# Atrial dysplasia in the atria of humans without cardiovascular disease

Guo-Liang Li,[1,2] Guy Fontaine,[2] Jine Wu,[1] Shuanliang Fan,[3] Chaofeng Sun,[1] Ardan M Saguner[4]

[1]Department of Cardiovascular Medicine, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China
[2]Cardiology Institute, Rhythmology Unit, Hôpital Universitaire La Pitié-Salpêtrière, Paris, France
[3]Forensic Medical College, Xi'an Jiaotong University, Xi'an, China
[4]University Heart Center Zürich, Zürich, Switzerland

**Correspondence to**
Dr Guo-Liang Li, Department of Cardiovascular Medicine, the First Affiliated Hospital of Xi'an Jiaotong University, 277 Yanta West Road, 710061, China; liguoliang_med@163.com

G-LL and GF contributed equally.

Accepted 17 January 2019



**To cite:** Li G-L, Fontaine G, Wu J, *et al*. *J Investig Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jim-2018-000916

## ABSTRACT

Research on atrial histology of humans without cardiovascular disease is scarce. Therefore, our aim was to study human atrial histology in subjects without cardiovascular disease. Histology of the right atrium, left atrium or atrial septum was studied in eight patients (one newborn infant and seven adults) who died of a non-cardiac cause and who were not known to suffer from any cardiovascular pathology. Staining with hematoxylin phloxine saffron or Masson's trichrome was performed to have a better identification of fibrosis and H&E for better identification of lymphocytes. Atrial histology was compared with the histology of the left ventricle and was taken from a collection of standard glass slides. Common light microscopic examination and numeric image processing was performed in all samples. Left atrial histology showed a substantial amount of adipocytes and interstitial fibrosis, associated with replacement fibrosis in some of these cases including one case of lymphocytic infiltrates, similar to the histologic changes of the right ventricle (RV) known in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVD). Furthermore, we identified a perpendicular orientation of atrial myocardial fibres, which is also a feature of the thin RV free wall. A similar histologic substrate to the RV myocardium known in ARVD is found in the atria of humans without an overt cardiovascular pathology. This may explain the high prevalence of atrial fibrillation in the general population.

## Significance of this study

**What is already known about this subject?**

- The right atrium of patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVD) has a similar histologic structure as compared with the right ventricle (RV) of these patients, which may explain the high prevalence of atrial arrhythmias in ARVD.
- Little is known about human atrial histology in subjects without cardiovascular disease.

**What are the new findings?**

- Atrial histology of humans without overt cardiovascular disease showed a substantial amount of adipocytes and interstitial fibrosis, associated with replacement fibrosis in some of these cases including one case of lymphocytic infiltrates, similar to the histologic changes of the RV known in patients with ARVD.
- A perpendicular orientation of atrial myocardial fibers, which is also a feature of the thin RV free wall, was identified. A similar histologic substrate to the RV myocardium known in ARVD is found in the atria of humans without an overt cardiovascular pathology.

**How might these results change the focus of research or clinical practice?**

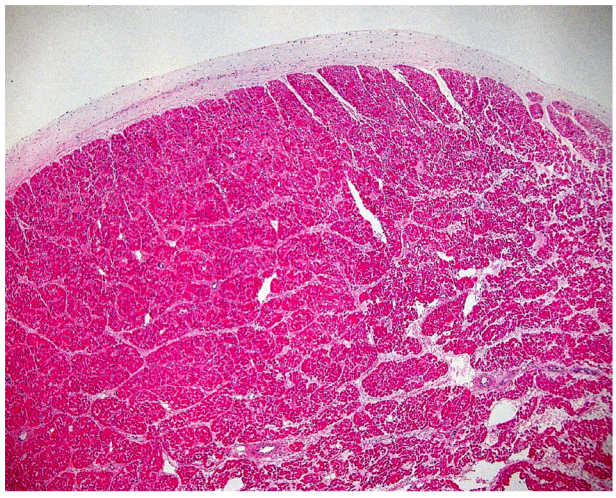
- Our findings may help to better understand the mechanisms underlying the high prevalence of atrial fibrillation in the general population.

