Roles of Transit-Time Flow Measurement for Coronary Artery Bypass Surgery

Yoshiyuki Takami1  Yasushi Takagi1

1 Department of Cardiovascular Surgery, Fujita Health University School of Medicine, Toyoake, Aichi, Japan


Address for correspondence Yoshiyuki Takami, MD, Department of Cardiovascular Surgery, Fujita Health University School of Medicine, 1-98 Dengakugakubo Kutsukake-cho, Toyoake, Aichi 470-1192, Japan (e-mail: mytakami@fujita-hu.ac.jp).

Abstract

Transit-time flow measurement (TTFM) has been increasingly applied to detect graft failure during coronary artery bypass grafting (CABG), because TTFM is less invasive, more reproducible, and less time consuming. Many authors have attempted to validate TTFM and to gain the clear cutoff values and algorithm in TTFM to predict graft failure. The TTFM technology has also been shown to be a useful tool to investigate CABG graft flow characteristics and coronary circulation physiology. It is important to recognize the practical roles of TTFM in the cardiac operating room by review and summarize the literatures.

Keywords

► coronary artery bypass grafting
► transit-time flow measurement
► graft flow
► coronary circulation

Introduction

Coronary artery bypass grafting (CABG) has contributed to the treatment of patients with ischemic heart disease to increase their survival and reduce ischemic complications. Anastomotic quality of CABG is directly associated with both perioperative and long-term clinical results.1 The failure of anastomosis was reported to occur in ~3% and 8% of the number of the grafts and patients, respectively.2 Increased number of patients with diffuse coronary artery disease associated with diabetes mellitus, renal insufficiency, cerebral, and peripheral artery disease has made it extremely important for cardiac surgeons to evaluate the quality of the anastomosis of CABG in the operating room. It is still more important in off-pump CABG (OPCAB) that is technically demanding.

It was traditionally common for a surgeon to determine the adequacy of the anastomosis based on palpation of the graft pulsation, hemodynamic stability, and electrocardiographic changes, which are all indirect and unreliable. To increase reliability, several methods have been advocated for intraoperative assessment of the anastomotic quality of CABG, including SPY system, electromagnetic flowmeter, and Doppler imaging using a direct contrast-indocyanine.3–5 Among these, transit-time flow measurement (TTFM) (Medi-Stim, Oslo, Norway) is considered to be more convenient, less invasive, more highly reproducible, and less time consuming.

Many authors have attempted to validate TTFM and to gain the clear-cut values and algorithm in TTFM to predict graft failure. TTFM has also been used as a tool to investigate CABG graft flow characteristics and coronary circulation physiology. In this article, we have reviewed the literatures regarding TTFM analysis of CABG graft flow to better understand the roles of TTFM in the cardiac operating room.

TTFM Principles

The TTFM is based on the principle that the time required for ultrasound to move through blood is slightly longer upstream than downstream.6 The TTFM utilizes the propagation time of the ultrasonic signal through the blood. A pair of ultrasonic transducers is installed on the outer surface of the flow probe as shown in Fig. 1. Each transducer of the probe works alternatively as both transmitter and receiver of ultrasonic signals. When the ultrasonic signal is transmitted toward the downstream side against the flow direction, more propagation time (T1) is required. However, when it is transmitted toward the upstream side with the flow direction, the propagation time (T2) is less. The difference in time between T1 and T2 is proportional to the flow velocity, and the flow volume can be calculated by multiplying it by the cross-sectional area, which is obtained by using the probe diameter. These processes are performed...
several hundred times per second, detecting the transit-time differences in picoseconds in transit time. Because the ultrasound beam is wider than the diameter of the vessel lumen, it is not necessary to know the vessel diameter or perform any complex calibrating procedures for zero correction. Historically, Franklin et al 14 and Plass 8 reported the flowmeters using this principle in the 1960s. Thereafter, several researchers verified the accuracy of the blood flow measurement using TTFM technology by in vitro and in vivo experiments.9,10

TTFM Parameters in CABG
The following parameters of TTFM in CABG are illustrated in Fig. 2 and summarized in Table 1.

