necessity remains an enigma[17] although the merits of this method were considered as prevention of distal embolism and reduction of subarachnoid bleeding at the time of intraprocedural rupture.[18] In group Pi, however, the territory of PICA was forced to be fed by retrograde blood flow via contralateral VA, which should run through coil mass when proximal flow control was performed.[19] The anxiety for thromboembolism in PICA territory might be the major reason for the smallest number of cases with this method in group Pi.

Stent-assisted coiling and stent monotherapy including the use of flow diverters are becoming an alternative method of NET for this disease and the initial results seem feasible.[20–22] Stent was used only in seven cases in JR-NET1, and unfortunately the use of stent was not in the collected datasets in JR-NET2. The number of stents use in ruptured VADA was considered to be small as stents designed for intracranial use were not available in Japan during the study period. A prospective, multi-centered study on the efficacy and safety of stenting along with antithrombotic therapy is strongly awaited.

This study has several limitations. This study was retrospective, and data were missing in some patients. The clinical evaluation during the study period and angiographic examinations were not evaluated by physicians who were blinded to the therapy. Furthermore, lack in unity in the datasets among two studies may have dimmed the influence of procedural/medical factors for favorable outcome. If all the datasets in JR-NET1 were collected in JR-NET2, influence of age, PICA-involved lesion, postprocedural antithrombotic therapy upon favorable outcome could be clarified for the better guidelines for NET and periprocedural management in ruptured VADA. Also, the determinants of favorable outcome after NET in poor grade patients might be presented.

Nevertheless, this study provides important information as to the current status of NET in Japan, especially the correlations among patients' status at onset, procedural results, and clinical outcomes.

Conclusion

Ruptured VADA treated by NET, mainly by proximal occlusion and internal trapping, resulted in high technical success rate up to 98.7%, and approximately 50% to 60% of the patients had a favorable outcome at 30 days after onset. Poor WFNS grade and intraprocedural complication were detected as negative factors for favorable outcomes. The results of this study may be used as baseline data for validation of future NET including the novel devices in Japan.

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Conflicts of Interest Disclosure

The authors declare that there are no conflicts of interest.

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

Recent Trends in Neuroendovascular Therapy in Japan: Analysis of a Nationwide Survey—Japanese Registry of Neuroendovascular Therapy (JR-NET) 1 and 2

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Abstract

The present study retrospectively analyzed the database of the Japanese Registry of Neuroendovascular Therapy 1 and 2 (JR-NET1&2) to determine annual trends, including adverse events and clinical outcomes at 30 days after undergoing neuroendovascular therapy. JR-NET1&2 are surveys that targeted all patients in Japan who underwent neuroendovascular therapy delivered by physicians certified by the Japanese Society of Neuroendovascular Therapy (JSNET) between 2005 and 2009. Medical information about the patients was anonymized and retrospectively registered via a website. Data from 32,608 patients were analyzed. The number of treated patients constantly increased from 5,040 in 2005 to 7,406 in 2009 and the rate of octogenarians increased from 7.0% in 2005 to 10.4% in 2009. The proportion of procedures remained relatively constant, but ratios of angioplasty slightly increased from 32.8% in 2005 to 33.7% in 2009. Procedural complications were associated more frequently with acute stroke (9.6%), ruptured aneurysms (7.4%), intracranial artery disease (ICAD) (5.4%), and arteriovenous malformation (AVM, 5.2%). The number of patients requiring neuroendovascular treatment in Japan is increasing and the outcomes of such therapy are clinically acceptable. Details of each type of treatment will be investigated in sub-analyses of the database.

Key words: nationwide survey, endovascular treatment, cerebral aneurysm, angioplasty, clinical outcome

Introduction

Neuroendovascular therapy is a less invasive method of treating various cerebrovascular diseases such as cerebral aneurysm, supra-aortic artery stenosis/occlusion, arteriovenous shunts, and acute stroke[1–8] that has become increasingly popular. However, the current status of this therapy including numbers of procedures, clinical outcomes, and adverse events remain unknown.[9,10]

The Japanese Society of Neuroendovascular Therapy (JSNET) established a board certification system in 2000 that certified physicians with ≥200 primary operator experiences, ≥10 presentations at medical meetings, and ≥3 publications as primary author as senior trainers and specialists through a board examination. The JSNET produced an expert consensus document in 2009 when a systematic review revealed a scarcity of high-quality clinical evidence in this field, especially in Japan. Thus, the society implemented retrospective studies (Japanese Registry of Neuroendovascular Therapy 1 and 2; JR-NET1&2) to clarify the general status of neuroendovascular therapy delivered by JSNET-certified physicians. Clinical and procedural data were retrospectively collected from January 2005 through December 2007 (JR-NET1) and from January 2008 through December 2009 (JR-NET2).

These studies aimed to determine annual changes in neuroendovascular treatment modalities and in major adverse events within 30 days thereafter.

Methods

I. Study design

JR-NET1 (2005–2006): This was the first nationwide survey of neuroendovascular treatments in Japan. The registry targeted all patients treated by JSNET board-certified physicians between January 2005 and December 2006, except for those whom their physicians judged unsuitable for this registry. Medical information about the patients was anonymized and retrospectively registered via a website (https://jr-net.tri-kobe.net/jr-net/).

JR-NET2 (2007–2009): This second nationwide survey of neuroendovascular treatment in Japan targeted all patients treated by JSNET board-certified physicians between January 2007 and December 2009. Medical information of the patients was anonymized and registered as described above.

Data were collected at the Translational Research Informatics Center (TRI, http://www.tri-kobe.org/). The study protocol, which is summarized briefly here, is available on line with the full text of this article (https://jr-net.tri-kobe.net/jr-net/). All members of the writing committee assumed responsibility for the accuracy and completeness of the data and for the fidelity of the study with regard to the protocol.

II. Patients

All patients treated by neuroendovascular treatment at participating centers during the study period were basically enrolled in the study. The local institutional review boards at each institution approved the study protocol before the investigators proceeded with the study.

III. Primary and secondary endpoints

The primary endpoint was activities of daily life (ADL) determined according to modified Rankin scale (mRS) scores. The secondary endpoints comprised the technical success of procedures and major adverse events (MAEs) that occurred within and at 30 days after procedures.

A score of 0 on the mRS indicates no disability, whereas scores of 1 or 2 indicate slight disability (some help required with ADL but basically independent), scores of 3 to 5 indicate moderate disability (some help required with ADL) to severe disability (bedridden or constant specific care required), and a score of 6 indicates death.

Adverse events were classified as minor and major when mRS scores deteriorated by 1 and ≥2 points, respectively.

IV. Statistical analysis

Data were statistically analyzed using JMP 7 software (SAS Institute, Cary, North Carolina, USA). The statistical significance of intergroup differences was assessed using the *t*-test for quantitative scales, Pearson's χ^2 test; $p < 0.05$ was considered significant.

Results

I. Backgrounds and characteristics of patients

A total of 32,068 patients (mean age, 63.5 ± 13.9

Table 1 Annual trends of JR-NET data

	2005	2006	2007	2008	2009	Total
Total number	n = 5,040	n = 6,174	n = 6,690	n = 6,758	n = 7,406	n = 32,068
Age	64.0+/–13.8	63.4+/–12.9	64.1+/–13.7	64.6+/–13.3	64.4+/–13.8	63.5+/–13.9
Female	2,341 (46.4%)	2,921 (47.3%)	3,109 (46.5%)	3,131 (46.3%)	3,495 (47.2%)	14,997 (46.8%)
mRS before treatment	0.7	0.7	0.7	0.6	0.6	0.7
Procedures	n = 4,500	n = 5,457	n = 6,466	n = 6,503	n = 7,232	n = 30,158
Aneurysm treatment	1,777 (39.5%)	2,396 (43.9%)	2,725 (42.1%)	2,668 (41.0%)	3,112 (43.0%)	12,678 (40.5%)
Dome embolization, ruptured	751 (16.7%)	963 (17.7%)	1,073 (16.6%)	1,091 (16.8%)	1,254 (17.3%)	5,132 (17.0%)
Dome embolization, unruptured	883 (19.6%)	1,105 (20.3%)	1,373 (21.2%)	1,302 (20.0%)	1,597 (22.1%)	6,260 (20.8%)
Dissection/parent artery occlusion	143 (3.2%)	328 (6.0%)	279 (4.3%)	275 (4.2%)	261 (3.6%)	1,439 (4.8%)
Angioplasty/stenting	1,476 (32.8%)	1,734 (31.2%)	2,275 (35.2%)	2,363 (36.3%)	2,438 (33.7%)	10,286 (34.1%)
Carotid artery	1,042 (23.2%)	1,281 (23.5%)	1,717 (26.6%)	1,855 (28.5%)	1,926 (26.6%)	7,821 (25.9%)
Vertebral/subclavian artery	203 (4.5%)	230 (4.2%)	281 (4.4%)	282 (4.3%)	254 (3.5%)	1,250 (4.1%)
Intracranial artery	231 (5.1%)	223 (4.1%)	277 (4.3%)	226 (3.5%)	258 (3.6%)	1,215 (4.0%)
Brain & spinal AVM embolization	217 (4.8%)	281 (5.1%)	204 (3.2%)	213 (3.3%)	259 (3.6%)	1,174 (3.9%)
DAVF embolization	317 (7.0%)	424 (7.8%)	468 (7.2%)	464 (7.1%)	525 (7.3%)	2,198 (7.3%)
Tumor embolization	347 (7.7%)	373 (6.8%)	317 (4.9%)	319 (4.9%)	382 (5.3%)	1,738 (5.8%)
Acute stroke treatment	366 (8.1%)	249 (4.6%)	277 (4.3%)	266 (4.1%)	281 (3.9%)	1,439 (4.8%)
Physicians in charge	n = 4,935	n = 5,988	n = 6,690	n = 6,758	n = 7,406	n = 31,777
Senior trainer, board certified	3,139 (63.6%)	3,573 (59.7%)	3,097 (46.3%)	3,277 (48.5%)	3,624 (48.9%)	16,710 (52.6%)
Specialist, board certified	1,355 (27.5%)	1,801 (30.1%)	3,103 (46.4%)	3,044 (45.0%)	3,358 (45.3%)	12,661 (39.8%)
Non-specialist	438 (8.9%)	617 (10.3%)	462 (6.9%)	375 (5.5%)	405 (5.5%)	2,297 (7.2%)

