MR-AF group, but there was no difference present between the MR-SR group and the MR-AF group (6 ± 2% and 8 ± 1%, $P = 0.347$).

The CVF of TIMP-2 increased significantly in the MS-AF group in comparison with that in the MS-SR group (4 ± 3% and 7 ± 2%, $P = 0.038$), but no difference in CVF of TIMP-2 was present between the total AF group and the total SR group (4 ± 2% and 6 ± 2%, $P = 0.412$), and no difference was present between the MR-SR group and the MR-AF group (5 ± 1% and 6 ± 2%, $P = 0.534$).

There were no differences in CVF of MMP-9 and TIMP-1 among the four groups.

## Electron microscope results

Electron microscopy was used to characterize structural alterations at higher resolution. Representative electron micrographs of left atrial appendages tissue samples from patients with different types of MVDs and AF or SR can be seen in *Figure 3*. In the SR groups (*Figure 3A*, *C*), atrial myocytes were connected mainly at the true end of the cell via intercalated discs. Normal, regularly structured sarcomeres were evident, surrounded by rows of mitochondria. Cardiomyocytes were often tightly assembled. Contrastingly, cardiomyocytes in the AF groups (*Figure 3B*, *D*) tended to be loosely packed due to the presence of fibrotic bands, which served to separate individual cardiomyocytes. In the AF group, the following typical structural changes were observed: (i) perinuclear accumulation of glycogen; (ii) numerous abnormally shaped

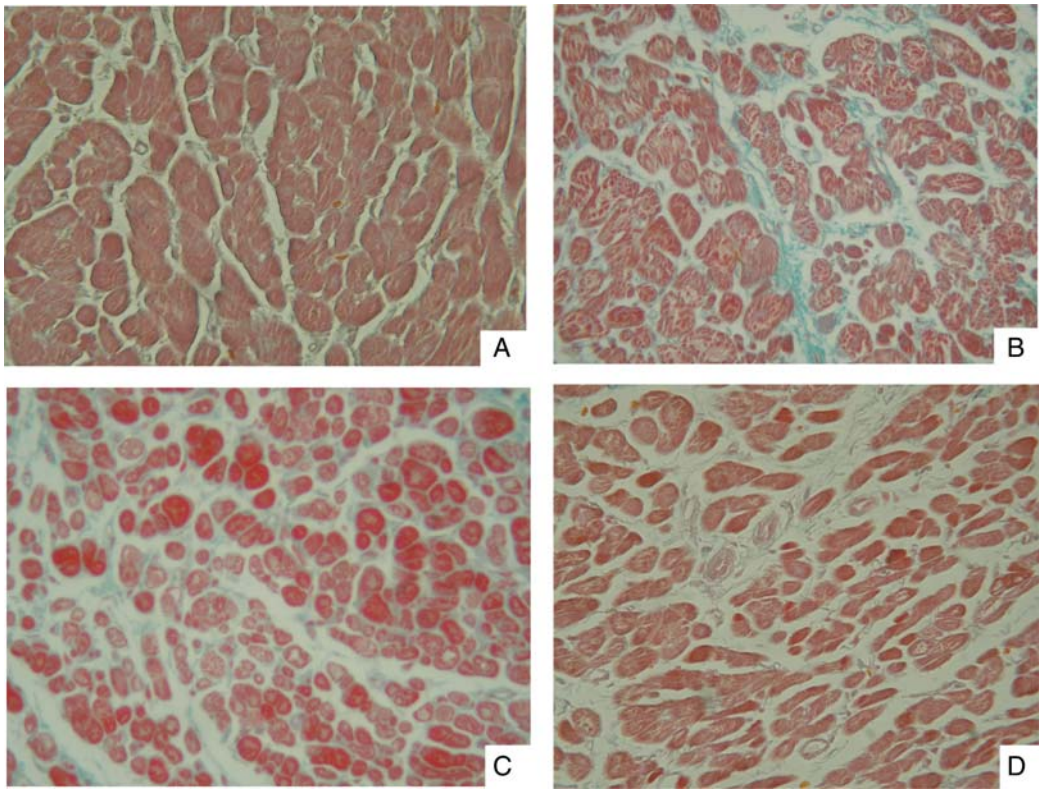


**Figure 1** (*A*) MS-SR, (*B*) MS-AF, (*C*) MR-SR, and (*D*) MR-AF, Masson's trichrome stained results. Compared with the SR groups (*A* and *C*), remarkable fibrosis was present in the AF groups (*B* and *D*). In the AF groups (*B* and *D*), fibrosis was even more pronounced with individual myocytes separated by fibrotic tissue in MS-AF patients (*B*). Magnification ×400. MS, mitral stenosis; SR, sinus rhythm; AF, atrial fibrillation; MR, mitral regurgitation.

