図2　No. 4心臓超音波検査所見（術後6週間目）
左：弁の閉鎖が確認できる．中央：弁の開放が確認できる．右：肺動脈弁逆流は認められない．

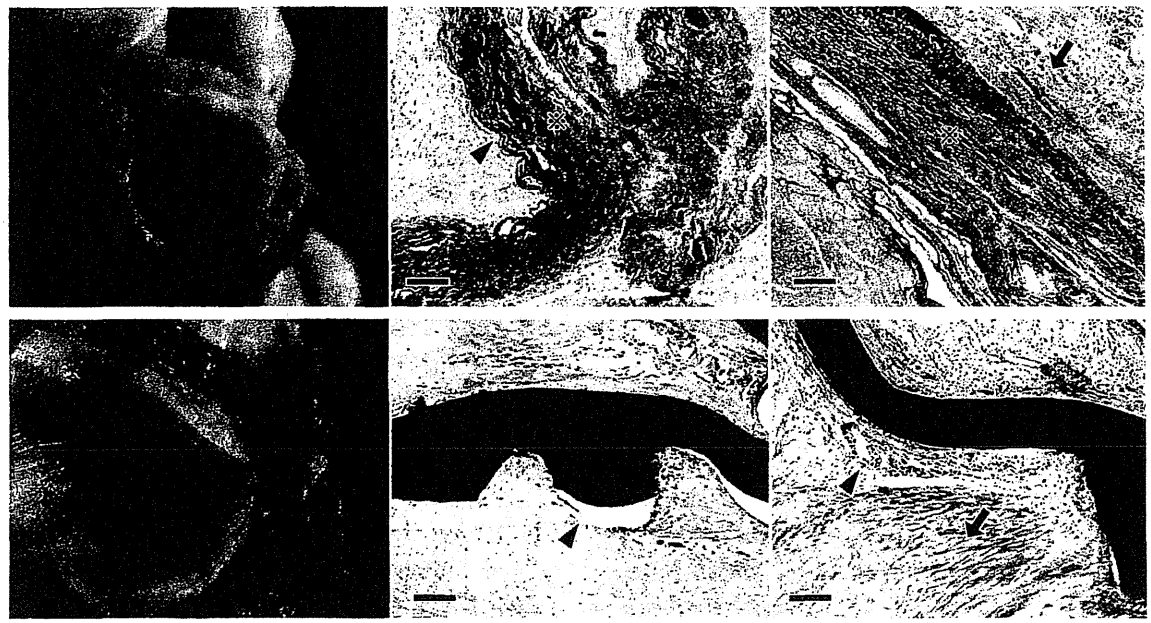

図3　移植弁の病理検査所見
上段：No. 2デナコール処理済み生体膜の組織学的検査（左：肉眼所見，中央：HE染色，右：MT染色，Bar＝400 μm）．
肉眼所見では，弁の肥厚が確認された．写真はともに弁縫着部の流出路領域．中央に弁（※）を認め，HE染色で血管内皮細胞の新生（矢頭）が認められ，縫着した弁と内皮細胞との結合は強固であった．MT染色で，線維の侵入（矢印）が認められた．左下領域に流出路を認めアーティファクトにより，弁との一部離開部分を認める．
下段：No. 3 ePTFEパッチの組織学的検査（左：肉眼所見，中央：HE染色，右：MT染色，Bar＝400 μm）．
肉眼所見では，弁の変化は認められなかった．写真は弁縫着部の流出路領域．HE染色，MT染色ともに血管内皮細胞の新生（矢頭）と線維の侵入（矢印）が認められた．

使用して行った．No. 3, 4ではePTFEパッチを使用し，流出路拡張術はデナコール処理済み生体膜を使用して行った．

切開した流出路に弁付導管をあてがい円筒下端の全周を流出路内壁に6-0モノフレン縫合糸で縫合した．弁付導管は二尖弁とし，上端は合わせ目部分とその対側部分に一部折り返した部分を作成した．対側部分の折り返しは内壁にマットレス縫合にて固定した（図1）．その後，肺動脈縦切開部に合わせて弁付導管を6-0モノフレン縫合糸で縫合し，弁付導管置換及び流出路拡張術を行った．

流出路縫合終了後，大動脈の鉗圧を解除し，心臓拍動を再開させた．体温を37℃に復温させながら，徐々にポンプ流量を減少させポンプを停止した．各カニューレを抜去した．硫酸プロタミン（ノボ硫酸プロタミン®，アベンティス ファーマ㈱，東京）0.2mg/kgをゆっくりと投与開始した．ACTが200秒以下になったことを確認したのち，ドレーンを留置し，定法にしたがって閉胸した．胸腔ドレーンは出血がないことを確認し，術後3日以内に抜去した．

術後2，4，6週間で，血液検査，心電図検査，心臓超音波検査を行った．術後2カ月で心臓カテーテル検査

(中心静脈圧，右室圧，肺動脈圧)，心臓超音波検査を行った．術後3，4及び5カ月で一般的身体検査及び心臓超音波検査を行った．術後6カ月で心臓超音波検査及び安楽死後に組織学的検査を行った．ヘマトキシリン・エオジン（HE）染色及び，マッソン・トリクローム（MT）染色で弁付導管縫合部位の評価を行った．

成　　績

全実験犬で，術後定期的に行った一般身体的検査，血液検査並びに心電図検査で異常は認められず，心臓超音波検査で弁の良好な可動性が確認できた．心臓超音波検査では，No. 1に軽度の弁の肥厚が確認されたが，逆流は認められなかった．No. 2では，同じく弁の肥厚を認め，縫着部付近での軽度の逆流を認めたが，逆流が弁尖部分からではなく，弁付導管の壁に沿うように生じていたため，縫着部からのリークの可能性が示唆された．No. 3では弁の肥厚は認めなかったが，縫着部付近での軽度逆流を認め，No. 2と同様に縫着部からのリークが疑われた．No. 2及びNo. 3で認められた縫着部での逆流は術後6カ月の心臓超音波検査でも，継続して同程度確認された．No. 4では弁の肥厚を認めず，逆流も認めなかった（図2）．心臓カテーテル検査では，No. 1で中心静脈圧：4/3/3mmHg（収縮期血圧，平均血圧，拡張期血圧），右心室圧：26/18/12mmHg，肺動脈圧：15/11/7mmHg，No. 2で中心静脈圧：0/0/0mmHg，右心室圧：25/7/0mmHg，肺動脈圧：14/7/1mmHg，No. 3で中心静脈圧：0/−1/−2mmHg，右心室圧：36/14/3mmHg，肺動脈圧：12/9/5mmHg，No. 4で中心静脈圧：1/0/0mmHg，右心室圧：20/8/0mmHg，肺動脈圧：12/9/6mmHgであった．No. 3で肺動脈と右心室の圧較差で軽度上昇を認めた．組織学的検査では肉眼的には，No. 1では置換した肺動脈弁は変色，肥厚し湾曲し，変化が著しかった．HE染色で置換した弁付導管の流出路内壁に接している部分に，線維芽細胞を含む内皮形成が認められた．MT染色で，弁付導管の円筒の下端を縫合した流出路に一部，膠原線維の侵入が認められた．縫合糸の辺縁で一部石灰化が認められた以外は，明瞭な石灰化，血栓は肉眼的にも，組織学的にも認めなかった．No. 2では弁は置換した時点よりも肥厚しており，色調も灰白色に変化していた（図3上段）．HE及びMT染色で，弁自体は均一な膠原線維で占められて肥厚しており，血管の弁尖への侵入を認めなかった．弁付導管縫着部では血管新生を伴う内皮細胞の発達と，線維の顕著な侵入が認められた．明らかな石灰化は認められなかった．No. 3及びNo. 4ではePTFEパッチ弁に肉眼的な変化や石灰化は認められなかった（図3下段）．HE及びMT染色で弁付導管縫着部には血管新生を伴う内皮細胞の発達が認められ結合組織の侵入が顕著であった．

考　　察

肺動脈狭窄症に対する狭窄の解除及び肺動脈弁逆流の予防を目的として自己新鮮生体膜とデナコール処理済み生体膜及びePTFEパッチを使用して肺動脈弁置換術の基礎的検討を行った．

今回作成した弁付導管は，長方形にトリミングした材料を円筒形にすることで，簡便に二尖弁を形成した．特別な器具を必要とせず，血流の確保と逆流を防ぐことができる弁付導管が作成できた．ただし，縫着部からのリークが残るものもあり，弁付導管下端の縫着を十分にする必要性があると考えられた．

ePTFEパッチは，強靭であり，抗血栓性を有し，生体適合性が高いことが特徴としてあげられる．ePTFEパッチ弁付導管では，心臓超音波検査で弁の可動性と閉鎖性が確認できた．また，肉眼的所見でも弁自体の変性，肥厚等は認めなかった．ePTFEによる三弁付導管を用いた右室流出路置換術においても良好な結果が報告されている［16］．これらのことから，ePTFEパッチ弁付導管の有用性が示唆された．

デナコール処理済み生体膜は生体反応が少なく，抗血栓性，抗石灰化能を有し，弾性・伸展性に富み，縫合しやすいなどの特徴をもつ［17-21］．本研究においては，心臓超音波検査で弁の開閉は良好であったが，弁の軽度肥厚が認められた．肉眼的所見でも弁自体は肥厚し，灰白色に変色していた．これは常に血流ストレス下のもと，弁の開閉による機械的ストレスが加わったためと考えられた．