AVM: arteriovenous malformation, DAVF: dural arteriovenous fistula, mRS: modified Rankin Scale.

years; female, 46.8%) were registered in this study (Table 1), which involved 200 and 256 board-certified physicians at 122 and 150 centers in JR-NET[11] and in JR-NET2, respectively (Appendix). Figure 1 shows the proportions of treated patients within various age groups. Although patients aged between 40 years and 70 years were the main recipients of treatment, the rate of octogenarians increased annually from 7.0% in 2005 to 10.4% in 2009 ($p < 0.001$). In contrast, the ratio of younger patients (< 40 years) remained constant ($p = 0.361$; Fig. 1).

II. Procedures

Among a total of 32,068 neuroendovascular procedures implemented between 2005 and 2009, angioplasty and treatment for aneurysms accounted for 34.1% and 40.5%, respectively. Embolization of brain and spinal arteriovenous malformations (AVMs), dural arteriovenous fistulae (dAVF), tumors, and treatment for acute stroke accounted for 3.9%, 7.3%, 5.8%, and 4.8% of procedures, respectively. Carotid artery stenting (CAS) accounted for 25.9% of all procedures (Table 1). The proportions of treatments remained relatively constant, except for CAS, which slightly increased from 23.2% in 2005 to 26.6% in 2009 ($p < 0.001$; Fig. 2).

Elective or emergency procedures: The total numbers of elective and emergency procedures increased annually, but the rate of emergency treatment remained relatively constant between 28% and 30% throughout the study period (Fig. 3).

Physicians in charge: Senior trainers certified by JSNET were in charge of 63.6% and 48.9% of procedures during 2005 and in 2009 (Table 1), respectively. The total number of treatment procedures with JSNET senior trainers and specialists in charge increased annually, but the rate of procedures supervised by JSNET senior trainers gradually decreased, although the difference did not reach significance. However, treatment delivered with JSNET non-specialist in charge decreased from 8.9% in 2005 to 5.5% in 2009 ($p = 0.029$).

mRS scores before and after treatment: Figure 4A and 4B shows the overall proportions of mRS scores before and after treatment. Before treatment, ≥90% of patients were in relatively good condition, with mRS scores of 0–2 (Fig. 4A). At 30 days after undergoing procedures, >80% of patients maintained mRS scores of 0–2 (Fig. 4B).

mRS scores after each type of procedure: Figure 5 shows the outcomes of each type of treatment

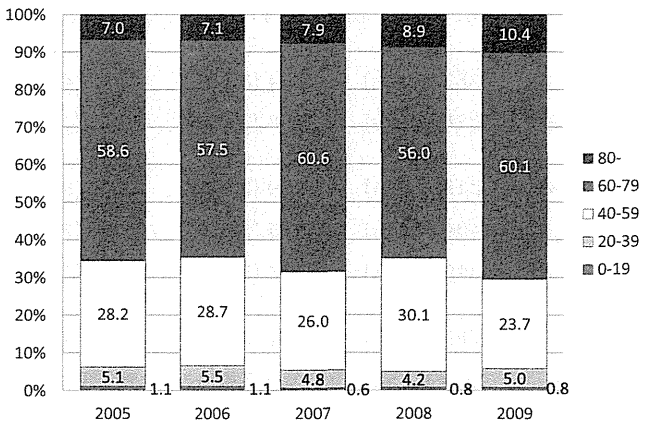

Fig. 1 Annual changes in patients' age during JR-NET1&2. Rates of octogenarians increased annually from 7.0% in 2005 to 10.4% in 2009 ($p < 0.001$), whereas the ratio of younger patients (< 40 years) remained constant ($p = 0.361$). JR-NET1&2: Japanese Registry of Neuroendovascular Therapy 1 and 2.

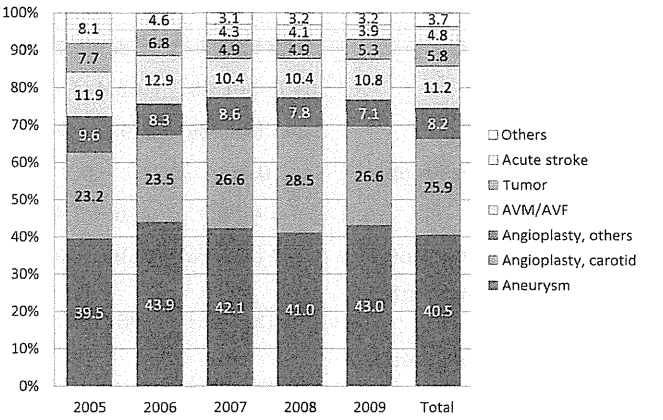

Fig. 2 Annual changes in the types of procedures. The proportion of treatments remained relatively constant, but carotid artery stenting (CAS) slightly increased from 23.2% in 2005 to 26.6% in 2009 ($p < 0.001$).

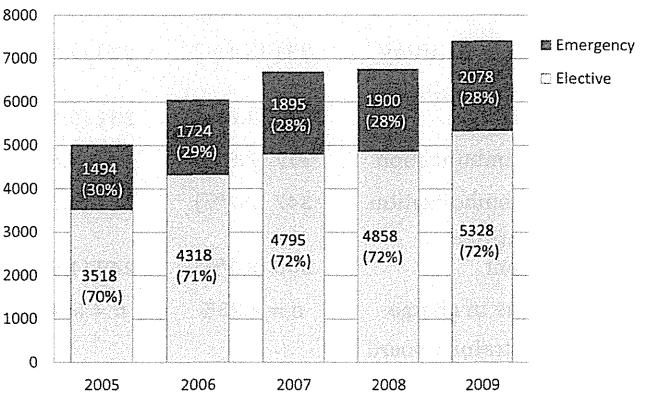

Fig. 3 Number of elective and emergency procedures. The total numbers of elective and emergency procedures increased annually, although the overall rate of emergency treatment remained between 28% and 30% throughout the period.

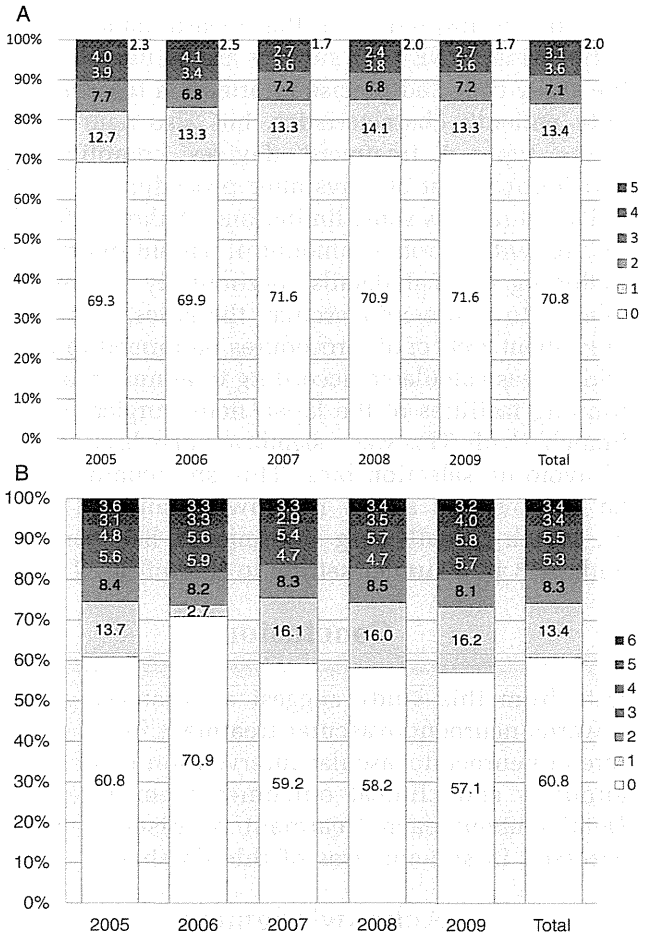

Fig. 4 Proportions of modified Rankin scale (mRS) scores before and after procedures. Ratio of patients with mRS 0–2 was ≥90% before therapeutic procedures (A), decreased at 30 days thereafter (B), but remained >80%.