Mean Graft Flow
The quantitative assessment study investigated the relationships between the intraoperative mean graft flow (MGF) values (mL/min) and postoperative angiographic findings of the CABG grafts.13 It revealed that the stenosis severity of the heel of graft anastomosis, which was greater than those of the toe, was significantly correlated with MGF values, suggesting that the MGF value reflects the quality of CABG graft anastomosis. This finding was supported with the study using intraoperative imaging by an ultrasound scanner, concluding that OPCAB causes a narrowing of the coronaries, especially at the anastomotic heel.12

However, when we see MGF, we must take into account other influencing factors than graft anastomotic stenosis, including graft diameter, perfusion area, myocardial viability, myocardial oxygen consumption, blood pressure, and coronary vascular resistance. Honda et al13 demonstrated that the MGF increased as coronary stenosis severity evaluated via fractional flow reserve (FFR) of the native coronary artery increased. Severe (FFR < 0.70), mild (0.70 ≤ FFR < 0.75), and nonstenotic lesions (FFR ≥ 0.75) referred directly to MGF values. In mild coronary artery stenosis, the chance of flow competition between the native coronary artery and the bypass graft increased.

MGF Threshold
In 1998, Walpoth et al14 reported that MGF of > 20 mL/min was the predictor for early graft failure in CABG. Thereafter, several authors accepted lower threshold values, with an MGF of <15 mL/min and <10 mL/min, respectively.15,16 In 2010, European Association for Cardio-Thoracic Surgery (EACTS)/European Society of Cardiology (ESC) Guidelines17 recommend an MGF of ≥20 mL/min as acceptable.

MGF and Target Coronary Artery
The cutoff values of MGF may vary with the target coronary arteries. As Gregg et al18 demonstrated in the normotensive dog at rest, the pulsatile right coronary artery (RCA) blood flow pattern differed in appearance from left coronary artery (LCA) flow patterns. Lowensohn et al19 also revealed that RCA systolic flow was significantly greater than LCA systolic flow, according to the relationships between coronary perfusion pressure and intramyocardial tension. Therefore, an antegrade flow occurs more easily during cardiac systole in a graft to RCA than to LCA. Tokuda et al20 reported that the optimal cutoff values of grafts to the LCA and that to right coronary arteries were MGF of 15 mL/min and 20 mL/min, respectively.

MGF and Graft Conduits
The cutoff values of MGF also vary with the graft conduits, including internal thoracic artery (ITA), saphenous vein (SV), radial artery (RA), and right gastroepiploic artery (RGEA). Lehnert et al21 defined the MGF threshold of ITAs > 20 mL/min, with an observed 4% decreased risk of graft failure for every 1 mL/min increase in MGF. Honda et al13 pointed out that reduced MGF of <15 mL/min was found to be nonpatent ITA grafts at follow-up. As Shin et al22 indicated, vasospasm is so
frequently observed in ITAs that MGF values of the ITA grafts are relatively lower, even with no anastomotic problems and other indicators such as pulsatility index (PI). In an experimental animal model, Pagni et al.\(^23\) also showed that competitive blood flow decreased graft flow rate on ITAs than on SV grafts, which is particularly evident during diastole.

As for SV grafts, Lehnert et al.\(^21\) recommended MGF of > 40 mL/min. Une et al.\(^24\) identified that MGF of < 31 mL/min was associated with 50% 1-year SV graft occlusion. Therefore, acceptable MGF for SV grafts should probably be higher than for ITA grafts.

Contrary to ITAs and SV grafts, Lehnert et al.\(^21\) did not find any correlation between MGF and RA graft failure, but general conclusions are limited due to the small number of the studies. Similarly, Uehara et al.\(^25\) found no significant differences in MGF values of occluded versus patent RGEA grafts to the RCAs. They suggested that the MGFs of patent RGEA grafts are relatively lower than the value obtained with ITA or SV grafts, because RGEA is a visceral artery and the fourth branch of the aorta. Although variable, intraoperative TTFM profiles of the functional in situ GEA grafted to RCA are classified into four types as systolic protruded, trapezoidal, sine-waved, and diastolic-dominant biphasic, according to the disease severity of the target RCA to be grafted.\(^26\)

