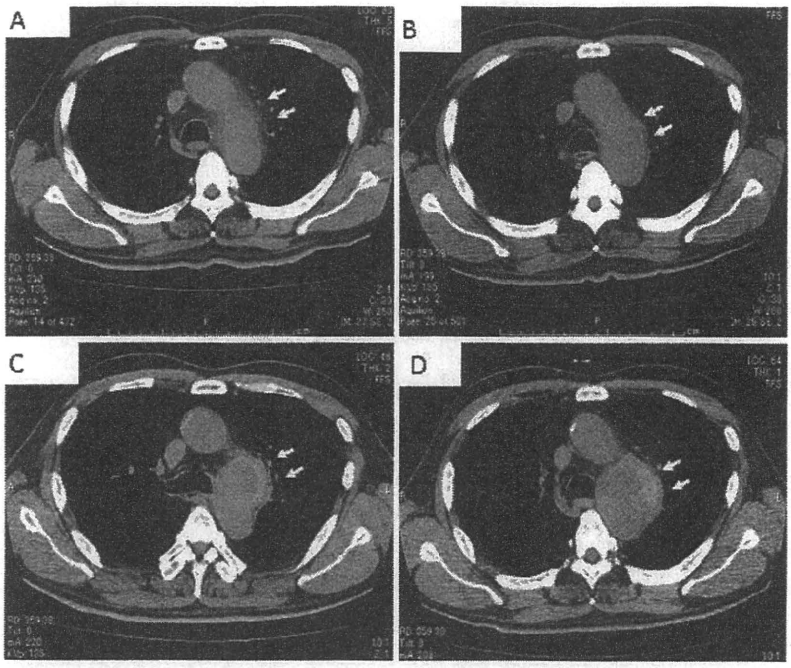

Figure 2. The course of disease as shown through changes in chest axial computed tomography (CT) scans. A: On admission, the CT image showed visible mediastinal soft tissue swelling originating from the aortic arch with mediastinitis (white arrow). B: Day 14, the swelling of the aortic arch appears to have improved. C: Day 33, a pseudoaneurysm with periaortic infiltration (white arrow) visible in the upper mediastinum. D: Day 40, the aortic arch aneurysm was more dilated than the previous day (white arrow).

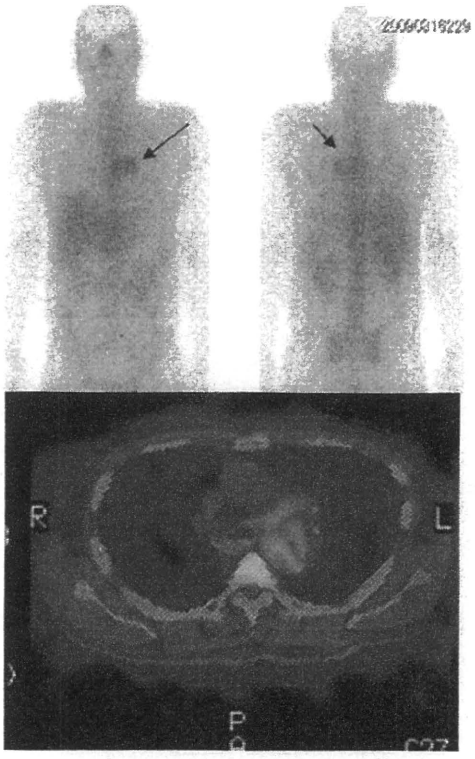

Figure 3. Ga-67 and CT fusion imaging. A. Ga-67 image shows abnormal accumulation at the upper mediastinum. (black arrow) B. Ga-67 SPECT and CT (Fig. 2A) fusion image of the infected aorta (red region).

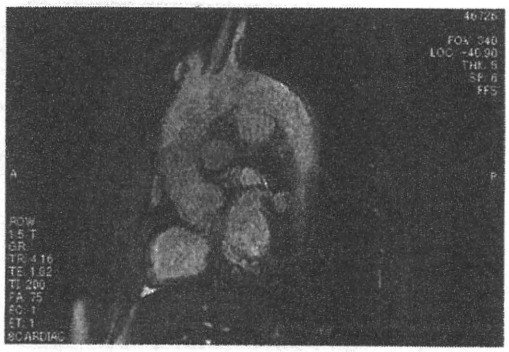

Figure 4. Chest longitudinal magnetic resonance imaging on day 34. The image clearly shows a saccular aneurysm in the aortic arch.

rysms being of the mycotic type (1-4); the incidence of mycotic aneurysms in the aortic arch is even lower (5). Infected aorta is also notoriously difficult to diagnose, and its detection requires strict attention to the patient's symptoms. It can be caused by the following: 1) formation of mycotic aneurysms secondary to septic microemboli in the vasa vasorum; 2) extension from a contiguous infected focus; 3) hematogenous seeding of the intima during bacteremia originating from a distant infection; and 4) direct contamination following trauma to the arterial wall (6, 7). Most infected aortic atherosclerotic aneurysms occur in elderly men. A large percentage of patients have underlying diseases or

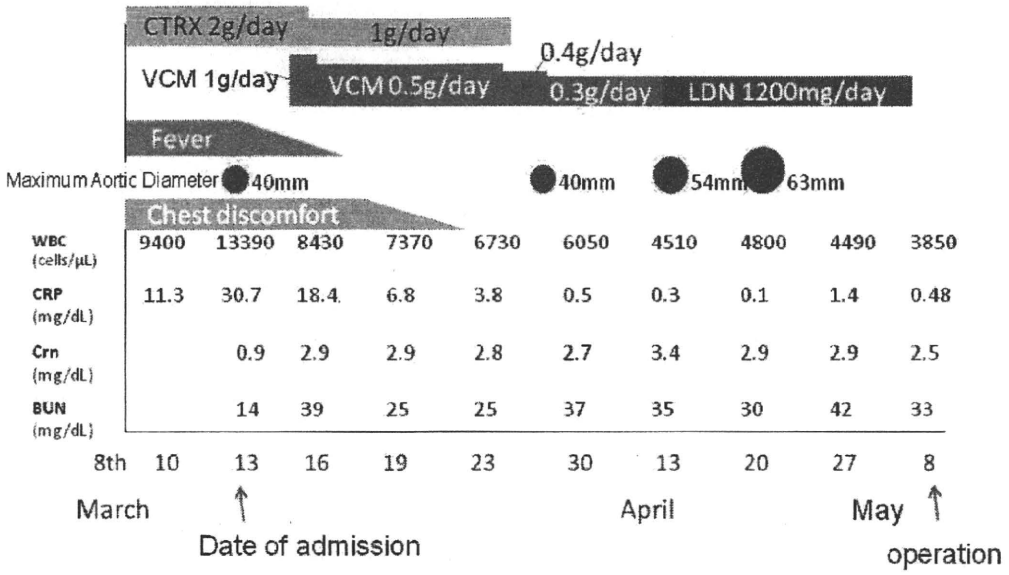

Figure 5. Clinical course of the patient. CTRX: ceftriaxone, VCM: vancomycin, LDN: linezolid, WBC: white blood cell count, CRP: C-reactive protein, Crn: Creatinine, BUN: Blood urea nitrogen

other relevant factors that increase their risk of the development of arteriosclerosis. These disease or factors include diabetes mellitus, hypertension, heavy smoking, or long-term corticosteroid therapy (2, 4, 7, 8). In general, the arterial intima is very resistant to infection; however, if this intimal lining is altered by atherosclerotic plaques or ulcers, resistance of arterial intima to infection is lowered, and its surface may become colonized by blood-borne organisms. Secondary infection of a pre-existng aneurysm occurs most commonly in the abdominal aorta, the site of 70% of such cases, because this portion of the aorta is most frequently and severely damaged by atherosclerosis. Both ascending and descending aortic aneurysms individually account for about 15% of secondary infection cases (9). When primary bacteremia is the cause, it most commonly originates from a distal infection in soft tissue or an infection in the lung, bone, or joint tissue. At the site of a preexisting aneurysm, the wall of the aorta is thinned and can be further weakened by focal acute and chronic inflammation; therefore, this site is as likely to develop into an infected pseudoaneurysm, as is its propensity to rupture (2-7, 10).

Approximately 60%, of infected aortic aneurysms are caused when a previously atherosclerotic vessel is colonized by gram-positive organisms, while 35% are caused by gram-negative bacilli colonization, especially salmonellae. Staphylococci are implicated in 40% of cases overall; more than two-thirds of which involve Staphylococcus aureus (1-4, 6, 9). In the present patient, we suspected colonization by methicillin-resistant Staphylococcus aureus, because VCM and linezolid were effective but CTRX was not. Patients with infected aortic aneurysms usually also have leukocytosis and increased CRP, but these associated conditions are nonspecific. Occult-infected aneurysms have also been identified in patients with fever of unknown origin.

