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A Long-term Porcine Model for Evaluation of Prosthetic Heart Valves

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ABSTRACT

Background: Animal experimental testing is imperative for preclinical evaluation of prosthetic heart valves and implantation techniques. Because human and pig cardiovascular structures including mitral valves show remarkable anatomical similarity, these animals are good candidates for preclinical testing. Previous attempts to establish such long-term models were hampered by both intra- and postoperative difficulties. Our aim was to overcome these difficulties to develop a porcine model for mitral valve replacement (MVR) and furthermore to investigate the practical feasibility of 3 chordal reconstruction procedures.

Methods: Sixteen 60-kg pigs were allocated to undergo 1 of 3 surgical procedures, (1) preservation of the entire subvalvular apparatus (n = 8), (2) preservation of the secondary chordae only (n = 4), or (3) excision of the native valve and papillary resuspension with sutures (n = 4). St. Jude Medical valves (29 mm) were implanted during extracorporeal circulation and cold cardioplegic arrest. Postoperative anticoagulation was administered by subcutaneous heparin injections.

Results: Fourteen animals survived 1 month, thriving and without signs of heart failure. One animal was euthanized due to irreversible bleeding in the tracheal tube, and another animal died on the third postoperative day owing to valve thrombosis.

Conclusion: A practically feasible long-term porcine model of MVR has been established. Because the pig is superior to other species with respect to anatomical and physiological similarity to humans, we consider this model as an optimal platform for experimental preclinical testing of heart valve prostheses.

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INTRODUCTION

Implantation of prosthetic heart valves has been used for treatment of valve diseases for more than 4 decades. Current designs and implantation techniques constitute a broad range of generally safe therapeutic options. However, serious side effects still exist, such as (1) bleeding and thromboembolic complications for mechanical valves, (2) structural degeneration of biological valves, and (3) left ventricular dysfunction after mitral valve replacement. Therefore, refinement and further development of current practice is necessary.

Prior to clinical implementation, standardization organizations [CEN 2004, ISO 2004] have defined a set of minimum requirements to be met by new designs. Although in vitro testing is employed for standardized and precise comparison of different designs mainly in terms of flow characteristics and mechanical durability, the biological impacts of implantation, including thrombogenecity, long-term biological durability, and effect on cardiac pump function, can be assessed only by animal experimental testing.

A number of different species including dogs [Bianco 1986], goats [Bjork 1986], sheep [Irwin 1993] and pigs [Hazekamp 1993, Gross 1997b] have been used in experimental models; however, no single model has yet elucidated all aspects of human valve-related complications. The use of dogs and goats has been largely abandoned, and although sheep are currently used most widely, profound shortcomings to the use of this species also exist. A long-term sheep model study failed to reveal the thrombogenecity of a new valve design (the Medtronic Parallel), which was consequently withdrawn from clinical use because of high incidence of thromboembolic complications in human patients [Bodnar 1996]. Furthermore, anatomical dissimilarities [Walmsley 1978] between human and sheep cardiovascular structures (lack of proper ascending aorta and a human-incompatible mitral valve apparatus) render this species less favorable for preclinical testing.

Because pigs and humans are very similar in terms of heart size, cardiac output, and blood pressure [Swindle 1998], our

laboratory has used porcine models for investigation of a broad range of cardiovascular fields including acute aortic and mitral valve replacement [Hasenkam 1988, Lomholt 2002]. Recent studies have furthermore shown that the porcine mitral valve apparatus is very similar to its human counterpart regarding size and arrangement of leaflets as well as number and distribution of chordae [Rijk-Zwikker 1994, Lomholt 2002]. Coagulation and inflammatory systems are comparable [Reverdiau-Moalic 1996, Gross 1997a]. Pigs are inexpensive and fairly easy to handle, and the use of this species in animal experimental research poses only minor ethical problems. Because of the widespread similarities, we hypothesized that pigs would constitute an ideal human compatible substrate for long-term evaluation of prosthetic heart valves. However, previous attempts to provide a practically feasible protocol in pigs have been hampered by intraoperative technical [Swan 1971a, Swan 1971b, Gross 1997b] as well as postoperative difficulties [Hazekamp 1993, Gross 1997b, Grehan 2000]. Therefore, the specific aim of this study was to establish a long-term model of MVR incorporating safe and reproducible surgical, anaesthesiological, and postoperative (including anticoagulant) procedures. Furthermore various chordal reconstruction techniques were performed for assessment of the pig as a suitable substrate in forthcoming experimental trials. This study presents a working and practically feasible long-term porcine model of MVR with mechanical prostheses.

