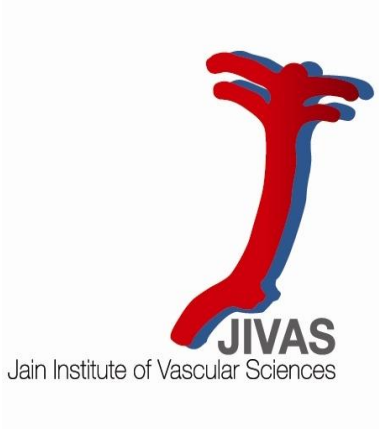
QUALITATIVE ASSESSMENT OF CARBON DIOXIDE AS A CONTRAST AGENT FOR INFRA-INGUINAL ARTERIAL DIAGNOSTIC AND THERAPEUTIC PROCEDURES IN CRITICAL LIMB ISCHEMIA.



DEC 2017

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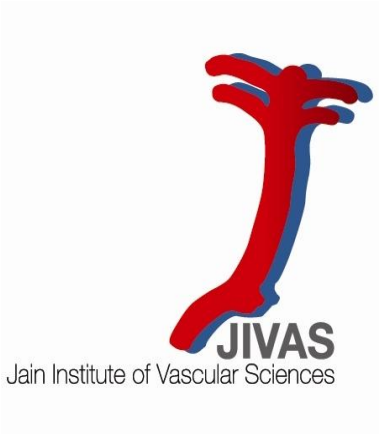
Qualitative Assessment of Carbon Dioxide As A Contrast Agent For Infra-Inguinal Arterial Diagnostic And Therapeutic Procedures In Critical Limb Ischemia.

Dissertation submitted to the National Board of Examinations, New Delhi, in partial fulfillment of the requirements for the award of the Diplomate of National Board in the super specialty of Peripheral Vascular Surgery



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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation titled **"Qualitative Assessment of Carbon Dioxide As A Contrast Agent For Infra-Inguinal Arterial Diagnostic And Therapeutic Procedures In Critical Limb Ischemia"** is a bonafide and genuine research work carried out by me under the guidance and supervision of **Dr. Sumanthraj Kolalu** Vascular Surgeon, Jain Institute of Vascular Sciences (JIVAS), Bhagwan Mahaveer Jain Hospital, Bangalore in partial fulfillment of the requirement of National Board of Examinations regulation for the award of the Degree of DNB in ***Peripheral Vascular Surgery.***

This has not formed the basis for the award of any degree or diploma to me before and I have not submitted this to any other university or board previously.

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Place: Bangalore

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This is to certify that the dissertation titled **"Qualitative Assessment of Carbon Dioxide As A Contrast Agent For Infra-Inguinal Arterial Diagnostic And Therapeutic Procedures In Critical Limb Ischemia"** is a bonafide research work done by **Dr. Dharmeshkumar B. Davra, MBBS, MS (General Surgery)** under my guidance at Jain Institute of Vascular Sciences (JIVAS), a unit of Bhagwan Mahaveer Jain Hospital, Bangalore in partial fulfillment of the requirement of National Board of Examinations regulation for the award of the degree of DNB in super specialty of ***Peripheral Vascular Surgery.***

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Place: Bangalore

Dated:

Dharmeshkumar

List of Abbreviations

AAA = Abdominal Aortic Aneurysm
ABI = Ankle Brachial Index
ACS = Acute Coronary Syndrome
ACT = Activating Clotting Time
AI = Aorto-Iliac
ATA = Anterior Tibial Artery
AV= Arterio-Venous
BTK = Below The Knee
CAD = Coronary Artery Disease
CFA = Common Femoral Artery
CIN = Contrast Induced Nephropathy
CLI = Critical Limb Ischemia
CO2 = Carbon Dioxide
CO2A = CO2 Angiography
CTA = Computed Tomography Angiography
CVD = Cerebro-Vascular Disease
DM = Diabetes Mellitus
DPA = Dorsalis Pedis Artery

