TITLE: Outcome of bioprosthetic valve replacement in dogs with tricuspid valve dysplasia

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Objectives: to describe the short term and long term outcome in dogs with tricuspid valve dysplasia (TVD) undergoing tricuspid valve replacement under cardiopulmonary bypass (CPB).

Methods: data were collected from the hospital records of all dogs that had undergone tricuspid valve replacement under cardiopulmonary bypass between 2006-2012. Dogs were considered candidates for TV replacement if they had severe tricuspid valve regurgitation associated with clinical signs of cardiac compromise.

Results: 9 dogs of 6 different breeds were presented. Median age was 13 months (range 7-61 months), median weight 26.5kg (range 9.7-59 kg). Eight bovine pericardial valves and 1 porcine aortic valve designed for use in the mitral position in man were used. One non-fatal intra-operative complication occurred. Complications during hospitalisation occurred in 6 dogs, 4 of which were fatal. Of the 5 dogs discharged, one presented dead due to haemothorax after minor trauma 7 days later. The 4 remaining dogs survived a median of 533 days; all of these dogs received a bovine pericardial valve.

Clinical significance: based on our results, TVR with bovine or porcine prosthetic valves is associated with a high incidence of complications. Until better techniques are devised for controlling the canine coagulation system or less thrombogenic valve materials are developed, bioprosthetic valve replacement using this protocol remains a high risk treatment in dogs.

Introduction

Tricuspid valve dysplasia is an uncommon congenital malformation in small animals, accounting for approximately 3% of congenital cardiac malformations in dogs (Oliveira et al. 2011). It is more common in larger dogs, with Labrador Retrievers, English Bulldogs and Golden Retrievers amongst others predisposed (Famula et al. 2005, Oliveira et al. 2011). A spectrum of valvular lesions are possible with the most common being thickened, immobile septal leaflets that are effectively tethered to the ventricular septum (Liu & Tilley 1976). The resulting valvular dysfunction leads to progressive right atrial and ventricular volume overload, with chamber dilatation and dilatation of the tricuspid annulus, which further exacerbates the valvular incompetence. Treatment options for canine tricuspid valve dysplasia typically consist of medical therapy for right sided heart failure (Adin 2008). In the human literature both valve repair and valve replacement are reported with the decision based on the specific valvular morphology and whether repair is feasible. In man, both techniques have advantages and disadvantages. There is one report describing the surgical treatment of tricuspid valve dysplasia in the veterinary literature to date (Arai et al. 2011) which documents the outcome of bioprosthetic valve implantation, under conditions of cardiopulmonary bypass (CPB) in 12 dogs. In that study, dogs were considered candidates for tricuspid valve replacement if they had severe tricuspid valve regurgitation associated with clinical signs of cardiac compromise such as severe exercise intolerance and ascites, and required on-going medical therapy (Arai et al). Ten of the dogs survived surgery with a further two euthanatised at 10 and 13 months post-operatively due to inflammatory pannus formation and consequent failure of the bioprosthesis. The purpose of the study reported here is to describe the short and long term outcomes in a further cohort of dogs.

Materials and Methods

Similar to Arai et al.'s description (2011), tricuspid valve replacement was undertaken in dogs that had severe tricuspid valve incompetence associated with right heart failure and whose owners fully accepted the risks associated with this treatment, along with the financial obligations associated with surgery. Written client consent was obtained from all owners. Data were collected from the medical records of all dogs that had undergone tricuspid valve replacement under CPB at the RVC between 2006 and 2012. Data gathered included: signalment, clinical signs, previous and current medication, echocardiographic findings, duration of anaesthesia, CPB and cross clamp time, type and size of valve used, pre- and post-operative complications and time to discharge. Follow up data were obtained from the medical records for subsequent visits to our referral centre, and long term outcome was obtained from either the medical record if the patient was known to be deceased, including post mortem data if applicable, or by referring veterinarian or owner contact. Minor complications were defined as those requiring no surgical intervention; major complications were those requiring surgical intervention or resulting in death.

