Figure 4A.3.4 Time course of induced pluripotent stem (iPS) cell generation from human T cells.

(Takahashi et al., 2007; Yu et al., 2007). However, recent studies have shown that other human somatic stem cells can also be used (Aasen et al., 2008; Eminli et al., 2009; Kim et al., 2009). Although these methods represent significant scientific breakthroughs, it is difficult to obtain human somatic stem cells; thus, a method of iPS cell generation that can be readily applied in clinical settings is needed. Blood sampling is a minimally invasive technique that can provide a source of cells. It has been reported that hematopoietic stem/progenitor cells are a useful cell source for iPS cells (Giorgetti et al., 2009; Haase et al., 2009; Loh et al., 2009), but it is difficult to obtain human hematopoietic stem/progenitor cells from patients or healthy volunteers. In the mouse, terminally differentiated B and T cells can be reprogrammed into iPS cells (Hanna et al., 2008; Hong et al., 2009). These studies reported that B cells needed C/EBPα and that T cells needed p53 knockout in addition to the introduction of the four pluripotency factors for the successful generation of iPS cells. Recently, various groups have reported on the reprogramming of human peripheral blood cells (Brown et al., 2010; Loh et al., 2010; Staerk et al., 2010; Kunisato et al., 2011). In these studies, human T cell reprogramming into iPS cells was achieved using retroviral or lentiviral vectors, but the reported efficiency of reprogramming was extremely low. We hypothesized that efficient gene transfer would result in the successful generation of human iPS cells from T cells. SeV vectors have been introduced into activated T cells with a high efficiency (Okano et al., 2003) and SeV-mediated gene transfer into fibroblast cells successfully generates iPS cells (Fusaki et al., 2009). Thus,

we used these methods to generate human iPS cells from human circulating peripheral T cells. The SeV-mediated transfer of reprogramming genes into T cells is very efficient, enabling the efficient generation of human iPS cells.

Troubleshooting

If no ES-like colony is obtained in the culture dish after SeV-mediated introduction of the four reprogramming factors, the following should be considered.

First, the density of the mononuclear cells before T cell activation in step 3 may not be appropriate. Too high a density of mononuclear cells leads to cell death, interfering with the proper activation of T cells; too low a density of mononuclear cells also disturbs the proper activation and proliferation of T cells. Proper activation of T cells is crucial for SeV infection; thus, the mononuclear cell culture should be checked and cell density adjusted accordingly.

Second, the MEF feeder layer may not withstand long periods of culture. Generating iPS cells takes a long time, and the MEF feeder layer has to last for at least 3 weeks in culture. If the MEF feeder cells are passaged many times before they are irradiated, they will not be able to withstand long periods of culture. Thus, MEF feeder cells that have been passaged only a few times should be used.

Third, the virus dosage may not be sufficient. The efficiency of TiPS cell colony generation depends on the dosage of the virus used for gene introduction. If no ES-like colonies are observed after SeV infection, the dosage of the virus can be increased up to an MOI of 20.

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Anticipated Results

The efficiency of reprogramming human T cells depends on the condition of the T cell culture and the dosage of the SeVs. Proper culture conditions and high dosages of the SeVs will generate ~50 colonies from 5×10^4 cells, a frequency of 0.1%.

Time Considerations

It takes 3 to 4 weeks from blood sampling for the TiPS cell colonies to emerge (Fig. 4A.3.4). These TiPS cells are passaged every 5 to 7 days. It takes a further 3 to 4 weeks for TiPS cells to proliferate until sufficient numbers of colonies are obtained that can be frozen as stock.

Acknowledgments

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Manipulation of Potency

4A.3.9

CASE REPORT

Successful percutaneous coil embolization of coronary–pulmonary, –carotid, and –internal mammary artery fistulas

Yohei Numasawa · Akio Kawamura · Subaru Hashimoto ·
Ayaka Endo · Shinsuke Yuasa · Yuichiro Maekawa ·
Sachio Kuribayashi · Keiichi Fukuda

Abstract We herein describe a 57-year-old man with coronary–pulmonary artery fistulas that had abnormal connections between the left common carotid artery and the left internal mammary artery. The patient was treated with percutaneous coil embolization using antegrade (via the coronary artery) and retrograde (via the pulmonary artery) approaches. Coronary artery fistulas have diverse anatomical variations, and it is important to thoroughly evaluate the anatomy before beginning any mode of treatment, surgical or endovascular. In the case reported herein, multislice computed tomography played a pivotal role in the preprocedure evaluation.

Y. Numasawa (✉) · A. Kawamura · A. Endo · S. Yuasa ·
Y. Maekawa · K. Fukuda
Department of Cardiology, Keio University School of Medicine,
35 Shinanomachi, Shinjuku-ku, Tokyo, Japan
e-mail: numasawa@cpnet.med.keio.ac.jp

A. Kawamura
e-mail: kawamura@cpnet.med.keio.ac.jp

A. Endo
e-mail: ayakaendo@cpnet.med.keio.ac.jp

S. Yuasa
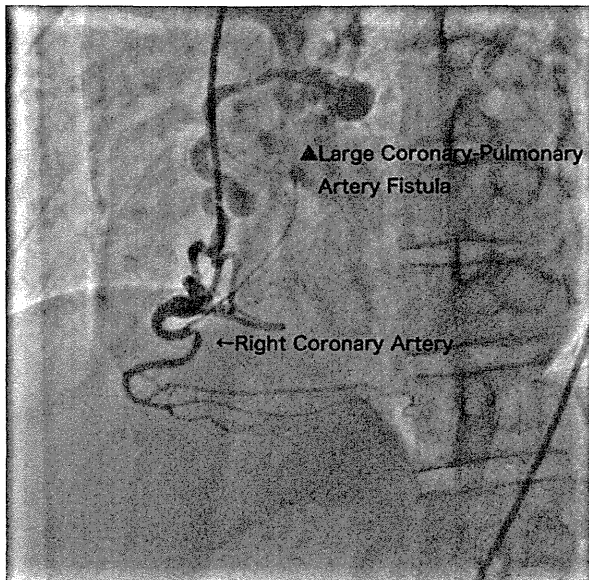e-mail: shinsuke@cpnet.med.keio.ac.jp

Y. Maekawa
e-mail: ymaekawa@gmail.com

K. Fukuda
e-mail: kfukuda@sc.itc.keio.ac.jp

S. Hashimoto · S. Kuribayashi
Department of Radiology,
Keio University School of Medicine, Tokyo, Japan
e-mail: subaru@sc.itc.keio.ac.jp

S. Kuribayashi
e-mail: skuribay@sc.itc.keio.ac.jp

Introduction

Coronary artery fistulas are relatively rare, occurring as an incidental finding in 0.06–0.2% of coronary angiograms [1–3]. Symptomatic coronary artery fistulas are managed with either transcatheter or surgical intervention. Whether endovascular or surgical treatment is planned, understanding the anatomy of the fistula is important. The majority of coronary artery fistulas originate from the right coronary artery or the left anterior descending artery, and are most likely to have a connection with the pulmonary artery, pulmonary vein, cardiac chambers, coronary sinus, or vena cava [4]. To the best of our knowledge, this is the first case report of concurrent coronary–pulmonary, –carotid, and –internal mammary artery fistulas. We report successful percutaneous embolization of these anatomically complex coronary artery fistulas using a bidirectional approach from the coronary artery and the pulmonary artery; computed tomography (CT) angiography provided vital preprocedure information.