## INTRODUCTION

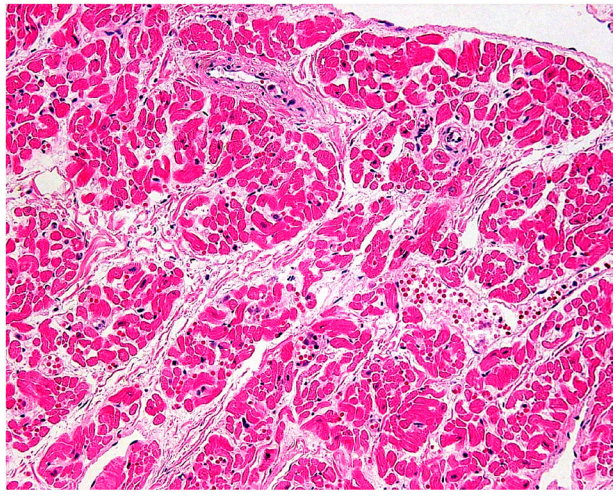
The right atrium (RA) of patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVD) has a similar histologic structure as compared with the right ventricle (RV) of these patients, which may explain the high prevalence of atrial arrhythmias in ARVD.[1] However, the prevalence of atrial fibrillation (AF) is also high in the general population, particularly with advancing age, with AF constituting the most common arrhythmia in the human species.[2] However, the mechanisms underlying this high prevalence in the general population remain less well defined. This relates to the paucity of research on atrial histology of humans without cardiovascular disease, and the difficulty to identify a pathologic substrate within the atria by current imaging modalities.[3] Therefore, in this study, we aimed to investigate the histology of right and left atria, which is considered the gold standard for assessing the pathologic substrate, with respect to the presence of fibrosis, fatty infiltration and inflammation, in a total of seven adults and one newborn infant, who died of non-cardiac causes and who did not previously suffer from an overt cardiovascular pathology.

## METHODS

Atrial histology of the RA and left atrium (LA) was studied in seven adult cases and one



A



B

**Figure 1** The pathologic samples were obtained from a healthy young man who died due to a car accident at the age of 18 years. His medical history was unremarkable. The low magnification displays the full thickness of the right atrial free wall (A: H&E, magnification ×40), and the high magnification was chosen to search for lymphocytes (B, H&E, magnification ×200).

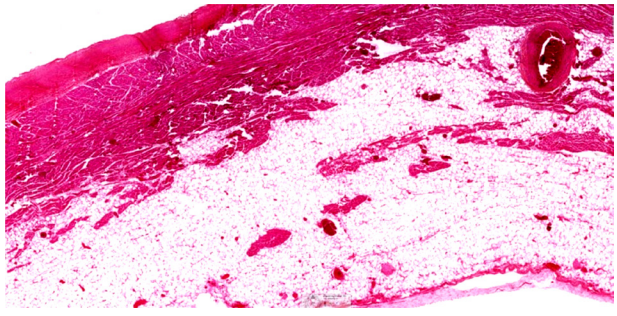
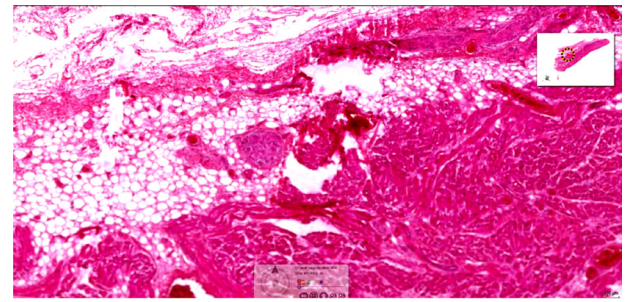
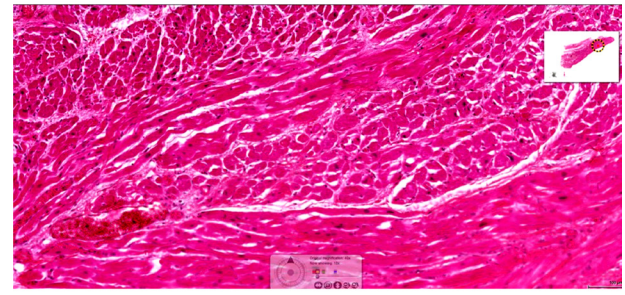


**Figure 2** Evidence of fat with strands of cardiomyocytes (without fibrosis) in the right atrium of case 1 similar to the fat dissociation syndrome found in the normal right ventricle (see text for details).



