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Biometal muscle to restore atrial transport function in a permanent atrial fibrillation animal model: a potential tool in the treatment of end-stage heart failure

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Abstract

Background: Half of the patients with end-stage heart failure suffer from persistent atrial fibrillation (AF). Atrial kick (AK) accounts for 10—15% of the ejection fraction. A device restoring AK should significantly improve cardiac output (CO) and possibly delay ventricular assist device (VAD) implantation. This study has been designed to assess the mechanical effects of a motorless pump on the right chambers of the heart in an animal model. **Methods:** Atripump is a dome-shaped biometal actuator electrically driven by a pacemaker-like control unit. In eight sheep, the device was sutured onto the right atrium (RA). AF was simulated with rapid atrial pacing. RA ejection fraction (EF) was assessed with intracardiac ultrasound (ICUS) in baseline, AF and assisted-AF status. In two animals, the pump was left in place for 4 weeks and then explanted. Histology examination was carried out. The mean values for single measurement per animal with ±SD were analysed. **Results:** The contraction rate of the device was 60 per min. RA EF was 41% in baseline, 7% in AF and 21% in assisted-AF conditions. CO was 7 ± 0.5 l min^{-1} in baseline, 6.2 ± 0.5 l min^{-1} in AF and 6.7 ± 0.5 l min^{-1} in assisted-AF status ($p < 0.01$). Histology of the atrium in the chronic group showed chronic tissue inflammation and no sign of tissue necrosis. **Conclusions:** The artificial muscle restores the AK and improves CO. In patients with end-stage cardiac failure and permanent AF, if implanted on both sides, it would improve CO and possibly delay or even avoid complex surgical treatment such as VAD implantation.

Keywords: Artificial muscle; Chronic heart failure; Ventricular assist device; Atrial fibrillation

1. Introduction

Congestive heart failure (CHF) afflicts nearly 15 million people worldwide and half of the patients with end-stage heart failure suffer from persistent atrial fibrillation (AF) [1—4]. The prevalence of AF increases with advancing functional severity of heart failure and is present in nearly 30% of patients with the New York Heart Association (NYHA) class III [5] and in as many as 50% of patients with the NYHA class IV heart failure [6]. Similarly, heart failure is prevalent in patients with AF. Therefore, heart failure increases the risk for AF, and AF increases the risk for heart failure. In patients with CHF and AF, when endovascular and/or surgical ablation techniques have failed to restore the atrial kick (AK), the only possible treatment of AF consists in the ventricular rhythm control and anticoagulation therapy to avoid clot formation due to blood pooling into atria. So far, there are no mechanical tools that are able to restore the AK in such patients. AK accounts for 10—15% of the normal ventricle ejection fraction (EF) [7]. Any device able to restore the AK should significantly improve the cardiac output (CO) of a patient with CHF and possibly delay ventricular assist device (VAD) implantation and/or heart transplantation. A motorless, volume—displacement pump based on artificial muscle technology could reproduce the AK when placed onto a fibrillating atrium. This study has been designed to assess the mechanical effects of this pump on the right chambers in an animal model of AF.

2. Material and methods

2.1. Description of the atrial assist device

Atripump (Nanosin Sarl, Switzerland) is a dome-shaped, silicone-coated nitinol actuator, 5×45 mm, controlled by a

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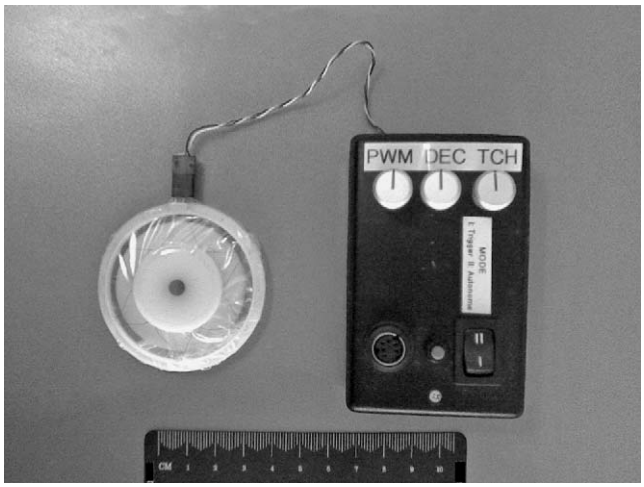

Fig. 1. The Atripump components are the dome (on the left) made of nitinol fibres embedded in a silicone rubber and the control unit (on the right).

