HEART RHYTHM DISORDERS

Mechanoelectrical feedback regulates the arrhythmogenic activity of pulmonary veins

S-L Chang, Y-C Chen, Y-J Chen, W Wangcharoen, S-H Lee, C-I Lin, S-A Chen

Heart 2007;**93**:82–88. doi: 10.1136/hrt.2006.089359

See end of article for authors' affiliations

Correspondence to: Dr Yi-Jen Chen, Division of Cardiovascular Medicine, Taipei Medical University-Wan-Fang Hospital, 111, Hsin-Lung Road, Sec 3, Taipei, Taiwan; yjchen@tmu.edu.tw

Accepted 7 August 2006
Published Online First 11 August 2006

Background: Atrial fibrillation is commonly associated with dilated pulmonary veins. Stretch has been shown to have mechano-electrical effects.
Objective: To investigate whether stretch can increase the arrhythmogenic activity of the pulmonary veins.
Methods: The transmembrane action potentials were recorded from rabbit pulmonary veins before and after stretch (100 and 300 mg). Gadolinium and streptomycin (stretch-activated ion channel blockers) were each perfused into the pulmonary veins under a 300-mg stretch.
Results: Stretch (0, 100 and 300 mg) force dependently increased the incidence of spontaneous activity (22%, 48% and 83%; $p<0.05$), mean (standard deviation (SD)) firing rates of spontaneous activity (1.7 (0.2), 2.1 (0.3) and 3 (0.2) Hz; $p<0.05$) and incidence of early post-depolarisations (9%, 26% and 61%; $p<0.05$) and delayed post-depolarisations (0%, 4% and 30%; $p<0.05$) in 23 pulmonary veins. In the seven preparations with spontaneous activity after the 300-mg stretch, gadolinium (1, 3 and 10 μmol/l) decreased the incidence of spontaneous activity by 43%, 29% and 14%, respectively ($p<0.05$), and decreased the firing rate from 2.9 (0.1) Hz to 0.8 (0.4), 0.3 (0.1) and 0.1 (0.1) Hz, respectively ($p<0.05$). Streptomycin (10 and 40 μmol/l) decreased the incidence of spontaneous activity by 71% and 29%, respectively ($p<0.05$), and decreased the firing rate from 2.9 (0.1) Hz to 1.6 (0.4) and 0.5 (0.3) Hz, respectively ($p<0.05$).
Conclusion: Stretch is an important factor in the electrical activity of the pulmonary vein. Stretch-induced arrhythmogenic activity of the pulmonary vein may contribute to the genesis of atrial fibrillation.

Atrial fibrillation is the most common cardiac arrhythmia in clinical practice, and can induce cardiac dysfunction and strokes. Atrial dilatation is an important risk factor for the genesis of atrial fibrillation.[1 2] The enlargement of atrial size is highly associated with the occurrence of atrial fibrillation, and avoidance of atrial enlargement may be important in preventing atrial fibrillation.[1 2] Mechanoelectrical feedback as a result of atrial enlargement alters the atrial refractoriness and dispersion and increases the vulnerability for atrial fibrillation.[3–5] On the other hand, stretch-activated ion channel (SAC) blockers were shown to decrease the vulnerability to atrial fibrillation.[6 7] These findings indicated the importance of mechanoelectrical feedback in the pathophysiology of atrial fibrillation.

Pulmonary veins are important sources of ectopic beats for the initiation of paroxysmal atrial fibrillation.[8] Other studies have suggested that pulmonary veins play a part in the maintenance of atrial fibrillation.[9] Previous anatomical and electrophysiological studies on isolated specimens of pulmonary veins have shown that pulmonary veins contain a mixture of pacemaker cells and working myocardium.[10–12] Isolated single pulmonary vein cardiomyocytes have distinct electrophysiological characteristics and high arrhythmogenic activity.[13 14] Mechanisms of re-entrant or non-reentrant focal electrical activity are suggested to underlie the arrhythmogenic activity of the pulmonary veins.[15–19] Dilated pulmonary veins are associated with a high stretch level, which may contribute to the initiation of atrial fibrillation.[20] An increase in the atrial pressure would accelerate the firing rates in pulmonary veins and result in the genesis of atrial fibrillation.[21] This evidence suggests that stretch may increase the arrhythmogenic activity of the pulmonary veins, which may induce atrial fibrillation. However, knowledge on the electrophysiological effects of stretch on the pulmonary veins is limited. It is not clear whether SAC blockers may reduce the arrhythmogenic potentials of the pulmonary veins. The purpose of this study was to investigate the role of stretch and SAC blockers in the electrical activity of the pulmonary veins.

METHODS

Rabbit pulmonary vein tissue preparations

This investigation conformed to the institutional Guide for the Care and Use of Laboratory Animals. Rabbits (weighing 1–2 kg) were anaesthetised with an intraperitoneal injection of sodium pentobarbital (40 mg/kg). A midline thoracotomy was then performed, and the heart and the lungs were removed. For the dissection of the pulmonary veins, the left atrium was opened by an incision extending from the coronary sinus to the septum while immersed in normal Tyrode's solution consisting (in mM) of 137 NaCl, 4 KCl, 15 $NaHCO_3$, 0.5 NaH_2PO_4, 0.5 $MgCl_2$, 2.7 $CaCl_2$ and 11 dextrose. The pulmonary veins were separated from the atrium at the left atrium–pulmonary vein junction and separated from the lungs at the end of the pulmonary vein myocardial sleeve. One end of the preparation, consisting of the left atrium–pulmonary vein junction, was pinned to the bottom of a tissue bath. The other end was connected to a Grass FT03C force transducer (Grass Instruments, Quincy, Massachusetts, USA) with silk thread. The adventitia of the pulmonary veins faced upwards, and the length of the un-stretched pulmonary vein specimens was around 10 mm. The tissue was superfused at a constant rate (3 ml/min) with Tyrode's solution saturated with a 97% O_2–3% CO_2 gas mixture. The temperature was maintained constant at 37°C and the preparations were allowed to equilibrate for 1 h before performing the electrophysiological study.

