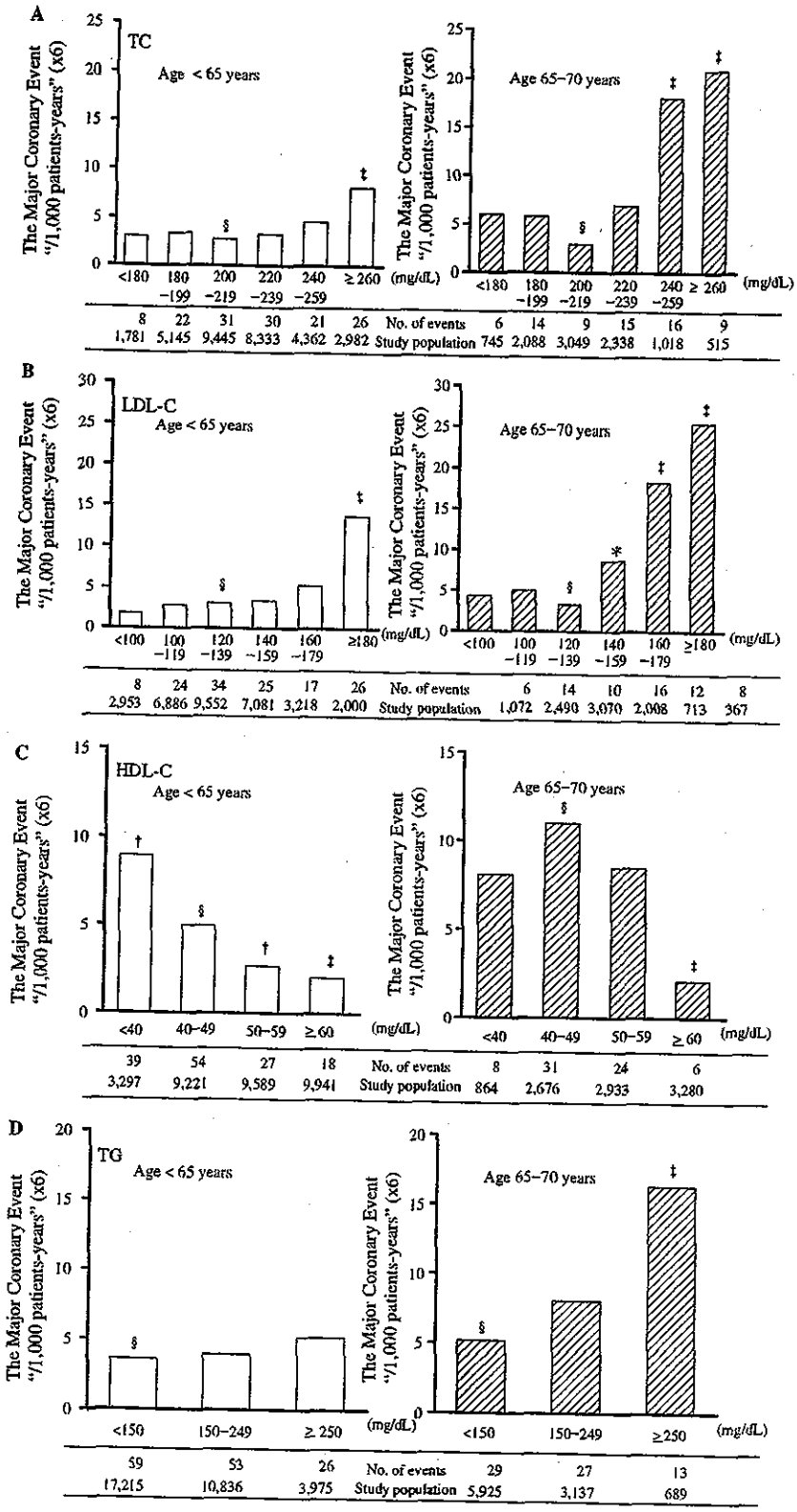

Figure 1. The relationship between the incidence of major coronary events and (A) serum total cholesterol TC, (B) low density lipoprotein-cholesterol LDL-C, (C) high density lipoprotein-cholesterol (HDL-C), and (D) triglyceride (TG) levels in the older and younger groups. The incidence rate of major coronary events was assessed using a Cox proportional hazards model according to stratified mean lipid levels during the follow-up period as indicated in the figures. These data were adjusted for sex, hypertension, diabetes mellitus, and smoking. *$P<.05$; †$P<.01$; ‡$P<.001$ versus reference category. Reference categories: TC = 200–219 mg/dL, LDL-C = 120–139 mg/dL, HDL-C = 40–49 mg/dL, and TG = <150 mg/dL.

coronary events increased as serum TC level elevated, and the increase was accentuated in patients with levels of 240 mg/dL or greater in the older group and 260 mg/dL or greater in the younger group (Figure 1A). Similarly, major coronary events increased in an LDL-C level–dependent manner in both groups, and the increase was accentuated in patients with levels of 140 mg/dL or greater in the older group and 180 mg/dL or greater in the younger group (Figure 1B). In a linear regression model, the incidence rate of major coronary events increased by 1.7% with an elevation of each 1 mg/dL LDL-C level in both age groups, although the absolute risk was higher in the older group (data not shown).

Major coronary events decreased as HDL-C level increased in the younger group, whereas in the older group major coronary events were higher in patients with levels lower than 60 mg/dL and declined abruptly in patients with levels of 60 mg/dL or greater (Figure 1C). Major coronary events in the younger group were not correlated with TG level. In the older group, major coronary events increased as TG level increased (Figure 1D).

DISCUSSION

The J-LIT study was the first successful large-scale prospective observational study in Japan. The overall results of the study clearly showed that the risk of CHD was positively correlated with LDL-C level and inversely correlated with HDL-C level in Japanese patients with hypercholesterolemia.[14,15] In this report, the J-LIT data of patients aged 65 to 70 without prior CHD were compared with those of patients aged 35 to 64. It was demonstrated that cholesterol-lowering treatment with simvastatin for older Japanese patients was as safe and effective as for the younger patients and that the absolute risk of CHD in older patients was approximately twice that of younger patients at any LDL-C level. Nonetheless, the LDL-dependent increase of the relative risk of CHD was similar.

Mean baseline TC (267 mg/dL) and LDL-C (181 mg/dL) levels in the older group decreased to 215 mg/dL (−19.5%) and 130 mg/dL (−28.2%), respectively, during the treatment. These values were similar to those in the younger group. In the J-LIT study, most patients (97%) took 5 mg/d of simvastatin. Why such a low dose of simvastatin reduced LDL-C levels by 28% in Japanese patients is not clearly understood.