Case report

A 57-year-old man with a history of hypertension had been suffering from exertional dyspnea, chest pain, and palpitation for 2 years. In 2003, he underwent cardiac catheterization in another hospital, and coronary angiography revealed two coronary–pulmonary artery fistulas. He was advised to undergo surgery because of his symptoms and future risks of heart failure and rupture of the aneurysmal

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Fig. 1 Angiogram of the coronary artery fistulas (selective angiogram of anterior–posterior view). One large fistula originated from the proximal portion of the right coronary artery, and it was remarkably dilated at the drainage site
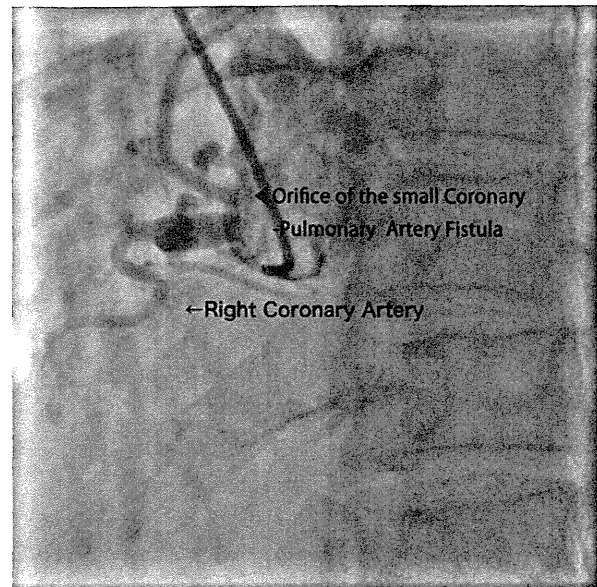
Fig. 2 Angiogram of the coronary artery fistulas (nonselective angiogram of left anterior oblique view). Another small fistula originated directly from the ascending aorta

fistula, but he refused surgical treatment. In 2009, his symptoms worsened and he was referred to our hospital. His medications were 10 mg of nifedipine, 5 mg of enalapril, 5 mg of bisoprolol for hypertension, and 100 mg of aspirin to prevent thrombosis.

The physical examination findings were normal with the exception of a continuous murmur heard at the left upper sternal border. The blood examination showed a slightly elevated brain natriuretic peptide (BNP) level (67.9 pg/ml).

Diagnostic coronary angiography revealed two coronary artery–pulmonary artery fistulas. One large fistula originated from the proximal portion of the right coronary artery, and it was remarkably dilated (Fig. 1). The smaller fistula originated directly from the ascending aorta and seemed to be derived from the isolated conus artery (Figs. 2, 3). The patient had dominant left coronary arteries, and the right coronary artery was small. There was no significant stenosis of his coronary arteries. Right heart catheterization with oximetry revealed a normal pulmonary arterial pressure, and the pulmonary-to-systemic flow ratio was 1.3.

Multislice CT angiography was performed to obtain more precise information regarding the fistulas. It confirmed that the 2 coronary–pulmonary artery fistulas originated from the proximal right coronary artery (Figs. 4, 5). In addition, other abnormal vessels had connections among the right coronary artery, the left common carotid artery, and the left internal mammary artery. We could not

recognize these abnormal arterial connections at the time of diagnostic angiography.

Although a treadmill exercise test and stress myocardial perfusion magnetic resonance imaging did not show clear evidence of myocardial ischemia, we elected percutaneous intervention for the fistulas because of the patient's symptoms and risks of future endocarditis and rupture of the aneurysmal vessel.

First, we attempted to occlude the small fistula that originated directly from the aorta in the vicinity of the right coronary orifice. A 6-Fr IMA guiding catheter (Cordis, Miami, FL, USA) was inserted into the femoral artery and engaged in the ostium of the fistula. A guidewire was introduced into the fistula, and a 2.7-Fr Progreat α (Terumo, Tokyo, Japan) was successfully advanced into the vessel. Four Micronester coils (3 mm in diameter) (Cook Medical, Inc., Bloomington, IN, USA) were then placed in the fistula (Fig. 6).
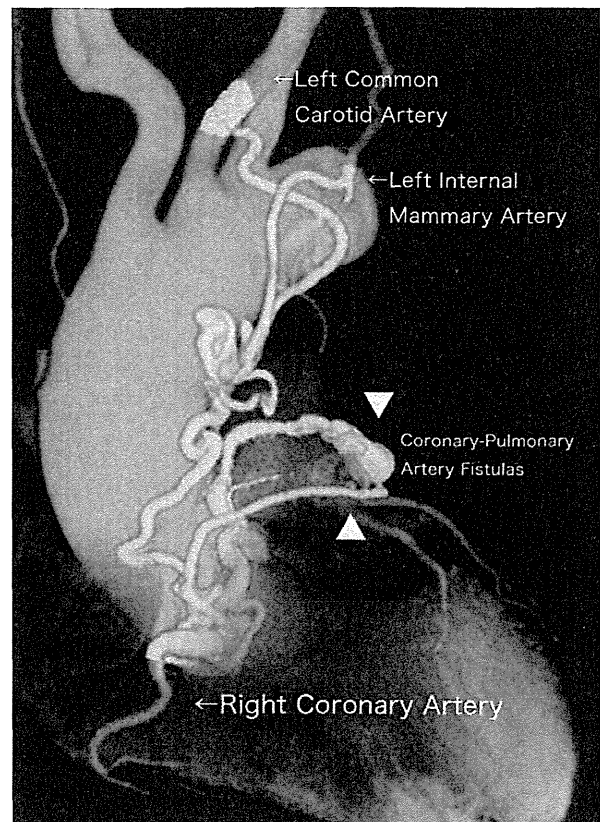
Because of severe bends of the remaining large fistula, it was difficult to perform coil embolization via the right coronary artery. Thus, we decided to occlude the second fistula via the pulmonary artery (retrograde approach, transfemoral vein). A 7-Fr Arrow 65-cm sheath (Arrow International, Inc., Reading, PA, USA) was placed in the main pulmonary artery, and a 5-Fr Mikaelson guiding catheter (Cook Medical, Inc.) was cannulated into the pulmonary arterial side orifice of the fistula. A 2.7-Fr Progreat α (Terumo, Tokyo, Japan) was successfully advanced into the fistula. Then one 6-mm, one 4-mm, and
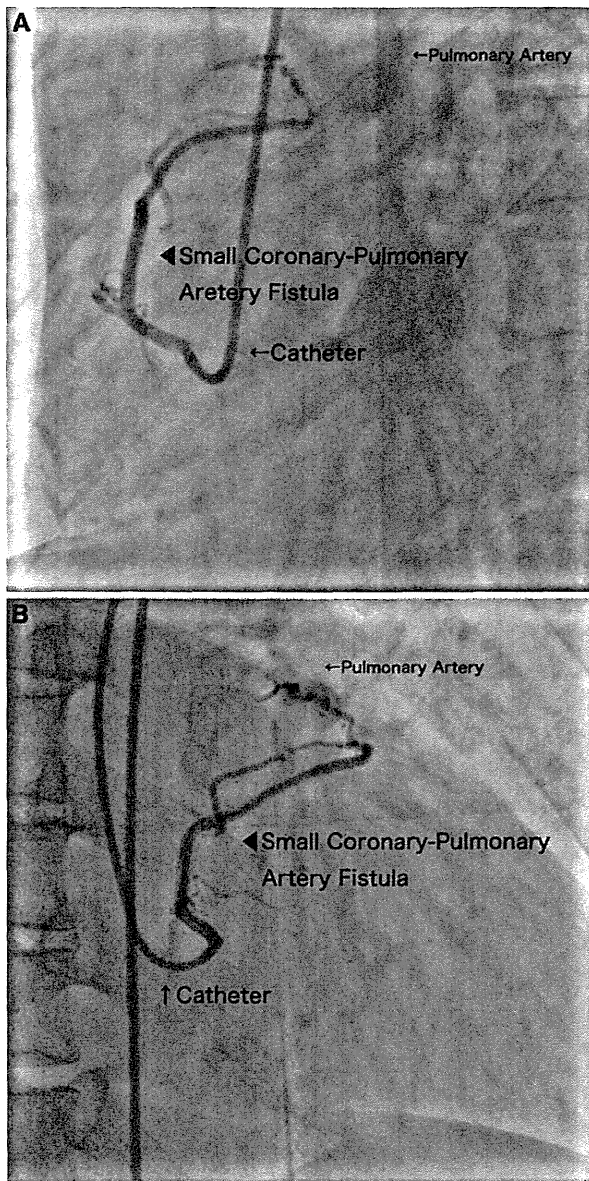
Fig. 3 Selective angiogram of the small coronary–pulmonary artery fistula (a left anterior oblique view, b right anterior oblique view). The small coronary–pulmonary artery fistula seemed to be derived from an isolated conus artery