Abbreviations: APA, amplitudes of the action potential; APD, action potential duration; DAD, delayed afterrepolarisation; EAD, early afterrepolarisation; MDP, membranous diastolic potential; SAC, stretch-activated ion channel

Electrophysiological and pharmacological studies

To investigate the effects of different tensions on the pulmonary veins, the transmembrane action potentials were recorded before and after successive stretch (100 and 300 mg) by glass capillary microelectrodes filled with 3 M of KCl and connected to a WPI model FD223 electrometer, as described previously.[17] The preparation was stretched until force began to develop. The electrical activities of pulmonary veins (at more than 20 sites) were recorded sequentially at a distance of 0.2 mm (in the horizontal and longitudinal direction) in the pulmonary vein myocardial sleeve. The electrical and mechanical events were displayed simultaneously on a Gould 4072 oscilloscope and a Gould TA11 recorder (Gould Instruments, Valley View, Ohio, USA). The signal was recorded with DC coupling and a 10-kHZ low-pass filter cut-off frequency using a data-acquisition system. Signals were recorded digitally with 16-bit accuracy at a rate of 125 kHz. An electrical stimulus (2 Hz) with a 2-ms duration and suprathreshold strength (30% above the threshold) was provided using a Grass S88 stimulator through a Grass SIU5B stimulus isolation unit. The amplitudes of the action potential (APA), the duration of action potential at a repolarisation of 90% (APD_{90}) and at 50% of the APA (APD_{50}), and membranous diastolic potential (MDP) were measured only during a steady-state action potential achieved without interference from the spontaneous activity of the pulmonary vein. The spontaneous activity of the pulmonary vein was determined by recording the automatically occurring electrical activity. To study the effects of the SAC blockers and compare them with those of L-type calcium channel blockers on the electrical activity of the pulmonary veins, gadolinium (1, 3 and 10 μmol/l), streptomycin (10 and 40 μmol/l) and verapamil (0.1 μmol/l) were given.

Statistical analysis

All quantitative data are expressed as mean (standard error of the mean). A paired t test or one-way repeated analysis of variance was used to compare the differences before and after the stretch or drug administration in the pulmonary vein preparations. Multiple comparisons were analysed with Fisher's least significant difference test; $p<0.05$ was considered significant.

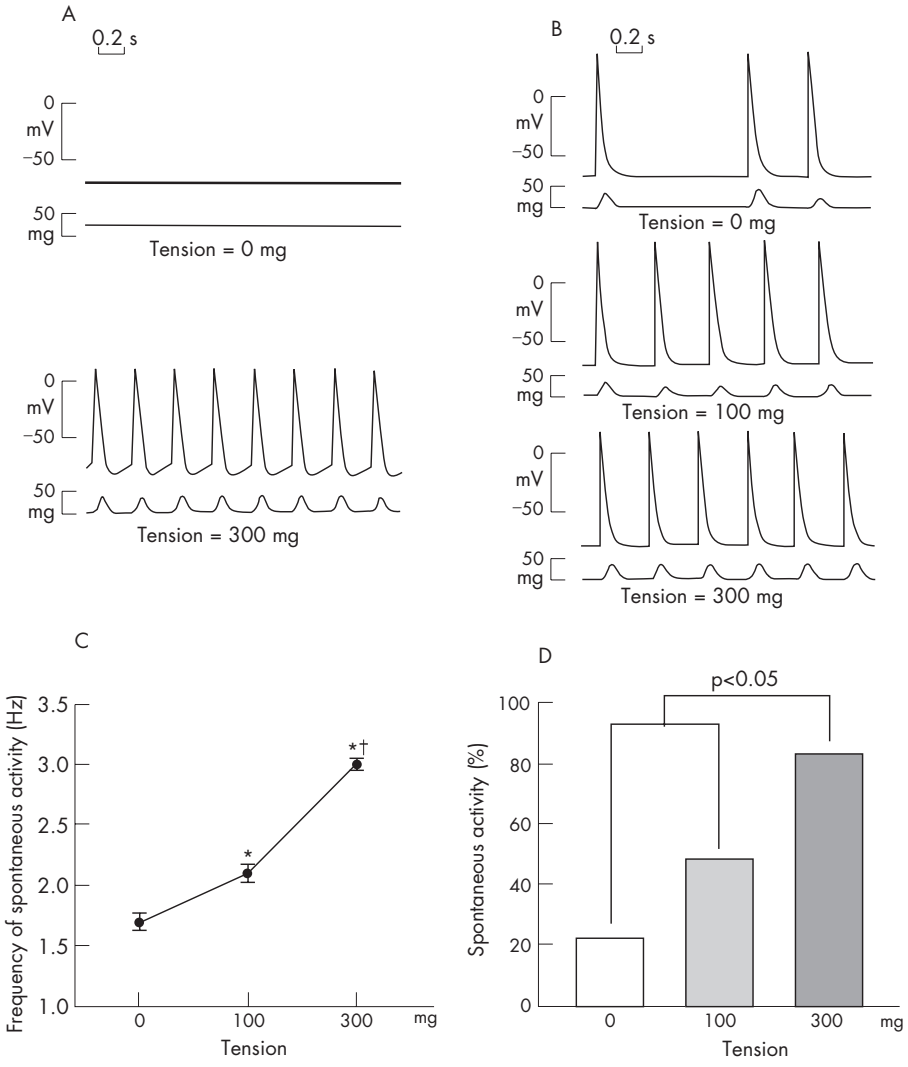

Figure 1 Effects of stretch on the electrical activityof a pulmonary vein (PV). (A) Tracings of stretch (300 mg) inducing the occurrence of spontaneous activity of the PVs. There was no spontaneous activity before the stretch. (B) Stretch force dependently increased the firing rate of the spontaneous activity of the PVs. (C, D) Firing rates and average incidence during the different stretch levels.