The incidence of major coronary events, including fatal and nonfatal MI, and sudden cardiac death was 1.30 per 1,000 patient-years in the older group and 0.80 per 1,000 patient-years in the younger group. There were fewer men in both groups, possibly because more women than men are treated for hypercholesterolemia in Japan.[25] Additionally, there was a lower percentage of men in the older group than in the younger group (21.2 vs 35.1%). In male patients, the incidence rate of major coronary events was 2.45 per 1,000 patient-years in the older group and 1.41 per 1,000 patient-years in the younger group. In female patients, the incidence rate was 1.00 per 1,000 patient-years and 0.47 per 1,000 patient-years, respectively. The incidence rate of major coronary events in the older group was approximately twice as high in both sex subgroups.

The incidence rate of coronary events was potentially underestimated in the J-LIT study compared with that in the general Japanese population because all subjects were taking simvastatin, which might have direct antiatherosclerotic effects on coronary vessels[26,27] in addition to reducing lipids. In Western countries, statin treatment has been shown to reduce coronary events by 30% to 40% in primary[3,19] and secondary prevention studies.[2,17,20] If this reduction rate could be applied to the J-LIT results, the incidence of coronary events would be predicted to be approximately 1.4 to 1.6 times higher in the general Japanese population. Nevertheless, the incidence rate of coronary events in this study is much lower than in Western populations.[1,3,19] In the West of Scotland Coronary Prevention Study (WOSCOPS),[3] Scottish male hypercholesterolemic patients aged 45 to 64 (mean age 55) were followed with or without pravastatin treatment. In the pravastatin group, baseline TC level was 272 mg/dL and decreased by 20% during the follow-up period.[3] Mean age, baseline TC level, and reduction rate of TC of the pravastatin group were similar to those of the younger male group (mean age 54.9) in the J-LIT study. The incidence rate of coronary events was 11/1,000 patient-years for the pravastatin group in the WOSCOPS whereas the rate was 1.41/1,000 patient-years for the younger male group in the J-LIT study. Although there were differences in study conditions, the incidence of coronary events in Japanese male patients under statin treatment was one-eighth that of Scottish male patients.

The relative risk of major coronary events increased by 1.7% with an elevation of each 1 mg/dL in LDL-C level in both age groups, whereas the absolute risk at any level of TC and LDL-C was higher in the older group. The incidence rate of major coronary events markedly increased with TC level above 240 mg/dL and LDL-C level above 140 mg/dL in the older group. These TC and LDL-C levels were 20 and 40 mg/dL lower than those in the younger group, respectively. Generally, high-risk patients are good candidates for preventive medicines. In this viewpoint, elderly patients might receive more benefit from lipid-lowering therapy, but lipid intervention trials are required to establish the therapeutic benefits and strategies in elderly Japanese.

The preventive effect of HDL-C was also observed in the Japanese population. In the older group, the incidence of major coronary events decreased with HDL-C level above 60 mg/dL, whereas the incidence was HDL-C level–dependent in its wide range in the younger group. The role of TG level for the development of coronary events is controversial,[28] although the evidence is accumulating.[29] In the J-LIT study, TG level above 250 mg/dL was associated with a greater risk of major coronary events in the older patients, whereas no such relationship was observed in the younger group.

The incidence rate of ischemic cerebrovascular events, including cerebral thrombosis and infarction, transient ischemic attack, and reversible ischemic neurological deficit, was 2.61 per 1,000 patient-years in the older group and 1.29 per 1,000 patient-years in the younger group. The ratio of the incidence rate of ischemic cerebrovascular events (the older group/the younger group, 2.02) was larger than that of major coronary events (1.63), suggesting that aging may affect the occurrence of ischemic cerebrovascular events more strongly than of coronary events in the Japanese population.

In summary, the LDL-C level–dependent increase of the relative risk of CHD was similar in elderly and younger patients, whereas the absolute risk at any TC and LDL-C level in elderly patients was twice as high as in younger patients. Further lipid intervention trials would be required to establish the therapeutic benefits and strategies in elderly Japanese.

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Feasibility of the Inoue single-branched stent-graft implantation for thoracic aortic aneurysm or dissection involving the left subclavian artery: Short- to medium-term results in 17 patients

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Objective: This study assessed the short- to medium-term clinical results of the Inoue single-branched stent graft for repair of thoracic aortic aneurysms or dissections involving the left subclavian artery.
Methods: A retrospective review of experiences at two institutions was performed. We analyzed the data of consecutive 17 patients with thoracic aortic aneurysms or dissections who underwent endovascular repairs with the Inoue single-branched stent graft between July 1999 and April 2004. Complete baseline and follow-up data were available on all patients. The mean age was 71 ± 9 years, and 13 of the patients (76%) were men. Eight patients (47%) were considered unfit for open surgery because of advanced age or the presence of comorbid diseases.
Results: The stent grafts were successfully delivered and deployed in all 17 patients. Periprocedural major complications, defined as those that caused any persistent disorder, occurred in one patient who developed spinal ischemia. A postoperative computed tomographic scan revealed three attachment site endoleaks; two endoleaks were from the proximal attachment sites and one endoleak was from the distal attachment site. The mean follow-up period was 26 months (range, 7 to 65 months). Two deaths occurred in the follow-up period from cerebral bleeding and pneumonia, both considered unrelated to the stent grafting. Two patients with attachment site endoleaks needed secondary stent-grafting; one patient required the implantation of a straight stent-graft in the distal attachment site and the other, the implantation of a double-branched stent-graft. Another patient with attachment site endoleak was considered very high-risk for open surgery or secondary stent grafting and did not undergo secondary intervention. The aneurysmal sac size of the patient has been stable for 28 months. The branched section of the stent graft was patent in all patients in the follow-up period.
Conclusion: The results demonstrate the feasibility of the Inoue single-branched stent graft for thoracic aortic aneurysms or dissections involving the left subclavian artery. (J Vasc Surg 2005;41:206-12.)

Open surgical repair is considered the traditional treatment for patients with thoracic aortic aneurysms. Despite recent advances in surgical techniques and anesthetic management, the surgical repair of thoracic aortic aneurysms is still associated with significant mortality and morbidity.[1] Endovascular stent grafting of thoracic aortic aneurysms is emerging as an alternative method for repair in selected patients.[2,3] Although endovascular stent grafting is less invasive than open surgical procedures, involvement of branch vessels in the aortic arch limits the application of stent grafting.

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Competition of interest: Dr Kanji Inoue holds all patents of the Inoue stent graft, which was developed and made by Dr Inoue. Dr Kanji Inoue is the only author who holds patents of the stent graft.
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Thoracic aortic aneurysms that involve the left subclavian artery are not rare. In the combined results of the EUROSTAR and the United Kingdom Thoracic Endograft registries, it was necessary to place a stent graft over the left subclavian artery in 17% of the patients.[4] Thurnher et al[5] reported that they required subclavian artery transposition in 24% of their cases.

Our method of managing the left subclavian artery is to provide a stent graft with a side branch. This method does not require the surgical revascularization of the left subclavian artery. This study assessed the short- to medium-term clinical results of Inoue single-branched stent-graft implantations for thoracic aortic aneurysms involving the left subclavian artery.