The technique for tricuspid valve replacement has been previously reported by Arai and others (Arai et al. 2011). The protocols for anaesthesia and cardiopulmonary bypass used in this study, have also been reported previously (Griffiths et al. 2005, Orton et al. 2001). All dogs were administered peri-operative antibiotics (cefuroxime (Zinacef; GlaxoSmithKline) n=8, imipenem (Primaxin; Merck Sharp & Dohme Ltd), n=1). Briefly, a right fifth intercostal thoracotomy was performed. The pericardium was opened and pericardial basket sutures placed. Venous drainage was achieved through two right angle cannulas placed in the cranial and caudal vena cavae through purse-string sutures in the adjacent right atrial myocardium. The arterial limb of the circuit was completed with arterial cannula in the right external carotid. Cardiopulmonary bypass was initiated and the dogs were cooled to an oesophageal temperature of 28º C. Rummel tourniquets of umbilical tape were used to form a seal around the intracaval part of the venous cannulas and the azygous rummel was tightened to stop flow through the azygous vein. An 18g cardioplegia cannula was inserted into the aortic root through a horizontal mattress suture of 5-0 polypropylene (Prolene; Ehicon) with expanded polytetrofluoroethylene (ePTFE) pledgets. Following aortic cross-clamping, cold (4º C) cardioplegia solution (Cardioplegia infusion; Martindale), combined with blood from the bypass circuit, was infused into the aortic root. Cardioplegia was delivered at 20 minute intervals or whenever mechanical cardiac muscular activity was observed.

The right atrial incision was made along a line parallel with the atrioventricular groove and equidistant from it and the dorsal pericardial reflection of the right atrium. Stay sutures of 3-0 polyglactin 910 (Vicryl; Ethicon) were placed around the atrial incision to maintain exposure of the tricuspid valve orifice. The tricuspid valve was inspected and the septal leaflet excised. Interrupted mattress sutures of 2-0 braided polyester with 7mm x 3mm PTFE pledgets (Ti-Cron Davis and Geck) were placed around the tricuspid annulus such that the edges of the pledgets were closely approximated on the ventricular side of the annulus, (Figure 1). The mural valve leaflet was “gathered” or “reefed” to preserve chordal attatchments but prevent the valve leaflet impinging on the artificial valve. Once all the sutures had been placed around the annulus, a valve “sizer” was gently inserted into the annulus so that the correct valve size could be selected. The pre-placed sutures were then passed through the suturing ring of the correctly sized artificial valve at even space intervals, and tied,

(Figure 2). The valve holding apparatus was removed, the heart was de-aired by allowing it to fill with blood from the azygous vein. The atriotomy incision was closed using 4-0 polypropylene (Prolene; Ethicon) with ePTFE pledgets in a continuous mattress suture oversewn by a simple continuous suture. Two suture strands were used, one starting from each end of the atriotomy and the sutures were tied in the middle of the incision following a final de-airing of the atrium.

