Research Article

Correlation between increased atrial expression of genes related to fatty acid metabolism and autophagy in patients with chronic atrial fibrillation

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Word count: 3,373 words, **Number of Tables and Figures**: 9

Short title: Fatty acid metabolism & autophagy in AF

Grants: This study was supported by KAKENHI Grant-in-Aid for Young Scientists (B) (#JP24791453 to Y.S.), the Cardiovascular Research Fund (to Y.S.), and the Center of Innovation Program from the Japan Science and Technology Agency (#JPMJCE1301 to T.Y.).

Abstract

Atrial metabolic disturbance contributes to the onset and development of atrial fibrillation (AF). Autophagy plays a role in maintaining the cellular energy balance. We examined whether the altered atrial expression of genes related to fatty acid metabolism is linked to that related to autophagy in chronic AF. Right atrial tissue was obtained during heart surgery from 51 patients with sinus rhythm (SR, n=38) or chronic AF (n=13). Preoperative fasting serum free-fatty-acid levels were significantly higher in the AF patients. The atrial gene expression of fatty acid binding protein 3 (*FABP3*), which is involved in the cells' fatty acid uptake and intracellular fatty acid transport, was significantly increased in AF patients compared to SR patients; in the SR patients it was positively correlated with the right atrial diameter and intra-atrial EMD, parameters of structural and electrical atrial remodeling that was evaluated by an echocardiography. In contrast, the two groups' atrial contents of diacylglycerol (DAG), a toxic fatty acid metabolite, were comparable. Importantly, the atrial gene expression of microtubule-associated protein light chain 3 (*LC3*) was significantly increased in the AF patients, and autophagy-related genes including *LC3* were positively correlated with the atrial expression of *FABP3*. In conclusion, in chronic AF patients, the atrial expression of *FABP3* was upregulated in association with autophagy-related genes without altered atrial DAG content. Our findings may support the hypothesis that dysregulated cardiac fatty acid metabolism contributes to the progression of AF and induction of autophagy has a cardioprotective effect against cardiac lipotoxicity in chronic AF.

Key words: atrial fibrillation; atrial remodeling; autophagy; fatty acid metabolism; lipotoxicity

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and its presence is associated with increased risks of death, heart failure, and stroke [1-3]. With the current increased prevalence of AF, the prevention of AF is important not only for public health but also to reduce the associated economic burden [4]. The risk factors for AF are diverse, including higher serum levels of free fatty acids (FFAs), obesity, hypertension, inflammation, and oxidative stress [5-7]. The mechanisms underlying the onset and development of AF have not been fully elucidated.

The pathophysiology of AF is complex and involves electrical, structural, contractile, and neurohormonal remodeling [8, 9]; metabolic disturbance in the atrial cardiac muscle is a recent focus of AF research, as the heart has a very high energy demand due to its organ-specific feature involving the constant activation of mitochondrial oxidative phosphorylation. In particular, fatty acids are the major fuel for the heart; their use depends on their uptake into the cells, transport from the cytosol into the mitochondria, and β-oxidation in the mitochondria. Prior research has shown that an elevated level of circulating FFAs is a strong risk factor for AF and AF-related stroke [6, 10] and can be a trigger of cardiac lipotoxicity, which is defined as the excess accumulation of toxic fatty acid metabolites such as diacylglycerol (DAG) in the heart. This may occur when the influx of FFAs exceeds the intracellular fatty acid oxidation,

71 which leads to cardiac dysfunction, cardiac remodeling, and arrhythmias [11]. However,
72 it is still unclear how metabolic disturbances including abnormal fatty acid metabolism
73 contribute to the development of AF.

74 Autophagy, the process of the degradation of intracellular components (e.g.,
75 proteins) in lysosomes, plays an important role in cellular homeostasis via cellular
76 quality control. Autophagy was also shown to contribute to the cellular energy balance,
77 in particular through a mechanism of fatty acid metabolism termed "lipophagy" (the
78 degradation of excess lipids by autophagy) and the degradation of lipid stores in the
79 cells [12]. Accordingly, autophagy may regulate the fatty acid metabolism in
80 cardiomyocytes. Alterations of the autophagy in the atrial muscles of patients with
81 persistent AF [13, 14] or post-operative AF have been reported [15]. Although it is still
82 controversial whether the induction of autophagy has a cardioprotective or detrimental
83 effect in AF, it is possible that autophagy is involved in metabolic remodeling in the
84 atrium in chronic AF patients.

85 We conducted the present study to determine: (1) whether the expression of
86 genes related to fatty acid metabolism and autophagy are altered in the atria of patients
87 with chronic AF, and (2) whether changes in these gene expression patterns are
88 correlated with each other. We used human atrial tissue excised from patients during

89 cardiac surgery, and our findings provide new insight into the pathophysiology of AF,

90 focusing on fatty acid metabolism and autophagy in the human atrium.

91

92

Materials and Methods

Patients

This study was conducted at Hokkaido University Hospital and Teine Keijinkai Hospital and included 51 consecutive patients: 38 with sinus rhythm (SR) and 13 with chronic AF who underwent cardiovascular surgery between 2013 and 2019 at either of these hospitals. All of the patients were Japanese. The patients with SR in the present series partly overlap with those of our recently published report [16].

After the establishment of a cardiopulmonary bypass (10 min after the infusion of heparin 300 IU/kg), right atrial myocardial tissue (approx. 100 mm^2) was excised from the right atrial incision site or the insertion point of a drainage cannula. The tissue was frozen and stored at −80°C until analysis.

Type 2 diabetes was defined as a fasting glucose level ≥7.0 mmol/L and/or taking antidiabetes medications. Coronary artery disease was evaluated by coronary angiography, and stenosis ≥75% was defined as significant; a patient with a history of percutaneous coronary intervention was also regarded as having coronary artery disease.

The study protocol was approved by the Ethics Committees of Hokkaido University Hospital and Teine Keijinkai Hospital and performed according to the Declaration of Helsinki. Written informed consent was obtained from each patient

111 before the surgery. This study was registered in the UMIN Clinical Trials Registry:
112 UMIN000012405 and UMIN000018137.
113

114 Transthoracic echocardiography

115 A Vivid Seven system (GE/Vingmed, Milwaukee, WI, USA) with an M3S (2.5–
116 3.5 MHz) transducer, an Aplio system (Toshiba Medical Systems, Tokyo) with a
117 2.5-MHz transducer, or a Philips system (Philips Ultrasound, Bothell, WA) with a
118 2.5-MHz transducer was used for the pre-operative echocardiography. The left
119 ventricular and atrial diameters were measured from the parasternal long-axis view. The
120 right atrial diameter (the largest minor-axis diameter in the four-chamber view) was
121 obtained at end-systole [17].
122 The electromechanical delay (EMD) of the right atrium was assessed in all but
123 one of the SR patients as a time interval (T1) from the beginning of the P-wave on
124 surface ECG to the beginning of the late diastolic wave (A') of the tricuspid annulus
125 [17]. T2 was the time interval from the beginning of the P-wave on the surface ECG to
126 the A' of the septal mitral annulus. The intra-atrial EMD was the interval from T1 to T2,
127 expressed as T2-T1 (msec). The left ventricular ejection fraction (LVEF) was measured
128 using the biplane method of disks. The mitral regurgitation grade was defined by the

129 regurgitation jet area-to-left atrium ratio (mild, <20%; moderate, 20%–40%; severe,
130 >40%).