MATERIALS AND METHODS

The protocol was developed as an iterative process. Although methods described below were used throughout this study, minor adjustments were made contemporarily. The following sections describe the procedures of the final protocol.

Animals

Sixteen mixed Danish Landrace/Yorkshire female pigs (body weight 60-65 kg, age 4.5-5 months) were used for MVR. The same number and race pigs (body weight 40 kg, age 3.5 months) were used as blood donors. All animals received 500 mg ampicilline (Pondocillin) perorally 2 times daily for 4 days preoperatively to prevent pneumonia and were kept fasting 12 hours preoperatively.

Valves

Mechanical heart valves (mitral, size 29; St. Jude Medical, St. Paul, MN, USA) were used in all MVR experiments of this study.

Anesthesia

Donor animals received 20 mg midazolam (Dormicum 5 mg/mL, 0.5 mg/kg) and 160 mg azaperone (Stresnil 40 mg/mL, 4 mg/kg), and MVR animals received 30 mg midazolam (0.5 mg/kg) and 240 mg azaperone (4 mg/kg) intramuscularly as preanaesthetic before being transported from farming facilities to the experimental laboratory. On arrival, an intravenous (IV) access was obtained through an ear vein. Donor animals also received 20 mg of midazolam (0.5 mg/kg) and 100 mg of ketaminol (2.5 mg/kg). Thereafter, a heavy gauged needle was inserted into the brachiocephalic vein plexus through the midline skin immediately anterior to the jugular notch for aspiration of blood (approximately 2 L) by means of air-evacuated bottles. The animal was then killed with 6 g pentobarbital IV (200 mg/mL, 100 mg/kg). One liter of donor blood was added to the cardiopulmonary bypass (CPB) prime solution; remaining blood was infused postoperatively.

MVR animals received 30 mg midazolam (0.5 mg/kg) and 300 mg ketaminol (5 mg/kg) IV as induction anaesthesia and were thereafter endotracheally intubated and coupled to a ventilator (Siemens Servo ventilator 900 D; Siemens-Elema AB, Solna, Sweden). Ventilated minute volume was kept at 150 mL/kg with a positive end-expiratory pressure (PEEP) of 4 cm H_2O and an FiO_2 of 50%. Immediately after ventilator adjustment and every 60 minutes during surgery, 12 mg pancuronium (Pavulon 2mg/mL, 0.2 mg/kg) was given as muscle relaxant. Continuous anesthesia consisted of 4.2 mg/kg per hour propofol IV (10 mg/mL), and analgesia was obtained by 10 μg/kg per hour fentanyl IV (Haldid, 50 μg/mL). A total of 500 mg methylprednisolone (SoluMedrol 500 mg), 250 mg IV and 250 mg in CPB prime, was given in order to reduce post-CPB inflammatory reactions. Cefuroxime 1.5 g (Zinacef 1500 mg) was given as prophylactic antibiotic. A 12-F urinary catheter was installed. Cardiac rhythm and frequency were monitored continuously (Cardiomed Flowmeter; Cardiomed A/S, Oslo, Norway).