METHODS

Patients. Between July 1999 and April 2004, endovascular grafting with the Inoue single-branched stent graft was undertaken in 17 patients with thoracic aortic aneurysms or dissections at Kokura Memorial Hospital, Kokura and Kyoto University Hospital, Kyoto, Japan. All patients gave their informed consent in conformance with the protocols approved by the institutional review board of each

Table I. Demographics and comorbidities of the patients

Patients	*Sex*	*Age*	*Etiology*	*Maximum diameter of aneurysm (mm)*	*Unfit for open surgery*	*Risk of open surgery*
No. 1	M	77	degenerative	50	No	
No. 2	F	66	aneurysmal degeneration of a long standing aortic dissection	64	No	
No. 3	M	60	chronic aortic dissection	60	No	
No. 4	M	48	chronic aortic dissection	47	No	
No. 5	M	81	aneurysmal degeneration of a long standing aortic dissection	62	Yes	Advanced age*
No. 6	M	69	acute aortic dissection	46	No	
No. 7	M	80	degenerative	61	Yes	Advanced age
No. 8	M	79	degenerative	75	No	
No. 9	M	75	chronic aortic dissection	70	No	
No. 10	M	67	degenerative	68	Yes	Cerebrovascular disease Prior thoracotomy
No. 11	M	73	degenerative	43	No	
No. 12	M	66	acute aortic dissection	39	Yes	Traumatic injury (rib fracture)
No. 13	—	74	degenerative	50	Yes	Lung disease
No. 14	F	71	degenerative	56	No	
No. 15	M	81	degenerative	70	Yes	Advanced age
No. 16	M	70	degenerative	60	Yes	Lung disease
No. 17	F	78	Ductus diverticulum	68	Yes	Lung disease

F = female; *M* = male.
*Advanced age was defined as over 79 years.

hospital. The mean age was 71 ± 9 years, and 13 patients (76%) were men. Eight patients (47%) were considered unfit for conventional surgical repair because of advanced age or the presence of comorbid diseases. The remaining nine patients rejected open surgery and strongly preferred endovascular repair.

The etiologies of the aneurysms were atherosclerotic aneurysms in nine patients, chronic dissecting aneurysms with patent false lumens in four patients, aneurysmal degeneration of long-standing aortic dissections with thrombosed false lumens in two patients, one traumatic acute aortic dissection, and one aneurysm of the ductus diverticulum.

The Inoue single-branched stent graft was placed into the distal aortic arch, including the origin of the left subclavian artery and the descending aorta. The proximal and distal landing zones required at least 10 mm in length. The front part of the proximal landing zone was at least 5 mm distal to the left common carotid artery. The mean diameter of the aneurysms was 58 ± 11 mm. The demographics and comorbidities of the patients are presented in Table I. Complete baseline and follow-up data are available on all patients.

Device. The Inoue endovascular grafting system consists of a stent graft, a detachable carrying wire, two detachable traction wires, a balloon catheter, and an introducer sheath (Fig 1). The size of the introducer sheath was determined individually, but was usually 20F to 24F.

The Inoue stent graft is constructed from a woven Dacron polyester fabric cylinder. The outside surface of the stent graft is supported with multiple rings of extra-flexible nickel titanium wire covered by Dacron filaments. Small Dacron cuffs are attached to the first and second rings from each end to improve the sealing function. The Inoue single-branched stent graft consists of an aortic section and a branched section. The aortic section and the branched section are sewn together.

The Inoue stent grafts were custom made. We used a specialized computer system for designing the Inoue stent graft.[9] A three-dimensional model was constructed from helical computed tomography (CT) images for the aneurysm. The stent graft was designed and positioned endoluminally on the computer (Fig 2). The diameter and length of each section of the stent graft was determined for each patient. The diameter of the aortic section of the graft was usually oversized by 2 mm and the branched section by 1 mm to achieve effective sealing. The ring of nickel titanium wire attached to the graft was oversized by more than 2 mm.

Each section of the stent graft was individually folded using loops of thread and nickel titanium wire. By removing the nickel titanium wire, each section of the stent graft was unfolded. Three detachable wires were also attached to the stent graft. A carrying wire was attached to the proximal end of the aortic section, and a traction wire was attached to the distal end of the aortic section. Another traction wire was attached to the branched section. The Inoue stent graft was delivered through the introducer sheath with the aid of the carrying and traction wires. A large compliant balloon was used in the dilatation of the aortic graft section. The balloon was custom made and inserted via the introducer sheath (Fig 1).

Implantation technique. All 17 procedures were performed in the cardiac catheterization laboratory under local anesthesia. The patient's femoral artery was surgically iso-

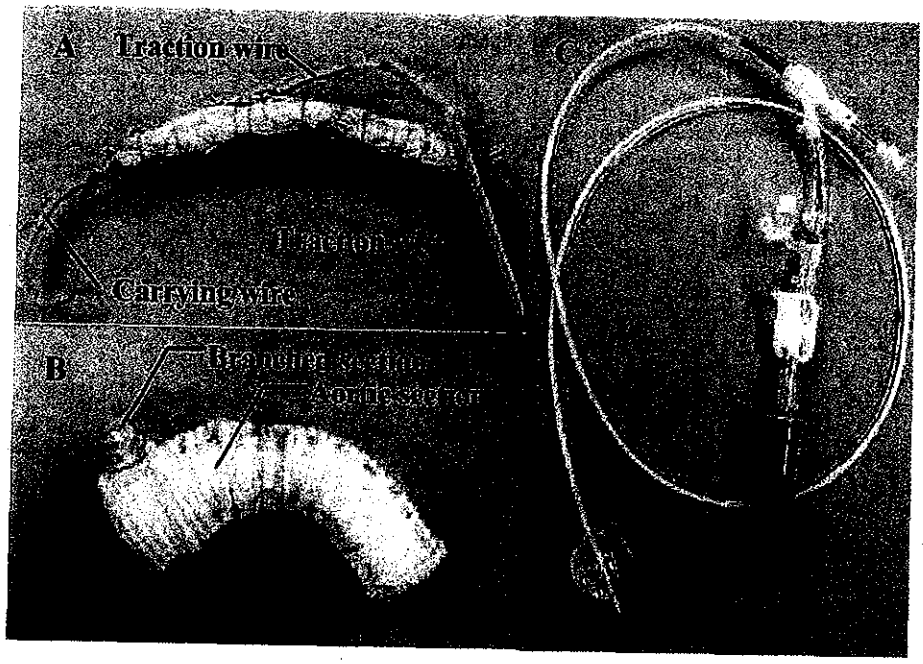

Fig 1. The Inoue single branched stent-graft (*A* and *B*) and the balloon (*C*). A. The folded state. The carrying wire is attached to the proximal end of the aneurysm. Each traction wire is attached to the branched section and the aortic section. B. The unfolded state. The stent-graft consists of the aortic section and the branched section.

lated and a transverse arteriotomy performed. A 7F sheath was inserted percutaneously in the left brachial artery. The introducer sheath was inserted through the femoral artery and advanced to the descending thoracic aorta under fluoroscopic guidance. After administration of 10000 U of heparin, the folded stent graft was introduced into the sheath, advanced to the descending thoracic aorta, and released from the sheath. The folded graft was then pushed to the distal aortic arch.