今回の研究期間では，石灰化はデナコール処理済み生体膜でも，ePTFEパッチでも認められなかったが，今後は長期の経過観察が必要である．

本研究では，弁付導管の材料として新鮮生体膜，デナコール処理済み生体膜及びePTFEパッチを使用し，肺動脈弁位へ置換したが，それぞれ例数が少ないため材料に関する考察，比較は十分に行うことができておらず，今後の検討課題が残る．しかし，同じデザインの弁付導管を置換した後の弁の可動性は6カ月間良好であったことから本デザインの弁付導管の臨床応用への可能性が示唆された．

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Pulmonary Valve Replacement with Valved Conduit

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SUMMARY

The aim of this study was to evaluate the mobility, calcification, and anti-thrombotic properties of valved conduits for the surgical palliation of pulmonic stenosis in dogs. This study included four healthy dogs and valved conduits with two leaflets on the inner side. The three valved conduit types used in this study were autologous pericardium, denacol-treated bioprosthetic valve, and ePTFE. Postoperative echocardiography demonstrated the smooth movement of the leaflets in all valved conduit types. Histological examination of the specimens obtained six months after implantation did not show any thrombus or marked calcification. The surface of the conduit was covered by neointima, including fibroblasts, and was formed at the anastomosis of the valve. However, the long-term outcome of these implanted valved conduits requires further investigation. Nevertheless, these valved conduits may have potential applications for the surgical palliation of pulmonic stenosis in dogs.

—— Key words : artificial valve, congenital heart disease, extracorporeal circulation, open heart surgery, implantation.

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Original Article

The pathological implications of heart transplantation: Experience with 50 cases in a single center

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Heart transplantation started in Japan in 1999. Since then, 50 transplants have been performed at our center. We performed histopathological analyses of the 50 explanted hearts and the post-transplant biopsy specimens. The median age of recipients was 39 years. The primary diseases before transplant were idiopathic dilated cardiomyopathy in 33 patients (66%), hypertrophic cardiomyopathy in seven (14%), restrictive cardiomyopathy in one, arrhythmogenic right ventricular cardiomyopathy in one, and secondary cardiomyopathy in eight (16%). Before transplantation, 47 patients (94%) had left ventricular assist devices. No severe cardiovascular failure due to allograft rejection occurred. The post-transplant survival rate was 97.6% at 1 year and 93.1% at 10 years. One recipient was lost to sepsis from myelodysplastic syndrome in the fourth year, one died of multiple organ failure and peritonitis 8 months after transplant. Another patient died of recurrent post-transplant lymphoproliferative disorders (PTLD). Mild cardiac dysfunction occurred in seven recipients in the early postoperative period. Moderate acute cellular rejection occurred in six patients (12%), and antibody-mediated rejection occurred in three (6%). The number of heart transplants performed in Japan is very small. However, the outstanding 10-year survival rate is due to donor evaluation and post-transplant care resulting in low grade rejection. Pathological evaluation has also greatly contributed to the results.

Key words: acute rejection, cardiomyopathy, endomyocardial biopsy, heart transplantation

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The world's first heart transplantation (HTx) was performed in 1967 in South Africa. Heart transplants have become a standard therapeutic option for the treatment of profound heart failure since the 1980s, mainly in Western countries, with 3000–4000 performed annually worldwide.[1] In Japan, the first HTx from a brain-dead donor was performed at Osaka University Hospital 2 years after the Organ Transplant Law of Japan was enacted in 1997. Since then, until the end of September 2012, 141 HTx have been performed at seven institutes in Japan (Fig. 1). Of these, 50 were performed at the National Cerebral and Cardiovascular Center (NCVC), Osaka, Japan. The clinical course after transplantation has been good, and patients have been able to return to social activity such as work, school, and housekeeping. Our 10-year survival rate following HTx is 93.1%, which are excellent results compared with international reports (Fig. 2). The important factors associated with this success, in addition to recipient selection, are careful management of transplant candidates, identification of donors, donor and recipient surgeries, perioperative care and post-transplant management. Diagnosis and treatment, including assessment of acute rejection mainly through regular postoperative endomyocardial biopsies (EMB), is also thought to have contributed to the excellent results. However, a shortage of donors means that many patients die while waiting for HTx without having reached the stage of transplantation. Based on our experience with 50 HTx at NCVC, we discuss the implications of HTx from the pathologists' point of view, and describe the important role of pathology in the diagnosis and management of HTx candidates both before and after the transplant.

MATERIALS AND METHODS

This was a retrospective pathological study of 50 heart transplants performed at our center, between May 1999 and

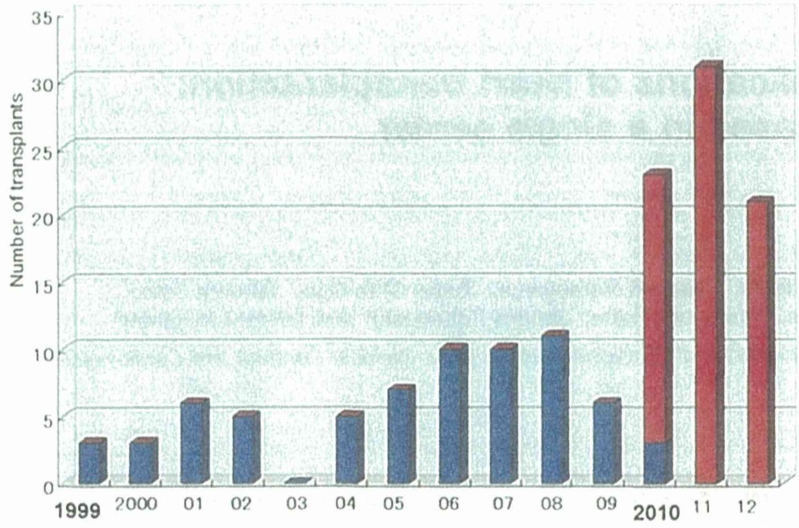

Figure 1 Number of HTx by year in Japan as of September 2012. The number has been dramatically increasing after the revision of organ transplant law in 2010. ▬, Before the revision of Organ Transplant Law (69 cases); ▬, After the revision of Organ Transplant Law (72 cases).

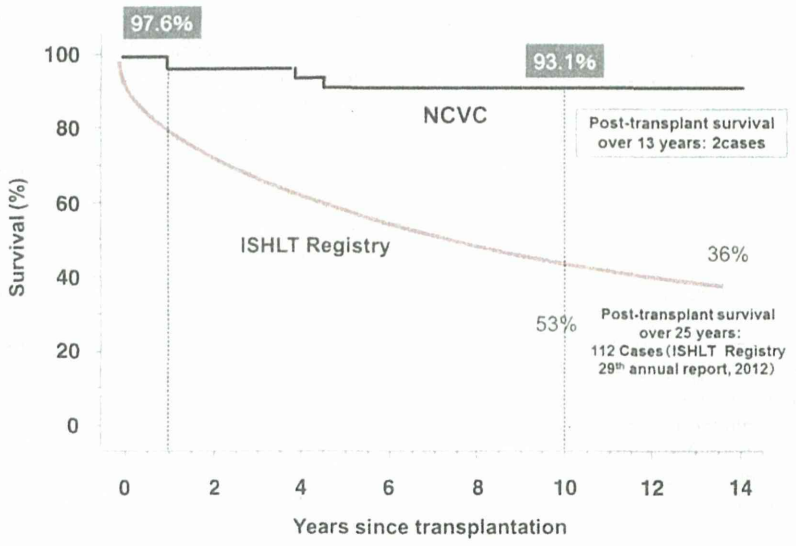

Figure 2 Kaplan-Meier long-term survival curves after heart transplants of patients in the International Society for Heart and Lung Transplantation (ISHLT) Registry and our institute, National Cerebral and Cardiovascular Center (NCVC). The ISHLT Registry data were obtained from http://www.ishlt.org/registries and Reference 1.

October 2012, with the approval of our institutional review board.

