CARDIOVASCULAR MEDICINE

Expression of connexins 40 and 43 in human left atrium in atrial fibrillation of different aetiologies

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Objective: To test the hypothesis that atrial fibrillation (AF) is associated with changes in the expression of connexins 40 and 43 in the left atrium with more pronounced changes in mitral valve disease than in lone AF.

Methods: Protein concentrations of connexin 40 and connexin 43 were analysed in left atrial tissue of patients undergoing cardiac surgery. One group of patients had lone AF ($n = 41$), one group had AF and mitral valve repair ($n = 36$), and one group in sinus rhythm served as controls ($n = 15$).

Results: Western blot analysis of connexin 40 and connexin 43 expression showed an increase of both gap junctional proteins (connexin 43 > connexin 40) in patients with AF of all forms compared with patients in sinus rhythm ($p = 0.01$ and $p = 0.011$, respectively). Subgroup analysis showed increased concentrations of connexin 40 in lone AF and AF with mitral valve disease compared with sinus rhythm ($p = 0.06$ and $p = 0.029$, respectively), whereas the same analysis for connexin 43 reached significance only in the mitral valve disease group ($p = 0.031$). No differences in connexin 40 and connexin 43 expression were detectable between lone AF and AF with mitral valve disease. Within the groups connexin 40 and connexin 43 expression did not differ between patients with paroxysmal AF and patients with chronic AF.

Conclusion: The present study shows for the first time that AF can induce changes in the left atrium with increased connexin expression. Furthermore, no systematic differences between patients with paroxysmal and chronic AF were detected.

Atrial fibrillation (AF) is very common in patients with mitral valve disease (MVD), although in many cases no specific cause of AF can be found—so called lone AF. AF of whatever cause leads to alterations in the electrophysiological properties of the atrial tissue, referred to as electrical remodelling, with a reduced effective refractory period, action potential duration, and conduction velocity, thereby increasing the stability of re-entrant circuits and promoting its own perpetuation.^{1–4} Conduction depends on cell to cell communication, which is determined by gap junction channels. In cardiac tissue connexins 40, 43, and 45 have been detected, with connexins 40 and 43 being the main components of the atrial gap junctions.^{4–8} Given the major role of these connexins in electrical conduction, and taking into consideration the observed pronounced electrical remodelling in AF, we proposed to find differences in connexin 40 and 43 expression between patients with AF and patients in sinus rhythm (SR). So far there are only limited and contradictory data on the role of connexins in electrical remodelling, especially in AF and mostly in the right atrial tissue.^{9–21} To test the hypothesis that AF is associated with changes in the expression of connexins 40 and 43 in the left atrium (as the typical origin of AF) with more pronounced changes in MVD than in lone AF, we analysed connexin 40 and connexin 43 protein expression in atrial tissue of patients with SR, lone AF, and AF in MVD. We also compared paroxysmal (PAF) with chronic AF (CAF).

METHODS

Patients

The study group comprised patients undergoing cardiac surgery for lone AF (lone AF group, $n = 41$: 21 with PAF and 20 with CAF), for mitral valve repair or replacement in

conjunction with intraoperative radiofrequency ablation of AF (MVD with AF group, $n = 36$: seven with PAF, 29 with CAF), and patients in SR undergoing cardiac surgery for coronary artery bypass grafting (CABG), valve replacement, or valve repair (detailed in table 1) (SR group, $n = 15$: eight with CABG or aortic valve replacement as the control group for the lone AF group, seven with SR and additional MVD). The majority of operations were minimally invasive. All tissue samples were obtained at the same stage of the surgical procedure during extracorporeal circulation.