Surgical Procedures

The heart was exposed through a midline sternotomy. The pericardium was thereafter suspended by stay sutures to the left sternal edges to expose the left atrium. Adventitia between the aorta and the pulmonary trunk was divided to enable placement of purse-string sutures (2-0 Ticron 3185-51, USS; Tyco Healthcare Group, Norwalk, CT, USA) distally in the aortic arch (Figure 1). A second purse-string (2-0 Ticron 3185-51, USS) was placed in the right atrial appendage. After heparinization (40,000 IU heparin [5000 IU/mL]; activated coagulation time >350 seconds), aortic (DLP arterial cannula 24-F, Medtronic, Inc., Minneapolis, USA) and venous (MC2 2-stage venous cannula 36/46 F; Medtronic) cannulation was made in the aortic arch and right atrial appendage, respectively. Lines were connected and normothermic CPB instituted (Stöckert-Shiley roller pump; Sorin Biomedica, Via Crescentino, Italy; Quadrox HMO 1010 Hollow Fibre membrane oxygenator; Jostra AG, Hirrlingen, Germany) with flows of 4.5 to 5.5 L/minute adjusted according to blood gas parameters. Mechanical ventilation was maintained throughout CPB; however, PEEP was reduced to 2 cm H_2O in order to partially deflate the lungs for optimized exposure. A cardioplegia cannula (aortic root cannula 9-F; Medtronic) was placed in the ascending aorta and secured with a purse-string (4-0 Surgipro VP 975, USS). Aortic cross-clamping was then performed and 1 L of 4°C crystalline cardioplegia (Kardioplex; H/S Apoteket, Copenhagen, Denmark) delivered; 300 mL of additional cardioplegia was administered after 15 minutes. The left atrial appendage was opened immediately to decom-

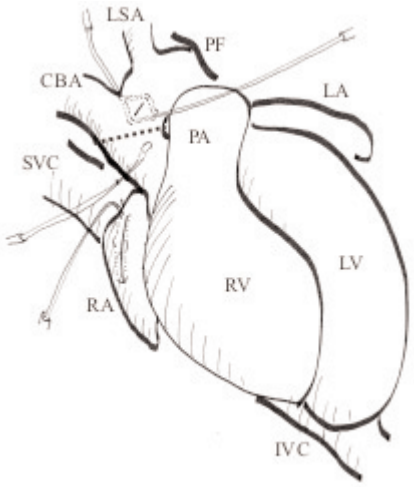

Figure 1. Schematic view of the porcine heart. Aortic cannulation in the arch for easy placement of cross-clamp (dotted line) and cardioplegia cannula. LSA indicates left subclavian artery; PF, pericardial fold (with phrenic nerve); CBA, common brachiocephalic artery; LA, left atrium; PA, pulmonary artery; SVC, superior vena cava; LV, left ventricle; RA, right atrium; RV, right ventricle; IVC, inferior vena cava.

press the left ventricle through the mitral orifice. A cardiotomy suction catheter was placed in the left lower pulmonary vein for drainage (Figure 2). MVR was thereafter performed (see "Chordal Reconstruction Procedures" below). Double-armed pledgeted valve sutures (2-0 Ticron 3323-56, USS) were placed evertedly through the mitral annulus and passed through the sewing ring of the mechanical valve, which was tied down and seated antianatomically. The atriotomy was closed using mattress and over-and-over technique (4-0 Surgipro VP 975, USS). The left ventricle was thereafter vented with a needle through the apex, and the left atrium was manipulated to expel any air. The cross-clamp was removed and 50 J DC conversion performed if necessary. During the subsequent 45-minute reperfusion the right internal mammary artery and vein were dissected free at the midsternal level and cannulated with vascular sheaths (8F Avanti+; Cordis, Miami, FL, USA). Disposable lines were inserted in the hemostatic ports of the sheaths and tunneled out through the abdominal skin for continuous intravascular pressure measurement and central venous access. Atrial and ventricular pace electrodes (3/0 temporary pacemaker electrodes, bipolar; Johnson & Johnson, Birkerød, Denmark) were placed and tunneled out through the abdominal skin. After confirmation of overall satisfying ventricular function (sinus rhythm, concentrical contractility pattern as visible from the surgeon's view) and absence of air in the coronary arteries as well as hemodynamic and biochemical stability, the animal was gently weaned from CPB. Heparinization was reversed by 250 mg of protamine sulphate (Protaminsulfat 10 mg/mL). Drains were placed in the mediastinum and pleurae and tunneled out through the abdominal skin. The sternum was closed with 12 steel-wire sutures (7.0 metric CV 320; Sherwood, Davis & Geck, Gosport, UK) and osteosynthesis was performed through the heads of the 2 cranial costae with 1 spongiosa screw (6.5 cancellous bone screw/32 mm, stainless steel; Stratec Medical A/S, Herlev, Denmark). Muscle and subcutis were closed in layers with running sutures (0 Polysorb CL 817, USS), and the skin was closed using both running intracutaneous technique (3-0 Biosyn SM 822, USS) and additional running sutures (3-0 Surgipro SP 675, USS) to strengthen the wound.