A



B

**Figure 3** (A) Presence of adipose tissue and fibrosis similar to ARVD but located in left atrial myocardium of case 2. (B) Perpendicular orientation of right atrial myocardial fibers (see text for details). ARVD, arrhythmogenic right ventricular cardiomyopathy/dysplasia.

newborn infant after atrial tissue preservation during autopsy. This was a retrospective study. The glass slides of four cases (cases 1, 2, 3 and 4) were obtained from GF's personal collection over the past decades of normal adult hearts. The exact age and gender was not available for those cases, but we know that these cases were all >40 years of age (personal communication, 2018). The samples in cases 1, 2, 3 and 4 were taken from the RA and/or LA free wall. For cases 5, 6, 7 and 8, at least two samples were collected from the interatrial septum close to the foramen ovale, the RA free wall and the LA free wall each. The latter four cases (cases 5, 6 7 and 8) were obtained from the pathologic collection of the Forensic Medical College of Xi'an Jiaotong University Health Science Center, China and they had no documented cardiovascular disease and other systemic disease, including, but not limited to, obesity, diabetes, smoking, valvular abnormalities (especially mitral valve disease), left ventricular dysfunction or chronic kidney disease.

Staining was perfomed with hematoxylin phloxine saffron or Masson's trichrome to have a better identification of fibrosis, and H&E for better identification of lymphocytes. Examination of slides was perfomed with a common light microscope (Leica, Wetzlar, Germany) and with numeric image processing.

Analysis of all slides was made at low and high magnification with special respect to adipocytes, interstitial or replacement fibrosis, as well as high magnification for detection of clusters of lymphocytes isolated in myocardium or embedded in fibrosis, which represents the chronic-active form of myocarditis. Please note the value of low magnification to display the full thickness of the atrial free wall (figure 1A) and the value of high magnification to search

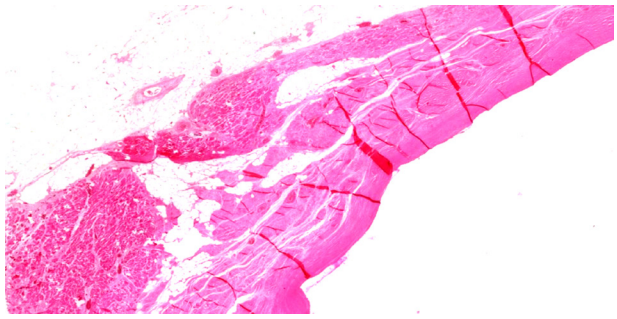


**Figure 4** Presence of adipocytes and fibrosis in the right atrium similar to RV myocardium of patients with ARVD. Please note the presence of major replacement fibrosis on the right. ARVD, arrhythmogenic right ventricular cardiomyopathy/dysplasia; RV, right ventricle.

for lymphocytes or evaluation of small coronary arteries (figure 1B).

Histology of the compact left ventricle (LV) from deceased cases without cardiovascular disease served as a 'healthy' control and was compared with the atrial histology, because the healthy RV shows a pattern of ARVD in up to 3.7% of cases or is infiltrated by fatty tissue in up to 60.9% of cases.[4]

## RESULTS

In case 1 (figure 2), both atria showed evidence of fat with strands of cardiomyocytes (without fibrosis) similar to the fat dissociation syndrome found in the normal RV.[4]