Patient characteristics

The median age of the 50 heart transplant recipients was 39 years (range, 17–61 years), and 39 (78%) were men. Meanwhile, the median age of the donors was 41 years (range, 16–68 years), and 28 (56%) were men. In the patients evaluated in this study, left ventricular assist systems (LVAS) were employed in 47 (94%) recipients due to the shortage of donors and the prolonged waiting period. Of those, 41 were implanted with Nipro-Toyobo extracorporeal systems and 6 were implantable LVAS (2 HeartMate VE, 1 Novacor, 1 EVAHEART, 1 Jarvik-2000, and 1 HeartMate II) following the Japanese guidelines.[2] At our hospital, before submitting an application for HTx to the Japanese Circulation Society, clinical conferences to discuss the transplant candidate were frequently held, which included specialists from various departments, such as internal medicine, cardiac surgery, pediatrics, pathology and nursing. Besides evaluation of cardiac function by echocardiography and cardiac catheterization, EMB provided important information in evaluation of severe heart failure patients as a candidate for HTx. The key pathology findings looked for in the EMB specimen before HTx were: (i) degree of

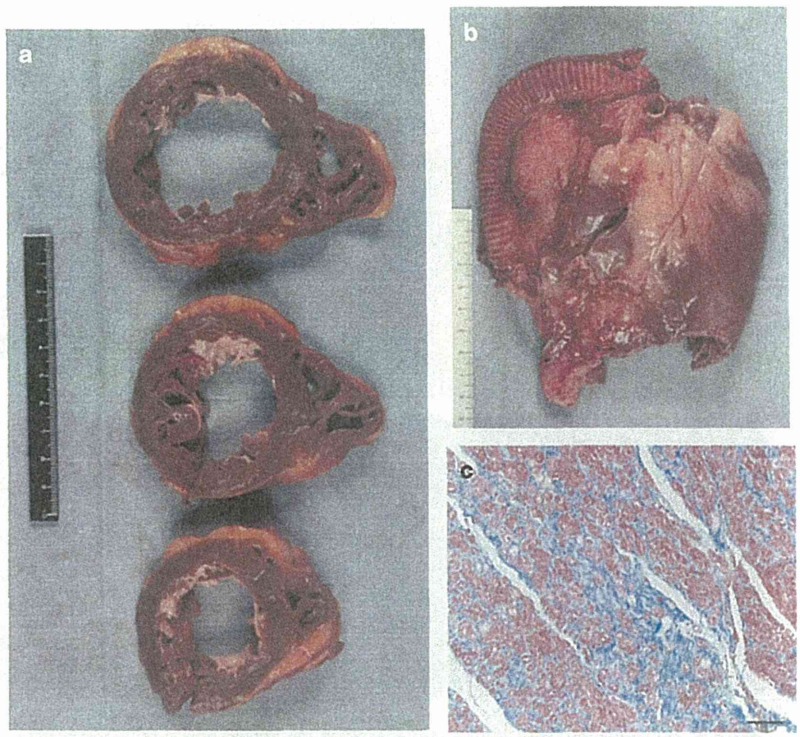

Figure 3 (**a**) A photomacrograph of explanted heart transverse section from a case of DCM. Dilatation of left ventricle with endocardial fibrosis. (**b**) Most parts of both atria of the explanted heart are left in recipient for anastomosis to donor's heart. Heart weighing is 380 g without apex where conduit of LVAS had been inserted. (**c**) A photomicrograph of representative part of LV. Diffuse interstitial and perimyocytic fibrosis is seen. Masson's trichrome staining. Bar = 100 μm.

fibrosis; (ii) degree of degeneration of cardiomyocytes; (iii) degree of myocardial hypertrophy; (iv) presence of inflammatory cell infiltration (resolution of inflammation is particularly important in patients with a clinical diagnosis of myocarditis); and (v) presence of secondary cardiomyopathies (evaluation for amyloidosis, sarcoidosis and other conditions). When EMBs of candidates showed histological evidence of myocarditis or secondary cardiomyopathies, those patients were excluded as candidates of HTx.

Preparation of explanted hearts

The recipients' hearts were observed in an unfixed state for gross findings by pathologists in the operation room immediately after their removal. The hearts, including their valves and great vessels, were examined to determine whether there was any structural abnormality before cryopreservation. Because the operative procedure currently performed at our center is the modified bicaval method,[3] surgeons resected both atria at the level of the upper 2–3 cm of both the atrioventricular valves. Explanted hearts were finally presented with two intact outflow tract semilunar valves with both major vessels and two atrioventricular valves with some part of both atria. The explanted hearts were weighed and a transverse section was made in the axial plane; photomacrographs of the sliced heart were taken before fixation. After fixation in 15% neutralized buffered formalin solution, histopathological specimens were prepared and assessed histologically (Figs 3–5).

EMB after HTx for assessment of acute rejection

In EMB, tissue samples 2–3 mm in size were taken from four to five pieces from the right ventricular wall of the interventricular septum with a bioptome percutaneously. This is based on a report that when three sites were sampled, the false-negative rate was 5%, and with four samples it was 2%.[4] To make a diagnosis within 6 h, the EMB samples were placed in 10% neutral buffered formalin solution and microwaved for 2 min at 45°C, put in an incubator for 20 min at 55°C, and embedded in paraffin. Within 6 weeks after the transplant, one of the biopsied tissue samples was frozen with optimum cutting temperature (OCT) compound, and an immunofluorescent immunohistochemistry analysis was done for immunoglobulin and complement (C4d and C3d), to detect antibody mediated rejection (AMR).[5–8] In the method used for histological examination of paraffin sections, the tissue depth was changed for a minimum of three levels, and three sections were prepared for each level.[9] Acute cellular rejection (ACR) is generally diagnosed with hematoxylin and eosin (H&E)-stained samples, although Masson's trichrome stain is also used since it is very helpful in distinguishing fibrosis and cardiomyocyte damage. EMB was normally done

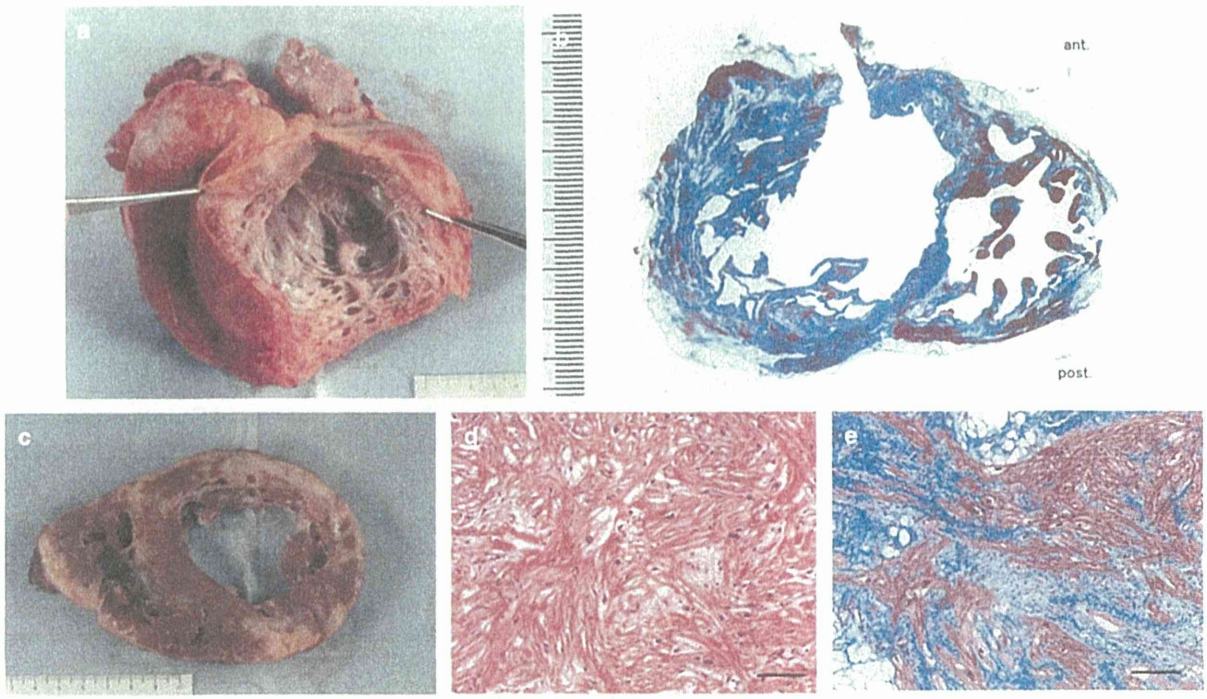

Figure 4 An explanted heart from a teenage girl in the dilated phase of hypertrophic cardiomyopathy. (**a**) Outflow tract view of excessive hypertrophied LV. Trabeculae are hyperorganized. The heart weight is 580 g. (**b**) A loupe view of transverse section with Masson's trichrome stain. Extensive fibrosis and hypertrabeculated ventricle are shown. ant, anterior wall; post, posterior wall. (**c**) A transverse slice from middle ventricle. Ivory part of LV free wall shows massive fibrosis. (**d**) Diffuse cellular disarray is seen in interventricular septum. H&E staining. Bar = 100 μm. (**e**) Interstitial replacement fibrosis and fatty infiltration of the right ventricle is present. Masson's trichrome staining. Bar = 200 μm.

weekly from 7 days after surgery to 3 weeks, then at intervals of 2, 4 and 8 weeks. From 6 months after transplantation, EMB was performed every 90 days, and from 1 year onwards, it was performed every 6 to 12 months. Assessment of ACR depended on the 1990 classification criteria and the 2004 simplified version of the International Society for Heart and Lung Transplantation (ISHLT) (Table S1).[10–12] The 1990 ISHLT grading system included: Grade 0, no rejection; Grade 1A, focal infiltrate without myocyte damage; Grade 1B, diffuse infiltrate without myocyte damage; Grade 2, one focus of infiltrate with associated myocyte damage rejection; Grade 3A, multifocal infiltrate with myocyte damage; Grade 3B, diffuse infiltrate with myocyte damage; and Grade 4, diffuse, polymorphous infiltrate with extensive myocyte damage. The 2004 revised categories of ACR were as follows: Grade 0 R; Grade 1R, mild rejection (compatible with 1990 Grades 1A, 1B and 2); Grade 2R, moderate rejection (1990 Grade 3A); and Grade 3R, severe rejection (1990 Grades 3B and 4). In addition, the evaluation of AMR was recommended as AMR 1 or AMR 0 with the presence or absence of humoral rejection in 2004.[5–8] In 2011, the ISHLT working formulation for pathological diagnosis of AMR was reported.[13,14] Then, diagnosis of AMR was made according to 2011 ISHLT consensus described in the following: histological evaluation for endothelial 'activation', intravascular macrophages, and capillary destruction. Additionally, immunofluorescence (C3d, C4d, HLA class I and II) and immunoperoxidase (C4d, CD68) were necessary for evaluation of AMR. AMR grading categories were: pAMR 0, negative; pAMR 1, (I +) immunohistologic AMR alone, (H +) histologic AMR alone; pAMR 2, pathologic AMR both (H +) and (I +); and pAMR 3, severe pathologic AMR (Table S2).