pacemaker-like unit and powered with a lithium-ion external battery (Fig. 1). The control unit is able to detect cardiac activity from epicardial wires as a classic pacemaker does, and delivers a given current to the nitinol wire, according to a predetermined algorithm. When electrically heated, the nitinol wire reduces its length, thus causing a shortening of the dome concavity. Once the current is switched off, the wire goes back to its initial length, restoring the initial concavity of the dome. The changes in dome concavity result in volume displacement. Similar to natural muscles, the nitinol fibres reduce their length when electrically stimulated; hence, the concept of motorless motion or artificial muscles. This concept, the technical characteristics of the device and the preliminary *in vitro* results have been extensively described in our previous publications [8,9].

2.2. Study design

The animal study was performed in compliance with the 'Principles of Laboratory Animal Care', formulated by the National Society for Medical Research and the 'Guide for Care and Use of Laboratory Animals', published by the National Institute of Health (NIH publication 85-23, revised 1985). In adult sheep, under general anaesthesia and electrocardiographic (ECG) monitoring, the right atrium (RA) was surgically exposed through right anterior thoracotomy. The actuator (dome) was sutured onto the external surface of the RA with six 4/0 interrupted sutures. A temperature probe was inserted at the apex of the dome, between the silicone membrane and the epicardium. A second temperature probe was inserted into the oesophagus. A Swan Ganz catheter was inserted into the right jugular vein to acquire data on central venous pressure (CVP) and pulmonary artery pressure (PAP). A 10F intracardiac ultrasound probe (ICUS, Acuson, AcuNav, Siemens) was inserted into the left jugular vein and advanced into the RA to acquire data on RA EF. The RA EF is an estimator of the right atrium volume changes during the cardiac cycle. We measured the cross-sectional area of the RA keeping the insertion of the septal leaflet as a reference point and the probe at the superior vena cava–RA junction. Specifically, the RA EF was calculated as follows: EF = (end-diastolic area − end systolic area/end diastolic area) × 100. The same physician carried out all measurements. A 12G catheter was inserted in a side branch of the carotid artery to monitor systemic blood pressure. Pacemaker wires for epicardic temporary stimulation were placed on the RA and connected to an external pacemaker (Biotronic Inc., Pittsburgh, PA, USA). The haemodynamic effect of AF was obtained using rapid epicardic pacing (600 beats min^{-1}) without affecting ventricular rate response. Sinus rhythm re-appeared a few minutes after the rapid pacing was switched off.

2.3. Data acquisition

Three sets of measurements were obtained: baseline, AF-equivalent condition and assisted-AF condition. During the assisted-AF condition, both the rapid pacing and the Atripump, were activated. Each set included the acquisition of the heart rate, CVP, PAP, RA EF, and central body and epicardium temperatures. Each set of measurements lasted for 30 min. Four consecutive sets of measurements were carried out.

At the end of the experience, some of the animals (acute group) were sacrificed and histology of the RA underneath the dome was performed using haematoxylin–eosin and three-chromic staining. To assess whether the dome causes chronic lesions on the heart surface, other animals (chronic group) had the cable connecting the dome to the control unit and power source passed under the skin up to the cervical region where it pierced the skin. In this way, both the control unit and the power source were outside the body. The animals were then transferred to the farm and followed up for 4 weeks. The follow-up checklist also included monitoring of the weight, heart rate, temperature of the surface of the atrium underneath the dome and dome functioning. A reduction in the daily consumption of food of greater than 50% was considered as a sign of chronic pain. The experiment would have been terminated if it caused the animal to lose more than 5% of its initial weight. At the end of the experience, the chronic group underwent the same sacrifice protocol as the acute group.

2.4. Statistical analysis

Student's paired *t*-test was used to test for a difference in scores between the three sets of measurements. Mean values for single measurement per animal with ±SD were analysed.

3. Results

The experiment has been conducted in eight sheep weighing 68 ±4 kg. All animals were in sinus rhythm at the beginning of the experiment.

The dome's contraction rate was 60–80 min^{-1} with power supply of 10 V, 300 mA for 100 ms. The mean temperature on the RA's surface was 39 ± 1.5 °C. The mean body temperature was 38 ± 1 °C. RA EF was 41% in baseline conditions, 7% and 21% in AF and assisted-AF, respectively. Detailed haemodynamic results are presented in Table 1.

