

Research Article

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Long Term Follow up After Successful Recanalization of Coronary Artery Chronic Total Occlusion Using Antegrade Versus Retrograde Approach by Single Photon Emission Computed Tomography

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ABSTRACT

Background: Coronary chronic total occlusions (CTOs) represent the most technically challenging lesion subset that interventional cardiologists face. CTOs are identified in up to one third of patients referred for coronary angiography and remain seriously undertreated with percutaneous techniques. The complexity of these procedures and the suboptimal success rates over a long period of time, along with the perception that CTOs are lesions with limited scope for recanalization, account for the underutilization of CTO Percutaneous Coronary Intervention (PCI).

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Introduction

Coronary Artery Disease (CAD) (or atherosclerotic heart disease) is the end result of the accumulation of atheromatous plaques within the walls of the coronary arteries that supply the myocardium with oxygen and nutrients. It is sometimes also called Coronary Heart Disease (CHD) [1].

As the degree of coronary artery disease progresses, there may be near-complete obstruction of the lumen of the coronary artery, severely restricting the flow of oxygen-carrying blood to the myocardium. Individuals with this degree of coronary artery disease typically have suffered from one or more myocardial infarctions (heart attacks), and may have signs and symptoms of chronic coronary ischemia, including symptoms of angina at rest [1].

A distinction should be made between myocardial ischemia and myocardial infarction. Ischemia means that the amount of blood supplied to the tissue is inadequate to supply the needs of the tissue. When large areas of the myocardium become ischemic, there can be impairment in the relaxation and contraction of the myocardium. Infarction means that the tissue has undergone irreversible death due to lack of sufficient oxygen-rich blood [2].

Periprocedural myocardial injury (PMI) is one of the noticed complications of percutaneous coronary intervention (PCI). PMI was defined as the subset of patients who had evidence of prolonged ischemia as demonstrated by persistent chest pain (>20 minutes), new pathological Q waves seen on the electrocardiogram, or cardiac troponin level elevation using various cutoffs. Higher

mortality rates have been associated with this complication, even when patients do not develop symptoms or electrocardiographic changes [3].

One of the most technically challenging interventions is PCI of chronic total occlusions (CTOs) which may require use of advanced crossing techniques, resulting in high rates of PMI. Coronary CTOs were defined as coronary lesions with thrombolysis in myocardial infarction (TIMI) grade 0 flow for a duration of at least 3 months [4].

Furthermore, while in non-CTO PCI PMI is associated with higher immediate and long-term morbidity, the prognostic implications of PMI in CTO PCI remain unclear [4].

Systematic evaluation of cardiac biomarkers after CTO PCI was done in a few studies which showed that PMI occurs more commonly than previously reported after CTO PCI. PMI is also more frequent when the retrograde approach is used and is associated with worse subsequent clinical outcomes [6].

^{99m}Tc sestamibi scintigraphy can be used to accurately quantify the extent of myocardial scarring. Furthermore, the relative sestamibi activity in perfusion defects, measured several hours after administration, is a good indicator of myocardial viability determined with microscopy [7].

Aim of the Work

A comparative study between antegrade versus retrograde recanalization of coronary chronic total occlusion, with special concern to ischemic burden assessment by SPECT pre-procedure and six months after.

Coronary Chronic Total Occlusion

Coronary chronic total occlusions (CTOs) represent the most technically challenging lesion subset that interventional cardiologists face. CTOs are identified in up to one third of patients referred for coronary angiography and remain seriously undertreated with percutaneous techniques. The complexity of these procedures and the suboptimal success rates over a long period of time, along with the perception that CTOs are lesions with limited scope for recanalization, account for the underutilization of CTO Percutaneous Coronary Intervention (PCI).

The duration may be difficult to determine if there is no prior angiogram demonstrating presence of the CTO. In such cases, estimation of the occlusion duration is based upon first onset of angina or dyspnea and/or prior history of myocardial infarction in the target vessel territory.

CTO remains the unresolved dilemma in interventional cardiology. Considering the recent development of catheter based technologies specific for CTO recanalization and the introduction of drug-eluting stents to reduce restenosis and re-occlusion, these lesions are now recognized as the last barrier to percutaneous revascularization success [8].

Compared to intervention of non-occluded stenoses, recanalization of chronic total occlusions requires more experienced operator, longer procedure duration, more amount of contrast material and more radiation dose for the patient and medical staff.

Indications and Potential Clinical Benefits of CTO PCI

Deciding to perform CTO PCI should depend on the patient's clinical presentation and risk benefit ratio and not the patient's anatomy, as experienced operators using contemporary CTO PCI techniques can be expected to be successful in the great majority of patients (80-90%), even among the most complex CTO lesions.

Successful CTO PCI Can Provide Numerous Benefits

1. Improve symptoms, such as angina and dyspnea.
2. Decrease the need for CABG surgery.
3. Decrease the need for anti-anginal medications.
4. Reduce mortality (compared to patients with failed CTO PCI).
5. Improve left ventricular function.
6. Decrease the risk for arrhythmias.
7. Improve tolerance of acute coronary syndromes that may occur in the future.

The experience in CTO interventions is increasing and learning curve is going up to the extent that made Japanese centers reach a success rate of 92.2% in opening CTOs.

Angiographic and Clinical Definitions

CTO of the coronary arteries is defined as angiographically documented or clinically suspected complete interruption of antegrade coronary flow (Thrombolysis In Myocardial Infarction-TIMI- 0 flow) of greater than 3 months [9].

Occasionally, bridging collaterals may provide antegrade flow to the vessel beyond the occlusion, giving the false impression of a functional sub-occlusive lesion. Careful examination of the occlusion in multiple views delineates the position of these collaterals outside the vessel architecture.

The interpretation is often complicated by the presence of intraluminal micro channels, which are demonstrated pathologically in the majority of cases, and may play a role in facilitating wire

crossing, but mostly remain below the resolution of angiography (100 μ m) and do not generally traverse the entire occluded segment or they violate the TIMI 0 criterion [10].

Since the time of the occlusion cannot be known, CTOs are usually distinguished into three levels of certainty [11]:

- a. **Certain (Angiographically Confirmed):** A previous angiogram has confirmed the presence of TIMI 0 flow for 3 months prior to the planned procedure.
- b. **Likely (Clinically Confirmed):** an acute myocardial infarction in the territory of the occluded artery distribution or acute coronary syndrome or deterioration of anginal threshold without other possible culprit arteries ≥ 3 months before the current angiogram.
- c. **Possible (Undetermined):** a CTO with TIMI 0 flow and angiographic anatomy suggestive of long-standing occlusion (collateral development, no contrast staining) with stable unchanged anginal symptoms in the last months or silent ischemia or, in case of recent acute ischemic episodes (acute myocardial infarction or unstable angina or worsening effort angina), with the presence of a culprit artery different from the occluded vessel.

Histology and Pathophysiology [12]

Typical chronic total occlusion may be classified as: soft, hard or a mixture of both.

Soft Plaques consist of cholesterol-laden cells and foam cells with loose fibrous tissue and neovascular channels; more frequent in younger occlusions (<1 year old) and are easier to be treated.

Hard Plaques are characterized by dense fibrous tissue and often contain large fibrocalcific regions without neovascular channels. These lesions are thus more likely to deflect guide wires into the subintimal area, creating dissection planes. Hard plaques are more prevalent with increasing CTO age (>1 year old).

An important CTO pathological feature is the extensive process of "neovascularization" which occurs throughout the extent of the whole lesion and the vessel wall.

Neoangiogenesis increases with occlusion age starting from adventitia till reaching the media, they are called "Bridging collaterals".

Such neovascular process may usually lead to the formation of relatively large capillaries measuring from 100 to 500 μ m that are defined as "microchannels"; these vessels can be frequently found through the CTO's body, can partially recanalize the distal lumen and may serve as a route for a guidewire to reach the distal vessel and hence may have an important therapeutic value.

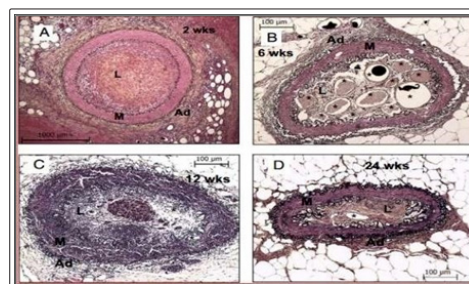


Figure 1: Neoangiogenesis in CTO; Low power view demonstrating central lumen, intimal plaque and adventitial neovascular channels formation over time [12].

There are therefore 4 important components of the occlusion: the proximal cap which can be hard to penetrate due to dense fibrous tissue, calcifications which vary in density from a CTO to another and can be a barrier for passage of the guide wire, microvessels which may be beneficial or harmful during intervention and the distal cap which is probably the worst part of CTO crossing, especially in very long and tortuous occlusions as the torque control of the wire becomes relatively reduced [13].

Revascularization Strategies [11]

Timing: In general, CTO PCI should not be performed ad hoc in order to:

- Allow time for thorough procedural planning and preparation, which is essential for success.
- Minimize the amount of contrast and radiation administered.
- Minimize patient and operator fatigue.
- Allow for a detailed discussion with the patient and family about the indications, goals, risks, and alternatives (such as medical therapy and coronary artery bypass graft surgery) to the procedure. Risks that may be increased in CTO PCI compared to non-CTO PCI include radiation injury and perforation.

In some cases, however, ad hoc PCI may be the best option, such as in patients who present with an acute coronary syndrome due to failure of a highly diseased saphenous vein graft, in whom treatment of the native coronary artery CTO is considered to be the preferred treatment strategy.

Generally, asymptomatic patients are more liable to be left on medical therapy rather than being percutaneously revascularized. However, this therapeutic strategy might not be clinically appropriate and the decision to treat a CTO in an asymptomatic patient should be driven by a non-invasive functional imaging test, in order to clarify the amount of myocardial viability and severity and extension of myocardial ischemia.

On the other hand symptomatic patients represent the greatest challenge for clinical decision making and different scenarios need to be considered:

When the CTO is the only culprit lesion in the coronary tree, and presence of viability and/or ischemia by non-invasive functional test has been shown, PCI is highly recommended.

Underestimating the CTO clinical impact in a single vessel disease may lead to catastrophic consequences. Indeed, although the CTO might be supplied by collateral circulation without ischemia at rest, acute donor vessel occlusion might cause large myocardial necrosis with an unfavorable prognosis for the patient.

In case of multivessel disease, the presence of a CTO should not be a sufficient reason to deny percutaneous revascularization in the absence of significant left main disease and when the other lesions are suitable for PCI.

In this situation, if the decision to perform a PCI is taken, a staged approach should be a reasonable strategy in order to avoid excessively long procedures and the use of large amount of contrast media. In this case, consideration of which artery to tackle first should be based on the importance of the occluded vessel. When complete revascularization is to be achieved, it is suggested to start PCI with the CTO vessel, as in case of failed attempt, patient might be fully revascularized by surgery.

Patient might also present two CTO vessels at the same time. In these cases if CTOs angiographic characteristics are favorable and the patient does not present any clinical contraindications such as renal failure or other co morbidities, PCI may be performed on both CTOs during the same procedure, paying careful attention to the amount of contrast media administered and to the duration of radiation exposure. Patient's compliance is another important issue to consider in these patients, and probably the most frequent reason to abort the procedure, prematurely.

CTO decision-making for PCI requires an individualized risk/benefit analysis, considering clinical, angiographic and technical features.

The consensus document from Euro CTO Club underlines that "PCI CTO should be attempted after careful review of clinical history, results of provocative tests, coronary anatomy and personal experience" and "with average recanalization success rate of >70% in experienced hands with contemporary techniques, the presence of a CTO should not be sufficient reason to switch from PCI with DES to surgery in multivessel disease".

Collateral Circulation

Coronary collateral vessels are believed to originate either from maturation of preexisting arteriolar connections (arteriogenesis) or occasionally from sprouting of new vessels from neighboring blood vessels (angiogenesis). The path of collateral arteries can be epicardial or intramyocardial and these vessels can serve as contralateral or ipsilateral conduits.

Classification

A large number of methods were utilized over the past years to classify collateral circulation. An old method of classification that is still used utilized the grade of occluded segment opacification [14]:

- Grade 0 = no filling.
- Grade 1 = filling of side branches of the artery to be dilated via collateral channels without visualization of the epicardial segment.
- Grade 2 = partial filling of the epicardial segment via collateral channel.
- Grade 3 = complete filling of the epicardial segment of the artery being dilated via collateral channel.

Another newer method of classification utilized evaluation of the size of the collateral connection (CC) diameter assessed by three grades:

- ✓ CC0, no visible continuous connection between donor and recipient artery
- ✓ CC1, continuous, threadlike connection.
- ✓ CC2, continuous, small side branch-like size of the collateral throughout its course.

Although coronary angiography is the standard method to visualize collateral arteries, this has a limited resolution; visible collaterals have a diameter from 0.3 up to 0.5 mm, thus arterioles < 100 µm are invisible to the human eye.

Collaterals in Healthy and Ischemic Individuals

The human coronary circulation is not an end-arterial system as it was previously considered. Indeed, collateral arteries may occur in neonates and in healthy individuals without CAD [15].

De novo collateral arteries formation after an acute myocardial occlusion takes at least 24 hours and generally it becomes

angiographically visible within 10 to 14 days after an acute occlusion [16].

Factors such as angiopoietin - 1, angiopoietin - 2 (more important), and their receptor Tie-2b have been identified and they seem to be involved in collateral development and maintenance. In cardiovascular disease, up-regulation of these factors in patients with acute coronary syndrome (ACS) has been reported [17].

On the other hand, some patients with long standing CTOs do not have well developed collateral circulation. Some of those patients exhibit high levels of angiogenic inhibition factors as endostatin [17].

Role in Ventricular Functions

Many cardiologists believe that collateral circulation preserves ventricular viability and function at rest and during stress conditions. Therefore they repute presence of collateral circulation a sufficient reason to deny interventional complete revascularization. However, during stress conditions an important process related to the function of collateral circulation occurs which may cause myocardial ischemia; the so-called "coronary steal". This is a complex phenomenon in which regional myocardial hypoperfusion occurs through diversion of coronary blood flow to adjacent coronary beds. It is usually mediated by collateral arteries [18].

Recovery of impaired LV functions after CTO recanalization is not directly related to the quality of collateral function, as collateral circulation development does not appear to require the presence of viable myocardium. Thus, decision for revascularization should not be based on the quality of collateral supply.

Changes after CTO Recanalization

CTO recanalization by re-establishing the antegrade blood flow which leads to an increase of resistance in the collateral vessels.

It is possible that the collateral function would gradually improve during persistent re-occlusion. Therefore, in case of acute re-occlusion, collateral compromised circulation may be unable to preserve ventricular viability. For this reason, an acute thrombosis in a previously occluded artery can lead to an acute coronary syndrome [19].