CT, MRI, and Ga-67 scintigraphy are modalities that have been used to localize intra-arterial infections (11-14). CT conveys anatomical information and SPECT reveals functional changes; these two modalities may be used complementarily. Thus, a Ga-67 SPECT/CT fusion image was quite useful in establishing the diagnosis for this patient. Our diagnosis of infected thoracic aorta was based on the patient's fever and elevated inflammatory signs along with the Ga-67 SPECT/CT fusion image. As infected aortic aneurysms usually develop rapidly even while the patients' inflammatory signs are improving, follow-up CTs are very important to determine whether an aneurysm is forming (2, 4). The possible routes of pathogenesis and the speed of growth in mycotic aneurysm remain unclear (1, 2). In the present case, a severe arteriosclerotic plaque was seen on the inner surface of the aorta during the operation, which was much more than that was extensive than that revealed by CT imaging. We conjecture that sclerotic plaque became infected when the bacteremia developed and the aortic wall was subsequently ruptured by the infection (1), and also that the pseudoaneurysm had developed rapidly even though infection was controlled. It thus follows that, one should not rely on the results of imaging alone for the understanding and treatment of infected aortic aneurysms.

Infected aortic aneurysms usually require treatment with both intravenous antibiotics, and surgical excision, because antibiotic therapy alone is usually insufficient. The mortality rate among patients with infected aortic aneurysms treated with antibiotics alone has been reported at 16% - 44% (5, 15). The critical points in the management of infected aortic aneurysm are the optimal timing of surgical procedure and the antibiotic strategy. The incidence of vascular complications was shown to be clearly associated with ruptured aneurysm and extensive periaortic infection at the

time of surgery (1, 2). Thus, complete excision of the affected aorta is the key to curative treatment (5, 16). Cases of successful endoluminal treatment of mycotic aortic aneurysms have been also reported (17, 18). In general, surgical procedures are associated with substantial mortality rates as well as a risk of recurrent infection although there are several exceptions (16, 19). After surgery, survival is primarily influenced not by the type of reconstruction but by the status of aneurysmal rupture; about 30-50% of aneurysms are reported to rupture (1, 2, 5, 16). The outcome is worse when the aneurysm has already ruptured or penetrated, and when it penetrated leading to formation of pseudoaneurysm. The required length of the follow-up period is not well established; recommendations range from 6-12 weeks to lifelong (1, 2, 4, 6).

In conclusion, increased clinical awareness of this condition among practitioners, immediate and follow-up CT evaluation, and prompt surgical intervention under appropriate and intensive antibiotic therapy appears to offer the best chance of survival for patients with infected aortic aneurysm.

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Three-Dimensional Architecture of Cardiomyocytes and Connective Tissue in Human Heart Revealed by Scanning Electron Microscopy

Yumiko Kanzaki, MD, PhD; Fumio Terasaki, MD, PhD; Makoto Okabe, MD, PhD; Shuichi Fujita, MD; Takashi Katashima, MD, PhD; Kaoru Otsuka, MD, PhD; Nobukazu Ishizaka, MD, PhD

Scanning electron microscopy is a useful modality to directly observe the 3-dimensional structures of cells at high resolution. Scanning electron microscopy enables visualization of the surface features of cardiomyocytes after removal of the surrounding connective tissue[1] and the connective tissue skeleton after removal of the nonfibrous elements.[2] In addition, backscattered electron emission with heavy metal staining[3] helps to provide high-quality images of the intracellular architecture of the cardiomyocyte.

In this study, we present the 3-dimensional structure of the human left ventricular myocardium from subjects without apparent cardiac abnormalities at the time of autopsy. Backscattered electron emission provides a high-contrast picture of the subsarcolemmal sarcomeres and intercalated discs as seen in longitudinally arranged cardiomyocytes (Figure 1A). The cardiomyocytes are seen to be branched and connected with the adjacent cells via intercalated discs. At higher magnification, in the sarcomeres, the A bands can be identified as broad bright zones, the I bands are seen as dark zones, and the Z bands are demonstrated as indistinct thin lines in the middle of I bands (Figure 1B).

After the removal of the nonfibrous elements, interstitial connective tissue surrounding the cardiomyocytes and small vessels can be clearly observed (Figure 2A). The perimysium, located around the bundle of cardiomyocytes, and the endomysium tether surrounding the individual cardiomyocytes are clearly demonstrated[4] (Figure 2B and 2C). At high magnification, collagen fibers are identified as forming a complex network and providing the strength sufficient to support the 3-dimensional structure comprising cardiac muscle fibers and neighboring vascular tissues (Figure 2D).

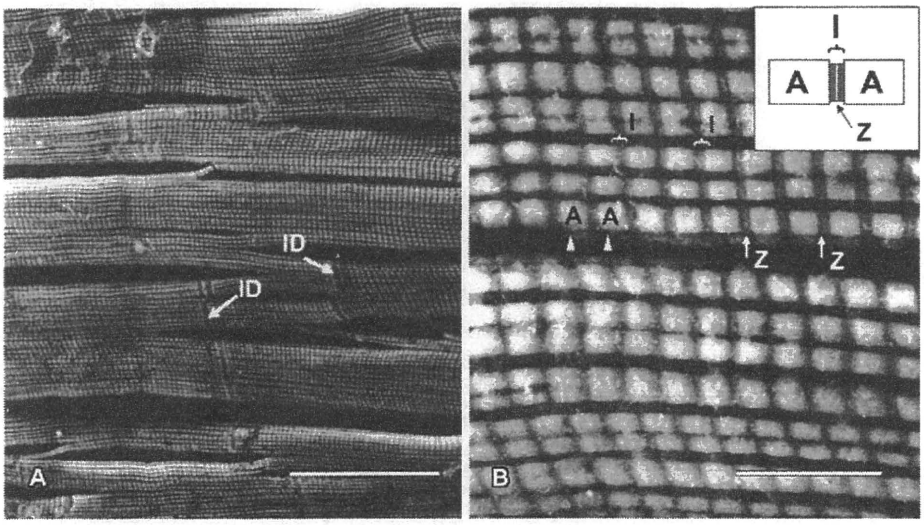

Figure 1. Backscattered electron imaging of normal human left ventricular cardiomyocytes. A, Intercalated discs (arrows) and sarcomere striations are clearly seen. Bar=50 μm; magnification ×600. B, Higher magnification of the sarcomeres; A bands (arrowheads) are seen as broad bright zones, I bands as dark zones, and Z band (arrows) as indistinct thin lines in the middle of the I bands. The schema is presented in the boxed area. Bar=10 μm; magnification ×3000. ID indicates intercalated disc; A, A band; I, I band; and Z, Z band.

From the Department of Internal Medicine III, Osaka Medical College, Osaka, Japan.
Correspondence to Fumio Terasaki, MD, PhD, Department of Internal Medicine III, Osaka Medical College, 2-7, Daigaku-machi, Takatsuki 569-8686, Japan. E-mail in3012@poh.osaka-med.ac.jp
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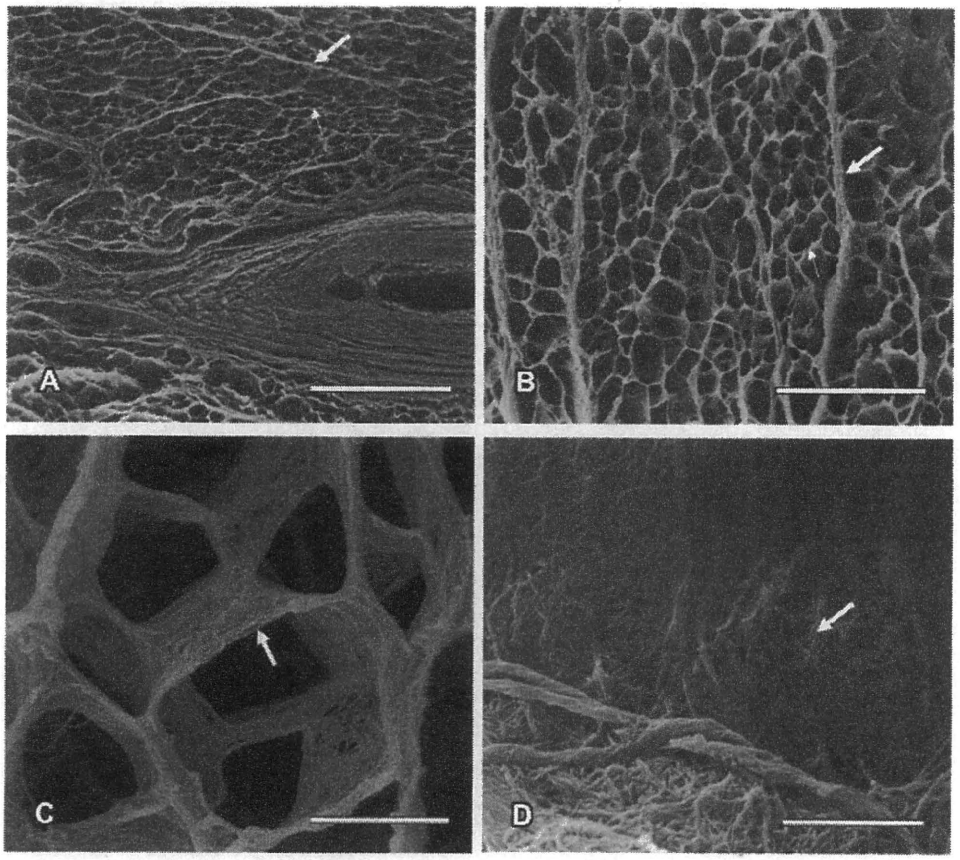

