EuroIntervention

Percutaneous Transvenous Mitral Annuloplasty (PTMA) with the Viking device reduces pacing-induced mitral regurgitation

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KEYWORDS
Mitral valve repair, mitral regurgitation, valvuloplasty, percutaneous annuloplasty.

Abstract

Objectives: The new percutaneous mitral annuloplasty Viking device was evaluated in surviving sheep with pacing-induced mitral regurgitation.

Methods and results: Twenty sheep were subjected to rapid ventricular pacing for one to three months, leading to cardiomyopathy and mitral regurgitation. Device implantation could be successfully performed in 11 of these animals after pacemaker treatment for 64±7 days. The device-related procedure time was 12±2 min. The mean follow-up time was 58±8 days after implantation of the device. Mitral annulus septo-lateral diameter was significantly reduced after insertion of the device, from 35±1 mm before implantation to 30±1 mm at the final follow up intracardiac echocardiography ($P = 0.0097$). The degree of mitral regurgitation (on a scale from 0 to 4) was 2.6±0.2 before device implantation and decreased to 0.8±0.2 after treatment ($P = 0.0039$), and the vena contracta was reduced from 7±0.4 mm to 3±0.8 mm ($P = 0.0019$). Angiography showed no signs of impairment of the coronary arteries. No thrombosis was observed.

Conclusions: These results indicate that the septo-lateral diameter of the mitral annulus, and the degree of experimentally induced mitral regurgitation, can be significantly reduced with a percutaneous catheter technique in surviving sheep.

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Introduction

Enlargement of the mitral annulus, alone or in conjunction with structural valve abnormalities, is an important factor in mitral regurgitation (MR). The annular dilatation occurs primarily in the posterior part of the annulus due to less attachment of this region to the fibrous skeleton of the heart[1,2]. An increased septo-lateral diameter caused by posterior dilation prohibits coaptation between the anterior and posterior mitral leaflets, resulting in MR. Beside other reparative measures of the leaflets and the chordae tendinae, surgical mitral valve repair today routinely involves an annuloplasty to correct this dilatation. A frequently used method is to suture a flexible prosthetic band along the posterior circumference of the valve, incorporating the fibrous trigones, or to suture a complete ring (rigid or flexible) along the entire circumference of the valve. By either of these methods the septo-lateral diameter is reduced, leading to increased coaptation of the mitral leaflets and reducing or eliminating the MR. Surgical annuloplasty requires general anaesthesia, extracorporeal circulation and open heart surgery, with considerable associated morbidity and mortality, particularly in patients with severe congestive heart failure or in combination with CABG. Less invasive procedures would therefore be advantageous.

We present a percutaneous transvenous method which takes advantage of the proximity of the coronary sinus (CS) to the posterior part of the mitral annulus. From the CS-ostium in the right atrium to the great cardiac veins interventricular part, the CS runs immediately adjacent and almost parallel to the two thirds of the mitral valve attachment that normally is pulled forward during surgical annuloplasty procedures. The purpose of the study was to evaluate the efficacy of this method in an animal model with mitral regurgitation induced by means of rapid pacing[3].

Methods

Pacemaker-induced mitral regurgitation

Twenty sheep of a native domestic Swedish breed and a mean weight of 67±11 kg were used. All the animals received humane care in compliance with the "Principles of Laboratory Animal Care" by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" by the Institute of Laboratory Animal Resources, National Research Council, National Academy Press, 1996. Each animal was sedated with 5 mg Midazolam (Roche, Switzerland) and 500 mg ketamine hydrochloride (Pfizer, Sweden) intramuscularly. The animal was secured on the operating table in dorsal recumbency. Anaesthesia was induced with thiopental (Abbott, USA) 5-8 mg/kg, given in a peripheral vein and maintained with a mixture of O_2 and isoflurane (Abbott, Sweden). An infusion of propofol (Braun, Germany), fentanyl (Pharmalink, Sweden), and ketamine was administered when applicable.