### MGF and Outcomes

Early graft failure may result from reduced initial MGF associated with anastomotic error, lesions of the conduit, competitive flow, insufficient distal runoff, and reduced target vessel diameter.\(^23\) Although TTFM is useful to identify grafts at risk during the early postoperative period, the correlation between TTFM and late graft failure remains questionable, because there are multifactorial.\(^28\)

### Pulsatility Index

The PI is defined according to the equation; PI = (maximum flow volume – minimum flow volume/mean flow volume). The PI value is considered to reflect the vascular resistance. Therefore, a high PI value is an indicator of poor graft quality or poor anastomosis. When the graft flow is competitive, PI is high because the minimal flow volume is negative. While Jokinen et al.\(^29\) and Di Giammarco et al.\(^30\) reported a PI > 3.0, Tokuda et al.\(^20\) reported a PI > 5.0 as a predictor for early graft failure. Kim et al.\(^31\) also reported a PI > 3 in the left coronary territories and > 5 in the right coronary territories as criteria for detection of abnormal graft flow. In 2010 EACTS/ESC Guidelines,\(^17\) a PI of > 5.0 was indicated as technically inadequate. However, competitive native coronary blood flow may affect PI values.\(^13\)

### Diastolic Filling Index

By synchronizing with electrocardiogram signals, it is accurate to identify the diastolic and systolic components of the graft flow waveform. The diastolic filling (DF) index (%) is defined by the equation; DF = [total diastolic flow/total diastolic flow + total systolic flow]. In animal experiments by Morota et al.,\(^32\) the same index of diastolic component as DF index showed higher specificity and sensitivity than the indicators such as PI in detecting anastomotic stenosis. Gregory\(^33\) advocated that the DF value should be > 50% and ideally > 65%. Furthermore, when both PI and DF index display good values, the graft quality must be excellent. The DF index of > 50% seems to be acceptable in all but one study with a recommended DF of at least 25%.\(^15,16,24\)

### Systolic Reverse Flow

The systolic reverse flow (SRF) or backward flow is the percentage of the flow curve area below the zero line, allowing to identify an oscillatory flow through the graft.\(^13,34\) There seems to be a correlation of an increased backward flow through the grafts and a worse outcome at follow-up. A SRF of ≥ 3% was proposed a parameter to detect graft failure.\(^13,30,33\) Tokuda et al.\(^20\) also reported that a backward flow of ≥4.1% was a predictor for early graft failure in grafts to LCA, and that the optimal cutoff value of grafts to RCA was 4.6%. In addition, Handa et al.\(^15\) introduced the
maximal graft flow acceleration (max df/dt) as a new reliable indicator to determine graft failure.

Fast Fourier Transforms Analysis
Some reports demonstrated that graft flow waveform is also important in relation to graft patency, because graft flow waveform affects the perfusion area of target vessels, coronary resistance, graft resistance, and quality of anastomosis. To express the flow pattern as the numeric value, fast Fourier transforms (FFT) analysis has been introduced. FFT analysis is based on the principle that all periodic waveforms can be broken down into a series of pure sine waves or harmonics. Harmonics exist at frequencies that are multiples of the frequency of the original waveform (the fundamental frequency) and are described in terms of amplitude and phase. The pulsatile waveforms of graft flow in CABG can be considered to be periodic with a fundamental frequency (the heart rate).

As a parameter representing gradual decrease in power of the harmonics of the fundamental frequency, a FFT ratio ([F_0] / [H_1], where [F_0] is a power of the fundamental frequency and [H_1] is a power of the first harmonic) was proposed. A patent graft showing smooth attenuation of the FFT spectrum curve has a [F_0] / [H_1] value of > 1.0, while a stenotic or occluded graft showing uneven attenuation has a [F_0] / [H_1] value of < 1.0. Using the Transonic Inc. TTFM, Koenig et al. reported in the animal experiment of ITA-LCA grafting in dogs that FFT analysis of blood flow is useful to detect anastomotic failures. In addition, Hatada et al. reported that the sum of 10 harmonic spectrum powers is useful to detect graft failures.