Predictors of Successful Intervention

Clinical Predictors:

- **Duration of occlusion:** more significant lesion organization with deposition of fibrous tissue, occurring in the course of time from occlusion, might lead to a lower possibility of recanalization [20].
- **Previous failed attempt;** with a special consideration to experience of the operator at the first attempt, the feasibility of different approaches and techniques, the availability of dedicated materials and devices. Previous dissection or perforations created during the first attempt might also heal in few months and a new collateral circulation might develop, enabling to choose a different strategy of approach and affecting the procedural outcome [11].
- **Patient tolerance and Co-morbidities;** CTO revascularization requires long time procedure and the patients must lie on supine position for a long time. Presence of associated co-morbidities such as musculo-skeletal pain, psychiatric disorders, cardiac or respiratory failure limits the patient ability to lie flat for prolonged periods, especially in older patients [21].

Angiographic Predictors

- The proximal fibrous cap; shape (blunt or tapered), presence of side branches and calcifications.
- Body of occlusion; length, calcifications and presence of bridging collaterals.
- The distal cap; shape and calcifications
- CTO location; Ostial location is unfavorable rather than proximal or mid due to the low guiding catheter support achievable when employing standard techniques. Also, very distal CTO location might also be considered unfavorable in some case, due to poor maneuverability of guide wires.
- Small vessel size; size < 3 mm is unfavorable with more risk of perforation and higher incidence of reocclusion [11].
- Vessel tortuosity proximal to occlusion; one bend > 150° or two bends >90° cause loss of pushability, trackability and steerability of the guidewire and support devices.
- Vessel tortuosity at the site of occlusion; causes loss of visualization of vessel path and consequently high risk of dissection when using the penetration wire techniques.
- Distal vessel disease: In case of proximal-mid occlusion with faint distal opacification, the presence of a stenosis distal to the occlusion cannot be easily assessed. Also, the presence of tandem occlusions which are defined as two occlusions in the same segment divided by an island of no disease vessel increases difficulty as two proximal and distal caps need to be crossed in the setting a CTO.

Role of MSCT

MSCT with the rapid developments in its technology in the past few years have been utilized in more than one study trying to derive predictors of success in CTO intervention. Numerous variables have been studied in this issue like ostial position, characters of the artery proximal to CTO, proximal cap (shape, calcification, side branches...etc.), CTO segment (length, calcification, etc.), distal cap (shape and calcification) and characters of the artery distal to CTO. However, still no consensus about definite predictors of success is settled. Some authors proposed predictive scores for CTO PCI success derived from MSCT [22].

Basic Materials for CTO PCI

Guidewires [23]

Two groups of wires are usually used for CTO: Plastic jacket guide wires and spring coil wires (medium and hard-tipped) designed for CTO only.

The *plastic jacket guidewire* is coated from base to tip with a polymer, and then also covered with a hydrophilic coat. These wires are typically useful in lesions which have visible microchannels, and when there are markedly tortuous vessel and lesions.

Once the lesion is successfully crossed, these plastic hydrophilic wires will easily track through the small and under perfused distal vessel course easily. Also, this type of wires can be used in the Subintimal Tracking and Reentry (STAR) technique and in retrograde approach to selectively engage collateral vessels.

However, this wire is difficult to manipulate intentionally by the operator, and as soon as the wire reach the hard tissue may automatically enter the surrounding subintimal space which is relatively soft, thus creating long dissections and perforations.

Spring wires are soft, medium or hard-tipped. Non coated wires are easier to direct and provide better tactile feel compared with hydrophilic wires. Therefore, higher friction of these wires may reduce the chance to create a false lumen. However, when using

stiffer non coated guidewires, less tip resistance is transmitted to operator increasing the likelihood to create a dissection.

Guidewire Selection for CTO Stepwise Approach Explore with Soft Tip or Medium Wire

- Asahi: Soft or medium 2 gram
- Guidant: 0.14” intermediate 2 gram or 0.14” Standard 4 gram
- Boston Sci: Choice PT (Hydrophilic) 2 gram. PT Graphix (Hydrophilic) 3-4 gram.

Medium to Heavy Wire

- Asahi: Miraclebros 3, 4.5, 6-gram Medtronic Vasc.: Persuader 3, 6 grams.
- Cordis: Shinobi (Hydrophilic) 2, 4-gram Guidant: Cross it 10.

Heavy Wire (Distal Cap)

- Asahi: Miraclebros 6, 9 gram, Confianza 8, 12 grams
- Confianza Pro 9, 12 gram Guidant: Cross-IT 300 4 gram, Cross-IT 400 6 gram.

Following successful crossing to true lumen, Exchange for soft-tipped wire (avoid hydrophilic).

Sion and Gaia Guidewires

Are “composite core” wires, which have a dual coil construction designed to enhance torquability, maneuverability and tip shape retention.

Sion is a soft guidewire designed for collateral vessel crossing, both septal and epicardial. There are several cases in which a Fielder FC wire (the traditional “gold standard” for collateral crossing) would not cross, whereas the Sion did, although there are opposite examples as well. The Sion blue is a variation of the Sion with softer tip and more supportive body and is often used as a workhorse guidewire.

The Gaia Wires

Represent the evolution of the Miracle and Confianza line of wires. The Gaia are stiff wires with tapered tips and high penetration power. Three types are available (Gaia First, Gaia Second and Gaia Third) with increasing tip stiffness. The distal 1-mm tip is pre-shaped to a 45-degree angle, and due to the composite core construction, it has excellent shaping memory and retention. These wires appear to be excellent for crossing long tortuous occlusions, but may require slower, more precise manipulation compared with previously used stiff guidewires.

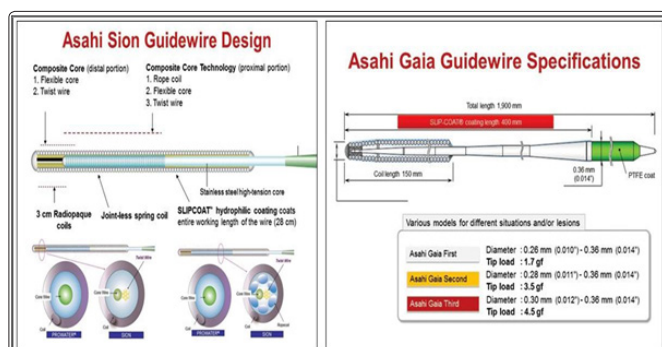


Figure 2: Sion and Gaia guidewires (adopted from Asahi network Site).

Over The Wire (OTW) devices [23]:

Wires should be always used with an OTW device which is either a balloon or a microcatheter in order to facilitate torque to the tip response, prevent flexion, kinking or prolapsing of guide wire, improve penetration ability and permit modifying the guide wire curve, reshaping, and exchange during the procedure.

Once the stiff wire has crossed the CTO and reached the distal true lumen, the use of OTW devices allows exchange of a stiff wire with a floppy one, minimizing the risk of distal wire perforation or dissection.

Microcatheters have the advantages of better tip flexibility than OTW balloons, providing better wire manipulation due to their larger inner lumen which reduces friction and a radiopaque marker at the tip which helps to avoid advancing too far into the lesion (a mistake that occurs frequently with OTW balloon).

Microcatheters with smaller shaft diameter and softer construction might be dedicated for retrograde approach or when approaching CTO with antegrade microchannels, while those of bigger size shaft diameter and stiffer construction may be employed in hard complex lesions for their greater support with stiffer wire.

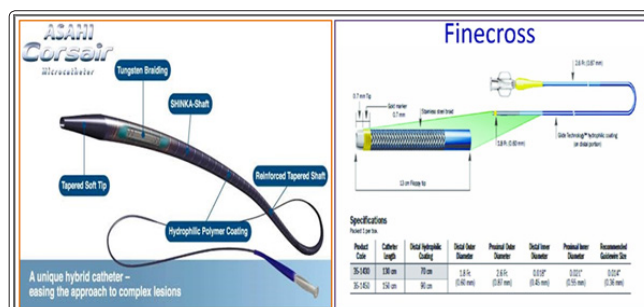


Figure 3: Finecross and corsair microcatheters (adopted from asahi site)

Special dedicated microcatheters have been developed for special uses in CTO as *Tornus*TM catheter for severe hard lesions, *Corsair*TM catheter for engaging collaterals in retrograde approach, *Twin-Pass*TM catheter for accessing different main branches at the same time and *Venture*TM catheter in case of difficult angulations.

OTW balloons are strongly recommended when starting dilatation of CTO after passage of the wire. Many parameters are important in differentiating different types of OTW balloons as: entry tip profile, balloon crossing profile, balloon size diameter and length, shaft diameter and length, hydrophilic coating and addition of reinforcer core wire.

Non-Compliant Balloons [23]

These balloons exert a high-pressure localized force within the vessel wall without overexpansion of the size of the balloon, leading to controlled localized plaque fissuring and dissection. These balloons are generally used with very resistant occlusive calcified lesions, especially when vessel size is not easily predictable because of the long standing occlusive status.

Stents

Restenosis rates markedly dropped by transition from CTO intervention using balloon angioplasty alone to angioplasty with stenting. However, despite technology advancements in wires, stents and catheters together with increased operators’ skills, success rates remained stable and rather disappointing until the introduction of drug eluting stents (DES).

Nowadays, Practice has shifted to routine DES implantation in CTOs because of the high restenosis rate after bare metal stents (BMS). There are large amount of data demonstrating significant reduction in restenosis and reocclusion compared to BMS. An example of these data can be seen in the results of the PRISON II trial [24].

Rotablation

Its main role in CTO PCI is debulking of superficial calcification in case of balloon un-crossable lesions. In DES era it is used for sufficient plaque modification needed for stent delivery and proper deployment. The main limitation with it is failure to pass the rotator specific wire through the lesion either due to failure of the stiff wire to cross or due to failure of the OTW device to cross the lesion with subsequent failure to exchange the stiff wire with the rotator wire.

Role of Intravascular Ultrasound (IVUS)

IVUS has been shown to be a powerful asset in accomplishing successful recanalization of CTOs. Employing IVUS in branching vessel disease, true and false lumen detection, and as a guide to salvage a failed revascularization attempt clearly demonstrates its usefulness for CTOs. The ultimate use of IVUS rests in its ability to evaluate disease extent and vessel size and to guide proper balloon and stent selection to maximize lumen gain in these complex scenarios. Technologic advances promise to open doors to techniques that will further improve rates of successful intervention of CTOs [25].

Antegrade Approach [23]

This is the first approach preferred in most CTO PCI procedures. Different techniques are used in the antegrade approach like:

Single Wire Technique: Utilizing plastic wires in case of microchannels or hard wires in absence of microchannels using the drilling or penetration methods.

Parallel Wire Technique: When passage of the first wire in subintima is confirmed, another wire is used keeping the dissection channel closed and acts as a marker for advancement of the second wire.

See Saw Technique: When the second wire in parallel wire technique also passes to subintima, the second wire can be used as landmark and retry to pass the first wire to true lumen with repeated change in role between both wire still one of them succeed to reach true lumen.

Side Branch Technique: Applied when a side branch is arising at the CTO level and IVUS guided technique is not feasible because of too short or angulated vessel.

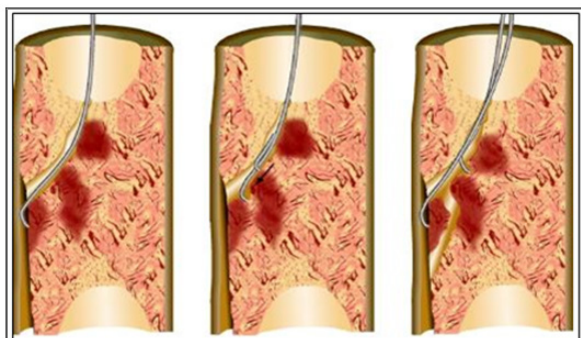


Figure 4: Parallel wire technique [23].

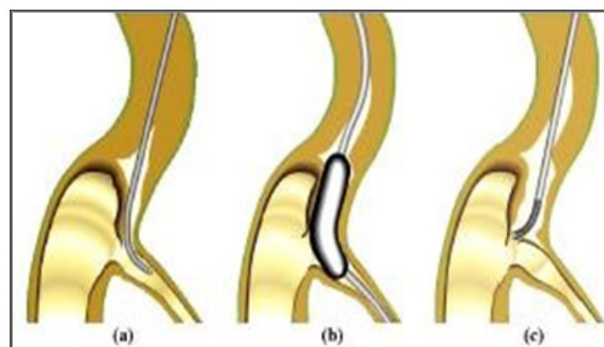


Figure 5: Side branch technique [23].

Subintimal Tracking and Re-entry (STAR) Technique: Utilizes a subintimal dissection track created by a stiff wire with or without intention. The stiff wire is replaced by a hydrophilic wire with a pronounced J tip “umbrella handle shape”. The hydrophilic wire is pushed more into the subintimal space and its loop will turn around the occluded lumen guided by the softest areas of subintimal space till finally it passes to the true lumen distally because Non diseased segments is thinner than proximal diseased ones making the wire face lower resistance towards true lumen than towards adventitia.

Microchannel Technique: Using hydrophilic wires in lesions within straight segment, having concave proximal fibrous cap and without severe calcifications [26].

Guiding Techniques to Increase Support

Child in Mother System: Inserting a 130 cm 5F catheter in a 6 or 7F catheter to increase backup support. In such a way the smaller catheter is deeply engaged into the proximal part of the target artery and balloons can be easily advanced across resistant lesions [27].

Anchor Balloon Technique: Inflating a balloon on the main guidewire at the proximal part of the major vessel before CTO. In the “anchor side branch technique” a catheter larger than 6F is used, a floppy wire is advanced to the side branch and a 1.5 mm diameter balloon is inflated over it at 4-8 atm. Giving extreme support for wires and balloons to cross the lesion [28].

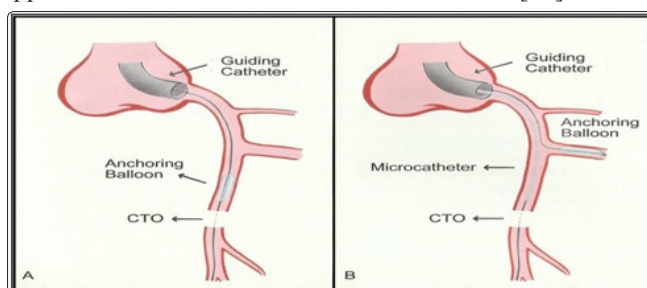


Figure 6: Anchor balloon technique (A: anchor balloon, B: anchor side branch balloon [28].

Retrograde Approach [29]

This approach requires an intercoronary channel between the occluded coronary and another patent one, this channel may be a septal or epicardial collateral or a bypass graft.

In presence of a good retrograde collateral channel and absence of much calcium, a difficult CTO in the antegrade approach may appear very easy in retrograde approach.

Criteria for easy collateral channel crossing include choosing well visible channel, non-tortuous channel, proximal septal collateral, preferably from LAD to RCA and to be sure that blood flow is not exclusively originating from the channel used.