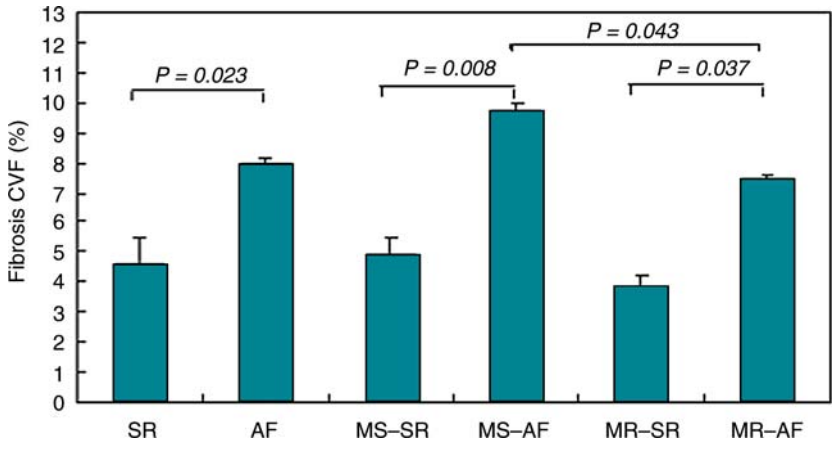


**Figure 2** CVF of fibrosis by heart rhythm status with different types of MVDs. CVF, collagen volume fraction; MVD, mitral valvular disease.

mitochondria (mitochondria took on an elongated shape with longitudinal-orientated cristae); (iii) remnants of sarcoplasmic reticulum, sarcomere disruption; (iv) numerous secondary lysosome-like bodies; (v) widening of the undifferentiated portions of the intercalated discs; (vi) hypertrophy of atrial myocytes; and vii) enlarged and lobulated nucleoli.

Although abnormal structural changes were present in AF patients, variable typical structural changes were observed between the different groups (MS-AF and MR-AF). In AF patients with MS, the most prominent structural change was the presence of muscle bundles surrounded by thick connective tissue fibres. These thick fibres were also present between the single muscle