Chordal Reconstruction Procedures

Three different procedures were used in a nonrandomized manner. We wanted to investigate the practical feasibility of each, in order to perform randomized studies later. Eight pigs received MVR with preservation of the entire native mitral valve apparatus (Figure 3A). Four pigs had MVR with partial preservation of the subvalvular apparatus (Figure 3B). Primary chordae tendineae and leaflet coaptation zones were excised, and the annuloventricular continuity was preserved by the remaining secondary chordae. Four pigs received MVR with excision of the entire native valve and papillary resuspension by pledgeted sutures (3-0 Ticron3323-56, USS) (Figure 2C).

Postoperative Care

Immediately after surgery animals were placed in lateral recumbency and alternately turned every 45 minutes to facilitate chest drainage. Residual blood from the heart-lung machine as well as remaining donor blood was infused via a custom-made roller-pump system as needed. Furosemide (Furix, 10 mg/mL) was given in doses of 5 to 10 mg, in order to maintain an hourly diuresis of 100 mL. In case of

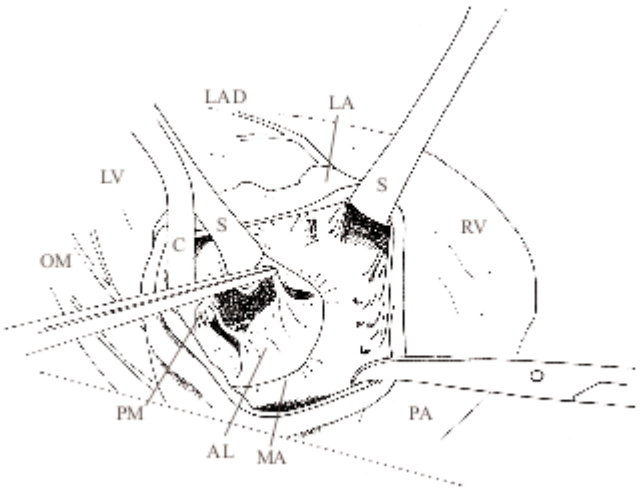

Figure 2. Access to the mitral valve through a left auricular incision continued backward toward the left pulmonary veins. Exposure was facilitated by sideholders pulling the auricle and annulus gently rightward. The anterior (septal) leaflet assumes a posterior position. The cardiotomy suction catheter (C) is placed in the lower left pulmonary vein for drainage and better exposure. LAD indicates left anterior descending artery; LA, left auricle; LV, left ventricle; S, sideholders; RV, right ventricle (collapsed); OM, obtuse marginal; PM, papillary muscle; PA, pulmonary artery; AL, anterior leaflet; MA, mitral annulus.