During atriotomy closure the dogs were warmed to an oesophageal temperature of 37^0C. At the end of atriotomy closure, the aortic cross clamp was removed and the myocardium allowed to re-perfuse. If normal sinus rhythm did not resume, ventricular fibrilliation was managed by direct internal electrical defibrillation (20 – 50J) and asystole was managed by the placement of temporary epicardial pacing leads (Ethicon temporary pacing leads (2-0)), and pacing begun at 100 beats per minute. The dogs were weaned from bypass, a thoracostomy tube was placed and the thoracotomy closed in a routine fashion. Ventilatory support was provided using a mechanical ventilator that provided inspiratory pressure support (2 to 8 cm H_2O) along with supplemental oxygen. The level of ventilatory support and supplemental oxygen required was determined by results of arterial blood gas analysis. The dogs were recovered from anaesthesia in the intensive care unit where their therapy was adjusted according to perceived needs based on changes in arterial blood gas measurements, blood pressure, urine production and fluid retrieved from the chest drain. Once the thoracostomy tube had been removed and all post-operative bleeding had stopped, heparin (100 U kg^{-1} SC q 8h) was administered in all but one dog (which received aspirin alone). Warfarin (0.1 mg kg^{-1} PO q 24hrs), was initiated the day after heparin was started and was continued for three months after valve implantation. Heparin therapy was discontinued three days after initiation of warfarin treatment at which stage aspirin was started and continued for the remainder of the dogs life. The dose of warfarin was adjusted according to changes in the measured prothrombin time and subsequent calculation of the international normalized ratio (INR) with the goal of maintaining the INR between 2.5 and 3.5. The INR was calculated 72 hours after initiating warfarin and checked weekly to 4-6 weeks depending on the result of the INR at each check.

Dogs remained in the ICU for a minimum of five days. Unless complications were encountered, echocardiography was repeated at 48 hours post-operatively and on alternate days thereafter for the remainder of their hospitalisation.

Results

Nine dogs met the inclusion criteria with their owners electing surgery. A variety of breeds were represented, with Labrador Retrievers (n=3) being the most common, followed by Golden Retrievers (n=2) and one each of Dogue de Bordeaux, Rhodesian Ridgeback, Rottweiler and Bassett Hound, (Table 1).

Six males, (two neutered) and three females, (all entire) were treated. Median age at surgery was 13 months (range 7-61 months). Median weight was 26.5kg (range 9.7-59 kg), (Table 1). Six dogs had a history of CHF prior to surgery and three had atrial fibrillation. In one dog, electrical cardioconversion was attempted prior to surgery but was unsuccessful. A variety of clinical signs were present including exercise intolerance, polyuria/polydipsia, distended abdomen, lethargy, stunted growth, dyspnoea and cachexia. All dogs apart from one were receiving a combination of medications prior to surgery; furosemide (Frusedale; Dechra, Frusemid; Millpledge, Frusol; Rosemont), (n=6), pimobendan (Vetmedin; Boehringer Ingelheim), (n=3), enalapril (Enacard; Merial), (n=8), digoxin (Lanoxin; Asper Pharma trading), (n=3), spironolactone (Prilactone; Ceva), (n=1).

The grade of heart murmur was recorded in 6 dogs pre-operatively, and was a grade V/VI in five and III/VI in one. On echocardiographic examination no dogs had evidence of apical valve displacement and all dogs had tethering of the septal valve leaflet to the septal wall. The free wall leaflets varied in appearance, ranging from thin and tethered to very thick, with variable chordae tendinae attachments. Eight dogs had tricuspid regurgitation, and the remaining dog had tricuspid stenosis.

Cross clamp and total bypass times were available in 8 dogs with a median of 65 minutes (range 45-90) and 98.5 minutes (range 65-120) respectively. One dog had a patent foramen ovale closed during the procedure. Eight bovine pericardial valves were used (27-33mm sizes), (Perimount Plus; Carpentier-Edwards) and one 25 mm porcine aortic valve prosthesis (Baxter).