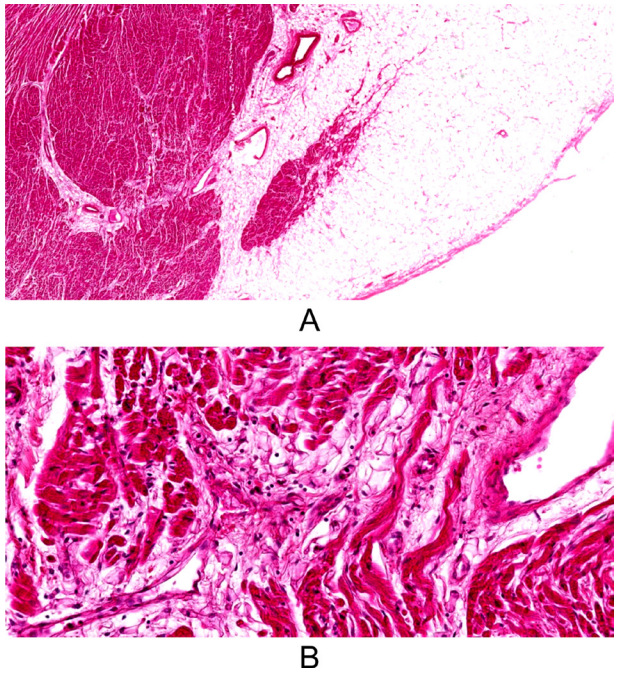



**Figure 5** (A) Left atrial specimen: almost complete absence of cardiomyocytes surrounded by fatty tissue. (B) Evidence of a right atrial focus of fibrosis containing lymphocytes classified as the chronic-active form of myocarditis clearly visible after high magnification (×200).

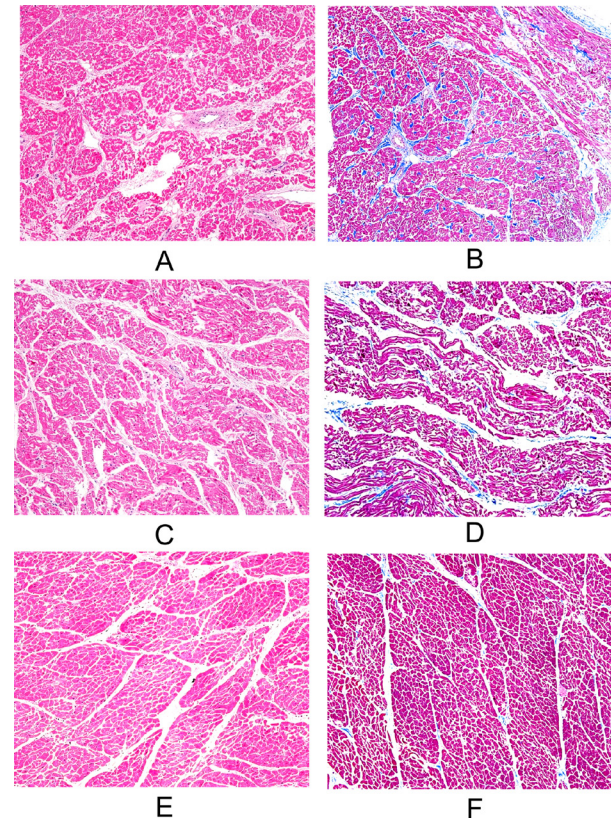



**Figure 6** H&E and Masson's trichrome stainings of samples from the right atrium (A: H&E; B: Masson), interatrial septum (C: H&E; D: Masson), and left atrium (E: H&E; F: Masson), respectively, indicating minor fibrosis without the presence of adipocytes (magnification ×40 for all slides). The samples were obtained from the same individual as in figure 1.

In case 2, there was presence of adipose tissue and fibrosis similar to ARVD but located in the atrial myocardium (figure 3).

In case 3, there was presence of adipocytes and fibrosis in both atria similar to RV myocardium in ARVD (figure 4). The presence of major replacement fibrosis was visible in the RA of this case.

In case 4, there were almost no residual cardiomyocytes in this LA specimen showing extensive fatty infiltration without major fibrosis, except for an oblique cut of a clear strand of cardiomyocytes (figure 5).

In case 5, the pathologic samples were obtained at autopsy from an 18-year-old man who died from a motorbike accident. His medical history was unremarkable. Histopathology, H&E and Masson's trichrome stainings of samples from the RA (figure 6A,B), interatrial septum (figure 6C,D), and LA (figure 6E,F) indicated less fibrosis as compared with the previous cases and no adipocytes.

In case 6 (figure 7), the samples were obtained from a 23-year-old man who died from a severe central nervous system infection. Histopathology from the RA (figure 7A,B), interatrial septum (figure 7C,D), and LA (figure 7E,F) are similar to case 5 and indicated less fibrosis without adipocytes.

In case 7 (figure 8), the samples were obtained from a 1-day newborn female infant, who died by an accident.