Figure 2. Connective tissue skeleton of human heart (transverse section). A, The collagen network around cardiomyocytes and small vessels is clearly observed. Bar=200 μm; magnification ×150 (thick arrow, perimysium; thin arrow, endomysium). B, The interstitial connective tissue consisting of perimysial and endomysial components presents a honeycomb shape. The perimysium (thick arrow) surrounds groups of cardiomyocytes, and the endomysium (thin arrow) surrounds each cardiomyocyte. Bar=100 μm; magnification ×300. C, The endomysium supports and connects individual cardiomyocyte fascicles. Bar=10 μm; magnification ×3000. D, At higher magnification, collagen fibers show interconnections on the surface of cardiomyocytes. Thin collagen strands are probably collagen III (arrow). Bar=3 μm; magnification ×10 000.

Disclosures

None.

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Expert Opinion

Periodontitis and cardiovascular diseases

Jun-ichi Suzuki†, Norio Aoyama, Masahito Ogawa, Yasunobu Hirata, Yuichi Izumi, Ryozo Nagai & Mitsuaki Isobe
†*University of Tokyo, Department of Advanced Clinical Science and Therapeutics, Tokyo, Japan*

Periodontitis is characterized by gingival inflammation and periodontopathic bacteria generate immunological inflammatory responses. Recent epidemiological reports suggest that periodontitis is one of the key risk factors for the onset of cardiovascular diseases. Several studies reported that periodontal bacteria in cardiovascular specimens were frequently detected. We revealed that patients with acute coronary syndrome showed significantly higher serum IgG titers to a strain of periodontopathic bacteria compared with patients with chronic coronary disease. Periodontopathic bacteria were also present in a high percentage of specimens of diseased arteries from patients with Buerger disease or abdominal aortic aneurysm. Although periodontopathic bacteria may play a role in the development of cardiovascular diseases, the influence of these bacteria on the disease has not yet been proven. In this article, we review the relationship between periodontopathic pathogens and cardiovascular diseases to conduct further clinical and experimental investigations in near future.

Keywords: aorta, bacteria, cytokine, inflammation, periodontitis

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1. Introduction

Periodontitis is a chronic inflammatory disease that degrades the attachment apparatus of the teeth, leading to tooth loosening. Clinical signs of the disease are often seen in middle age and it is a very common disease in adults [1,2]. Epidemiological studies showed that periodontitis significantly increased the risk of cardiovascular disease (CVD) [3-6]. Although data was adjusted for known CVD risk factors such as smoking, diabetes, hypertension and socioeconomic conditions, other points might still explain the apparent association. Levels of risk markers for CVD have been reported to be elevated in patients with periodontitis. Furthermore, animal studies demonstrated an association between the prevalence of periodontal pathogens, bacterial products, periodontitis and the incidence of CVD-related events [7,8]. Although DNA from oral bacteria has been found in atherosclerotic plaque in animal experimental models [9] and humans [10], the contribution of these bacteria to plaque formation remains unknown. Periodontal pathogens and their products were reported to be a trigger of the atherosclerotic process in animal studies [7,8]. However, their effects in the human system remain unclear. The release of host-derived inflammatory mediators, such as cytokines from the chronically inflamed periodontal tissues into the circulation, may provide a link between periodontal disease and CVD [11,12]. Altered serological profiles of risk markers in patients with periodontitis may result from an invasion of bacteria. Additionally, entry of their products from the periodontal lesion into the blood stream and the consequential induction and maintenance of a chronic inflammatory state also contribute to the progression of CVD.

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In this small article, we review pathological and immunological influence of periodontal pathogens to CVD and some promising methodologies for prevention of the disease.

2. Coronary arterial disease and periodontitis

Recent studies suggest that chronic inflammation plays an important role in the development of coronary arterial disease (CAD). Because periodontal disease is an enhancer of several chronic inflammatory factors such as MMPs [13-15], an etiological relationship between periodontal disease and CAD was proposed. For these reasons, there is strong interest in evaluating whether periodontal disease is independently associated with CAD [16-18]. Humphrey *et al.* revealed that periodontal disease is associated with increased risk of CAD using a meta-analysis [19]. They concluded that periodontal disease is a risk factor or marker for CAD, and is independent of traditional CAD risk factors. Nakajima *et al.* also revealed that periodontitis is associated with increased risk of CAD through dysfunction of endothelial cells, induced by either periodontopathic bacteria or their products [20]. CRP concentrations were higher among patients who subsequently developed myocardial infarction compared with those without the disease. However, there was no report to elucidate the relationship between specific gingival bacteria infection and CAD.

We recently revealed that there is an association between periodontitis and CAD, particularly acute coronary syndrome (ACS). A total of 28 CAD patients participated in the study. Coronary angiography, periodontal examination and dental radiography were performed in all patients. Subgingival plaque, saliva and blood samples were analyzed for the periodontopathogens *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola,* and *Prevotella intermedia* using PCR. Specific serum antibody titers to the five periodontal pathogens were determined by ELISA. We found that 33% of the ACS patients harbored *A. actinomycetemcomitans* in oral samples, whereas no *A. actinomycetemcomitans* was found in the patients with chronic CAD. Furthermore, ACS patients showed significantly higher serum IgG titers to *A. actinomycetemcomitans* compared with chronic CAD patients. Thus, we concluded that a specific periodontal pathogens may play a crucial role in the development of ACS [21].

3. Peripheral arterial disease and periodontitis

There are several papers demonstrating the relationship between peripheral arterial disease (PAD) and periodontitis. Buhlin *et al.* revealed the association by determining the plasma levels of some risk markers for PAD in cases with periodontitis [22,23]. Statistical analyses revealed a significant association between periodontitis and high levels of C-reactive protein (CRP), fibrinogen, IL-18 and antibodies against heat shock protein (Hsp) 65 and 70. They also showed the effect of infection control of periodontitis on the prevalence of the risk factors. One year after the initial treatment, IL-18 and other levels decreased. Thus, standard treatment for periodontal disease induces systemic changes in several biochemical markers that reflect the risk for PAD.

Chen *et al.* also revealed that periodontitis was associated with PAD using tissue specimens [24]. They identified *P. gingivalis, T. denticola, A. actinomycetemcomitans, P. intermedia* in tissue specimens taken from the anastomotic site of distal bypasses PCR. In the study, periodontopathic bacteria were detected in 52% of atherosclerotic specimens. Severe (Fontaine grade III or IV) patients showed higher detection frequency of *P. gingivalis* than mild (Fontaine grade II) patients. After adjusting for age, sex, diabetes and smoking, periodontitis increased fivefold the risk of having PAD. They also showed that periodontitis was associated with increased serum IL-6 and TNF-α concentrations.

Buerger disease also showed the significant relationship to periodontitis. Iwai *et al.* revealed that DNA of oral bacteria was detected in 13 of 14 arterial samples and all oral samples of patients with Buerger disease [25]. While *T. denticola* was found in 86% of the arterial samples, other pathogens were found in 14 to 43% of the samples. A pathological examination revealed that arterial specimens showed the characteristics of an intermediate-chronic-stage or chronic-stage lesion of Buerger disease. They reported that the patients with Buerger disease had high prevalence of severe periodontitis with higher serum IgG titers against *T. denticola, P. gingivalis* and *A. actinomycetemcomitans* [26]. They also found that the patients had increased titers of serum anti-cardiolipin antibody compared with healthy subjects [27]. These results suggest that periodontitis influences the development of PAD.