131 Tricuspid regurgitation was graded using the regurgitation jet area (mild, <5 cm^2;
132 moderate, 5–10 cm^2; severe, >10 cm^2). Aortic stenosis was defined using the valve area
133 (mild, >1.5 cm^2; moderate, 1.0–1.5 cm^2; severe, <1.0 cm^2). Aortic regurgitation was
134 determined using a combination of the jet width/outflow tract, the pressure half-time,
135 and the diastolic reverse flow at the abdominal aorta (mild, moderate, severe) [18].

136

137 Blood biochemistry

138 Blood was collected from each patient early in the morning after a 10-hr fast
139 within 2 days before surgery. The blood glucose, hemoglobin A1c, insulin, and FFA
140 levels were measured by an enzymatic reaction involving glucose oxidase,
141 high-performance liquid chromatography, an enzyme immunoassay, and the enzymatic
142 method, respectively. Total cholesterol and triglycerides were assessed by enzymatic
143 methods. The plasma levels of B-type natriuretic peptide (BNP) were evaluated by a
144 chemiluminescent enzyme immunoassay.

145

146 The atrial expression of genes related to fatty acid metabolism
147 and autophagy

148 The atrial expression of the following genes related to fatty acid metabolism and
149 autophagy was determined by reverse transcription-polymerase chain reaction
150 (RT-PCR): cluster of differentiation 36/fatty acid translocase (*CD36*), carnitine
151 palmitoyltransferase 1B (*CPT1B*), fatty acid-binding protein 3 (*FABP3*),
152 autophagy-related gene 5 (*ATG5*), Unc-51-like kinase 1 (*ULK1*), Beclin-1 (*BCLN1*),
153 and microtubule-associated protein light chain 3 (*LC3*). Myocardial mRNA was isolated
154 from frozen tissue using a High Pure RNA Tissue Kit (Roche, Penzberg, Germany) and
155 was then reverse-transcribed into cDNA using a Transcriptor First Strand cDNA
156 Synthesis Kit (Roche).
157 The RT-PCR was performed using FastStart Essential DNA Probes Master
158 (Roche) and the Real-time Ready Assay (Roche Assay ID: *CD36,* 144833; *CPT1B*,
159 126501; *FABP3*, 118811; *ATG5*, 125999; *ULK1*, 109914; *BCLN1*, 100115; *LC3*,
160 144582; *TBP*, 143707). PCR amplification was then performed with a reaction volume
161 of 20 µL using a LightCycler Nano (Roche) under the conditions specified by the
162 manufacturer. After the initial denaturation and activation of the enzyme for 10 min at
163 95°C, 45 cycles of denaturation at 95°C for 10 sec, and annealing and extension at 60°C
164 for 30 sec were performed. *TBP* (TATA-binding protein) was used as a reference gene,
165 as we confirmed that TBP is not influenced by the occurrence of AF.
166

The atrial enzymatic activities of the mitochondrial TCA cycle and fatty acid β-oxidation

We spectrophotometrically determined the activity levels of both citrate synthase (CS), a key enzyme in the tricarboxylic acid (TCA) cycle, and β-hydroxyacyl CoA dehydrogenase (β-HAD), a key enzyme in fatty acid β-oxidation, in the myocardial samples as described [19]. Due to the lack of atrial muscle samples, these enzymatic activities were measured in 20 of the 38 patients with SR and eight of the 13 patients with AF.

The atrial DAG content

Heart tissue was homogenized in 1.5 mL of methanol, followed by mixing with 2.25 mL of 1 M NaCl and 2.5 mL of chloroform. The mixture was centrifuged at 1,500 g for 10 min at 4°C, and the organic phase was dried. DAG was then detected with a DAG assay kit (Cell Biolabs, San Diego, CA) following the manufacturer's instructions. Due to the lack of atrial muscle samples, the atrial DAG content was measured in six patients with SR and six patients with AF.

Statistical analyses

Values are presented as the mean ± standard deviation (SD) or the median (interquartile range [IQR]) as appropriate. We used Student's t-test for continuous variables that are normally distributed and the Mann-Whitney U-test for other continuous variables. The chi-square test or Fisher's exact test were used for categorical variables. We conducted a Pearson's correlation analysis to determine linear relationships between continuous variables. The statistical analyses were performed using GraphPad Prism ver. 8 (GraphPad Software, San Diego, CA), and significance was defined as $p<0.05$.

Results

Patient characteristics

The characteristics of the SR and AF patients are summarized in **Table 1**. The median duration of AF was 12 years (range 1–16 years). Except for the use of medications, all parameters including cardiovascular risk factors were comparable between the two groups. The surgical procedures performed after the excision of atrial specimens included aortic valve replacement in 30 cases, total arch replacement in eight cases, coronary artery bypass grafting in 10 cases, aortic root replacement in six cases, and mitral valve repair in 12 cases. Multiple procedures were performed in some patients.

Transthoracic echocardiography

As shown in **Table 2**, the diameters of the left and the right atria were significantly increased in the AF group. The left ventricular size (i.e., left ventricular end-diastolic diameter [LVDd]) and the left ventricular systolic function (i.e., the LVEF) were comparable between the two groups. Regarding valvular heart disease, the grade of mitral regurgitation was higher in the AF group than in the SR group.

The serum levels of FFA and the atrial expression of genes

related to fatty acid metabolism

The serum FFA levels were significantly higher in the AF group compared to the SR group (719 ± 107 vs. 416 ± 37 μmol/L, p=0.001, **Fig 1**).

The expressions of genes related to fatty acid metabolism in the right atrial muscle are shown in **Fig 2**. The gene expression of *CD36*, which facilitates fatty acid uptake across the plasma membrane, tended to be higher in the AF group than in the SR group (**Fig 2A**). The gene expression of *FABP3*, which facilitates fatty acid uptake into the cell and intracellular fatty acid transport, was significantly increased in the AF group (**Fig 2B**), but there was no significant difference between the two groups in the atrial expression of *CPT1B*, which is located on the outer mitochondrial membrane for fatty acid transport into the mitochondria (**Fig 2C**).

In the SR patients, *FABP3* gene was positively correlated with the right atrial diameter (**Fig 3A**) and the intra-atrial EMD (**Fig 3B**), indicating that increased atrial gene expression related to intracellular fatty acid transport was associated with structural and electrical atrial remodeling.

