Three-dimensional assessment of papillary muscle displacement in a porcine model of ischemic mitral regurgitation

Henrik Jensen, MD, PhD,[a,c] Morten O. Jensen, PhD,[a,f] Morten H. Smerup, PhD,[a] Steffen Ringgaard, PhD,[b] Thomas S. Sørensen, PhD,[c,d] Niels T. Andersen, PhD,[e] Per Wierup, MD, PhD,[a] J. Michael Hasenkam, MD, PhD, DMSc,[a] and Sten L. Nielsen, MD, PhD, DMSc[a]

Objective: Papillary muscle displacement relative to mitral annulus is pivotal in chronic functional ischemic mitral regurgitation. Analysis of 3-dimensional papillary muscle displacement has relied on invasive measurement. In this study, we used noninvasive clinically applicable 3-dimensional morphology cardiac magnetic resonance imaging to define papillary muscle position in a 3-dimensional matrix.

Methods: Fifty pigs (approximately 50 kg) were subjected to posterolateral myocardial infarction and tachycardiac stress. Fourteen animals survived 6 weeks: 10 acquired chronic functional ischemic mitral regurgitation at least grade II and 4 did not. Animals were examined by 3-dimensional morphology cardiac magnetic resonance imaging, and dedicated software enabled assessment of anterior and posterior papillary muscle positions relative to anterior and posterior trigones and posterior mitral annulus. Animals with functional ischemic mitral regurgitation were compared with those without and with 10 healthy controls.

Results: Relative to controls, animals with functional ischemic mitral regurgitation at end systole had significantly higher displacements of the posterior papillary muscle from anterior and posterior trigones in lateral and posterior directions, and of anterior papillary muscle from anterior and posterior trigones in apical direction. Relative to animals without functional ischemic mitral regurgitation, there was significantly higher posterior papillary muscle displacement from posterior trigone in lateral direction. Interpapillary muscle distance was the strongest predictor of regurgitant volume ($r^2 = 0.85$, $P < .001$).

Conclusions: Three-dimensional morphology cardiac magnetic resonance imaging enabled detailed analysis of local left ventricular remodeling effects causing functional ischemic mitral regurgitation. (J Thorac Cardiovasc Surg 2010;140:1312-8)

ACD

Chronic functional ischemic mitral regurgitation (FIMR) is observed in 20% to 25% of patients after acute myocardial infarction,[1] and long-term survival is directly related to its severity.[2] FIMR at the time of coronary artery bypass grafting increases mortality as much as 4-fold even with revascularization.[3] Furthermore, persistent or recurrent FIMR has been reported in 13% to 59% of patients late after standard downsized ring annuloplasty,[4] and optimal surgical treatment is therefore still debatable.[5] To improve surgical outcome the fundamental mechanisms of chronic FIMR have been examined. Although the exact mechanism causing chronic FIMR is still elusive, clinical[6] and experimental[7] studies have focused on 2 central pathways, annular dilatation and papillary muscle (PM) displacement. Annular dilatation impedes leaflet coaptation by pulling the leaflets apart, most notably in septolateral directions (Carpentier type I dysfunction). The posterior PM has been shown to be displaced away from the annulus in the lateral and posterior directions in FIMR experimental models[7] and in patients.[8] PM displacement causes mitral valve tethering into the left ventricle (LV), which impairs coaptation (Carpentier type IIIb dysfunction). Posterior PM displacement[9] and continued LV remodeling[10] have been shown to predict recurrence of FIMR after ring annuloplasty. Because standard downsized ring annuloplasty primarily addresses annular dilatation and not PM displacement, Kron and colleagues[11] introduced surgical PM relocation as an adjunct procedure to downsized ring annuloplasty to relieve leaflet tethering and potentially improve durability of ring annuloplasty. PM geometry relative to mitral annular structures varies among patients, however, depending on

From the Department of Cardiothoracic and Vascular Surgery T,[a] and The Magnetic Resonance Imaging Research Centre,[b] Aarhus University Hospital, Skejby, Denmark; the Institute of Clinical Medicine[c] and the Departments of Computer Science,[d] and Biostatistics (Faculty of Health Sciences),[e] Aarhus University, Århus, Denmark; and the Department of Biomedical Engineering,[f] Engineering College of Aarhus, Århus, Denmark.

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Address for reprints: Henrik Jensen, MD, PhD, Senior Registrar, Department of Cardiothoracic and Vascular Surgery T and Institute of Clinical Medicine, Aarhus University Hospital, Skejby, 8200, Denmark (E-mail: hjensen@dadlnet.dk).

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Abbreviations and Acronyms

3D = 3-dimensional
FIMR = functional ischemic mitral valve regurgitation
LV = left ventricle
MRI = magnetic resonance imaging
PM = papillary muscle
RegVol = regurgitation volume

biologic variation and severity of remodeling. Therefore a detailed preoperative 3-dimensional (3D) analysis of the entire mitral valve apparatus is mandatory for planning surgical strategy. Experimentally, this has been achieved by epicardial ultrasonography,[12] videofluoroscopy,[13] and sonomicrometry.[14] These techniques, however, require direct surgical access to the heart and therefore lack clinical applicability. In the clinical setting, 2-dimensional echocardiography is the preferred method of assessing PM position, and 3D echocardiography has recently been introduced[15]; however, assessment of discrete geometric changes in PM geometry requires very precise 3D positioning of scan planes. Handheld echocardiographic probe positioning to assess subvalvular geometry is limited by the need for an appropriate acoustic window and by operator experience, inducing high risks of intraobserver and interobserver variability. Cardiac magnetic resonance imaging (MRI) provides superior image quality and allows operator-independent positioning of scan planes with great accuracy in 3 dimensions without the need for an acoustic window. In this study, we used a noninvasive 3D morphology cardiac MRI technique[16] for detailed geometric analysis of papillary muscle position in a pig model of FIMR. We aimed to identify the subvalvular geometric culprits responsible for the development of FIMR to provide a surgical planning tool for dedicated correction of FIMR.