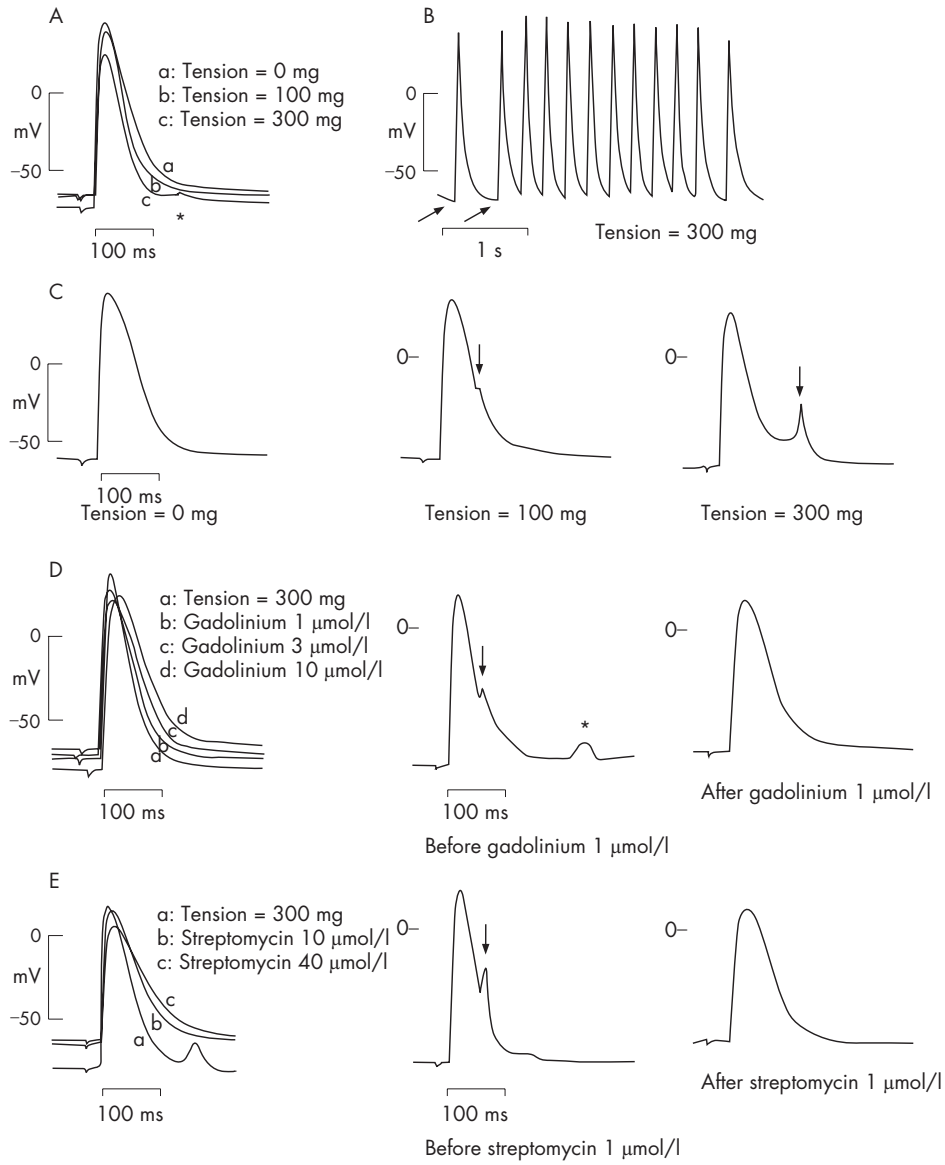

Figure 2 Effects of stretch and stretch-activated ion channel blockers on the action potential (AP) configuration of the pulmonary veins (PV). (A) Superimposed tracings in which stretch force dependently decreased the amplitude and duration of the AP and induced delayed after-depolarisations (DAD; start). (B) Stretch (300 mg) induced the genesis of early after-depolarisation (EAD) and resulted in the occurrence of burst firings in PVs. Arrow indicates electrical stimuli (2 Hz). (C) Tracings of the APs before (left) and after the stretch (100 mg, middle; 300 mg, right). Stretch force dependently increased the genesis of EADs (arrows). (D) Superimposed tracings in which gadolinium dose dependently increased the AP duration in the PVs with 300 mg of stretch (left); inhibited the stretch-induced DADs (start; middle) and EADs (arrow; right) in the PVs. (E) Superimposed tracings in which streptomycin increased the AP duration and inhibited the stretch-induced DADs in the PVs with 300 mg of stretch (left). The middle and right panels show the inhibition of stretch-induced EADs (arrow) in the PVs during the administration of streptomycin.

RESULTS

Effect of the stretch on the spontaneous activity of the pulmonary veins

In 23 isolated pulmonary vein preparations, 5 pulmonary veins had spontaneous activity before the stretch. During a 100-mg stretch, 11 pulmonary veins had spontaneous activity, and during a 300-mg stretch, 19 pulmonary veins had spontaneous activity. Figure 1A shows an example of the stretch-induced occurrences of the spontaneous activity of the pulmonary veins. Figure 1B shows an example in which the stretch force dependently increased the firing rates in a pulmonary vein. The incidence of the spontaneous activity of the pulmonary veins and the firing rates increased force dependently (fig 1C,D).