The atrial enzymatic activities of the mitochondrial TCA cycle and fatty acid β-oxidation

Fig 4 illustrates the enzymatic activities related to the mitochondrial fatty acid

β-oxidation and TCA cycle in the right atrial muscle. The CS activity was comparable between the SR and AF groups (**Fig 4A**), as was the β-HAD activity (**Fig 4B**).

The atrial DAG content

Despite the higher serum levels of FFA and the upregulated atrial gene expression of *FABP3* in the AF group, there was no significant difference in the atrial content of DAG, a major toxic fatty acid metabolite, between the SR and AF groups (**Fig 5**).

The atrial expression of autophagy-related genes

The gene expression of *LC3* in the right atrial muscle was significantly higher in the AF group than in the SR group (**Fig 6D**), but there was no significant difference in other autophagy-related genes including *ATG5*, *ULK1*, and *BCLN1* between the SR and AF groups (**Figs 6A–6C**).

The linear relationship between the atrial expression of FABP3 gene and autophagy-related genes

The gene expression of *FABP3* was positively correlated with autophagy-related genes including *LC3* gene in all patients (**Fig 7**). Similar correlations were observed

between *FABP3* gene and autophagy-related genes even when they were analyzed separately for the SR group (*FABP3* and *ATG5*: r^2=0.510, p<0.001; *FABP3* and *ULK1*: r^2=0.622, p<0.001; *FABP3* and *BCLN1*: r^2=0.740, p<0.001; *FABP3* and *LC3*: r^2=0.384, p<0.001) and the AF group (*FABP3* and *ATG5*: r^2=0.670, p<0.001; *FABP3* and *ULK1*: r^2=0.790, p<0.001; *FABP3* and *BCLN1*: r^2=0.768, p<0.001; *FABP3* and *LC3*: r^2=0.534, p=0.005).

Discussion

Our findings demonstrated that the atrial expression of a gene involved in fatty acid metabolism, *FABP3*, was upregulated in patients with chronic AF compared to the SR patients. In the SR patients, the increased atrial expression of *FABP3* was positively correlated with the right atrial diameter and the intra-atrial EMD, which are parameters of structural and electrical remodeling of the atrium. In contrast, there was no increase in the atrial content of DAG despite the increased atrial expression of *FABP3* and higher serum levels of FFA in our patients with chronic AF. Intriguingly, the atrial expression of a gene related to autophagosome maturation, *LC3*, was increased in the chronic AF patients, and autophagy-related genes including *LC3* were positively correlated with the atrial expression of *FABP3*. To the best of our knowledge, this is the first study showing that the atrial expression of *FABP3* gene is increased in association with autophagy-related genes in patients with chronic AF.

The dysregulated fatty acid metabolism in the atrium of chronic AF patients

Compared to the SR patients, the chronic AF patients had higher serum FFA levels. The Cardiovascular Health Study has reported that an increase in the plasma levels of FFA by 200 μmol/L presents an 11% higher risk of AF occurrence even after

adjustment for confounding risk factors including age, sex, race, physical activity, body mass index, coronary heart disease, congestive heart failure, smoking, alcohol use, log-C-reactive protein, diabetes mellitus, and hypertension in older adults [6]. Accordingly, elevated FFA levels can be an independent risk factor of AF.

The fatty acid-binding proteins (FABPs) reversibly bind to fatty acid and other lipophilic molecules. FABPs, which are located on the plasma membrane, facilitate fatty acid uptake into the cells, and intracellular FABPs transport fatty acid to other locations such as the nucleus and mitochondrion. Among the 10 isoforms of FABPs distributed in various tissues in mammals, FABP3 is most predominantly expressed in the heart [20]. Here, we observed that the gene expression of *FABP3* in the right atrial muscle was enhanced in chronic AF patients, which may indicate increased fatty acid uptake into the cells and increased intracellular fatty acid transport in the atrial muscle in chronic AF. In contrast, the gene expression of *CPT-1B* (which facilitates fatty acid transport across the outer mitochondrial membrane) and β-HAD activity (an enzymatic activity of mitochondrial fatty acid β-oxidation) in the atrium were comparable between our AF and SR groups.

The association of the atrial expression of FABP3 with structural and electrical atrial remodeling

298 The results of our analyses revealed that the expression of *FABP3* in the right
299 atrial muscle was positively correlated with the right atrium diameter and the intra-atrial
300 EMD in the SR patients. The intra-atrial EMD is the time delay from the electrical
301 activation to the actual motion of the atrial myocardium, and a delayed intra-atrial EMD
302 indicates excitation-contraction uncoupling in the atrium. Prolonged intra-atrial EMD
303 after cardioversion was reported to predict AF recurrence in patients with persistent AF,
304 and histopathological changes characterized by myocardial fibrosis in the atrium appear
305 to be a major determinant of the prolonged intra-atrial EMD [21].
306 Boldt et al. revealed that the atrial expression of collagen type I is enhanced in
307 patients with lone AF, indicating that the occurrence of AF can directly increase the
308 expression of collagen type I and cause myocardial fibrosis in the atrial muscle [22].
309 Although we did not conduct histopathological evaluations, previous reports and our
310 present findings raise the possibility that the dysregulation of atrial fatty acid
311 metabolism is linked to structural and electrical atrial remodeling, which may contribute
312 to a future onset or recurrence of AF.
313

314 Altered autophagy in the atrium in chronic AF

315 Garcia et al. first reported impaired cardiac autophagy characterized by reduced
316 LC3 processing (i.e., a reduced protein expression of LC3B Ⅱ) with an accumulation of

lipofuscin deposit — a potential trigger of AF — in the atrial myocardium in patients with post-operative AF [15]. A pair of studies have shown that in chronic AF patients, the cardiac autophagy characterized by an increased protein expression of LC3B Ⅱ is induced in the atrial myocardium in association with AMPK or endoplasmic reticulum (ER) stress [13, 14]. Our present findings demonstrated that the atrial gene expression of *LC3* was upregulated in the patients with chronic AF. Taking these results together, we speculate that altered cardiac autophagy in the atrium may be involved in the progression of AF.

Implications of the association between the atrial expression of FABP3 and autophagy

The intracellular lipid content is generally deteremined by an imbalance between the uptake and the utilization of fatty acid, and thus the increased atrial expression of *FABP3* that we observed might contribute to the accumulation of lipids including DAG in the atrial myocardium in chronic AF. However, we did not detect an accumulation of DAG in the atrium in our patients with chronic AF as was reported in another study [23]. Autophagy has been shown to play a role in the regulation of fatty acid metabolism via the degradation of excessive intracellular lipids, termed “lipophagy” [12]. Our findings of an association between the atrial expression of *FABP3* gene and

autophagy-related genes in chronic AF patients may support our hypothesis that in chronic AF, autophagy at least in part contributes to the prevention of the accumulation of toxic fatty acid metabolites via a degradation of intracellular lipids. Further research is necessary to clarify the mechanistic roles of cardiac autophagy in the atrium in AF progression.