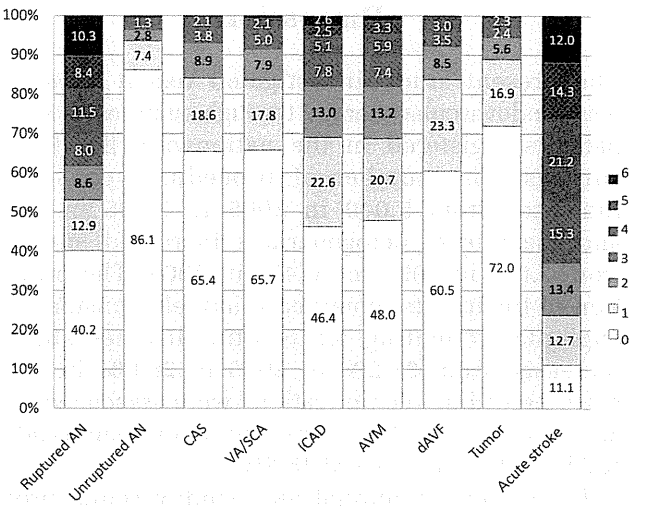

Fig. 5 Proportions of modified Rankin scale (mRS) scores at 30 days after various procedures. Outcomes were favorable (mRS 0–2) for 61.7% and 96.3% of patients with ruptured and unruptured aneurysms respectively. Ratios of favorable outcomes of carotid artery stenting (CAS), vertebral artery (VA)/SCA (subclavian artery), dural arteriovenous fistula (dAVF), and tumor embolization were >90%. On the other hand, the ratios of favorable outcomes were 82.0%, 81.9%, and only 37.2% in intracranial artery disease (ICAD), arteriovenous malformation (AVM) and acute stroke, respectively.

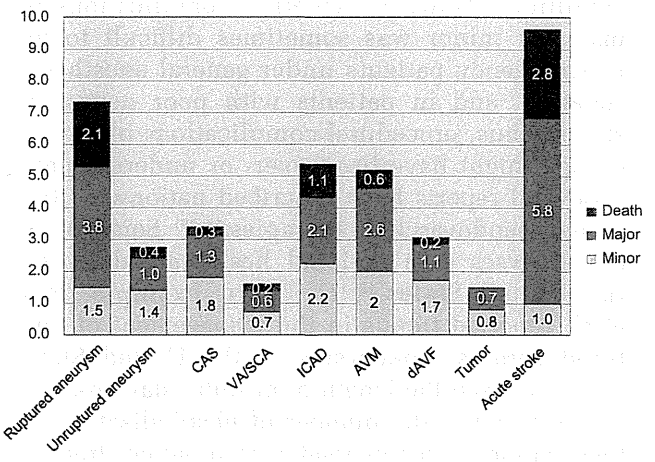

Fig. 6 Complications associated with each procedure. Complication rates were higher after procedures for ruptured aneurysm (7.4%) and acute stroke (9.5%), but less frequent for those that treated unruptured aneurysms (2.8%), VA/SCA (1.5%), and tumor embolization (1.5%).

according to mRS scores. Outcomes were favorable for 61.7% and 96.3% of patients with ruptured and unruptured aneurysms, respectively, (mRS 0–2) and for ≥90% those after CAS, VA/SCA, dAVF, and tumors. On the other hand, 82.0%, 81.9%, and 37.2% of those treated for intracranial artery disease (ICAD), in AVM, and acute stroke had favorable outcomes.

Procedural complications of each treatment: Figure 6 shows the frequency of procedural complications after each type of treatment. Death, major and minor procedural complications occurred in 7.4% and 2.8% of patients treated for ruptured and unruptured aneurysms, respectively. Among angioplasties, procedural complications occurred in 3.4%, 1.5%, and 5.4% in the carotid artery, the VA/SCA and in ICAD, respectively. Among arteriovenous shunt diseases, complications developed in 5.2% and 3.0% of those treated for AVM and dAVF, respectively. The rate of complications of tumor embolization was 1.5%, and none of the patients died of procedure-related complications. On the other hand, complications developed at a rate of 9.6% in patients treated for acute stroke, including 2.8% who died.

Discussion

The present study investigated recent trends in neuroendovascular therapy through analyses of 32,608 patients registered in the nationwide JR-NET1&2 surveys. The number of procedures constantly increased from 5,040 in 2005 to 7,406 in 2009, and the rate of octogenarians increased annually from 7.0% in 2005 to 10.4% in 2009. The proportion of treatments remained relatively constant, but angioplasty/stenting for carotid diseases slightly increased from 23.2% in 2005 to 26.6% in 2009. More procedural complications were associated with acute stroke (9.5%), ruptured aneurysm (7.4%), ICAD (5.4%), and AVM (5.2%).

The number of annual neuroendovascular procedures increased by 46.9% (from 5,040 to 7,406). The annual numbers of procedures required to treat intracranial aneurysms and angioplasty/stenting for atherosclerotic disease between 2005 and 2009 increased by 75.1% (from 1,777 to 3,112) and 65.2% (1,476 to 2,438), respectively. The mRS scores after procedures remained favorable in >80% of the patients each year. Clinical outcomes and complication rates significantly differed among procedures. Rates of favorable outcomes of procedures to treat ruptured aneurysms and acute stroke were around 60% and < 40%, respectively, and more procedural complications were also associated with these conditions. However, whether complications were major or minor was sometimes difficult to judge in emergency patients under general anesthesia or sedation, and in patients with poor neurological status. Thus, procedural complications in these two groups might have been over- or underestimated.

Several reports have described nationwide trends in neuroendovascular therapies.[12–19] Some of them are analyses of a national healthcare database in the United States.[12–15,17,20] For example, Huang et al. reported trends in the management of unruptured cerebral aneurysms in the United States.[15] They analyzed the length of hospital stay, in-hospital mortality rates, the number of hospitalizations, and total national charges related to inpatient treatment. Their findings provide valuable information regarding trends, but obtaining clinical data about neurological status, neuroendovascular procedures, and follow-up results might be difficult. Detailed evaluations and analyses could be achieved if areas or centers were selected. Higashida et al. described endovascular treatment for unruptured intracranial aneurysms in 18 of 47 states in the United Staes during 2007.[21] Qureshi et al. described how class I evidence (ISAT) from a nationwide impact survey impacted clinical practice. Their database was derived from stratified sampling at 20% of US hospitals.[20] In that regard, data from the nationwide JR-NET1&2 surveys are valuable because the study collected precise information regarding not only patient's characteristics, but also neurological status, types of treatment, devices, complications, and follow-up at 30 days after procedures.

This study has some limitations. Although JR-NET 1&2 provided a robust amount of patient information including clinical details, particularly information related to neuroendovascular therapies, it covered only about 35% of all procedures performed in Japan, which was calculated according to annual reports of training facilities of the Japan neurosurgical society (unpublished). This was a significant drawback in terms of avoiding selection bias. This shortcoming might be improved in a new nationwide survey (JR-NET 3), which is collecting information between 2010 and 2013 in a similar setting to that of JR-NET 1&2.

Conclusion

Data from this study suggest an increasing trend towards neuroendovascular treatment in Japan. The rate of neuroendovascular intervention is increasing annually and clinical outcomes seem acceptable. Details about each treatment or disease will be assessed in sub-analyses of this database.

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Conflicts of Interest Disclosure

All authors who are members of The Japan Neurosurgical Society (JNS) have registered self-reported COI disclosure statements through the website for JNS members.

This manuscript has not been published or presented elsewhere in part or in entirety, and is not under consideration by another journal.