RESULTS

Pathological diagnosis of explanted hearts

Among the 50 HTx recipients, LVAS was implanted in 47 (94%) for a mean period of 903.2 ± 332.9 days. Median weight of the 50 explanted hearts was 378 g (range, 225–804 g). Fibrosis area in the myocardial layer of the heart wall was present in 19–45% of the each recipient. The final pathological diagnosis in four cases (8%) was different from the clinical diagnosis with pathological findings from RV wall biopsy before HTx. Indeed, two of the cases with a clinical diagnosis

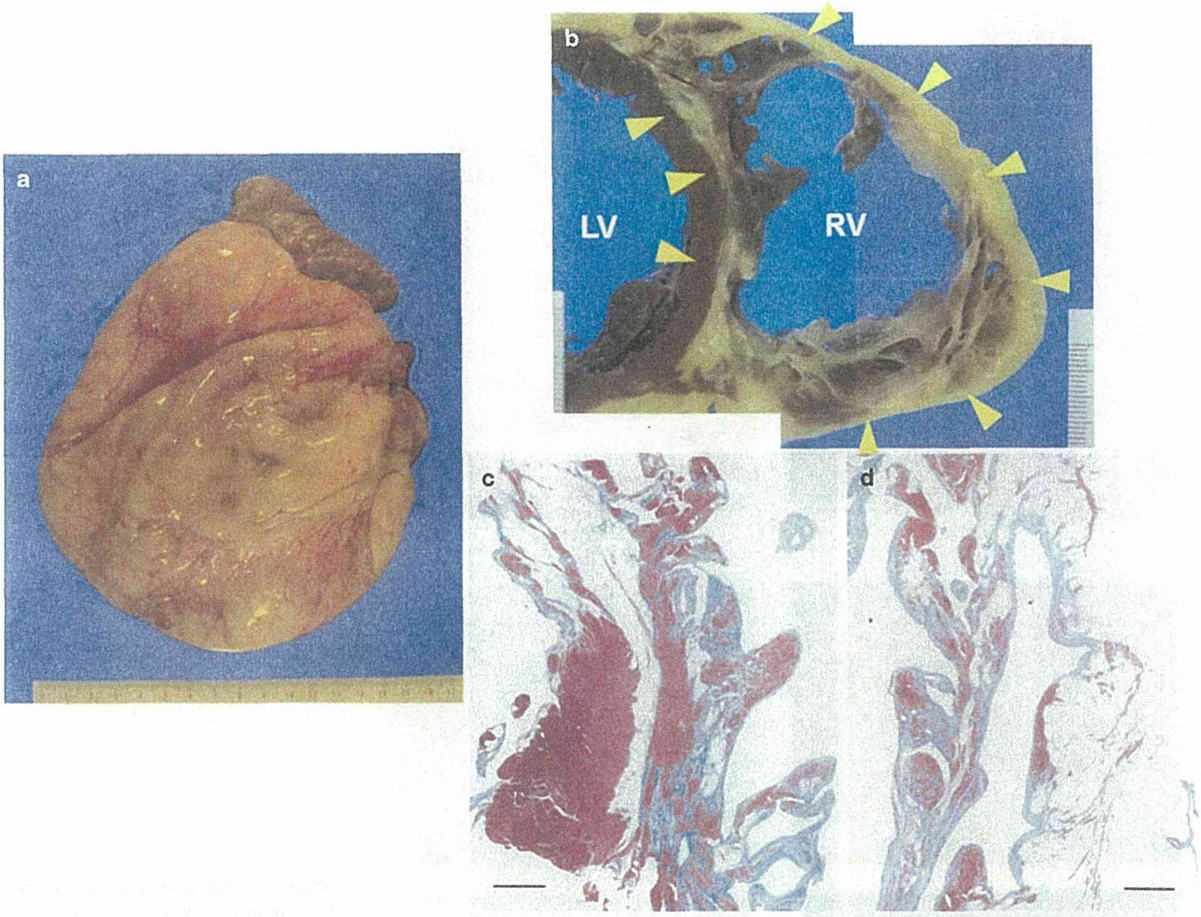

Figure 5 (**a**) An explanted heart from a middle aged female recipient with arrhythmogenic right ventricular (RV) cardiomyopathy. LVAS is not used in this case. The whole epicardium is covered with fat. The enlarged heart weighs 455 g. (**b**) Marked epicardial fat and fatty infiltration of the myocardium of the RV and interventricular septum (IVS) are observed (arrow head). (**c**) A photomicrograph from IVS. Marked fat infiltration in the middle layer of IVS. Masson's trichrome staining. Subendocardial fibrosis of RV site of IVS. Bar = 500 μm. (**d**) A photomicrograph from right ventricular wall. Myocytes are left only in subendocardium and trabeculae. Masson's trichrome staining. Bar = 500 μm.

of DCM were actually cardiac sarcoidosis and one was revealed to be inflammatory dilated cardiomyopathy. Moreover, the pathological diagnosis of one case that was clinically diagnosed as hypertrophic cardiomyopathy (HCM) was found to be a glycogen storage disease. These secondary cardiomyopathy cases were not diagnosed by endomyocardial biopsies before heart transplantation. The underlying diseases for heart transplant indication were dilated cardiomyopathy in 33 patients (66%) (Fig. 3), the dilated phase of hypertrophic cardiomyopathy in seven patients (14%) (Fig. 4), restrictive cardiomyopathy in one patient, arrhythmogenic right ventricular cardiomyopathy in one patient (Fig. 5), and secondary cardiomyopathy in eight patients (16%), including sarcoidosis in two, Becker type of muscular dystrophy in two, ischemic cardiomyopathy in two, cardiac anomaly in one, and glycogen storage disease in one.

Evaluation of rejection based on EMB of transplanted hearts

Over the 13-year study period, 668 EMB samples (7 to 32 times per patient, the median number of times was 13) after HTx were obtained from the 50 recipients. ACR in mild degree sometimes appeared within 3 weeks after transplantation; 15 patients (30%) showed Grade 1R (Grade 1A, 1B and 2) rejection in 3 weeks after HTx. In addition, 37 patients (74%) showed Grade 1R rejection in 3 months. However, there were no cases of hyperacute rejection soon after transplant resulting in severe cardiac dysfunction and presenting as graft failure. Grade 2R (Grade 3A) ACR occurred in 6 patients (12%) (Fig. 6), but it resolved with steroid pulse therapy in all cases. When an ACR of Grade 2R or more was seen, additional EMB was performed to determine the

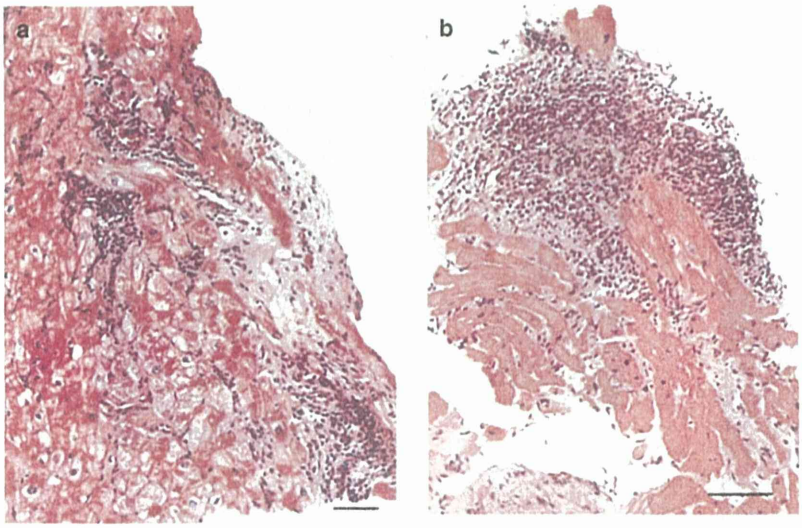

Figure 6 (**a**) A photomicrograph demonstrating Grade 2R acute cellular rejection (grade 3A of 1990). Two foci of cardiomyocyte injury with lymphocytic infiltration and one focus of perivascular lymphocytic infiltration are present. H&E staining. Bar = 50 μm. (**b**) Another case of Grade 2R (grade 3A of 1990) ACR with intensive infiltration of lymphocytes destroying the myocytes is seen. H&E staining. Bar = 100 μm.