Fig. 4 Multislice computed tomography. Multislice CT angiography showed two tortuous coronary artery fistulas, and revealed abnormal vessels that had connections with the right coronary artery, the left common carotid artery, and the left internal mammary artery

the embolized coronary–pulmonary artery fistulas were not detectable.

Discussion

Coil embolization of anatomically complex coronary artery fistulas was successfully accomplished with a bidirectional approach. The first successful transcatheter closure of a coronary artery fistula was reported in 1983 [5]. Since then, this treatment method has become more popular and is now widely available [6–11].

Since there are limited numbers of patients with coronary artery fistulas, the management is controversial and there is no guideline for the therapeutic method. In general, antiplatelet therapy is recommended, especially in patients with distal coronary artery fistulas and abnormally dilated coronary arteries [12]. Surgical closure or percutaneous intervention for coronary artery fistulas are recommended for patients with clinical symptoms, myocardial ischemia, or to prevent occurrence of endocarditis [14], rupture of the

three 3-mm Micronester coils (Cook Medical, Inc.) were deployed in the fistula (Fig. 7). The final coronary angiogram showed complete resolution of the shunt flow.

After the procedure, the patient's symptoms and cardiac murmur disappeared. The pulmonary-to-systemic flow ratio improved to 1.1, and the BNP value decreased to 14.7 pg/ml. Aspirin was discontinued after the procedure to promote thrombus formation in the embolized fistulas. One year later, multislice CT angiography was performed, and
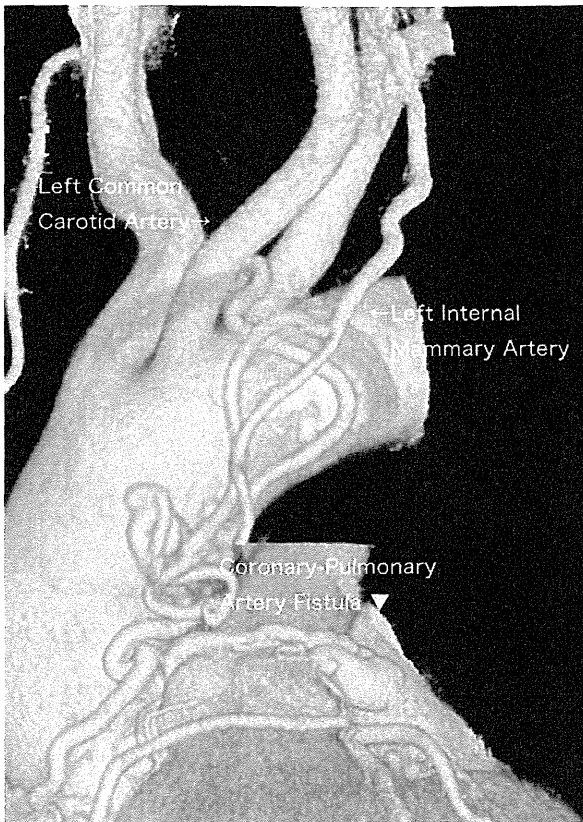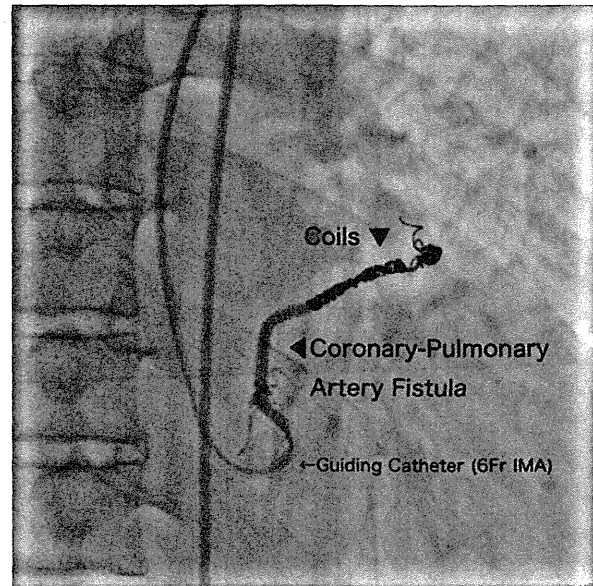
Fig. 5 Multislice computed tomography. This figure is an enlargement of the abnormal vessels that had connections with the right coronary artery, the left common carotid artery, and the left internal mammary artery

Fig. 6 Post-coil embolization angiogram (selective angiogram of the right anterior oblique view). Percutaneous coil embolization of the fistula that originated from the ascending aorta was successfully performed with an antegrade (from the arterial side) approach