An endotracheal tube was inserted and mechanical ventilation initiated with tidal volumes set at 8-10 ml/kg body weight with a 100 ml compensation for dead space, at a rate of 12-15 cycles per minute. Fluid support (Lactated Ringers Solution) was delivered intravenously maintaining the systolic blood pressure over 90 mmHg. The external jugular vein was exposed and a screw-in pacemaker lead (KY II 67C unipolar, Sulzer Medica, USA) was inserted into the vein through a purse string suture and an introducer. The lead was placed and fixed in the right ventricle. A single-chamber pacemaker (Actros SR, Biotronic, Germany) was placed at the place of insertion and ventricular pacing (VVI) with a frequency of 180 min^{-1} was started. The wound was closed with resorbable suture and the animal was observed for 24 hours and then returned to the breeder.

Echocardiography

Transthoracic echocardiography, TTE (Acuson Cypress, Siemens, USA) was performed preoperatively and monthly after pacemaker implantation until a significant MR was observed. The degree of MR was estimated on a scale from 0 to 4. An MR of degree 2 or higher was considered significant and qualified the animal for device implantation. The septo-lateral diameter of the mitral annulus was measured in diastole in a parasternal view. Five measurements were made each time, and the mean value of these was calculated. The vena contracta, the diameter of the left atrium, and the diameter of the left ventricle in systole and diastole were also measured. At the time of device implantation and at sacrifice a probe for intracardiac echocardiography, ICE, (AcuNav, 10F, Siemens, USA) was introduced via the external jugular vein into the right atrium. Measurements were performed as described above, except for the projection for measuring the mitral valve size, where a view from the right atrium just above the tricuspid valve was used. The left ventricular volumes were calculated according to the formula: $V = D^3 \times 7/(2.4 + D)$, where V = left ventricular volume and D = left ventricular diameter. The ejection fraction (EF) was calculated according to the Teichholtz formula: EF = (EDV-ESV)/EDV x 100, where EDV is the end-diastolic volume and ESV is the end-systolic volume.

The annuloplasty device

The mitral annuloplasty Viking device (Edwards Lifesciences, Irvine, CA, USA) is made of Nitinol, a shape memory alloy of nickel and titanium. The device is intended for percutaneous, intravenous repair of mitral valve regurgitation by indirect remodeling of the mitral valve annulus from the CS and the great cardiac vein. The system is a catheter-deployed device consisting of a 12F outer diameter (O.D.) guide catheter, dilator, delivery catheter, and the therapy device. The system is compatible with a 0.035" maximum O.D. guide wire. The annuloplasty therapy device itself consists of an 8.8 F coaxial over-the-wire delivery system with the self-expanding Nitinol annuloplasty device mounted in the distal segment. A middle segment of the device has spring-like shortening properties due to the memory properties of the Nitinol alloy, and the stent-shaped end-segments have anchoring properties (Fig. 1). The memory of Nitinol is activated by body temperature. The middle segment is cut in a specific pattern leaving gaps in this segment. A biodegradable material fills the gaps and acts as a spacer, thus keeping it in its elongated phase for 3-4 weeks. This time will allow secure incorporation of the anchors into the wall of the CS before contraction of the device begins. The device is provided in a number of different lengths and anchor diameters.

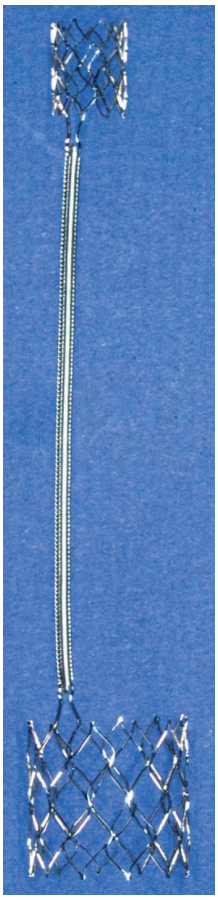


Figure 1. The Viking annuloplasty device. A middle segment of the device has spring-like shortening properties due to the memory properties of the Nitinol alloy, and the stent-shaped end-segments have anchoring properties.

Deployment

The animals were sedated, anaesthetized and intubated as above. A TTE was performed to confirm a significant MR. An electrocardiogram was taken. A 12 F introducer sheath (Medikit, Japan) was placed in the external jugular vein with the Seldinger technique. The ICE was performed through this access. A 10 F guide catheter (Edwards Lifesciences, USA) was then introduced and placed in the orifice of the CS. Sheep have a left-sided hemiazygos vein emptying into the CS close to the orifice. For this reason, the branching site was localized and the continuation of the CS catheterized with a JR 4 catheter, through which a 0.035 inch guide wire was introduced into the great cardiac vein. A CS venogram was performed, the JR 4 catheter was withdrawn, and the device was inserted over the guide wire. The device was placed with one anchor in the anterior interventricular vein, and the other at the orifice of the CS. After deployment of the device all catheters were retracted and the animal was allowed to wake up. After an observation period of one day the animal was returned to the breeder. A bolus of 10,000 IU of heparin was given intravenously before device insertion. Acetylsalicylic acid 75 mg (Pharmacia, Sweden) and Clopidogrel 75 mg (sanofi-aventis, France) was given daily throughout the study, starting on the morning before implantation.