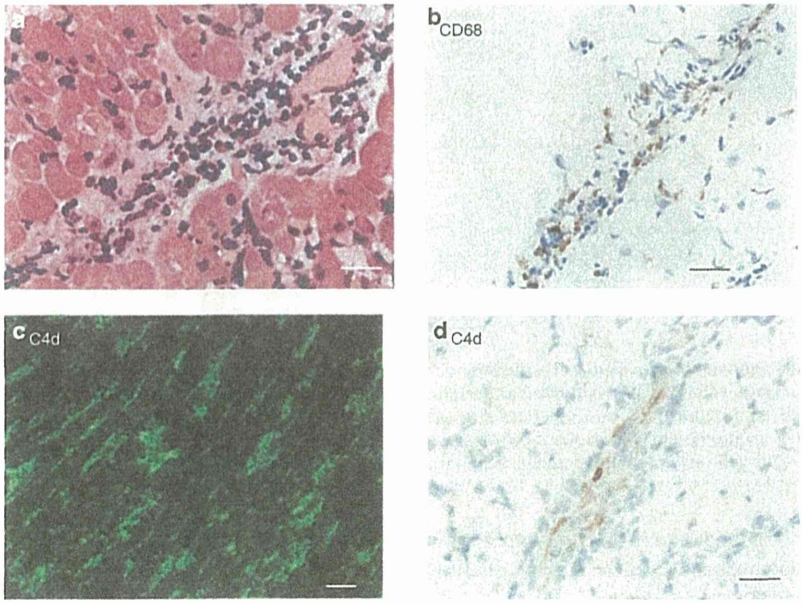

Figure 7 Photomicrographs of endomyocardial biopsy from a case of AMR 1-week post-HTx. (**a**) Hypertrophied endothelial cells and capillaries filled with macrophages, lymphocytes and eosinophils are shown. H&E staining. Bar = 20 μm. (**b**) CD68 immunohistochemistry shows accumulation of macrophages in the capillary. Bar = 20 μm. (**c**) Immunofluorescence of C4d is positive in the capillary endothelium in frozen section. Bar = 40 μm. (**d**) Immunohistochemistry of C4d in a serial section of (**a**). Bar = 20 μm.

treatment effect after 1–2 weeks.[11] Among 668 EMBs, 65% were assigned Grade 0.

Antibody-mediated rejection (AMR)

AMR was diagnosed from the findings of interstitial edema, endothelial cell enlargement and damage, and extravasation of red blood cells, although less lymphocyte infiltration was seen as compared to that observed in the cases of cellular rejection. Immunohistochemical demonstration of C4d and C3d deposition in the vessel walls and endothelial cells of the capillary in EMB specimens was diagnosed as AMR (Fig. 7). Among 50 recipients, three cases (6%) pathologically diagnosed as pAMR2 without hemodynamic changes were successfully treated by plasmapheresis and additional immunosuppressants.

Opportunistic infections

Due to the use of long-term immunosuppression to recipients, Cytomegalovirus (CMV) gastric ulcer and gastritis

occurred in two recipients. Asymptomatic polyoma virus cystitis developed in 14 recipients and 3 cases experienced herpes zoster infection.

Prognosis

There were three deaths after HTx. One recipient died of sepsis secondary to myelodysplastic syndrome 4 years after the transplantation, one recipient with situs inversus died of peritonitis and sepsis 8 months after transplant, and the other recipient died of recurrent post-transplant lymphoproliferative disorders (PTLD) after 3 years and 5 months. However, all other patients are alive and there were no deaths or severe cardiovascular failure from acute rejection. The postoperative course was good in nearly all the patients, enabling them to return to normal life in society. Mild controllable cardiovascular dysfunction with no relation to rejection occurred in seven patients in the acute phase after transplant. PTLD occurred in one case after Epstein-Barr virus seroconversion 14 months after HTx, which was treated with Rituximub. This case was diagnosed as polymorphic PTLD (P-PTLD) according to the WHO classification.[15] The primary tumor of PTLD was in the mediastinal lymph nodes. After remission of the primary tumor, the PTLD recurred in anterior mediastinum and left lung, and the patient died of respiratory failure. The autopsy revealed that the massive PTLD tumor occupied the mediastinal space and invaded the left lung and pericardium.

Cardiac allograft vasculopathy of coronary arteries

Cardiac allograft vasculopathy (CAV) of coronary arteries occurs over a long period of time after HTx.[16,17] Among the 50 recipients, coronary angiography and intravascular ultrasound (IVUS) demonstrated intimal thickening of coronary artery lesions in four patients. One case required stent deployment in stenotic lesions of the coronary artery. Another case underwent coronary aortic bypass graft. Because IVUS could detect intimal thickening even in an early stage of atherosclerosis, baseline evaluation was conducted within the first 5 weeks to 3 months after HTx at our center, following which IVUS was done every year. Autopsy of a patient who died 4 years post-transplant showed marked fibrotic intimal thickening of the afferent intima histologically, with little damage in the internal elastic layer and with no remarkable changes in the smooth muscle cells of the media. Therefore, the CAV of this autopsy case was assessed as mild degree.

Autopsy results in 48 HTx candidates

A total of 48 candidates with LVAS implantation died before HTx in the period from 1997 to 2012. The causes of death as seen on the autopsy reports included sepsis (n = 18), intracranial hemorrhage (n = 15, including two subdural hemorrhages and two subarachnoid hemorrhages due to rupture of septic emboli), cerebral hemorrhagic infarct (n = 12), and multiple organ failure due to systemic emboli (n = 3) as previously reported.[18] Manifestations of chronic heart failure, such as chronic congestion and infection, were seen in visceral organs, especially in the lungs and liver.

DISCUSSION

The number of HTx undertaken in Japan remains very small compared with Western countries. Despite the limited number, however, heart transplantation in Japan is well established, with a high long-term post-transplant survival by international standards.[1] Although therapies for end-stage heart failure such as drug therapy and implantable artificial heart devices are developing, HTx using allografts is still the most efficacious and the gold standard therapy in end-stage heart failure. Nevertheless, only a few candidates receive the benefits of HTx due to the lack of donors.

The underlying diseases for HTx reported in ISHLT world data were idiopathic cardiomyopathy (54%), ischemic cardiomyopathy (37%) and others.[1] The analysis of candidates for heart transplant in Japan, on the other hand, showed mostly idiopathic cardiomyopathy (82%), such as dilated cardiomyopathy (DCM) (66%) or hypertrophic cardiomyopathy (HCM) (16%), as the leading underlying disease. Development of ischemic heart disease in Japan is mainly seen in the elderly. Thus, the main indication for HTx is idiopathic cardiomyopathy, including DCM and dilated phase of HCM, which occurs most often in younger people. In our institute, only two (4%) of the HTx patients had ischemic cardiomyopathy as the underlying disease. The introduction of HTx in Japan was late compared to other Western countries. In Japan, donations of organs from a brain-dead donor became possible as a result of the enactment of the Organ Transplant Law in 1997. However, this law requires the confirmation of the intent to donate and there have been few organ donations. Up to December 2013, only 185 cases of HTx have been performed in Japan because of donor shortage. On the other hand, approximately 3700–3800 HTx operations are performed worldwide per year. Yet, the 10-year survival rate after HTx in the international registry reaches over 50%,[1] while the survival rate approaches 90% in Japan, and an especially high survival rate of 93.1% has been achieved in our center. Detailed post-transplant follow-up by the transplant team including immunosuppressive therapy and pathological monitoring for rejection using myocardial biopsies contributed to the excellent prognosis at our center.

In 1990, ISHLT proposed diagnostic criteria for acute rejection of transplanted hearts by EMB.[10] In 2004, the ISHLT

modified and simplified the acute cellular rejection (ACR) criteria to include only three grades.[11] Due to the accumulation of a large number of cases to date, globally diagnosis can be made in the same way according to these diagnostic criteria, and reflected in treatment.[19] EMB is a rather invasive modality compared to other tests such as echocardiography and MRI.[20] However, it is still the most important examination, being the 'gold standard' to monitor acute rejection.[21] In our study population, 23 patients (46%) experienced mild and moderate ACR, and three patients (6%) had AMR within the first year. Previously, AMR was known as humoral rejection.[22,23] This type of rejection is caused by recipient antibodies to the allograft, with the majority of cases occurring within 2 weeks of transplantation, although later occurrence is also reported. We encountered three cases of AMR in the early stage, all of which were detected early by immunological monitoring and pathological testing, and all recovered with plasmapheresis.

Most of the opportunistic infections[24,25] that developed in our patients were viral infections, of which CMV gastritis and CMV ulcers were the most important among HTx recipients diagnosed by gastric biopsy in whom CMV infection was positive in blood tests. Subclinical papilloma virus infection of the urinary tract was frequently recognized in 28% of the urine tests of recipients. Ischemic myocardial damage due to perioperative ischemic conditions may lead to graft failure in the early stage and to coronary artery lesions in the chronic phase, although there is currently no generally accepted theory.[26] In our investigation of patients undergoing HTx at NCVC, ischemic myocardial damage was recognized in EMB specimens from all patients by the fifth week after transplantation. No relationship was seen between the extent of the spread of ischemic myocardial damage and acute rejection. The possibility has been suggested that the amount of catecholamine used before transplantation and ischemic time for transplantation affect the extent of ischemic myocardial damage.