A 7F catheter with a gooseneck wire was inserted through the 7F sheath in the left brachial artery. The free end of the traction wire attached to the tip of the branched graft section was caught by the gooseneck wire and then pulled back into the left subclavian artery. The carrying wire and the traction wire were manipulated to properly position the aortic and branched graft sections.

After unfolding the graft, the aortic section and the branched section of the graft were dilated by a compliant balloon. The balloon was custom made and inserted via the introducer sheath. We did not use hypotension to place the graft or for balloon inflation. The carrying wire and the traction wires prevented migration of the stent graft during balloon inflation.

The sheath was removed, and the incision was closed. Fig 3 shows a successful implantation. Detailed information concerning the implantation techniques is available in previous reports.[7,8]

Follow-up protocol. *All patients were examined with* contrast enhanced helical CT scans before hospital discharge. The scans were repeated every 6 months. The mean follow-up period was 26 months (range, 7 to 65 months).

RESULTS

The stent grafts were successfully delivered and deployed in all patients. The mean procedure time, measured *from the incision of the skin to surgical closure of the* femoral access site, was 219 ± 68 minutes. The mean contrast media used in the procedures was 249 ± 99 mL.

All patients were transferred immediately to the ward without staying in the intensive care unit. Four patients required a blood transfusion. Major complications, defined as that caused any persistent disorders, occurred in one *patient. The patient developed paraparesis that was prob*ably caused by the accidental embolization of the Adamkiewicz artery. The graft of the patient was too short to cover the location of the Adamkiewicz artery, and the preprocedural images showed irregular, shaggy mural thrombus in the thoracic aorta.

Three access site complications occurred: a lymphor*rhea, a pseudoaneurysm, and an intimal injury of the iliac* artery. The lymphorrhea was resolved without aspiration. The pseudoaneurysm was successfully repaired by surgery. The intimal injury required a metallic stent implantation in the iliac artery. The three patients with minor complications were discharged without any disorders.

Complete exclusion of the inlet of the aneurysm or the primary entry tear of the aortic dissection at the time of the first postoperative CT scan was achieved in 14 patients

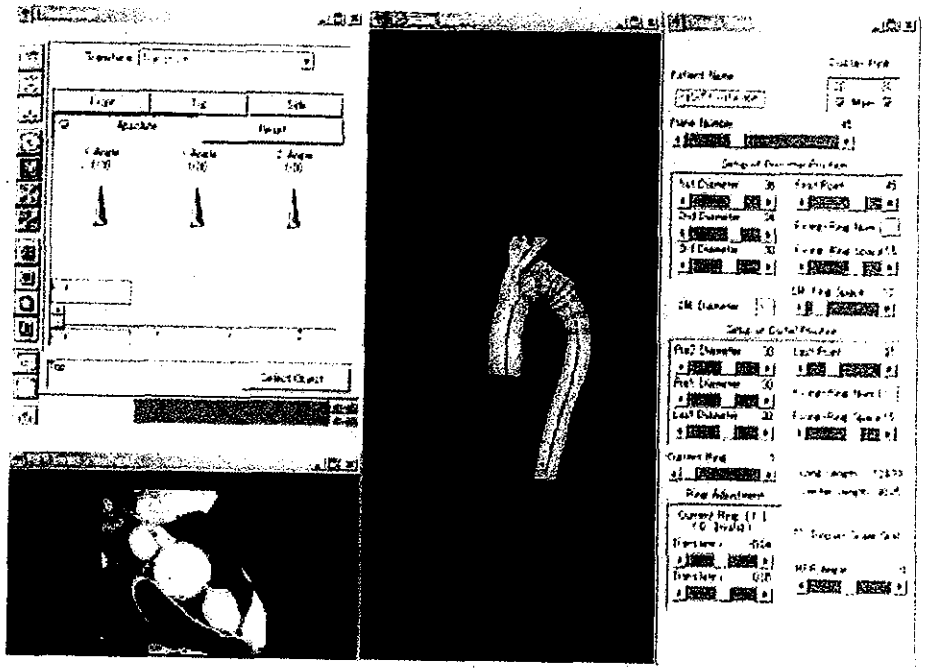

Fig 2. Monitor display of the computer program used to design the Inoue stent graft.

(82%). Attachment site endoleaks were revealed in three patients; two leaks were from the proximal attachment sites, and one leak was from the distal attachment site. The cause of the two endoleaks in the proximal attachment sites was considered unrelated to the branched section; they were instead considered caused by difficulties in implanting the stent graft in a curved position. The primary endoleak rate was 18%.

The average hospital stay after the procedure was 19 ± 27 days (range, 2 to 120). The patient who developed paraparesis required a distinctly prolonged hospital stay of 120 days for rehabilitation. All patients were discharged alive, and the 30-day mortality was 0%.

The mean follow-up period was 26 months (range, 7 to 65 months). More than a 3-mm sac size change was defined significant. Significant sac size shrinkage was achieved in 8 patients (47%). Sac size change was measured at the most recently obtained CT scan. Two of the three patients with attachment site endoleaks at the first postoperative CT scan required secondary stent grafting; one patient required implantation of a straight stent graft at the distal attachment site; the other patient required implantation of a double-branched stent graft.

Another patient with attachment site endoleak had a history of cerebral infarction, which occurred during previous open surgical replacement of a thoracoabdominal aortic aneurysm. We estimated that the risk of a repeat open surgery or secondary stent grafting procedure outweighed the risk of rupture. The aneurysmal sac size of the patient has not changed for 28 months.

Enlargement of the aneurysmal sac or secondary endoleak requiring secondary intervention has not been revealed in any of the other patients. CT scan confirmed that the branched section of the stent graft was patent in all cases. No stent graft migration occurred in any patient.

Two deaths occurred in the follow-up period. The cause of death was cerebral bleeding and pneumonia, both considered unrelated to the stent grafting. The initial and follow-up results are summarized in Table II.

DISCUSSION

Endovascular repair of thoracic aortic aneurysms may reduce morbidity and mortality.[2,3] The procedure is considered most suitable when the proximal end of the aneurysm is 1 to 2 cm from the left subclavian artery. Implantation can be difficult when the landing zone distal to the left subclavian artery is not sufficient.