Retrograde approach is indicated when antegrade wiring seems very difficult (complex CTO) or as re-attempt after a previous failed antegrade trial taking in consideration that the donor vessel must be healthy, and collaterals must be visible and continuous (CC1 and CC2).

Multiple techniques can be used when employing the retrograde approach, from which the most popular will be discussed.

Pure Retrograde Technique: Recanalization using retrograde approach with a single wire without simultaneous antegrade approach. After recanalization, antegrade wire is passed through the occlusion and standard PCI is done. Its success rate markedly improved by the use of “Corsair” channel dilator microcatheter. This technique is preferred in ostial lesions and retrograde bypass graft reopening due to lack of antegrade engagement.

Kissing Retrograde Technique: Used when retrograde wire stops at the middle of the occlusion. The position of distal true lumen is recognizable with the retrograde wire and lesion is crossed by antegrade approach under guidance from retrograde wire.

Knuckle Technique: Same principle of the STAR technique with the beneficial absence of flow that can propagate dissection distally. Dissection of subintimal space is done by formation of a loop in the retrograde wire (preferably a soft hydrophilic one) then advancing it to the occlusion. Then, an antegrade stiff wire is used to get through the dissected lumen created by the knuckle wire. After passage of the antegrade wire to the true lumen, PCI is done in standard techniques.

Controlled Antegrade and Retrograde Subintimal Tracking (Cart) Technique: Combines simultaneous use of antegrade and retrograde approaches by creating a subintimal dissection with limited extension only at the site of the CTO [30].

Reverse Cart Technique: Balloon dilatation of subintimal space within CTO antegradely instead of retrogradely. The advent of channel dilator “Corsair” microcatheter made this approach much easier with higher success rates.

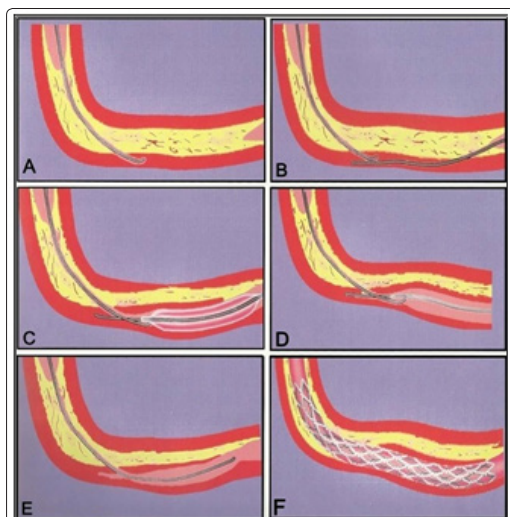


Figure 7: CART technique [30].

Drawbacks of the Retrograde Approach

The need for another guiding catheter in the donor artery usually $\geq 7F$ which may cause proximal dissection with its tip.

Tight or even moderate lesions in the donor artery have to be treated before treating CTO to prevent severe ischemia during procedure making incomplete revascularization a possibility in case of failure of CTO recanalization.

Thrombosis in the donor artery due to long stasis or handling of guiding catheter, wires or balloons.

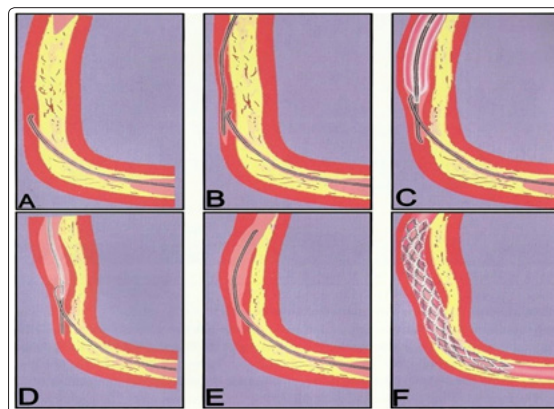


Figure 8: Reverse CART technique [30].

Complications of CTO PCI

Major Adverse Cardiac Events (MACE)

The safety and success of CTO PCI has increased steadily over the last decade. However, one of the key barriers to referral remains a perception of increased periprocedural complications compared to non-CTO PCI. A meta-analysis of 65 CTO PCI studies including more than 18,000 patients over an 11 year period demonstrated an overall MACE rate of 3.1%, comprising a 0.2% risk of death, 0.1% risk of emergency CABG, < 0.01% risk of stroke and a 0.2% risk of Q-wave MI (2.5% risk for any cardiac biomarker rise) [5]. Vascular Access Complications: Including haematoma formation, uncontrolled bleeding (either evident or into retroperitoneal space), pseudoaneurysm, arteriovenous fistula and dissection at access site.

Procedure Related Complications

Coronary Perforation: This complication has various predictors which may be patient related (old age and female gender), angiographic related (heavy calcification and inaccurate assessment of vessel diameter) or device related (use of atheroablative debulking devices, cutting balloons, IVUS balloon, embolic protection devices, stiff wires and hydrophilic wires [31].

Coronary Ostium Dissection: More in case of using a high back-up guiding catheter e.g. Amplatz catheters. Also common in cases of donor artery cannulation in the retrograde approach.

Coronary Thrombosis: More in retrograde approach and with use of multiple guidewires and devices. Prevention can be done by administration of unfractionated heparin keeping ACT above 300 seconds. Careful observation of angiogram must be done to detect and manage as early as possible.

Entrapment of a Device inside a Lesion: A microcatheter or a balloon may be entrapped after CTO wire crossing especially in highly calcified and tortuous vessels.

Single-photon Emission Computed Tomography (SPECT)

Single-photon emission computed tomography (SPECT) myocardial perfusion imaging is a well-established method of evaluating for coronary artery disease with over 30 years of experience supported by literature validating its diagnostic and prognostic value [32].

The most widely used nuclear cardiology procedure is myocardial perfusion imaging (MPI) using SPECT study. It is a non-invasive imaging modality routinely used in the diagnosis of and for assessing the prognosis of coronary artery disease and heart muscle damage following an infarction. MPI SPECT images provide a visual three-dimensional image of the perfused myocardium for assessment. In addition, if the MPI SPECT studies are gated to the electrocardiogram (ECG) it is possible to make a functional assessment of the perfusion images. The clinical success of MPI SPECT, and gated MPI SPECT, relies on an understanding of the physics and technical aspects of SPECT imaging, as well as the technical [33].

The excellent procedural and clinical guidelines published by ACCF and ASNC have made this testing modality widely available in the outpatient and inpatient setting. In the United States, more than 6 million SPECT MPI studies performed annually. This versatile technique may be combined with exercise, dobutamine or vasodilator stress, providing stress, providing flexibility for various patient populations [34].

To perform MPI a patient is intravenously given a radio-pharmaceutical or tracer (a pharmaceutical labelled with a small amount of radioactivity, which emits gamma rays). The ideal tracer would have the following desirable properties:

1. Distribute in the myocardium in linear proportion to blood flow.
2. Efficient myocardial extraction from the blood on the first pass through the heart.
3. Stable retention within the myocardium during the scan but also rapid elimination allowing repeat studies under different conditions.
4. Be readily available; and have good imaging characteristics, limitations and quality assurance requirements of the system.

SPECT (tomography) imaging produces full 3D images and has several advantages over planar imaging. In particular, tomography allows separation of target regions from overlying structures, and therefore gives improved diagnostic results over planar imaging. By performing MPI SPECT, it is possible to create a 3D volume representation of the perfused myocardium. By selecting appropriate planes through the myocardium, the cardiac shape can be assessed, together with regional and global perfusion patterns. The sensitivity of CAD detection has been shown to be far superior with SPECT (93%) than with planar imaging (77%). Specificity is also improved in SPECT compared with planar imaging (88% and 82%, respectively). SPECT is, however, a much more complex technique, and there is scope for more image artifacts to appear during the image acquisition and subsequent image processing. However, by paying strict attention to detail throughout the whole imaging procedure (acquisition and processing) and by regularly performing quality control tests on the gamma camera, the chance of these image artifacts appearing is much reduced [33].

Other advantages of SPECT image over planar one include ability to differentiate overlying and underlying structures, ability to reconstruct image in same orientation irrespective to cardiac position and ability to reconstruct images in format comparable

with other cardiological images [35].

ACCF/ASNC 2009 Appropriate use criteria (AUC) consist of 67 most common clinical scenarios, and scored based on the level of appropriateness, using a rigorous scientific method (33 appropriate, 9 uncertain and 25 inappropriate). An appropriate imaging study is one in which the expected incremental information, combined with clinical judgment, exceeds the expected negative consequences by a sufficient margin for a specific indication. A hierarchical approach facilitates the use of AUC so that the patients are classified for a true clinical indication as some might fall into clinical figure. (Figure (9))

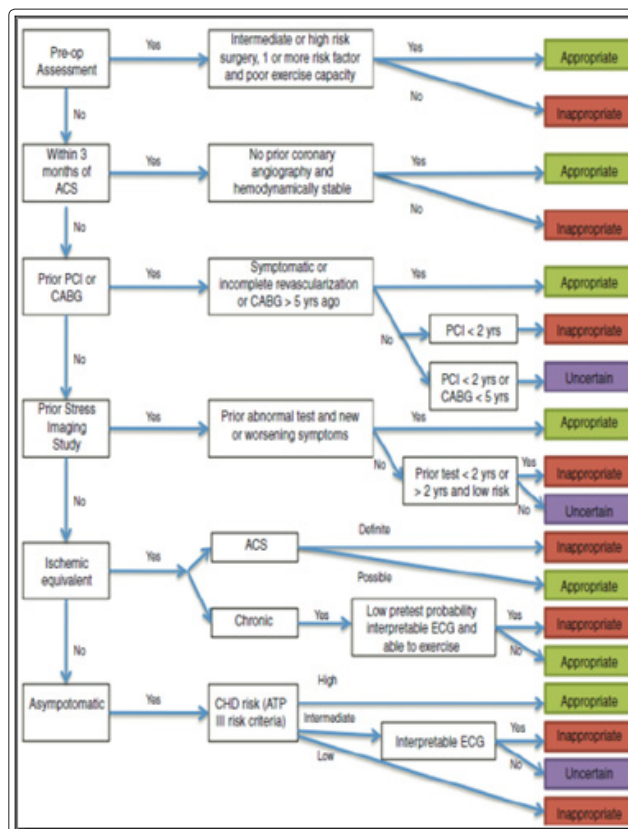


Figure 9: Hierarchical approach for test ordering using AUC [36].

Gated SPECT

Gated SPECT scans have increased temporal resolution, and so it is possible to analyse individual phases of the cardiac cycle. In a gated acquisition each phase of the cardiac cycle are associated with a temporal frame within the computer. Reconstruction of each interval of a gated MPI SPECT into a tomographic image set allows for visual or quantitative estimation of functional parameters, such as myocardial motion and thickening. The most common gating rate is eight frames per R-R interval per projection, although 16 frames are sometimes used. Gated MPI SPECT wall motion is often visualized using bulls eye plots or a 3D surface display or mesh method [38].

In 1971 Strauss et al. introduced the concept of using ECG to trigger image frame acquisition. Combined perfusion/function studies became commonplace in the late 1980s with the advent of Tc-99m labeled myocardial perfusion agents and has rapidly evolved into a standard for myocardial perfusion imaging in the USA [37].

In its position paper in March 1999, The American Society of Nuclear Cardiology recommended the routine incorporation of

ECG gating during SPECT cardiac perfusion scintigraphy [37]. Over 90% of all myocardial perfusion SPECT studies in the USA are now gated.

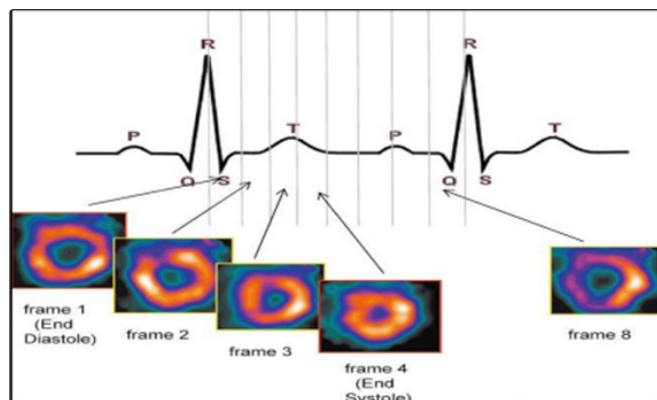


Figure (10): 8 Frames ECG gated SPECT study [38].

DePuey and Rozanski demonstrated that false-positive perfusion studies could be reduced from 14% to 3% by incorporating regional wall motion data in the interpretation of perfusion imaging. In women, where the false-positive rate of stress ECGs is relatively high and breast soft-tissue attenuation artifact is common, ECG gating has been shown to further enhance the diagnostic specificity of ^{99m}Tc perfusion imaging from 84% to 94% [39].

Smano et al. demonstrated that the number of “borderline-normal” or “borderline-abnormal” interpretations was significantly reduced. In patients with a low likelihood of CAD, the normalcy rate increased from 74% to 93%. In patients with a high likelihood of CAD, the trend was also toward a higher number of unequivocally abnormal interpretations [40].

In the case of multivessel disease or left main disease, balanced global hypoperfusion comes into play. According to several reports, only 13–50% of patients with three-vessel CAD or left main disease actually have perfusion abnormalities in multiple territories. In the setting of diffuse ischemia, a perfusion defect may not be seen, because of image normalization. Transient ischemic dilatation (TID) in myocardial perfusion imaging (MPI) refers to a significant enlargement in left ventricular (LV) size on the stress images compared with the rest images. In the case balanced ischemia, TID due to stunning results in an increase in ESV and a decrease in EF. This is helpful to correctly identify significant CAD for predicting severe proximal left anterior descending artery or multivessel critical coronary lesion, even though there is no perfusion abnormality due to balanced ischemia [41].

Advantages of gated SPECT [42]

1. Allows the reporting physician to distinguish between fixed defects from artifacts.
2. End diastolic and end-systolic images or polar map displays also help assess apparent perfusion abnormality.
3. Used to calculate the end-diastolic and end-systolic volumes, and as a result, calculate the left ventricular ejection fraction (LVEF), which is a fundamental diagnostic and prognostic predictor of CAD.
4. Assessment of both perfusion and function in a single injection, single acquisition sequence.
5. Gated SPECT helps to differentiate soft tissue attenuation artifact from scar. Artifact showed normal function and thickening, while scar showed as a fixed defect, with diminished or lack of wall thickening and motion.

Indications of gated SPECT [43]

Known or Suspected CAD

1. Diagnosis of physiologically significant CAD (presence and severity).
2. Determine prognosis (risk stratification based on extent and severity of myocardial perfusion abnormalities and left ventricular function).
3. Differentiate between coronary and non-coronary causes in patients with acute chest pain syndromes seen in the emergency rooms.