Appendix

Participants, their hospitals, and the number of registered patients in JR-NET2 are listed when >100 patients were registered; names of investigators are listed when < 100 patients were registered. This information has already been reported for JR-NET1.[11]

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K Haraguchi, H Manabe, M Hayashi, O Kikuchi, S Iihoshi, K Miyata, J Sakurai, S Yamauchi, A Takahashi, N Tamagawa, J Moroi, A Shimada, K Asakura, H Shimaguchi, O Miyagi, M Matsumoto, A Kojima, T Takahashi, S Ishihara, S Kohyama, F Yamane, T Dembo, R Kanazawa, K Nakai, M Katayama, S Kittipong, M Tanaka, Y Numaguchi, M Fujimoto, A Uemura, T Saguchi, O Tone, Y Sato, K Shigeta, Y Yoshida, T Ohashi, K Amari, Y Sakata, S Tateshima, Y Ito, T Sorimachi, S Inagawa, K Morita, K Kitazawa, M Arai, N Minamide, Y Hirota, Y Takabatake, K Kanemaru, J Yamada, H Kitajima, S Fukazawa, T Okamoto, T Nakano, A Tsurumi, T Kojima, M Negoro, A Sadato, M Hayakawa, T Watanabe, K Irie, T Tanaka, T Hattori, N Kobayashi, A Tsuji, M Kawanishi, M Yamada, M Hirai, K Owada, M Ohashi, T Ota, K Maeno, S Sakamoto, T Kuroiwa, K Murao, K Nakazawa, J Kobayashi, N Nakagawa, T Fukawa, A Fujita, K Matsumoto, Y Yoshida, I Yamaura, A Masuda, H Minami, K Uchida, M Shirakawa, H Nakagawa, I Nakagawa, H Takeuchi, S Kawada, A Handa, M Koyanagi, K Yoshida, S Matsubara, T Mizogami, K Migita, H Yasuda, S Kato, K Satoh, M Hanaoka, N Hayashi, K Yoshino, A Nishida, T Shiraishi, O Nishizaki, M Iwanaga, T Higashi, M Iwaasa, M Okawa, K Nakahara, T Yoshioka, M Kaji, Y Hori, T Asano, M Okahara, A Kashiwagi, H Kiyosue, S Tanoue, T Kubo, and H Yonaha.

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Plasma atrial natriuretic peptide is an early diagnosis and disease severity marker of myxomatous mitral valve disease in dogs

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ABSTRACT

The aim of this study was to retrospectively assess the clinical usefulness of plasma atrial natriuretic peptide (ANP) concentrations for determining the severity of myxomatous mitral valve disease (MMVD) in dogs. Plasma ANP levels were found to be significantly higher in dogs with MMVD compared to healthy dogs, and plasma ANP levels increased significantly in dogs with progressive heart failure. In dogs with MMVD, stepwise regression analysis revealed that the left atrium/aorta ratio and fractional shortening could be used to predict the plasma ANP concentration. These results indicated that plasma ANP rose with an increase in the volume overload of the left side of the heart. Plasma ANP discriminated cardiomegaly from non-cardiomegaly caused by asymptomatic MMVD. We conclude, therefore, that plasma ANP concentrations may be a clinically useful tool for early diagnosis of asymptomatic MMVD in dogs.

1. Introduction

Myxomatous mitral valve disease (MMVD) in dogs is the most commonly acquired heart disease (Serfass et al., 2006). MMVD causes mitral regurgitation due to rupture of chordae tendineae and poor coaptation of the mitral valve leaflets during systole. Mitral regurgitation leads to the left atrial and the left ventricular dilatation, and causes pulmonary congestion (Gouni et al., 2007). This mechanical stress imparted on the cardiomyocytes stimulates the synthesis and secretion of atrial natriuretic peptide (ANP) (Edwards et al., 1988). Normally, ANP is secreted mainly by atrial cardiomyocytes, ventricular contribution corresponding to less than 3% (Nakayama, 2005). However, heart failure stimulates ANP release from ventricular cardiomyocytes to a level equivalent to the atrial cardiomyocytes. This small peptide plays an important role in intravascular volume homeostasis, such as natriuresis, vasodilation, and inhibition of the renin–angiotensin–aldosterone system (Ruskoaho, 2003). Precisely, release of ANP is a protective mechanism against ventricular volume overload (de Almeida et al., 2012).

Heart diseases in dogs are associated with high concentration of ANP in the bloodstream. For instance, plasma ANP level increases with pulmonary capillary wedge pressure, a measure of left atrial pressure in dogs (Asano et al., 1999; Hori et al., 2010). Häggström et al. reported that left atrial enlargement causes an increase in plasma ANP concentration, and ANP level was a good indicator of decompensation in Cavalier King Charles Spaniels with mitral regurgitation (Häggström et al., 1994, 2000). In addition, Greco et al. reported that plasma ANP level reflects survival in dogs with heart failure including dilated cardiomyopathy and MMVD (Greco et al., 2003). These studies suggest plasma ANP may be a marker of severity of heart disease in dogs.

The aim of this study was to test the potential of plasma ANP levels as diagnostic marker of MMVD severity in dogs. First, we determined the relationship between plasma ANP levels and MMVD severity. Second, the accuracy as a diagnostic indicator of MMVD severity was determined by the sensitivity and specificity of plasma ANP levels.

2. Materials and methods

2.1. Study population

The study population consisted of client-owned dogs that presented with systolic murmur in the mitral area (grade > 2) and owner consent was obtained for all dogs included in this study. Five veterinary cardiology practices prospectively recruited dogs between October 2009 and May 2010. Both healthy dogs (healthy group) and dogs with MMVD (MMVD group) were recruited for

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this study. The healthy dogs were considered healthy on the basis of results of physical examination, including cardiac auscultation, and blood test; total protein, albumin, complete blood count, urea nitrogen, creatinine, aspartate amino transferase, and alanine aminotransferase. Exclusion criteria included congenital heart disease and acquired heart disease other than MMVD. For the MMVD group, dogs with liver disease, kidney disease, or systemic disease were excluded from the study. Dogs with prerenal azotemia associated with MMVD were included in the study.

2.2. Assessment of cardiac disease severity

All dogs with MMVD underwent thoracic radiography and 2-D, M-mode, and color-flow Doppler echocardiography. The left ventricular end-diastolic diameter (LVEDD), the left ventricular end-systolic diameter (LVESD), the aortic diameter (Ao), and the left atrial diameter (LA) were measured by standard echocardiographic techniques (Hansson et al., 2002; Thomas et al., 1993). LA to Ao ratio was calculated (LA/Ao). The left ventricular fractional shortening (FS) was calculated with LVEDD and LVESD. LVEDD and LVESD values were divided by the Ao to normalize them to the size of the dog (LVEDD/Ao and LVESD/Ao, respectively). In dogs with MMVD, the severity of heart failure was classified according to the International Small Animal Cardiac Health Council (ISACHC) recommendations based on clinical symptoms and thoracic radiographs (International Small Animal Cardiac Health Council, 1999).

2.3. Blood sampling and measurement of ANP

Blood samples were obtained from the jugular or cephalic vein and were immediately collected in a tube containing aprotinin and EDTA and centrifuged at 3000 rpm for 10 min. The supernatant (plasma) was transferred to a plastic tube and stored at −80 °C. Plasma ANP concentrations were determined with a chemiluminescence enzyme immunoassay for human α-ANP (Shionoria-ANP, Shionogi Co., Osaka, Japan) (Hori et al., 2011). The detection limit of plasma ANP concentrations assay was 5 pg/mL.

2.4. Statistical analysis

Values are presented as the median and the interquartile range (IQR, 25th–75th percentile). Mann–Whitney's *U* test was used to compare plasma ANP concentrations between healthy dogs and dogs in each ISACHC Class of MMVD. The Kruskal–Wallis test, followed by the Dunn multiple comparison test, was used to compare physical examination results, echocardiography variables, and plasma ANP concentrations among dogs in each ISACHC Class of MMVD. Differences in the numbers of dogs receiving medical treatment in each ISACHC Class were determined by use of the chi-square test.

Pearson's correlation coefficient test was used to examine correlations between plasma ANP concentration and heart rate, LA/Ao, LVEDD/Ao, LVESD/Ao, and FS. The Spearman rank correlation was calculated to assess the correlation between plasma ANP concentration and heart murmur grade. Stepwise multiple regression analysis was performed to identify continuous variables associated with plasma ANP concentration.

Receiver operating characteristic (ROC) analyses were performed to determine the optimal cut-off values for plasma ANP concentration in discriminating between dogs with MMVD and healthy dogs. Furthermore, ROC analyses were performed to assess the predictive accuracy of the plasma ANP concentration for detecting left atrium enlargement and pulmonary edema. ROC curves were drawn by plotting all the sensitivity values against their corresponding 1 − specificity values. The area under the ROC curve and the 95% confidence interval (CI) of the prediction of the area were calculated. All analyses were performed with standard software (Prism version 5.0c, GraphPad Software Inc., CA, USA) and values of $P < 0.05$ were considered significantly different.

3. Results

A total of 36 healthy dogs and 127 dogs diagnosed with MMVD were included in this study. Both groups were comparable in terms of mean age, gender ratio and body weight, as well as breed variety. The healthy group comprised of male ($n = 16$, 44.4%) and female ($n = 20$, 55.6%), adult aged (median, 56 months; IQR, 42–87 months), and small-breed dogs (median, 9.0 kg; 5.4–11.9 kg). Breeds consisted of 16 Beagles, seven Miniature Dachshunds, three Mixed breeds, two Yorkshire Terriers, and one French Bulldog, Labrador Retriever, Maltese, Papillon, Shetland Sheepdog, Shiba, Toy Poodle, and Welsh Corgi. The MMVD group was mostly composed of male ($n = 81$, 63.8%), adult aged (median, 145 months; IQR, 115–161 months), small-breed dogs (median, 5.5 kg; 3.8–7.7 kg). Breeds consisted of 17 Mixed breeds, 16 each of Maltese and Cavalier King Charles Spaniels, 14 Shih Tzus, 13 Miniature Dachshunds, 12 Chihuahuas, eight each of Yorkshire Terriers and Pomeranians, six Shibas, five Toy Poodles, three each of Beagles and Miniature Schnauzers, two Papillons, and one Akita, American Cocker Spaniel, Japanese Chin and West Highland White Terrier.