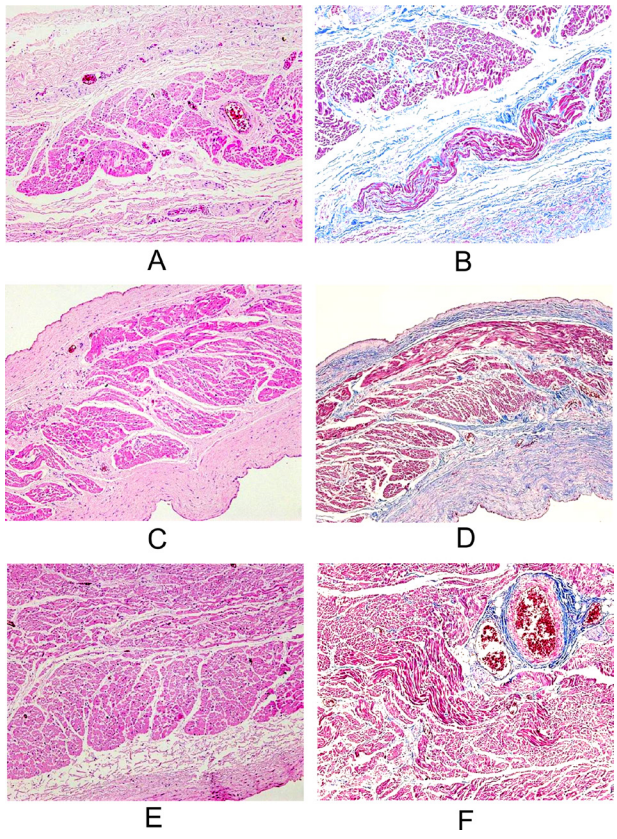



**Figure 7** H&E and Masson's trichrome stainings of samples from the right atrium (A: HE; B: Masson), interatrial septum (C: HE; D: Masson), and left atrium (E: H&E; F: Masson), respectively, indicate minor fibrosis without presence of adipocytes (magnification ×100 for all slides). The histopathologic characteristics are similar to figure 6.

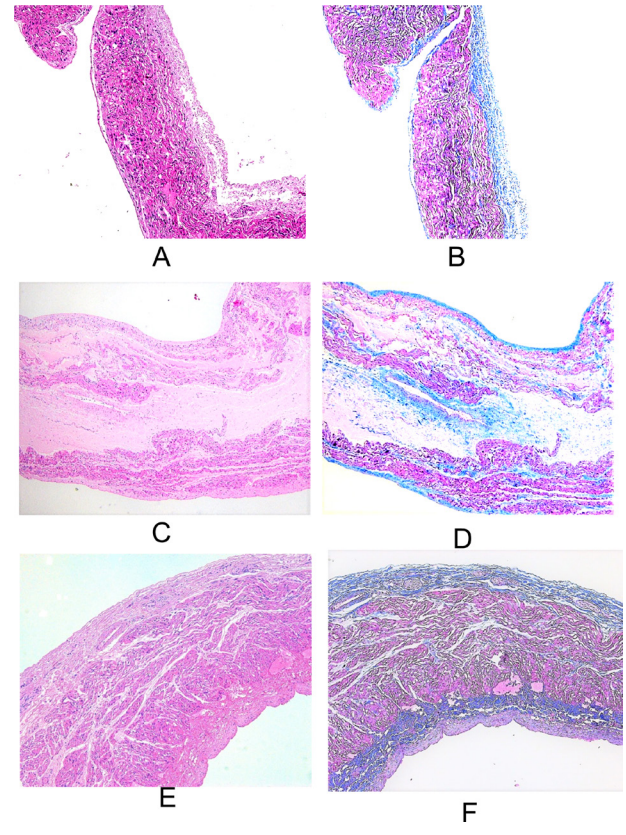



**Figure 8** H&E and Masson's trichrome stainings of samples from the right atrium (A: H&E; B: Masson), interatrial septum (C: H&E; D: Masson), and left atrium (E: H&E; F: Masson), respectively, show almost no fibrosis and no adipocytes (magnification ×100 for all slides). The histopathologic characteristics of the atria from this newborn infant can be considered as healthy.

