Percutaneous coronary intervention (PCI) is the first choice for treating simple coronary artery lesions because of the progress of coronary stent techniques in recent years. Coronary artery bypass grafting is recommended for patients with multiple, diffuse and severely diseased coronary lesions. The most important goals of coronary artery bypass grafting are complete revascularization and long-term graft patency without reintervention. The left internal thoracic artery has demonstrated superior graft patency and provided excellent clinical results compared with saphenous vein graft. Moreover, bilateral internal thoracic artery grafting has better survival benefits than single internal thoracic artery grafting and patency rates and survival benefits are satisfactory when bilateral internal thoracic artery grafts are used. However, bilateral internal thoracic artery use rate remains low for reasons including the complexity of graft configuration and risk of sternal wound infection. This review aims to address the advantages and disadvantages of using the bilateral internal thoracic artery in coronary artery bypass grafting.

KEY WORDS: coronary artery bypass grafting, internal thoracic artery

I. Introduction and background

Percutaneous coronary intervention (PCI) is the first choice for treating simple coronary artery lesions because of the progress of coronary stent techniques in recent years. Coronary artery bypass grafting (CABG) is considered a class I recommendation for all types of stenosis location except for "one vessel disease without proximal LAD stenosis" \(^9\). CABG remains the superior method for treating selected patient groups.

Saphenous vein graft (SVG) is the most popular graft used in CABG. A survey of the Japanese Association for Coronary Artery Surgery demonstrated that SVG is used more than 40% in patients undergoing CABG \(^10\). However, SVG shows poor patency rates and does not improve long-term morbidity \(^11\). Conversely, the left internal thoracic artery (ITA) has superior graft patency and excellent clinical results \(^12\). Several trials reported a 10-year patency of the left ITA of 90%–95% compared with 50% in SVG \(^13, 14\). The use of arterial conduits in CABG has been hypothesized to improve long-term results \(^15\). Therefore, some arterial grafts have been used as bypass grafts including the right ITA \(^16\), radial artery \(^17\) and right gastroepiploic artery. \(^18\). Various combinations of these arterial grafts have been employed (Fig. 1) and many retrospective studies have supported their safety and effectiveness. These findings suggest that arterial grafts are better suited for coronary bypass grafts than venous grafts. Among the arterial grafts used for CABG, ITA has the greatest long-term patency rate. Many factors regarding resistance to the development of atherosclerosis in ITA have been indicated by numerous studies: structurally, its endothelial layer shows fewer fenestrations, lower intercellular junction permeability, greater antithrombotic molecules such as heparin sulfate and tissue plasminogen activator and higher endothelial nitric oxide production. These are some of the unique ways that make the ITA impervious to the transfer of lipoproteins, which are responsible for atherosclerosis development \(^19-29\). In comparison, the radial artery has a relatively thick media and a tendency for distal intimal hyperplasia \(^30\). Therefore, the use of bilateral ITA is theoretically reasonable for CABG in terms of long-term patency and survival. Numerous observational studies and meta-analyses have demonstrated the superiority of bilateral ITA in terms of survival compared with single ITA. Current guidelines therefore recommend bilateral ITA for CABG as class IIa \(^9, 31\).

In this review, the advantages and disadvantages of using bilateral ITA in CABG are discussed. Moreover, the only randomized trial comparing bilateral and single ITA to date is reviewed.

II. Advantages of bilateral ITA grafting

Many retrospective comparative studies have investigated the
outcomes of bilateral and single ITA grafting in patients undergoing isolated CABG. In 1999, the Cleveland Clinic group conducted a long-term comparative analysis between bilateral ITA and single ITA including more than 2000 patients in each group\textsuperscript{16}. Patients undergoing single ITA grafting had a significantly higher rate of death and revascularization compared with patients undergoing bilateral ITA. This group further reported in 2004 a study comparing 1,152 propensity-matched pairs of patients receiving single and bilateral ITA\textsuperscript{37}. The mean follow-up time of this study was 16.5 years. They found that single ITA grafting was a continuous risk factor for long-term mortality during the follow-up period. Further supportive studies including meta-analyses have been reported.