The difference in the atrial expression of FABP3 between post-operative AF and chronic AF

We observed that the atrial gene expression of *FABP3* was reduced in patients with post-operative AF in our prior study [16]; this is inconsistent with our present results regarding chronic AF patients. One of the possible explanations is a difference in pathophysiology between post-operative AF and chronic AF. It was demonstrated that in patients with metabolic syndrome, impairment in the mitochondrial respiratory capacity in the atrial tissues predicts the occurrence of post-operative AF [24]. In contrast, the mitochondrial respiratory capacity in the atrium was reported to be increased in chronic AF patients [25]. Taken together, these findings indicate that impaired energy metabolism (including reduced fatty acid utilization) in the atrial muscle might be a primary pathogenesis of post-operative AF, but in chronic AF,

354 excessive fatty acid uptake into the atrial cells seems to play a crucial role in AF
355 progression.
356

357 Study limitations

358 Several limitations of this study should be addressed. First, most of the patients
359 had valvular heart diseases, and the results of this study thus cannot be directly applied
360 to patients with lone AF. Second, we were unable to perform western blotting to assess
361 the protein levels of the autophagic marker due to the limited number of specimens.
362 Therefore, based on our results alone we cannot definitively show whether autophagic
363 flux is activated in the atrium. Finally, we cannot conclude that there is a causal
364 relationship between fatty acid metabolism and autophagy in the atrium.
365
366

Conclusions

Our study is the first to demonstrate that compared to patients with SR, the atrial expression of *FABP3* gene was upregulated in association with autophagy-related genes in patients with chronic AF. We also observed that the atrial gene expression of *FABP3* was related to structural and electrical remodeling in SR patients. Despite the increased atrial expression of *FABP3* with higher serum levels of FFA, atrial contents of DAG were not increased in patients with chronic AF. These findings provide new insights into the pathophysiology of chronic AF, and they suggest that dysregulated cardiac fatty acid metabolism might contribute to the progression of AF and induction of autophagy might have a cardioprotective effect against cardiac lipotoxicity in chronic AF.

Acknowledgements

We thank Haruki Niwano for the technical assistance.

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459

460

Figure legends

Fig 1: Preoperative levels of serum FFA.

Lines indicate the median with the interquartile range (IQR) in each group (SR, n=35; AF, n=12). AF, atrial fibrillation; FFA, free fatty acids; SR, sinus rhythm.

Fig 2: Gene expression related to fatty acid metabolism in the right atrial myocardium.

(**A**) *CD36*, (**B**) *FABP3*, and (**C**) *CPT1B*. Lines indicate the median with IQR in each group (SR; n=38, AF; n=13). *CD36*, cluster of differentiation 36 (fatty acid translocase); *CPT1B*, carnitine palmitoyltransferase 1B; *FABP3*, fatty acid binding protein 3.

Fig 3: Association between gene expression levels of *FABP3* in the right atrial myocardium and parameters of atrial remodelling in patients with SR.

(**A**) *FABP3* and RA diameter (n=38) and (**B**) *FABP3* and intra-atrial EMD (n=37). EMD, electromechanical delay; *FABP3*, fatty acid binding protein 3; RA, right atrium.

Fig 4: Enzymatic activities related to the mitochondrial TCA cycle and fatty acid β-oxidation in the right atrial myocardium.

(**A**) CS activity and (**B**) β-HAD activity. Lines indicate the median with IQR in each group (SR, n=20; AF, n=8). β-HAD, β-hydroxyacyl CoA dehydrogenase; CS, citrate synthase.

Fig 5: DAG contents in the right atrial myocardium.

Lines indicate the median with IQR in each group (SR, n=6; AF, n=6). DAG, diacylglycerol; RFUs, relative fluorescence units.

Fig 6: Gene expression related to autophagy in the right atrial myocardium.

(**A**) *ATG5*, (**B**) *ULK1*, (**C**) *BCLN1*, and (**D**) *LC3*. Lines indicate the median with IQR in each group (SR, n=37 except for *ATG5* [n=38]; AF, n=13). *ATG5*, autophagy-related gene 5; *BCLN1*, beclin-1; *LC3*, microtubule-associated protein light chain 3; *ULK1*, Unc-51-like kinase 1.

Fig 7: Association between the expression levels of *FABP3* gene and autophagy-related genes in the right atrial myocardium in patients with SR or AF.

(**A**) *FABP3* and *ATG5* (SR; n=13; AF, n =38), (**B**) *FABP3* and *ULK1* (SR, n=13; AF, n=37), (**C**) *FABP3* and *BCLN1* (SR, n=13; AF, n=37), and (**D**) *FABP3* and *LC3* (SR,

497 n=13; AF, n=37). *FABP3*, fatty acid binding protein 3. Other abbreviations are

498 explained in the Fig 6 legend.

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Table 1. Characteristics of the SR and AF patients

	SR (n=38)	AF (n=13)	p-value
Age, yrs	70 ± 13	69 ± 9	0.775
Male	18 (47%)	8 (62%)	0.378
BMI, kg/m^2	22.8 ± 3.4	24.8 ± 4.3	0.097
Heart rate, bpm	67 ± 10	73 ± 13	0.134
Systolic blood pressure, mm Hg	118 ± 19	115 ± 18	0.643
Diastolic blood pressure, mm Hg	60 ± 12	68 ± 13	0.051
Diabetes mellitus	7 (18%)	2 (15%)	0.804
Coronary artery disease	13 (34%)	2 (15%)	0.198
Medications			
Diuretics	18 (47%)	13 (100%)	0.001
β-blockers	14 (37%)	9 (69%)	0.043
Statins	18 (47%)	4 (31%)	0.297
Total cholesterol, mmol/L	4.7 ± 0.9	4.4 ± 0.7	0.357
Triglycerides, mmol/L	1.4 ± 0.7	1.0 ± 0.5	0.052
Fasting blood glucose, mmol/L	5.5 (0.8)	5.7 (0.7)	0.802
Insulin, μU/mL	5.0 (4.0)	5.8 (8.9)	0.612
HbA1c, %	5.7 ± 0.8	5.9 ± 0.6	0.324
BNP, pg/mL	79 (270)	249 (321)	0.060

Data are mean±SD, median (interquartile range), or n (%). AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; HbA1c, hemoglobin A1c; SR, sinus rhythm.