Fig. 7 Post-coil embolization angiogram (selective angiogram of the anterior-posterior view). Percutaneous coil embolization of the main fistula was successfully performed with a retrograde (via the pulmonary artery) approach
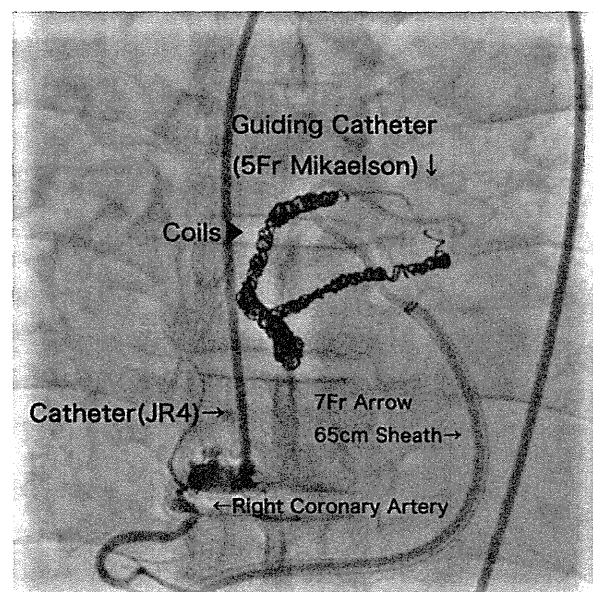
aneurysmal vessel [15–17], and heart failure [18]. However, recommendations are based on anecdotal cases or small retrospective series. There is no evidence that percutaneous coil embolization for the coronary artery fistula can reduce the risks of those complications. However, it is generally considered that disappearance of the shunt flow can reduce the risks of endocarditis and heart failure as well as those with patent ductus arteriosus. As to the management of adult patent ductus arteriosus, there is a class A indication of percutaneous closure even if it is small and asymptomatic [19].

Percutaneous intervention for coronary artery fistulas is a good choice, especially for a fistula with a single origin and drainage site and without extreme tortuosity [20, 21]. If a patient has multiple coronary artery fistulas or additional heart disease requiring surgery (e.g., ventricular septal defect, coronary artery aneurysm, or atherosclerotic coronary artery disease requiring a coronary artery bypass graft), surgical treatment is preferred [20–23].

Coronary artery fistulas have diverse anatomical variations. There have been a few case reports about internal

mammary artery to pulmonary vasculature fistulas, especially after coronary artery bypass grafting [24, 25]. However, to the best of our knowledge, this is the first case report of a congenital coronary–pulmonary artery fistula

that also had connections to both the common carotid and internal mammary arteries. The pathological meanings of the connections among the coronary artery, common carotid artery, and internal mammary artery are unclear, but seem to be minimal because each of these vessels is a part of the systemic arterial system and there are no pressure gradients among them. This was the reason why embolization was not performed for these arteries in our case. After the successful embolization of the coronary–pulmonary artery fistulas, our patient's symptoms disappeared. Thus, it seems that these abnormal arterial connections were not related to either his symptoms or coronary steal phenomenon.

Our patient had anatomically complex coronary artery fistulas. We evaluated the entire anatomy of the fistulas prior to treatment, and the procedure was successful. Multislice coronary CT angiography played a pivotal role in the preprocedure evaluation. Sometimes the origin and the precise course of the anomalous vessel are unclear during coronary angiography. We could not recognize the abnormal arterial connections between the right coronary artery, the left common carotid artery, and the left internal mammary artery at the time of diagnostic angiography. Multislice CT angiography provides a better understanding of complex anomalous anatomy before intervention by a three-dimensional display of anatomy. Datta et al. [26] reported that multislice CT angiography unequivocally demonstrated the origin of 20 anomalous coronary arteries and their courses in relation to the great vessels. Multislice CT angiography has recently become an essential noninvasive method for not only preoperative evaluation of abnormal vessels [27, 28], but also postoperative evaluation of graft patency [29, 30]. In addition, CT is useful not only for morphological diagnosis, but also for functional evaluation [31]. With the growing popularity of multislice CT angiography, more coronary–pulmonary artery fistulas with abnormal connections to other systemic arteries may be found.

The covered stent graft is another option for occlusion of coronary artery fistulas [8, 32]. In this case, it was not suitable because intravascular ultrasound showed that the size of the right coronary artery was beyond the working range of the stent. In addition, because one fistula originated from the ascending aorta, a covered stent graft was not available. Larger devices, such as the Amplatzer occluder [33] and the Chinese self-expandable occluder [34], have recently become available for larger shunts.

Percutaneous intervention of coronary artery fistulas has become a safer and more useful alternative to surgery because of improvements in endovascular techniques and devices. Whichever treatment is planned, it is essential to thoroughly evaluate the anatomy of coronary artery fistulas before treatment.

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CASE REPORT

Successful coronary intervention of chronic total occlusion of the right coronary artery by ipsilateral injection via an isolated conus artery

Takahide Arai · Akio Kawamura · Shinsuke Yuasa · Yuichiro Maekawa · Keiichi Fukuda

Abstract A conus artery is sometimes a good collateral source for the left anterior descending coronary artery and the right coronary artery (RCA). In some cases, the conus artery arises independently of the RCA from a separate orifice, which is called an isolated conus artery. The conus artery is often missed by angiography for RCA if a catheter is deeply engaged. This case report describes a percutaneous coronary intervention of chronic total occlusion of the proximal RCA with good collateral circulation from an isolated conus artery by super-selective ipsilateral injection via the artery.

Keywords Conus artery · Chronic total occlusion · Right coronary artery

Introduction

In patients with occlusion of the left anterior descending coronary artery (LAD) or right coronary artery (RCA), the conus artery often serves as a principal source of collateral circulation [1]. However, selective coronary angiography for RCA may miss the conus artery if a catheter is deeply engaged [2]. Failure to visualize the artery can result in underestimation of the collateral circulation, as well as overestimation of the length of the chronic total occlusion (CTO). While the conus artery is usually a branch of the RCA, it is reported to arise independently of the RCA from

T. Arai (✉) · A. Kawamura · S. Yuasa · Y. Maekawa · K. Fukuda
Division of Cardiology, Department of Medicine,
Keio University School of Medicine, 35 Shinanomachi,
Shinjuku-ku, Tokyo 160-8582, Japan
e-mail: tarai@cpnet.med.keio.ac.jp

a separate orifice in the right sinus of Valsalva in 45–50% of human hearts [3]. In these cases, it is called an isolated conus artery. The present case report describes a successful percutaneous revascularization of CTO of the RCA by super-selective ipsilateral injection via the isolated conus artery.