In 2001, Tuggart et al. reported a meta-analysis of seven studies comprising 15,962 patients (SITA 11,269, BITA 4,693)\textsuperscript{33}. The overall finding was significantly improved survival in the bilateral ITA group (HR, 0.81; 95% CI, 0.70–0.94). Iribarne et al. reported a multicenter retrospective analysis of 1297 propensity-matched patients undergoing bilateral ITA grafting and single ITA in each group\textsuperscript{34}. The median duration of follow-up was 13.2 years. Among the matched cohort, 19.4% (n=252) of patients receiving SIMA underwent repeat revascularization, whereas this frequency was 15.1% (n=196) among patients receiving BIMA (P=0.004). Moreover, bilateral ITA grafting was associated with reduced all-cause mortality at 12 years of follow-up (HR, 0.79 [95% CI, 0.69–0.91]; P=0.001). Buttar et al. conducted a meta-analysis comprising 89,399 patients and found that the bilateral ITA cohort had significantly improved long-term survival compared with the single ITA cohort (HR 0.78; p<0.00001)\textsuperscript{35}. Furthermore, the bilateral ITA cohort also had significantly reduced hospital mortality rates (1.2% vs 2.1%, p=0.04), cerebrovascular accidents (1.3% vs 2.9%, p=0.0003) and need for revascularization (4.8% vs 10%, p=0.005). Long-term cardiac-free, myocardial infarction-free and angina-free survival was also superior for the bilateral ITA cohort. More recently, Saran et al. reported a single-center analysis comparing bilateral ITA and single ITA using propensity score matching\textsuperscript{36}. The effect of bilateral ITA use on survival in high-risk patients (ejection fraction <40%, body mass index >30, age >70 years, diabetes, chronic lung disease, cerebrovascular accident) was also evaluated. The study showed a survival advantage for bilateral ITA over single ITA (HR, 0.81; 95% CI, 0.66–0.99; P=0.043). Moreover, none of the high-risk subsets of patients showed adverse effects of bilateral ITA on survival. Many observational studies support the use of bilateral ITA for long-term survival. We also routinely use bilateral ITA for patients undergoing isolated CABG unless patients have absolute contraindications for bilateral ITA.

**III. Technical aspects of bilateral ITA**

At many Japanese institutions, ITA grafts are usually harvested in skeletonized fashion using an ultrasonic scalpel. This technique minimizes chest wall trauma, preserves sternal blood flow and obtains maximum length compared with pedicled ITA. Moreover, complex grafting techniques including composite and sequential grafting can be easily performed with skeletonized ITA. When two ITAs are used to revascularize the left coronary artery, two strategies are generally considered; (1) in situ bilateral ITA and (2) in situ left ITA with free right ITA.

1. When both ITAs are used as in situ grafts, there are two ways to use bilateral ITAs as in situ grafts to the left coronary system: in situ left ITA to the left anterior descending artery and in situ right ITA to the left circumflex artery (Fig. 2A) or in situ right ITA to the left anterior descending artery and in situ left ITA to the left circumflex artery (Fig. 2B). There is no universal consensus as to which strategy is better. In situ left ITA with skeletonization can reach any branch in the left coronary system and can be used to create sequential anastomoses to several branches; for example, in situ left ITA to the diagonal branch and left anterior descending artery or in situ left ITA to the obtuse marginal branch and posterolateral branch of the left circumflex artery. Generally, however, in situ left ITA is used for the left anterior descending artery because its course is straight and parallel to the left anterior descending artery. Conversely, in situ right ITA is limited in its length even with skeletonization. In situ right ITA is usually used for the mid left anterior descending artery, the diagonal branch, the proximal part of the obtuse marginal branch or the posterolateral branch when it is used for the left coronary artery system. Moreover, when it is used for left
circumflex artery, it is usually passed through the transverse sinus. In situ right ITA grafts are sometimes at risk of injury at reoperation. The right ITA should be wrapped in thymic tissue and covered with mediastinal fat at the end of the surgery to prevent injury upon reopening. In situ right ITA to left anterior descending artery is therefore not recommended for patients with high probability of repeat surgery, such as valve operations.

(2) When right ITA is used as free graft, it can be used for multiple grafting for the left circumflex artery (Fig. 3A and B). With this strategy, proximal anastomosis of the free right ITA is performed to the in situ left ITA, to another graft (RA or SVG) or directly to the aorta. Conversely, the left ITA is merely used as a free graft. If it is not suitable for use as in situ graft, it is used as free graft, such as injury during harvesting, subclavian artery stenosis or radiation injury. Tatoulis et al. demonstrated that the 10-year patency rates of in situ (n = 450, 89%) and free (n = 541, 91%) right ITA grafts are similar (p = 0.44)\(^\text{39}\). Furthermore, in our previous analysis, follow-up angiographic results of sequential grafts were as good as those of individual grafts\(^\text{39}\). The most popular site of proximal anastomosis of the free right ITA is the in situ left ITA using a T or Y configuration because anastomosis between two ITAs is simple as the wall characteristics are the same. The free right ITA can reach the posterior descending artery when its proximal anastomosis is conducted on the left ITA\(^\text{39}\).