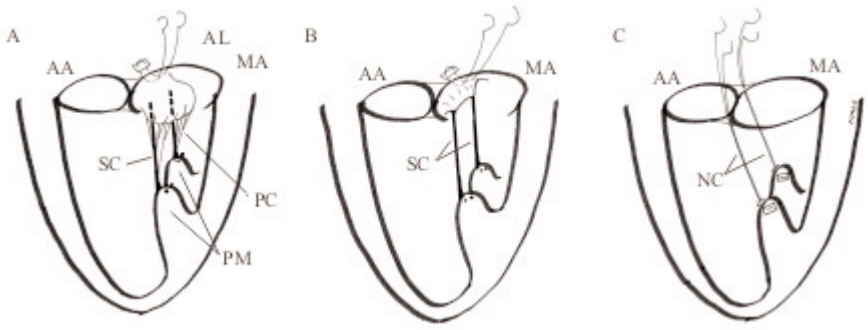

Figure 3. A, Preservation of the entire subvalvular apparatus (posterior leaflet not shown). B, Preservation of the secondary chordae only. C, Papillary resuspension with pledgeted 3-0 Ticron sutures, which are passed through the fibrous trigones and secured in the valve sewing ring. AA indicates aortic annulus; AL, anterior leaflet; MA, mitral annulus; SC, secondary chordae; NC, 3-0 Ticron neo-chordae; PC, primary chordae; PM, papillary muscles.

bradyarrhythmia, a pacemaker (Temporary Pulsegenerator Medtronic 5346DDD) was instituted in atrial or atrioventricular mode (80-90 impulses per minute). Anesthesia was continued until the animals were hemodynamically stable and had acceptable blood gasses and drain production had ceased. Thereafter drains were removed and the animals were placed in an oxygen cage. Intravascular lines and pace electrodes were removed and extubation performed when allowed by spontaneous respiration. Analgesic therapy constituted a combination of agents. First, flunixine (50 mg/mL, 4 mg/kg), a potent veterinary nonsteroidal anti-inflammatory drug, was administered intramuscularly at a dosage of 240 mg daily for 2 weeks. Second, buprenorphine 1.8 mg (Anorfin 0.3 mg/mL) was given IV every 4 to 6 hours in the first 24 hours postoperatively. Third, 2 daily doses of paracetamol 2 g (Panodil Retard 500 mg, 4 g/day) were administered perorally for 4 weeks postoperatively. Postoperative anticoagulation was maintained by daily subcutaneous injection of 10,000 IU of unfractionated heparin. Antibiotic therapy consisted of IV cefuroxime 1.5 g, 3 times daily for 3 days, and thereafter peroral ampicilline 500 mg, 3 times daily for 2 weeks.

Approximately 24 hours after surgery, the animals were transported to their farming facilities for continuous observation for 5 days postoperatively, whereupon they were observed a minimum of 3 times daily during feeding. The veterinary technicians maintained in close contact with the study leader during the postoperative period, and any signs of pain, infections, or heart failure (fatigue, dyspnea, coughing) were immediately reported. Animals were followed for 1 month postoperatively. Animal handling was performed according to the guidelines given by the Danish Inspectorate for Animal Experimentation and after specific approval from this institution.

RESULTS

Cross-clamping times, CPB times, skin-to-skin times, chest drainage times and production volume, time on ventilator, and recovery times are shown in Table 1. Intraoperative as well as early- and late-recovery hemodynamics and blood gas parameters are shown in Table 2. No intraoperative deaths occurred in the 16 MVR pigs. One animal was sacrificed in the early postoperative period because of bleeding in the airways presumably caused by the tracheal tube (this caused desaturation while the pig was still artificially ventilated). Fifteen (94%) of 16 animals were transported to the farming facilities the day after surgery. One pig died on the 3rd postoperative day. Post mortem examination showed excessive thrombus formation on the atrial aspect of the prosthetic valve in the hinge regions. No animals, including the pig that died of thrombus formation, did at any time of the study exhibit signs of stress, pain, infection, sternal dislocation, or heart failure.

DISCUSSION

This study is the first to present a practically feasible long-term model for MVR in pigs with survival rates that equal those of acute experiments. Fourteen of 16 pigs survived 1 month postoperatively with neither thrombotic nor bleeding complications. Because these results have been achieved after thorough revision of initial experimental protocols, we feel confident to address a number of specific items regarding anaesthesiological, surgical, and CPB procedures. We must, however, emphasize the iterative nature of this project; adjustments are still being made in an ongoing fashion.