DSA = Digital Subtraction Angiography
DUS = Duplex Ultra Sound
$^{e}C_{Cr}$ = estimated creatinine clearance
eGFR = Estimated Glomerular Filtration Rate
ETCO2 = Endotracheal Tube CO2
EVT = Endovascular Therapy
GA = General Anesthesia
GFR = Glomerular Filtration Rate
HbA1c = Glycated haemoglobin
HDL = High Density Lipoprotein
HTN = Hypertension
IA = Intra-Arterial
ICM = Iodine Contrast Material
IV = Intra-Venous
IVUS = Intra-Vascular Ultrasound
KDOQI = Kidney Disease Outcome Quality Initiative
LA = Local Anesthesia
MAC = Monitored Anesthesia Care
MDRD = Modification of Diet in Renal Disease
MRA = Magnetic Resonance Angiogram

NAC = N-acetyl Cysteine
NOMI = Non-occlusive mesenteric Ischemia
PA = Popliteal Artery
PAD = Peripheral Arterial Disease
PCI = Percutaneous Coronary Intervention
PTA = Percutaneous Transluminal Angioplasty
PTA = Posterior Tibial Artery
PVR = Pulse Volume Recording
RA = Regional Anesthesia
RAS = Renal Artery Stenting
SCr = Serum Creatinine
SFA = Superficial Femoral Artery
TBI = Toe Brachial Index
TOF = Time of Flight
TPT = Tibio-Peroneal Trunk
USG = Ultrasonography

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Introduction

INTRODUCTION

Patients presenting with Peripheral arterial disease (PAD), often have coexisting renal, cardiac, diabetic, and other medical co-morbidities. The number of patients with chronic kidney disease (CKD) complicated with PVD is significantly increasing. In these patients, iodinated contrast will likely increase the risk of contrast-induced nephropathy (CIN). CIN is an acute renal injury and may lead to irreversible loss of renal function. Following percutaneous cardiovascular intervention therapy, CIN was observed in 8%–15% of total patients and 40%–50% of high-risk patients depending on the prevalence of risk factors and used definition[1]. The most important effective preventive strategy for CIN is reduction in iodine contrast material (ICM) volume.[1]

Hawkins pioneered the use of CO2 as an intra-arterial contrast agent and interest developed because it represented a safe, effective, inexpensive alternative to the relatively toxic ionic contrast agents available at that time. Despite this, CO2 angiography has never been widely used. This is due to two factors- First the angiographic image quality is limited due to the low intrinsic radio-opacity of CO2 gas and second there is a perception that gas contrast is difficult to use. Modern angiographic equipment is capable of high resolution and image summation. This has increased the scope for CO2 angiography.[2]

CO_2 is a nontoxic, non-flammable, buoyant, compressible gas that has low viscosity and is produced endogenously at approximately 200 cc to 250 cc per minute. It is a natural by-product and there are approximately 120 litter of CO_2 stored in the soft tissues at one time. It is transported in the blood to the lungs by three mechanisms: dissolution directly in the blood (7%), bound to haemoglobin (10%), or

predominantly carried as a bicarbonate ion (85%). Because CO_2 is present endogenously there is no concern for allergy or renal toxicity, which has been confirmed by numerous animal and human studies. Its viscosity is 1/400 that of iodinated contrast and it is also highly soluble, roughly 20 times to 30 times greater than O_2. Therefore it is less occlusive than other gases. When administered intravascularly, it tends to dissolve within a vessel in 30 seconds to 60 seconds. In intravenous administration it is also removed from the lungs in one pass. If CO_2 persists in a vessel for more than 30 seconds it is either trapped or there is room air contamination. [3,4,5]

As opposed to traditional liquid agents, carbon dioxide does not mix with blood. In fact, CO_2 is lighter than blood and floats anterior to it. To render a representative image it must displace the blood in the vessel. As a result, the vessel is less dense and a negative image is obtained with digital subtraction angiography. The quality and accuracy of the image will depend on the amount of blood displaced by the CO_2. Smaller vessels, especially those 10 mm or lesser, demonstrate a better correlation with iodinated contrast. [3,4,5]

Although CO2 angiography is considered to be a safe and effective method, the evaluation and treatment of lower extremity arterial disease has not gained pervasiveness. With the advancements in interventional techniques and imaging technology over time and with increase in population of CKD and PVD patients, the utility of CO2 angiography needs to be readdressed.