Patients of the control group were matched to the AF groups according to age, left atrial size, and left ventricular function. Patients were enrolled in the study only if they had preserved left ventricular function and, in the lone AF group, if they had a left atrial size of ≤ 45 mm as assessed by echocardiography. Patients with impaired left ventricular function or very enlarged left atria (> 55 mm) and additional cardiac diseases such as coronary artery disease or aortic valve disease were not included in the study group. Left ventricular function had to be normal in the control group. The surgical procedure and the concept of intraoperative ablation of AF have been described in detail previously.²² All patients gave informed consent. The institutional ethics committee approved the study. The investigation conforms with the principles outlined in the Declaration of Helsinki. Table 1 summarises clinical data of the patients.

Abbreviations: AF, atrial fibrillation; CABG, coronary artery bypass grafting; CAF, chronic atrial fibrillation; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HEPES, hydroxyethylpiperazine-ethanesulfonic acid; MVD, mitral valve disease; PAF, paroxysmal atrial fibrillation; SR, sinus rhythm

Table 1 Summary of patient data

	Lone AF group (n = 41)	MVD group (n = 36)	Control group (n = 15)	p Value
PAF	21	7	0	
CAF	20	29	0	
Cardiac surgery	IRAAF	MVR+IRAAF	MVR 6, MVR+CABG 1, CABG 6, AVR+CABG 2	
Age (years)	50 (12)	63.5 (10)	61 (8)	<0.05*, NS†
LVEF (%)	60 (7)	56 (15)	55 (15)	NS
Left atrium (mm)	43 (6)	55 (11)	44 (7)	<0.05*, NS†

Data are mean (SEM) or number.

AF, atrial fibrillation; AVR, aortic valve repair or replacement; CABG, coronary artery bypass grafting; CAF, chronic atrial fibrillation; IRAAF, intraoperative radiofrequency ablation of atrial fibrillation (placement of linear lesions within the left atrium²²); LVEF, left ventricular ejection fraction; MVD, mitral valve disease; MVR, mitral valve repair or replacement; NS, not significant; PAF, paroxysmal atrial fibrillation.

*Lone AF versus MVD; †versus control.

Tissue preparation

During cardiac surgery for intraoperative ablation or mitral valve repair, left atrial tissue samples were obtained from the left sided atriotomy. In the control group only in patients undergoing CABG (n = 8), samples were taken from the right atrial appendage. The material was immediately frozen in liquid nitrogen and stored at -80°C until further investigation.

Western blot analysis

For protein extraction frozen atrial tissue samples were homogenised in hydroxyethylpiperazine-ethanesulfonic acid (HEPES) buffer with the addition of protease inhibitors (0.5 mg/ml leupeptin, 10 $\mu\text{g}/\text{ml}$ aprotinin) and 1 mM phenylmethylsulfonyl fluoride (Boehringer, Mannheim, Germany). A total of 50 μg protein was separated on a 12% sodium dodecyl sulfate polyacrylamide gel and blotted on to nitrocellulose membranes (Roth, Karlsruhe, Germany) with a tank blotting system (BioRad, Munich, Germany). Membranes were blocked with 5% milk powder (Roth) in tris buffered saline with 0.5% Tween 20 for one hour. After washing (three times for five minutes in Tween 20 and tris buffered saline) membranes were incubated with the primary antibodies rabbit anti-human connexin 40 and rabbit anti human connexin 43 (Alpha Diagnostics, San Antonio, Texas, USA) and mouse anti-human glyceraldehyde-3-phosphate dehydrogenase (GAPDH; Hytest, Turku, Finland) for two hours. After a second washing step, membranes were incubated with secondary antibodies conjugated with horse-radish peroxidase for one hour, goat anti-rabbit IgG

(Dianova, Hamburg, Germany), or rabbit anti-mouse IgG (Sigma, Deisenhofen, Germany). Membranes were washed three times in Tween 20 and tris buffered saline and subsequently developed with Super Signal Reagent (Pierce, Rockford, Illinois, USA). The specificity of the antibodies has been determined previously.²¹

Densitometric analysis

Immunoblots were exposed to x ray film (Eastman Kodak Co), developed, and analysed by ONE-Dscan 1.0 Software (Scanalytics, Los Angeles, California, USA). The relative amount of connexin in each sample was determined by comparing the grey scale values of connexin with GAPDH. The housekeeping protein GAPDH was used to assure that the same amounts of cellular protein were assessed in each sample. To avoid measurement mistakes by different x ray exposure all values were normalised to the grey scale value of an internal standard.