4. Aortic aneurysm and periodontitis

Abdominal aortic aneurysm (AAA) is a common and lethal disorder in the aging population [28,29]. Inflammation and MMPs appear to play a critical role in AAA development and progression [30]. Human AAA tissue samples demonstrated severe inflammatory infiltrates in both the media and adventitia [31,32]. An increased expression of MMPs has been observed in human aneurysm tissue specimens [33-37]. It is well known that MMPs play key roles in periodontal diseases. Periodontopathic bacteria generate host immunological inflammatory responses, thus resulting in the secretion of cytokines and MMPs [38], and eventually leading to the extracellular matrix destruction of the periodontal tissues [39]. Some studies reported the detection of periodontal bacteria in AAA specimens. Periodontopathic bacteria, especially *P. gingivalis* was present in a high percentage of specimens of AAA and were also found throughout the whole aneurysmal wall [40]. Thus, periodontopathic bacteria may play a role in the development of AAA, but the influence of these bacteria on the aneurysmal wall has not yet been

proven. To determine the effect of the periodontal microorganism on the AAA, we made a novel murine AAA model, which was produced by the periaortic application of 0.25 M $CaCl_2$. The mice received inoculations of either live *P. gingivalis*, *A. actinomycetemcomitans* or vehicle. Four weeks after the application of $CaCl_2$, the *P. gingivalis*-challenged mice showed a significant increase in the aortic diameter in comparison with the vehicle control mice while the *A. actinomycetemcomitans*-challenged mice showed no significant increase. Immunohistochemically, the CD8- and MOMA2-positive cells and the level of MMP-2 in the aneurysmal samples of *P. gingivalis*-challenged mice were also significantly higher than that inoculated with vehicle. We found that the *P. gingivalis*, but not *A. actinomycetemcomitans*, infection accelerated the progression of AAA due to the increased expression of MMPs (Aoyama N, unpublished).

5. Vitamin D is a key factor for periodontitis and cardiovascular diseases

Although vitamin D is well known to regulate calcium and phosphorus metabolism, it also has a physiological effects beyond its role in skeletal homeostasis. Recently, it was revealed that vitamin D is an immunomodulator which targets various immune cells, and modulates both innate and adaptive immune responses. Thus, vitamin D plays a crucial role in maintenance of immune homeostasis [41]. Several epidemiological studies have linked inadequate vitamin D levels to a higher susceptibility to immune-mediated disorders [42,43], including cardiovascular diseases [44]. It is believed that maintaining adequate vitamin D levels might in part prevent these common diseases [45]. It has been reported that low serum vitamin D levels were independently associated with periodontal and cardiovascular diseases [46,47]. Notably, vitamin D insufficiency is associated with increased circulating CRP levels, and vitamin D supplementation decreases circulating CRP levels [48]. Thus, the elevated CRP levels observed in periodontal and cardiovascular disease might be a surrogate for vitamin D insufficiency.

6. Conclusion

In this brief article, we have demonstrated the relationship between periodontopathic pathogens and cardiovascular diseases. We have also elucidated that each gingival bacterium caused different condition of cardiovascular diseases.

7. Expert opinion

Although several periodontopathic bacteria play a serious role in the development of cardiovascular diseases, the influence of these bacteria has to be elucidated because of the lack of appropriate investigations. Thus, further experimental and clinical studies should be conducted to elucidate the pathophysiology and relationship between periodontitis and cardiovascular diseases. Meanwhile, clinicians should optimize the periodontal conditions in patients with cardiovascular risk factors for primary and/or secondary prevention. Finally, it is plausible that this simple treatment of periodontitis might provide as much or even more benefit than the standard treatments for cardiovascular diseases.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Affiliation

Jun-ichi Suzuki[†1], Norio Aoyama[2], Masahito Ogawa[1], Yasunobu Hirata[1], Yuichi Izumi[2], Ryozo Nagai[4] & Mitsuaki Isobe[3]
[†]Author for correspondence
[1]University of Tokyo, Department of Advanced Clinical Science and Therapeutics, 7-3-1 Hongo, Bunkyo, Tokyo 113-8655, Japan
Tel: +81 3 5800 9116; Fax: +81 3 5800 9182; E-mail: junichisuzuki-circ@umin.ac.jp
[2]Tokyo Medical and Dental University, Department of Periodontology and GCOE Program, Tokyo, Japan
[3]Tokyo Medical and Dental University, Department of Cardiovascular Medicine, Tokyo, Japan
[4]University of Tokyo, Department of Cardiovascular Medicine, Tokyo, Japan

人工血管

*1東京大学大学院医学系研究科心臓外科，*2同　重症心不全治療開発講座
竹谷 剛*1，西村 隆*2
Tsuyoshi TAKETANI, Takashi NISHIMURA

1. はじめに

「人は血管とともに老いる」とは言い古された言葉であるが，現在，先進国において動脈硬化性疾患は死因のほぼ半分を占めており[1]，老化した血管をすべて人工血管に置き換えられれば，老い・死をかなりの部分，制御できるかもしれない。図1は，大動脈疾患が死亡原因となることが多く，一昔前は平均寿命が30歳台前半とされたマルファン症候群の50歳女性患者のCT画像である。このように現在では，大動脈とその主要分枝の基部をすべて人工血管ないしステントグラフトに置き換えた人でも，手術さえ乗り切ればその耐久性の範囲内で何不自由なく生活できる。

現在，人工血管における課題は，閉塞しない小口径人工血管をいかに作るかという点と，それなりに満足できるレベルにある大口径人工血管をいかにさらに良いものにするか（手術時の出血/低侵襲性，耐久性等）という点にある。

人工臓器一般について言えることであるが，人工血管には，①人工材料（繊維）として，②再生医学・生体組織工学の対象として，③臨床使用される製品として等，様々な観点がある。1950年代にDubost, DeBakey, Cooleyらにより黎明期を迎えた人工血管移植手術には，ほどなくダクロン（ポリエステル）人工血管が登場し，1970年代半ばにはテフロン（ポリ4フッ化エチレン）ePTFE人工血管が登場した。基布の織り方や成形の方法には多くの改良がなされてきたが，①の人工材料としての観点からは，その後際立った進歩は見られていない[2]。では②の観点ではどうであろうか。数十年前から現在に至るまで，日本の研究者を含め世界で綿々と研究が続けられており[3)～6)]，国内外の心臓血管外科の学会に参加すると，tissue engineeringによる小口径人工血管に関する演題をほぼ必ず目にする。これらは，ポリエステルやePTFE人工血管では短期に閉塞してしまう可能性の高い小口径血管の再建を主な目的としたものであるが，未だ現実に臨床使用されるには至っていない。③の観点では，近年も様々な改良が主に企業によって続けられており，我々外科医は新しい製品が出るたびにその恩恵を少しずつ感じている。本稿では，ここ2～3年以内の人工血管/ステントグラフトの進歩について総説する。

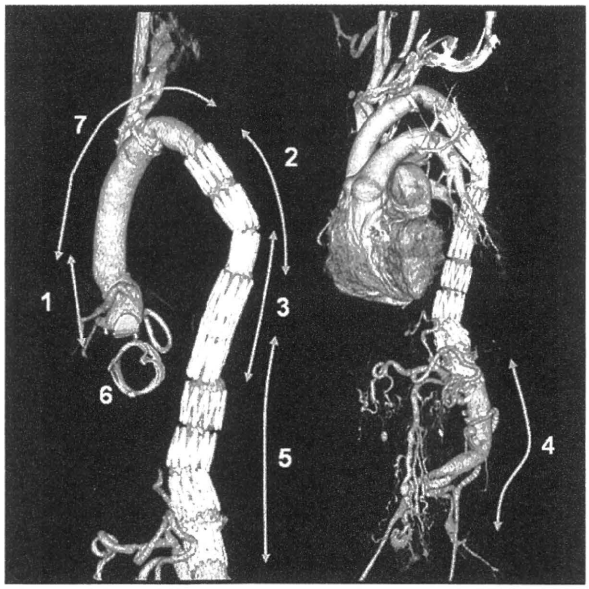


図1　7回の手術により，大動脈基部から両側腸骨動脈がすべて人工血管またはステントグラフトに置換された50歳女性患者のCT画像
分枝は，腕頭動脈，左総頸動脈，左鎖骨下動脈，腹腔動脈，上腸間膜動脈，左右腎動脈，肋間動脈がそれぞれ人工血管により再建されている。

■著者連絡先
東京大学大学院医学系研究科心臓外科
（〒113-0033　東京都文京区本郷7-3-1）
E-mail. ttaketa-tky@umin.ac.jp