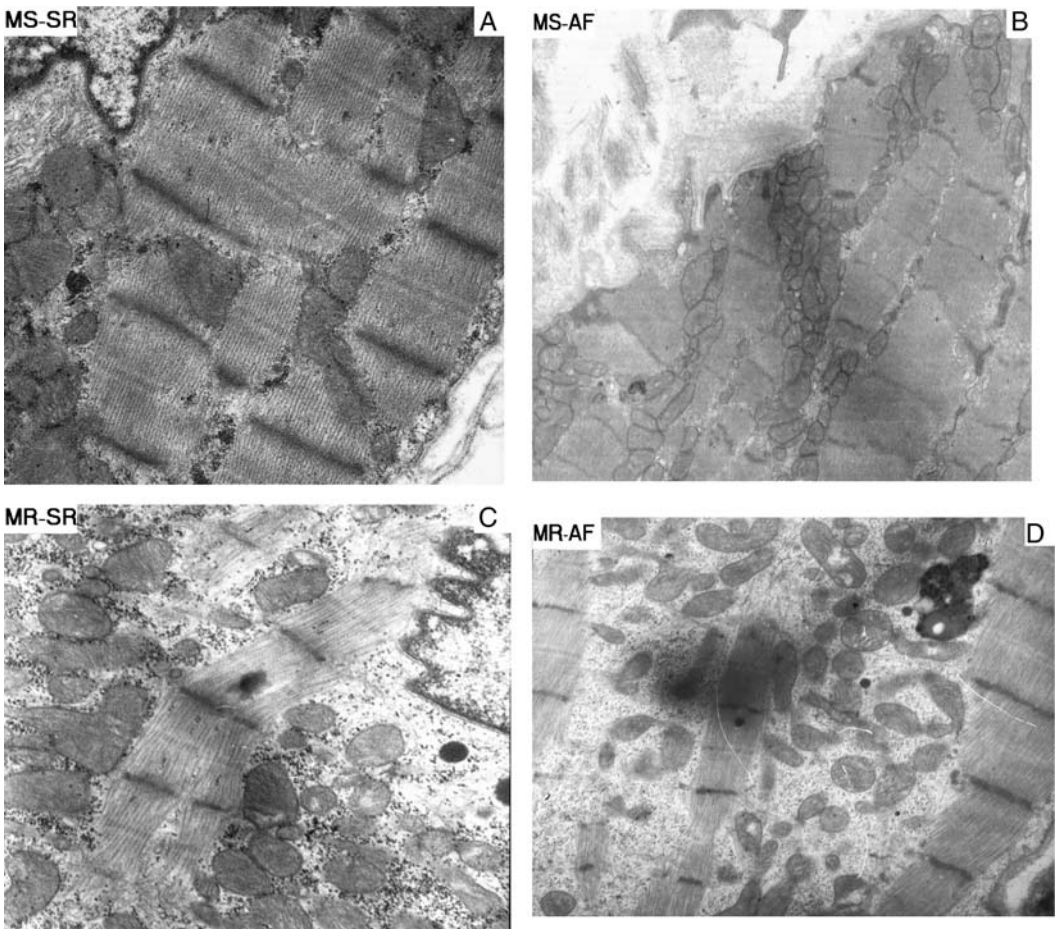


**Figure 3** (*A*–*D*) Electron microscopy results. In the SR groups (*A* and *C*), atrial myocytes with regular sarcomere organization and muscle striations could be seen clearly. Few collagen fibres showed between muscles cells (*A*). The cell nucleus was oval shaped, glycogen accumulated slightly in some region. Mitochondria showed diffused distribution (*C*). In the AF groups (*B* and *D*), mitochondria proliferated and gathered into clusters, and muscle bundles were surrounded by thick connective tissue fibres. These thick fibres were also present between the single muscle cells or cardiomyocytes separating cells from each other (*B*). Perinuclear accumulation of glycogen and disruption of cardiac muscle fibres could be seen (*D*). Original magnification, ×10 000 (*A*), ×8000 (*B*), ×15 000 (*C*), and ×10 000 (*D*). SR, sinus rhythm; AF, atrial fibrillation.

cells or cardiomyocytes separating cells from each other (*Figure 3B*). Samples from MR-AF patients exhibited typical degenerative features including numerous secondary lysosome-like bodies, myolytic areas with glycogen accumulation, and numerous abnormally shaped mitochondria. Disruption of cardiac muscle fibres was also evident. (*Figure 3D*).

## Discussion

To the best of our knowledge, this is the first study to report a relationship between structural remodelling and persistent AF with different types of MVDs. Fibrosis and ultrastructural alterations are two important features of structural remodelling.[8,9] We found that the interstitial fibrosis increased to different extents in AF patients with different types of MVDs. Interestingly, electron microscopy also revealed different ultrastructural alterations in AF patients with different types of MVDs.

Fibrosis is a hallmark of structural remodelling. Once atrial fibrosis has occurred, it is only partly reversible and contributes to sustain AF.[10] Atrial fibrosis is characterized by excessive deposition of extracellular matrix that can occur as a result of mechanical overload of the tissue combined with the action of other profibrotic factors or tissue damage.[11] The major components of the extracellular matrix are collagen I and collagen III.[12] Collagen I is the major collagenous product of cardiac fibroblasts and accounts for ~80% of total cardiac collagen content. Collagen Type III is relatively abundant in the myocardium, where it constitutes to 10% of total collagen content.[13] In our study, concordant changes existed between the extent of interstitial fibrosis and collagen Type I. We found that both collagen Type I and III content were significantly enhanced in AF patients with MVDs compared with SR patients with MVDs. However, AF patients with different types of MVDs exhibited different degrees of increase in collagen content. The increase in collagen Type I was more pronounced in AF patients with MS than in those with MR. The increase in

collagen Type III content was slightly more pronounced in the MR-AF group patients, but not significantly so. These findings highlight the association between atrial fibrosis and AF in patients with different types of MVDs.