One intra-operative complication occurred: a tear in the aorta at the insertion site of the cardioplegia cannula which was successfully repaired with sutures. All dogs survived surgery but six dogs experienced complications during hospitalisation, and four of these were fatal. Of the minor complications, one dog developed partial tongue necrosis, minor wound dehiscence and a supraventricular tachycardia, all of which resolved. The other dog developed a pneumothorax after thoracostomy tube removal which was successfully managed by a period of continuous pleural drainage. This dog also developed a large right atrial thrombus but remained stable with a good cardiac output and was discharged 29 days post-operatively. Of the dogs experiencing fatal complications, one dog developed acute central nervous system (CNS) signs on the morning of planned hospital discharge (day five post-operatively). He subsequently became acutely hypotensive with low output heart failure after an uneventful initial recovery, presumed to be due to a thrombus on the valve. The cause of the neurological signs was thought likely due to a transient hypoxia either due to low output heart failure or a pulmonary embolus. This dog was treated with a thrombolytic agent (Tenecteplase (TNKase®; Genentech)) at a dose according to the recommendations in people, but developed profuse haemorrhagic diarrhoea and was euthanatised. Post mortem evaluation confirmed the presence of thrombus on this dog's valve as a cause of acute valve failure (Figure 3). This dog was the only case that had a porcine aortic valve implanted, and was also the only dog to receive just aspirin rather than heparin and warfarin as well. The second dog developed hypotension, hypoxia and oliguria approximately 12 hours post-operatively. Despite aggressive supportive care this dog continued to deteriorate and was euthanatised at approximately 20 hours post-operatively. The third dog initially recovered well but remained in the hospital while warfarin treatment was stabilised. He became pyrexic on the 8th post-operative day and on day 11, a positive blood culture confirmed highly resistant strains of Enterobacter cloacae and Escherichia coli. This dog experienced a suspected brain stem haemorrhage, with the loss of brain stem auditory evoked responses on day 14 and was euthanatised. The fourth dog also made a good recovery initially but became pyrexic on the fourth post-operative day and died from a cardiorespiratory arrest. Again, a multi-resistant Enterobacter cloacae and Acinetobacter baumanii were cultured from ante mortem blood samples.

Five dogs were discharged from the hospital. One dog collapsed after a minor fall at home and was returned to the hospital seven days after discharge, and was dead on arrival. At post mortem examination this dog had a large volume intrathoracic haemorrhage, likely due to minor trauma in conjunction with the anti-coagulant medications. Despite this fatal haemorrhage, this dog had thrombus covering his valve, (Figure 3). Of the four remaining dogs, one dog had a low volume pleural effusion at three months post-operatively at which stage he was started on furosemide. He remained well for the following month, and at 4 months post-operatively he had no evidence of a thrombus or micro clots, and had only mild tricuspid regurgitation. At 8 months post-operatively he was presented in congestive heart failure and atrial fibrillation; a very large thrombus was found on the valve causing valvular stenosis and the dog was euthanatised. The second dog had an echocardiogram performed four months post-operatively, which showed improved right ventricular function and a reduction in his heart murmur from a grade IV/VI to a grade I/VI, but was euthanatised due to metastatic osteosarcoma at 246 days after surgery. Revision surgery was attempted in the third dog 12 months post-operatively, but she was euthanatised on the table when it became clear that explanting the valve would be impossible due to extensive inflammatory tissue engulfing the prosthesis. Inflammatory pannus was confirmed histologically at post mortem examination (Figure 4). The final dog collapsed and died 1277 days post-operatively whilst exercising. A post mortem examination was declined but three months prior to this a repeat echocardiogram of the valve showed no abnormalities, (Table 1).

Discussion

In the group of dogs undergoing cardiopulmonary bypass for tricuspid valve replacement in the study reported here, only 5/9 dogs survived to discharge. Of the five dogs that died in the short term, three died because of problems associated with coagulation (thrombus formation, n=1), or anticoagulation (fatal hemorrhage, n=2).

Two dogs developed pyrexia with positive blood cultures, and it is assumed they were septicaemic, several days after apparently uneventful recovery. Of the four dogs that survived in the long term, two died as a result of stenosis of the valve with the presence of fibrous tissue (inflammatory pannus/organized thrombus) confirmed histopathologically, the cause of one death was unknown and one death (euthanasia because of osteosarcoma) was unrelated to cardiac disease.