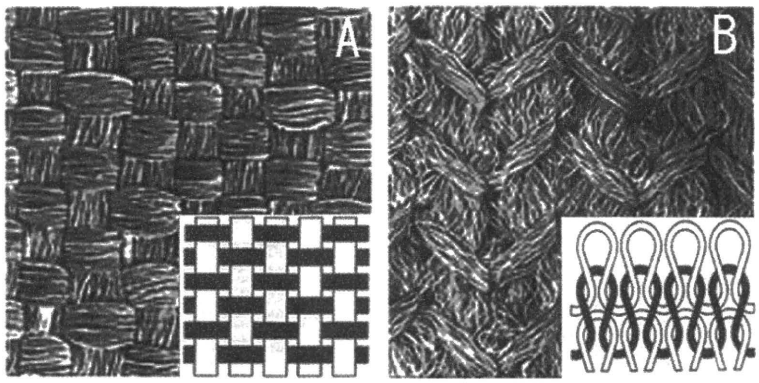


図2　織り（woven）人工血管（A）と編み（knitted）人工血管（B）の構造

表1　Wovenおよびknitted graftの特性

	Porosity	生体適合性	針穴	ハンドリング	ほつれ	耐拡張性	主用途
Woven	小さい	低い	大きい	やや硬い	ほつれやすい	高い	胸部領域
Knitted	大きい	高い	小さい	やわらかい	ほつれ難い	低い	腹部・末梢

2.　シールドグラフトと，その最近の進歩

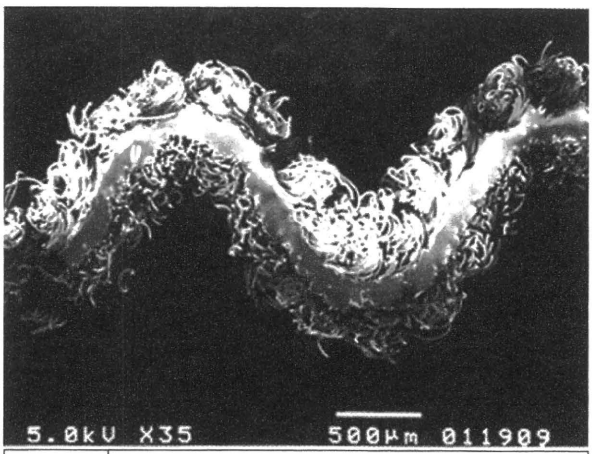
大動脈手術に使用する人工血管について我々外科医が感じる問題点は，出血（人工血管胴体および針穴から）と術後の発熱である。「大動脈の手術であること」のみならず，大動脈解離等に伴う急性凝固障害，長時間の人工心肺，低体温，循環停止等，止血を困難にする要因が揃い，術後は人工血管感染が致命的となることの多い大動脈手術においては，ハンドリングの良さやさらなる強度・耐久性の向上は二の次に考える外科医が多いのではなかろうか。

ダクロン人工血管にはweave（織り：woven）とknit（編み：knitted）構造（図2）があり，それぞれ表1に掲げる特徴を有する。Woven graftは主に胸部大動脈に，knitted graftは主に腹部大動脈や末梢血管に使われてきたが，図2を見て直感的に理解できるように，wovenはporosityが小さく（＝胴体からの出血が少ない）耐拡張性に優れる半面，ほつれや針穴の拡大が生じるという短所を持つ。また，porosityが小さいということは，ここに自己組織が入り込むことによる組織修復が得られにくいことを意味する。

ダクロン（ポリエステルの布）製人工血管は，ある意味Yシャツのようなものであるから，porosityの比較的小さなwoven graftでさえも，そのままであれば血液の漏出が生じる。1990年代半ばまでは，この血液漏出を防ぐために患者の血液を人工血管表面に塗り，凝固させてまた血液を塗るということを繰り返すこと（プレクロッティング）により，このporosityを埋める作業が手術室で行われていた。1986年頃より牛由来のコラーゲンやゼラチン，アルブミンによりシールドされた人工血管が登場し，プレクロッティング操作は次第に必要なくなっていったが，この生体材料に対する免疫反応，またそれらを人工血管に固定するための架橋剤（ホルムアルデヒドやグルタールアルデヒド）による炎症反応により，発熱や浸出液貯留が遷延するという問題が起きている。発熱はシールド材の分解に伴い解消するものであるが，術直後の患者にとって苦痛となるのはもちろんのこと，感染に伴う発熱との区別が困難であるため，入院期間や抗生剤使用量が無意味に多くなるという弊害がある。

この問題に対しては，シールド材の量を減少させたり，シールド材が含有するエンドトキシン量を減らした人工血管[7),8)]，さらに動物由来蛋白の代わりに高分子化合物をシールド材として用いる人工血管（図3）が近年登場し，筆者も術後発熱の減少を実感している。また，それら新しい人工血管は，織り方の改良により基布のporosityを下げることや[8)]，knitted graftでありながら人工高分子化合物の層を挟むことで，胴体および針穴からの出血が少なくなった。

こういった改良以外にも，製品としての人工血管はvarietyを増やしている。従来からある直管，1分枝管，4分枝管，Y字管に加え，大動脈基部置換術用のValsalvaグラフト（図4A），胸腹部大動脈置換術用のCoselliグラフト（図4B）等が発売された。従来は直管をトリミング[9)]ないし枝を縫着して同様の形態を作っていたのであるが，こういった出来合いの人工血管を使用することは単に外科医の手間



内層	ニット ポリエステル繊維
中層	スチレン系エラストマー（弾性樹脂）
外層	ニット ポリエステル繊維

図3 高分子化合物（エラストマー樹脂）をknitted graftの中間層としてサンドイッチした構造の人工血管（Vascutek- テルモ：トリプレックス）
従来のwoven graftの問題であった生体材料による術後発熱，針穴出血・ほつれ，生体適合性において改善が図られている。

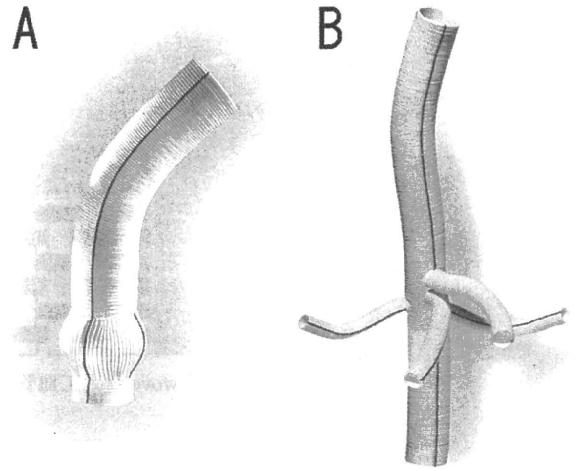


図4 大動脈基部置換術用のValsalvaグラフト（A）と，胸腹部大動脈置換用のCoselliグラフト（B）
各術式に応じた既製の人工血管を使用することで，手術時間，出血を減らすことが期待できる。

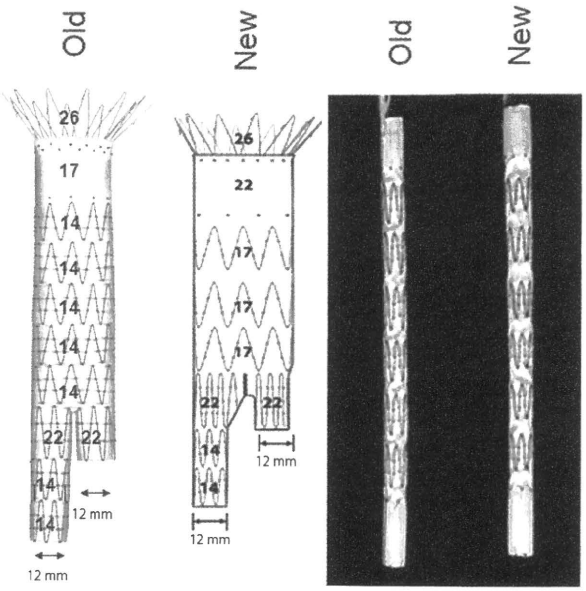


図5 Zenith®システム（Old）とZenith Flex®システム（New）
ステント間の間隔を大きくすることで，柔軟性を増している。

を省くのみならず，針穴や吻合を少なくすることで出血を減らすという利点がある。

大口径人工血管は，進化がほぼplateauに達し，ステントグラフトの出現により需要も頭打ちになりつつあると思われるが，出血しない人工血管をめざしてさらなる改良も期待される。