Table 1
Hemodynamic changes during baseline conditions, atrial failure induce by rapid right atrial pacing (AF) and assisted atrial failure (assisted-AF). Results are expressed with SD differences between the adjacent values are evaluated with Student's paired *t*-test.

	Baseline	*p* value	AF	*p* value	Assisted-AF
Mean heart rate	68 ± 10	0.01	90 ± 10	ns	95 ± 11
Mean arterial pressure (mmHg)	75 ± 22	ns	70 ± 13	ns	69 ± 22
Mean pulmonary pressure (mmHg)	16 ± 2	ns	15 ± 2	ns	17 ± 3
Central venous pressure (cmH_2O)	12 ± 2	ns	15 ± 6	ns	12 ± 5
Right ventricle output (l/min)	7 ± 0.5	0.01	6.2 ± 0.5	0.01	6.7 ± 0.5
RA systolic surface (cm^2)	4 ± 0.3	0.01	6.1 ± 0.1	0.01	5.1 ± 0.3
RA diastolic surface (cm^2)	6.8 ± 0.3	0.01	6.5 ± 0.1	0.01	6.4 ± 0.2
RA ejection fraction (%)	41% ± 5	0.01	7% ± 2	0.01	21% ± 3

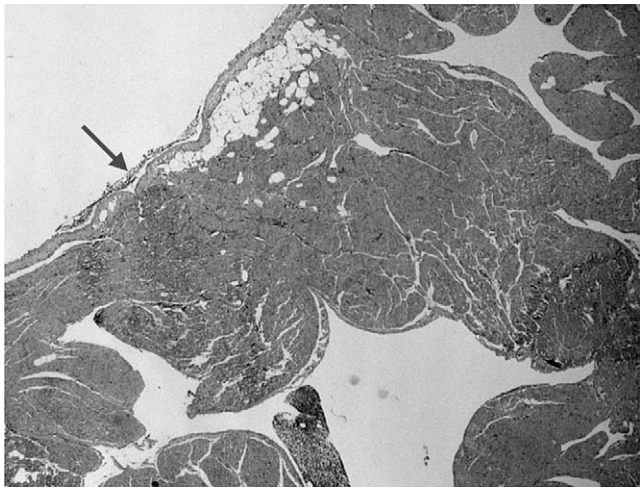

Fig. 2. Acute group. Haematoxylin–eosin stain slice (25×) of the right atrium in contact with the artificial muscle. Any relevant histological changes are visible. Note a thin layer of fibrin deposition on epicardial side (arrow). Rare lymphocytes are present.

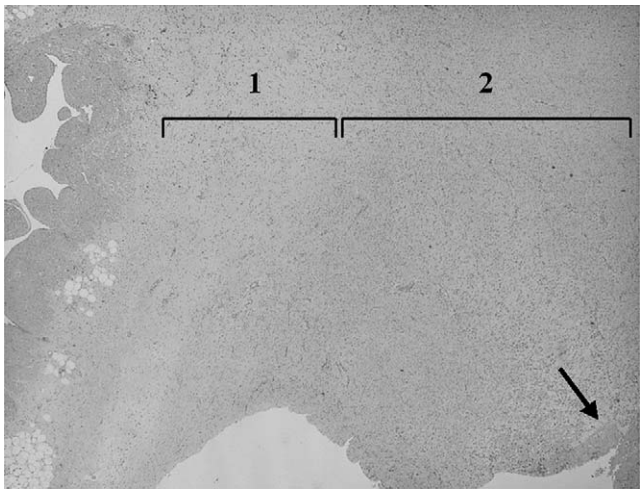

Fig. 3. Chronic group. Haematoxylin–eosin slice (25×) of the right atrium that has been in contact with the artificial muscle for 4 weeks. Note a thick layer of fibrous tissue on the epicardial side. Fibrous tissue presents a gradual maturation. The deeper layer is more mature (1) with respect to the external surface (2) where immature fibroblasts and fibrin are visible (arrow). There is not evidence of tissue necrosis.

The *t*-test had a significant *p* value (<0.001) for RA EF in baseline versus AF and in assisted-AF versus AF conditions. We also found statistical differences between CO in baseline versus AF and AF versus assisted-AF. In two animals (chronic group), the device was left in place for 4 weeks, activated in fix mode 60 min^{-1}. No technical failure occurred. The activation was painless as demonstrated by the normal food intake and the behaviour of the animal. The maximal temperature of the surface of the atrium was 41.4 °C.