Effect of stretch on the action potentials of the pulmonary veins

Table 1 summarises the action potential parameters of the pulmonary vein specimen before and after applying stretch of different amounts. The APA, APD_{50} and APD_{90} of the pulmonary veins decreased force dependently. The incidence of early after-depolarisations (EADs) and delayed after-depolarisations (DADs) in the pulmonary veins also increased force dependently. Figure 2A and C shows examples in which the stretch changed the action potential configuration and the induction of EADs and DADs in the pulmonary veins. The EADs could result in the occurrence of burst firing in pulmonary veins (fig 2B).

Table 1 The action potential parameters of the pulmonary veins before and after the stretch

Tension (mg)	0	100	300	p Value
APA (mV)	110 (10)	101 (9)*	86 (7)*†	<0.005
APD_{50} (ms)	63 (9)	58 (8)*	47 (11)*†	<0.005
APD_{90} (ms)	137 (16)	129 (15)*	110 (14)*†	<0.005
MDP (-mV)	70 (5)	72 (6)*	81 (6)*†	<0.005
Incidence of EADs (%)	2/23 (9%)	6/23 (26%)	14/23 (61%)*†	<0.005
Incidence of DADs (%)	0/23 (0%)	1/23 (4%)	7/23 (30%)*†	<0.005

APA, amplitudes of the action potential; APD, action potential duration; APD_{50}, action potential at a repolarisation of 50%; APD_{90}, action potential at a repolarisation of 90%; DADs, delayed after-repolarisation; EADs, early after-repolarisation; MDP, membranous diastolic potential.
Action potentials of the pulmonary veins (n = 23) elicited by electrical stimuli (2 Hz), *p<0.05 versus tension = 0; †p<0.05 versus tension = 100 mg.

Effect of gadolinium and streptomycin on spontaneous activity of the pulmonary vein

Twelve pulmonary veins with a 300-mg stretch received gadolinium, and 5 of the 12 preparations had spontaneous activity before the stretch and 7 of the 12 preparations had spontaneous activity after the stretch. Figure 3A shows an example in which gadolinium (1, 3 and 10 μM) did not change the firing rate of the spontaneous activity in an unstretched pulmonary vein. In the five preparations with spontaneous activity before stretch, gadolinium (1, 3 and 10 μmol/l) did not change the spontaneous activity and firing rates of the pulmonary vein. Figure 3B shows another example in which gadolinium (1, 3 and 10 μmol/l) dose dependently decreased the firing rates of the spontaneous activity in a stretched pulmonary vein. In the seven preparations with spontaneous activity after stretch, gadolinium dose dependently decreased the incidence of the spontaneous activity of the pulmonary vein and reduced the mean (SD) firing rates by 71% (13%), 91% (6%), and 98% (2%), respectively (fig 3C,D). This effect was reversible after a washout of the gadolinium over 10 min. The half-maximal inhibitory concentration of gadolinium was 0.45 μmol/l.

Similarly, fig 4A shows an example in which streptomycin (10 and 40 μmol/l) dose dependently decreased the firing rate of the spontaneous activity in a stretched pulmonary vein. In the pulmonary veins with spontaneous activity after a 300-mg stretch (n = 7), streptomycin (10 and 40 μmol/l) dose dependently decreased the incidence of the spontaneous activity and reduced the mean (SD) firing rate by 44% (15%) and 82% (11%), respectively (fig 4B,C). This effect was reversible after a washout of the streptomycin over 20 min.

Figure 4D shows an example in which the calcium channel blocker verapamil (0.1 μmol/l) slightly decreased the firing rates of the spontaneous activity in a stretched pulmonary vein. Verapamil (0.1 μmol/l) reduced the firing rates only by 14 (1%) (from 2.9 (0.1) to 2.5 (0.1) Hz; n = 7; p<0.05) in the pulmonary veins with spontaneous activity after a 300-mg stretch. This effect is significantly less than those of gadolinium (1, 3 and 10 μmol/l) and streptomycin (10 and 40 μmol/l).