Table 2. Echocardiographic parameters of the SR and AF patients

	SR (n=38)	AF (n=13)	p-value
LVDd, mm	48 (20)	59 (17)	0.209
LVDs, mm	31 (22)	41 (20)	0.132
LVEF, %	59 ± 14	54 ± 14	0.268
Left atrial diameter, mm	41 ± 7	53 ± 9	<0.001
Right atrial diameter, mm	34 ± 6	42 ± 9	0.007
Aortic stenosis:			0.130
Mild	1 (3%)	0 (0%)	
Moderate	1 (3%)	1 (8%)	
Severe	15 (39%)	1 (8%)	
Aortic regurgitation:			0.306
Mild	18 (47%)	4 (31%)	
Moderate	4 (11%)	2 (15%)	
Severe	10 (26%)	2 (15%)	
Mitral regurgitation:			0.002
Mild	29 (76%)	5 (38%)	
Moderate	2 (5%)	5 (38%)	
Severe	2 (5%)	3 (23%)	
Tricuspid regurgitation:			0.133
Mild	26 (68%)	6 (46%)	
Moderate	3 (78%)	3 (23%)	
Severe	0 (0%)	1 (8%)	

Data are mean±SD, median (interquartile range), or n (%). AF, atrial fibrillation; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; SR, sinus rhythm.