Case report

An 84-year-old male with unstable angina was referred for cardiac catheterization, which revealed a CTO of the proximal RCA (Fig. 1). The LAD provided only faint collateral circulation to the RCA. The length of the occlusion was estimated to be more than 40 mm. Because dye reaching the distal RCA through the collateral vessel was moving back and forth, other potential collateral sources were considered. With a 5-Fr right Judkins catheter withdrawn from the ostium of the RCA and rotated anteriorly, a conus artery was visualized and found to take off directly from the aorta a few centimeters above the origin of the RCA (Fig. 2). The isolated conus artery was connected to the right ventricular branch, providing good collateral filling to the distal part of the chronically occluded RCA. Percutaneous coronary intervention (PCI) of the RCA was performed by super-selective ipsilateral injection into the isolated conus artery because non-selective angiograms did not adequately opacify the distal lumen. For cannulation of the conus artery, a 6-Fr right Judkins catheter was selectively engaged to the conus artery. A 0.014-in. Fielder FC (Asahi Intec, Nagoya, Japan) was advanced distally into the isolated conus artery. Next, a 1.8-Fr Finecross microcatheter (Terumo Medical, Tokyo, Japan) was advanced over the guidewire. After the guidewire was withdrawn, blood was allowed to exit back from

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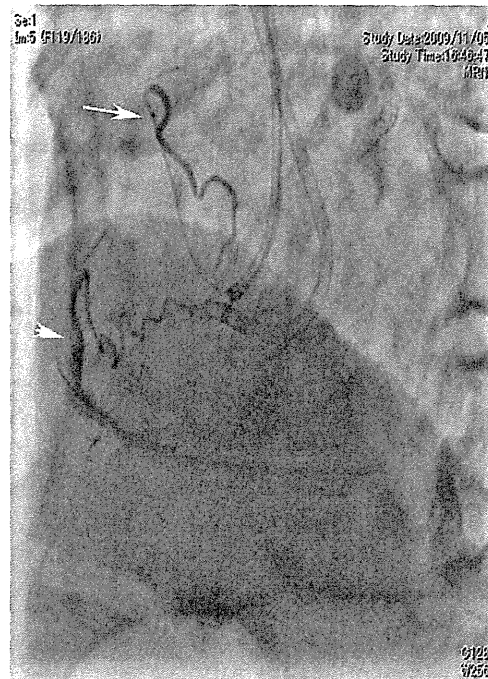Fig. 1 Diagnostic angiogram showing a chronic total occlusion of the right coronary artery (RCA)
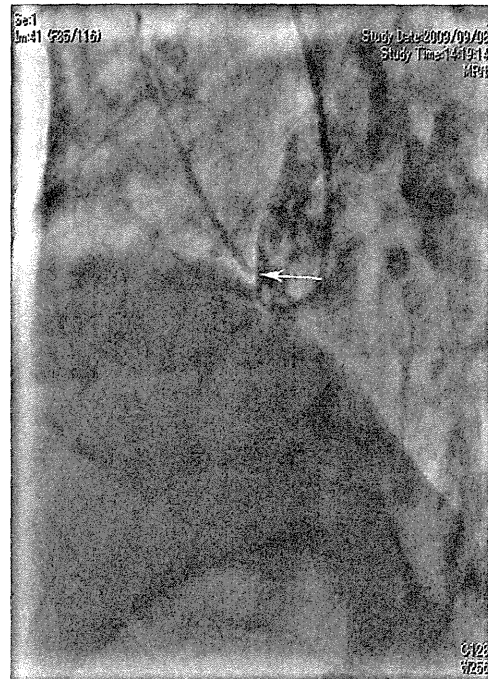
Fig. 2 Non-selective injection to visualize the isolated conus artery (*arrow*), which take off directly from the aorta a few centimeters above the origin of RCA

Fig. 3 Super-selective injection through a microcatheter in the conus artery, which was connected to the RV branch, providing collateral filling to the distal part of the chronically occluded lesion. *Arrow* shows the tip of a microcatheter and *arrowhead* shows the distal part of the chronic occluded RCA

the microcatheter. Ipsilateral injection was performed gently through the microcatheter with a minimal amount of contrast each time, providing clear visualization of the distal lumen (Fig. 3). At this point, it was evident that the occluded segment was a maximum of 20 mm in length. No major arrhythmia was induced by the injection. Finally, the occluded segment was successfully crossed with a 0.014-in. Conquest Pro guidewire (Asahi Intec, Nagoya, Japan), and three sirolimus-eluting Cypher stents (Cordis Corp., Miami Lakes, FL, USA) were deployed (Figs. 4, 5, 6).
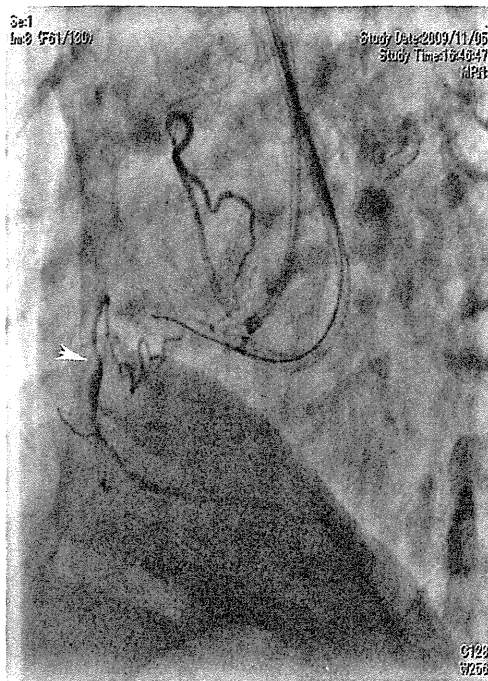
Discussion

For PCI of CTO, precise evaluation of the length and course of a totally occluded segment is crucial. The conus artery is an important collateral pathway to the LAD and RCA. For the CTO of LAD, Monopoli et al. [4] reported the case that an isolated conus artery provided a good collateral flow to an occluded LAD. For the CTO of RCA, Kerensky et al. [5] reported a CTO case with an ostial RCA occlusion with excellent collaterals directly to the proximal RCA via the conus artery. In our case, collateral circulation reached the proximal RCA via the conus artery and right ventricular branch.
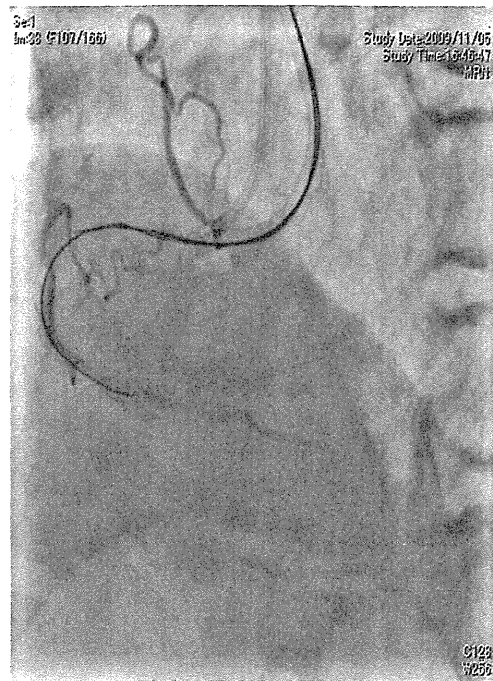
While the artery is usually a branch of the RCA, it arises directly from the aorta in approximately 50% of human

Fig. 4 A guidewire was advanced distally, while ipsilateral injection provided clear visualization of the distal part of the chronic occluded lesion (*arrowhead*)

Fig. 5 The occluded lesion was successfully crossed with a 0.014-in. guidewire

hearts based on autopsy [6]. This is called an isolated conus artery, which can be missed at the time of coronary angiography in 20% of cases. Although nonselective angiography is helpful, it can be challenging to find a relatively small conus artery if the origin is distant from the RCA. Multislice computed tomography was recently proposed to be a useful tool for detecting the isolated conus artery. Andreini et al. [7] reported that an isolated conus artery was present in 10.6% of 2,757 patients analyzed using multislice computed tomography.