Statistical analysis

All data are represented as mean (SEM). Statistical evaluation was done by two way multivariate analysis of variance. Values of $p < 0.05$ were considered significant. All measurements were done in triple and mean values were used for further analysis.

Figure 1 Connexin 40 (Cx 40) and connexin 43 (Cx 43) protein concentrations in patients with atrial fibrillation (AF) compared with sinus rhythm (SR). Concentrations are expressed as the ratio of Cx to glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a housekeeping protein. All data are mean (SEM).

Figure 2 Cx 40 and Cx 43 protein concentrations in patients with lone AF and AF with mitral valve disease (MVD+AF) compared with SR. Concentrations are expressed as the ratio of Cx to GAPDH and are given as mean (SEM).

Figure 3 Cx 40 expression in paroxysmal (PAF) and chronic atrial fibrillation (CAF) in the lone AF and the MVD+AF groups. Concentrations are expressed as the ratio of Cx to GAPDH and given as mean (SEM). ANOVA, analysis of variance.

RESULTS

Patients

Table 1 presents clinical data of the patients. Patients in the lone AF group were younger and had smaller left atrial sizes than patients in the MVD group ($p < 0.05$). Left ventricular function was similar in both groups. Control patients were matched according to age and left atrial size. There were no significant differences in clinical data between the control group and the study groups.

Influence of AF on connexin 40 and connexin 43 expression

Western blot analysis of connexin 40 and connexin 43 expression presented a clear increase of both gap junctional proteins in patients with AF of either cause (lone AF and MVD, $n = 77$) compared with patients in SR with and without MVD ($n = 15$). The protein concentration of connexin 40 in left atrial tissue was slightly but significantly increased ($p = 0.01$) in patients with AF. More clearly, connexin 43 protein was significantly enhanced ($p = 0.011$) in patients with AF compared with all patients in SR (fig 1).

Next we analysed patient subgroups. Comparing connexin 40 expression between SR control patients with lone AF, we

Figure 4 Cx 43 expression in PAF and CAF in the lone AF and the MVD+AF groups compared with SR control patients. Concentrations are expressed as the ratio of Cx to GAPDH and given as mean (SEM).

Figure 5 Cx 40 and Cx 43 protein concentrations in patients without MVD (including all patients with lone AF and SR controls without MVD) compared with patients with MVD (AF and SR group).

found an almost significant increase in lone AF ($p = 0.06$). In the MVD and AF group the increase in connexin 40 compared with the SR group was significant ($p = 0.029$). There were no differences in connexin 40 concentration in left atrial tissue between patients with lone AF and patients with MVD and AF ($p = 0.89$) (fig 2).

The same comparisons for connexin 43 expression showed an increase (though not significant) in the lone AF group and a significant increase in the MVD with AF group compared with the SR group ($p = 0.12$ and $p = 0.031$, respectively) (fig 2). There were also no significant differences in connexin 43 expression between the lone AF and the MVD with AF group ($p = 0.54$).

To investigate the influence of the PAF and CAF forms of AF on the protein expression of connexin 40 and connexin 43 we compared patients with PAF and CAF within the groups. No significant differences in either connexin 40 or connexin 43 expression were found when comparing patients with PAF versus CAF within the lone AF and the MVD group (figs 3 and 4).

Influence of MVD on connexin 40 and connexin 43 expression

Lastly, to determine the influence of MVD on connexin expression in general, we compared all patients without MVD (SR and lone AF, $n = 49$) with all patients with MVD (MVD and SR, and MVD and AF, $n = 43$) and did not detect any changes in either connexin 40 or connexin 43 protein expression (fig 5).