Review of Literature

REVIEW OF LITERATURE

Iodinated contrast angiography continues to be the gold standard for vascular imaging, although significant advances in ultrasound, CTA, and MRA imaging, it has not replace conventional contrast angiography. Angiography with iodinated contrast is the imaging modality of choice for performing interventional peripheral vascular procedures, and frequently is used for nonvascular intervention[6,7].

Worldwide, >200 million patients are affected by peripheral arterial disease (PAD). Patients may present without symptoms, with intermittent claudication and with rest pain or tissue loss due to critical limb ischemia (CLI). Persons with chronic kidney disease (CKD) have higher rates of incident and prevalent PAD[8]. O'Hare and colleagues reported that 24% of persons with CKD stage 3 or greater (creatinine clearance of <60 ml/min/1.73m^2) had PAD. This is 6-fold higher prevalence rate compared to persons with a creatinine clearance of >60 ml/min/1.73m^2 (4%)[9]. Since the 1980s, endovascular interventions have emerged as the first-choice treatment in symptomatic PAD. As a result, increased use of contrast media in diagnostic and interventional procedures is observed. In particular, patients with more complex problems or more severe stages of PAD are likely to undergo several angiograms and endovascular interventions make them prone to contrast-induced nephropathy[8].

Contrast-induced nephropathy (CIN) is defined as an increase in serum creatinine by >25% or 44μmol/L (>0.5 mg/dl) within the first 3 days of the procedure[10.11]. CIN characteristically manifests 3 days after administration of the contrast medium, with a peak in renal function decline 3-5 days after contrast exposure[12]. Besides surgery and hypotension, administration of radio contrast is the third most common cause of acute kidney injury[13]. Many studies show that patients

developing CIN have a greater risk of prolonged hospitalization, cardiovascular events, and death[14]. Furthermore, when patients with acute kidney injury require dialysis, mortality is higher compared with those not requiring dialysis. Owing to an increasingly elderly patient population the incidence of CIN is likely to increase rapidly[8].

Comprehensive literature is available regarding CIN following coronary intervention, with an incidence ranging from 11.3% to 14.5%[15]. In comparison, CIN following peripheral interventions has been shown to vary between 5.4% and 13.5%[16]. However, limited data are available regarding CIN after endovascular interventions in patients with symptomatic PAD. Only one small retrospective study investigated the incidence of acute kidney injury in patients treated with balloon angioplasty for femoropopliteal PAD[17].

❖ CONTROVERSY AND LIMITATIONS INHERENT IN THE LITERATURE OF CIN

Given the inaccuracy of defining CIN based on serum creatinine, random variations in daily creatinine measurement, lack of an adequate control group or long term (>72 h) follow-up in most published studies, and heterogeneous definitions of CIN throughout the literature, the actual incidence and clinical significance of CIN has been called into question[18,19]. Newhouse et al examined the random fluctuations of serum creatinine in 32,161 hospitalized patients who had 5 days of consecutive serum creatinine measurements without any intravascular administration of contrast in the preceding 10 days[20]. Depending on the definition, 6 to 35% of those patients would have fit criteria for being diagnosed with CIN. These rates are not substantially different from the rates of CIN in the published literature. Indeed, recent publications have highlighted two earlier studies by Cramer et al and Heller et al that included matched

controls who did not receive intravascular contrast[20,21,22,23]. These studies demonstrated no substantial differences in CIN (defined as serum creatinine increase of >50%) between the contrast and non-contrast control groups. Acknowledging the limitations of these studies, these observations suggest that the incidence of CIN in the published literature has likely been overestimated. Despite these controversies, however, the vast majority of published literature, consensus panels, and published guidelines all agree that CIN is a clinically significant problem that does have a substantial impact on patient outcome[24].

❖ PATHOPHYSIOLOGY OF CIN

Although there are many complex pathways involved in the development of CIN, the end result is thought to be ischemic injury to the renal medulla. Under normal conditions, the renal medulla is poorly oxygenated and operates in a near hypoxic environment. After administration of contrast, renal blood flood temporarily increases, then decreases over a prolonged period. These changes are mediated by a complex interplay of many factors. Renal vasoconstriction plays a major role and is mediated by vasoactive substances such as endothelin, adenosine, nitric oxide, and prostaglandins. Direct cytotoxic and osmotic effects of contrast on renal tubules also play a role and may be partly mediated by free radical formation. Increased intra tubular pressure, increased urine viscosity, and tubular obstruction further contribute to renal injury[25,26].