There is only one other report in the veterinary literature describing tricuspid valve replacement in dogs (Arai et al. 2011). The mortality rate in the study reported here was higher in the short term (n=5/9) when compared to Arai et al. 2011 (n=2/12). The reason for this difference is unknown; the surgical technique including cannulation methods are identical between both centers, indeed, the surgery, perfusion and post operative care team from Colorado State University performed the first tricuspid valve replacement at the Royal Veterinary College (RVC), alongside the RVC team. These nine dogs, along with 12 dogs that underwent open patch grafting of the right ventricular outflow tract to treat pulmonic stenosis and double chambered right ventricle (unpublished data), represent the first 21 dogs operated on at the RVC under cardiopulmonary bypass and so it would be reasonable to expect a higher incidence of technical failures initially, but similarly, it would be expected that these would reduce as familiarity with the techniques developed.

Most of the deaths in the dogs in our study were related to problems with blood clotting (inadequate haemostasis and thrombogenic complications), despite our attempts to use the anti-coagulation therapy previously reported, which consisted of heparin and warfarin once post-operative bleeding had ceased. The only difference between the protocol used in the study reported here and that reported by Arai et al.

(2011), was that warfarin therapy was started the day following heparin initiation in our population, compared with the second post-operative day in the study reported by Arai et al. (2011). One of the dogs in our study only received antiplatelet therapy (aspirin) following immediate post-operative heparin therapy, based on the recommendation of an experienced human cardiac surgeon; and this was the dog that died as a result of acute valve failure secondary to thrombus formation. Although only one case, it would appear that aspirin alone is not an effective strategy in dogs, despite its success in humans. This was also the only dog in our paper to have a porcine aortic valve implanted. One of Arai et al.'s (2011) conclusions was that inflammatory pannus was more likely with implantation of a bovine pericardial valve (2/4 developed this in their cases), as opposed to a porcine aortic valve (0/5 developed this), however because the only case that received a porcine valve was also the only case treated with aspirin alone, the finding of tricuspid valve thrombus on post mortem should be interpreted cautiously. In contrast with our findings, humans appear to have a relatively low risk of death or embolic complications in the first three months following surgery for aortic valve bioprosthesis replacement (Brennan et al. 2012). This study showed that the combination of aspirin and warfarin relative to aspirin alone had a lower adjusted risk of death and embolic events, however this group of patients had a higher risk of bleeding (Brennan et al. 2012). A meta-analysis from 2001 on humans with prosthetic heart valves, concluded that adding low dose aspirin to warfarin decreases the risk of embolism or death, with a slightly increased risk of bleeding, and concluded that there was a favorable risk to benefit ratio with this protocol (Massel & Little 2001). Even in human medicine, controlling the balance of the coagulation cascade post-operatively is clearly still a challenge, however, on the evidence of the dogs reported here, much work is needed before we can recommend the use of valves that require even short-term anticoagulation in dogs.

The reason tissue valves were chosen as the prosthesis for these dogs was because human patients with tissue valves do not require life-long anticoagulant therapy once the exposed elements of the valve are coated with native endothelium, (Bloomfield 2002). In addition, Orton et al. (2005) concluded that long term anticoagulant therapy was difficult to monitor and control in a report of a series of dogs that underwent mitral valve replacement using a bi-leaflet mechanical valve; with thrombus-related valve failure seen as a frequent event (Orton et al. 2005). Again, it is not clear why our results differ from those of Arai et al. (2011) as the variation in anticoagulant therapy (with the exception of one dog) is minor and would have been more likely to reduce coagulation related problems. The group at Colorado State have published several reports on the use of warfarin in dogs, (Arai et al. 2011, Monnet & Morgan 2005, Orton et al. 2005), so we conclude that some of the complications we saw associated with anticoagulation were due to our relative inexperience, but also that this remains problematic even in the hands of those more experienced in its use.