Follow-up

Pacing with a frequency of 180 min^{-1} was continued for the entire follow up period. At the 2-month follow-up the animals were anaesthetized, intubated and prepared for sacrifice. If an animal showed signs of suffering, sacrifice was performed earlier. An ICE was performed first. Then a 6 F introducer sheath was placed in the femoral artery and a selective coronary angiogram was performed by means of a JL 4 catheter. The animal was then sacrificed by means of an intravenous injection of potassium chloride and autopsied. A coronary angiogram was performed on the explanted heart *ex vivo*. The heart was dissected and studied macroscopically with photo documentation and then preserved in formaldehyde for microscopic examination. Specimens were also taken from each lung for microscopy.

Analysis of data

All results are presented as means ± standard error of the mean (SEM), and n refers to the number of animals. The difference between all variables measured pre and post were analysed using the Wilcoxon Signed Rank test., with *P* values less than 0.05 being considered significant.

Results

Pacemaker treatment

Of 20 pacemaker treated animals, one had not developed MR after 3 months and was sacrificed, one animal had a wound infection and lost the pacemaker, and six animals died before device implantation could be done. The treatment time before device implantation averaged 64±7 days.

Device implantation and clinical follow-up

Twelve animals were thus alive and had developed a significant MR after pacemaker treatment and were eligible for device insertion. One implantation was unsuccessful due to improper function of the delivery system, and the animal was kept as a control. The remaining eleven animals received devices. The mean total procedure time was 84±14 min (n = 11), whereof the device-related procedure time was 12±2 min (n = 11). The mean follow-up time was 58±8 days. The weight of the animals before implant was 65±3 kg and at the time for sacrifice 64±3 kg (n.s.). Guide wire perforation of the CS was seen in one animal. A small amount of blood was seen in the pericardium at ultrasound, and no treatment was necessary. All animals were up and standing immediately after the procedure. Three animals were suffering from CHF and two were sacrificed according to the protocol on day 24 and 25 respectively. Both these sheep had normal coronary angiograms, and echocardiography showed no MR, compared to MR of grade 3 and 2-3, respectively, before device implantation. The third animal showed MR grade 2, and post-mortem examination showed the large anchor to be located within the right atrium instead of in the CS. This was due to incorrect sizing at implant, leading to use of a too long device. The foreshortening of the middle segment could therefore not correct the MR effectively. Angiography showed normal

coronary arteries. One animal aspirated and died during induction of anaesthesia for the follow-up, why no echocardiography could be obtained. Post-mortem angiography of the sheep showed an intact device and normal coronary arteries as well.

Echocardiography

Pacemaker treatment increased the mitral annulus septo-lateral diameter 23%, from 26±2 mm to 35±1 mm on the TTE. The degree of mitral regurgitation increased from 0.2±0.2 to 2.6±0.2 and the vena contracta increased from 1±1 mm to 7±0 mm. The ejection fraction (EF) decreased from 52±4% before pacemaker implantation to 28±3%. The diameter of the left atrium increased from 35±2 mm to 57±2.

The Viking device reduced the septo-lateral diameter of the mitral annulus with 15%. The diameter decreased from 35±1 mm before implantation to 30±1 mm at the follow up (n = 10, P = 0.0097). The degree of MR decreased from 2.6±0.2 on ICE to 0.8±0.2 (n = 10, P = 0.0039) and the vena contracta was reduced from 7±0.4 mm to 3±0.8 mm (n = 10, P = 0.0019).