Difficulties with PCI to CTOs are largely influenced by the degree to which collateral circulation is opacified. It is important to evaluate the total length of the occluded segment and to clarify the location of the distal part, which is the goal for the guidewire to reach. In our case, the LAD provided only faint collateral circulation to the RCA. The guidewire passage would have been more challenging without super-selective ipsilateral injection via the isolated conus artery. Furthermore, we could reduce the amount of contrast medium by using super-selective injection. Matejka et al. [8] reported that the use of a minimum amount of contrast medium is necessary to prevent contrast-induced kidney injury. Although we used super-selective ipsilateral injection via the isolated conus artery for the guidewire passage, super-selective contralateral injection from LAD might be also helpful. Selective conus artery catheterization

Fig. 6 Final angiogram after deployment of sirolimus-eluting stents

can cause fatal arrhythmias. Yamagishi et al. [9], however, reported that the isolated conus artery was selectively engaged and visualized in 45 patients without causing

ventricular arrhythmias. Furthermore, Kawamura et al. [10] reported that PCI of the CTO of the LAD with collateral circulation from an isolated conus artery by selective contralateral injection via the artery was successfully performed without any arrhythmias. We also performed super-selective injection from a microcatheter to obtain adequate opacification of the distal segment. A small amount of contrast was gently injected over a short duration so as not to induce major arrhythmias. Thus, we could complete PCI of the CTO of the proximal RCA by selective ipsilateral injection via the isolated conus artery without any complications (Figs. 4, 5).

Whenever sufficient collateral filling is not visualized in a chronically occluded RCA, the presence of an isolated conus artery should be suspected. Super-selective injection into an isolated conus artery can play a crucial role in successful PCI of CTO of the RCA (Fig. 6).

Conflict of interest None.

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Outcomes of Intravascular Ultrasound-Guided Percutaneous Coronary Intervention With Drug-Eluting Stents Versus Bare Metal Stents for Acute Coronary Syndrome in Octogenarians
Yuichiro Maekawa, Akio Kawamura, Shinsuke Yuasa, Yohei Ohno, Takahide Arai, Yohei Numasawa, Ayaka Endo and Keiichi Fukuda

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Outcomes of Intravascular Ultrasound-Guided Percutaneous Coronary Intervention With Drug-Eluting Stents Versus Bare Metal Stents for Acute Coronary Syndrome in Octogenarians

Yuichiro Maekawa, MD, PhD[1], Akio Kawamura, MD, PhD[1],
Shinsuke Yuasa, MD, PhD[1], Yohei Ohno, MD[1], Takahide Arai, MD[1],
Yohei Numasawa, MD[1], Ayaka Endo, MD[1], and
Keiichi Fukuda, MD, PhD[1]

Abstract

The number of percutaneous coronary interventions (PCI) performed for octogenarians with acute coronary syndrome (ACS) continue to increase. The short- and long-term outcomes of intravascular ultrasound (IVUS)-guided PCI with drug-eluting stents (DES) or bare metal stents (BMS) for ACS in octogenarians, however, remain largely unknown. We analyzed clinical outcomes of octogenarians undergoing IVUS-guided PCI for ACS with either DES or BMS. During the study period, a total of 776 patients with ACS underwent IVUS-guided PCI and 75 of them were octogenarians. In-hospital mortality tended to be lower in the DES group than in the BMS group. Between 6 months and 1 year of follow up, treatment with DES compared with BMS tended to result in fewer target lesion revascularizations. Major adverse cardiac events were similar between patients receiving DES and BMS. In octogenarians with ACS treated with IVUS-guided PCI, DES appears as safe as BMS, providing similar short- and long-term outcomes.

Keywords

IVUS-guided PCI, acute coronary syndrome, octogenarians

Introduction

The elderly population continues to increase in developed countries. Therefore, the number of octogenarians with acute coronary syndrome (ACS) has also increased and primary percutaneous coronary intervention (PCI) is frequently performed.[1,2] Octogenarians with ACS tend to have more concomitant diseases, such as cerebrovascular disease, chronic obstructive pulmonary disease, and cancer, compared to younger patients with ACS, which strongly affects the prognosis of octogenarians and may influence the PCI results.[2,3] Intravascular ultrasound (IVUS)-guided PCI has reduced thrombosis in drug-eluting stents (DES) and the need for repeat revascularization.[4] Although the use of DES in patients with ACS results in a favorable outcome, it remains unknown whether the use of DES compared to the use of bare metal stents (BMS) in octogenarians with ACS results in a favorable outcome. Therefore, we analyzed the short- and long-term outcomes of octogenarians undergoing IVUS-guided PCI for ACS with either DES or BMS.

Patients and Methods

Patient Population

Between January 2005 and December 2009, we retrospectively enrolled 776 consecutive patients who underwent IVUS-guided PCI for ACS in our institute. Of these, 75 patients were octogenarians. Of the 75 octogenarians treated with PCI, 46 were implanted with DES.

Stent Implantation Procedures

Before beginning the procedure, all patients were administered 5000 IU heparin intravenously. Additional heparin was

[1] Keio University School of Medicine, Tokyo, Japan

Corresponding Author:
Yuichiro Maekawa, Department of Cardiology, Keio University School of Medicine, Shinanomahi 35, Shinjuku-ku, Tokyo 160-8582, Japan
Email: ymaekawa@gmail.com

administered every hour during the procedure to maintain an activated clotting time of 300 seconds. Coronary angiography in all patients was performed using a 5F catheter via the femoral approach. Stent deployment was performed according to conventional methods using a 6F or 8F guiding catheter, a 0.014-inch guidewire, and a monorail balloon catheter. All patients were evaluated with IVUS. Patients underwent stent implantation after balloon predilation and received either DES or BMS. After stenting, further balloon upsizing and/or higher inflation pressures were used. Following the procedures, all patients received aspirin (81 to 100 mg/day) and either clopidogrel (75 mg/day) or ticlopidine (200 mg/day). Intravascular ultrasound catheters were inserted in target vessels and were carefully advanced distal to the culprit lesion under angiographic guidance. Continuous ultrasound imaging was performed during withdrawal of the catheter through the arterial segment at a constant rate of 0.5 mm/s.[5] Platelet glycoprotein IIb/IIIa inhibitors were not used in this study. When angiographic no-reflow occurred, intracoronary and intravenous nicorandil was used. Intra-aortic balloon pumping was used when angiographic no-reflow persisted after the final procedure. The minimum lumen diameter inside the stent and reference diameter were used to calculate diameter stenosis after the final balloon dilation. Two independent, experienced angiographers who were blinded to all other clinical data evaluated all of the coronary angiograms.