The MMVD dogs were classified according to disease severity based on the ISACHC classification. A total of 57 dogs (44.9%) had asymptomatic disease (Class I), 47 dogs (37.0%) were in ISACHC Class II, and 23 dogs (18.1%) were in ISACHC Class III. The heart murmur rate gradually doubled with disease severity, from a median value of 2 for Class Ia to 4 for Class IIIb. Heart rate also increased significantly with disease severity, but the most dramatic increase was detected for Class IIIa, and not Class IIIb. The healthy dogs were not taking any medication. In contrast, the MMVD dogs at baseline, 96 (75.6%) dogs were receiving medical treatment for their cardiac disease. Twenty-nine dogs were receiving monotherapy with angiotensin converting enzyme (ACE) inhibitor. Sixty-seven dogs were receiving combination therapy with more than two of the following drugs: ACE inhibitor, carvedilol, digoxin, diuretics (furosemide or torsemide), spironolactone, and/or pimobendan. A higher proportion of dogs in ISACHC Class II (91.5%) were receiving medical treatment compared with dogs in ISACHC Class I (63.2%, $P < 0.01$) and Class III (73.9%, $P < 0.05$) MMVD. Ventricular overload increased linearly starting with Class Ib as detected in terms of LA/Ao, LVEDD/Ao, and LVESD/Ao. The most remarkable finding is the drastic age difference between Class Ia and Class Ib, which marks a change in the rate of disease progression. Seventeen dogs presented with pulmonary edema in ISACHC Class III. Baseline values of the continuous variables for the 127 dogs at first examination are summarized in Table 1.

The relationship between MMVD and plasma ANP concentration was demonstrated by comparing the median values of the healthy dogs to those of each Class of MMVD dogs. Table 2 shows that all MMVD Classes of dogs exhibited a median plasma ANP level significantly higher than healthy dogs. Also, plasma ANP levels were significantly higher in Classes Ib, II, IIIa and IIIb, compared to Class Ia, showing a gradual progression with disease severity.

Regression analyses were conducted to determine whether an increase in plasma ANP level correlates with the increase of ventricular overload in MMVD dogs. Table 3 shows that plasma ANP level was correlated significantly with heart rate, LA/Ao, LVEDD/Ao, and FS, but not LVESD/Ao that is reflected by pressure overload and systolic function. Stepwise multiple regression analysis revealed that the LA/Ao ratio and FS could be used to predict the plasma ANP concentration.

Table 1
Baseline characteristics of the study population including 127 dogs with myxomatous mitral valve disease.

	ISACHC				
Variable	Ia (n = 31)	Ib (n = 26)	II (n = 47)	IIIa (n = 14)	IIIb (n = 9)
Age (months)	115 [94-157]	141 [114-151]	148* [130-171]	153 [134-170]	145 [103-161]
Body weight (kg)	5.5 [3.8-8.0]	6.8 [4.4-7.9]	5.0 [3.9-8.2]	4.9 [3.7-10.9]	3.6 [2.8-5.6]
Heart murmur grade	2 [2–3]	3** [3–4]	4***,† [4–5]	4*** [4–5]	4*** [4–5]
Heart rate (bpm)	131 [107–150]	146 [121–152]	140*** [120–168]	180***,††,§ [155–214]	144** [108–172]
Medication	15	21	43	11	6
LA/Ao	1.4 [1.3–1.5]	1.7** [1.6–1.9]	2.0***,† [1.8–2.3]	2.4***,†† [2.1–2.7]	2.6***,†† [2.2–3.0]
LVIDD/Ao	1.6 [1.5–1.9]	1.9* [1.7–2.5]	2.3*** [2.0–2.6]	2.3** [2.0–2.9]	2.9***,†† [2.6–3.0]
LVISDAo	0.9 [0.7–1.0]	1.1 [0.9–1.2]	1.1** [0.9–1.3]	1.2 [0.7–1.5]	1.3* [1.0–1.6]
FS (%)	45.8 [41.5–53.6]	47.7 [39.7–52.0]	49.6 [44.0–57.8]	43.1 [38.7–57.6]	49.0 [45.0–63.4]

Data are given as medians and 25th–75th percentiles.
ISACHC, International Small Animal Cardiac Health Council; n, number of dogs for which variables were available; LA/Ao, left atrium to aortic root ratio; LVEDD, left ventricular diameter in diastole; LVESD, left ventricular diameter in systole; FS, left ventricular fractional shortening.
Statistics were calculated by Kruskal–Wallis test, followed by the Dunn multiple comparison test.
* $P < 0.0.05$ compared with Class Ia.
** $P < 0.01$ compared with Class Ia.
*** $P < 0.001$ compared with Class Ia.
† $P < 0.05$ compared with Class Ib.
†† $P < 0.001$ compared with Class Ib.
§ $P < 0.05$ compared with Class II.

Table 2
The plasma atrial natriuretic peptide (ANP) concentrations in healthy dogs and in dogs with myxomatous mitral valve disease grouped on the basis of International Small Animal Cardiac Health Council (ISACHC) Class.

	Median	IQR (25th–75th)
Healthy	15.8	11.0–26.3
ISACHC		
Class Ia	33.8	23.5–58.9
Class Ib	53.0	33.4–111.3*
Class II	77.0	43.4–173.0*
Class IIIa	228.0	165.5–446.0*,†,§§
Class IIIb	222.0	99.5–347.5*,†,§

Mann–Whitney's U test was used to compare plasma ANP concentrations between healthy dogs and dogs in each ISACHC Class of MMVD. All ISACHC Classes of dogs exhibited a median plasma ANP level significantly higher than healthy dogs.
Statistics were calculated by Kruskal–Wallis test, followed by the Dunn multiple comparison test, to compare plasma ANP concentrations among dogs in each ISACHC Class of MMVD.
* $P < 0.001$ compared with Class Ia.
† $P < 0.01$ compared with Class Ib.
§ $P < 0.01$ compared with Class II.
§§ $P < 0.05$ compared with Class II.

Table 3
Correlations between plasma atrial natriuretic peptide concentration and various parameters (n = 127).

	Correlation coefficient (r)	r^2	P value
Heart rate (bpm)	0.35	0.12	<0.001
LA/Ao	0.68	0.46	<0.001
LVEDD/Ao	0.35	0.12	<0.001
LVESD/Ao	0.09	0.01	NS
FS (%)	0.34	0.12	<0.001

n, number of dogs for which variables were available; r^2, coefficient of determination; LA/Ao, left atrium to aortic root ratio; LVEDD, left ventricular diameter in diastole; LVESD, left ventricular diameter in systole; FS, left ventricular fractional shortening; NS, not significant. Statistics were calculated by Pearson's correlation coefficient test.

Receiver operating characteristic (ROC) analysis was performed to determine the cut-off value of plasma ANP concentration, which is different between healthy dogs and MMVD dogs (Table 4 and Fig. 1). The highest sensitivity and specificity (83% and 86%) were found for a plasma ANP cut-off concentration of 30.7 pg/mL in the whole population. Plasma ANP concentrations >27.0 pg/mL identified dogs with ISACHC Class Ib MMVD with a sensitivity of 88% and a specificity of 81%. The optimal plasma ANP cut-off concentrations were different when dogs with asymptomatic MMVD (27.0 pg/mL) and dogs with symptomatic MMVD (40.8 pg/mL) were studied separately. A plasma ANP concentration >59.9 pg/mL could identify dogs with left atrial enlargement (LA/Ao ≥ 1.7) with a sensitivity of 81% and a specificity of 79% (Fig. 2). Use of plasma ANP concentration >182.5 pg/mL to identify dogs with pulmonary edema had a sensitivity of 94% and a specificity of 79% (Fig. 3).

4. Discussion

Congestive heart failure caused by MMVD is commonly reported in dogs over 10 years old. Since MMVD is a progressive degenerative disease, the aim of this study was to identify a simple and sensitive diagnostic assay that could detect MMVD early to improve the survival of these dogs through proactive interventions. Plasma ANP was selected because this small peptide is released from cardiomyocytes in response to cardiac overload. The present study provides evidence that plasma ANP can be used as early diagnostic tool and marker of disease severity for dogs with MMVD.

In the present study, plasma ANP levels in dogs with mitral regurgitation are significantly elevated compared with those in healthy dogs and this result is consistent with a previous study (Häggström et al., 1994; Hori et al., 2011). Furthermore, the present study showed that plasma ANP levels were able to discriminate

Table 4
Sensitivity and specificity of plasma atrial natriuretic peptide concentrations to discriminate dogs with myxomatous mitral valve disease from healthy dogs.