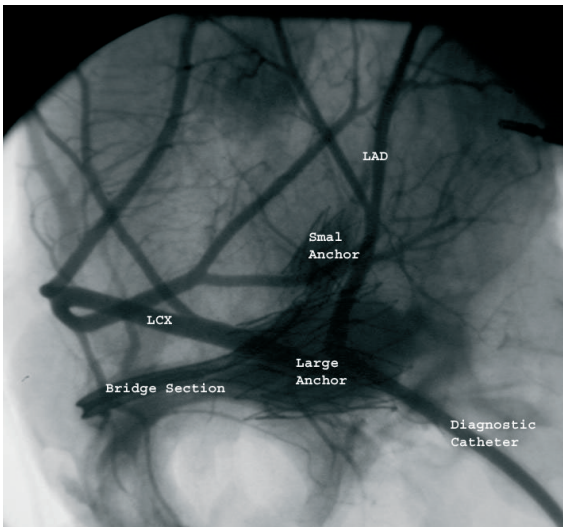
The EF increased from 28±3% at implantation to 39±4% at the last follow up (n = 10, P = 0.0371). No mitral stenosis could be seen. The diameter of the left atrium changed from 57±2 mm to 46±3 mm (n = 10, P = 0.0156). Normal flow was seen in the CS by Doppler in all cases. The animal in which implantation was unsuccessful due to failure of the delivery system was followed according to the protocol and used as a control. In this animal the MR increased from grade 3 to grade 4, and the MV septo-lateral diameter increased from 34 mm to 41 mm, and the EF decreased from 38 to 33% during the 2 month follow-up.

Angiography

A coronary angiogram was obtained in-vivo pre implant and pre sacrifice well as a post mortem *ex vivo* angiogram in all animals. All showed normal left-dominant coronary arteries, fully open with no signs of stenosis, neither in the proximity of the anchors, nor in the middle segment. In particular, the region where the circumflex artery crosses the coronary sinus was studied. The intermediate space was projected free, showing no signs of compression on the circumflex artery (Fig. 2).

Macroscopic findings

Apart from the case described above, where the large anchor was misplaced into the right atrium, all anchors appeared to have healed well, into the wall of the coronary sinus, with no signs of thrombosis. The middle segment was firmly attached to the wall of the vessel and covered by a sheath of fibrous tissue and endothelium.



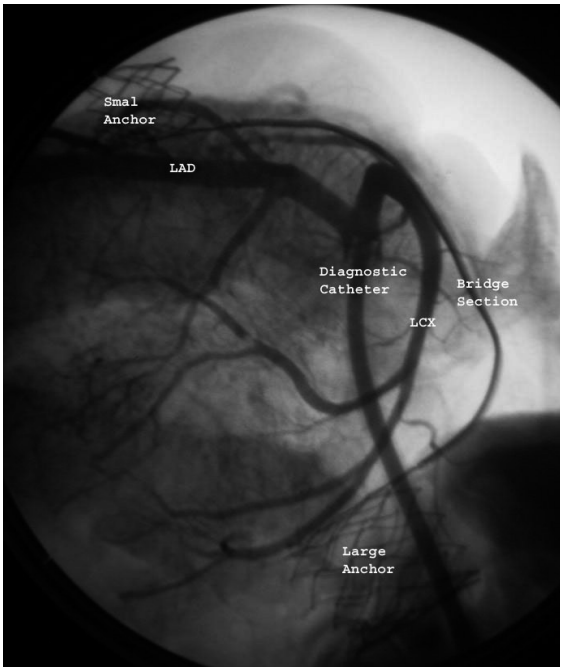


Figure 2.
A. Coronary angiogram showing the region where the coronary sinus, with the middle segment of the device (bridge), crosses the circumflex artery (LCX). Due to the projection the anchors are superimposed on each other. The small anchor is situated next to the left anterior descending artery (LAD).

B. Different projection of the same coronary angiogram showing that the lumina of the LCX and the LAD are unaffected by the device.

Discussion

The survival of patients with severe left ventricular dysfunction is significantly decreased when accompanied by mitral regurgitation[4,5], with one-year mortality reported to be as high as 54-70%[6]. Mitral valve surgery improves symptoms and survival in these patients[7,8]. Bolling *et al.* also proposed that undersizing the annulus acutely remodels the base of the heart, giving it a more ellipsoid shape[8]. Three-dimensional echocardiographic findings in sheep support this hypothesis[9].

Mitral annuloplasty is most commonly achieved by either suturing a complete ring, rigid or flexible, along the entire annulus, or suturing a flexible band along the posterior annulus incorporating both fibrous trigones. The rationale for the latter method is the assumption that the anterior portion of the annulus does not dilate.