The analysis of cause of death after HTx was difficult to discuss here because we had only three deaths. In general, the most frequent cause of death in the early postoperative period is primary graft failure; however, there was no graft failure in our 50 recipients. Follow-up is required after HTx for neoplasms such as PTLD, which occurs in young recipients.[27] The PTLD of our lost recipient became overt clinically in his twenties. Myocardial infarct as a major complication in late phase after HTx could be fatal due to CAV of coronary arteries, because recipients feel no heartache because of the denervation by the transplant operation. In our hospital, frequent follow-ups by angiography or IVUS may prevent unexpected myocardial infarct. As pathologists, we must precisely document the cause of long-term death.[28,29] In conclusion, we described the current pathological examinations related to HTx that are conducted at our medical center. The underlying disease for HTx was mostly idiopathic cardiomyopathy, and LVASs were implanted in most candidates, including recipients. All 50 HTx recipients have not shown high-grade ACR and only 6% of the recipients experienced pathological AMR. In addition to monitoring ACR and AMR by EMB, histopathologic assessments of patients awaiting HTx, autopsy investigations among cases that did not reach transplantation and explanted hearts from recipients are also very helpful for the evaluation of underlying diseases of the candidates, which sometimes differ from clinical diagnoses. Pathological assistance plays a very important role in pre- and post- HTx medical care.

ACKNOWLEDGMENTS

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 The International Society for Heart and Lung Transplantation (ISHLT) 1990 grading and more simply modified 2004 grading system for Acute Cellular Rejection (ACR) of heart transplant.[11]

Table S2 ISHLT recommendation for Acute Antibody-Mediated Rejection (AMR) of heart transplant in 2011.[13]

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Special Theme Topic: Japanese Surveillance of Neuroendovascular Therapy in JR-NET/JR-NET2—Part II

Endovascular Treatment for Ruptured Vertebral Artery Dissecting Aneurysms: Results from Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and 2

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Abstract

In treating ruptured vertebral artery dissecting aneurysms (VADAs), neuroendovascular therapy (NET) represented by coil obliteration is considered to be a reliable intervention. However, there has been no multi-center based study in this setting so far. In this article, results of NET for ruptured VADA obtained from Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and 2 were assessed to elucidate the factors associated with favorable outcome. A total of 213 in JR-NET1 and 381 patients in JR-NET2 with ruptured VADA were included, and they were separately analyzed because several important datasets such as vasospasm and site of dissecting aneurysms in relation to the posterior inferior cerebellar artery (PICA) were collected only in JR-NET1. The ratio of poor World Federation of Neurosurgical Societies (WFNS) grade (4 and 5) was 48.8% and 53.9%, and the ratio of favorable outcome (modified Rankin scale, mRS 0 to 2) at 30 days after onset was 61.1 % and 49.1% in JR-NET1 and 2, respectively. In both studies, poor WFNS grade and procedural complication were independently correlated as negative factors for favorable outcome. In JR-NET1, PICA-involved lesion was also designated as a negative factor while elderly age and absence of postprocedural antithrombotic therapy was detected as other negative factors in JR-NET2. The ratios of favorable outcome in poor grade patients were 25.4% in JR-NET1 and 31.3% in JR-NET2, which seemed compatible with the previous studies. These results may provide a baseline data for the NET in this disease and could be useful for validating the benefits of novel devices.

Key words: vertebral artery, dissecting aneurysm, subarachnoid hemorrhage, neuroendovascular therapy, nationwide survey

Introduction

Vertebral artery dissecting aneurysm (VADA) is nowadays increasingly recognized as a cause of subarachnoid hemorrhage and ischemic stroke.[1)] In patients with ruptured VADAs, a high incidence of rebleeding and a high mortality rate at the time of rebleeding was reported.[2,3)] Recently, catheter-based neuroendovascular approach has emerged as first-line therapy for ruptured VADA along with the development of new techniques and devices and their results are favorable so far.[4–10)]

There was no report, however, as to the detailed data of the relationship between NET and patient's outcome in a large multi-center based study.

This study was aimed to clarify the current status and results of NET for ruptured VADA in Japan from the data of Japanese Registry of Neuroendovascular Therapy

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(JR-NET) 1 and 2, thereby extracting a clue for elucidating the appropriate therapy for this harmful disease.

Materials and Methods

The data in this study were collected from JR-NET1 and 2. Briefly, JR-NET1 was the registration of therapeutic procedures and outcomes from the certified board members of Japanese Society for Neuroendovascular Therapy (JSNET) between 2005 and 2006 while JR-NET2 was that of JSNET board members between 2007 and 2009. The Institutional Review Board at each center approved the use of retrospective data from the patients.

The total numbers of registration were 11,213 cases in JR-NET1 and 20,751 cases in JR-NET2. Among all the datasets, the incidence of ruptured VADA was 213 (1.9%) and 381 (1.8%) in JR-NET1 and JR-NET2, respectively.

The following factors were collected in both studies: age, sex, and World Federation of Neurosurgical Societies (WFNS) grade on admission as patient-derived factors while the timing of neuroendovascular therapy (NET), mode of anesthesia, technical success which was defined as the absence of blood flow to the ruptured lesion, participation of board members as in charge of the procedure, intraprocedural use of heparin, postprocedural antithrombotic therapy, and ischemic/hemorrhagic complications as periprocedural factors. No detailed information about used devices for the lesion such as coils (bare platinum or surface modified), stents, and balloons were collected in both studies. A modified Rankin scale (mRS) score at 30 days after the onset was used for evaluation of patients' outcome and defined as the primary endpoint. The point of 0 to 2 in mRS, which means independence of the patients, was considered as a favorable outcome.

The relationship between factors listed above and mRS scores at 30 days were analyzed to clarify the influencing factors for favorable outcome.

As the datasets collected only in JR-NET1 noted above were expected to influence on the outcome, we analyzed the data of each study separately.

Statistical analysis

Analyses were performed using JMP version 9.0 (SAS Institute, Cary, North Carolina, USA). Statistical significance for intergroup differences was assessed using the z test for categorical variables and the Mann-Whitney U test for continuous variables. A logistic regression analysis was carried out using the factors with statistically significant differences by univariate analyses to determine any factors that were significantly related to the favorable outcome. P values < 0.05 were considered to indicate a significant difference.

Results

I. Patient characteristics

The patients' demographics are shown in Table 1. The mean age was 52.5 and 54.6 years in JR-NET1 and JR-NET2, respectively. Male preponderance was noted in both studies. As to WFNS grade on admission, the incidence of poor grade (Grades 4 and 5) was 48.9% and 52.0% in JR-NET1 and JR-NET2, respectively.

Table 2 summarized the timing of intervention. 49.2% of the cases in JR-NET1 while 74.3% in JR-NET2 were treated within 24 hours after onset, which had a significant difference ($p < 0.0001$)

Table 1 Patients' baseline characteristics in JR-NET1 and 2

	JR-NET1 (n = 213)	JR-NET2 (n = 381)	p value
Age (SD)	52.5 (± 10.4)	54.6 (± 11.7)	0.17
Male (%)	143 (67.1)	232 (60.9)	0.13
WFNS grade (%)			
1	20 (9.4)	33 (8.7)	
2	52 (24.4)	72 (18.9)	
3	37 (17.4)	71 (18.6)	
4	47 (22.1)	89 (23.4)	
5	57 (26.8)	109 (28.6)	
Poor (4 and 5, %)	104 (48.9)	198 (52.0)	0.46
Unknown (%)	0 (0.0)	7 (1.8)	

JR-NET: Japanese Registry of Neuroendovascular Therapy, WFNS: World Federation of Neurosurgical Societies.

Table 2 Interval from admission to treatment in JR-NET1 and 2

	JR-NET1 n = 213	JR-NET2 n = 381	p value
< 24 h	105 (49.2)	283 (74.3)	< 0.0001
24 h to 72 h	68 (32.0)	57 (15.0)	
< 72 h	*173 (81.2)*	*340 (89.3)*	*0.006*
Days 3 to 7	14 (6.6)	13 (3.4)	
Days 8 to 14	8 (3.8)	8 (2.1)	
After day 14	16 (7.6)	20 (5.2)	

Figures in the parentheses indicate column percentages. h: hours, JR-NET: Japanese Registry of Neuroendovascular Therapy.

between the two studies.

Approximately three-fourth of the cases were under general anesthesia (74.6% and 80.1% in JR-NET1 and JR-NET2, respectively).

II. Therapeutic demographics

Technical success was noted in 98.6% and 98.7% in JR-NET1 and JR-NET2, respectively.

As shown in Table 3, intraprocedural use of heparin was noted in 88.3% and 78.8% of the cases in JR-NET1 and JR-NET2, respectively. In more than half of the cases with heparin use, the administration of heparin was performed after the placement of sheath introducers. Postprocedural antithrombotic therapy was performed in approximately two-third of the cases (63.4% in JR-NET1 and 63.5% in JR-NET2). The ratios of anticoagulant use were 53.3% and 43.4% in JR-NET1 and JR-NET2, respectively. Antiplatelet agents were used approximately in 80% of all the cases in both studies, and concomitant use were observed approximately in one-third of the cases throughout two studies.

Procedural complication was observed in 9.9% and 10.8% in JR-NET1 and JR-NET2, respectively. The clinical outcome at 30 days after the onset was favorable in 61.0% and 49.1% whereas fatal in 15.5% and 14.4% in JR-NET1 and JR-NET2, respectively (Table 4).