Limitation of TTFM
A randomized trial reported a low sensitivity of 25% and a specificity of 98% to detect > 50% graft stenosis or occlusion by TTFM, using the following cutoff values: MGF > 10 mL/min, PI < 5, and DF > 50%. Walker et al. reported that normal TTFM values were observed in cases of distal anastomotic occlusion with pathological antegrade, but preserved retrograde coronary flow. TTFM cannot detect a proximal or distal coronary stenosis. Une et al. reported the low diagnostic accuracy of MGF for SV grafts with a sensitivity of 63.6% and a specificity of 67.4%. This concerns us about unnecessary graft revisions by using TTFM. Therefore, surgical judgment is critically important in addition to TTF analysis when deciding whether an individual graft should be revised. Since a common definition for critical graft failure remains obscure as these findings showed, the current EACTS/ESC guidelines in 2014 include TTFM for direct intraoperative quality control in CABG surgery with class IIb recommendation and level of evidence C, although the guidelines in 2010 recommend an MGF of ≥ 20 mL/min as acceptable.

Although MGF is theoretically independent from the vessel diameter, it does not mean that MGF is independent of the probe’s size. There may be differences in MGF values when a “little bit smaller” probe is used for a “little bit larger” graft and when a “little bit larger” probe is used for a “little bit smaller” graft. Therefore, it is recommended to immerse the part of the graft with a “little bit larger” probe in warm water filled in the mediastinum during intraoperative TTFM, to avoid the interference in graft diameter.

To increase diagnostic accuracy of TTFM, high-resolution epicardial ultrasonography (HR-ECUS), with a 15 MHz probe incorporated into VeriQC (Medi-Stim AS, Oslo, Norway) for TTFM, has been recently implemented in the intraoperative graft verification procedure. By color-flow mapping along with a longitudinal and a cross-sectional scan of a 3-cm distance across the coronary anastomosis, it is able to reveal morphological failures at graft body and anastomotic site, including suture crossover, intimal flap, purse-string effect, and deep stitch at the toe or heel level. Di Giammarco et al. recommended the simultaneous use of the two methods provides functional (TTFM) and morphological (HR-ECUS) information with maximal increase in diagnostic accuracy of the graft verification procedure.

Studies Using TTFM
Its convenience, reliability, and reproducibility enable TTFM to be a useful tool to obtain the data of the coronary circulation as well as graft blood flow in CABG. TTF technology gave the possibility to investigate the functional behavior of CABG.

Effects of IABP upon Graft Blood Flow in CABG
There have been some studies regarding hemodynamic effects of intra-aortic balloon pumping (IABP) upon CABG graft flows. In an animal model, IABP increased diastolic flow by 75% in aorto-coronary (A-C) bypass grafts and by 38% in ITA grafts. Clinical studies, Onorati et al. found significant increases of 50% to 90% in blood flow in all types of grafts, and Rubino et al. reported an increase in
graft flow of 55% to 95% with IABP after CABG. Takami et al.\(^4\) also reported that (1) the IABP assist device significantly increases graft flow by 23% and its diastolic components of all types of grafts, (2) the degree of increase in flow is greater in the in situ ITA onto the left anterior descending (LAD) than in the A-C grafts anastomosed with other coronary arteries, and (3) the effect of IABP to increase the diastolic component is greater with the A-C grafts than with the in situ ITAs.

In contrast to these studies, Nakajima et al.\(^4\) reported no significant difference in graft flow between on IABP and off IABP after OPCAB. They suggested that autoregulation may be preserved or minimally damaged during OPCAB, in contrast to ONCAB. Therefore, the increase in flow with IABP with the increase in diastolic pressure may be attributable to a hyperemic state induced by cardiopulmonary bypass and cardiac arrest.