Clinical Assessments

Medical records, including medical history, physical examination, laboratory tests, 12-lead ECG, and, when available, echocardiographic findings were carefully reviewed. The following data were obtained: age; gender; coronary risk factors, including cigarette smoking, hypertension as defined by the Joint National Committee VII,[6] dyslipidemia (considered present if the total cholesterol concentration on admission was higher than 220 mg/dL or the low-density lipoprotein–cholesterol concentration on admission was higher than 140 mg/dL), diabetes mellitus as defined by the World Health Organization study group,[7] and a family history of premature coronary artery disease, defined as myocardial infarction or sudden death in a first relative, male younger than 55 years and female younger than 65 years; and concomitant medications before and after hospitalization including aspirin, clopidogrel, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins. Creatinine levels were measured just before and within 24 hours after PCI, and renal function was assessed based on the creatinine clearance using the Cockcroft–Gault formula: creatinine clearance (mL/min) = [([140 − age] × weight [kg])/72 × serum creatinine (mL/min)] (×0.85 for women).[8] Cardiac enzymes (creatine kinase and troponin T) level was measured and 12-lead ECG findings (ST shifts, T-wave changes, and Q-wave formation in all leads) were examined. In-hospital complications included pump failure (a grade of class 2 or greater according to Killip's classification or subset II or greater according to Forrester's classification) and

Table 1. Baseline Characteristics

Variable	BMS (n = 29)	DES (n = 46)	P Value
Age, year	84 ± 4	83 ± 3	.29
Male, gender (%)	66	74	.44
Hypertension (%)	72	74	.93
Dyslipidemia (%)	48	73	.14
Diabetes mellitus (%)	40	38	.87
Current smoking (%)	17	6	.22
Family history of CAD (%)	0	15	.03
Previous MI (%)	14	37	.03
Previous PCI (%)	7	37	.002
Previous CABG (%)	0	9	.10
Atrial fibrillation (%)	7	7	.95
sCr before PCI (mg/dL)	1.1 ± 0.3	1.0 ± 0.4	.72
CCr before PCI (mL/min)	47 ± 15	49 ± 16	.65
sCr after PCI (mg/dL)	1.1 ± 0.3	1.1 ± 0.4	.73
CCr after PCI (mL/min)	49 ± 15	48 ± 17	.89
Medication before PCI			
Aspirin (%)	79	95	.05
Clopidogrel (%)	42	46	.98
Beta-blockers (%)	42	79	.002
ACEI/ARB (%)	38	49	.34
Statins (%)	38	72	.005

Abbreviations: BMS, bare metal stent; CAD, coronary artery disease; DES, drug-eluting stent; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; sCr, serum creatinine; CCr, creatinine clearance; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

cardiac death.[9] Follow-up data, including the history of myocardial infarction, target lesion revascularization (TLR), and cardiac deaths related to sudden death were obtained through direct contact at an outpatient clinic, telephone interview or by reviewing the medical records of surviving patients. Major adverse cardiac events (MACE) were defined as cardiac death, myocardial infarction, or TLR. The study protocol was conducted in agreement with the guidelines of the ethics committee of our institution.

Statistical Analyses

All of the data are expressed as mean ± SD. Comparisons between 2 groups were performed using the unpaired t test or nonparametric means test for continuous variables and the chi-square test for categorical variables. All tests were 2-tailed, and a P value of .05 was considered to be statistically significant. All statistical analyses were performed using Statview 5.0 software (SAS Institute Inc) and Microsoft Office Excel (Microsoft).

Results

Baseline Characteristics

We retrospectively enrolled 776 consecutive patients in our institute who underwent PCI for ACS. Of these, 75 patients were octogenarians. Of 75 octogenarians treated with PCI, 46 were treated with DES implantation. Baseline characteristics for both groups are listed in Table 1. The mean age of the BMS

Table 2. Baseline Angiographic Variables

Variable	BMS (n = 29)	DES (n = 46)	P Value
Coronary artery disease (%)			
1 Vessel	52	26	.02
2 Vessels	17	43	.02
3 Vessels	31	31	.96
Multivessel diseases	48	73	.02
Infarct-related artery (%)			
Left anterior descending artery	59	39	.10
Left main stem	0	13	.05
Right coronary artery	31	24	.50
Left circumflex artery	10	24	.14
Reference diameter (mm)	3.2 ± 0.4	2.9 ± 0.3	.14

Abbreviations: BMS, bare metal stent; DES, drug-eluting stent.

Table 3. Procedural Variables

Variable	BMS (n = 29)	DES (n = 46)	P Value
Stent size (mm)	3.3 ± 0.4	3.2 ± 0.4	.05
Stent length (mm)	19.8 ± 5.3	18.9 ± 5.4	.47
No. of stents implanted per patient	1.3 ± 0.6	1.9 ± 0.9	.93
Maximal balloon inflation pressure (atm)	14 ± 2	16 ± 3	.03
IABP insertion (%)	10	11	.93
Final TIMI 3 flow grade (%)	93	96	.63
Reference diameter (mm)	3.3 ± 0.4	3.1 ± 0.5	.09
Luminal diameter (mm)	3.2 ± 0.5	3.0 ± 0.4	.08
Residual stenosis (%)	5.1 ± 0.7	5.4 ± 0.5	.14
Procedural success (%)	93	96	.63
Contrast (mL)	288	340	.10

Abbreviations: BMS, bare metal stent; DES, drug-eluting stent; IABP, intraaortic balloon pumping; TIMI, thrombolysis in myocardial infarction.

Table 4. Major Adverse Cardiac Events[a]

	BMS (n = 29)	DES (n = 46)	P Value
In-hospital			
Death (%)	14	4	.14
Pump failure (%)	17	17	.99
1 Year			
Death (%)	17	11	.43
Myocardial infarction (%)	0	0	1.00
TLR (%)	7	4	.63
Composite MACE (%)	24	15	.33

Abbreviations: BMS, bare metal stent; DES, drug-eluting stent; TLR, target lesion revascularization; MACE, major adverse cardiac events.
[a] Composite MACE included death, myocardial infarction, and TLR.

group was 84 ± 4 years (range 80 to 98), and that of the DES group was 83 ± 3 years (range 80 to 95). The prevalence of coronary risk factors including hypertension, dyslipidemia, diabetes, and current smoking was similar between groups. Significantly more patients in the DES group had a history of myocardial infarction and PCI compared to the BMS group. There were no significant differences in serum creatinine and creatinine clearance before and within 24 hours after the procedure between the 2 groups. Use of beta-blockers and statins was more common in the DES group than in the BMS group. Table 2 shows the baseline angiographic variables of both groups. Patients in the DES group had a higher rate of multivessel disease. There was no significant difference in the location of infarct-related arteries between the 2 groups.

Procedural Results

There were no significant differences in the implanted stent size and stent length between the BMS and the DES groups. The number of stents implanted per patient was higher in the DES group than in the BMS group. Maximal balloon inflation pressure was higher in the DES group than in the BMS group (Table 3).

Short-Term Prognosis

The number of patients with pump failure was not significantly different between groups. Patients in the BMS group tended to have higher rates of in-hospital mortality compared with the DES group (Table 4).

Long-Term Prognosis

Mean follow-up period was 12 ± 4 months. During the follow-up period, the incidence of cardiac death tended to be greater in the BMS group than the DES group (17% and 11%, respectively, $P = .43$), whereas no patients in either group suffered myocardial infarction or stent thrombosis during the follow-up period. The composite major adverse cardiac events did not differ between the BMS and DES groups (24% and 15%,

respectively, $P = .33$). The Kaplan-Meier curves for major adverse cardiac events are shown in Figure 1.