Follow-Up of Patients with Known CAD

1. Evaluate the immediate and long-term effect of:
 - a. Revascularization procedures (such as coronary artery bypass grafting, angioplasty, stent placement, use of angiogenic growth factors, etc.).
 - b. Medical or drug therapy, whether designed to prevent ischemia (e.g., drugs that alter myocardial metabolic oxygen supply/demand relationship) or modify lipids and other features of atherosclerotic plaque (e.g., statin drugs).

Known or Suspected Congestive Heart Failure

1. Differentiate ischemic from idiopathic cardiomyopathy.
2. Help assess whether patient has sufficient viable myocardium overlying the infarction to consider revascularization.

Stress Modalities of SPECT Study

Exercise Stress Test

This is usually performed with a treadmill or bicycle ergometer with continuous patient monitoring and it is the preferred stress modality in patients who can exercise to an adequate workload. Exercise testing has a limited value in patients who cannot achieve an adequate heart rate and blood pressure response due to non-cardiac physical limitations such as pulmonary, peripheral vascular, musculoskeletal abnormalities or due to a lack of motivation. A treadmill is the most widely used exercise modality, with Bruce and modified Bruce being the most widely used exercise protocols. Departments may decide not to offer exercise stress MPI routinely if the patient population within the catchment area of the department is likely to include a high proportion of patients with non-cardiac physical limitation [44].

It allows for a physiologic assessment of functional capacity, symptoms and hemodynamics. When compared to pharmacologic stress testing, exercise is associated with less extensive hepatic and gastrointestinal tracer uptake, which significantly improves image quality [36]. However, for several reasons plain exercise ECG may not be adequate and in such conditions it should be combined with an imaging modality to increase the sensitivity and specificity of diagnosis like electronically paced ventricular rhythm, Pre-excitation syndrome example Wolff Parkinson-White, 1 mm of ST segment depression at rest, Previous PCI/CABG and Left bundle branch block [36].

Myocardial perfusion imaging (MPI) with exercise stress testing enhances diagnostic sensitivity and specificity, particularly among patients with resting ECG abnormalities that preclude the interpretation of ST-segment deviation. MPI helps to differentiate true-positive from false-positive ST-segment depression and provides a more accurate assessment of the extent and severity of disease. Importantly, it can also localize ischemia to a particular vascular distribution. MPI is useful when patients are unable to achieve their target heart rate during exercise, because myocardial

perfusion abnormalities in response to stress occur earlier than ECG changes [45].

When combined with exercise, MPI not only improves diagnostic capability, but it is also predictive of short- and long-term cardiac events. This prognostic ability does not apply to ECG interpretation without concurrent use of the Duke treadmill score [46].

Duke treadmill score = Exercise time (in minutes) – 5 × maximum ST depression – 4 × angina score (0 = none, 1 = present, 2 = reason for test termination)

Low risk: > 5

Intermediate risk: = -10 to +4

High risk: < -10

The indications and contraindications for exercise MPI are listed in (Table (1), Table (2) respectively.

Table 1: Indications of exercise stress myocardial perfusion imaging [34]:

Diagnosis of ischemic heart disease in patients with intermediate pretest probability of CAD and/or risk stratification of patients with intermediate or high pretest probability of CAD based on age, gender, and symptoms :	Class
Identify location, severity, and extent of ischemia	I
In patients with Intermediate Duke treadmill score	I
Assessment of functional significance of intermediate (25–75%) coronary lesion	I
Repeat testing in patients whose symptoms have worsened/changed to redefine the risk for cardiac event.	I
Repeat testing every 1–3 years in high likelihood patients.	IIb
Asymptomatic patients who have a high-risk occupation.	IIb
Severe coronary calcification with uninterpretable ECG.	IIb
Screening of asymptomatic patients with low probability of CAD.	III
Prior to non-cardiac surgery Class:	
Intermediate risk surgery or vascular surgery AND risk factors with poor functional capacity.	IIb
Intermediate risk surgery or vascular surgery and adequate functional capacity (≥ 4 METS).	III
Low risk surgery.	III
Assessment of therapy and interventions in ischemic heart disease:	
3–5 years after revascularization in high risk, asymptomatic patients.	IIa
Evaluation of therapeutic efficacy (anti-ischemic drug therapy)	IIb
Routine assessment after PCI or CABG in asymptomatic patient	III

Table 2: Contraindications of exercise stress testing [36]:

Absolute	Relative
Acute myocardial infarction (within 2 days)	Left main coronary stenosis or it's equivalent
Unstable angina	Electrolyte abnormalities
Acute pulmonary embolism or infarction	LBBB, pacemaker or pre-excitation
Symptomatic severe aortic stenosis	Moderate valvular stenosis
Uncontrolled symptomatic heart failure	HCM or other forms of out flow tract obstruction
Acute myocarditis or pericarditis	High-degree atrioventricular block
Aortic dissection	Significant tachy- or bradyarrhythmias
Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise	Mental or physical impairment leading to inability to cooperate
Patient unable to sign consent	Extreme obesity, with weight exceeding the recommendations of the equipment capacity (usually >159 kg [350 lb])
Uncontrolled hypertension (systolic ≥ 200 mmHg and/or diastolic ≥ 110 mmHg)	Respiratory distress
Pregnant or breastfeeding	

Pharmacological Stress Test

The pharmacological stress test has proven to be an excellent alternative to the physical exercise test and can be performed using vasodilator agents (such as Dipyridamole or Adenosine) or Dobutamine. Adenosine is a direct coronary vasodilator and leads to a 3.5 to 4-fold increase in myocardial blood flow and is routinely given as a continuous infusion at a rate of 140 µg/kg/min over 6 minutes. Patients who cannot perform exercise stress for various reasons and those who are on concomitant treatment with medications which blunt the heart rate response (such as beta-blockers and calcium channel blockers) are better suited to Adenosine stress. Dipyridamole is an indirect coronary artery vasodilator that increases the tissue levels of Adenosine by preventing the intracellular reuptake and deamination of Adenosine [47].

It induces hyperemia, which lasts for more than 15 minutes. Although the incidence of side effects is less than with Adenosine, they last for a longer period and additional intervention such as IV Aminophylline may be required to reverse side effects. The onset and duration of action of dipyridamole are usually prolonged. The peak pharmacological effects occur about 6 to 8 minutes following initiation of the infusion [48].

Effects persist for 15 to 30 minutes but may last as long as 60 minutes. Half-life of dipyridamole is approximately 12 hours. Prolonged pharmacological activity could occur in the setting of hepatic insufficiency. The heterogeneity in blood flow in dipyridamole-induced ischaemia is probably due to the steal phenomenon, where the normal coronary arteries dilate and augment blood flow leaving a reduced pressure for flow of blood across the compromised arteries. It is reported that during pharmacological stress, dipyridamole (0.56 mg/kg dose) increases heart rate by 11± 7 beats/ minute and the mean arterial blood pressure decreases by – 10 ± 3 mmHg [49].

Patients should be without oral intake for at least 6 h prior to the test and caffeine ingestion should be restricted for at least 12 h. Additionally, if the test is being carried out to establish a diagnosis of coronary artery disease, all anti-anginal medications should be withheld. Adverse effects are common with pharmacologic stress testing (50–80% incidence), although these are usually mild and predominantly bothersome, not issues of safety. Death and major cardiac complications are very rare (<1/10,000) in properly selected patients [50].

Indications and contraindications are listed in (Table 3).

Table 3: Indications and contraindications of pharmacologic stress testing [51]:

A. Indications for Pharmacologic stress testing	B. Contraindications for Pharmacologic Stress Imaging
Contraindications to exercise testing Unsteady gait Critical aortic stenosis Large abdominal aortic aneurysm Left Bundle Branch Block Ventricular Paced Rhythm Pre-excited pattern Inability to perform adequate exercise Orthopedic, neurologic limitations Underlying lung disease (i.e. COPD, asthma) Medication limiting heart rate response Poor motivation Peripheral vascular disease	Hypotension Hypersensitivity to the stress agent Recent ACS Decompensated heart failure Severe aortic stenosis Severe hypertension (vasodilators are acceptable) Uncontrolled atrial fibrillation (vasodilators are acceptable) Asthma or COPD with ongoing wheezing (dobutamine is acceptable) Methylxanthine use such as caffeine (dobutamine is acceptable) Dipyridamole use (dipyridamole or dobutamine is acceptable) High grade AV block (dobutamine is acceptable)

Interpretation and Reporting

The interpretation of myocardial perfusion SPECT images should be performed in a systematic fashion to include: (1) evaluation of the raw images in cine mode to determine the presence of potential sources of image artifact and the distribution of extracardiac tracer activity; (2) interpretation of images with respect to the location, size, severity, and reversibility of perfusion defects as well as cardiac chamber sizes, and, especially for Tl-201, presence or absence of increased pulmonary uptake; (3) incorporation of the results of quantitative perfusion analysis; (4) consideration of functional data obtained from the gated images; and (5) consideration of clinical factors that may influence the final interpretation of the study. All of these factors contribute to the production of a final clinical report

Display

It is strongly recommended that the reading physician use the computer monitor screen rather than hard copy (e.g., paper or film) to interpret the study. A computer monitor is capable of displaying more variations in gray scale or color, making it easier to discern smaller variations in activity. Moreover, it is not possible to properly view moving images (e.g., raw cine data or gated images) on hard copy. A linear gray-scale translation table is generally preferred to color tables since the gray-scale demonstrates more consistent grades of uptake, but this is also dependent on the familiarity of the individual reader with a given translation [52].

Evaluation of the Images for Technical Sources of Error Patient Motion

The experienced reader should be familiar with the normal appearance of raw planar images and be able to identify motion artifact. In patients who have had a technetium-based perfusion agent with negligible myocardial redistribution (e.g., Tc-99m sestamibi or Tc-99m tetrofosmin), consideration should be made for repeating the image acquisition when significant motion is detected. Alternatives, such as planar imaging or prone positioning may also be considered [53].

Attenuation and Attenuation Correction

The most common being diaphragmatic in men and the breast in women. Breast attenuation artifact is most problematic when the left breast position varies between the rest and stress images (i.e., shifting breast attenuation artifact). When the apparent perfusion defect caused by breast attenuation artifact is more severe on the stress images than on the resting images, it is difficult to exclude ischemia. Breast attenuation artifact can be confirmed by repeating the acquisition with the left breast repositioned [54].

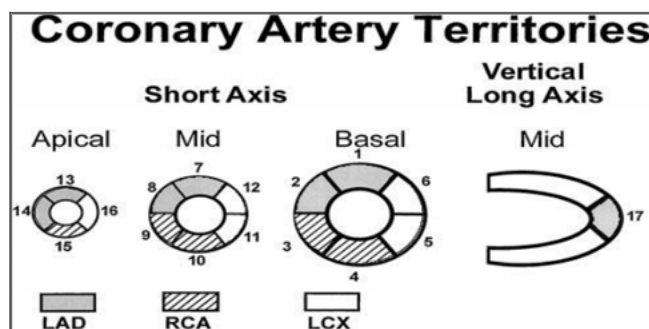


Figure 11: Left ventricular wall segmentation and assignment of vascular territories [55].

The nomenclature of short, vertical long and horizontal long axes has been used for the cardiac planes generated by SPECT, PET, cardiac CT, and CMR. The heart is segmented to 17 segments for assessment of myocardium and ventricular cavity (Figure (11)). Left ventricle should be divided into equal thirds perpendicular to the long axis of the heart. This will generate 3 circular basal, mid-cavity, and apical short axis slices of the left ventricle. Myocardial segments should be named and localized with reference to both the long axes of the ventricle and the 360° circumferential locations on the short-axis views. The names basal, mid-cavity, and apical identify the location on the long axis of the left ventricle. The circumferential locations in the basal and mid-cavity are anterior, anteroseptal, inferoseptal, inferior, inferolateral, and anterolateral. By using this system, for example segments 1 and 7 identify the locations of the anterior wall at the base and mid-cavity.

Segments 1, 2, 7, 8, 13, 14, and 17 are assigned to the left anterior descending coronary artery distribution. Segments 3, 4, 9, 10, and 15 are assigned to the right coronary artery when it is dominant. Segments 5, 6, 11, 12, and 16 generally are assigned to the left circumflex artery. The greatest variability in myocardial blood supply occurs at the apical cap, segment 17, which can be supplied by any of the 3 arteries [55].

Blood Supply of the Heart

The heart receives blood from left coronary arteries (LCA) and right coronary arteries (RCA) (Figure (12)).

Left Coronary Artery

The left coronary artery arises from the left aortic sinus (at an acute angle from the aorta) as a single short main artery (left mainstem). The LCA bifurcates to form the left anterior descending artery (LAD) and left circumflex (LCx). The LAD anastomoses with the posterior descending artery (PDA) a branch of the right coronary artery (RCA). The LAD supplies the interventricular septum (anterior two-thirds), the apex, and the anterior aspects of the right and left ventricle and right and left bundle branches. The LCx has a major branch, the left marginal artery. In around 10–15% of the population, the LCx anastomoses with the RCA to give rise to the PDA. In general, the LCx supplies the posterior aspect of the left atrium and superior portion of the left ventricle [56].

Right Coronary Artery

The RCA arises from the right aortic sinus and has major branches such as: a) PDA (supplying the posterior third of the interventricular septum and AV node).

1. Nodal artery (supplying the right atrium and the SA node).
2. Right marginal artery (supplying a portion of the right ventricle, the inferior left ventricular wall, and the PDA).
3. In the majority (80–90%) of cases, the RCA supplies the atrioventricular node (AV node) [57].
4. In general, the RCA is dominant in 60–65% of cases because it gives off a PDA branch (balanced coronary circulation). In about 10–15% of cases, the LCx gives rise to the PDA (left predominant circulation) [56].

Technetium Tc99m

Technetium is produced by process called elution. The ^{99}Mo - $^{99\text{m}}\text{Tc}$ generator is the most commonly used radionuclide generator system in nuclear medicine. The generator consists of ^{99}Mo absorbed onto an alumina column. ^{99}Mo decays by beta emission to $^{99\text{m}}\text{Tc}$ with a half-life of 67 hours. To minimise radiation exposure from the emitted beta particles and gamma radiation, the alumina column is shielded, typically by depleted uranium. The $^{99\text{m}}\text{Tc}$ can be removed from the column, as sodium pertechnetate ($\text{Na}^{99\text{m}}\text{TcO}_4$) by drawing a solution of sodium chloride through the column. This process is known as elution or ‘milking’ of the generator [58].

Technetium Tc 99m-labeled myocardial perfusion tracers were introduced in the clinical arena in the 1990s. $^{99\text{m}}\text{Tc}$ emits 140 keV of photon energy and has a physical half-life of 6 hours. Despite the excellent myocardial extraction and flow kinetic properties of thallium, its energy spectrum of 80 keV is suboptimal for conventional gamma cameras (ideal photopeak in the 140-keV range). In addition, thallium's long physical half-life (73 hours) limits the amount of thallium that may be administered to stay within acceptable radiation exposure parameters. Thus, $^{99\text{m}}\text{Tc}$ -labeled tracers improve on these two limitations of thallium. Although three $^{99\text{m}}\text{Tc}$ -labeled tracers (sestamibi, teboroxime, and tetrofosmin) have received U.S. Food and Drug Administration (FDA) approval for detection of CAD, only sestamibi and tetrofosmin are available for clinical use at present [59].