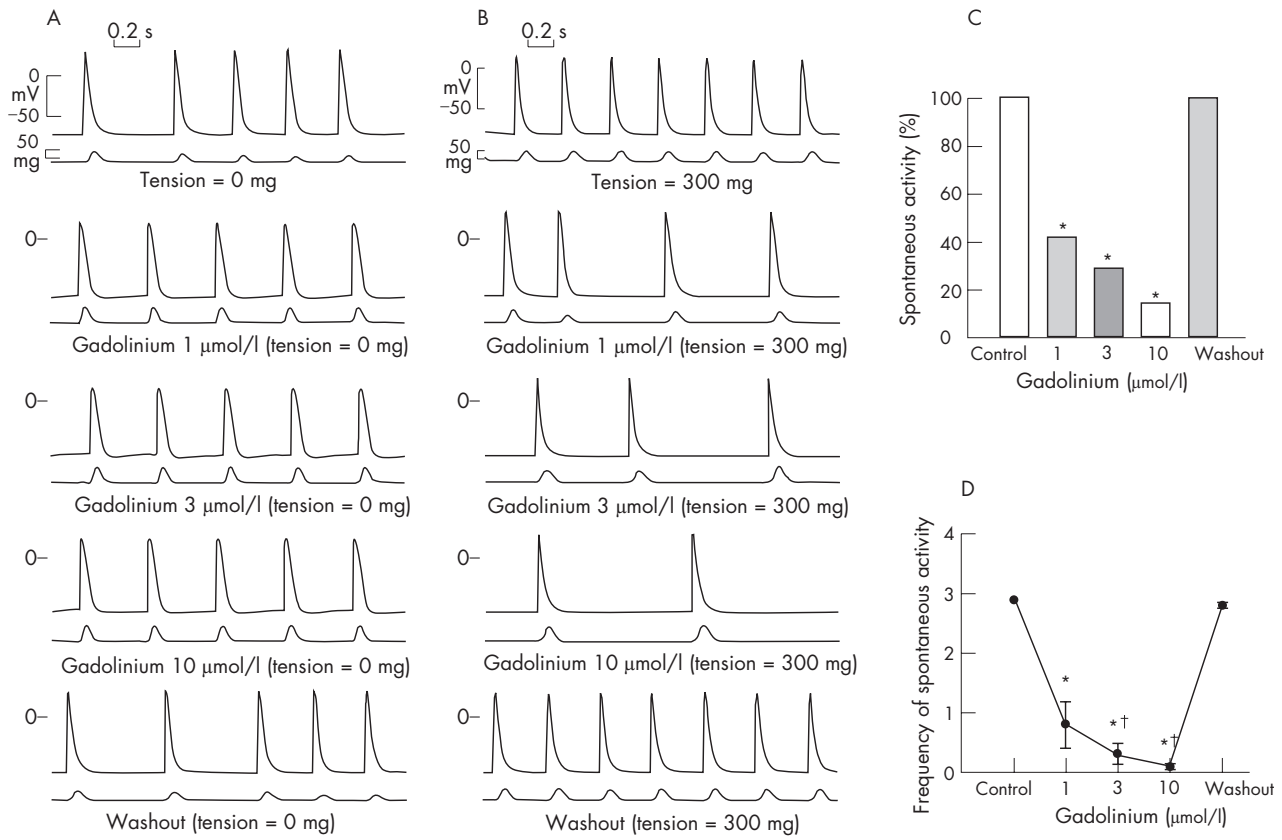

Figure 3 Effect of gadolinium on the stretch-induced spontaneous activity of a pulmonary vein (PV). (A) Tracings in which gadolinium had little effect on the PVs presenting with spontaneous activity without stretch. (B) Tracings in which gadolinium (1, 3 and 10 μmol/l) decreased the firing rates of the spontaneous activity of the PV after the stretch. This effect was reversible after a washout of the gadolinium. (C, D) The effect of gadolinium on the incidence and firing rates in the stretch-induced spontaneous activity of a PV. *p<0.05 versus 0 μmol/l gadolinium; †p<0.05 versus 1 μmol/l gadolinium.

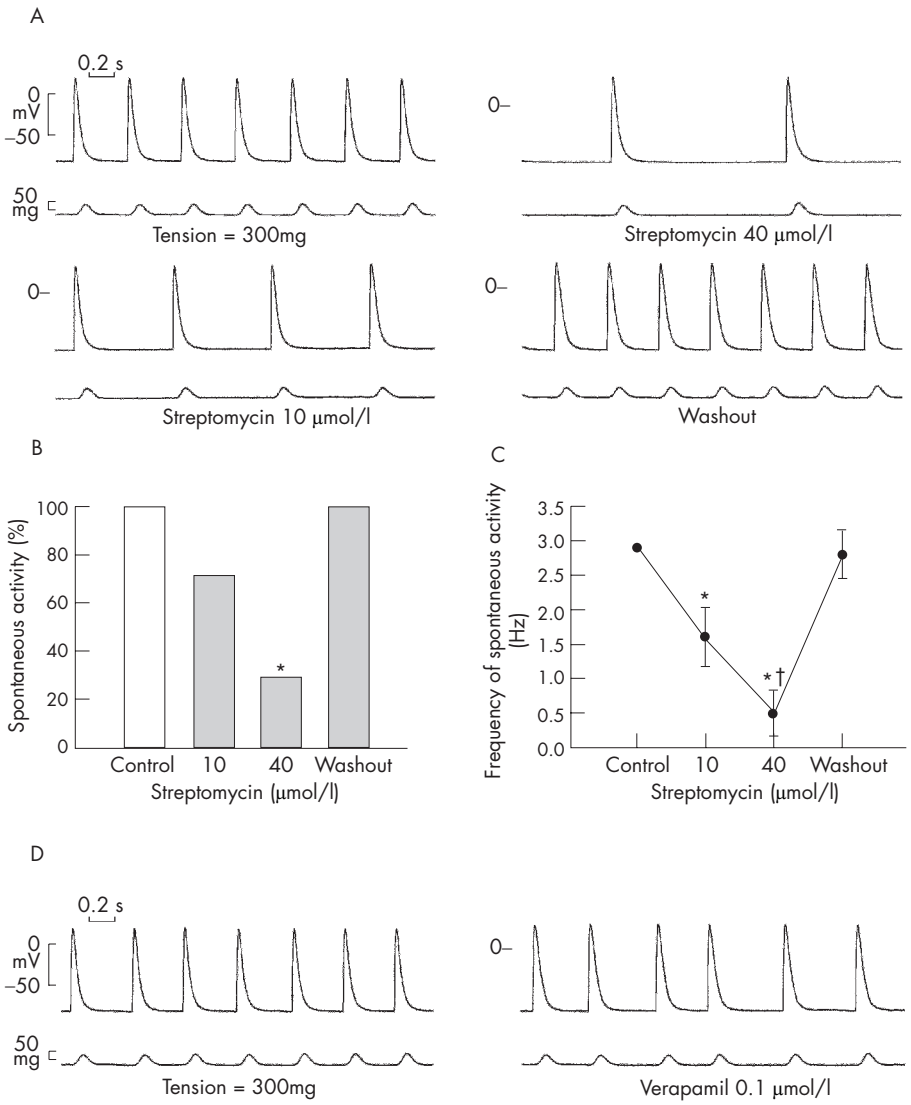

Figure 4 Effect of streptomycin on the stretch-induced spontaneous activity of a pulmonary vein (PV). (A) Streptomycin (10 and 40 μmol/l) decreased the firing rate of the spontaneous activity of the PV after the stretch. This effect was reversible after a washout of the streptomycin. (B, C) Effect of streptomycin on the incidence and firing rate in the stretch-induced spontaneous activity of the PV. (D) Tracings in which verapamil (0.1 μmol/l) reduced the firing rate (from 2.8 to 2.4 Hz) in the stretch-induced spontaneous activity of the PV. *p<0.05 versus. 0 μmol/l streptomycin, †p<0.05 versus 10 μmol/l streptomycin.