MATERIALS AND METHODS

This study was conducted as a long-term intervention–control study on female Danish Landrace pigs. All animal experiments were conducted according to the guidelines given by the Danish Inspectorate for Animal Experimentation and after specific approval from this institution. Qualified animal caretaker personnel monitored the health status of the animals at all times during the study period. Analgesics were administered whenever an animal showed any sign of pain. In cases of refractory pain or poor thriving, animals were humanely killed.

Surgical Technique

The chronic FIMR animal model has recently been developed at our institution.[17,18] Figure 1 displays survival and inclusion of animals during the study period. Fifty pigs weighing approximately 50 kg each were anesthetized with intramuscular injections of midazolam (0.5 mg/kg) and ketamine (5 mg/kg). Then intravenous access was obtained through an ear vein, and etomidate (Hypnomidate, 0.6 mg/kg) was given to allow intubation. The animal was coupled to a ventilator, and sevoflurane inhalation was adjusted to a minimum alveolar concentration of 1% for continuous anesthesia. A continuous fentanyl drip (10 μg/[kg · h]) was used for analgesia. Transthoracic echocardiography was performed to confirm mitral competence. Six animals were excluded for mitral regurgitation at baseline. In the remaining 44 animals, a 7F sheath was placed in the right common carotid artery with the Seldinger technique. Coronary angiography was for performed, and a posterolateral LV wall infarction was induced by placing 2 to 3 metal coils in the circumflex artery proximal to the first obtuse marginal. A loading dose of amiodarone (300 mg) and potassium chloride (10 mEq) was given during the 20 minutes before induction of infarction as prophylaxis against ventricular arrhythmias, and pancuronium bromide (0.2 mg/kg) was given as muscle relaxant. Sixteen animals died of ventricular fibrillation refractory to direct current conversion. Forty-five minutes after coil placement, a pacemaker with a right ventricular lead was implanted; starting on postoperative day 10, pacing intervals were conducted to promote LV remodeling (2 sequences of 7 days of pacing at 160 beats/min and 7 days off). Cefuroxime (1.5 g) was administered both preoperatively and postoperatively to prevent infection. Postoperative analgesia was achieved with intramuscular injections of flunixin (INN flunixine, 0.4 mg/kg daily for 4 days) and acetaminophen (INN paracetamol , 1 g twice daily for 14 days). Buprenorphine (0.3 mg/mL) was administered intramuscularly to animals showing signs of pain. Amiodarone (200 mg for 5 days) was given to reduce the risk of arrhythmia. During the period of intermittent pacing, animals were given furosemide (40 mg twice daily) to avoid pulmonary congestion and potassium chloride (750 mg twice daily) to prevent potassium depletion. Fourteen animals died or were humanely killed because of severe symptoms of heart failure during the next 6 weeks. Fourteen animals survived 6 weeks to be returned to the laboratory and were sedated, intubated, and coupled to a ventilator as described previously.

The presence of a mitral regurgitation jet was assessed by transthoracic echocardiography (Vivid 7; GE Vingmed Ultrasound, Horten, Norway). Severity of mitral regurgitation was graded as I through IV according to the American Heart Association and American College of Cardiology guidelines.[19] Ten animals were considered to have FIMR of at least grade II (FIMR-positive group), whereas 4 were not (FIMR-negative group). The animals were then examined with cardiac MRI and subsequently allocated to further study. Ten weight-matched healthy female pigs (53 kg) served as controls. These animals underwent transthoracic echocardiography and cardiac MRI. No control animals had mitral regurgitation.

Cardiac MRI

MRI was conducted with a Philips Achieva 1.5-T MR Scanner (Philips Medical Systems BV, Best, The Netherlands), with electrocardiography used to synchronize data acquisition. Cine images were used to assess hemodynamics and mitral valve leaflet geometry and were acquired with the Balanced Steady-State-Free-Precession sequence with 30 heart phases, a slice thickness of 5 mm, a pixel size 2.0×2.0 mm^2, a repetition time of 3.2 ms, an echo time of 1.6 ms, and a flip angle of 65°. Aortic flow was assessed with a 2-dimensional phase-contrast sequence with a slice thickness of 8 mm, a pixel size 2.5×2.5 mm^2, a repetition time of 5.1 ms, an echo time of 3.1 ms, a flip angle of 15°, and a velocity encoding of 100 cm/s, which prevented aliasing in all scans. No animals had aortic regurgitation. The 3D morphology scans were acquired with the Balanced Steady-State-Free-Precession sequence. The field-of-view was $330 \times 330 \times 130$ mm^3, the repetition time 4.0 ms, the echo time 2.0 ms, and the flip angle 90°. Online identification of end diastole and end systole was necessary for planning of 3D morphology scans. End diastole was defined as the time of R-wave onset in the electrocardiogram, and end systole was defined as the time of maximum septal contraction.

Hemodynamics

LV stroke volume was obtained by subtracting LV volumes at end diastole and end systole on the basis of a 12-slice cine short-axis scan covering the LV from the apex to the center of the atrium. Mitral regurgitation volume (RegVol) and regurgitation fraction was obtained by subtracting the LV