Population considered	Area under ROC curves	95% CI	Cut-off points (pg/mL)	Sensitivity (%)	Specificity (%)
Whole population (n = 127)	0.93	0.887–0.966	>30.7	83	86
ISACHC					
Class I (n = 57)	0.87	0.797–0.937	>27.0	77	81
Class Ia (n = 31)	0.82	0.728–0.921	>27.0	68	81
Class Ib (n = 26)	0.92	0.851–0.985	>27.0	88	81
Class II, III (n = 70)	0.98	0.952–0.998	>40.8	90	97

ROC, receiver operating characteristic; CI, confidence interval; ISACHC, International Small Animal Cardiac Health Council. Statistics were calculated by ROC analysis.

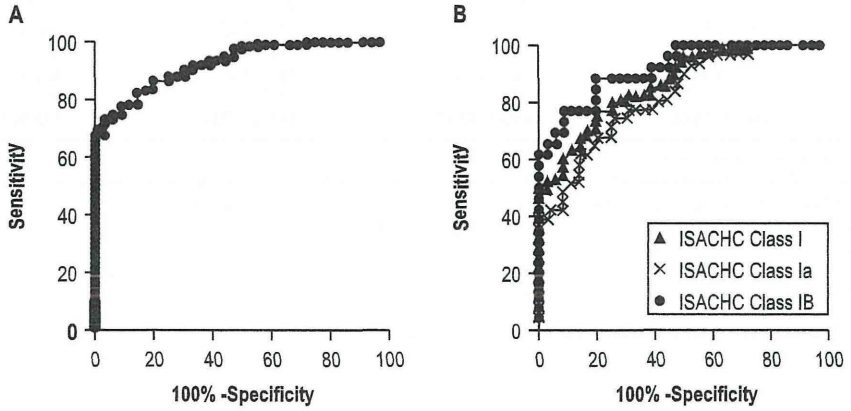

Fig. 1. Receiver operating characteristic (ROC) curve showing the sensitivity and specificity of using plasma atrial natriuretic peptide concentrations to distinguish healthy dogs from dogs with myxomatous mitral valve disease. The abscissa and the ordinate of each point represent the sensitivity and 100% – specificity rates for specific cutoff. Each curve was generated by calculating the sensitivity and 100% – specificity rates. Plasma ANP discriminated cardiomegaly from non-cardiomegaly caused by asymptomatic MMVD. (A) ROC curve for the whole population (n = 127). (B) ROC curve for ISACHC Class I (combined Class Ia and Ib, n = 57), Class Ia (n = 31) and Class Ib (n = 26).

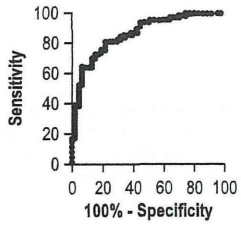

Fig. 2. Receiver operating characteristic (ROC) curve displaying sensitivity and specificity of using plasma atrial natriuretic peptide (ANP) concentrations to distinguish dogs with myxomatous mitral valve disease (MMVD) and left atrial enlargement (LA/Ao ≥ 1.7) from dogs with MMVD and LA/Ao < 1.7. The abscissa and the ordinate of each point represent the sensitivity and 100% – specificity rates for specific cutoff. Each curve was generated by calculating the sensitivity and 100% – specificity rates. An ANP value of 59.9 pg/mL was associated with a sensitivity of 81% and a specificity of 79%. Area under the curve = 0.87.

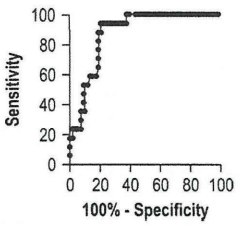

Fig. 3. Receiver operating characteristic curve displaying sensitivity and specificity of using plasma atrial natriuretic peptide (ANP) concentrations to distinguish symptomatic dogs with myxomatous mitral valve disease (MMVD) and pulmonary edema from symptomatic dogs with MMVD without pulmonary edema. The abscissa and the ordinate of each point represent the sensitivity and 100% – specificity rates for specific cutoff. Each curve was generated by calculating the sensitivity and 100% – specificity rates. An ANP value of 182.5 pg/mL was associated with a sensitivity of 94% and a specificity of 79%. Area under the curve = 0.88.

dogs with ISACHC Class Ib MMVD from healthy dogs with high sensitivity and specificity. Similar result was reported by Hori et al. (2011). Plasma ANP concentration differentiates ISACHC Classes Ib, II and III from Class Ia with high sensitivity and specificity, regardless of heart disease (including MMVD, dilated cardiomyopathy, patent ductus arteriosus, and ventricular septal defect) (Hori et al., 2011).

ANP is secreted in response to the stretching of the atrium that results from volume overload in the heart (Edwards et al., 1988; Hori et al., 2010). Plasma ANP concentration increased concomitantly with increase in the cardiothoracic ratio, vertebral heart score, LA/Ao, in dogs with heart disease (Hori et al., 2011; Häggström et al., 1994). In the present study, plasma ANP concentrations showed a moderate positive correlation with LA/Ao, and >59.9 pg/mL, and could discriminate the left atrial enlargement (LA/Ao ≥ 1.7) with a sensitivity of 81% and a specificity of 79%. These results indicate that plasma ANP concentration differentiates asymptomatic MMVD with enlarged heart.

The present study demonstrated that the plasma ANP concentration increases gradually with the progression of MMVD. These data are supported by a number of previous studies. For instance, the Cavalier King Charles Spaniel with naturally acquired decompensated mitral valve regurgitation, N-terminal pro-atrial natriuretic peptide (Nt-proANP) levels rose gradually during compensation and reached their highest levels in early decompensated congestive heart failure (Häggström et al., 1997).

Progression of heart failure in dogs with MMVD leads to left atrial and ventricular enlargement (Gouni et al., 2007; Lord et al.,

2010), and Perrella et al. showed a stepwise increase in left atrial ANP expression throughout the progression of congestive heart failure (Perrella et al., 1992). In addition, the stretching of the heart walls induces release of ANP from the ventricles. Luchner et al. demonstrated that left ventricular ANP gene expression and plasma ANP levels increased following the left ventricular wall stress in dogs with experimentally induced congestive heart failure (Luchner et al., 2000). These results suggest that ANP levels are elevated in dogs with congestive heart failure.

Conversely, several studies have indicated that there is reduced atrial storage of ANP in dogs with pacing-induced heart failure (Moe et al., 1989, 1991). One possible explanation is extensive cardiac tissue fibrosis associated with acute pacing-induced heart failure in dogs (Ogawa et al., 2007). Post-mortem examination revealed that cardiac tissue fibrosis is also extensive in MMVD dogs with congestive heart failure (Falk et al., 2010; O'Leary and Wilkie, 2009). Mitral regurgitation produced by mitral valve avulsion has been reported to promote the formation of interstitial fibrosis and inflammation in dog left atrium (Verheule et al., 2003). These recent research suggest that plasma ANP level affected not only cardiac enlargement but also time course and cardiac fibrosis. Therefore, acute or chronic severe mitral regurgitation may indicate lower plasma ANP level.

In summary, the present work demonstrates that the measurement of plasma ANP concentration can be used for early diagnosis and monitoring of MMVD severity. An earlier study reported a greater median survival in dogs with heart failure and plasma ANP <95 pg/mL (Greco et al., 2003). In contrast, the ROC analysis presented here identifies, for the first time, a cut-off value that can be used to identify MMVD even before the emergence of symptoms. The prognosis of dogs with MMVD is currently very poor, with a median survival time of 6–7 months after diagnosis (Borgarelli et al., 2008; Serres et al., 2007). Regular monitoring of plasma ANP levels of dogs over the age of 9 years might detect the onset of MMVD disease before irreversible damage to the heart. This examination might provide a window of opportunity for successful early intervention.

In conclusion, plasma ANP levels correspond to the severity of MMVD, including asymptomatic MMVD, and with left atrial enlargement.

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短　報

抗血栓療法で良好に維持している左心室腔内血栓症の犬の1例

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要　　約

犬の血栓塞栓症はまれである．われわれは，末梢性動脈血栓塞栓症及び左心室腔内における血栓形成が疑われる犬に遭遇した．症例はボーダー・コリー，避妊雌，4歳9カ月齢，両後肢の起立困難，肢端の冷感が突然認められたことから末梢性動脈血栓塞栓症が疑われた．また，心臓超音波検査にて左心室腔内心尖部に突出した腫瘤（20.6 × 18.5mm）が認められ，その経過から左心室腔内血栓を疑い，ダルテパリンナトリウム及び塩酸オザグレルの投与を行った．投与後7日で腫瘤は13.1 × 4.9mmまで縮小し，第58病日から歩行可能となり，第79病日に腫瘤は消失した．血栓の確定診断は，外科的除去による病理学的検査が必要だが，内科療法により短期間で消失したことから，腫瘤は血栓であると判断した．本症例では抗血栓療法による血栓形成の抑制により血栓を溶解に導くことができたと考えられた．