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Figure 1

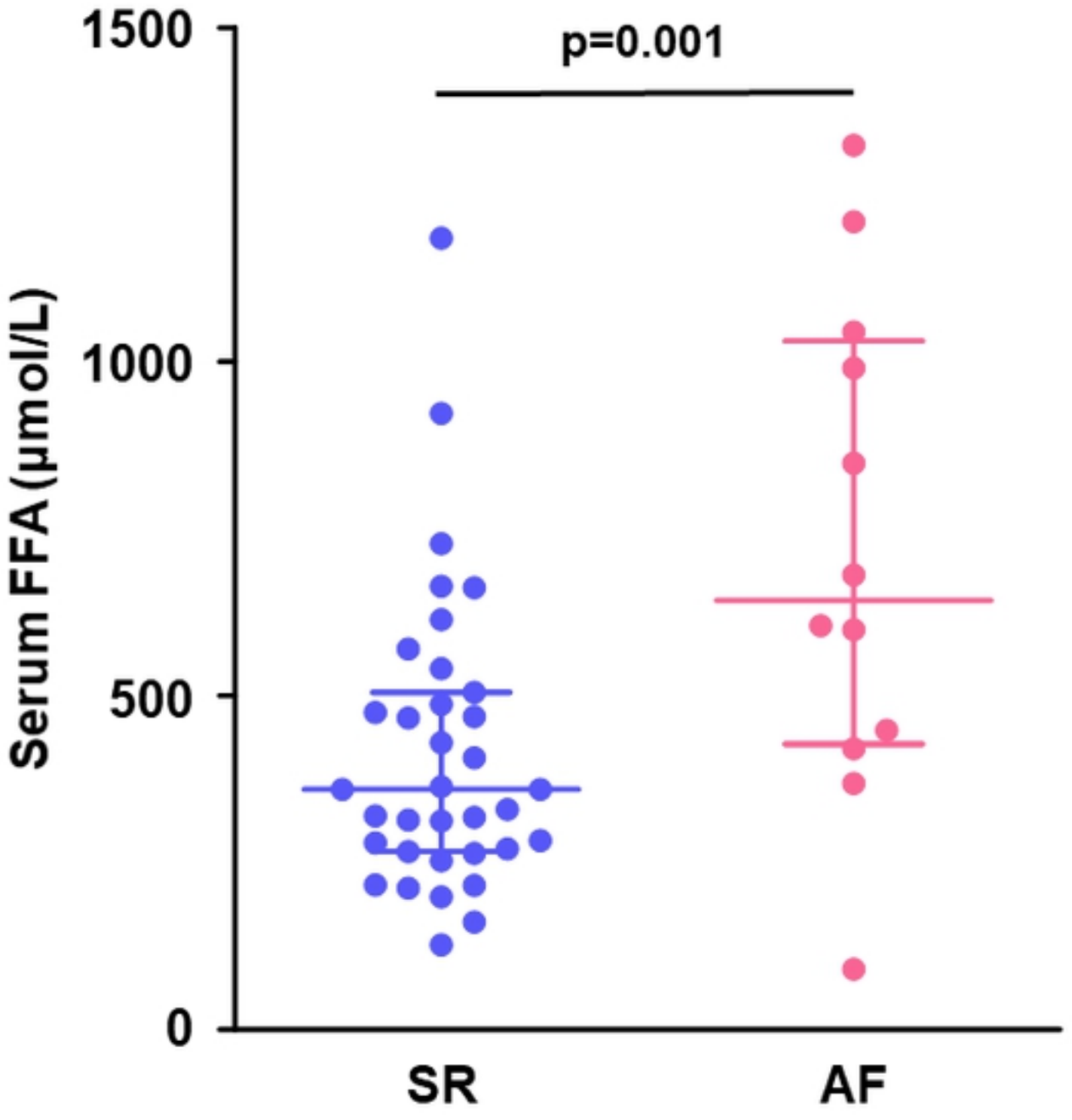

Figure 1

Figure 2

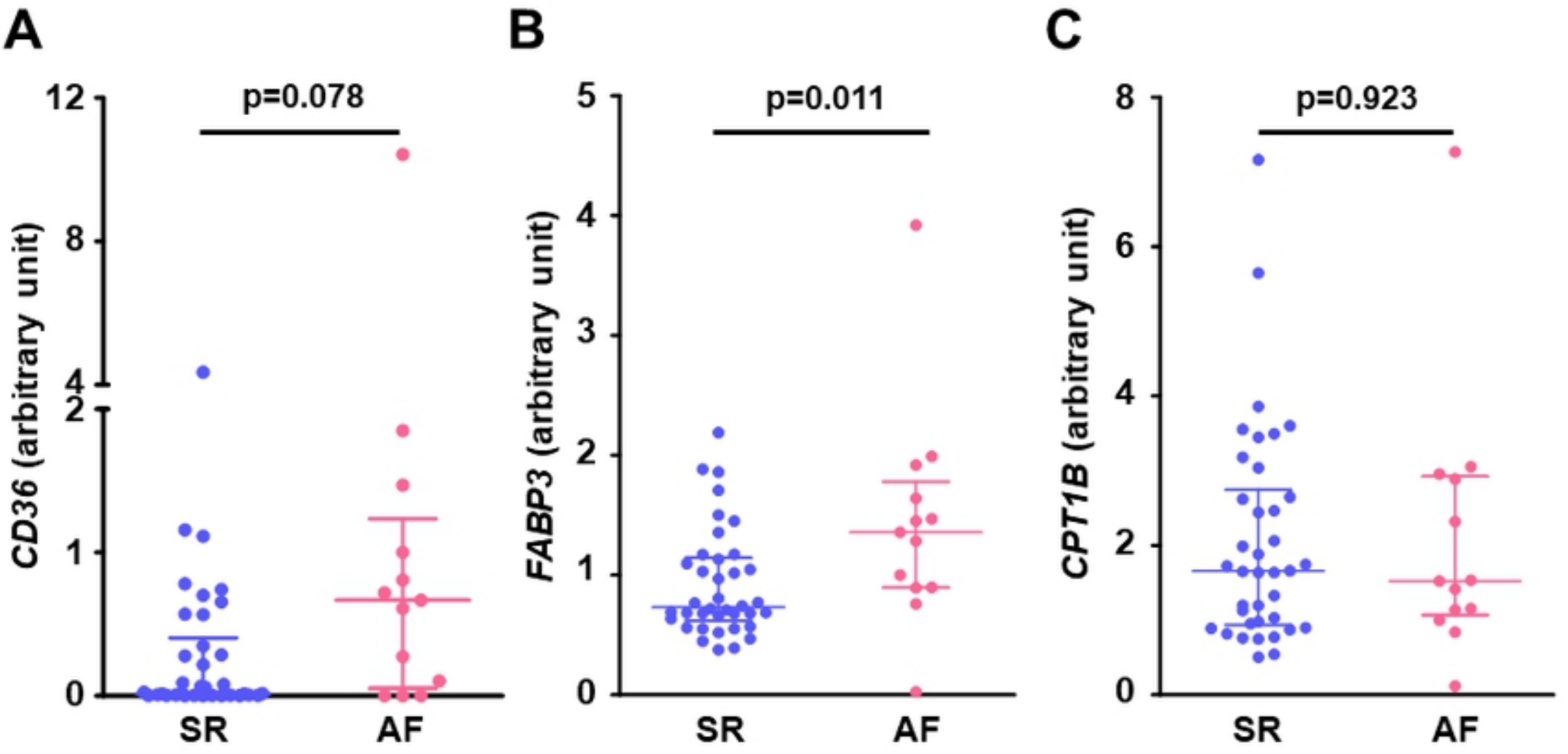