Several options have been proposed to overcome this problem. The most traditional is prophylactic transposition or bypass graft placement to provide flow to the arm.[9-11] Some recent reports have described the safety of the intentional occlusion of the left subclavian artery by the stent graft without prophylactic surgical transposition. If arm, hand, or cerebral symptoms develop after coverage of the left subclavian artery, surgical revascularization of the subclavian artery is performed.[12-14] Although the early results of this option suggest that it is safe in most patients, some patients require transposition of the left subclavian artery in the follow-up.

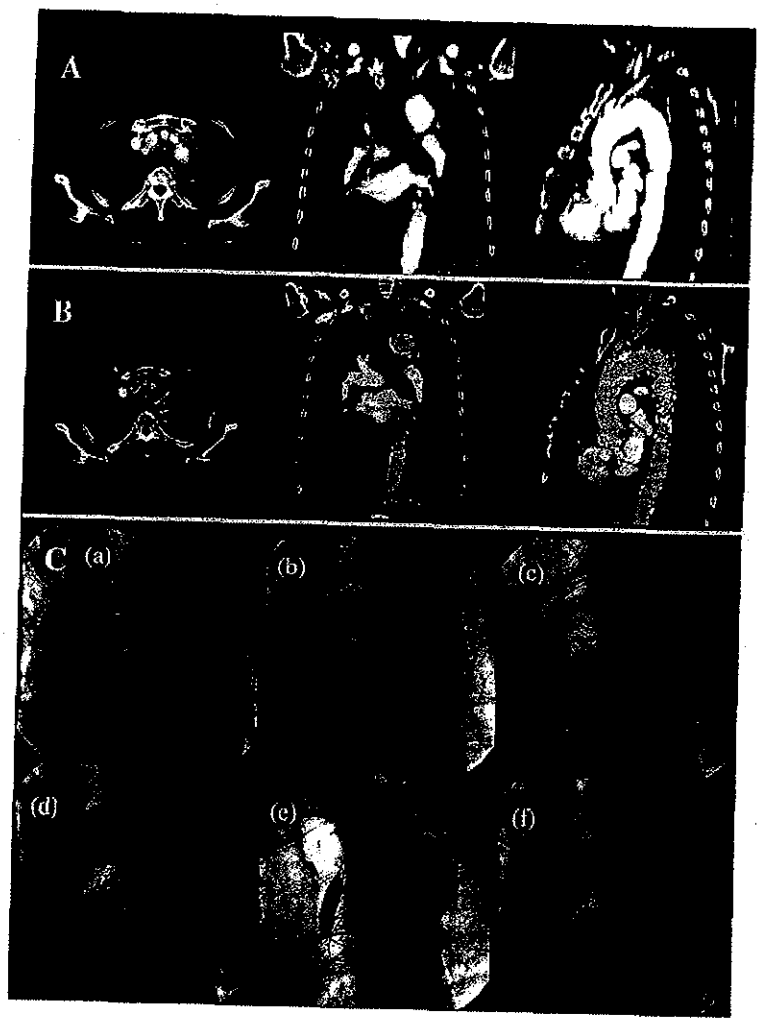

Fig 3. The successful implantation of the Inoue single-branched stent graft is shown for patient 16 in Table I. **A,** Enhanced computed tomography (CT) scan before treatment. **B,** Enhanced CT after treatment. **C,** Angiogram during the procedure. *a,* The folded Inoue stent-graft was delivered and positioned. *b,* The distal part of the aortic section of the graft was unfolded. *c,* After unfolding the proximal part of the aortic section of the graft, the distal neck was dilated. *d,* The proximal part of the aortic section was dilated. *e,* The branched section was dilated. *f,* The final angiogram revealed complete exclusion of the aneurysm.

Tiesenhausen et al[14] reported on eight patients who underwent thoracic aortic stent grafting without revascularizations of the left subclavian arteries. No immediate neurologic deficit or left arm ischemia occurred, but three patients required surgical revascularization of the left subclavian artery during follow-up. Furthermore, the occluded subclavian artery poses another problem: it may be a potential source of retrograde inflow into the excluded aneurysms or the false lumen.

Another option is to cross the origin of the left subclavian artery with the uncovered lesion of the stent graft.[15] The Talent LPS stent graft (Medtronic AVE, Santa Rosa, Calif) is usually used in this option. This option has limitations, however. The uncovered proximal stent aids in anchoring—not sealing—and leaks may occur. The uncovered stent may erode through the aorta.

Our option is to provide a stent graft with a side branch to the left subclavian artery.[7,8] This method does not require surgical transposition of the left subclavian artery and is widely applicable. However, except for the Inoue stent grafts, reports of endovascular techniques of complex aneurysm repair with branched stent grafts have been limited to animal studies and incidental case reports.[16,17]

In their initial experience with the branched stent-graft implantations, Inoue and colleagues[8] reported embolic cerebrovascular accident as the major complication. We consider that the risk of cerebral infarction is very low in the placement of a stent graft with a side branch to the left subclavian artery.

Table II. Initial and follow-up results of the patients. Corresponding patients' numbers are shown in Table I.

Patients	*Etiology*	*Hospital stay (day)*	*Complication*	*Endoleak at the first postoperative CT scan*	*Follow-up period (month)*	*Event in the follow-up period*
No. 1	Degenerative	19	No	No	65	Sac size stable
No. 2	Aneurysmal degeneration of a long standing aortic dissection	7	No	Yes (from the distal attachment site)	9	Sac size increased Secondary stent-grafting
No. 3	Chronic aortic dissection	4	No	No	54	Sac size reduced
No. 4	Chronic aortic dissection	3	No	No	53	Sac size reduced
No. 5	Aneurysmal degeneration of a long standing aortic dissection	3	No	No	50	Sac size stable
No. 6	Chronic aortic dissection	2	No	Yes (from the proximal attachment site)	35	Sac size increased Secondary stent-grafting
No. 7	Degenerative	26	Pseudoaneurysm	No	14	Sac size stable Death (cerebral bleeding)
No. 8	Degenerative	120	Paraparesis	No	9	Sac size stable Death (pneumonia)
No. 9	Chronic aortic dissection	8	No	No	35	Sac size reduced
No. 10	Degenerative	21	No	Yes (from the proximal attachment site)	28	Sac size stable
No. 11	Degenerative	29	Lymphorrhea	No	21	Sac size stable
No. 12	Acute aortic dissection	19	No	No	17	Sac size reduced
No. 13	Degenerative	13	No	No	17	Sac size reduced
No. 14	Degenerative	17	No	No	14	Sac size reduced
No. 15	Degenerative	14	No	No	13	Sac size stable
No. 16	Degenerative	10	No	No	9	Sac size reduced
No. 17	Ductus diverticulum	16	Intimal injury of the iliac artery	No	7	Sac size reduced

CT, computed tomography.

In normal human anatomy, the right common carotid artery and the right subclavian artery branch from the brachiocephalic artery, whereas the left common carotid artery and the left subclavian artery branch from the aorta directly. The right subclavian artery involves the common carotid artery, but the left subclavian artery does not. Thus, the single-branched stent-graft implantation is much safer than the double- or triple-branched stent-graft implantation in terms of the risk of cerebral infarction.