3. ステントグラフト

2006年に，わが国でも保険医療で企業製のステントグラフトが使用できるようになった。以降，その普及には目を見張るものがあり，日本ステントグラフト実施基準管理委員会の追跡調査に登録されたデータだけでも，直近，腹部は年間4,000例ペース，胸部は年間1,700例ペースで内挿術が行われている（日本ステントグラフト実施基準管理委員会のホームページ：http://stentgraft.jpによる）。現在使用可能な企業製ステントグラフトについては，その開発から製品としての特性まで，2007年の加藤[10]，2009年の樋上ら[11]により本誌にて詳述されている。その中で，Cook社製の腹部大動脈瘤治療用ステントグラフトZenith®に関しては，2010年に新たな改良がなされた。Gore社製のステントグラフト（Excluder®，TAG®）と比較した際のZenith®の1つの欠点は，蛇行した血管に挿入する際の屈曲性の乏しさにあった。そこで図5の如く，Zenith Flex®ではメインボディにおいてステントの1st gapおよび2nd gapに5～6 mmの間隔をおき，レッグにおいてもステント間の間隔を従来の2～3 mmから5 mmに延長することで，屈曲の曲率半径を小さく（＝柔軟性を高く）している。

日本ステントグラフト実施基準管理委員会が公開した予後調査結果によると，2006年7月1日～2008年6月30日の2年間に治療を受け登録完了された1,724人の患者のうち，術中死亡は0，入院死亡は9人であった。これは海外で行われた代表的な前向き臨床試験[12)～14)]におけるステントグラフト治療群，開腹治療群と比較してもはるかに良好な

成績であり，日本の実施基準を満たす治療医のレベルの高さを示すものと言えよう。デバイス（ステントグラフト本体，デリバリーシステム）依存性の高い本治療法は，デバイスの改善によりさらに普及し，開胸/開腹手術を凌駕していくことは想像に難くない。

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SURGERY TODAY

How to Do It

Successful Endovascular Repair in Two Cases of Graft Limb Occlusion After Endovascular Aneurysm Repair for Abdominal Aortic Aneurysms

KATSUYUKI HOSHINA[1,2], MASAAKI KATO[1], AKIYOSHI MIKURIYA[1], and NOBUKAZU OHKUBO[1]

[1]Department of Cardiovascular Surgery, Morinomiya Hospital, Osaka, Japan
[2]Department of Vascular Surgery, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Abstract
Among 148 abdominal aortic aneurysm patients who underwent endovascular aneurysm repair at our institution, two cases of graft limb occlusion (GLO) were identified and successfully treated with endovascular repair. Guidewire cannulation against the occluded limb is the most important aspect of the procedure. After a thrombectomy, balloon dilatation is performed followed by stent-graft deployment. Various procedures such as thrombectomy, thrombolysis, and extra-anatomical bypass have been adopted for the treatment of GLO. Our use of endovascular techniques, including overlapping stent grafts, has some benefits, namely, better patency of anatomical route revascularization, decreased risk of ipsilateral shower embolization due to the stent graft's sealing over the irregular remnant thrombus, and easy access to angioplasty for tortured iliac arteries. However, shower embolization during catheter handling or future fabric failure due to friction is the potential complication associated with endovascular techniques. Intravascular repair techniques and stent-graft use should therefore be an early step of the GLO treatment algorithm.

Key words Endovascular aneurysm repair · Graft limb occlusion · Abdominal aortic aneurysm · Stent graft

Introduction

Graft limb occlusion (GLO) is a complication associated with endovascular aneurysm repair (EVAR) of abdominal aortic aneurysms. The culprit thrombus is thought to be caused by kinking of the stent graft or tortuosity of the iliac artery;[1] however, the precise etiology of GLO is still unclear. Although it is not a rare complication, optimal therapeutic strategies are largely unknown. In cases of acute occlusion, a thrombectomy would be the easiest and most effective treatment strategy. However, in cases of chronic occlusion, other methods such as thrombolytic therapy or extra-anatomical bypass are often adopted[2] because thrombectomy of a hardened thrombus has an increased potential of failure. Bare stent coverage is another treatment option,[3] although this procedure might result in shower embolization of the remnant thrombus.

We herein report two successful cases of chronic GLO treated by endovascular technique. We passed a guidewire through the hard thrombus using various methods. Thereafter, balloon dilatation and stent-graft leg deployment were performed.

Reprint requests to: K. Hoshina (address 2)
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Case Reports

Case 1

A 77-year-old man who had undergone EVAR for an abdominal aortic aneurysm in December 2006 complained of coldness and intermittent claudication in the lower right extremity. He had also undergone graft replacement for a right common iliac artery aneurysm 10 years before. The symptoms appeared in January 2008, when he underwent treatment for brain infarction at another hospital, and GLO was diagnosed 3 months later. On physical examination, the patient suffered mild coldness and no pain in the lower right extremity. The ankle-brachial index (ABI) at this time was lower (0.5) than the ABI in the preoperative data (0.8). Computed tomography (CT) angiography performed after the EVAR procedure revealed no severe tortuosity of the right graft limb (Fig. 1), while the most recent CT displayed right GLO from the flow divider at the bifurcation of the aortic endograft (Fig. 2). The cause of the

occlusion was unclear from a hemodynamic perspective. A repair operation was performed in May 2008.

An open puncture of the right common femoral artery was performed and a 6-F sheath was inserted. We utilized both angled and straight 0.035-inch guidewires in order to pass through the thrombus. After the cannulation, the puncture site was cut and extended under hemorrhage control with a vascular clamp. A thrombectomy was performed with a Fogarty thru-lumen catheter (Edwards Lifesciences, Irvine, CA, USA), and a large thrombus was removed. However, intra-arterial contrast agent revealed the irregular shape of the inner lumen of the graft leg. After balloon dilatation with an ATB Balloon Catheter (Cook Medical, Bloomington, IN, USA), a 12-F sheath was carefully inserted. The stent-graft leg (the contralateral leg of the Gore iliac extender [Gore Medical, Flagstaff, AZ, USA]) was overlapped from the flow divider to the external iliac artery where the irregular internal lumen persisted. A balloon catheter was used for touching up the stent graft. After the procedure, the pedal pulse was palpable, and a CT scan revealed patent blood flow with no endoleak (Fig. 3).

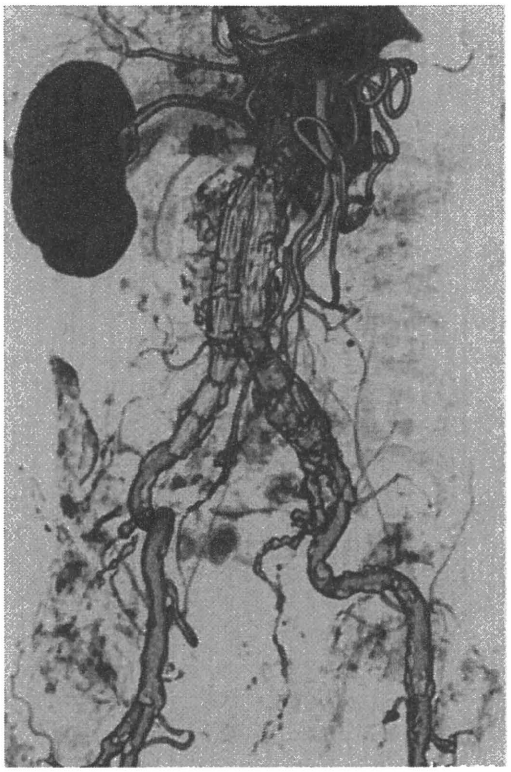

Fig. 1. Preoperative three-dimensional computed tomography (3D-CT) scan revealed no evidence of severe tortuosity of the right graft limb

Case 2

A 63-year-old woman underwent EVAR for an infrarenal abdominal aortic aneurysm with a Zenith endovascular graft (Cook Medical) in July 2008. A preoperative MR scan had shown severe tortuosity at the terminal aorta (Fig. 4). The procedure was performed with intravascular ultrasound (IVUS) guidance because of renal dysfunction, as her creatinine (Cr) level was over 3 mg/dl. An X-ray revealed kinking of the left stent-graft leg, but the left femoral artery pulse was palpable. Sixteen days after the operation, she was readmitted to our hospital complaining of coldness and pain in the lower left extremity. Her ABI dropped from 0.80 immediately after the operation to 0.45 when she was readmitted. A physical examination revealed coldness of the foot, a weak right femoral artery pulse, and inter-