Tc 99 m to be used as indicator of coronary blood flow, it must be labeled by another compound either sestamibi or tetrofosamine that selectively concentrates in the myocardium [60].

Sestamibi is a lipophilic monovalent cation with a trade name of cardiolite. Sestamibi will not be extracted by non-viable myocardium and in plasma, less than 1% is protein bound. Hyperpolarized state of plasma membrane and mitochondrial potentials increases the uptake and retention of $^{99\text{m}}\text{Tc}$ -sestamibi. The first pass extraction fraction for $^{99\text{m}}\text{Tc}$ -sestamibi is approximately 65%, which is lower than that for thallium. Only about 1–2% of the injected dose localizes to the myocardium at rest. However, this lower extraction fraction is overcome by injecting a larger dose, which in turn results in a higher count rate. The uptake in myocardium is proportional to blood flow in the physiologic flow range. However, at higher flow rates there is a plateau in extraction [61].

Myocardial clearance of $^{99\text{m}}\text{Tc}$ -sestamibi is slow and the agent does not redistribute like ^{201}Tl . The main route of excretion is hepatobiliary (approximately 33%) with a half-life of approximately 30 minutes. This high hepatic concentration may result in liver-dominant SPECT images with compromised cardiac resolution; so fatty meal used to speed hepato-biliary clearance of the Tc 99 m sestaMIBI and, additional fluids will help gastrointestinal motility moves activity away from the heart. However, there can be very intense activity in the colon many hours later, especially in patients with a high splenic flexure, which would also affect myocardial imaging, considering that during exercise, splanchnic blood flow lessens, resulting in less splanchnic uptake than at rest. Therefore, imaging is best done after a brief waiting period to allow for some liver and biliary clearance but before significant accumulation can occur in the transverse colon. Typically, imaging is begun 30 minutes after peak injection and 45 to 60 minutes after rest one. The organs at risk are the gallbladder and kidneys. Although the breast takes up $^{99\text{m}}\text{Tc}$ -sestamibi, there is only minimal transfer to breast milk and cessation of breast-feeding is not essential [62].

Gamma Camera

The standard camera used in nuclear cardiology studies, a gamma camera, captures the gamma ray photons and converts the information into digital data representing the magnitude of uptake and the location of the emission. The photoemissions collide along their flight path with a detector crystal. There, the gamma photons are absorbed and converted into visible light events (a scintillation event). Emitted gamma rays are selected for capture and quantitation by a collimator attached to the face of the camera-detector system. Most often, parallel hole collimators are used so that only photon emissions coursing perpendicular to the camera head and parallel to the collimation holes are accepted (Figure (12) [63].

This arrangement allows better appropriate localization of the source of the emitted gamma rays. Photomultiplier tubes, the final major component in the gamma camera, sense the light-scintillation events and convert the events into an electrical signal to be further processed. The final result of SPECT imaging is the creation of multiple tomograms, or slices, of the organ of interest, composing a digital display representing radiotracer distribution throughout the organ. With SPECT myocardial perfusion imaging (MPI), the display represents the distribution of perfusion throughout the myocardium [64].

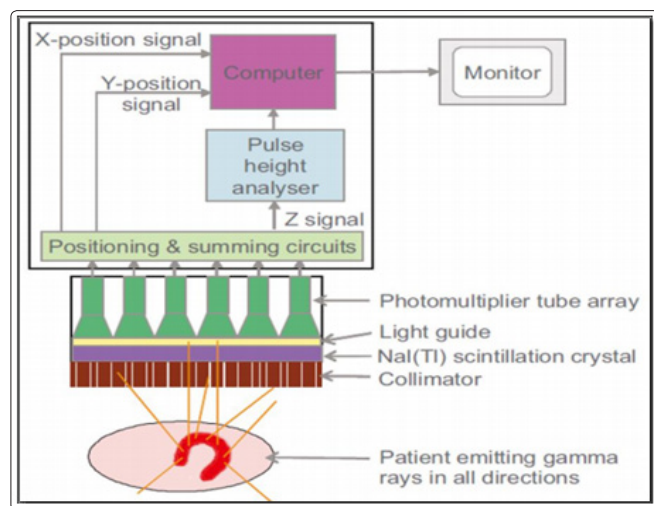


Figure 12: Schematic diagram of Gamma camera [63].

Structure of Gamma Camera

The gamma camera consists of a large, relatively thin (9–25 mm) sodium iodide scintillation crystal that is doped with a small amount (~0.7%) of thallium to form NaI(Tl). Gamma rays emitted in all directions and some of these gamma rays pass through the collimator and enter the gamma camera detector where they strike the NaI(Tl) scintillation crystal and are converted to flashes of light. The light photons are then viewed by all of the photomultiplier tubes (PMTs), the amount of light detected by the array of PMTs is transformed into three electronic signals (called X, Y and Z). The X and Y signals represent the location of where the gamma ray hit the crystal. The Z signal represents the gamma ray energy deposited in the crystal. Gamma rays passed through a pulse height analyser to determine if it is within the range of values expected for the specific radiopharmaceutical used. Gamma rays represented by dots in the monitor of the Gamma camera. Thousands of gamma rays are detected, and so thousands of dots appear on the monitor to eventually create an image [65].

Collimators

Important part of Gamma camera what is called collimator. This important part consists of a lead plate with thousands (30 000 to 60 000) of tiny holes (0.8 to 1.5 mm diameter) through it. The lead walls between the holes are called septa. Each hole accepts gamma rays from only a limited angle, and those gamma rays not travelling in the preferred direction are absorbed by the lead septa and never reach the detector. This means that a large proportion of emitted gamma rays do not contribute to the imaging process [66].

Two principal parameters describing collimator performance are resolution and sensitivity. Unfortunately, it is not possible to optimise both sensitivity and resolution simultaneously. For example, if the hole size of collimator is wide the sensitivity (the proportion of gamma rays incident on the collimator that actually pass through to the detector) increased and the resolution deteriorate, but if the hole length increased the sensitivity is decreased and the resolution improved. So, the collimator is manufactured by specific parameters for specific functions. The septal thickness is determined by the energy of the gamma ray to be imaged and is chosen to prevent gamma rays from crossing from one hole to the next. High resolution collimators with thin (short) septa and small holes are used for ^{99m}Tc high resolution cardiac imaging, whereas for ^{201}Tl scans, due to the low energy of the ^{201}Tl gamma rays, a low energy general purpose collimator is more appropriate [67].

According to the position of the collimator there are 2 types: parallel collimator and converging collimator. The parallel one is the most widely used collimator. Converging collimators have a field of view that magnify the object within the field of view but there is also some image distortion due to the fact that different planes of the object are at different distances from the collimator [68].

The spatial resolution of the image is comprised of intrinsic resolution (resolution of detector alone) and the collimator resolution. The intrinsic resolution is determined by the thickness of the scintillation crystal. As crystal thickness increases, the spatial resolution deteriorates but detection efficiency increases. In order to overcome the long time of the test, gamma camera with multiple detectors are often used. Cameras with two or even three detectors allow two or three angular projections to be acquired simultaneously. This allows the image to be acquired in half or one-third of the time required for a single detector camera [69].

Periprocedural Myocardial Injury (PMI)

Percutaneous coronary intervention (PCI) is performed in high-risk patients with complex lesions, recently, more than ever before. New armamentarium is used to accomplish this; for example, in the presence of calcified lesions, the use of some debulking technologies is becoming popular. This intense instrumentation of the coronary vessels brings as a consequence some periprocedural myocardial injury; when it is severe, it impairs myocardial function.

On the other hand, the introduction of new drug-eluting stents (DES) with thinner struts has impacted the rates of myocardial injury after PCI. In the last two decades, the Universal Definition Myocardial Infarction (UDMI) group, Academic Research Consortium (ARC), and Society for Cardiovascular Angiography and Interventions (SCAI) have attempted to provide standardized definitions for periprocedural myocardial infarction (PMI) after PCI to inform clinical decisions and harmonize clinical trial reporting.

It is, therefore, very relevant and timely to revise the mechanisms, prognosis, and prevention of myocardial injury after PCI.

Evolution of the Definition of PMI

Periprocedural myocardial injury occurs as a complication of any procedure involving PCI, such as using stents, balloons (or any other debulking/scoring technology) angioplasty, thrombolysis, or angiographic imaging.

In 2000, a joint European Society of Cardiology (ESC)/American College of Cardiology committee proposed its first UDMI and encouraged routine measurement of cardiac troponin (cTn) before and after PCI with the 99th percentile upper reference limit (URL) threshold to diagnose periprocedural MI [70].

Several subsequent studies questioned the importance of such small biomarkers increases on the long-term outcomes, while others were able to show a correlation to clinical outcomes using various cutoffs of different cardiac biomarkers [71-77]. Alternatively, in 2007, the ARC defined PCI-related PMI as troponin or creatine kinase-MB (CK-MB) > three times the URL [78].

Subsequently, the UDMI was revised in 2007 and again in 2012 [79,80]. In the third UDMI (2012), PMI was arbitrarily defined as an increase in cardiac troponin cTn of more than five times the

upper limit of normal (ULN) during the first 48 hour post-procedure in addition to specific clinical changes, electrocardiogram (ECG) features, or imaging evidence of infarction [80]. Similar definition was adopted in the recent fourth UDMI [81].

In 2018, the ARC-2 initiative revisited its first PMI definition [82]. ARC-2 proposes a common ≥ 35 URL threshold for cTn for both PCI- and coronary artery bypass grafting-related PMI as a reasonable threshold. However, ancillary criteria were required in addition to the ≥ 35 cTn rise to fulfill the definition of PMI. The ancillary criteria are one or more of the following: “flow-limiting” angiographic complications in a major epicardial vessel or >1.5 -mm-diameter branch, new significant Q-waves (or equivalent) related to the procedure, or a “substantial” new wall motion abnormality on echocardiography related to the procedure.

Mechanisms of Periprocedural Myocardial Injury

PMI occurs as a complication of any coronary intervention [83-85]. It is understood that PMI can be caused by a variety of mechanisms that occur either independently or concurrently (Figure 13). During PCI, the most commonly implicated mechanisms are distal microembolization of plaque debris, large flow limiting dissections and side-branch occlusion (SBO) [86-89]. Other mechanisms that have been described include the release of vasoactive substances, coronary spasm, no-reflow, and prolonged ischemia in presence of intraluminal thrombus [87-89].

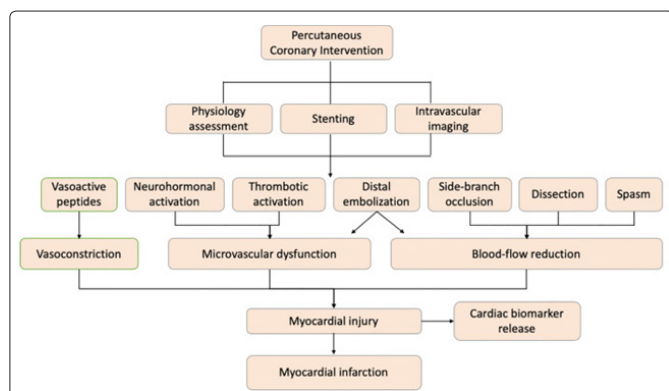


Figure 13: Mechanisms underlying periprocedural myocardial injury.

Distal Embolization of Plaque Debris

Embolization of atheromatous or thrombotic material into the distal vascular bed is a well-studied phenomenon that has been reported to occur in 40% to 70% of cases involving periprocedural myonecrosis [89-91]. In this process, high-risk atherosclerotic plaques are disrupted during PCI and dislodging debris travels downstream and causes microvascular obstruction [91-93]. This process is largely dependent on a vulnerable substrate that has certain characteristics, including a large necrotic core and unstable plaque composition [93,94]. There is some evidence showing a lower risk of post-procedural biomarker rise in restenotic lesions, supporting the central role of distal embolization to PMI [95]. Restenotic lesions possess a higher fibrotic-to-atherosclerotic content ratio than native atherosclerotic plaques and are thus less likely to embolize [95].

Conventional angiography can be used to assess and quantify coronary flow. One method is through examining contrast opacification within epicardial and myocardial microcirculations, quantified as TIMI flow grade or myocardial blush grade (MBG) respectively [96]. When performed before the coronary intervention, a low baseline TIMI flow grade (0 to 2) is highly

predictive of PCI-related myonecrosis. When performed toward the end of PCI, it can allow for evaluation of coronary reperfusion and assess for any potential myocardial damage. Low MBG (0 to 2) and TIMI (0 to 1) grades have been identified as independent predictors of PMI. Patients with low TIMI flow grades <3 are subject to the slow-flow or no-reflow phenomenon. In this phenomenon, inadequate myocardial reperfusion after PCI is reflected clinically by signs and symptoms of ischemia, ECG findings, and other sequelae similar to those of PMI [97-99].

The advancement of different imaging modalities has helped in assessing the risk of PMI before PCI, as well as early detection of myocardial injury during or after the procedure. Such imaging techniques can be invasive or non-invasive. The former includes optical coherence tomography (OCT), near-infrared spectroscopy (NIRS), intravascular ultrasound (IVUS and IVUS-derived imaging modalities such as virtual histology [VH-IVUS] and integrated backscatter IVUS [IB-IVUS]), angiography, and intracoronary Doppler ultrasound. Non-invasive modalities include coronary computed tomography angiography (CTA), Single-photon emission computed tomography (SPECT), cardiac magnetic resonance (CMR), and echocardiography (Figure 14).

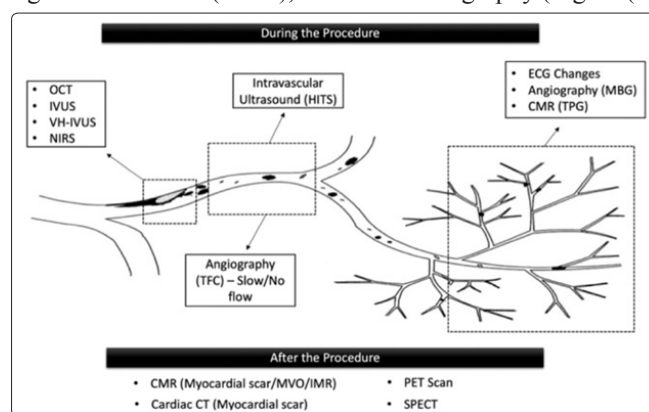


Figure 14: Different modalities that can be used to assess the occurrence and etiology of peri-procedural myocardial injury during the intra-procedural and post-procedural phases. OCT=optical coherence tomography; VH-IVUS=virtual histology-intravascular ultrasound; NIRS=near-infrared spectroscopy; HITS=high-intensity transient signals; TFC=TIMI frame count; ECG=electrocardiogram; MBG=myocardial blush grade; TPG=transmural perfusion gradient; MVO=microvascular obstruction; IMR=index of microcirculatory resistance; CT=computerized tomography; PET=positron emission tomography; SPECT=single-photon emission computerized tomography.