Two dogs in the study reported here died of septic complications, one dog four days after surgery and the other dog ten days after surgery. Both of these dogs had recovered uneventfully initially, having received cefuroxime (Zinacef; GlaxoSmithKline), during the perioperative period. In both dogs, multi resistant enterobacteriaciae were involved in the infection. It is assumed, therefore, that these were nosocomial infections that gained access to the body through either the intravenous access sites, chest drain or urinary catheter. Whilst we endeavored not to leave such catheters in longer than necessary, the critical nature of the first 24 -48 hours recovery period necessitates intensive monitoring and such “instrumentation” is essential. Clearly, in any busy hospital, it is advisable to remove any instrumentation as soon as it is reasonable to do so, to eliminate or reduce the risk of ascending infection. Imipenem was used in the case subsequently to these two cases for 48 hours, based on the above dogs’ culture and sensitivity and the presumption that these were hospital acquired. We have subsequently reverted back to the protocol of using cefuroxime and now de-instrument dogs sooner if they are stable.

The reasons for the poorer outcome in the study reported here remain unclear. With so many variables (surgery team, anaesthesia team, cross clamp time, bypass time, total surgery time, valve type used, weight, etc) that could affect outcome, a larger number of dogs undergoing this procedure would have to be studied. Based on the results reported here, we have to conclude that at least in our hands, bioprosthetic tricuspid valve replacement in dogs has poor results with a high short term mortality rate and a short survival time postoperatively.

No conflicts of interest have been declared

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Table 1: Signalment and survival details

Case	Breed	Age at surgery (months)	Body weight at surgery (kg)	Survival (days)
1	Rhodesian ridgeback	61	52	246
2	Rottweiler	7	19·5	5
3	Labrador retriever	12	25	370
4	Bassett hound	36	18·5	240
5	Labrador retriever	13	28	1277
6	Golden retriever	10	23	1
7	Labrador retriever	36	34	14
8	Dogue de Bordeaux	13	59	4
9	Golden retriever	13	30	?

Figure 1: Sutures of 2-0 TiCron placed in the tricuspid annulus with pledgets on the ventricular side