**Effect of Sympathetic Stimulation upon RGEA Graft Flow**

The RGEA is an alternative arterial graft because its anatomic location and vessel diameter allows it to be used as an in situ graft to the posterior coronary arteries. However, blood flow through the RGEA graft may be compromised and fail to meet demands when sympathetic tone increases during exercise or emotional stress. Ryu et al.\(^5\) evaluated the effect of sympathetic stimulation with noradrenaline infusion on blood flow through an RGEA graft in comparison to an ITA graft after OPCAB. They demonstrated that sympathetic stimulation increased, rather than compromised, both the absolute blood flow and blood flow in proportion to cardiac output through the RGEA graft after coronary revascularization.

**Effects of Graft Design upon Graft Flow**

Use of multiple arterial grafts improves long-term outcomes after CABG.\(^6\) The current trend in CABG is to achieve a complete coronary revascularization that maximizes arterial and sequential graftings. However, the patency of the distal end-to-side anastomosis of the sequential bypass may be inferior to that of an individual graft. Using intraoperative TTFM, Gwozdziewicz et al.\(^7\) compared blood flow through an individual SV graft with that in a distal segment of the sequential SV graft performed on the beating heart. They showed that the flow through an individual bypass was comparable with that through the distal segment (end-to-side anastomosis) of a sequential bypass, even if the sequential bypass graft is anastomosed to the coronary artery with a large perfusion area. As for a sequential bypass, Nordgaard et al.\(^8\) found increased blood flow in sequential SV graft (SVG) compared with single SVG. They also revealed that the blood flow increased according to the number of distal anastomoses, that this observation was consistent for both male and female patients, with male patients exhibiting the highest flows, and that there was no difference in PI between sequential and single grafts.

Composite conduits with either a Y or T configuration have been advocated to maximize the benefits of ITA revascularization. However, concerns have been raised regarding the possibility of hypoperfusion when these composite conduits are adopted. Using TTFM, Gaudino et al.\(^9\) investigated the flow reserve of a Y graft of bilateral ITAs after the injection of a bolus of 20 μg/kg dobutamine. They showed that new reserve after dobutamine load is ≥ 2.0 not only in the main stem of the ITA but also in each ITA branch. This finding may verify the safety of Y conduits in terms of hemodynamic potential. To confirm the
appropriateness of blood supply with the composite configuration, Onorati et al\textsuperscript{55} investigated TTFM at baseline and during 1:1 IABP in the patients receiving the RA as an A-C bypass or as a Y-graft with the left ITA. Baseline minimum diastolic flow, MGF, minimum systolic flow, and PI were comparable. However, IABP-induced graft flow reserve was more highly recruited in composite Y-conduits than in A-C grafts, regardless of the grafted territory and the perfusion strategy.

**Effects of Cardiopulmonary Bypass upon Graft Flow**

A study compared the quality of anastomoses performed in OPCAB with those performed in conventional CABG using the intraoperative TTFM,\textsuperscript{56} demonstrating significantly lower flows in all coronary territories in grafts performed using OPCAB in comparison with those performed conventionally. This finding was postulated that there is myocardial ischemia causing coronary vasodilatation in cases of on-pump CABG (ONCAB) and cardioplegic arrest, whereas in cases of OPCAB vasoconstrictors are commonly given, causing coronary vasoconstriction and consequently less flow. However, Hassanein et al\textsuperscript{57} reported no difference in flow in the LAD territory despite of significant differences in other territories, associated with less accessibility to the circumflex territory in OPCAB. They showed significantly lower flows and higher pulsatile indices in anastomoses performed in OPCAB in comparison with conventional CABG.

Balacumaraswami et al\textsuperscript{58} investigated arterial pressure and blood flow in bypass grafts and compared ONCAB with OPCAB. After ONCAB, graft flow was significantly higher for all grafts than after OPCAB, and the flow/pressure ratio was greater for all grafts after ONCAB. Increased graft flow despite of lower arterial pressure may result from reactive hyperemia and impairment of autoregulation due to cardiopulmonary bypass and myocardial ischemia.

**Effects of Atrial Fibrillation upon Graft Flow**

Shin et al\textsuperscript{59} investigated the direct effects of atrial fibrillation on the bypass graft flow by inducing atrial fibrillation by high frequency atrial pacing during CABG. The TTFM showed that atrial fibrillation significantly reduced the graft flow. The effect was much greater in ITA grafts with strong high diastolic dependence than in SV grafts.