Pigs, especially if unaccustomed to human contact, have a tendency to develop severe acute stress symptoms (malignant

Table 1. Timing of Events and Drain Production*

	All Procedures, Mean (Range)
Cross-clamping time, min	35.6 (24-55)
Cardiopulmonary bypass time, min	94.7 (75-115)
Skin-to-skin time, min	179.3 (138-215)
Drainage time, min	290.7 (220-525)
Drain production, mL	308.5 (200-600)
Time on ventilator	10 h 58 min (9 h-13 h 40 min)
Recovery time	12 h 46 min (10 h 10 min-18 h 20 min)

*Drainage time is the interval from chest closure to drain removal. Recovery time is the interval from intubation until the animal is on its feet again.

Table 2. Hemodynamic and Blood Gas Parameters during and after CPB

	Steady-State CPB	Intraoperative (Post-CPB)	Early Postoperative	Late Postoperative
Systolic pressure, mm Hg		87 ± 10 (70-100)	99 ± 12 (80-110)	130 ± 13 (110-140)
Mean pressure, mm Hg	61 ± 15 (38-88)	65 ± 10 (50-80)	75 ± 10 (60-90)	95 ± 8 (80-100)
Diastolic pressure, mm Hg		55 ± 10 (40-70)	63 ± 12 (50-80)	85 ± 8 (70-90)
CPB flow rate, L/min	4.8 ± .5 (3.7-5.4)			
Heart rate, min^{-1}		79 ± 17 (55-110)	81 ± 10 (65-100)	81 ± 14 (60-110)
pH	7.47 ± .08 (7.38-7.65)		7.48 ± .06 (7.41-7.59)	7.43 ± .03 (7.35-7.49)
pCO_2, kPa	4.58 ± .65 (3.66-5.84)		5.19 ± .61 (4.26-6.15)	6.35 ± .62 (5.38-7.46)
pO_2, kPa	20.65 ± 5.16 (13.16-35.1)		44.58 ± 12.26 (6.77-55.55)	15.57 ± 6.21 (8.54-30.78)
$SatO_2$, %	100 ± 0 (0)		98.9 ± 4.3 (82.9-100)	98.7 ± 2.8 (92.0-100)
Hematocrit, %	25.2 ± 4.2 (20.6-34.0)		25.7 ± 4.0 (19.2-32.9)	33.9 ± 4.0 (23.8-41.3)
Base excess, mmol/L	1.2 ± 4.4 (-6.6-8.3)		5.2 ± 2.9 (.3-9.7)	6.9 ± 2.9 (-1.0-10.7)
K^+, mmol/L	3.9 ± .5 (2.6-4.8)		4.4 ± .8 (3.0-6.1)	4.2 ± .5 (3.5-5.2)
Lactate, mmol/L	5.4 ± 3.6 (1.7-15.2)		2.7 ± 1.3 (1.0-5.4)	1.6 ± 1.1 (.6-5.1)
Donor hematocrit, %	26.5 ± 1.6 (24.6-29.8)			

*Values are shown as mean ± standard deviation (range). CPB indicates cardiopulmonary bypass.

hyperthermia, tachyarrhythmias) [Mitchell 1982] during instrumentation. To avoid this condition, we previously used high dosages for pre- and continuous infusion anesthesia. By using azaperone, midazolam, and ketaminol for pre- and induction and thereafter propofol (which has a short half-life, $t_{1/2}$ = 0.5-1 hours) for continuous infusion we combine beneficial effects for achieving immediate satisfactory sedation, and recovery was not hampered by slow awakening. Animals were usually able to walk around as well as eat and drink effortlessly within 2 hours of extubation (Table 1). Pigs tend to tolerate and therefore require higher doses of opioids than humans [Swindle 1991]; we have not seen any adverse effects to the use of fentanyl or buprenorphine in this study. For achievement of long-term analgesia, paracetamol and Flunixine proved very effective.