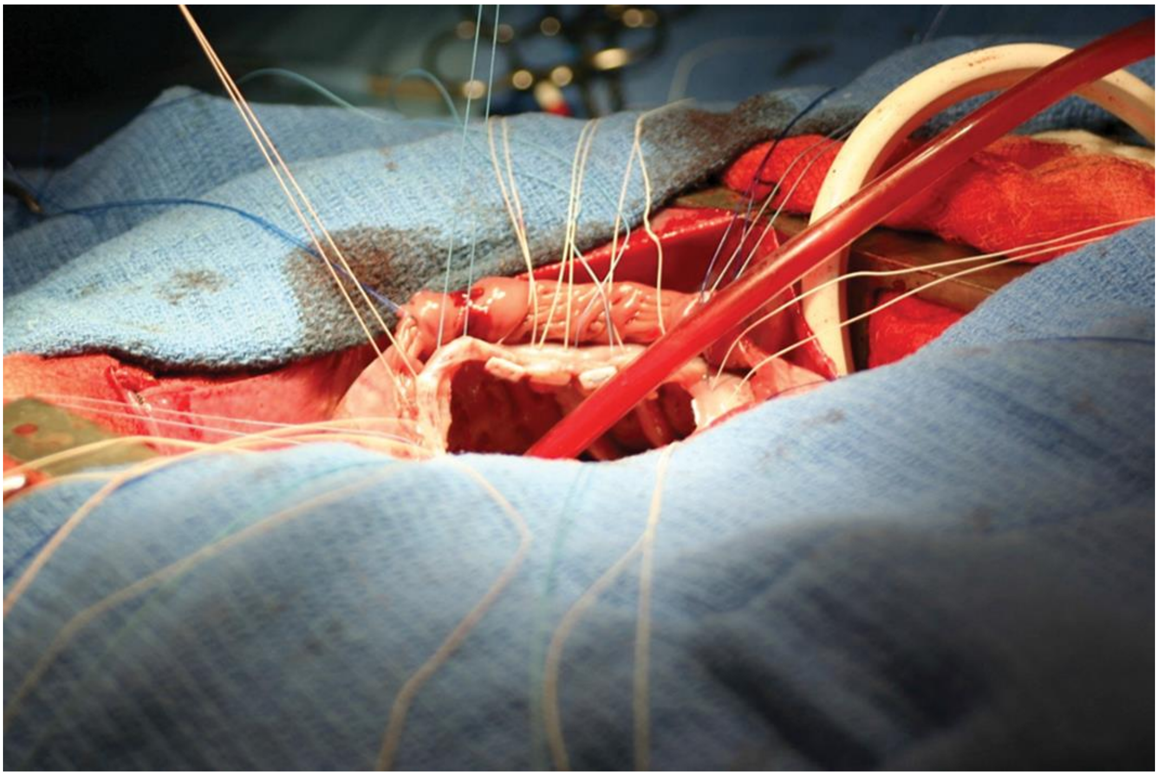

Figure 2: Prosthetic valve mounted on handle, after preplaced sutures have been passed through suturing ring

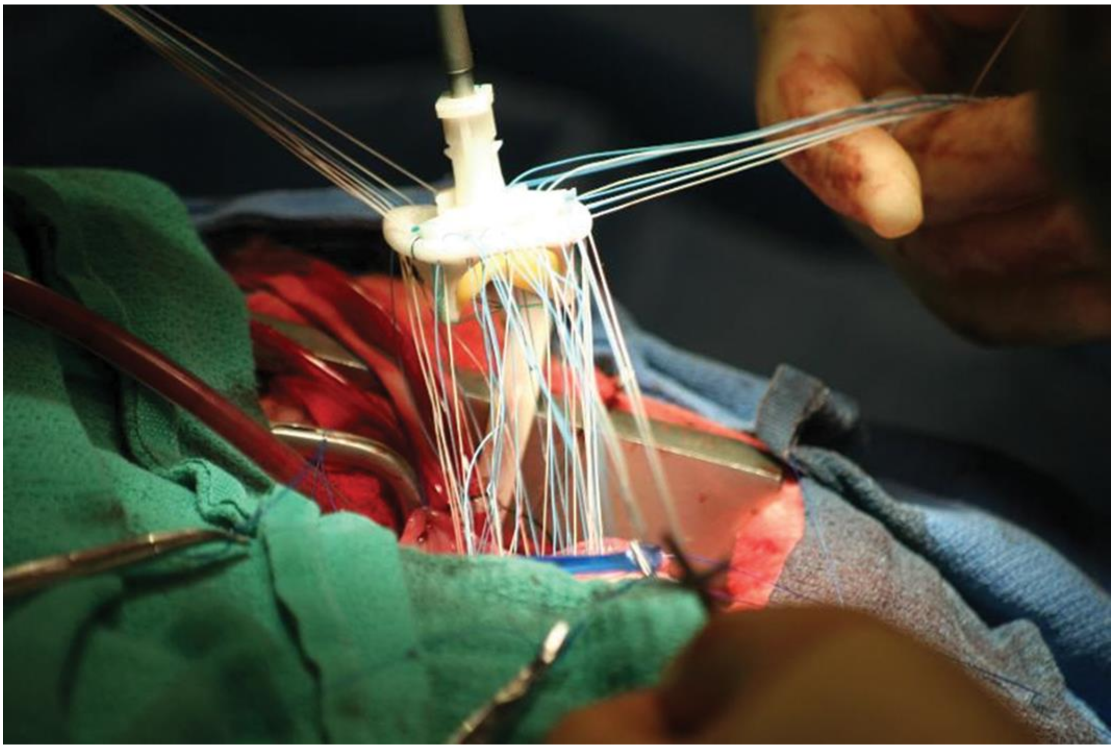

Figure 3: Post-mortem picture of thrombus on valve (day four postoperatively, case 8)