――キーワード：低分子ヘパリン，心筋梗塞，塩酸オザグレル，血栓症．

日獣会誌　66，52～56（2013）

血栓塞栓症は心臓内や血管内で形成された血栓により血流が遮断される疾患である．人においては血栓症の発症要因としてVirchowの3要因，すなわち①血管壁の性状変化，②血液成分の変化，③血流の変化が提唱されている［1］．血栓塞栓症は猫における発生が多く［2］，犬における血栓塞栓症はまれである．犬における血栓塞栓症の危険因子として，感染性心内膜炎が一般的であるが，副腎皮質機能亢進症，免疫介在性溶血性貧血，敗血症，蛋白漏出性腎症または蛋白漏出性腸症に併発する傾向がある［3, 4］．治療方法は，直接血栓を除去する外科療法，ヘパリン，ワルファリンなどの抗血栓療法，組織型プラスミノーゲンアクチベーター（t-PA）製剤などの血栓溶解療法がある［5, 6］．しかし，各治療法の問題点として，①外科療法は麻酔の危険性及び手術侵襲，②抗血栓療法は非侵襲的ではあるが効果が不十分なこと，③血栓溶解療法は虚血再灌流障害による高カリウム血症や代謝性アシドーシスなどを起こして死亡することが挙げられる［7, 8］．このため，人及び犬において標準的な治療指針はいまだ確立されていない．

われわれは，原疾患が明らかでない犬における左心室腔内血栓症及び末梢性動脈血栓塞栓症を経験した．抗血栓療法のみで症状の改善が認められ，良好な経過を観察しているのでその概要を報告する．

症　　例

症例は，ボーダー・コリー，避妊雌，4歳9カ月齢，

表1　第6病日から第420病日までの血液検査

病　日		6	13	22	30	79	100	420
RBC	($10^4/\mu l$)	389	287	521	501	550	601	734
WBC	($10^2/\mu l$)	328	488	202	176	132	116	56
Hct	(%)	28	23	38	36	40	41	44
PLT	($10^4/\mu l$)	7.5	40.4	34.5	41.8	47.2	39.3	36.0
CRP	(mg/dl)	6.2	5.2	5.7	7.7	3.1	0.0	0.1
総蛋白	(g/dl)	5.4	7.0	8.2	7.6	7.3	6.8	7.0
ALB	(g/dl)	1.1	1.6	2.2	2.3	2.4	2.7	3.4
ALKP	(IU/l)	244	243	322	263	205	166	79
ALT	(IU/l)	296	59	25	16	＜10	＜10	35
AST	(IU/l)	67	41	7	24	11	39	27
BUN	(mg/dl)	22	20	20	16	18	208	18
CREA	(mg/dl)	0.8	0.7	0.7	0.8	0.8	0.8	1.0
CK	(IU/l)	270	—	—	—	—	61	60
PT	(秒)	10.2	—	—	—	10.1	—	—
APTT	(秒)	24.2	—	—	—	＜15	—	—
Fibrinogen	(mg/dl)	246	—	—	—	443	—	—
AT	(%)	56	—	—	—	87	—	—
FDPs	(μg/ml)	10	—	—	—	—	—	—

基準範囲：PT 6～9秒，APTT 15～21秒，
Fibrinogen 200～400 mg/dl，AT 75～135%，
FDP 4 μg/ml 以下
—：検査実施せず

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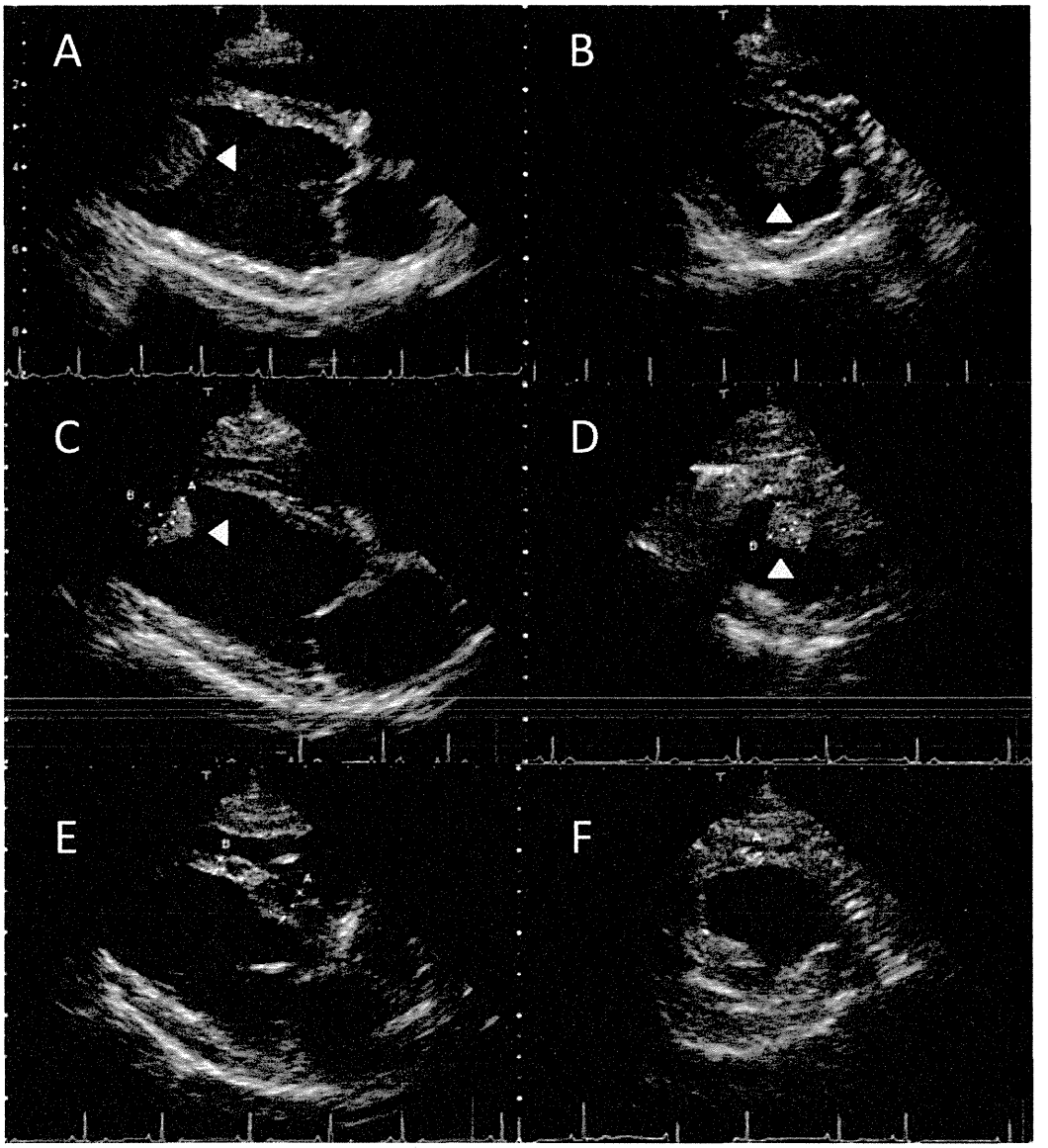

図1　心臓超音波検査所見

第6病日（A，B），第30病日（C，D），第79病日（E，F）の心臓超音波検査所見を示す．第79病日で腫瘤状エコー病変部（白矢頭）が消失した．A，C，Eは右側傍胸骨長軸四腔断面像，B，D，Fは右側傍胸骨短軸断面像乳頭筋レベルである．

体重14.5kg．2010年8月上旬に近医にて左後肢前十字靱帯損傷のためメロキシカム及びフィロコキシブが投与されていた．投薬24日目に総白血球数（34,900/μl）増加，投与27日目（第0病日）に突然の両後肢起立困難となり，股動脈圧の触知不可，爪床及び肉球の蒼白及び排尿排便困難が認められた．臨床徴候より末梢性動脈血栓塞栓症を疑った．ヘパリン，ジピリダモール，グリチルリチン酸モノアンモニウム，グルタチオン，シルデナフィルクエン酸塩が投与され，輸液として乳酸リンゲルが処置された．第6病日に日本大学付属動物病院循環器科に紹介された．

来院時の一般検査では，元気消失，起立不能，両後肢の疼痛，浮腫及び冷感があった．股動脈圧は微弱だが触知可能であった．血液検査では，総白血球数32,800/μl，C反応性蛋白濃度（CRP）6.2mg/dl，クレアチニンキナーゼ270IU/lは高値を示し，ヘマトクリット値28％，血小板数75,000/μl，アルブミン値1.1g/dlは低値を示した（表1）．また，線溶系及び血液凝固検査ではプロトロンビン時間（PT）10.2秒，活性化部分トロンボプラスチン時間（APTT）24.2秒，血漿フィブリノーゲン濃度246mg/dl，アンチトロンビン（AT）56％，フィブリン分解産物（FDP）10μg/mlであった．SpO_2は右後肢が96％，左後肢が95％であり，心電図検査（α6000 AX-D，フクダ エム・イー工業㈱，東京）にて不整脈は認められなかった．胸部X線検査にて心拡大は認められず（椎骨心計測比：10.5v，心胸郭比：63.7％），肺野