Intracoronary imaging can inform of the likelihood of distal embolization based on plaque morphology, plaque composition, and even characteristics within the vessel. Such an assessment can provide useful information on a patient's pre-procedural risk of PMI based on different parameters. These suggested imaging findings and their effects on PMI are summarized in Supplemental Table 1.

Plaque burden visualization with IVUS can help to identify high plaque volume and assessing the volume of echo-attenuated plaque (EAP). Patients with PMI are more likely to have higher plaque burden at the minimal lumen area, greater plaque volume, and presence of EAP [30,100-102]. Examining plaque composition by NIRS has shown that a greater lipid burden, measured as the maximal lipid core burden index (LCBI) over 4 mm of plaque, is

associated with PMI [101]. Similarly, large necrotic cores seen by radiofrequency IVUS have been implicated in the target lesions of patients with PMI [91,100].

As mentioned above, non-invasive imaging modalities have also been shown to provide valid information regarding plaque morphology and the risk of PMI. Despite being non-invasive, CTA can be used to visualize and characterize coronary plaque. CTA has identified low attenuation, high remodeling index, and spotty calcification as significant predictors of PMI [103]. CTA can also measure high coronary artery calcification score (CACS) as a risk factor associated with postprocedural biomarker elevation [91]. Here, it is thought that coronary calcium phosphate crystals cause inflammation and cardiac muscle cell damage, which eventually leads to destabilized atherosclerotic plaques [104].

CMR has been used to characterize high-intensity plaques (HIP) and to calculate a coronary plaque-to-myocardium signal intensity ratio (PMR) [105]. HIP is thought to directly reflect positive remodeling and thus represent an unstable coronary plaque [105]. The presence of HIP and a greater PMR have both been reported to predict PMI accurately [106].

Postprocedural analysis can be done to evaluate long-term functional and histological sequelae of myocardial microinfarction. Again, both non-invasive and invasive approaches are available to assess the degree of reperfusion and characterize the detrimental effects of myocardial injury.

A simple 12-leads ECG can be used post-procedurally and is most useful when detecting new Q-waves. In stable patients undergoing PCI, the presence of a new Q-wave with or without biomarker elevation was a powerful predictor of both short- and long-term mortality [107]. The presence of significant intracoronary ST-segment shift (≥ 1 mm shift from baseline) post-procedurally is also associated with worse outcomes and a higher risk of major adverse cardiovascular events (MACE) [108].

Imaging studies, such as CMR, computed tomography (CT), nuclear medicine, and positron emission tomography (PET), can evaluate certain parameters of the myocardium, providing information on prognosis and risk stratification after infarction has occurred. However, many of these studies investigating long-term myocardial changes have been performed in patients with ACS treated by PCI. Fewer studies in this area have focused on PMI patients. Nevertheless, for the purpose of discussing long-term outcomes after PMI, these lessons learned from ACS patients will be extended to stable patients suffering PMI, with the presumption that long-term sequelae due to acute MI and PMI are similar.

As with CMR, CT can be used post-procedurally for myocardial evaluation. Delayed enhancement multidetector CT (DE-MDCT) identifies areas of hypoenhancement that represent MVO, suggesting irreversible damage to the myocardium and worse long-term outcomes (109). Finally, SPECT represents a one of best method for providing a quantitative assessment of myocardial blood flow (MBF) after PCI [110]. There has been increasing interest in characterize the cellular immune response to myocardial damage and repair after PCI. Evidence suggests that this combined approach is a valid indicator of long-term prognosis.

Pre-Procedural versus Post-Procedural Risk and Prognostic Significance of Biomarker Elevation

The practice of cardiac biomarker assessment after routine PCI has changed over the past decade. The routine measurement of postprocedural enzymes was widely adopted in the catheterization

laboratories. It was, in fact, proposed by many societies in certain situations such as after procedure with evidence of “no-reflow” or compromised side-branch flow [111]. The routine acquisition of serial cardiac enzymes has gradually fallen out of favor as elective PCI started to increasingly become an ambulatory procedure in addition to the introduction of higher sensitive assays that introduced further uncertainty on the clinical consequence of biomarker elevation after PCI.

Furthermore, the prognostic implications of PMI and its effect on mortality have been subject to conflicting conclusions [112]. Some have suggested no relationship between PMI and long-term outcomes, whereas others have reported a non-linear relationship in which mortality becomes more likely only after a certain threshold [26,113]. However, the majority of these studies included several confounding factors that may muddle the true relationship between PMI and mortality. These include patients with ACS presentation, elevated baseline troponins, complex PCI procedures, or in-hospital complications [30]. Although still not yet perfect, the definition of PMI has been fine-tuned over the years, such that many of the older studies would now probably not be valid based on their study definition of PMI. In this context, it is also important to consider the delicate interplay between the PMI definition and its prognostic value. As others have indicated, a lower threshold will detect more overall cases of PMI; a higher threshold for PMI will capture fewer cases overall, but also most likely the sickest [114]. This again emphasizes the importance of a thoughtful, evidence-based definition of PMI.

The arrival of hs-TnT assays has introduced further complexity to this notion and has not yet been incorporated into all recent definitions of PMI. Hs-TnT can detect subtle troponin increases from minor myocardial damage after coronary intervention. At the same time, non-ACS patients might also have baseline hs-TnT elevations.

Prevention of Periprocedural Myocardial Infarction

There have been several strategies and therapeutic interventions that have been tested to prevent the incidence of PMI. These include, among others, antiplatelet drugs, statins, adenosine, beta-blockers, ischemic preconditioning, and different approaches that have been found in selected studies to reduce PMI.

Patients and Methods

Thirty patients with CTO were treated by an antegrade approach procedure, and another thirty patients with CTO were treated by a retrograde approach.

Each patient in the two groups was examined clinically, doing resting ECG, transthoracic echo, stress ECG before CTO approach.

99mTc sestamibi scintigraphy was done for each patient before CTO approach to detect the viability of the myocardium and to detect the size of reversible ischemia, and after six months of CTO approach was done for detection the effect of antegrade and retrograde approach for CTO on the viability of the myocardium and reversible ischemia.

Technical Design

- Site of study:** Cardiology Department, Al-Azhar University Hospitals in collaboration with National Heart Institute.
- Sample size**
- Total patients: 60 patient 30 patient antegrade approach and 30 patient retrograde approach
- Subjects included in the study**

Inclusion Criteria

1. Patients who have moderate to severe ischemia.
2. Patients who have had a successful CTO PCI.
3. Single vessel CTO.

Exclusion Criteria

1. Failed CTO PCI.
2. Renal Failure.
3. Heart failure with reduced ejection fraction.
4. Non-viable CTO territory.
5. Any DAPT contraindications.
6. Standard contraindications to coronary angiography.

Tools and Instruments

Electrocardiogram, transthoracic echocardiography, stress ECG, 99mTc sestamibi scintigraphy for myocardial viability and CTO PCI for all the patients.

Operational Design

- a) Type of Study: Prospective cohort study.
- b) Steps of performance and techniques used:
 - Complete history taking.
 - Electrocardiographic examination.
 - Conventional Transthoracic Echocardiography
 - Stress Electrocardiogram.
 - 99mTc sestamibi scintigraphy scanning for myocardial viability
 - Cardiac biomarkers (Ck-MB) levels were done to all patients before and after the PCI.
 - CTO PCI was performed to all patients. Antegrade and retrograde approach

SPECT Myocardial Perfusion Imaging

All patients deemed were encouraged to come off their beta-blockers and calcium-channel-blockers (negative chronotropic) for 48 hours and nitrates for 24 hours prior to the study and were asked to fast for 4 hours.

We do a 2-day protocol and all patients except those who have a depressed systolic function less than 35% and known to be ischemic will start with stress day. The patient is asked to take off his/her clothes, to shave the chest hair in males, and to pull breasts up and outwards in females. The chest is scrubbed using alcohol swap then electrodes are connected to the chest wall. A cannula is inserted.

The patient did either treadmill stress test according Bruce protocol or pharmacological stress using dobutamine agents.

- In treadmill stress test the patient will be exercised according to Bruce protocol aiming to reach at least 85% max predicted heart rate according to the patient's age (220- the patient's age) plus at least 5 METs to inject the isotope intravenously.

- In pharmacological stress using dobutamine is infused incrementally starting at a dose of 5 or 10mcg/kg/ min, which is increased at 3-minute intervals to 20,30, and 40mcg/kg/ min. Radiotracer is injected at peak heart rate with dobutamine infusion continuing for 1-minute following tracer injection. As with exercise stress, achieving greater than 85% of the predicted heart rate is desirable.

Also, we use the Tc-99m Sesta MIBI as a tracer. The dose of the isotope is calculated according to the weight of the patient. A light fatty meal given 15-20 min after the injection and SPECT imaging acquired 1 hour following the injection of the radionuclide. Scintigraphy gated images obtained quantitatively by using either a dedicated software (Auto QUANT 6.0; Philips Medical Systems;

Cleveland; Ohio).

Sixty-four (thirty-two frames by the dual head camera) projection images were acquired using the stop-and-shoot method. An electrocardiogram R-wave detector provided a gate to acquire eighteen frames per cardiac cycle. Three sets of SPECT slices representing summed, end-diastolic, and end-systolic images formed for computer display.

If the patient has a homogenous perfusion imaging, normal systolic function and no SWMA, the patient will have a stress only day. If the patient has either a perfusion defect, SWMA or an abnormal systolic function, the patient will have another day with rest or rest with nitrate potentiation.

On the 2nd day the patient will come on full medical treatment and fasting for 4 hours. The patient will be injected and will be asked to have a light fatty meal and the SPECT images will be acquired after injection by 1 hour.

Initial image analysis and interpretation: The initial interpretation of the perfusion study should be performed without any clinical information other than the patient's gender, height and weight. Such an approach minimizes the bias in study interpretation. All relevant clinical data should be reviewed after a preliminary impression is formed.

Ventricular Dilation: Before segmental analysis of myocardial perfusion, the reader should note whether there is LV enlargement at rest or post-stress or not. Dilation of the LV on both the stress and resting studies usually indicates LV systolic dysfunction, although it may be seen in volume overload states (e.g. severe mitral or aortic regurgitation) with normal ventricular systolic function. An increased stress-to-rest LV cavity ratio, also referred to as transient cavity dilatation (TCD) or transient ischemic dilation (TID), has been described as a marker for high-risk coronary disease. It is actually apparent, and not true, dilatation of the ventricle with stress, and is most likely caused by diffuse subendocardial ischemia and can be seen in other conditions, such as microvascular disease, that cause diffuse subendocardial ischemia even in the absence of epicardial coronary disease. TID is typically described qualitatively but may also be quantified. Normal limits by quantitation will depend on perfusion imaging protocol, the image processing parameters, and the software algorithm used.

Lung Uptake: the presence of increased lung uptake after thallium perfusion imaging has been described as an indicator of poor prognosis and should therefore be evaluated in all patients when using this perfusion agent.

Right Ventricular Uptake: Right ventricular RV uptake may be qualitatively assessed on the raw projection data and on the reconstructed data. There are no established quantitative criteria for RV uptake, but in general, the intensity of the RV is approximately 50% of peak LV intensity. RV uptake increases in the presence of RV hypertrophy, most typically because of pulmonary hypertension. The intensity of the RV may also appear relatively increased when LV uptake is globally reduced. Regional abnormalities of RV uptake may be a sign of ischemia or infarction in the distribution of the right coronary artery. The size of the RV should also be noted, as RV dilation can provide a clue to the presence of right heart volume overload due to conditions such as atrial septal defect or severe tricuspid regurgitation.

Non-Cardiac Findings: Both thallium-and technetium-based agents can be concentrated in tumors, and uptake outside the

myocardium may reflect unexpected pathology. However, the sensitivity and specificity of myocardial perfusion imaging for diagnosing non-cardiac conditions have not been well established.

Perfusion Defect Location: Myocardial perfusion defects should be identified by the use of visual analysis of the reconstructed slices. The perfusion defects should be characterized by their location as they relate to specific myocardial walls that is, apical, anterior, inferior, and lateral. The term posterior should be avoided because it has been variably assigned to either the lateral wall (circumflex distribution) or to the basal inferior wall (right coronary distribution), and is thus ambiguous. Standardization of segment nomenclature is highly recommended.

Defect extent may be qualitatively described as small, medium, or large.

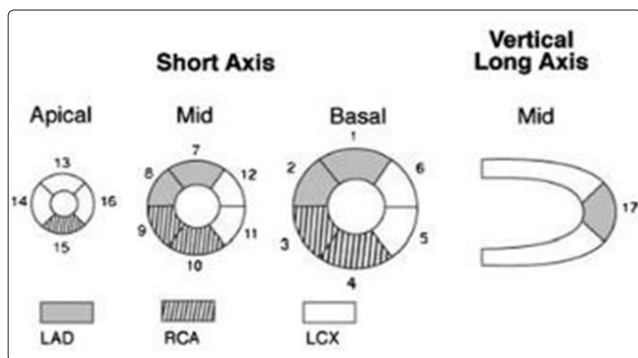


Figure 1: Territories of coronary arteries. LAD; left anterior descending artery. RCA; right coronary artery. LCX; left circumflex artery.

In semi-quantitative terms, small represents less than 5%, medium represents 5-9%, and large represents greater than or equal to 10% of the LV. Alternatively, defect extent may also be estimated as a fraction such as the “basal one half” or “apical one-third” of a particular wall or as extending from the base to the apex. Defects whose severity and extent do not change between stress and rest images are categorized as “fixed” or “nonreversible.” When perfusion defects are more severe and/or extensive on stress compared to resting images, a qualitative description of the degree of reversibility is required.

Semi-quantitative in addition to the qualitative evaluation of perfusion defects, it is recommended that the physician also apply a semi-quantitative segmental scoring system. This approach standardizes the visual interpretation of scans, reduces the likelihood of overlooking significant defects, and provides an important semi-quantitative index that is applicable to diagnostic and prognostic assessments.