Although this view has recently been challenged[10], follow-up studies of 1072 patients with degenerative mitral valve disease[11] and 585 patients with ischemic MR[12] at the Cleveland Clinic have shown that the choice of either of these methods did not influence repair durability.

The close anatomical relationship between the CS in the atrioventricular (AV) groove and the posterior mitral annulus lead us to hypothesize that a device placed in the CS could indirectly remodel the mitral annulus. The CS runs on the atrial side at a distance of 10 to 14 mm from the mitral annulus along the AV groove[13]. However, due to the sphericity of the filled left atrium and the base of the left ventricle *in vivo*, the AV groove is wedge-shaped. With the mitral annulus situated at the sharp angle of this wedge, and the CS at its base, contraction of the device in the CS will cause a force directed towards the sharp angle of the wedge, affecting the annulus. As a result, the septo-lateral diameter of the mitral annulus, as shown in this study, is reduced. The echocardiograms during the follow-up very clearly demonstrated the position of the contracted device deeper in the AV groove, in close proximity to the mitral annulus. Constriction or bulging of the left atrium was never seen. Rapid pacing was utilized in this study to induce a cardiomyopathy with secondary mitral regurgitation. The degree of mitral regurgitation achieved, as well as the increase in the septo-lateral diameter, is in agreement with previous findings with this model[14].

No animals where randomized to act as control which is a limitation in our study. The mitral annulus septo-lateral diameter and mitral regurgitation did however not decrease in the untreated animal during the follow-up period. In an ovine pacing study by Byrne *et al.*[15] where animals paced for 5 weeks were randomized to treatment with percutaneous annuloplasty or only continued pacing for another 28 days, the mitral annulus diameter and mitral regurgitation did not decrease in the non-treated group.

In the present study the septo-lateral diameter of the mitral annulus decreased 15%. In a study by Liddicoat *et al.*[16], acute ischemia was induced in sheep for 1-5 minutes, thereby causing temporary mitral regurgitation. When placing a rigid element in the lumen of a catheter in the CS (Viacor Inc), mitral regurgitation could be significantly reduced and the diameter decreased 20%. This was repeated in a subsequent study with chronic ischemia where six animals were followed for a period of 1 to 2 weeks[17]. In the above mentioned study by Byrne *et al.*[15] a cinching device by Nitinol was used for 4 weeks in 9 animals giving a 23.7% decrease of the diameter. The Viking device was designed for 20% reduction, a foreshortening calculated from ultrasound data obtained from patients undergoing MV repair at our institution. The device achieved 20% in bench-tests. The 5% loss might be explained with the difference in planes of the MV and the coronary sinus. However, 15% seems to be effective, indicating that the reduction during surgery might be overdone.

The coronary sinus is a delicate structure and one possible complication is perforation of the same. We had one perforation with the guide wire that needed no specific treatment, however in humans on heavy anticoagulation therapy, pericardial drainage could be necessary.

There was originally a concern that the device might affect the circumflex artery where it crosses under the CS. This was demonstrated in 3 out of 12 dogs in a previous study by Maniu *et al.* where an annuloplasty of a different design was positioned in the CS and cinched at deployment[18]. Coronary angiograms of all animals in the present study, *in vivo* and *ex vivo*, showed no signs of stenosis, neither in the circumflex artery nor in the left anterior descending artery, and the CS was clearly separated from the circumflex artery in multiple projections of the cross-over region in all animals (Fig. 2). This could be attributed to anatomical differences between sheep and dogs. It could also be due to the more gradual increase of tension over weeks with the device used in our study, possibly allowing movement of the circumflex artery within the groove. The stentlike anchors of the Viking device are also attached over a larger area of the CS which might counteract impingement on the arteries. There was a concern for the risk of thrombus formation in the CS, but this was not seen in any animal. This may be due to the relatively small amount of foreign material protruding into the lumen of the CS as well as the properties and to the slow release mechanism of the device itself.

The Viking device was evaluated in sheep with pacemaker-induced MR. Its safety and efficacy in models with ischemic MR remains to be investigated. Likewise, all possible anatomical differences between species must be taken into account before applying this method to patients.

These results indicate that the septo-lateral diameter of the mitral annulus, as well as the degree of experimentally induced mitral regurgitation, can be reduced with this new percutaneous catheter technique.

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