**Effects of Pacing upon Graft Flow**

D’Ancona et al\textsuperscript{60} investigated modifications of CABG grafts flow during two different pacing modalities, dual-chamber pacing (DDD), and ventricular pacing (VVI). The TTFM showed that the MGF during DDD pacing was significantly greater than that during VVI pacing, associated with improvement in systemic hemodynamics during DDD versus VVV pacing. Therefore, DDD mode should be preferred in patients requiring pacing immediately after CABG to allow for maximal grafts flow. Although systemic hemodynamics was not influenced by the atrioventricular (AV) delay value, grafts flows achieved an optimal level at 175 ms of AV delay and a minimum level toward 25 ms of AV delay.

**Effects of Collaterals upon Graft Flow**

Verhooye et al\textsuperscript{61} performed TTFM of flow across left coronary grafts to determine their contributions to collateral blood flow. In the patients with triple vessel disease and chronic occlusions of the RCA who underwent OPCAB, the flow through the left coronary grafts was measured before and after unclamping of the RCA bypass graft. They observed that a significant decrease in blood flow across the right ITA grafted onto the left circumflex artery after unclamping of the SV graft to the occluded RCA. Since a significant relationship between the differences in ITA flow before versus after unclamping and the collateral blood flow, the collateral to the occluded RCA proved to be provided by the left circumflex artery.

**Effects of Aortic Valve Replacement upon Graft Flow**

Hassanein et al\textsuperscript{62} reported the influence of prosthetic valve type on the flow in the bypass grafts implanted to the ascending aorta after concomitant aortic valve replacement and CABG. They demonstrated that the turbulence downstream flow profile in the ascending aorta affected the flow in the bypass grafts. Receiving a mechanical aortic valve, rather than a bioprosthesis, was found to be an independent risk factor for low flow in the bypass grafts.

**Application of Doppler Velocity Probe**

Doppler velocity measurement is also useful to locate intramyocardial vessels during CABG.\textsuperscript{63} It can be used for dissection of the mediastinal structures during redo procedures to identify the patent coronary grafts and to avoid graft injury.\textsuperscript{64} Using a 7.5-MHz Doppler probe incorporated into Veri QC, it was observed that the LAD flow is preserved at least 50% through a 1.5-mm intracoronary shunt, although the flow pattern was attenuated, during OPCAB anastomosis.\textsuperscript{65}

**Future Challenges**

Complex factors affecting the flow dynamics make it difficult to define the cutoff values of TTFM to detect early CAGB graft failure in the operating room, including graft diameter, perfusion area, myocardial viability, myocardial oxygen consumption, blood pressure, distal runoff, and coronary vascular resistance. Further scientific studies are needed to pursue the precise cutoff values by controlling these factors and by collaborating with cardiologists, anesthesiologist, and physiologist.

No studies revealed whether TTFM is useful to predict and improve the long-term outcomes after CABG. Further studies are needed to determine which parameter predicts long-term outcomes, MGF, PI, DF index, SFR, or FFT analysis. Otherwise, the TTF parameters may not be less important than the progression of coronary artery disease, uncontrolled diabetes mellitus, or higher low-density lipoprotein, to predict long-term outcomes.

**Conclusions**

For cardiac surgeons and anesthesiologists in the operating room, TTFM is a reliable, simple, and less invasive tool for...
diagnosis and research of CABG grafts and coronary circulation. In addition to flow measurement, a 15 MHz HR-ECUS probe and a 7.5-MHz Doppler probe incorporated into Veri QC are anticipated to be applied aggressively. Further investigation from both functional and morphological points of view will improve the quality of CABG surgery and enhance our knowledge of coronary physiology and pathology.

Conflict of Interest
None.

Financial Disclosure
None.

References
64 Lotus AA, Owens WA. Intraoperative Doppler velocity measurements to locate patent ITA grafts at reoperation. Ann Thorac Surg 2006;82(03):1108–1110

Role of TTFM for CABG

Takami, Takagi

433