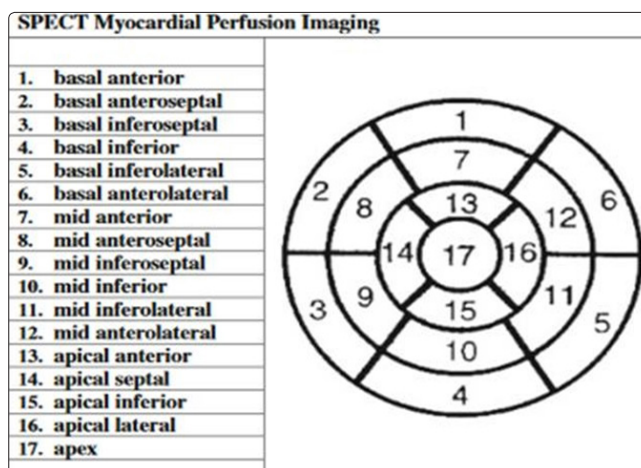


Figure 2: Myocardial segmentation on Bull's eye

The QA Committee of the American Society of Nuclear Cardiology has considered several models for segmentation of the perfusion images and has previously recommended either a 17- or 20-segment model for semi-quantitative visual analysis. In order to facilitate consistency of nomenclature with other imaging modalities, the 17-segment model is preferred and the 20-segment model should no longer be used.

The use of a five-point scoring system provides a reproducible semi-quantitative assessment of defect severity and extent. A consistent approach to defect severity and extent are clinically important because both variables contain independent prognostic information. Points are assigned to each segment according to the perceived count density of the segment. In addition to individual scores, it has been recommended that summed scores be calculated. The summed stress scores equal the sum of the stress scores of all the segments and the summed rest score equals the sum of the resting scores (or redistribution scores) of all the segments. The summed difference score equals the difference between the summed stress and the summed resting (redistribution) scores and is a measure of perfusion defect reversibility reflecting inducible ischemia. In particular, the summed stress score has been shown to have significant prognostic power, although the resting perfusion data provide incremental prognostic information as well.

Before scoring, it is necessary for the interpreting physician to be familiar with the normal regional variation in count distribution of myocardial perfusion SPECT in men and women.

Category	Score
Normal perfusion	0
Mild reduction in counts—not definitely abnormal	1
Moderate reduction in counts—definitely abnormal	2
Severe reduction in counts	3
Absent uptake	4

Figure 3: 5-point scoring system in semi-quantitative analysis

Quantitative analysis: it is useful to supplement visual interpretation. Most techniques of quantitative analysis are based on radial plots of short-axis slices, and analyze the apex separately. These plots are then normalized to allow comparison to a normal gender-specific database. Defect severity can be defined based

on the patient’s regional myocardial tracer activity compared to the mean regional activity of a normal database. Quantitation of the stress perfusion is compared to the resting perfusion to assess the extent and severity of ischemia. It is customary to use separate normal data bases specific to the patient’s gender as well as the perfusion agent used. This quantitative analysis is typically displayed as a “bull’s-eye” or polar plot.

Regional wall motion should be interpreted with a gray scale display. When computer edge analysis software is available, the physician may choose to analyze wall motion by use of the assigned endocardial and epicardial contours, but reference should also be made to the wall motion without computer-derived edges. Regional wall thickening may be analyzed in gray scale or in a suitable color scheme, although color displays may make it easier to appreciate changes in count intensity.

Gated SPECT: regional wall motion and thickening: Regional wall motion should be analyzed by the use of standard nomenclature: normal, hypokinesis, akinesis, and dyskinesis. Hypokinesis maybe further qualified as mild, moderate, or severe. A semi-quantitative is normal, 1 is mild hypokinesis, 2 is moderate hypokinesis, 3 is severe hypokinesis, 4 is akinesis, and 5 is dyskinesis. This is comparable to the 5-point scoring system used in both contrast and radionuclide ventriculography.

As in any assessment of regional ventricular function, one must be cognizant of expected normal and abnormal variations such as the reduced wall excursion at the base compared with the apex, the greater excursion of the basal lateral wall compared with the basal septum, and paradoxical septal motion, which may result from left bundle, post pericardiotomy or RV pacing. Normal myocardial wall thickness is below the spatial resolution of currently available SPECT systems. Because of the “partial volume effect,” regional wall thickening can be estimated by the count increase from end diastole to end systole.

It is more difficult to visually assess the severity of abnormality of myocardial wall thickening than it is to visually estimate abnormalities of wall motion. However, the evaluation of thickening with gated perfusion SPECT lends itself to quantitation because it is characterized by count changes. Wall motion and wall thickening are generally concordant. In addition to noting LV wall motion, wall thickening, and EF, the function of the RV should also be noted.

Quantitative normal databases are available for assessment of regional wall thickening. Left ventricular ejection fraction and volume.

LVEF and LV and RV chamber sizes should routinely be evaluated qualitatively, EF may be categorized as normal, mildly, moderately, or severely reduced. Volume may be categorized as normal, mildly, moderately or severely reduced. Alternatively, LVEF and end-diastolic and end-systolic volumes may be calculated with geometric models applied to the reconstructed data set.

Statistical Analysis

Statistical analysis was done by SPSS v25 (IBM Inc., Chicago, IL, USA).

Normality of data was checked with Shapiro-Wilks test and all variables were normally distributed.

Quantitative variables were presented as mean, standard deviation (SD) and range and were compared between the two groups utilizing Student's t- test.

Categorical variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square test or Fisher's exact test when appropriate.

P value < 0.05 was considered statistically significant.

Results

In this study, group A: 30 patients with CTO were treated by an antegrade approach procedure, and group R: 30 patients with CTO were treated by a retrograde approach.

Table 1: Patients' characteristics in both studied groups:

		Group A (n = 30)	Group R (n = 30)	P value
Age (years)	Mean ± SD	52.6 ± 5.84	53.4 ± 7.36	0.67
	Range	42-64	40-65	
Sex	Male	21 (70%)	18 (60%)	0.417
	Female	9 (30%)	12 (40%)	
Hypertension	HTN	17 (56.7%)	20 (66.7%)	0.426
	No HTN	13 (43.3%)	10 (33.3%)	
Diabetes mellitus	DM	19 (63.3%)	16 (53.3%)	0.432
	No DM	11 (36.7%)	14 (46.7%)	
Smoking	Smoker	24 (80%)	22 (73.3%)	0.542
	Not	6 (20%)	8 (26.7%)	
Previous MI	Previous MI	5 (16.7%)	7 (23.3%)	0.542
	No	25 (83.3%)	23 (76.7%)	
Previous PCI	Previous PCI	7 (23.3%)	5 (16.7%)	0.519
	No	23 (76.7%)	25 (83.3%)	
Chest pain	C/O chest pain	30 (100%)	30 (100%)	1
	No	0 (0%)	0 (0%)	

Patients’ characteristics (age, sex, hypertension, diabetes mellitus, smoking, previous MI, previous PCI and chest pain) were insignificantly different between both groups. [Table (1, Figure (1)]

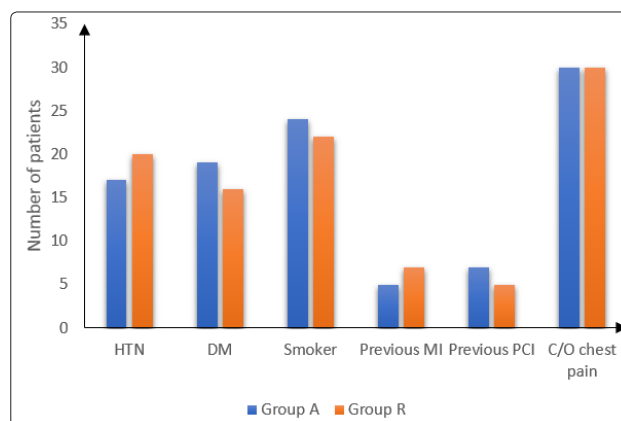


Figure 1: Past history of both groups

Table 2: PCI procedure in both studied groups:

		Group A (n = 30)	Group R (n = 30)	P value
Duration of PCI procedure (min)	Mean ± SD	86.2 ± 20.29	162 ± 25.78	<0.001*
	Range	60-120	120-205	
Target vessel	LAD	13 (43.3%)	17 (56.7%)	0.302
	LCX	8 (26.7%)	10 (33.3%)	0.571
	RCA	9 (30%)	3 (10%)	0.104
Number of stents implanted	1	9 (30%)	10 (33.3%)	0.555
	2	15 (50%)	17 (56.7%)	
	3	6 (20%)	3 (10%)	
Contrast volume of PCI procedure (mL)	Mean ± SD	335.3 ± 70.8	429.7 ± 68.3	<0.001*
	Range	250-450	300-550	

*significant as P value <0.05

Duration of PCI procedure and contrast volume of PCI procedure were significantly decreased in group A than group R (P <0.001). [Table (2), Figures 19, 22].

Target vessel and number of stents implanted were insignificantly different between both groups. [Table (2), Figures 20, 21].

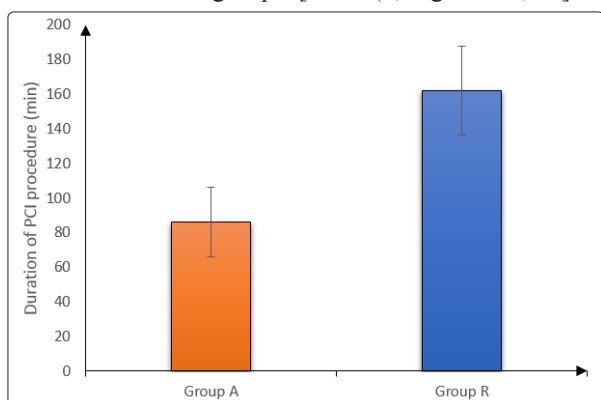


Figure 2: Duration of PCI procedure of both groups

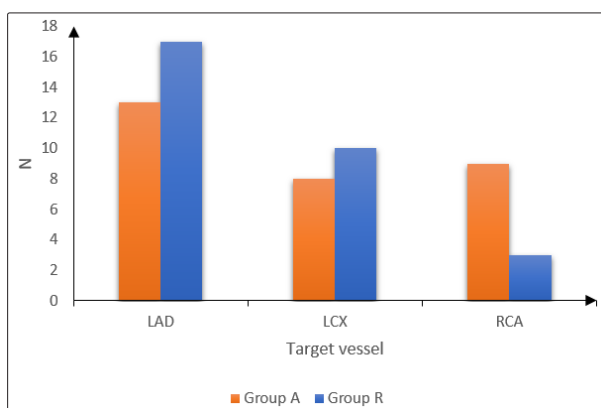


Figure 3: Target vessel of both groups

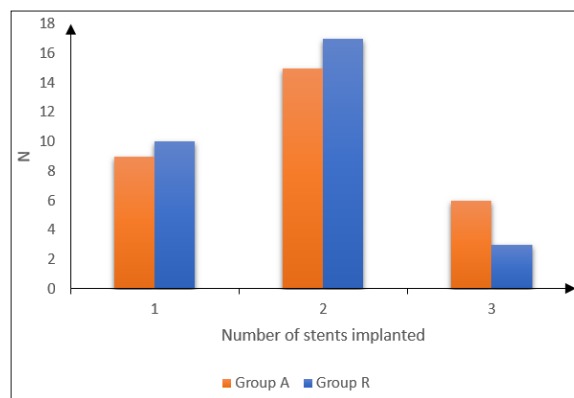


Figure 4: Number of stents implanted of both groups

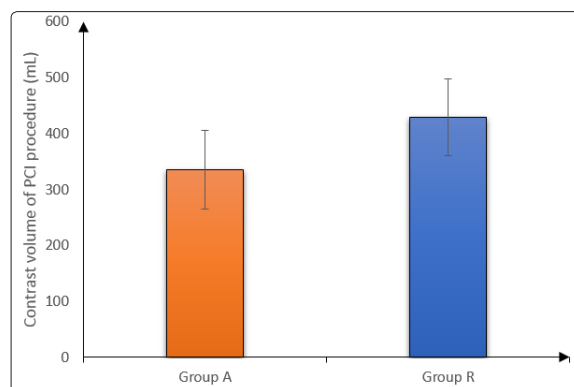


Figure 5: Contrast volume of PCI procedure of both groups

Table 3: Stress perfusion defect in both studied groups

		Before PCI	After PCI	Decrease
Group A (n = 30)	Mean	20.83	4.70	16.13
	± SD	3.77	2.60	1.17
Group R (n = 30)	Mean	19.33	6.67	12.67
	± SD	4.53	1.60	2.92
P value		0.169	0.001*	0.007*

*significant as P value <0.05

Stress perfusion defect before PCI was insignificantly different between both groups. Stress perfusion defect after PCI was significantly decreased in group A than group R (P = 0.001), stress perfusion defect decrease was significantly increased in group A than group R (P = 0.007). [Table (3), Figure (6)]

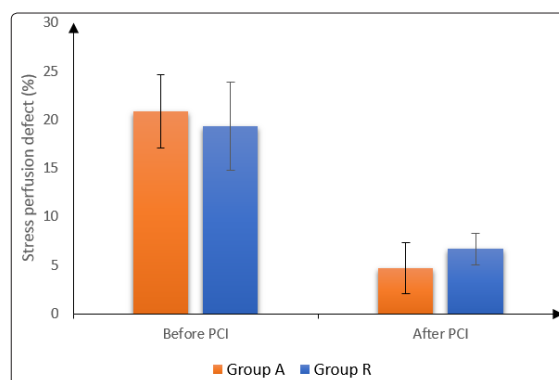


Figure 6: Stress perfusion defect of both groups

Table 4: Rest perfusion defect in both studied groups

		Before PCI	After PCI	Decrease
Group A (n = 30)	Mean	6.77	1.47	5.30
	± SD	2.30	1.01	1.29
Group R (n = 30)	Mean	6.60	1.90	4.70
	± SD	1.63	1.27	0.36
P value		0.747	0.148	0.323

Rest perfusion defect before PCI, after PCI and decrease were insignificantly different between both groups. [Table (4), Figure (7)]

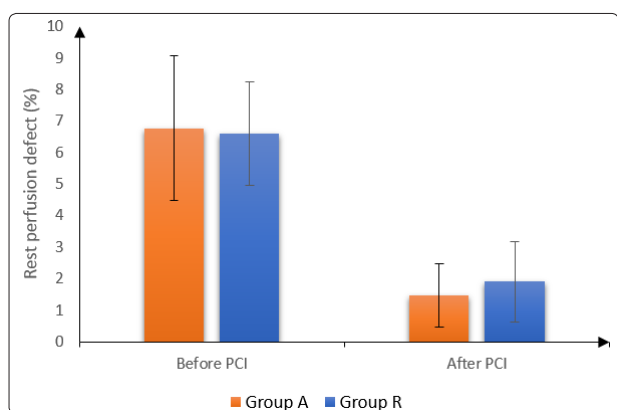


Figure 7: Rest perfusion defect of both groups

Table 5: Stress Rest perfusion difference in both studied groups

		Before PCI	After PCI	Decrease
Group A (n = 30)	Mean	14.07	3.23	10.83
	± SD	3.74	3.08	0.66
Group R (n = 30)	Mean	12.73	4.77	7.97
	± SD	4.23	1.77	2.45
P value		0.201	0.022*	0.030*

* significant as P value <0.05

Stress rest perfusion difference before PCI was insignificantly different between both groups. Stress rest perfusion difference after PCI was significantly decreased in group A than group R (P = 0.022), stress rest perfusion difference decrease was significantly increased in group A than group R (P = 0.030). [Table (5), Figure (8)]

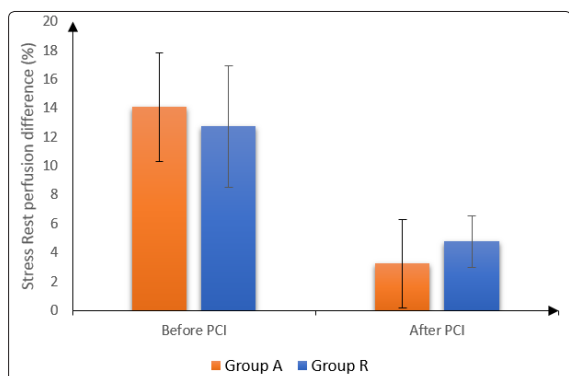


Figure 8: Stress Rest perfusion difference of both groups.