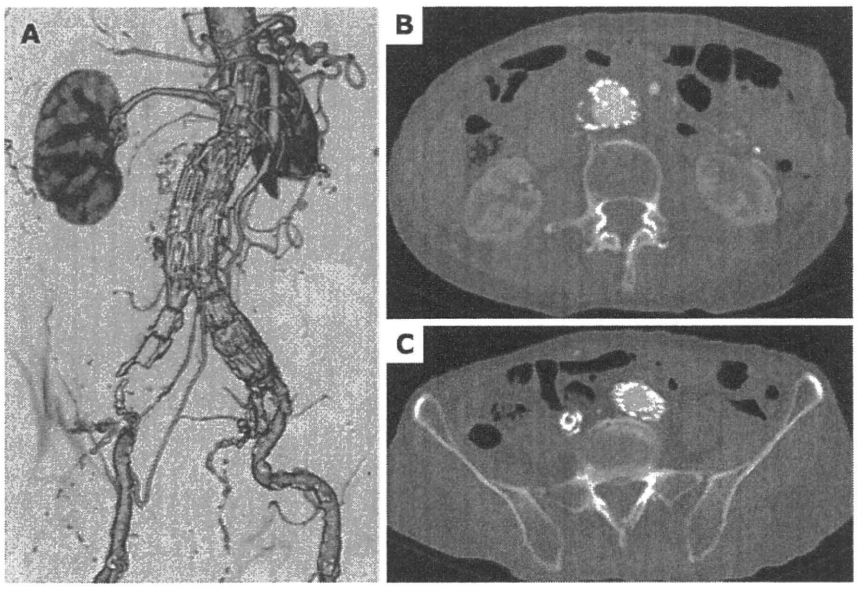

Fig. 2. The most recent CT revealed right graft limb occlusion (**A**) from the flow divider at the bifurcation of the aortic endograft (**B**) to the external iliac artery (**C**)

mittent claudication after walking 10m. An ultrasound scan showed severe stenosis of the left leg. The symptoms did not worsen, and the repair operation was performed two months after the EVAR.

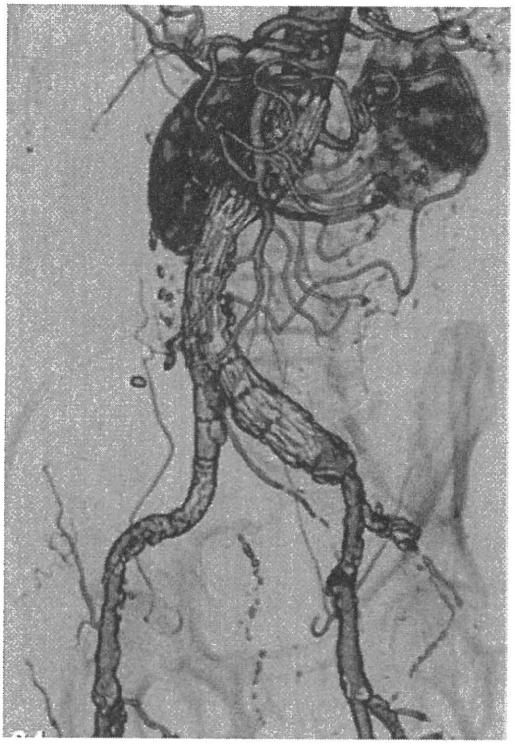

Fig. 3. Postoperative 3D-CT demonstrated patent blood flow of the right graft limb

The procedure was performed with IVUS guidance. The guidewire passed easily through the occluded lumen. A 4-F guiding catheter also passed over the flow divider along the guidewire. After confirming no blood pressure gradation between the radial artery and the level of the flow divider, a thrombectomy was performed with a Fogarty thru-lumen catheter. Balloon angioplasty was also performed to correct the kinking (Fig. 4). A Gore iliac extender was used to overlap the left leg. After the procedure, the ABI improved to 0.85. There was no indication of any endoleaks on an ultrasound scan. An X-ray revealed that the previous kinked stent graft was straightened.

Discussion

Graft limb occlusion after EVAR is a relatively common complication. We confirmed GLO in 2 of 148 cases (1.3%), which is slightly less than the rates reported in other studies,[1,2,4] possibly because we have the benefit of recent technological improvements. Maleux et al. reported nine GLO cases, among which three were treated with thrombolysis or stent insertion, five were treated with operation, and two were monitored.[4] According to the algorithm of the Trans Atlantic Inter-Society Consensus (TASC) 2, a thrombectomy is the first option for acute thrombosis.[5] However, as a thrombus in a stent graft lacks plasticity, it is difficult to remove completely and additional treatment is often necessary. An extra-anatomical bypass procedure, such

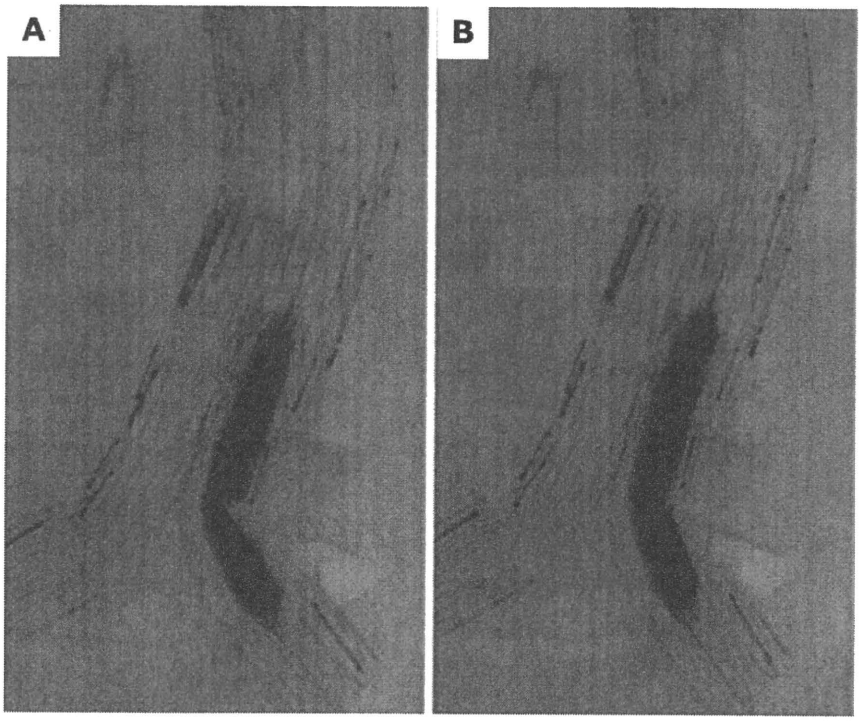

Fig. 4. A Intraoperative angiography revealed kinking of the stent-graft leg. **B** Balloon angioplasty was subsequently performed

as a femorofemoral bypass graft, would be the second option. However, this procedure is controversial because the patency is relatively low.[5] We chose to employ intravascular techniques for the treatment of GLO in order to achieve better patency by revascularization of the anatomical route. Furthermore, this procedure is less stressful for patients than open surgery,[3] and the ballooning of the stent graft can crush the remnant thrombus.[6] Finally, stent grafts can straighten tortuous iliac arteries. The use of bare stents can also bring about the same results,[3] but it may also cause shower embolization to the ipsilateral site from the crevice.

Shower embolization to the contralateral site during catheter handling is a possible complication of the procedure we utilized. We carefully observed the contralateral femoral pulse during operations in order to avoid embolization. The risk of future fabric failure by reinforcement of the stent has also been suggested as a possible complication.[1] However, using the same material for the stent-graft leg may minimize friction. The narrowing of the internal lumen is another potential problem of stent graft overlapping. Overlapping more than three times may cause reocclusion of the vessel. Touching-up with a noncompliant balloon may be necessary to create enough pressure on the overlapped site.

Cannulation of the occluded site is very important for the success of the procedure. We have found that guidewire cannulation is often possible within 2 or 3 months after limb occlusion. In Case 1, the thrombectomy was successful even after several months had passed. Various types of guidewire should be employed in order to pass through the thrombus. We usually initially use an angled Radifocus Glidewire (Terumo Medical, Shizuoka, Japan) and then carefully change to a straight guidewire to avoid arterial wall dissection. For better control of the guidewire, a thick, hard guiding catheter should be advanced around the thrombus edge.

Upon successful cannulation, a thrombectomy is usually possible. If the balloon catheter passes through the thrombus, a sheath thick enough to introduce the stent graft should be inserted. An additional stent-graft leg is subsequently deployed, and ballooning for touching up and angioplasty should be performed. Regarding the type of stent graft, we think that the structure and arrangement of the Gore Excluder endograft (Gore Medical) might be more tolerable than that of the Zenith endograft in regard of vascular tortuosity.