Table 3 Periprocedural antithrombotic therapy in JR-NET1 and 2

	JR-NET1 n = 213	JR-NET2 n = 381	p value
Intraprocedural use of heparin, yes	188 (88.3)	300 (78.8)	0.004
Timing	n = 188	n = 300	
After introduction of sheath	97 (51.6)	194 (64.7)	0.004
After navigation of a microcatheter	22 (11.7)	29 (9.7)	0.47
After placement of first coil	64 (34.0)	68 (22.7)	0.005
Others	5 (2.7)	9 (3.0)	
Postprocedural antithrombotic therapy, yes	135 (63.4)	242 (63.5)	0.97
Mode	n = 135	n = 242	
Anticoagulant only	27 (20.0)	21 (8.7)	0.001
Antiplatelet only	61 (45.2)	102 (42.1)	0.57
Anticoagulant and antiplatelet	45 (33.3)	84 (34.7)	0.79
Unknown	2 (1.5)	35 (14.5)	

Figures in the parentheses indicate column percentages. JR-NET: Japanese Registry of Neuroendovascular Therapy.

III. Relationship between patient characteristics, procedural factors and clinical outcome

In JR-NET1, univariate analysis showed that age, poor WFNS grade, posterior inferior cerebellar artery (PICA)-involved lesion, use of heparin, and procedural complication were significantly related to the favorable outcome. Among them, poor WFNS grade, PICA-involved lesion, and procedural complication were identified as independent factors by multivariate analysis (Table 5).

Similarly, univariate analysis showed that age, poor WFNS grade, postprocedural antithrombotic therapy, and absence of procedural complication were significantly related to the favorable outcome in JR-NET2. Multivariate analysis in this registry revealed that age, poor WFNS grade, postprocedural antithrombotic therapy, and procedural complication were independently correlated with the favorable outcome (Table 6).

In addition, factors associated with favorable outcome in poor grade patients were also analyzed. However, there were no significant factors detected as positive or negative factors for favorable outcome, except for the ischemic complication in JR-NET1 (Table 7).

IV. Relationship between location of the lesion and NET in JR-NET1

Information as to the locations of VADA and site of intervention in relation to the dissecting aneurysms which were only available in JR-NET1 study is shown in Table 8. Locations of VADA were classified into four groups: proximal to PICA (pP), distal to PICA (dP), PICA involved (Pi), and no PICA (nP). Coil placement in the aneurysmal dilatation (AD) were performed in 78.7% (37/47) of group pP, 95.2% (79/83) of group dP, 80% (40/50) of group Pi, and 100% (29/29) of group nP. Balloon guiding catheter

Table 4 Clinical outcome at 30 days in JR-NET1 and 2

	JR-NET1 n = 213	JR-NET2 n = 381	p value
mRS 0	80 (37.6)	101 (26.5)	
1	38 (17.8)	49 (12.9)	
2	12 (5.6)	37 (9.7)	
0–2	*130 (61.0)*	*187 (49.1)*	*0.005*
3	16 (7.5)	30 (7.9)	
4	23 (10.8)	42 (11.0)	
5	11 (5.2)	36 (9.4)	
6	33 (15.5)	55 (14.4)	
Unknown	0 (0)	31 (8.1)	

JR-NET: Japanese Registry of Neuroendovascular Therapy, mRS: modified Rankin scale.

Table 5 Results of univariate and multivariate analyses for favorable outcome in JR-NET1

Variable	Number	Favorable outcome	Univariate	Multivariate	
			p value	OR (95% CI)	p value
Age	54.2 (± 10.5)	50.6 (± 10.1)	0.034	0.99 (0.95–1.02)	0.46
Male	143/213 (67.1)	85/130 (65.4)	0.49		
Poor WFNS grade (4 and 5)	104/213 (48.8)	33/130 (25.4)	< 0.0001	0.066 (0.026–0.16)	< 0.0001
OTT					
> 24 h	103/192 (53.6)	62/124 (50.0)	0.23	1.61 (0.66–4.04)	0.29
24h to 72 h	67/192 (34.9)	45/124 (36.3)	0.098	0.62 (0.24–2.98)	0.81
> 72 h	22/192 (11.5)	17/124 (13.7)	0.23	1.16 (0.38–4.98)	0.62
Board members in charge of procedure	180/210 (85.7)	110/129 (85.2)	1.00		
PICA involved lesion	50/213 (23.5)	22/130 (16.9)	0.02	0.41 (0.15–1.05)	0.05
Use of heparin	188/210 (89.5)	121/129 (93.8)	0.01	2.41 (0.17–9.31)	0.17
Postprocedural antithrombotic therapy	135/207 (65.2)	89/128 (69.5)	0.09	1.26 (0.33–1.98)	0.67
Procedural complications	21/210 (10.0)	8/130 (6.2)	0.0007		
Ischemic	13/210 (6.2)	4/130 (3.1)	0.001	0.11 (1.59–59.9)	0.012
Hemorrhagic	5/210 (2.4)	0/130 (0.0)	< 0.0001	< 0.0001 (0–0.04)	0.039
Vasospasm	24/195 (12.3)	11/130 (9.5)	0.06	0.24 (0.04–1.08)	0.08

Standard deviation or percentages are in parentheses otherwise indicated. CI: confidence interval, h: hours, OR: odds ratio, OTT: Onset-to-treat time, PICA: posterior inferior cerebellar artery, WFNS: World Federation of Neurosurgical Societies.

Table 6 Results of univariate and multivariate analyses for favorable outcome in JR-NET2

Variable	Number	Favorable outcome (n = 187)	Univariate	Multivariate	
			p value	OR (95% CI)	p value
Age	54.6 (± 11.7)	50.8 (± 10.1)	< 0.0001	1.06 (1.04–1.09)	< 0.0001
Male	232 (60.9)	108 (57.5)	0.21		
Poor WFNS grade (4 and 5)	198 (52.0)	62 (31.3)	< 0.0001	0.13 (0.08–0.21)	< 0.0001
OTT					
> 24 h	283 (74.3)	141 (75.4)	0.21	0.74 (0.36–1.50)	0.4
24 h to 72 h	57 (15.0)	27 (14.4)	0.17	0.87 (0.33–2.33)	0.78
> 72 h	41 (10.7)	19 (10.2)	0.20	1.55 (0.71–3.46)	0.28
Board members in charge of procedure	341 (89.5)	167 (89.3)	1.00		
Use of heparin	300 (78.3)	150 (80.2)	0.13	0.97 (0.53–1.77)	0.91
Postprocedural antithrombotic therapy	211 (55.4)	122 (65.2)	0.0002	2.15 (1.32–3.54)	0.002
Procedural complications	41 (10.8)	15 (8.0)	0.09		
Ischemic	33 (8.7)	15 (8.0)	0.71	0.39 (0.16–0.92)	0.03
Hemorrhagic	8 (2.1)	0 (0.0)	0.007	< 0.0001 (0–0.19)	0.0005

Standard deviation or percentages are in parentheses otherwise indicated. CI: confidence interval, h: hours, OR: odds ratio, OTT: onset-to-treat time, WFNS: World Federation of Neurosurgical Societies.

Table 7 Results of univariate and multivariate analyses for favorable outcome in patients with poor WFNS grade on admission

Variable	JR-NET1 (n = 104)			JR-NET2 (n = 198)		
	Univariate	Multivariate		Univariate	Multivariate	
	p value	OR (95% CI)	p value	p value	OR (95% CI)	p value
Age	0.59	0.96 (0.92–1.02)	0.25	0.02	1.05 (0.98–1.09)	0.06
Male	0.82			0.53		
OTT						
> 24 h	0.49	0.55 (0.18–1.63)	0.28	0.29	0.85 (0.32–2.44)	0.75
24 h to 72 h	0.64	0.84 (0.15–5.18)	0.84	0.61	1.87 (0.60–7.15)	0.28
> 72 h	0.48	1.52 (0.29–9.19)	0.62	0.45	2.20 (0.51–10.7)	0.29
BM in charge of procedure	0.77	1.46 (0.35–6.06)	0.59	0.81	1.16 (0.42–3.53)	0.78
PICA involved lesion	0.64	0.68 (0.19–2.22)	0.54	n/a		
Use of heparin	0.78	2.11 (0.56–9.37)	0.28	0.35	1.28 (0.58–3.03)	0.55
Postprocedural AT	0.78	1.12 (0.39–3.29)	0.82	0.36	1.46 (0.78–2.79)	0.23
Procedural complications	0.01			0.23		
Ischemic	0.05	0.13 (0–0.008)	0.008	0.51	0.41 (0.05–1.93)	0.28
Hemorrhagic	< 0.0001	0.01 (0–11.7)	0.41	0.56	0.19 (0.02–2.35)	0.16
Vasospasm	0.08	0.25 (0.03–1.56)	0.14	n/a		

AT: antithrombotic therapy, BM: board members, CI: confidence interval, h: hours, JR-NET: Japanese Registry of Neuroendovascular Therapy, n/a: not applicable, OR: odds ratio, OTT: onset-to-treat time, WFNS: World Federation of Neurosurgical Societies.