Table 6: Post-exercise EF in both studied groups

		Before PCI	After PCI	Decrease
Group A (n = 30)	Mean	44.87	49.33	-4.47
	± SD	5.61	5.90	-0.29
Group R (n = 30)	Mean	44.27	51.50	-7.23
	± SD	4.08	4.85	-0.77
P value		0.638	0.126	0.065

Post-exercise EF before PCI, after PCI and decrease were insignificantly different between both groups. [Table (6), Figure (9)]

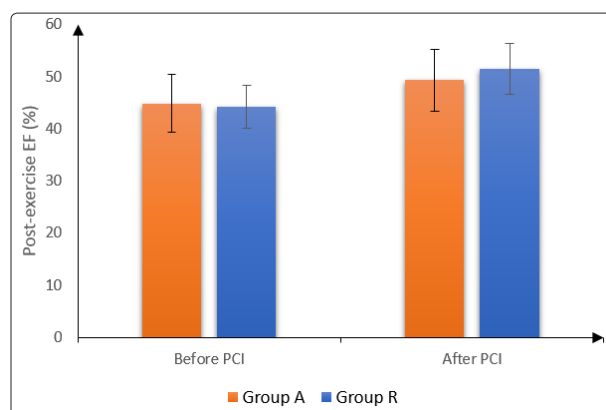


Figure 9: Post-exercise EF of both groups

Table 7: Rest EF in both studied groups

		Before PCI	After PCI	Decrease
Group A (n = 30)	Mean	50.90	55.10	-4.20
	± SD	5.55	5.92	-0.37
Group R (n = 30)	Mean	50.20	57.13	-6.93
	± SD	4.33	4.50	-0.17
P value		0.588	0.140	0.062

Rest EF before PCI, after PCI and increase were insignificantly different between both groups. [Table (7), Figure (10)]

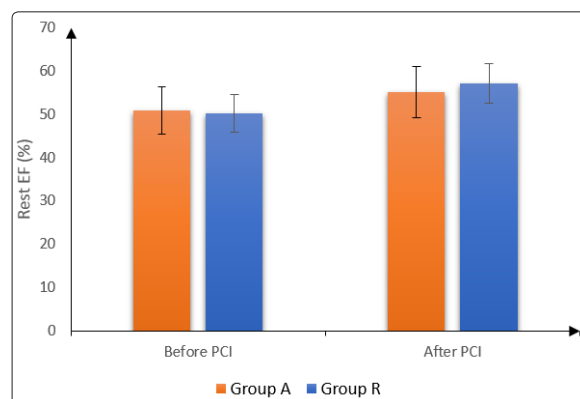


Figure 10: Rest EF of both groups.

Summary

Chronic total occlusions were defined as a lesion with thrombolysis in myocardial infarction (TIMI) grade 0 flow for at least 3 months duration, clinically estimated based on onset of angina symptoms, history of myocardial infarction, or documentation on invasive or computer tomography angiography.

With recent advances in interventional devices, procedural techniques, and operator experience, the technical success rate of modern CTO PCI is consistently above 90%, with low procedural complication rate. The retrograde approach has been developed and utilized worldwide in recent years, thanks to the development of modern guide-wires and micro-catheters allowing aggressive collateral channel tracking. However, many experts still use the antegrade approach as the default initial strategy, and reserve the retrograde approach only for reattempts.

During the past decade, there has been a renewed interest in treating coronary chronic total occlusions (CTOs) percutaneously after the development of both controlled antegrade dissection reentry (ADR) and retrograde recanalization techniques, which are often utilized in the treatment of more complex CTOs. Antegrade dissection reentry (ADR) refers to an attempt to cross a CTO lesion that leads to wire or equipment passage in the subintimal space followed by reentry to the distal true lumen.

The use of a retrograde approach and algorithm-driven CTO (chronic total occlusion) percutaneous coronary intervention (PCI) has become widespread, and many registries have reported good results.

We conducted this study to compare between antegrade versus retrograde recanalization of coronary chronic total occlusion, with special concern to ischemic burden assessment by SPECT pre-procedure and six months after.

In this study, group A: 30 patients with CTO were treated by an antegrade approach procedure, and group R: 30 patients with CTO were treated by a retrograde approach.

Our Results Showed That

Patients' characteristics (age, sex, hypertension, diabetes mellitus, smoking, previous MI, previous PCI and chest pain) were insignificantly different between both groups.

The duration and contrast volume of PCI procedure was significantly lower in group A than group R ($P < 0.001$). While target vessel and number of stents implanted were insignificantly different between both groups.

The stress perfusion defect after PCI was significantly decreased in group A than group R ($P = 0.001$), stress perfusion defect decrease was significantly increased in group A than group R ($P = 0.007$). Rest perfusion defect before PCI, and decrease were insignificantly different between both groups. Stress rest perfusion difference after PCI and stress rest perfusion decrease was significantly decreased in group A than group R ($P = 0.022$ & 0.030 respectively). Post-exercise EF and rest EF before PCI, after PCI and decrease were insignificantly different between both groups.

Conclusion

PCI CTO treatments are very demanding in terms of staff skills and equipment used. Retrograde approach had a higher duration and contrast volume of PCI procedure compared to antegrade approach but without differences in target vessel and number of stents implanted.

Retrograde approach had a higher stress perfusion defect and stress rest perfusion difference after PCI compared to antegrade approach but without difference in rest perfusion defect. Post-exercise EF and rest EF before PCI, after PCI and decrease were insignificantly different between both retrograde and antegrade approaches.

Limitations of the Study

1. There were no definite criteria for strategy selection, except for operators' experience, skills, and clinical judgments.
2. The cost-effectiveness of these 2 approaches was not analyzed in the present study.
3. This study was not a randomized controlled trial and the sample size was relatively small.

Recommendations

1. Conduction of larger, multicentric study was required to clearly explore the superiority of one approach over other.
2. More focus on acute procedural outcomes regarding success rate, complication and evaluate long-term prognosis after CTO PCI is needed.
3. More studies compared between both approaches on patients with associated comorbidities and anatomical abnormalities on coronaries will be required.

Discussion

Chronic total occlusions (CTOs) of coronary arteries are common and can be seen in 15–30% of patients with coronary artery disease. Percutaneous coronary intervention (PCI) of chronic total occlusion (CTO) remains one of the most challenging procedures in interventional cardiology. The main barriers to CTO PCI are: procedural complexity and uncertainties regarding its clinical benefit. CTO PCI is technically challenging and requires skill sets that are very different from non-CTO PCI. It is considered the "final frontier" of coronary intervention. Recently, there has been a growing interest in CTO revascularization as evidenced by developments of novel techniques and devices with improved success rates [116,117].

In case of antegrade failure to cross the CTO lesion, the retrograde approach may improve the success rate of such procedures. Using a retrograde approach, as originally described by the Toyohashi Heart Center group in 2006, has dramatically improved success rates of chronic total occlusion (CTO) percutaneous coronary intervention (PCI) [119,120].

However, there remains skepticism and controversy regarding the true clinical benefits of successful CTO revascularization. Single photon emission computed tomography (SPECT) can also be used in the assessment of both ischemia and viable myocardium. Two main tracers can be used: thallium-201 or technetium-99m. Prior clinical studies suggested that myocardial perfusion imaging with either thallium-201 or technetium-99m sestamibi can provide clinically important information pertaining to the status of myocardial viability when systolic dysfunction exists in the setting of severe coronary artery disease or after an acute myocardial infarction. This ability to identify ischemic or viable myocardium can help with identification of suitable patients to undergo CTO PCI [121].

We conducted this study to compare between antegrade versus retrograde recanalization of coronary chronic total occlusion, with special concern to ischemic burden assessment by SPECT pre-procedure and six months after.

In this study, group A: 30 patients with CTO were treated by an antegrade approach procedure, and group R: 30 patients with CTO were treated by a retrograde approach.

In the current study, duration and contrast volume of PCI procedure was significantly lower in group A than group R ($P < 0.001$). While target vessel and number of stents implanted were insignificantly different between both groups.

In harmony with current study, Lee et al., included patients that underwent 321 consecutive attempts. The antegrade approach was used in 152 patients, and retrograde in 169 patients. Their results showed that, the procedure and fluoroscopy times were significantly longer, with more radiation exposure and contrast medium consumption, in the retrograde group. But in disagree with our results, the target CTO lesions were located in right coronary artery (RCA) in 48.6% of the patients, left anterior descending artery (LAD) in 34.9%, and left circumflex artery (LCX) in 15.6%. With significant difference between groups [122]. Similarly, the different antegrade and retrograde techniques according to Pillai et al., showed no statistically significant association was seen between the occluded vessel targeted for intervention and the procedural success ($p = 0.13$ by chi-square test) [123].

Moreover, in study by Harding et al., the current radiation and contrast dose, and fluoroscopy time were all comparable [124]. In contrast with current study, baseline characteristics and comparison between those who underwent retrograde versus antegrade procedures are listed by Wu et al., they found number of stents implanted in CTO vessel was 2.1 in Antegrade versus 2.5 in retrograde with significant difference, $p < 0.001$. on the other hands, their results was similar to our finding regarding procedure time (minutes) which significantly prolonged in retrograde than antegrade. Also, Right coronary artery CTO was more commonly approached with retrograde (58% vs 38.2%) and in-stent restenosis cases were more commonly performed through an antegrade approach only (12.6% vs 5.7%) with significant difference. In addition, Karmpaliotis et al., reported that, the retrograde approach contributed to 28.7% of all technical success at a cost of more contrast (300 [220–404] versus 245 [180–320] mL; $P < 0.001$), longer procedure time (183 [128–234] versus 100 [68–135] min; $P < 0.001$), compared with antegrade-only cases, respectively [125,126].

In current study, stress perfusion defect after PCI was significantly decreased in group A than group R ($P = 0.001$), stress perfusion defect decrease was significantly increased in group A than group R ($P = 0.007$). Rest perfusion defect before PCI, and decrease were insignificantly different between both groups. Stress rest perfusion difference after PCI and stress rest perfusion decrease was significantly decreased in group A than group R ($P = 0.022$ & 0.030 respectively). Post-exercise EF and rest EF before PCI, after PCI and decrease were insignificantly different between both groups.

According to our knowledge, there was limited number of studies compared between both modalities in PCI. On the other hands, efficacy and operative outcome of either retrograde and antegrades technique of PCI was evaluated previously. In study by Tuma et al., ischemic stress-induced myocardial segments assessed by percutaneous retrograde coronary sinus perfusion (PRCSP) received. They found that, the median baseline area of ischemic myocardium by SPECT of 38.2% was reduced to 26.5% at one year and 23.5% at two years ($p = 0.001$). The median rest left ventricular ejection fraction by SPECT at baseline was 31.2% and improved to 35.5% at 2 year follow up ($p = 0.019$) [127].

Moreover, percutaneous retrograde coronary sinus perfusion (PRCSP) is a well-established technique for delivery of cardioplegia solution in cardiovascular surgery and for protection against myocardial ischemia in patients undergoing high risk percutaneous coronary intervention (PCI) in many studies [128-130].

And regarding to antegrade approaches, study by Pujadas et al., using cardiac magnetic resonance (CMR) had shown inducible

perfusion defects in 26 (79%) before PCI, while they were observed in 10 (30%) post-PCI CMR study ($p < 0.001$). The number of segments showing inducible perfusion defect (3.4 ± 2 prevs. 2.9 ± 4.5 post-PCI, $p = 0.002$) was significantly reduced in this group [131].

Our results was supported by many trails showed that, direct comparisons between gated single photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI) have shown excellent correlations for the evaluation of both global and regional left ventricular function [132,133]. Moreover, in those without prior history of myocardial infarction, stress-induced reversible perfusion defects are observed on single-photon positron emission CT (SPECT) imaging, as shown in a series by He et al.,(134) and Enein et al.,(135) with single vessel CTO. To detect reversible perfusion defects in CTO, adenosine SPECT imaging has been found to be more sensitive than exercise-induced stress imaging [136].

This was in line with Pillai et al., single-center non-randomized descriptive follow-up study on CTO PCI. Techniques employed were antegrade guide wire escalation approach, antegrade parallel wire, and dissection/re-entry. The conventional approach was antegrade in this series. An increase in left ventricular ejection fraction (LVEF) was noted following successful CTO PCI after complete revascularization in both groups equally [123].

This study was in disagree with Schumacher et al., compared outcomes in 193 patients who underwent chronic total occlusion (CTO) percutaneous coronary intervention (PCI) using different techniques: antegrade wire escalation, retrograde wire escalation, antegrade dissection and reentry (ADR), and retrograde dissection and reentry. They found increase in hyperemic MBF ($P=0.40$) and coronary flow reserve ($1P=0.84$) and decrease in defect size ($P=0.77$) were comparable between the 4 approaches. Although sometimes necessary to cross a complex CTO lesion, subintimal knuckle wiring and subintimal tracking and reentry resulted in less hyperemic MBF improvement compared with other subintimal crossing and reentry techniques [137].

Another opinion was reported by Riley and Yeh, as antegrade dissection and reentry (ADR) was initially adapted from the subintimal tracking and reentry (STAR) technique. This involved pushing a looped or knuckled guidewire within the CTO segment until it reentered the distal true lumen. This approach typically results in an uncontrolled reentry into the distal true lumen of the vessel, can result in poor runoff, and has been associated with high rates of target vessel failure when used as a primary revascularization strategy. One adaptation of subintimal tracking and reentry is limited antegrade subintimal tracking. This approach involves placement of a guidewire in a subintimal position. The subintimal space is then fenestrated into the true lumen with a stiff wire, followed by wiring the true lumen with a medium-weight polymer jacketed wire. However, similar to subintimal tracking and reentry, reentry with limited antegrade subintimal tracking has associated with relatively poor long-term outcomes. Evolving from these strategies, dedicated equipment for ADR has been developed to make subintimal reentry more reliable and has resulted in much more favorable, durable long-term results. Use of retrograde recanalization techniques are now standard techniques that associated with significant improvements by expert operators [138].

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