No cerebrovascular embolic events occurred in this study. Branched stent-graft implantation does not require surgical transposition of the left subclavian artery. Furthermore, this method offers another advantage: it may prevent the migration of the graft. Concerns about stent-graft migration in the long term have been reported.[18] Migration is associated with late aneurysm rupture, proximal endoleak, and graft kinking. The Inoue stent graft has no barbs to hold it in place. The branched section secures the proximal fixation and prevents later migration of the graft.

Our data suggest the feasibility of the single-branched stent-graft implantation for thoracic aorta. The Inoue single-branched stent graft offers an alternative mode of management for thoracic aortic aneurysms that involve the left subclavian artery and may expand the indication of thoracic stent grafting.

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INVITED COMMENTARY

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In the accompanying paper, Saito et al describe their use of the Inoue system, a novel prosthesis with a side branch to the left subclavian artery, to achieve promising results in 17 cases of distal aortic arch repair. The Inoue system has several unusual features that lend themselves to this particular application:

- *A supporting framework of nickel titanium rings confers great* flexibility and is capable of sealing within a very short attachment site between the left subclavian and left carotid arteries.
- A corset of diameter-restricting ties allows final adjustments in the orientation and position of the unsheathed, but still constrained, prosthesis, as the subclavian side-branch is retrieved using a transbrachial snare and drawn all the way into the subclavian artery.
- Once deployed, the fully embedded unibody side branch has less effect on proximal aortic implantation than a conventional (external) modular attachment cuff that would have to remain within the aorta.

Their results show that the technique appears to be both safe and effective in the short-to-medium term: serious complications were rare, aneurysm dilatation was rare, and most type I endoleaks were treatable by endovascular means. Yet, it is too early to say that this approach is clearly better than the endovascular alternatives.

The attachment means is one cause for concern. Unbarbed nickel titanium rings have not generally been effective in preventing late-occurring migration and type I endoleak. An oversized ring buckles, distorts the profile of the attached graft orifice, and induces dilatation of the surrounding aorta, whereas an undersized ring exerts no outward force and produces neither seal nor resistance to migration. The stated 2% oversizing used by Inoue et al contains no margin for error. Perhaps the side branch of the Inoue device helps secure stent-graft position, but it would help more if it had the stiffness of a stent rather than the flexibility of a series of rings.

Stroke is notably absent from the current report. In previous reports, endovascular repair of the distal arch has often been complicated by embolic stroke, and multibranched versions of the current system are no exception. The current single-branched version requires less manipulation but does not altogether avoid instrumentation of the ascending aorta and arch. I suspect this system could still produce a high stroke rate in less experienced hands, which together with the high cost of customized device manufacture, would impede widespread application.

The most widely practiced alternative involves stent-graft coverage of the subclavian artery origin. Some provision for subclavian flow must be made in any patient with an internal mammary coronary graft, a dominant left vertebral artery, a high risk of paraplegia (distal thoracic aortic aneurysm or dissection), subclavian steal, or left arm claudication. I remain to be convinced that the single side-branch is superior to carotid-subclavian bypass or transposition.

Circ J 2004; **68:** 1160–1164

Combined Measurements of Cardiac Troponin T and N-Terminal Pro-Brain Natriuretic Peptide in Patients With Heart Failure

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Background To examine the prognostic contribution of combined cardiac troponin T (cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients with heart failure (CHF) in the absence of acute coronary syndrome.

Methods and Results Between July 2001 and March 2002, 71 consecutive patients (mean age=68.4±1.4 years, 37 men), hospitalised for heart failure, were studied during hospitalisation and follow up until December 2002. Serum cTnT and NT-proBNP were measured on admission. Actuarial rates of adverse cardiac events, including sudden or CHF death, or rehospitalisation for CHF during follow up were compared with patients grouped according to initial serum cTnT and/or NT-proBNP concentrations. The adverse cardiac event-free rate among the 20 patients with cTnT≥0.01 ng/ml was significantly lower than the 51 patients with cTnT<0.01 ng/ml ($P<0.05$). Similarly, the adverse cardiac event-free rate among the 36 patients with NT-proBNP≥1,357 pg/ml (median) was significantly lower than the 35 patients with NT-proBNP<1,357 pg/ml ($P<0.01$). The 16 patients with high concentrations of both cTnT and NT-proBNP had a lower adverse cardiac event-free rate than the 31 patients with low cTnT and low NT-proBNP upon commencement of the study ($P<0.005$).

Conclusion Measurements of serum cTnT and NT-proBNP were reliable prognostic markers of adverse cardiac event in patients with CHF. (*Circ J* 2004; **68:** 1160–1164)

Key Words: Heart failure; Pro-brain natriuretic peptide; Prognosis; Troponin

Chronic heart failure (CHF) is associated with a dismal long-term prognosis and remains a major health concern world wide!,2 While various management strategies have become available, clinical tools to stage CHF remain few. The New York Heart Association (NYHA) functional classification, along with several tests, including chest roentgenogram, echocardiogram, myocardial scintigraphy, cardiopulmonary exercise, and hemodynamic measurements are useful to estimate the degree of CHF, although they are subject to inter-observer variations in interpretation[3,4] Serial measurements of reliable and objective biochemical markers would be advantageous to monitor the long-term prognosis of patients with CHF.

The troponin complex consists of 3 proteins attached to the actin thin filament, known as subunits I, T, and C, which regulate the force and velocity of muscle contraction. Cardiac troponin T (cTnT) is a highly sensitive and specific marker of myocardial injury in acute coronary syndromes, and a revised definition of acute myocardial infarction has been developed, based on rises in cardiac troponins in the blood[5,6] We found that patients with idiopathic dilated cardiomyopathy, who had a particularly poor prognosis, had increased serum concentrations of cTnT in the absence of significant coronary stenoses[7–10] Most patients with poor outcomes had persistently high cTnT. This often occurred during periods when CHF was stabilised by conventional treatment, and there was no evidence of dyspnea, roentgenographic and auscultatory signs of pulmonary congestion[8,9] Therefore, an increase in serum cTnT concentrations seems to be a reliable indicator of ongoing subclinical myocyte injury rather than an indicator

Table 1 Demographic and Baseline Clinical Characteristics of Study Population (n=71)

Age, mean±SE (years)	*68.4±1.4*
M/F	*37/34*
NYHA functional class I/II/III/IV	*10/22/22/17*
Underlying heart disease	
Dilated cardiomyopathy	*20 (28)*
Hypertrophic cardiomyopathy	*8 (11)*
Ischemic	*8 (11)*
Congenital or valvular	*22 (31)*
Hypertensive	*9 (13)*
Other	*4 (6)*
Oral drug regimen	
β-adrenergic blockade	*24 (34)*
ACEI or ARB	*33 (46)*
Spironolactone	*33 (46)*
Furosemide	*49 (69)*

Unless indicated otherwise, values are number (%) of patients. Other heart diseases include incessant tachyarrythmias (n=2), cardiac amyloidosis (n=1) and restrictive cardiomyopathy (n=1).
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NYHA, New York Heart Association.