DISCUSSION

The present study shows that AF is accompanied by significant changes in the protein expression of connexins 40 and 43 in the left atrium (connexin 43 > connexin 40). Subgroup analysis, however, showed a trend towards increased concentrations of connexin 40 in lone AF and significantly increased concentrations of connexin 40 protein in MVD and AF. Differences in connexin 43 expression were significant only in the MVD and AF subgroup. Interestingly, connexins 40 and 43 changed to a similar extent in patients with lone AF and in patients with AF with MVD, suggesting that AF alone may be enough to lead to changes of the atrium with increased expression of gap junctional proteins and that MVD does not induce further changes. Furthermore, no systematic differences between patients with PAF and patients with CAF were detected.

To our knowledge this is the first study of changes in connexin 40 and connexin 43 expression in human lone AF in the left atrium. So far only a limited number of studies on connexin expression in human AF are available. All of them

investigated only patients with advanced structural heart disease with an indication for cardiac surgery.^{14 15 17 20 23}

Regarding connexin 40 our data are in close accordance with data presented by Polontchouk *et al.*¹⁴ who observed a similar increase in connexin 40 in the right atrium of patients with CAF. Dupont *et al.*¹⁵ also found significantly higher connexin 40 concentration in patients susceptible to post-operative AF, although this arrhythmia and “naturally occurring” AF are probably caused by different pathophysiological mechanisms. On the other hand, Kostin *et al.*¹⁷ described a significant decrease of connexin 40 in the right atrial appendages of patients with AF and a slight but non-significant increase in the right atrial free wall of the same patients. Recently Nao *et al.*¹⁹ showed a significant reduction of connexin 40 protein and mRNA concentrations in the right atrial tissue of patients with MVD and AF compared with normal SR and MVD and normal controls (patients undergoing CABG), but they described a significant increase in serine phosphorylated connexin 40 in MVD and AF. In the goat model of pacing induced AF no quantitative changes in connexin 40 were found but there was a pronounced change in the distribution of connexin 40 from end to end junctions to the lateral wall.^{13 20}

The available data on connexin 43 are also inconclusive, since Kostin *et al.*¹⁷ described significant decreases in connexin 43 in patients with AF, whereas Polontchouk *et al.*¹⁴ Dupont *et al.*¹⁵ and Nao *et al.*¹⁹ in human material and van der Velden *et al.*^{18 21} in goats did not find any quantitative change in connexin 43 with AF. However, the source of the tissue (right or left atrium) should be taken into account. Only Elvan *et al.*¹² observed an increase in connexin 43 in pacing induced AF, which returned to normal after linear radiofrequency ablation within the right atrium. Several attempts have been undertaken either surgically or by catheter techniques to cure AF by linear ablation especially within the left atrium.^{22 24}

The functional consequence of our findings is not clear at the moment, since we do not know whether the expressed connexin 40 and connexin 43 proteins form functional gap junction channels and, if so, what kind of electrical alterations are caused by a higher number of gap junction channels. It is known from animal studies with knock out models that changes in connexin 40 are accompanied by changes in atrial electrical coupling and susceptibility to AF,^{25–28} whereas changes in connexin 43 lead to disturbances of ventricular electrical coupling.^{28 29} In cardiac diseases altering ventricular function, changes in connexin 43 have been observed. A common feature in ventricular function disturbance is a reduction in connexin 43 (the main ventricular connexin) and a change in gap junction distribution and size with an increase in side to side coupling and a decrease in end to end connections. Changes in gap junctional organisation or in the amount of connexin 43 are associated with an increased risk of arrhythmias in the diseased ventricle. In the atrium higher connexin 40 concentrations are associated with a higher risk of developing AF after cardiac surgery.^{11–13 30–37} According to these data one would expect to find only changes in connexin 40, the main atrial connexin, and not necessarily changes in connexin 43. However, in our study we clearly detected differences in connexin 40 and connexin 43 protein expression in patients with AF. If the increased expression of connexin 40 and connexin 43 protein leads to functioning gap junction channels both longitudinally and laterally at the cell wall, one would expect a change in the biophysical properties of the cells as shown by Polontchouk *et al.*³⁸ Further studies to examine the connexin distribution and function in the atria, and cell culture and animal studies analysing the electrophysiological properties of the changed gap junction channels, are needed.