Histopathology from the RA (figure 8A,B), interatrial septum (figure 8C,D), and LA (figure 8E,F) showed a preserved atrial architecture without fibrosis and adipocytes.

In case 8 (figure 9), the atrial samples were obtained at autopsy of a 33-year-old female who died due to severe postpartum haemorrhage. Histopathology from the RA (figure 9A,B), interatrial septum (figure 9C,D), and LA (figure 9E,F) showed evidence of fat with strands of cardiomyocytes and minor fibrosis similar to the fat dissociation syndrome found in the normal RV.[4 5]

Histologic myocardial specimen from the LV were also taken and analyzed in cases 5–8. They did not show any signs of myocardial disease, with the LV consisting of compact myocardium without relevant fibrosis, fat or inflammation.

## DISCUSSION

Research on the atrial histology of humans without cardiovascular disease is scarce, although AF is very common in the general population constituting the most common arrhythmia in the human species. We hypothesize that a pathologic substrate such as fibrosis, fatty infiltration or inflammation can explain the high prevalence of AF in the general population. Since current imaging modalities have limitations to identify a pathologic substrate, and histology is considered the gold standard, we carefully analyzed histologic specimen from the RA and LA in deceased probands without overt cardiovascular disease. To our surprise, we observed pathologic changes in both atria of apparently normal hearts in a considerable number of subjects who died of a non-cardiac cause and did not have an overt cardiovascular pathology. We hypothesize that atrial adipogenesis and fibrosis start in adulthood, but this is difficult to prove since exact age at autopsy was not known in 50% of patients. However, cases 1–4 were >40 years of age at the time of autopsy. Given this information and the normal histology of atrial tissue in the newborn infant and almost no fibrosis and no fat in the 18-year-old (case 5) and 23-year-old (case 6) cases of our series, we can assume that the process of fibro-fatty infiltration of the atria is age dependent. These changes were similar to those known in the RV in ARVD.[6] Cases 1–5 (figure 2) can be called 'atrial dysplasia'.[7] This term has been first reported in a single case where the dysplastic phenomenon in the atria was localized on a focal zone in a patient with myotonic dystrophy.[8] Case 1 showing strands of cardiomyocytes inside fatty tissue without fibrosis is the marker of production of fat instead of cardiomyocytes. This feature is typical of ARVD[6] and is also prevalent in some normal hearts. Its mechanism is unknown, but it is not always a benign anomaly.[4 8] Case 2 showed

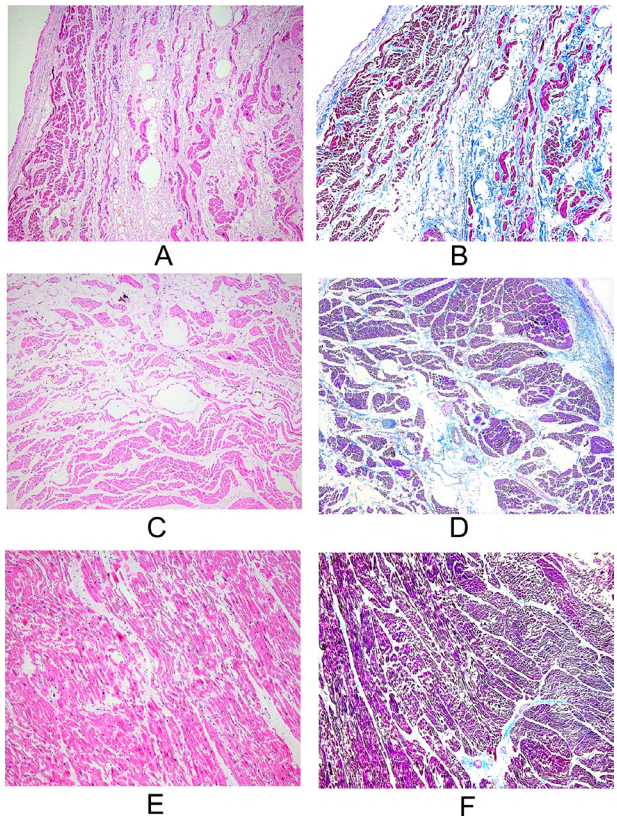



**Figure 9** H&E and Masson stainings of samples from the right, atrium (A and B), interatrial septum (C and D), and left atrium (E and F), respectively, showed evidence of fat with strands of cardiomyocytes (minor fibrosis) similar to the fat dissociation syndrome found in the normal right ventricle (magnification ×100 for all slides).