Figure 2

Figure 3

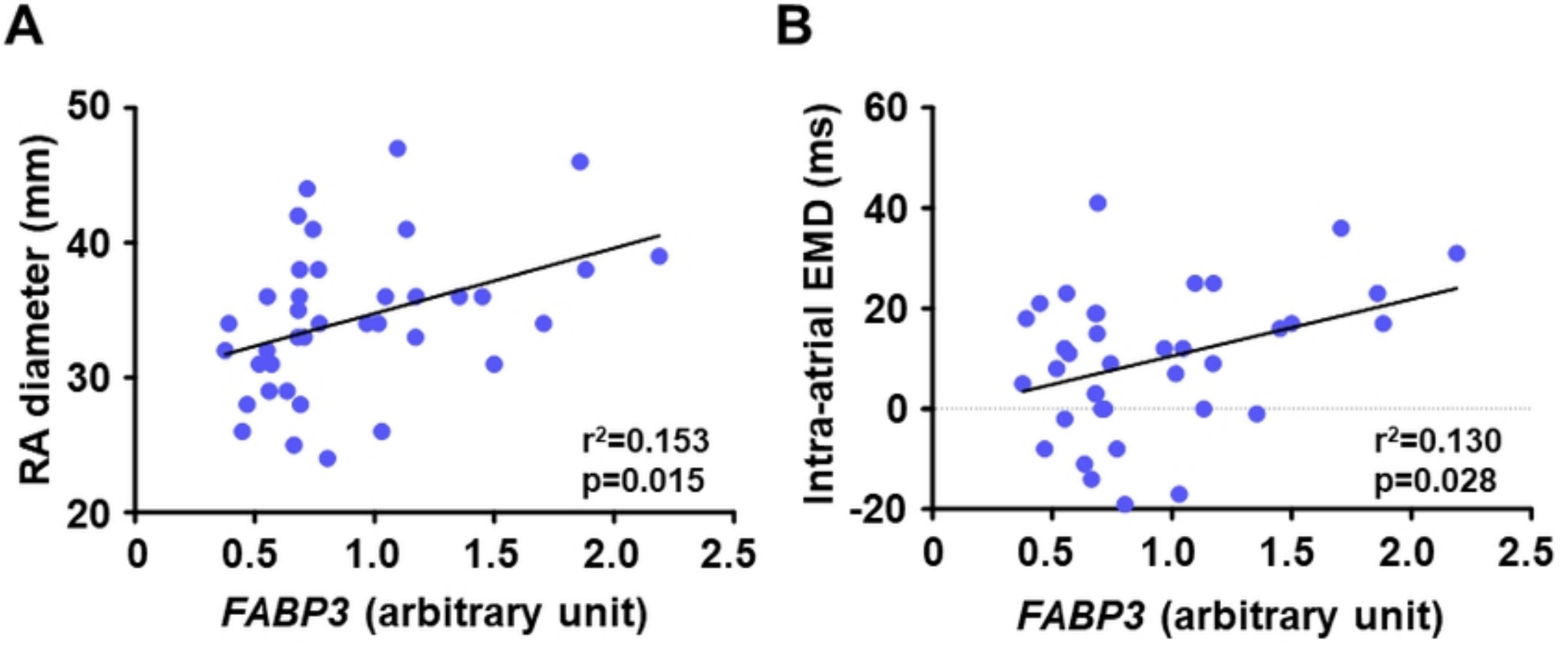

Figure 3

Figure 4

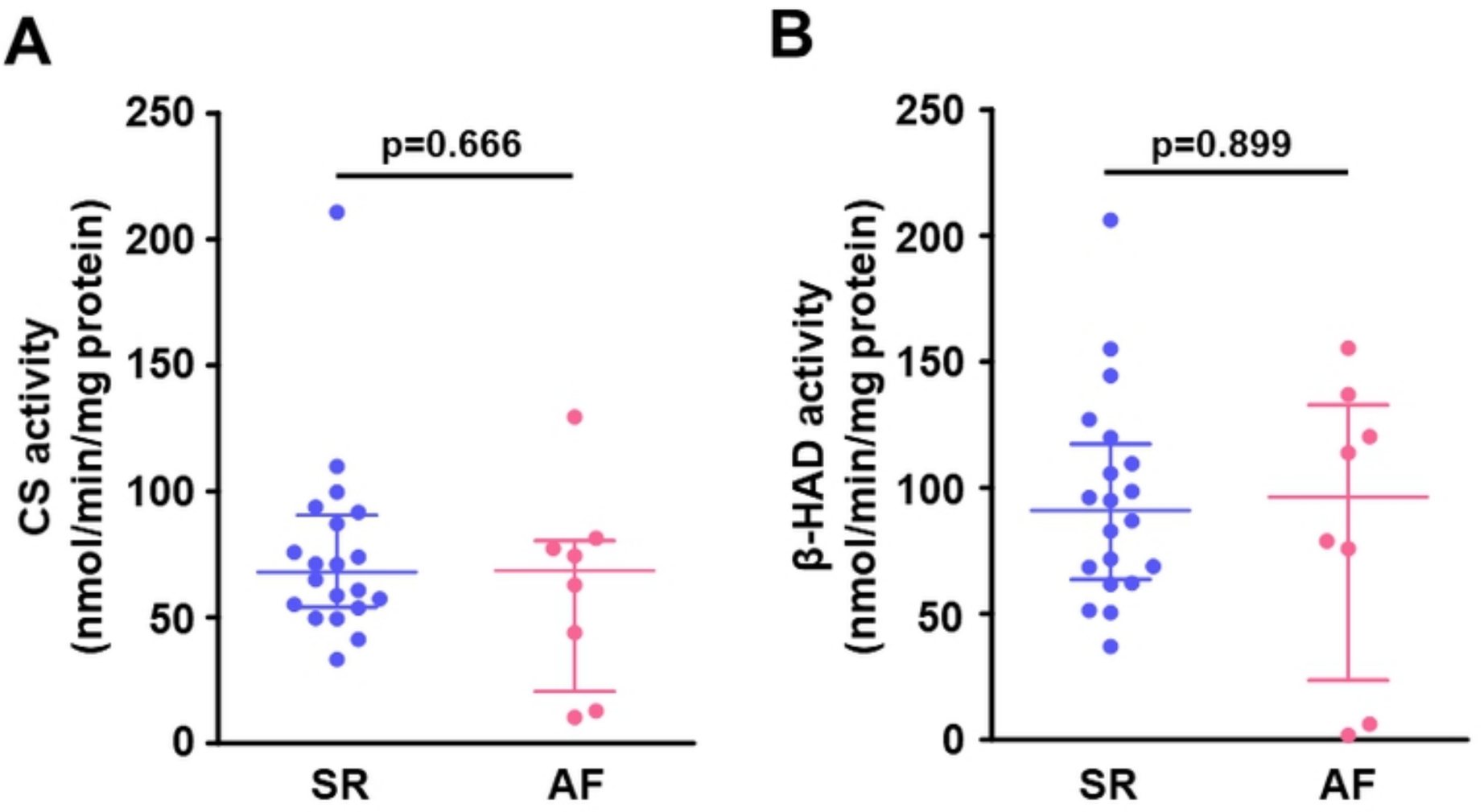

Figure 4

Figure 6