We have earlier noticed a tendency for porcine pulmonary tissue to develop large atelectases. We therefore routinely use PEEP levels of 4 to 6 cm H_2O as well as ventilation during CPB to avoid collapse. The lungs are manually hyperinflated prior to weaning from CPB as an additional means for prevention of atelectases.

From our past experience pigs are prone to a very rapid and self-increasing metabolic decline toward (lactemic) acidosis during extensive surgical procedures. In contrast to reported methods [Swindle 1998] we therefore used compensatory hyperventilation to maintain pH above 7.5 (Table 2). During CPB very large elevations in serum lactate (>15 mmol/L) can occur (Table 2) as a sign of possibly insufficient perfusion. This phenomenon always normalizes post-CPB and should be recognized as being relatively benign in the setting of normal pH values.

Pigs have been reported to react adversely to CPB with postperfusion pulmonary hypertension, right-sided heart failure, and cardiovascular collapse [Swan 1971a]. Guided by clinical implementation [Fillinger 2002], we started using 500 mg methylprednisolone preoperatively; none of the above-mentioned complications and side-effects was observed.

Domestic Landrace/Yorkshire pigs have low hematocrit compared to other pig breeds [Swindle 1998] and humans (Table 2). We found a mean hematocrit of 26.5% in sixteen 40-kg pigs (Table 2). To avoid post-CPB dilution, we use non–cross-matched allogenic donor blood in the prime solution. Remaining donor blood and residual blood from the heart-lung machine were transfused postoperatively. A mean late postoperative hematocrit of 34% was obtained after this practice (Table 2). No transfusion-related complications using this breed of pigs have occurred.

We used fairly straightforward and human-comparable surgical procedures; however, some points deserve attention. As noted by others [Swan 1971b, Gross 1997b] porcine vascular structures are extremely fragile and should be handled with delicacy. When repair of a suture line or cannulation site is necessary, we recommend pledgeted 4-0 prolene sutures. Regarding CPB cannulation, we find it beneficial to place the aortic cannula as far distal as possible in the aortic arch in order to provide space for the cardioplegia cannula and cross-clamping (Figure 1). Venous drainage to the CPB circuit should be so effective that the right ventricle collapses entirely for ease of mitral valve exposure. Because of the dextrorotation of pig hearts [Crick 1998] the left coronary ostium lies anteriorily in the aorta. This characteristic causes a tendency for air embolism in the left anterior descending artery when the cross-clamp is removed. The consequence is seen on the visible part of the left ventricle as systolic paradoxical movements of the nonperfused myocardium; proximal-distal massage to the arteries should be performed immediately. We always reperfuse 45 minutes or longer, always longer than cross-clamping time and always more than 15 minutes after visible paradoxical myocardial movements have ceased. Weaning from CPB should be done gradually with down-regulation of flow in 4 or 5 steps and cautious filling to avoid volume overload of the right ventricle. Apart from supplemental calcium and in contrast to others [Gross 1997b], we never use any inotropic support.

Cannulation of the internal mammary vessels is a handy and time-saving way to obtain intravascular access; lines are very easily removed postoperatively, and we have seen no complications (bleeding, infection, hampered sternal healing) to this technique.

Proper sternal stabilization is imperative for safe mobilization and healing (+12 steel wire sutures and costal osteosynthesis). We have seen no sternal dislodgement or infection in this series.

Regarding the various methods of chordal reconstruction, such procedures are performed within acceptable time limits (Table 1) and without obvious complications. Exposure of the porcine mitral valve orifice is easy through the auricle of the left atrium after slight rightward rotation of the heart (Figure 2). The porcine mitral valve apparatus is very similar to its human counterpart with respect to size and arrangement of leaflets as well as number and distribution of chordae and therefore constitutes a suitable substrate for future evaluation of chordal reconstruction techniques during MVR or valvular plasty.

In conclusion, a protocol for reproducible surgical, anaesthesiological, and postoperative procedures for MVR in pigs has been established. Because the pig is superior to other species with respect to anatomical and physiological similarity to humans, we consider this model as an optimal platform for experimental preclinical testing of heart valve prostheses.

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