Regulation of gap junctional expression, distribution, and function is still under investigation. A lot of factors such as phosphorylation and dephosphorylation, voltage gradients, and many signalling pathways seem to be involved.^{3–7 38} Gap junction channels have a very short half life and are therefore prone to regulatory mechanisms.^{6 7 33} Recently it was shown that the renin–angiotensin system is involved in the regulation of connexin expression through the AT1 receptor, hinting that altered connexin expression and arrhythmogenesis are linked to various cardiac diseases accompanied by changes in the renin–angiotensin system.^{6 33 34 38–40} Involvement of the renin–angiotensin system may allow new treatment options for the many patients with AF. The first clinical observations have already been made of reduced AF recurrences in patients treated with angiotensin converting enzyme inhibitors.

Study limitations

Our study had some limitations mainly caused by tissue sample availability. Because of ethical and surgical concerns it was not possible to analyse left atrial tissue from healthy patients in SR without MVD. So far there are no conclusive data on differential connexin expression in the left and right atrium. Therefore, we hypothesised that the distribution of connexins 40 and 43 and their changes in pathological processes are similar in left and right atrial tissue. However, according to the data of this study connexin 40 and connexin 43 protein expression needs to be compared in the left and right atrium; we are investigating this comparison in our laboratory.

Conclusion

Our study showed a significant up regulation of connexin 40 and even more of connexin 43 protein expression in the left atrial tissue of patients with AF without and with MVD. Changes were of about the same magnitude in lone AF and in AF with MVD with no significant differences between PAF and CAF. Changes in gap junctional protein expression may be important in the electrical and morphological remodelling processes in AF. A better understanding of the pathophysiological mechanisms in the development and perpetuation of AF will improve the management of arrhythmia.

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ELECTRONIC PAGES

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Treatment of unprotected left main coronary artery stenosis with a drug eluting stent in a heart transplant patient with allograft vasculopathy

G Matos, L Steen, F Leya

High risk angioplasty with drug eluting stent placement into an unprotected left main coronary artery in a heart transplant recipient with allograft vasculopathy is reported. Ten month angiographic follow up is reported. The literature is reviewed and current methods of revascularisation are described in detail. This is the first report of drug eluting stent use in this clinical situation.

(*Heart* 2005;**91**:e11) www.heartjnl.com/cgi/content/full/91/2/e11

Hypoplastic coronary artery disease: report of one case

N Amabile, A Fraisse, J Quilici

Hypoplastic coronary artery disease (HCAD) is a rare abnormality with a high rate of sudden death and poor outcome. HCAD was revealed by myocardial infarction in a teenager with objective evidence of silent ischaemia on myocardial scintigraphy. After four years of follow up, he suddenly collapsed during exercise and subsequently died.

Although HCAD is very uncommon, it should be actively excluded in children and young adults who experience sudden cardiac death. Aggressive treatment such as implantable cardioverter-defibrillator or heart transplantation may be indicated for this rare coronary abnormality.

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Contained myocardial rupture: a variant linking complete and incomplete rupture

T A Helmy, W J Nicholson, S Lick, B F Uretsky

Myocardial rupture is an uncommon complication of myocardial infarction, often with devastating haemodynamic consequences. Although rupture is usually fatal, when patients do survive, the majority present with a pseudoaneurysm in which the rupture is sealed by a haematoma on the epicardial surface of the heart. Cases in which all myocardial layers are dissected except the epicardium or visceral pericardium have been included under this subheading. The authors describe such a case and suggest the pathological description of a “contained myocardial rupture”. This link between complete and incomplete myocardial rupture may allow a more conservative management approach to be pursued.

(*Heart* 2005;**91**:e13) www.heartjnl.com/cgi/content/full/91/2/e13