Table 2 Effect of gadolinium and streptomycin on the action potential parameters of the pulmonary veins with 300-mg stretch

	Gadolinium (n = 12)					Streptomycin (n = 7)			
Concentrations (μmol/l)	**0**	**1**	**3**	**10**	**p Value**	**0**	**10**	**40**	**p Value**
APA(mV)	90 (3)	84 (3)*	81 (3)*†	77 (3)*†‡	<0.005	91 (2)	82 (1)§	80 (2)§*	<0.005
APD_{50} (ms)	48 (6)	54 (3)*	60 (5)*†	65 (6)*†	<0.005	48 (2)	55 (2)	62 (2)§¶	<0.005
APD_{90} (ms)	109 (13)	117 (4)	123 (6)*†	135 (9)*†‡	<0.005	115 (3)	119 (2.1)	132 (3)§¶	<0.005
MDP (−mV)	83 (4)	75 (5)*	71 (3)*†	66 (4)*†‡	<0.005	83 (2)	70 (2)§	68 (2)§	<0.005
Incidence of EADs (%)	9/12 (75)	6/12 (50)	2/12 (17)*	1/12 (8)*	<0.005	6/7 (86)	3/7 (43)	1/7 (14)§	<0.005
Incidence of DADs (%)	5/12 (42)	2/12 (17)	0/12 (0)*	0/12 (0)*	<0.05	4/7 (57)	2/7 (33)	0/7 (0)	0.06

APA, amplitudes of the action potential; APD_{50}, action potential at a repolarisation of 50%; APD_{90}, action potential at a repolarisation of 90%; DADs, delayed after-repolarisation; EADs, early after-repolarisation; MDP, membranous diastolic potential.
Gadolinium and streptomycin were given in different groups of tissue preparations. The action potentials of the pulmonary veins were elicited by electrical stimuli (2 Hz). *p<0.05 versus 0 μmol/l gadolinium; †p<0.05 versus 1 μmol/l gadolinium; ‡p<0.05 versus 3 μmol/l gadolinium; §p<0.05 versus 0 μmol/l streptomycin; ¶p<0.05 versus 10 μmol/l streptomycin.

Effect of gadolinium and streptomycin on the action potential of the pulmonary vein

Table 2 summarises the effects of gadolinium and streptomycin on the action potential parameters driven by electrical stimulation in the pulmonary vein specimens during a 300-mg stretch. Gadolinium (1, 3, and 10 μmol/l) dose dependently decreased the APA and MDP, and increased the APD_{50} and APD_{90}. Also, gadolinium dose dependently decreased the incidence of stretch-induced EADs and DADs. Figure 2D shows tracings of the action potential configurations in the pulmonary veins during a 300-mg stretch before and after giving gadolinium. Furthermore, streptomycin (10 and 40 μmol/l) dose dependently decreased the APA and MDP, and increased the APD_{50} and APD_{90}. Streptomycin also dose dependently decreased the incidence of stretch-induced EADs and DADs. Figure 2E shows tracings of the action potential configurations before and after giving streptomycin in the pulmonary veins during a 300-mg stretch.

DISCUSSION

Major findings

This study showed that stretch force dependently increased the automaticity of pulmonary veins, EADs, DADs, and shortened the duration of action potential. SAC blockers dose dependently inhibited the stretch-induced arrhythmogenic activity of the pulmonary veins.

Role of stretch on electrical activity of the pulmonary veins

Previous studies have shown that mechanoelectrical feedback plays an important part in cardiac electrophysiology.[3] Mechanoelectrical feedback is produced by the activation of SACs, which can affect both the inward and outward ionic currents and result in shortening the duration of action potential and increasing the automaticity.[4 22 23] In addition, stretch may induce a calcium overload and produce after-depolarisations in cardiomyocytes.[23] Although an increase in the atrial pressure has been shown to enhance the arrhythmogenic activity of the pulmonary veins, with an acceleration of the firing rates in pulmonary veins,[6] the underlying electrophysiological mechanisms are not known in detail. In this study, we showed that stretch changed the electrophysiological properties of the pulmonary veins, with the enhancement of the automaticity and triggered activity. These results would increase the arrhythmogenic activity of the pulmonary veins and further induce ectopic firing from the pulmonary veins that may contribute to the genesis of atrial fibrillation. Consistent with our results, Honjo *et al*[18] also found a low incidence of spontaneous activity in pulmonary veins without a stretch. Although the exact ionic currents underlying the stretch-induced arrhythmogenic activity of the pulmonary veins is not clear from this study, the generation of both EADs and DADs favour the role of stretch inducing a calcium overload. Although EAD is generally believed to be associated with prolonging the duration of the action potentials, an increased or prolonged Ca^{2+} transient during a shortened duration of action potential has been reported to give rise to EADs and triggered arrhythmia in pulmonary veins.[24] In addition, Burashnikov *et al*[25] also suggested that calcium overload may induce the genesis of EAD during the decrease in duration of action potential in the atrium. Therefore, the mechanoelectrical feedback may increase the Ca^{2+} transient to generate EAD during the shortening of the duration of the action potential. The genesis of re-entrant circuits may also contribute to the arrhythmogenic activity of the pulmonary veins.[15–17] The shortening of the APD_{90} and APD_{50} by stretch also facilitates the genesis of micro-reentrant circuits and further increases the arrhythmogenic activity of the pulmonary veins. These findings indicate the importance of stretch on the arrhythmogenic activity of the pulmonary veins. Previous studies have shown a higher incidence of atrial fibrillation in dilated atria and heart failure. Heart failure is known to be associated with an increasing stretch in pulmonary veins due to an increased pressure. The stretch-induced increase in the arrhythmogenic activity of the pulmonary veins may play an important part in these pathological situations. It is also possible that the patients treated with angiotensin receptor blockers or angiotensin-converting enzyme inhibitors have reduced atrial fibrillation through the effect of decreasing the stretch in the pulmonary veins by the mechanoelectrical feedback.[26]