Discussion

This retrospective study was performed to directly compare the outcomes of octogenarians with ACS treated with either BMS or DES. Treatment with DES compared with BMS tended to result in fewer incidences of target lesion revascularization at 1 year. Although in-hospital mortality tended to be lower in the DES group than in the BMS group, composite MACE was similar between the DES and BMS groups.

Many randomized controlled clinical trials have demonstrated that the use of DES compared with the use of BMS significantly reduces the TLR rate, but the use of DES does not reduce the rate of MACE, including myocardial infarction and death.[10-12] In patients with acute myocardial infarction, the use of DES significantly reduced the rate of TLR, but there was no significant difference between the DES and BMS groups in the rate of death and reinfarction or stent thrombosis. We demonstrated that MACE was similar between the BMS and DES groups. The results of our study are consistent with previous
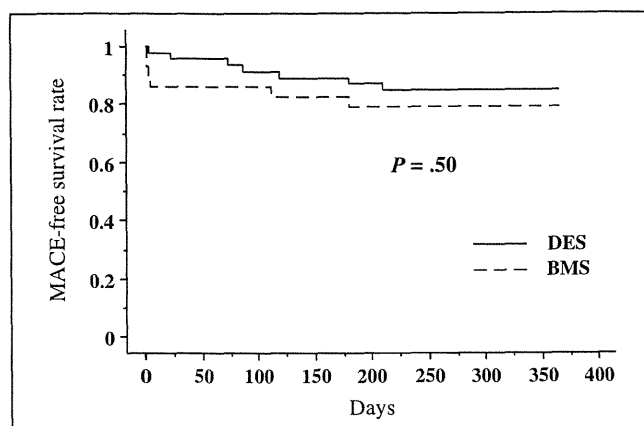
Figure 1. Major adverse cardiac events (MACE)-free survival rates. Kaplan-Meier curves of the incidence of MACE in patients with acute coronary syndrome (ACS).

findings, although the present study population comprised octogenarians.

In contrast to previous studies, no patients in the present study suffered myocardial infarction or stent thrombosis during the follow-up period. The use of IVUS for all patients and IVUS guidance during either BMS or DES implantation in the present study might have contributed to reduce the rate of myocardial infarction and stent thrombosis.[4] In addition, our results are consistent with the findings of previous studies of DES versus BMS in patients with acute myocardial infarction showing that there are no significant differences of the rate of myocardial infarction and stent thrombosis.[13,14]

Primary PCI for elderly patients has some problems.[15] The number of elderly patients with peripheral artery diseases has increased, making it difficult to perform PCI via transfemoral approach and increasing the incidence of vascular complications. The incidence of contrast-induced nephropathy is also greater in elderly patients because baseline renal function is lower in the elderly population than the younger population.[16] The prevalence of multivessel disease is more frequent in octogenarians, and may account for their poor clinical prognosis. Despite these disadvantages of PCI for elderly patients, patients in the present study did not have serious complications and complications did not influence the clinical outcome.

Study Limitations

Our study was a retrospective and observational study in a single center and the sample size was small. Therefore, the statistical power might not be strong enough to draw conclusions from any negative data. However, there are also few octogenarians undergoing IVUS-guided PCI for ACS.

Conclusions

In octogenarians with ACS treated with IVUS-guided PCI, DES appears as safe as BMS, providing similar short- and

long-term outcomes with regard to death and myocardial infarction.

Declaration of Conflicting Interests

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G-CSF influences mouse skeletal muscle development and regeneration by stimulating myoblast proliferation

Mie Hara,[1] Shinsuke Yuasa,[1,2] Kenichiro Shimoji,[1] Takeshi Onizuka,[1] Nozomi Hayashiji,[1] Yohei Ohno,[1] Takahide Arai,[1] Fumiyuki Hattori,[1] Ruri Kaneda,[1] Kensuke Kimura,[1] Shinji Makino,[1,2] Motoaki Sano,[1] and Keiichi Fukuda[1]

[1]Department of Cardiology and [2]Center for Integrated Medical Research, Keio University School of Medicine, Shinjuku, Tokyo 160-8582, Japan

After skeletal muscle injury, neutrophils, monocytes, and macrophages infiltrate the damaged area; this is followed by rapid proliferation of myoblasts derived from muscle stem cells (also called satellite cells). Although it is known that inflammation triggers skeletal muscle regeneration, the underlying molecular mechanisms remain incompletely understood. In this study, we show that granulocyte colony-stimulating factor (G-CSF) receptor (G-CSFR) is expressed in developing somites. G-CSFR and G-CSF were expressed in myoblasts of mouse embryos during the midgestational stage but not in mature myocytes. Furthermore, G-CSFR was specifically but transiently expressed in regenerating myocytes present in injured adult mouse skeletal muscle. Neutralization of endogenous G-CSF with a blocking antibody impaired the regeneration process, whereas exogenous G-CSF supported muscle regeneration by promoting the proliferation of regenerating myoblasts. Furthermore, muscle regeneration was markedly impaired in G-CSFR–knockout mice. These findings indicate that G-CSF is crucial for skeletal myocyte development and regeneration and demonstrate the importance of inflammation-mediated induction of muscle regeneration.

CORRESPONDENCE
Keiichi Fukuda:
kfukuda@sc.itc.keio.ac.jp

Abbreviations used: APRE, acute phase response element; EGFP, enhanced GFP; ERK, extracellular regulated kinase; G-CSFR, G-CSF receptor; JNK, c-Jun N-terminal kinase; MRF, myogenic regulatory factor.

Adult skeletal muscle has resident stem cells, called satellite cells, which are responsible for generating new muscle under both physiological and pathophysiologic conditions. Although these muscles have the capacity to regenerate, this capacity has some limitations (Le Grand and Rudnicki, 2007). There are several skeletal muscle diseases such as skeletal muscle dystrophy, myopathy, severe injury, and disuse syndrome for which there are no effective treatments (Shi and Garry, 2006). Although several studies have identified various growth factors and cytokines that regulate skeletal muscle development and regeneration, effective control of regeneration hasn't been achieved using these factors in the clinical setting (Buckingham and Montarras, 2008). Therefore, it is worth elucidating the mechanisms of skeletal muscle regeneration and developing novel regeneration therapies.

After injury to skeletal muscle, neutrophils, monocytes, and macrophages infiltrate the damaged area. Concomitantly, satellite cells differentiate into transient-amplifying myoblasts, which rapidly proliferate, fuse with one another, and regenerate skeletal myotubes. During these processes, inflammation and regeneration are tightly linked. Therefore, it is reasonable to assume that some factors expressed during the inflammatory process influence skeletal muscle regeneration. However, the precise mechanisms remain unknown.

Previously, when we looked for potent differentiation-promoting factors during embryonic stem cell differentiation (Yuasa et al., 2005, 2010), we noted a marked elevation in the expression of G-CSF receptor (G-CSFR; encoded

M. Hara and S. Yuasa contributed equally to this paper.

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