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Table 2 Mean NT-ProBNP, CK, Age, and LVEF Among Patients With High and Low cTnT Values at Time of Hospital Admission

	NT-proBNP (pg/ml)	CK (IU/L)	Age (years)	LVEF (%)
cTnT high (n=20)	13,260±5,035*	90.2±9.2	68.5±3.5	49.6±3.1
cTnT low (n=51)	1,847±311	91.8±6.1	68.3±1.5	53.9±2.7

*P<0.001, other between-group differences are not statistically significant.
CK, creatine kinase; cTnT, cardiac troponin T; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 3 Comparison Between Patients With and Without Cardiac Decompensation

	Decompensation (+) (n=45)	Decompensation (–) (n=26)
Age, mean±SE (years)	70.4±1.7	64.8±2.4
M/F	21/24	16/10
LVEF (%)	49.5±2.5	58.1±3.6
NYHA functional class I/II/III/IV	0/12/16/17	10/10/6/0
TnT positive (%)	16/45 (35)	4/26 (15)
Mean TnT of positive patients (ng/ml)	0.037±0.004	0.038±0.002
NT-proBNP (pg/ml)	7,233±2,369	1,303±291*
Creatinine (mg/dl)	1.1±0.1	1.0±0.1
Underlying heart disease		
Dilated cardiomyopathy	14 (31)	6 (23)
Ischemic	5 (11)	3 (11)
Congenital or valvular	14 (31)	8 (31)
Hypertensive	8 (17)	1 (4)
Oral drug regimen		
β-adrenergic blockade	12 (27)	12 (46)
ACEI or ARB	22 (48)	11 (42)
Spironolactone	26 (58)	7 (27)*
Furosemide	37 (82)	12 (46)**
Cardiac event (%)	10 (22)	0 (0)*

*P<0.05, **P<0.01
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; TnT, Troponin T.

of circulatory congestion.

However, N-terminal pro-brain natriuretic peptide (NT-proBNP) represents the N-terminal fragment of pro-BNP, the high molecular weight precursor of biologically active BNP. N-terminal pro-brain natriuretic peptide has a relatively long half-life and is stable in whole blood. Concentrations of NT pro-BNP are increased in patients with CHF and correlate with prognosis[11–13] Since CHF is a complex clinical syndrome, a single biomarker may not reflect all of its characteristics. Theoretically, cTnT is a marker of myocyte injury while NT-proBNP reflects cardiac load.

This study examines the contribution of combined measurements of cTnT and NT-proBNP in patients with CHF in absence of acute coronary syndrome.

Methods

Subjects

The study population consisted of 71 consecutive patients admitted to our hospital between July 2001 and March 2002 for the management or evaluation of decompensated CHF. No patient had suffered a myocardial infarction or unstable angina pectoris within 3 months prior to hospitalisation, and no electrocardiographic changes or increase in creatine kinase (CK) were present upon admission. The criteria for a diagnosis of left heart decompensation on initial presentation used in this study were: (1) dyspnea or orthopnea requiring emergency hospitalisation, intravenous furosemide, and infusion of nitrates or inotropic agents, and (2) roentgenographically apparent pulmonary oedema and presence of moist rales on auscultation. Patients with cancer and undergoing hemodialysis were excluded. The demographic and baseline clinical characteristics of the study population are presented in Table 1.

Serum cTnT and NT-proBNP were measured with commercially available immunoassay kits (Roche Diagnostics, Tokyo, Japan). All study procedures were in accordance with the ethical institutional guidelines of Kyoto University.

Long-Term Clinical Events

The subsequent incidence of adverse cardiac events was recorded until December 2002. Significant adverse cardiac events were defined as sudden death without apparent ischemia, death from CHF, or rehospitalisation of the patient for management of cardiac decompensation with pulmonary oedema. Information pertinent to a patient's death occurring outside the hospital between follow-up visits was obtained from the family.

Statistical Analysis

Data are expressed as mean±standard error. The study variables were compared by factorial analysis of variance for continuous variables. A receiver–operator characteristic (ROC) curve was used to determine the cut-off value of NT-proBNP which predicts cardiac decompensation and cardiac events. Adverse cardiac event-free rate, were constructed by Kaplan–Meier's method, log-rank test. A P value <0.05 was considered statistically significant.