Kalifa *et al*[21] used optical mapping to study stretch-related atrial fibrillation in sheep hearts, and found a rapid atrial activation originating from the pulmonary veins. Mapping experiments are able to investigate the source of spontaneous activity and evaluate the slowing in conduction, the changes in the rate of phase 4 depolarisation, and the responses of after-depolarisation to the stretch or SAC blockers. In this study, we did not perform mapping experiments because several spontaneous activities of pulmonary veins were only recorded in the deep layers of the pulmonary vein myocardial sleeve. In addition, the pulmonary veins possess anisotrophic conduction, and mapping experiments may not accurately present the electrical activity of the pulmonary veins from different muscle layers.[19]

Role of stretch-activated channel blockers in electrical activity of the pulmonary veins

SAC blockers have been shown to have several cardiac effects, with the inhibition of stretch-induced changes in action potential and after-depolarisations.[6 27 28] In addition, gadolinium can reduce the stretch-induced vulnerability to atrial fibrillation in a dose-dependent manner.[6] The more specific SAC blocker, GsMTx-4, found in the venom of the tarantula *Grammostola spatulata*, effectively reverses the effects of stretch-induced atrial fibrillation.[7] These results indicated that SAC blockers represent a novel antiarrhythmic approach to atrial fibrillation. In this study, both gadolinium and streptomycin could inhibit the stretch-induced automaticity of pulmonary veins and triggered activity in a dose-dependent manner. The reversal of stretch-induced shortening of the duration of the action potantial by gadolinium also prevents the genesis of micro-reentrant circuits in the pulmonary veins. These findings indicated that SAC blockers can reduce the genesis of atrial fibrillation by suppressing the arrhythmogenic activity of the ectopic foci. Although gadolinium also inhibits the L-type calcium channel, the relative lesser effects of verapamil on the stretch-induced electrical activity of the pulmonary veins than gadolinium and streptomycin indicate that these results are mainly caused by the SAC blockade. This mechanism is also suggested by the findings that gadolinium did not suppress the electrical activity of the pulmonary veins before the stretch.

Gadolinium is used as contrast agent (gadolinium chelates) for magnetic resonance imaging. The serum concentration of gadolinium is around 1–5 μmol/l,[29] which is similar to that in this study (1 and 3 μmol/l). Streptomycin is the drug used to treat mycobacterial infections. The therapeutic serum concentration of streptomycin is 20–50 μmol/l,[30] which is close to the concentration of the streptomycin (10, 40 μmol/l) used in this study. Therefore, both gadolinium and streptomycin may have an antiarrhythmic potential through their SAC-blocking effects.

CONCLUSION

Stretch plays an important part in the electrical activity of the pulmonary veins, which can be reversed by SAC blockers. The

enhanced arrhythmogenic activity of the pulmonary veins during stretch may underlie the genesis of dilated pulmonary vein-initiated atrial fibrillation.

Authors' affiliations

S-L Chang, W Wangcharoen, S-A Chen, Division of Cardiology and Cardiovascular Research Center, National Yang-Ming University School of Medicine and Veterans General Hospital, Taipei, Taiwan
Y-C Chen, Department of Biomedical Engineering, National Defense Medical Center, Taiwan
Y-J Chen, Taipei Medical University, School of Medicine; Division of Cardiovascular Medicine, Taipei Medical University-Wan-Fang Hospital, Taipei, Taiwan
S-H Lee, Shin-Kong Memorial Hospital; Department of Medicine, Fu Jen Catholic University
C-I Lin, Institute of Physiology, National Defense Medical Center, Taiwan

Funding: This work was supported by the NSC 92-2314-B010-052, NSC SC92-2314-B038-054, NSC 93-2314-B038-033, NSC 94-2314-B038-061, NSC 94-2314-B010-053, NSC 94-2314-B010-056, NSC 94-2314-B075-093, VGH92-238, VGH92-243, VGH91-260, VGH91-44, VTY 92-P5-34, VTY92-P5-29, VTY91-P5-44 and RFCM 91-02019 grants.

Competing interests: None declared.