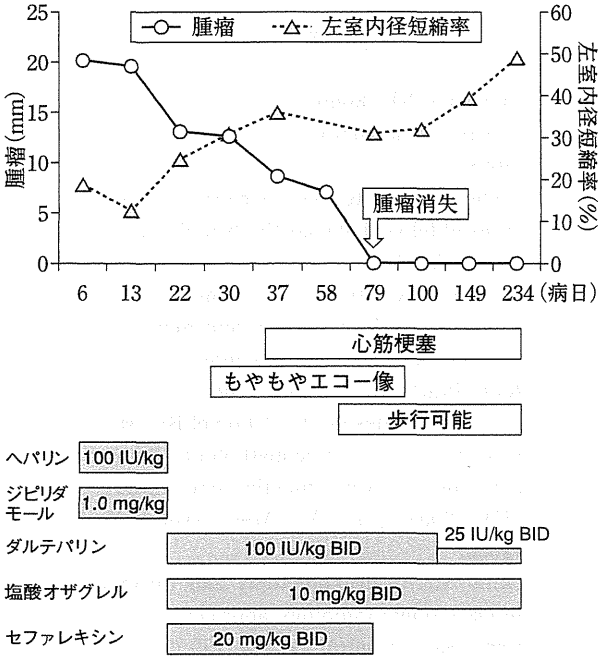

図2　腫瘤サイズ及び左室内径短縮率の推移．左縦軸は腫瘤サイズを，右縦軸は左室内径短縮率を示す．

に異常は認められなかった．心臓超音波検査（APLIO SSA-770A，東芝メディカルシステムズ㈱，栃木）では，左室内径短縮率は18.8％，左心房/大動脈比は1.46であり，心室中隔壁の高エコー性及び左心室腔内においてもやもやエコー像が認められた．また，左心室腔内心尖部に突出した高エコー性の腫瘤（20.6 × 18.5mm）が認められた．本腫瘤は左心室腔内心尖部に有茎状に付着し，血流に伴う可動性が確認された．心臓腫瘤の確定診断には外科的生検あるいは除去による病理学的検査が必要であるが，侵襲性が高い手技を選択しなければならない．そのため，本症例では心臓超音波検査及び血液検査の結果から心臓腫瘍あるいは血栓と仮診断した．

また，本症例では両後肢の疼痛，蒼白，股動脈圧消失，不全麻痺及び運動麻痺が認められたことから，末梢性動脈血栓塞栓症の発症も疑われた．末梢性動脈血栓の診断は超音波検査もしくは造影検査が必要であるが，本症例では臨床徴候から末梢性動脈血栓塞栓症と仮診断した．また，末梢性動脈血栓塞栓症の確定診断は，外科的除去術による病理学的検査が必要であるが，本症例では診断的治療として内科療法を選択した．

第13病日まで，ヘパリン加生理食塩水輸液，ジピリダモール，グリチルリチン酸モノアンモニウム，グルタチオン，シルデナフィルクエン酸塩の処置を継続したが，臨床徴候の改善は認められず，努力性呼吸が認められた．また，心臓超音波検査にて左室内径短縮率は12.6％，ヘマトクリット値は23％まで低下した．第14病日に輸血300m*l*を行い，ヘマトクリット値は33％まで上昇した．さらに，投薬内容をダルテパリンナトリウム注射液（100IU/kg, SC, BID），塩酸オザグレル（10mg/kg, PO, BID），セファレキシン（20mg/kg, PO, BID）に変更した．第22病日に呼吸状態は改善し，ヘマトクリット値は38％まで上昇した．血液検査では総白血球数20,200/μlが低下し，アルブミン値2.2g/d*l*は上昇した．また，心臓超音波検査にて，腫瘤は13.1 × 4.9mmに縮小したが，左心室腔内にもやもやエコー像が認められた．第30病日に心室中隔心尖部領域の運動性低下及び菲薄化が認められた．

本症例は第58病日から歩行可能となった．第79病日に左心室腔内に腫瘤は認められなくなり，第79病日の線溶系及び血液凝固検査ではPT 10.1秒，APTT＜15秒，血漿フィブリノーゲン濃度443mg/d*l*，AT87％であった．第95病日に左心室腔内のもやもやエコー像は消失した（図1，2）．第234病日までダルテパリンナトリウム（25IU/kg, SC, BID）及び塩酸オザグレル（10mg/kg, PO, BID）の投与は継続された．現在，第420病日が経過しているが，一般状態は良好で左心室腔内に腫瘤は認められず，心室中隔壁に大きな変化はない．血液検査の異常及びその他心臓に異常は認められない．

考　　察

本症例は，左心室腔内に腫瘤及び末梢性動脈血栓塞栓症を発症したが，抗血栓療法により両疾患ともに改善が認められた．

本症例では，第6病日に左心室腔内に腫瘤が確認され，心臓腫瘍あるいは血栓の可能性が考えられた．左心室腔内の高エコー性腫瘤は，粘液腫または血栓である可能性が高い．しかし，両者に超音波検査における診断的特徴はなく，確定診断には病理学的検査を必要とする［9］．心臓腫瘍であった場合は外科的除去術が有効であるが，侵襲が高い．血栓であった場合は内科的治療により改善する可能性もあるため，今回は外科的除去術を選択しなかった．また，組織型プラスミノーゲンに選択的に作用し血栓を特異的に分解するt-PA製剤などの血栓溶解療法は，出血傾向及び血栓溶解後に生じる虚血再灌流障害の発生率が高いことが報告されている［8］．特に獣医領域での血栓塞栓症は血流障害の発現から治療を開始するまで長時間経過している場合が多く，虚血再灌流障害を惹起する可能性が高い．このため本症例ではt-PA製剤などによる血栓溶解療法を実施しなかった．

本症例で選択した薬剤は，トロンボキサンA_2合成酵素阻害薬及び低分子ヘパリンである．血管内皮に接着した血小板は，トロンビン，トロンボキサンA_2，アドレナリンなどを遊離し，付近の血小板を凝集させるため［7］，血小板凝集抑制及び血管拡張作用を示すトロンボキサンA_2合成酵素阻害薬［10, 11］を選択した．また，APTT

を延長させずに第Xa因子を阻害する低分子ヘパリン[12]は，未分画ヘパリンに比較して作用が緩徐であり，腎不全，過体重，妊娠動物を除き，薬効モニタリングの必要性が低い利点がある．これら両薬剤の併用は持続性のトロンビン産生を抑制することが知られている[13]．本症例では左心室腔内の腫瘤が短期間で退縮したことから，腫瘤は血栓であったと考えられた．

左心室腔内血栓症に関連する疾患は，心筋梗塞，感染性心内膜炎の報告があるが，発症の原因はいまだ解明されていない[9]．本症例では起立困難を呈する（第0病日）前に総白血球数が増加し，第6病日に血小板数の低値，APTTの延長，ATの低値及びFDPの高値を示したことから播種性血管内凝固症候群（DIC）であったと考えられた．人において敗血症による感染性心内膜炎及びDICが，血行動態と微小血管の機能不全を誘引し，急性の冠状動脈血栓症を引き起こす[14]．また，犬においては感染性心内膜炎に続発する冠状動脈の敗血症性塞栓症が知られている．本症例では第6病日に左心室の可動性低下，第6病日から第13病日までに左室内径短縮率の低下，第22病日に左心室内もやもやエコー像，第30病日に心室中隔部の局所的な運動性低下，心室壁の菲薄化及び高エコー性所見が認められたことから敗血症による感染性心内膜炎により，冠状動脈の血栓塞栓症が生じ，急性心筋梗塞が生じたと示唆された．心筋梗塞後，心筋の局所的な運動性低下[15-17]が左心室腔内血栓症を誘引した．第30病日までに冠状動脈側副路の発達により冠状血流量が増加し心筋梗塞部位が縮小するとともに[18]，左室内径短縮率が改善したと考えられた．

また，犬の末梢性動脈血栓塞栓症はまれな疾患であり，好発犬種，雌雄差は認められない[19]．発症の原因はいまだ解明されていないが，敗血症による蛋白異化亢進は低アルブミン血症を誘引し，末梢性動脈血栓塞栓症の原因となる[20, 21]．さらに第0病日前に投与されていた選択的シクロオキシゲナーゼ-2阻害薬の投与は血管壁の性状変化及び血小板の活性化を誘引することで血栓塞栓症のリスク因子となる[22]．また末梢性動脈血栓塞栓症の基礎疾患として，血液粘稠度の亢進，血管炎などの炎症性疾患の存在を考慮する必要がある．本症例では心筋梗塞による左心室腔内の血液うっ滞，敗血症による血管内皮からの組織因子産生，抗凝固性蛋白であるトロンボモジュリンの発現及び血管内皮由来のプラスミノーゲンアクチベーターの産生抑制[23]，DIC，選択的シクロオキシゲナーゼ-2阻害薬などにより末梢性動脈血栓塞栓症を引き起こしたと考えられた．

本症例では，抗血栓療法により左心室腔内の血栓と思われる腫瘤を溶解させることができた．獣医療では，血栓塞栓症の標準的な治療法はいまだ確立されていないため，今後さらなる検討が必要である．

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