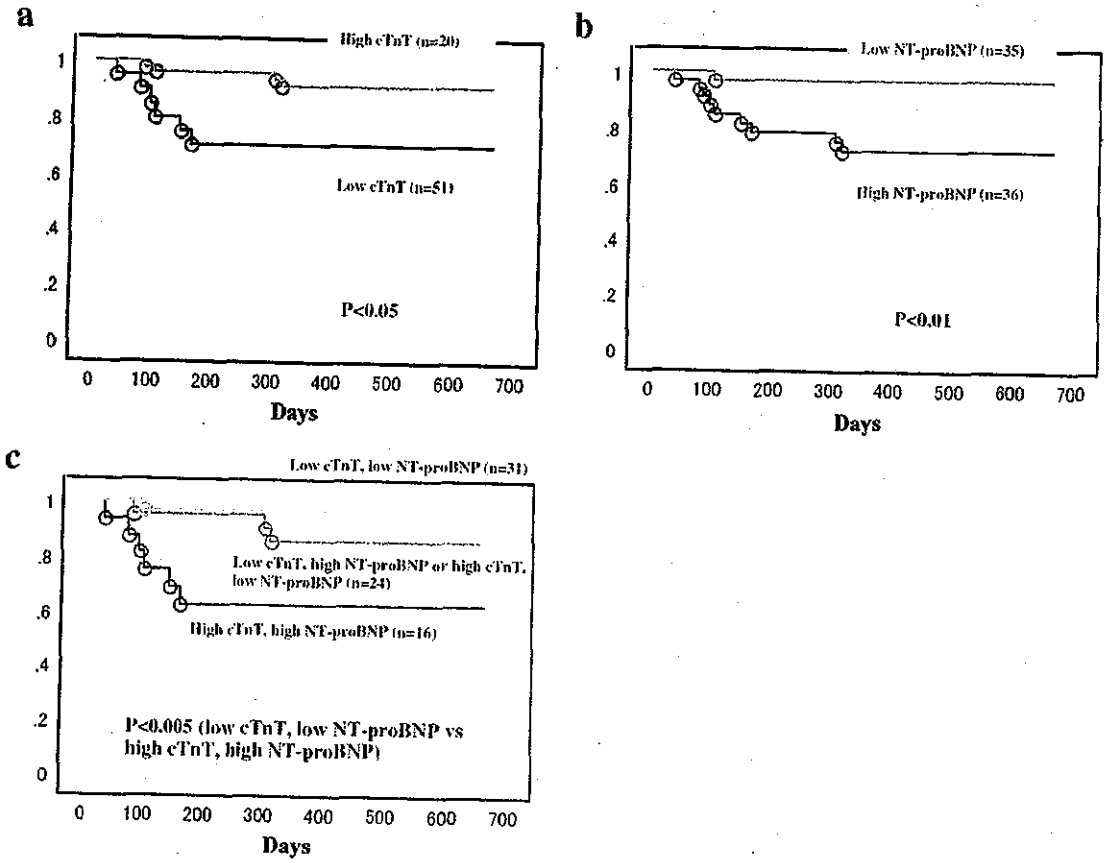

Fig 1. (a) Adverse cardiac event-free rate of patients with cTnT concentrations ≥0.01 ng/ml vs patients with cTnT concentrations <0.01 ng/ml. (b) Adverse cardiac event-free rate of patients with NT-proBNP concentrations ≥1,357 pg/ml vs patients with NT-proBNP concentrations <1,357 pg/ml. (c) Adverse cardiac event-free rate of patients with combined measurements of cTnT and NT-proBNP concentrations.

Results

Measurements of NT-ProBNP and TnT

The mean serum NT-proBNP concentration upon hospital admission of the 71 patients was 5,062±1,537 pg/ml (median=1,357 pg/ml). The mean NT-proBNP concentrations in patients of the NYHA functional class I, II, III, and IV were 954±361 (n=10), 1,673±473 (n=22), 2,902±771 (n=22), and 14,659±5,839 pg/ml (n=17), respectively. The cut-off value determined by ROC analysis for cardiac decompensation and cardiac events was 1,050 pg/ml (sensitivity 80%, specificity 67%) and 2,000 pg/ml (sensitivity 59%, specificity 67%), respectively. Age, CK concentration, and left ventricular ejection fraction and enddiastolic dimension measured echocardiographically did not correlate with NT-proBNP in this small population (data not shown).

The serum concentration of cTnT upon admission into the hospital was ≥0.01 ng/ml in 20 of the 71 patients (0.037±0.003 ng/ml). Cardiac troponin T was ≥0.01 ng/ml in 0/10 (0%), 6/22 (27%; 0.037±0.004 ng/ml), 7/22 (31%; 0.031±0.005 ng/ml) and 7/17 (41%; 0.046±0.008 ng/ml) patients in the NYHA functional classes I, II, III, and IV, respectively.

The mean serum concentration of NT-proBNP in the group of patients with high cTnT was significantly higher than in patients with low cTnT values (P<0.001). In contrast, age, CK and left ventricular ejection fraction were similar in both cTnT groups (Table 2). Comparisons between patients with and without cardiac decompensation are shown in Table 3. Concentrations of NT-proBNP in patients with cardiac decompensation were significantly higher than those in patients without (P<0.05).

Measurements of cTnT and NT-ProBNP, and Adverse Cardiac Events

Adverse cardiac events were observed in 10 patients (2 deaths from CHF and 8 cases of rehospitalisation for the management of cardiac decompensation with pulmonary oedema). The patients were divided into groups according to values of cTnT and NT-proBNP. The adverse cardiac event-free rate among the 20 patients with cTnT concentrations ≥0.01 ng/ml was significantly lower than the 51 patients with cTnT concentrations <0.01 ng/ml (P<0.05, Fig 1a). Similarly, the adverse cardiac event-free rate among the 36 patients with NT-proBNP concentrations ≥1,357 pg/ml was significantly lower than the 35 patients with NT-proBNP <1,357 pg/ml (P<0.01, Fig 1b). When groups were allocated according to both cTnT and NT-proBNP measurements, the 16 patients with high concentrations of both cTnT and NT-proBNP had a significantly lower adverse cardiac event-free rate than the 31 patients who had low cTnT and low NT-proBNP concentrations upon commencement of the study (P<0.005, Fig 1c).

Table 4 Hypothesis of Relationship Between Measurements of NT-ProBNP and TnT

	Low TnT	*High TnT*
Low NT-proBNP	*Without ongoing myocyte injury or myocardial load.*	*No myocardial load however, subclinical myocyte injury is ongoing. Patient is at risk of heart failure in the near future.*
High NT-proBNP	*Patient has heart failure without ongoing myocyte injury. Patient will stabilize with optimal treatment for heart failure.*	*Patient has heart failure with ongoing myocyte injury. If TnT concentrations do not decrease, heart failure may progress*

NT-proBNP, N-terminal pro-brain natriuretic peptide; TnT, Troponin T.

Discussion

In the present study, cTnT and NT-proBNP were reliable prognostic markers, both singly and in combination. Serum concentrations of cTnT≥0.01 ng/ml were considered significant.[14] Assay of NT-proBNP is a new technology and normal values were reported approximately as 20 pg/ml.[15,16] In our study, while mean NT-proBNP rose in the NYHA functional class, a similar correlation was not observed with mean cTnT concentrations. Moreover, 65% of patients with cardiac decompensation did not have a high serum cTnT concentration, and 15% had elevated concentrations despite being in a compensated state (Table 3). Troponin T seems to be a less sensitive marker of congestion.

We recently hypothesised that when managing heart failure, the therapeutic goals should be: (1) the relief of circulatory congestion and rapid lowering of markers of myocardial load, and (2) the mitigation of myocyte injury and lowering of markers of myocyte injury during long-term follow up.[17] In this hypothesis, cTnT and NT-proBNP are important biochemical markers. The relationship between TnT and BNP and heart failure, based on our hypothesis, is shown in Table 4. These markers are easy to determine within a few hours and can be repeated for patient follow up, without inter-observer variability. In the future, the combination of these tests may be used in bedside clinical settings.[18,19] Unfortunately, a multivariate analysis was not used to evaluate the prognostic value of these parameters because of our small sample numbers. Recently, Ishii et al reported that elevated cTnT and BNP on admission independently correlated with an increase in cardiac event rates in patients who were admitted to the coronary care unit for worsening chronic heart failure.[14]

Although the mechanism of myocyte injury and the release of cTnT in CHF is not completely understood, cTnT seems to reflect ongoing myocyte injury even during compensated periods of CHF.[7–10] Whether this indicates irreversible or reversible myocyte injury requires further investigation. The cytosolic pool for cTnT has been estimated at 6–8%. The release of protein may be because of a transient leak from the cytosol due to loss of sarcolemmal integrity during reversible ischemia, or from its continuous release when ischemic injury is irreversible.[20,21]

No guidelines have been issued regarding the use of biochemical markers as part of the management of CHF. Recently, Maeda et al reported that BNP after optimized treatment for heart failure, rather than BNP before treatment, is an independent risk factor for morbidity and mortality in patients with congestive heart failure.[22] We were unable to obtain follow up NT-proBNP data. While further studies are necessary, we anticipate that these assays will become the new monitoring standards in this patient population.

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