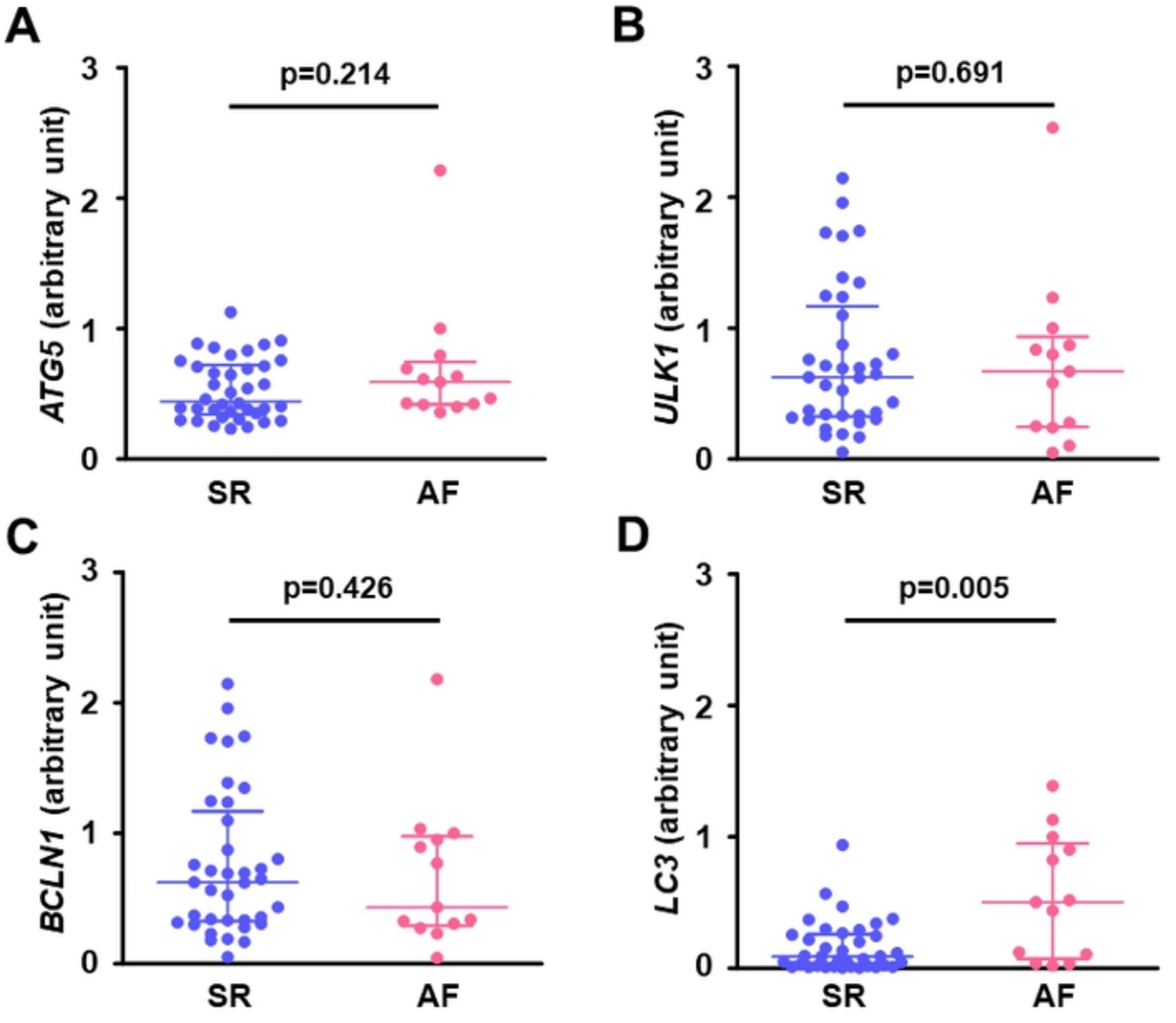

Figure 6

Figure 7

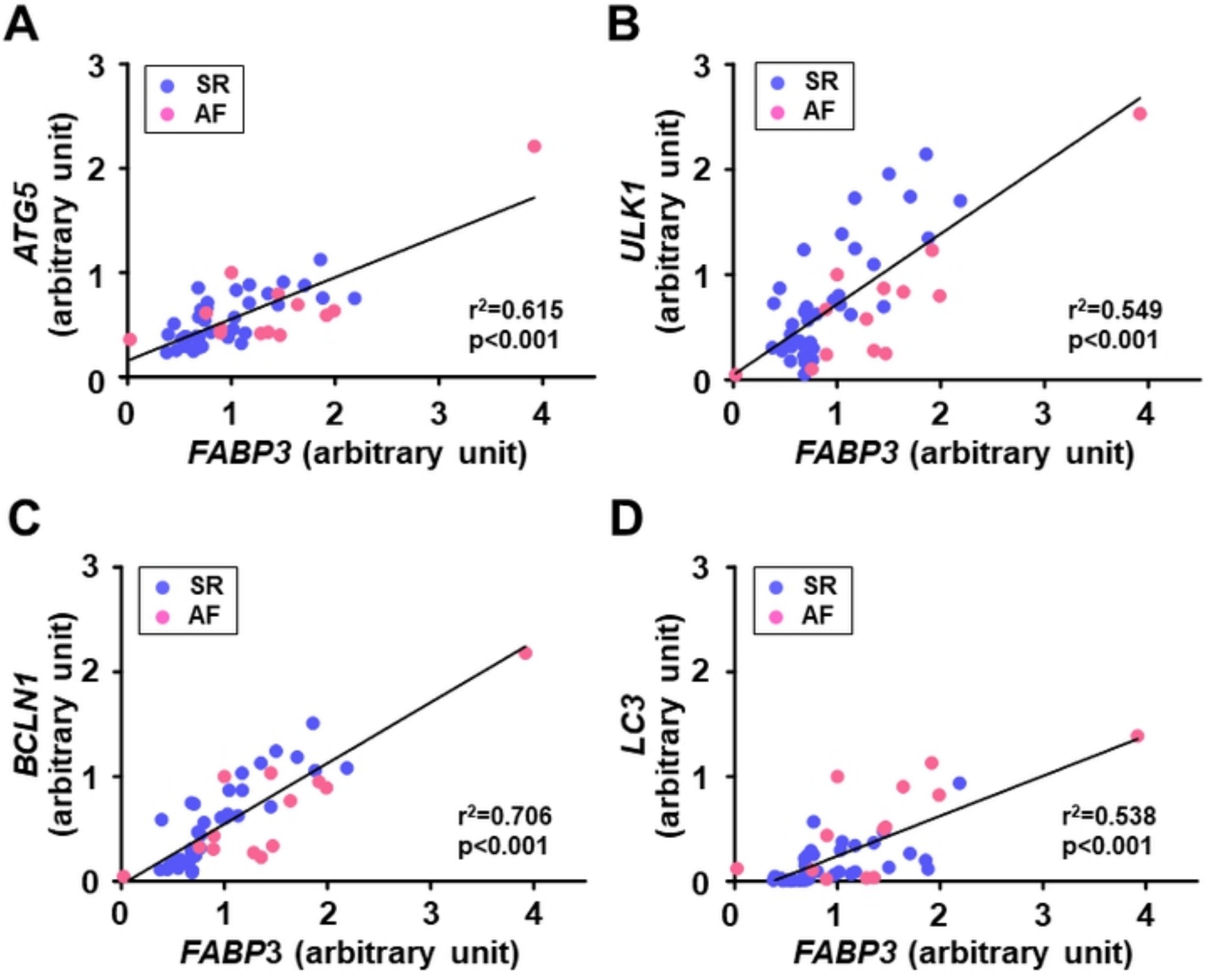

Figure 7

Figure 5

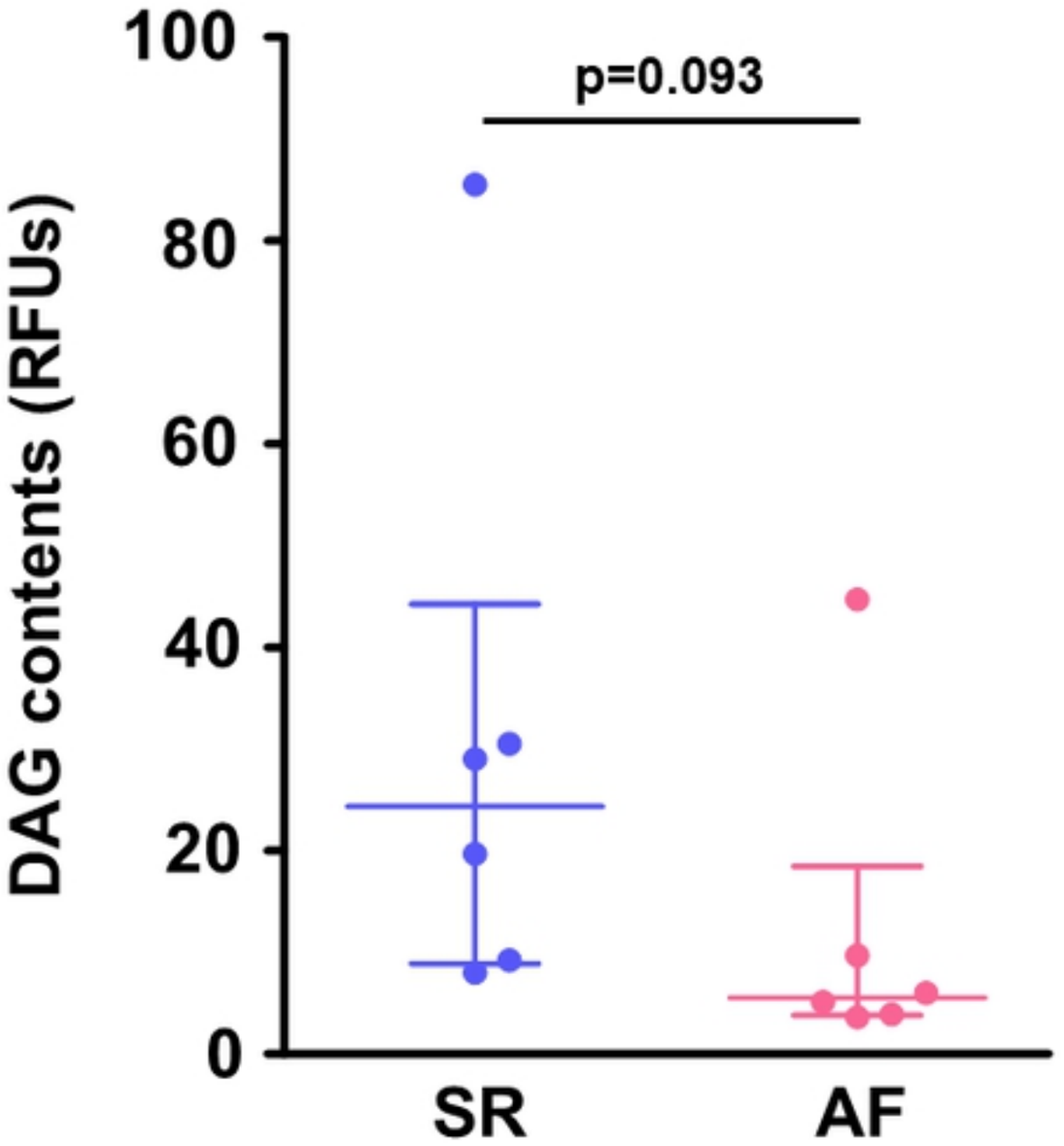

Figure 5