Table 8 Obliterated sites and location of aneurysmal dilatation in JR-NET1

	Proximal to PICA	Distal to PICA	PICA involved	No PICA	Unknown	p value
Number (%)	47 (22.1)	83 (39.0)	50 (23.5)	29 (13.6)	4 (1.9)	
Favorable outcome	30/47 (63.8)	56/83 (67.5)	22 (44.0)*	20 (69.0)	2 (50.0)	0.01
Obliterated site (%)	n = 47	n = 83	n = 50	n = 29	n = 4	
Proximal only	8 (16.8)	1 (1.2)	10 (20.0)	0 (0.0)	3 (75.0)	
AD only	14 (29.8)	54 (65.1)	24 (24.0)	13 (44.8)	1 (25.0)	
Distal only	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Proximal and AD	19 (40.4)	16 (19.3)	11 (22.0)	10 (34.5)	0 (0.0)	
Distal and AD	1 (2.1)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	
Proximal, distal, and AD	2 (4.2)	6 (7.2)	4 (8.0)	6 (20.7)	0 (0.0)	
AD and stenting	1 (2.1)	1 (1.2)	1 (2.0)	0 (0.0)	0 (0.0)	
Stenting only	1 (2.1)	3 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	
Use of balloon GC (%)	13 (27.7)	13 (15.7)	16 (34.0)	12 (41.4)	1 (25.0)	
Postprocedural status of PICA						
Preserved	46	83	23	10	1	
Occluded	1	0	23	0	0	
With bypass surgery	0	0	4	0	0	
Unknown	0	0	0	19	3	

AD: aneurysmal dilatation, GC: guiding catheter, PICA: posterior inferior cerebellar artery. *Statistically significant.

was used in 27.7%, 15.7%, 34.0%, and 41.4% in cases of group pP, dP, Pi, and nP, respectively.

In group Pi, the ratio of favorable outcome was smaller than other groups (44%, p = 0.01). The proportion of using a balloon guiding catheter was rather small, and PICA was sacrificed in approximately half of the cases. Ischemic complication was noted in 21.7% cases with sacrifice of PICA, resulting in smaller proportion of favorable outcome comparing with cases in which PICA was preserved (34.8% versus 52.2%) although there was no statistic difference in favorable outcome (p = 0.11, Table 9).

Discussion

It is well known that the prognosis of ruptured VADA is very poor. Two major reasons are poor grade on admission and high incidence of rerupture at ultra-early stage.[2,3] With the invent of NET, the first-line therapy for ruptured VADA has been shifted to NET in this decade because of its less invasiveness and time consciousness: direct access to the lesion without damaging the cerebellum and cranial nerves is possible and the therapeutic procedures can be performed in conjunction with the diagnostic angiography.[11]

This is the first nationwide survey of NET for ruptured VADA and provides important information about current status of NET and its relationship with clinical outcomes. Although the protocols were almost the same in JR-NET1 and 2, several datasets including the location of the lesion and vasospasm which were collected only in JR-NET1 seemed to be associated with favorable outcomes (Table 5). Thus, JR-NET1 and 2 were analyzed separately instead of analyzing these two studies as a composite to provide the accurate information.

Approximately 50% of all the cases in both studies were categorized as poor WFNS grade, which was compatible with previous reports.[4,12] There was a significant difference in terms of onset-to-treatment time (OTT) between two studies and approximately three-fourth of the patients were treated within 24 hours after onset in JR-NET2 (Table 2). This result may be due to widespread recognition as to the importance of preventing ultra-early rebleeding and nationwide prevalence of NET itself.

In both studies, poor WFNS grade and procedural complication were independently detected as negative factors for favorable outcome. This finding was compatible with previous studies on the outcome of subarachnoid hemorrhage including a recent study from our country,[13,14] and also with a single-center study regarding ruptured VADA[12] (Tables 5 and 6). The ratios of favorable outcome of patients with poor WFNS grade at onset were 25.4% and 31.3% in JR-NET1 and JR-NET2, respectively. These results were compatible with the previous studies as shown in Table 10, and were better than the result of PRESAT study, which dealt only with saccular aneurysms, whose ratio of favorable outcome in the patients with poor grade was 20.0%.[14] The clinical course of poor grade SAH caused by ruptured VADA might be more promising than SAH with ruptured, saccular aneurysms.

We also analyzed the relationship between collected datasets and favorable outcome in poor grade patients, only to find that the ischemic complication in JR-NET1 was negatively associated with favorable outcome. A possible explanation is that the determinants other than poor grade itself as detected in Tables 5 and 6 were less correlated with favorable outcome in this subgroup mainly due to sample size.

In JR-NET2, age and postprocedural antithrombotic therapy were demonstrated as independent factors for favorable outcome. As to age, the odds ratio was only 1.06 although elderly age is considered as an indicator for poor outcome in previous

Table 9 Procedural complication, favorable outcome, and postprocedural status of PICA in JR-NET1

	Procedural complication n = 9	Hemorrhagic complication n = 3	Ischemic complication n = 5	Favorable outcome	p value
PICA preserved	1/23 (4.3)	1/23 (4.3)	0/23 (0.0)	12/23 (52.2)	0.11
PICA occluded	8/23 (34.8)	2/23 (8.6)	5/23 (21.7)	8/23 (34.8)	
OA-PICA bypass	0/4 (0.0)	0/4 (0.0)	0/4 (0.0)	2/4 (50.0)	

Percentages are in parentheses, OA: occipital artery, PICA: posterior inferior cerebellar artery.

Table 10 Comparison of profiles and outcomes between previous studies on ruptured VADA and JR-NET studies

Series	Number	Age (mean)	Poor WFNS grade n (%)	Techniques used (n)	Used scale for outcome	Favorable outcome n (%)		Death n (%)
						All	Poor WFNS grade	
Kurata et al.[6]	18	52	9 (50.0)	IT (18)	GOS	14 (77.7)	3 (33.3)	3 (16.7)
Ravinov et al.[8]	21	52	6 (28.6)	IT (11), PO (7)	mRS	11 (52.4)	1 (16.7)	0 (0.0)
Yuki et al.[10]	27	45	8 (29.6)	IT (26), PO (1)	mRS	14 (51.8)	1 (12.5)	5 (9.3)
Sugiu et al.[9]	20	56	8 (40.0)	IT (19), SAC (1)	GOS	15 (75.0)	3 (37.5)	4 (20.0)
Endo et al.[11]	38	53	19 (50.0)	IT (38)	mRS	23 (60.5)	9 (47.4)	6 (15.8)
JR-NET1	213	54	104 (48.8)	IT (183), PO (23), SAC (3), SM (4)	mRS	130 (61.0)	33 (25.4)	33 (15.5)
JR-NET2	381	55	198 (52.0)	n/a	mRS	187 (49.1)	62 (31.3)	55 (14.4)

A favorable outcome is considered for patients with an mRS score of 0–2, or with GR or MD by GOS. GOS: Glasgow outcome scale, GR: good recovery, IT: internal trapping, JR-NET: Japanese Registry of Neuroendovascular Therapy, MD: moderate disability, mRS: modified Rankin scale, n/a: not available, PO: proximal occlusion, SAC: stent-assisted coiling, SM: stent monotherapy, VADA: vertebral artery dissecting aneurysm, WFNS: World Federation of Neurosurgical Societies.

studies listed above.[13,14] This might be explained by the fact that the age at onset in this disease was relatively young as compared with studies dealing with saccular aneurysms[6,7,12] (Table 6).

The efficacy and safety of antithrombotic therapy during and after the NET for ruptured aneurysms remains an unsolved issue. One systematic review suggested that the antiplatelet drugs reduced the risk of delayed cerebral ischemia in patients with subarachnoid hemorrhage.[15] On the contrary, a subanalysis of International Subarachnoid Aneurysm Trial (ISAT) revealed that antiplatelet therapy during or after endovascular coiling improved outcome in patients with SAH.[16] The majority of the procedures in our studies were parent artery occlusion, thus use of antiplatelets or anticoagulants might favor in avoiding thromboembolic complications especially with small branches originating from affected VA, and unfavorable outcomes such as re-rupture due to recanalization in acute stage might have occurred less frequently than coiling of saccular aneurysms.

However, this factor was not independently correlated with favorable outcome in JR-NET1 which had more variables; it seems to be premature to recommend postprocedural antithrombotic therapy. The detailed information of antithrombotic therapy especially such as dose, mode, and duration of the used drugs is needed to validate the efficacy of periprocedural antithrombic therapy for NET in ruptured VADA.

Comparing two studies, the proportion of patients with favorable outcome at 30 days decreased from 61.0% in JR-NET1 to 49.1% in JR-NET2 (Table 4). The reason for this decline is difficult to describe as there were no differences between two studies in the proportion of poor grade patients, technical success, and incidence of procedural complication. Although the OTT was shorter in JR-NET2, no correlation between OTT and favorable outcome was observed by either univariate or multivariate analysis. The participation of board members as in charge of the procedure also did not correlate with the outcome in each study. No major change was found in the used devices or techniques between two periods. According to the results shown in Table 10, it may be more reasonable to understand that the ratio of favorable outcome in patients with ruptured VADA who underwent NET lies between these numbers noted above.

Regarding the location of the lesion and the mode of the procedure in JR-NET1, the result in group Pi demonstrated that the occlusion of PICA did not affect the ratio of favorable outcome despite the increased incidence of ischemic complication (Table 9). This result should be dealt with special care as there was no information about the perfusion territory of the affected PICA in this series. Complete obliteration of the lesion might be preferred in group Pi in this study as the most important role of NET for ruptured VADAs was the prevention of rerupture. A recent report from Japan, however, demonstrated that the postoperative medullary infarction was associated with unfavorable outcomes after internal coil trapping for ruptured VADAs.[11] Furthermore, the fact that the hemorrhagic complication occurred only in one case (4.3%) in which PICA were preserved in this group may imply that the proximal occlusion may be enough for the prevention of rerupture in acute phase as proposed by authors.[5]

Regarding use of a balloon-guiding catheter, its