epicardial adipocytes and interstitial fibrosis embedding cardiomyocytes similar to the RV in classical ARVD. In addition, the perpendicular orientation of the two atrial layers can be considered a zone of weakness similar to the two perpendicular RV layers in ARVD. It is proposed that if the same desmosomal genes like in ARVD are involved at the interface between the two perpendicular layers of atrial myocardium, this can be a zone of weakness producing fat and fibrosis during adulthood. However, no desmosomal mutations have been observed in the normal heart. It is therefore possible to consider that genetic and epigenetic factors involved in the development and repair of atrial tissue are different from the RV.[9 10] During the development of the embryo, the RV is systemic, which is an explanation why ARVD begins in the mediomural RV layers.[11] We do not know if the same concept is valid for the atria of patients with ARVD, but atrial dysplasia is also present in patients with ARVD as previously shown by our group. Case 3 showed large zones of hyaline fibrosis suggesting healed myocarditis on top of the dysplastic phenomenon with adipocytes inside cardiomyocytes. Case 4 is the most complex form with all the components known from right ventricular dysplasia in ARVD, in this case being present in the atria of an apparently normal heart. Of note, high magnification was able to detect a focus of fibrosis containing typical lymphocytes, which is the hallmark of superimposed myocarditis.[12] It is also possible that these structural anomalies are increasing the susceptibility of this abnormal myocardium to attract inflammation.[13 14] Case 5 showed strands of cardiomyocytes with evidence of fat and less fibrosis similar to the 'fat dissociation syndrome' found in the normal RV. The atrial samples obtained from cases 5, 6, 7 and 8 who died at a younger age as compared with the subjects 1–4 showed almost no fibrosis and no fatty tissue, which can be considered as the true 'healthy atrium' prior to the onset of atrial remodelling with advancing age. This is particularly evident in the atria from the newborn infant. It is interesting to note that atrial dysplasia was absent in this newborn infant and two young male patients. Therefore, as dicussed above, the presence of atrial dysplasia in the human species may be age related. We have no clear evidence of an overt cardiovascular pathology in none of our subjects, suggesting that increasing age alone can lead to atrial remodelling and 'atrial dysplasia'. The absence of relevant fibrosis, fat and inflammation and the presence of compact myocardium in our LV samples in cases 5–8 underlines the assumption that no cardiovascular disease was present. Our observations help to understand why AF is the most common arrhythmia in the human species and its prevalence significantly rises with increasing age,[2 15] independent of cardiovascular risk factors such as systemic arterial hypertension or sleep apnea, among others.

## Limitations

Our study has some important limitations. First, we cannot provide exact information on gender and age for cases 1–4, all of which were collected by GFover the past decades. These were all adult cases >40 years of age at the time of autopsy without any known history of cardiovascular or systemic disease, and autopsy findings excluded any significant cardiovascular disease. Yet, given the retrospective nature of this study, we cannot fully exclude that these four cases had unrecognized cardiovascular or systemic diseases or risk factors, including, but not limited to, obesity, diabetes, valvular disease, left ventricular diastolic dysfunction and chronic kidney disease, which can all promote atrial remodeling. Second, atrial arrhythmia is associated with increasing age and increased atrial size. In our study, all samples of the right and left atria were retrospectively analyzed. Atrial volume was not measured prior to preparation of the atrial specimen during autopsy. Moreover, since the cases did not have any overt cardiovascular disease prior to their death, imaging data on atrial size was not available. Therefore, we cannot provide data on atrial size or volume, which is known to be associated with atrial remodeling. Third, assessment of fibrous and fatty infiltration was done by subjective visual assessment by GF, who was an expert in cardiac pathology, similar to the assessment of histologic diagnostic criteria in ARVD in the 2010 ARVD Task Force Criteria.[16] Last, this report was made from a small series of autopsy subjects given the difficulty of obtaining histologic specimen from both atria in subjects without an overt cardiovascular pathology.