REFERENCES

1 **Fraser HR**, Turner RW. Auricular fibrillation; with special reference to rheumatic heart disease. *BMJ* 1955;i:1414–18.
2 **Psaty BM**, Manolio TA, Kuller LH, *et al.* Incidence of and risk factors for atrial fibrillation in older adults. *Circulation* 1997;**96**:2455–61.
3 **Nazir SA**, Lab MJ. Mechanoelectric feedback and atrial arrhythmias. *Cardiovasc Res* 1996;**32**:52–61.
4 **Ravelli F**, Allessie M. Effects of atrial dilatation on refractory period and vulnerability to atrial fibrillation in the isolated Langendorff-perfused rabbit heart. *Circulation* 1997;**96**:1686–95.
5 **Chen YJ**, Tai CT, Chiou CW, *et al.* Inducibility of atrial fibrillation during atrioventricular pacing with varying intervals: role of atrial electrophysiology and the autonomic nervous system. *J Cardiovasc Electrophysiol* 1999;**10**:1578–85.
6 **Bode F**, Katchman A, Woosley RL, *et al.* Gadolinium decreases stretch-induced vulnerability to atrial fibrillation. *Circulation* 2000;**101**:2200–5.
7 **Bode F**, Sachs F, Franz MR. Tarantula peptide inhibits atrial fibrillation. *Nature* 2001;**409**:35–6.
8 **Haissaguerre M**, Jais P, Shah DC, *et al.* Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;**339**:659–66.
9 **Pappone C**, Rosanio S, Oreto G, *et al.* Circumferential radiofrequency ablation of pulmonary vein ostia: a new anatomic approach for curing atrial fibrillation. *Circulation* 2000;**102**:2619–28.
10 **Blom NA**, Gittenberger-de Groot AC, DeRuiter MC, *et al.* Development of the cardiac conduction tissue in human embryos using HNK-1 antigen expression: possible relevance for understanding of abnormal atrial automaticity. *Circulation* 1999;**99**:800–6.
11 **Cha TJ**, Ehrlich JR, Zhang L, *et al.* Atrial tachycardia remodeling of pulmonary vein cardiomyocytes: comparison with left atrium and potential relation to arrhythmogenesis. *Circulation* 2005;**111**:728–35.
12 **Cheung DW**. Electrical activity of the pulmonary vein and its interaction with the right atrium in the guinea-pig. *J Physiol* 1981;**314**:445–56.
13 **Chen YJ**, Chen SA, Chen YC, *et al.* Effects of rapid atrial pacing on the arrhythmogenic activity of single cardiomyocytes from pulmonary veins: implication in initiation of atrial fibrillation. *Circulation* 2001;**104**:2849–54.
14 **Chen YC**, Chen SA, Chen YJ, *et al.* Effects of thyroid hormone on the arrhythmogenic activity of pulmonary vein cardiomyocytes. *J Am Coll Cardiol* 2002;**39**:366–72.
15 **Hocini M**, Ho SY, Kawara T, *et al.* Electrical conduction in canine pulmonary veins: electrophysiological and anatomic correlation. *Circulation* 2002;**105**:2442–8.
16 **Zhou S**, Chang CM, Wu TJ, *et al.* Nonreentrant focal activations in pulmonary veins in canine model of sustained atrial fibrillation. *Am J Physiol Heart Circ Physiol* 2002;**283**:H1244–52.
17 **Chen YJ**, Chen SA, Chang MS, *et al.* Arrhythmogenic activity of cardiac muscle in pulmonary veins of the dog: implication for the genesis of atrial fibrillation. *Cardiovasc Res* 2000;**48**:265–73.
18 **Honjo H**, Boyett MR, Niwa R, *et al.* Pacing-induced spontaneous activity in myocardial sleeves of pulmonary veins after treatment with ryanodine. *Circulation* 2003;**107**:1937–43.
19 **Arora R**, Verheule S, Scott L, *et al.* Arrhythmogenic substrate of the pulmonary veins assessed by high-resolution optical mapping. *Circulation* 2003;**107**:1816–21.
20 **Tsao HM**, Yu WC, Cheng HC, *et al.* Pulmonary vein dilation in patients with atrial fibrillation: detection by magnetic resonance imaging. *J Cardiovasc Electrophysiol* 2001;**12**:809–13.
21 **Kalifa J**, Jalife J, Zaitsev AV, *et al.* Intra-atrial pressure increases rate and organization of waves emanating from the superior pulmonary veins during atrial fibrillation. *Circulation* 2003;**108**:668–71.
22 **Ruknudin A**, Sachs F, Bustamante JO. Stretch-activated ion channels in tissue-cultured chick heart. *Am J Physiol* 1993;**264**:H960–72.
23 **Sigurdson W**, Ruknudin A, Sachs F. Calcium imaging of mechanically induced fluxes in tissue-cultured chick heart: role of stretch-activated ion channels. *Am J Physiol* 1992;**262**:H1110–15.
24 **Patterson E**, Lazzara R, Szabo B, *et al.* Sodium-calcium exchange initiated by the Ca^{2+} transient: an arrhythmia trigger within pulmonary veins. *J Am Coll Cardiol* 2006;**47**:1196–206.
25 **Burashnikov A**, Antzelevitch C. Reinduction of atrial fibrillation immediately after termination of the arrhythmia is mediated by late phase 3 early afterdepolarization-induced triggered activity. *Circulation* 2003;**107**:2355–60.
26 **Madrid AH**, Peng J, Zamora J, *et al.* The role of angiotensin receptor blockers and/or angiotensin converting enzyme inhibitors in the prevention of atrial fibrillation in patients with cardiovascular diseases: meta-analysis of randomized controlled clinical trials. *Pacing Clin Electrophysiol* 2004;**27**:1405–10.
27 **Tavi P**, Laine M, Weckstrom M. Effect of gadolinium on stretch-induced changes in contraction and intracellularly recorded action- and afterpotentials of rat isolated atrium. *Br J Pharmacol* 1996;**118**:407–13.
28 **Gannier F**, White E, Lacampagne A, *et al.* Streptomycin reverses a large stretch induced increase in $[Ca^{2+}]i$ in isolated guinea pig ventricular myocytes. *Cardiovasc Res* 1994;**28**:1193–8.
29 **Cacheris WP**, Quay SC, Rocklage SM. The relationship between thermodynamics and the toxicity of gadolinium complexes. *Magn Reson Imaging* 1990;**8**:467–81.
30 **Peloquin CA**, Berning SE, Nitta AT, *et al.* Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. *Clin Infect Dis* 2004;**38**:1538–44.

Mechanoelectrical feedback regulates the arrhythmogenic activity of pulmonary veins

S-L Chang, Y-C Chen, Y-J Chen, et al.

Heart 2007 93: 82-88 originally published online August 11, 2006
doi: 10.1136/hrt.2006.089359