IV. Drawbacks of bilateral ITA grafting

Bilateral ITA has some drawbacks. Compared with single ITA patients, bilateral ITA patients have longer operation times and a higher rate of sternal complications. Even though the operation time is longer in bilateral ITA patients, operative mortality, stroke rate and blood transfusion rate are not higher\(^\text{34}\). The biggest reason for not using bilateral ITA is the higher sternal infection rate in bilateral ITA patients. Most studies comparing the outcomes of bilateral and single ITA have demonstrated a statistically significant risk increase for sternal wound infection. Buttar et al. reported results regarding sternal wound infections: bilateral ITA patients demonstrated a significantly greater risk of

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Fig. 2 Two ways for using bilateral ITA as in situ grafts to the left coronary system: (A) in situ left ITA to the left anterior descending artery and in situ right ITA to the left circumflex artery and (B) in situ right ITA to the left anterior descending artery and in situ left ITA to the left circumflex artery.
sternal wound infection than single ITA patients (1.8% vs 1.4%, OR 1.37, p=0.0008) \(^{(30)}\). Dai et al. found in a meta-analysis of 4,701 patients that the risk of sternal wound infection in bilateral ITA patients was significantly higher than that of single ITA patients (relative risk 0.62, 95% CI, 0.55–0.71) \(^{(40)}\). Moreover, bilateral ITA grafting was associated with a higher risk of sternal wound infection in diabetic and elderly patients. However, the rate of sternal wound infection was not significantly different between the two groups when bilateral ITA was harvested with the skeletonized technique. Bonacchi et al. investigated the risk factors for sternal wound infection in patients undergoing bilateral ITA grafting \(^{(41)}\). Their multivariable logistic regression analysis revealed that any single independent predictor of sternal wound infection, any combination of peripheral vascular disease, diabetes, chronic obstructive lung disease, obesity and female sex increased the risk. The American Society of Thoracic Surgeons guidelines on arterial revascularization state that "Use of bilateral ITAs should be considered in patients who do not have an excessive risk of sternal complications" (class IIa, level B) \(^{(42)}\). Therefore, we may generally need to consider contraindications of the use of bilateral ITA, such as obesity, diabetes, chronic obstructive lung disease and elderly female patients.

V. ART trial

The Arterial Revascularization Trial (ART) is the only randomized trial comparing bilateral and single ITA grafting \(^{(43)}\). In this study, 3,102 patients were enrolled. The primary outcome was death from any cause at 10-year follow-up. Secondary outcomes were the composite of death from any cause, myocardial infarction or stroke (in a time-to-event analysis), rate of repeat revascularization and safety outcomes (including bleeding and sternal wound complications). Moreover, information on quality of life, costs and cost effectiveness was also collected and is reported separately. In the bilateral ITA group, 83.6% of patients received bilateral ITA grafts (13.9% of patients received only a single ITA graft) and in the single ITA group, 96.1% of patients received a single ITA graft. Additional radial-artery grafts were used in 19.4% of patients in the bilateral ITA group and in 21.8% in the single ITA group. As a primary outcome, 315 deaths occurred by 10 years (20.3%) in the bilateral ITA group and 329 (21.2%) in the single ITA group (hazard ratio, 0.96; 95% confidence interval [CI], 0.82–1.12; P = 0.62). As a secondary outcome, the composite outcome of death from any cause, myocardial infarction or stroke, 385 patients (24.9%) had an event in the bilateral ITA group and 425 (27.3%) in the single ITA group (hazard ratio, 0.90; 95% CI, 0.79–1.03). In this study, the as-treated analysis compared patients who received multiple arterial grafts with those who received a single arterial graft, regardless of randomization assignment. In this sub-analysis, 315 deaths occurred among 1690 patients (18.6%) in the group with
two or more arterial grafts and 307 deaths among 1,330 patients (23.1%) in the group with a single ITA graft (adjusted hazard ratio, 0.81; 95% CI, 0.68–0.95). The composite outcome of death, myocardial infarction or stroke occurred in 399 patients (23.6%) in the group with two or more arterial grafts and in 385 patients (28.9%) in the group with a single ITA graft (adjusted hazard ratio, 0.80; 95% CI, 0.69–0.93).

As an intention-to-treat analysis, this study found no significant differences between the two groups in the rates of death from any cause or the rates of the composite endpoints. However, the results in the as-treated analysis were nearly identical to those of other large observational studies. Therefore, we should carefully interpret the findings of this first randomized trial. We await the results of another randomized study, the Randomization of Single versus Multiple Arterial Grafts (ROMA) trial. It includes only patients younger than 70 years of age undergoing CABG at experienced centers to test whether multiple arterial grafts results in a lower rate of the composite outcomes of death, myocardial infarction, stroke or repeat revascularization at 10-year follow-up than single ITA.

VI. Conclusions

Bilateral ITA grafting for coronary artery revascularization has better survival benefits than single ITA grafting and patency rates are favorable when bilateral ITA grafts are used compared with any other grafts. However, there remain some problems, including the increasing rate of sternal wound infection. Moreover, further study of which patients are suitable for bilateral ITA grafting and which coronary territory should be revascularized with bilateral ITA is necessary.

Conflicts of interest

Toshihiro Fukui has no conflict of interest.

References

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