Matrix metalloproteinases are a family of proteolytic enzymes that regulate the extracellular matrix turnover together with the inhibitory mediators of the MMPs called TIMPs.[14] We selected MMP-2, MMP-9, TIMP-1, and TIMP-2 to investigate the mechanism of fibrosis in AF patients with different types of MVDs in the present study. In this study, we observed an increase expression of MMP-2 in AF patients with MS and no change in AF patients with MR. Concordant changes between MMP-2 and fibrosis during MS suggest the involvement of MMP-2 in atrial structural remodelling in MS patients. This suggests that atrial volume overload due to MS may lead to an increased atrial MMP-2 expression, which in turn will lead to an increased presence of atrial fibrosis. On the basis of the data, MMP-2 is not responsible for patients with MR and AF. There were no differences in the CVF of MMP-9 among the four groups. We observed an increased expression of MMP-2 in MS-AF patients and no changes in MMP-9. Our findings are consistent with Xu who found an increased expression of MMP-2, and are in contrast with the previous studies from Nakano who reported an upregulation of MMP-9.[15,16] The differences between these studies and ours could be explained by the fact that they studied a heterogeneous AF population. Different types of MVDs with different cardiac rhythms lead to different activation extent of MMP-2. In addition, all our patients have already suffered for many years from mitral valve disease and/or AF. As for the TIMP-1 and TIMP-2, we demonstrated that the CVF of TIMP-2 only increased in the MS-AF group. We also demonstrated that the expression of the MMP-2 increased more in the atria of the MS-AF group than that of the MS-SR group. Together with our data, these observations suggest that the abnormal CVF of MMP-2 is a strong candidate for being associated with the atrial structural remodelling during MS with AF. As the MMP-2 overexpressed, the TIMP-2 compensatingly increased, but it did not catch up with the MMP-2 increase, and the MMP-2/TIMP-2 balance broke down, thus possibly resulting in fibrosis in MS with AF.

Ultrastructural alterations are another hallmark of structural remodelling. Bailey *et al.*[17] reported the first study in which atrial myocardium of living patients with AF was examined. Electron microscopic studies revealed that atrial myocyte structural alterations included the following: cardiomyocyte volume increase, myolysis, accumulation of glycogen, connexin alterations, mitochondrial shape changes, the absence of sarcoplasmic reticulum, and homogeneous distribution of chromatin.[17] Mary-Rabine *et al.*[18] described atrial ultrastructure in 121 patients who underwent cardiac surgery, 23 of whom had AF. Atrial biopsies obtained from patients with AF revealed ultrastructural abnormalities such as loss of myofibrils and disorganization of sarcoplasmic reticulum. Similar electron microscopic findings were observed in our study. In general, samples from different subgroups of patients with AF exhibited similar ultrastructural alterations; however, some differences did exist. The extent of ultrastructural alteration was greater in AF patients with MS than in AF patients with MR. A pathognomonic feature of AF patients with MS was fibrotic bands, which tended to separate individual cardiomyocytes and membrane invaginations of the sarcolemma. Samples from AF patients with MR exhibited typical degenerative features such as numerous secondary lysosome-like bodies, myolytic areas with glycogen accumulation, numerous abnormally shaped mitochondria, and clumping of nuclei. Disruption of cardiac muscle fibres was also evident. The presence of such extensive ultrastructural alterations suggests that the mechanisms initiating and maintaining AF may be diffusely located and be different in patients with MS and MR.

The interpretation of different atrial structural remodelling in patients with AF and MVDs is difficult. Atrial structural remodelling involves multifactorial processes that result from complex interactions among neurohormonal and cellular mediators.[19] At the same time, the different types of MVDs have different underlying pathophysiological or haemodynamic mechanisms. There are many different pathophysiological alterations in different forms of mitral lesions; pressure and volume overload occur in MS, while relatively pure volume overload occurs with MR.[20]

## Study limitations

The most important limitation of the study is sample size, since it might have been possible to observe further significant differences in a larger study sample. However, we believe that our results may help to clarify the relationship between structural remodelling and AF in patients with MVDs. Secondly, although our results indicate an association between structural remodelling and AF, a cause and effect relationship cannot be established.

## Conclusions

Atrial structural remodelling is associated with persistent AF patients with MVDs. The extent of atrial structural remodelling can be variable with different types of MVDs and heart rhythms. Different structural remodelling is a mechanism that may contribute to the increased risk of AF with MVDs. Our study provides new insight into the structural remodelling that occurs in patients with AF and MVDs. These findings may ultimately facilitate the development of strategies for the treatment of patients with AF and MVDs.

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