In the acute group, histology examination of the atrium in contact with the artificial muscle revealed signs of acute inflammatory reaction mediated by lymphocytes, but no signs of necrosis or apoptosis (Fig. 2). In the chronic group, the histology revealed chronic tissue inflammation and no sign of tissue necrosis or apoptosis (Fig. 3).

4. Discussion

Currently, about 20 000 patients in the United States would benefit from heart transplantation. However, the donor pool limits the number of transplant procedures to 2300 per year [10]. Epidemiologic studies reveal an annual incidence of heart failure in the United States and Europe between 0.3% and 1% [4]; and patients who are on continuous palliative inotropes have a 6-month mortality between 60% and 75% [2,3].

These data emphasise the urgent demand for new therapeutic options to reduce the costs of long-term mechanical support as a bridge to transplantation.

AF has been reported to be associated with decreased survival. Its prognostic importance in end-stage heart failure is controversial [11]. Ramdas and co-workers recently reported the results involving one of the largest cohort of patients suffering from AF (about 9000 patients over 10 years) suggesting that the effects of AF on mortality is absent in those with moderate and severe left ventricular (LV) dysfunction [12]. However, the haemodynamic effect of atrial contraction is well known and even if it could sometimes be overestimated, it cannot be denied.

According to an AHA report, the factors that markedly decrease CO during AF are loss of synchronous atrial mechanical activity, irregular ventricular response, rapid heart rate and impaired coronary flow [13]. Haemodynamic impairment due to variation in R–R intervals during AF has been demonstrated in a canine model with complete heart block, in which CO fell by approximately 9% during irregular ventricular pacing [7,14].

Another major sequel of AF results from the increased risk of embolism, with a five- to sixfold increase in the risk of stroke in non-rheumatic patients and a 17 times increase in the risk of stroke in rheumatic patients [5].

About half of the patients suffering from end-stage CHF have persistent AF despite ablation treatment [15]. In such a group of patients, any treatment that is able to restore the pump function of the atrium should theoretically increase the CO sufficiently to improve symptoms, prevent disease progression and eventually avoid the implantation of VADs as a bridge to transplant or destination therapy. In other words, the restoration of the AK could make the difference between being at the hospital under IV-drug therapy and waiting at home for the right donor.

The existing treatments of AF aim to restore the sinus rhythm or, at least to reduce the ventricular response. The only surgical intervention that potentially cures AF, rather than palliates, is the Maze procedure. Using thermo- or cryo-ablation techniques, either with percutaneous access or open surgery, it is possible to isolate the parts of the RA and left atrium (LA) where the foci triggering the AF are located. However, the rate of patients that maintain sinus rhythm is low in the long-term [16]. Moreover, because cardiomyocytes are destroyed or uncoupled after surgical and/or catheter ablation procedures, maintenance of sinus rhythm may not necessarily result in the complete restoration of atria transport function. Lemola et al. reported that LA EF after ablation of chronic AF remains significantly lower than normal [17]. Patients continue to require anticoagulation therapy for life and thus, are exposed to the risk of haemorrhagic complications.

The solution we propose is the first device intended to restore the pump function of fibrillating atria, introducing the concept of atrial-assist device. The device has been developed to be totally implantable in the human body with a transcutaneous energy-transfer system to recharge the implanted battery. Atripump links the classic pacemaker function (stimulation) to the muscles actuation function (contraction) using electrically activated nitinol fibres. The idea of using a nitinol actuator to rescue the weakened heart was first introduced by Sawyer and co-workers in 1976 [18] and, more recently, by Yambe and co-workers [19]. The VAD they developed was able to assist heart functions in the animal experimental set-up. However, contraction cycle, material fatigue, heating and energy supply were the major limitations faced. We learned a lot from their experiences and designed a pulsatile pump that overcomes the historical limitations of nitinol wire when used as the actuator. As previously published, the Atripump is able to pump approximately the volume of the normal atrium under physiologic conditions: this corresponds to 11—22 ml per systole [19], depending on ventricular filling pressure and preload. The Atripump stroke volume of 8 ml corresponds, therefore, to 75% of physiologic conditions. With a maximum output of about half a litre per minute, it clearly satisfies the haemodynamic needs of the normal atrium. However, one major difference with the natural muscle is the resistance to fatigue: human cardiac muscle might last for a hundred years and more, while wires we use with a kinetic distortion of 5% and a tensile strength of 0.8 Kgf can last for a few years.