Regarding the possible causes of GLO, Carroccio et al. suggested that the condition was due to device kinking, migration, or device elongation to the external iliac artery.[1] In Case 2, kinking of the left leg was shown in the X-ray. This kinking should have been corrected during the initial operation. The kinking was manipulated and dilated using balloon angioplasty during the subsequent operation. If either kinking or a tortured iliac artery is noted, balloon angioplasty should be performed in order to prevent future GLO. Furthermore, a completion angiogram with the least amount of contrast medium should be performed to ensure the success of the procedure. However, the patient in Case 1 was not at risk for GLO from a hemodynamic point of view. It was assumed that GLO occurred concurrently with the patient's brain infarction. Hemoconcentration frequently occurs in such situations, and might have caused the GLO in Case 1.

The present study indicated that intravascular repair techniques and the use of stent grafts should be an early step of the GLO treatment algorithm. However, careful follow-up for these cases is necessary, because the subsequent vascular patency has only been proved for up to 12 months.

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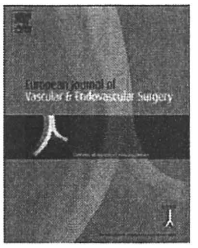

A Retrospective Study of Intravascular Ultrasound use in Patients Undergoing Endovascular Aneurysm Repair: Its Usefulness and a Description of the Procedure

K. Hoshina [a,b,*], M. Kato [b], T. Miyahara [a], A. Mikuriya [b], N. Ohkubo [b], T. Miyata [a]

[a] *Department of Vascular Surgery, The University of Tokyo Hospital, Tokyo, Japan*
[b] *Department of Cardiovascular Surgery, Morinomiya Hospital, Osaka, Japan*

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KEYWORDS
Intravascular ultrasound;
Endovascular aneurysm repair;
Contrast agents

Abstract *Objectives:* To verify the usefulness and limitation of intravascular ultrasound (IVUS) in endovascular aneurysm repair (EVAR).
Methods: A total of 112 consecutive patients, who underwent EVAR to treat abdominal aortic aneurysms, were examined retrospectively. Of these, 33 patients were assigned to the IVUS group because of renal failure, a suspected allergy to contrast agents or anatomical difficulties; the remaining 79 patients were assigned to the non-IVUS group.
Results: Patients in the IVUS group required fewer intra-arterial contrast agents (IACAs) than those in the non-IVUS group (67 ± 34 ml vs. 123 ± 50 ml; $p < 0.01$). Blood loss and operation time were comparable between the two groups. No patients died within 30 days of the operation. Three major renal complications occurred in the non-IVUS group. Renal deterioration evaluated by chronic kidney disease (CKD) stage was found to a greater extent in the non-IVUS group.
Conclusions: IVUS is a powerful auxiliary method in EVAR for reducing the required volume of contrast agents. The combination of IVUS and IACA usage showed good overall performance; thus, we propose the routine use of IVUS in EVAR procedures.

* Corresponding author. Department of Vascular Surgery, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Tel.: +81 3 5800 8653; fax: +81 3 3811 6822.
E-mail address: traruba@gmail.com (K. Hoshina).

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Introduction

Refinements in endovascular techniques have steadily improved perioperative survival rates among patients undergoing endovascular aneurysm repair (EVAR).[1] EVAR procedures require the use of intra-arterial contrast agents (IACA), which aid in verifying aortic aneurysm morphology and in identifying the ostia of renal and hypogastric arteries. However, IACA are not recommended for use in patients with renal dysfunctions or allergies to contrast agents. Since the 1990s, intravascular ultrasound (IVUS) has been used as an alternative to IACA.[2–4] Originally, IVUS images had low accuracy,[5–7] but recent improvements have resulted in very high-quality images of intra-aortic structures, which makes the use of IACA almost unnecessary.[8] An additional advantage of IVUS is that it facilitates the precise placement of stent grafts, because it is more accurate in locating hypogastric arteries and renal arteries,[2] which have parallax from the anteroposterior (A-P) view rather than from angiography.

We retrospectively studied 112 cases of EVAR performed in patients with non-ruptured infrarenal abdominal aortic aneurysms. The purpose of this study was to examine both the usefulness and limitations of IVUS, and also whether using IVUS in cases of EVAR can reduce the amount of IACA required without lowering the quality of the procedure. Furthermore, we aimed to provide a detailed description of the basic steps of the IVUS procedure to highlight its ease of use.

Patients and Methods

At Morinomiya Hospital (Osaka, Japan), 112 consecutive EVAR procedures were performed on patients with non-ruptured infrarenal abdominal aortic aneurysms (AAA) between January 2008 and November 2008. IVUS (Volcano Visions, PV 8.2F: Volcano Japan Inc., Tokyo, Japan) was used in 33 cases (i.e., the IVUS group) for the following reasons: (1) anatomical difficulties (16 cases; criteria included neck length < 15 mm, peripheral landing length < 10 mm, or overlapping aortic branches, defined as any case where aortic branches could not be clearly separated unless C-arm rotation of more than 45° was used), (2) renal dysfunction (14 cases; defined as serum creatinine level > 1.4 mg dl^{-1}) or (3) allergy to contrast agents (three cases). The remaining 79 patients received an EVAR with IACA-only (i.e., the non-IVUS group). Age, gender, aneurysmal diameter and co-morbid conditions of all patients are shown in Table 1. We also examined the factor of aortic wall condition. Shaggy aorta was defined by the presence of mural thrombus more than 3/4th of the circumflex of the thoracic aorta or the abdominal aneurysmal neck. Three shaggy aortas were observed (two thoracic and one abdominal) in the IVUS group and 21 (eight thoracic and 13 abdominal) in the non-IVUS group. Follow-ups of all cases continued for 12–24 months, postoperatively. No patients experienced severe allergic reactions to the contrast agents.

Two kinds of commercially available devices were used in this study: a Gore Excluder® AAA endoprosthesis (W.L. Gore and Associates, Newark, DE, USA) and a Zenith® endovascular graft (COOK Medical Inc. Bloomington, IN, USA). There were no definite criteria that dictated device selection. In general, we preferred to use the Excluder® for AAA with angulated aortic morphology because of its flexible stent framework. On the other hand, we preferred to use the Zenith® for AAA in cases of short aortic necks because its bare top stent facilitated firmer fixation.

Table 1 Patients' characteristics.

	IVUS	Non-IVUS	*p*-value
Age			
Gender (Male/Female)	75.1 ± 8.6	74.4 ± 8.9	N.S.
AAA diameter(mm)	52.8 ± 9.9	51.1 ± 10.9	N.S.
Risks			
Cardiac	5 (15%)	9 (11%)	N.S.
Cerebrovascular	7 (21%)	5 (6%)	0.02
Respiratory	9 (27%)	5 (6%)	<0.01
Renal	14(42%)	2(2%)	<0.01
Device			
Excluder®	24	39	
Zenith®	9	40	

The IVUS procedure steps used are summarised here. First, the bilateral common femoral arteries were exposed and a 9-F sheath introducer – the lowest profile adjusted to the 8.2-F of the outer diameter of the IVUS transducer – was inserted retrograde. A soft guidewire was used to introduce a calibrated pigtail catheter, graduated in centimetres, up to the thoracic aortic arch. The guidewire was then replaced with a stiff wire followed by IVUS insertion. IVUS was used to locate the renal arteries and hypogastric arteries by mapping them on the monitor; then, IVUS was switched to the calibrated catheter to determine the length of the main body. IVUS was introduced using the monorail system. In patients receiving IACA, a 4-F sheath was inserted into the left brachial artery to introduce the 4-F pigtail catheter, which was positioned with its tip near the ostium of the renal artery. After deployment of the main body, the soft guidewire was cannulated into the contralateral limb. The guidewire was replaced with the stiff wire, followed by the IVUS insertion (Fig. 1). The length of the contralateral site was determined by measuring the length from the edge of

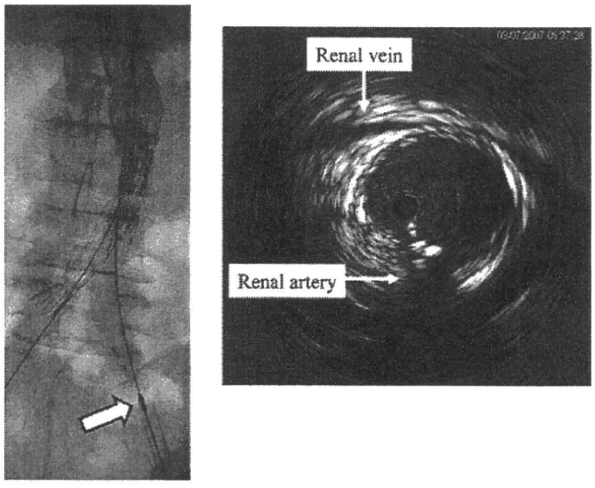

Figure 1 Transducer of the IVUS was detected on the intraoperative fluoroscopy. IVUS image showed the intra-aortic structures.