## CONCLUSIONS

Histologic anomalies in the ventricular myocardium as observed in ARVD can lead to ventricular arrhythmias including ventricular fibrillation and sudden cardiac death. A similar situation with the presence of a considerable amount of fibro-fatty tissue in the atrial myocardium, which can be called atrial dysplasia, seems to be common in older adults and can contribute to the high prevalence of AF in the general population.

**Acknowledgements** We dedicate this work to our great mentor and teacher Guy H Fontaine, who is deeply missed.

**Contributors** All authors listed have contributed sufficiently to the project to be included as authors and are responsible for the study design, manuscript content and editorial decisions. All authors reviewed and approved the final version.

**Funding** This study was supported by the Clinical Research Award of the First Affiliated Hospital of Xi'an Jiaotong University, China (XJTU1AF-CRF-2018-015).

**Competing interests** None declared.

**Patient consent** Next of kin consent obtained.

**Ethics approval** Forensic Medical College obtained the approved paperwork from the ethical committee of Xi'an Jiaotong University Health Science Center, China (approval number No.: 2018007).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** Not available.

## REFERENCES

1 Li G, Fontaine GH, Fan S, *et al*. Right atrial pathology in arrhythmogenic right ventricular dysplasia. *Cardiol J* 2018.
2 Go AS, Hylek EM, Phillips KA, *et al*. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;285:2370–5.
3 Pontecorboli G, Figueras I Ventura RM, Carlosena A, *et al*. Use of delayed-enhancement magnetic resonance imaging for fibrosis detection in the atria: a review. *Europace* 2017;19:180–9.
4 Fontaine G, Chen HS. Arrhythmogenic right ventricular dysplasia back in force. *Am J Cardiol* 2014;113:1735–9.
5 Fontaine G, Fontaliran F, Zenati O, *et al*. Fat in the heart. A feature unique to the human species? Observational reflections on an unsolved problem. *Acta Cardiol* 1999;54:189–94.
6 Mallat Z, Tedgui A, Fontaliran F, *et al*. Evidence of apoptosis in arrhythmogenic right ventricular dysplasia. *N Engl J Med* 1996;335:1190–7.
7 Bonny A, Lellouche N, Ditah I, *et al*. C-reactive protein in arrhythmogenic right ventricular dysplasia/cardiomyopathy and relationship with ventricular tachycardia. *Cardiol Res Pract* 2010;2010:1–7.
8 Pickering JG, Guiraudon C, Klein GJ. Focal right atrial dysplasia and atrial flutter in a patient with myotonic dystrophy. *Pacing Clin Electrophysiol* 1989;12:1317–23.
9 Darbar D, Roden DM. Genetic mechanisms of atrial fibrillation: impact on response to treatment. *Nat Rev Cardiol* 2013;10:317–29.
10 Nielsen JB, Thorolfsdottir RB, Fritsche LG, *et al*. Biobank-driven genomic discovery yields new insight into atrial fibrillation biology. *Nat Genet* 2018;50:1234–9.
11 Fontaine G, Charron P. Arrhythmogenic right ventricular cardiomyopathies. In: Zipes D, Jalife J, eds. *Cardiac electrophysiology: from cell to bedside*. 5th edn. Philadelphia: Saunders, 2009:689–97.
12 Saguner AM, Roland F, Li GL, *et al*. 1933Superimposed myocarditis leading to heart transplantation in a young patient with arrhythmogenic right ventricular dysplasia. *Eur Heart J* 2017;38:ehx495.1933.
13 Lopez-Ayala JM, Pastor-Quirante F, Gonzalez-Carrillo J, *et al*. Genetics of myocarditis in arrhythmogenic right ventricular dysplasia. *Heart Rhythm* 2015;12:766–73.
14 Chimenti C, Frustaci A. Contribution and risks of left ventricular endomyocardial biopsy in patients with cardiomyopathies: a retrospective study over a 28-year period. *Circulation* 2013;128:1531–41.
15 Kistler PM, Sanders P, Fynn SP, *et al*. Electrophysiologic and electroanatomic changes in the human atrium associated with age. *J Am Coll Cardiol* 2004;44:109–16.
16 Marcus FI, McKenna WJ, Sherrill D, *et al*. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation* 2010;121:1533–41.