The restoration of the AK should reduce the vortices and blood stagnation in the appendix far enough to considerably reduce thrombus formation. This concept of a mechanical anticoagulation device is new only from the engineering and therapeutic points of view, because, in practice, it reproduces exactly what nature does.

In clinical practice, the haemodynamic effect of atrial contraction is echo-assessed measuring the peak velocity and time—velocity integral of the left ventricular diastolic filling wave during the A-wave phase [16]. In our experimental set-up, this technique would have been less reliable than in a patient because the animal had the chest open, it was ventilated with positive pressure and the activation of the dome was not synchronised with the ventricular activity. Therefore, we decided to calculate the EF of the atrium directly, using the ICUS. In baseline conditions, the EF of the right atrium was 41% and dropped down to 7% when the atrial failure was induced with rapid pacing. During this phase, ICUS demonstrated spontaneous echo contrast in the right appendix signifying that blood flow velocity, at least in this area, was low enough to induce thrombus formation. When the artificial muscle was activated at a fixed rate of 60 min^{-1} and despite the persistency of atrial failure induced by rapid pacing, the spontaneous echo contrast in RA disappeared and the EF increased to 21%, proving that the AK was partially restored. Even if this experience has been conducted only in eight animals, the results were highly reproducible.

The effect of the pump on the output of the right ventricle was minimal (+0.5 l min^{-1}), but significant. However, the fact that also the rapid atrial pacing slightly reduced the CO could be due to the inadequacy of the animal model we used. A healthy sheep can compensate the lost of AK through the increase in HR and preload. We could speculate that, in a diseased heart, this small increase in CO would have much more impact on the clinical status and quality of life.

The atrial assist device represents a new therapeutic concept and it should not be considered a 'tiny VAD'. The major differences with existing VADs concern the invasiveness, the efficacy and the cost. Atripump is not in contact with the blood stream; therefore, it does not require anticoagulation and, theoretically, should not be associated with neurological disorders and infections that still constitute major problems with the VAD treatment modality [20,21]. We could speculate that patients with Atripump are less exposed to infections because Atripump is totally implantable maintaining the integrity of the skin barrier, which is not the case when tubes pierce the skin. The area where the driving line passes through the skin is definitely the most common source of infections in patients with VADs.

In our model, the device was inserted through a small thoracotomy and this approach is definitely minimally invasive. However, in a clinical setting, this access would not allow the exposure of the LA. In a clinical setting, a thoracoscopic approach would permit the minimally invasive implantation of the device on both atria.

Costs are probably one order of magnitude smaller than for the current VADs. However, the model's haemodynamic performance is significantly smaller than is the case with current VADs.

This study has several methodological limitations. Because the study has been conducted on the right side of

the heart, we can only speculate that this device is effective in increasing the CO of the left ventricle and prevents systemic embolism of cardiac origin in AF patients. The Atripump has been developed for the RA and its shape does not match the complex anatomy of the LA. The presence of the four pulmonary veins and the proximity of the oesophagus require a softer actuator having an oval or figure-eight shape. It should be possible with such an actuator positioned in between pulmonary veins to reproduce the natural haemodynamic effect also on the LA.

The pump has been activated in a fixed mode making the calculation of the peak velocity and time—velocity integral of the left ventricular diastolic filling (A wave) unreliable. This problem has been partially overcome by calculating the EF of the RA. The model of persistent AF we used has not been validated yet. Rapid atrial pacing (600 min^{-1}) induces atrial failure but it is neither associated with atrial dilatation nor with the contractile remodelling of the wall typically seen in chronic AF. The device presented is a prototype and its lifetime is short. However, components and technology are both reliable, providing appropriate functioning of the device for years.

Last, but not least, the model we used had normal ventricular function and did not reproduce the CHF conditions. We would have used the model proposed by other authors [14], inducing CHF with microinjections in coronary arteries. However, our veterinary authority policy tends to avoid the induction of two diseases (AF and CHF) in chronic animal models.

5. Conclusions

Placed on the right side, the artificial muscle restores the AK and improves CO. In patients with end-stage cardiac failure and permanent AF, if implanted on both sides, it would improve CO and possibly delay or even avoid complex surgical treatment such as VAD implantation; and it should reduce the re-hospitalisation rate. The Atripump is a small kick for weak hearts, a big help for patients waiting for a heart transplant.

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