❖ NATURAL HISTORY OF CIN

Most CIN is self-limited. Serum creatinine typically increases over 1 to 3 days, peaks at 4 to 5 days, and returns to baseline in 7 to 14 days[26,27]. More severe CIN, however, may be associated with a delayed

peak in serum creatinine and a slower return to steady state, which may remain above baseline values. These cases may be associated with oliguria. In a small subset of patients, temporary or permanent dialysis is required.

The median 2-year survival rate in patients who require dialysis is 19% and in-hospital mortality is as high as 36%[28]. Even with the development of mild CIN that does not require intervention, there is increased morbidity and mortality independent of other risk factors. Whether this effect is causal is unclear, and the development of CIN may simply reflect a poor overall prognostic marker for outcome[18]. However, there is an ongoing debate with regard to the causality of this association. It is currently unclear whether CIN is the cause of increased cardiovascular events and death, or that patients at increased risk of cardiovascular events and death are more prone to develop acute kidney injury, owing to their comorbidities[8].

❖ DEFINING AT-RISK POPULATIONS OF CIN

Contrast-induced nephropathy occurs most commonly in patients with identifiable risk factors. Many risk factors have been reported in the literature (Table 1), although few have been proven to be independent factors[18,20,26,29,30,31].

Table 1: Reported Risks for Contrast-Induced Nephropathy[24]

Non-modifiable risks	**Modifiable risks**
Primary Preexisting renal disease	Dehydration
Diabetes associated with renal disease	Recent contrast administration (<72 hours)
Acute kidney injury (esp. acute tubular necrosis)	Contrast volume
Hypotension/sepsis	Contrast type (HOCM>LOCM/IOCM)
Secondary Cardiovascular disease (esp. congestive heart failure)	Contrast administration route (IA > IV)
Cirrhosis	Nephrotoxic medications: Nonsteroidal antiinflammatory drugs, Aminoglycosides, vancomycin, amphotericin B, Loop diuretics
Nephrotic syndrome	
Myeloma	
Organ transplantation	Immunosuppressive: cyclosporine A
Human immunodeficiency virus	
Metabolic disorders (Hyperuricemia, hypercholesterolemia, Hypercalcemia)	

IA, Intra-arterial; HOCM, high-osmolar contrast media; IOCM, iso-osmolar contrast media; LOCM, low-osmolar contrast media; IV, intravenous.

❖ RISK STRATIFICATION TO REDUCE CIN

Although not without controversy, current trends suggest that risk stratification for preexisting renal disease should be performed with either estimated GFR (eGFR) or estimated creatinine clearance (eC_{Cr})[31,32]. Both values can be calculated from the serum creatinine (SCr) based on equations validated in adult populations. Because creatinine clearance estimates the GFR, both measurements can be used interchangeably for the purpose of risk stratification. These equations account for differences in muscle mass in adult populations based on several variables (age, gender, race, weight) and are thought to result in more sensitive and specific measurements of renal function than serum creatinine alone. It is important to remember that these formulas were developed for assessment of patients with chronic renal disease, not acute renal dysfunction.

Estimated GFR is most commonly calculated with the four variable Modification of Diet in Renal Disease (MDRD) formula and eC_{Cr} by using the Cockcroft-Gault formula (Figure 1)[24]. Numerous online calculators are available. Both formulas have limitations in those with extremes of body mass (i.e., muscle wasting or extreme obesity). The serum creatinine used for risk stratification should be a baseline value, prior to hydration or administration of NAC, which may falsely decrease serum creatinine levels.

When utilizing eGFR for risk stratification, there is general agreement that patient with eGFR >60 are at low risk for CIN, and those with eGFR <30 are at very high risk for CIN, regardless of the route of contrast administration (IV or IA). Patients with eGFR <30 have a 30 to 40% risk of CIN and a 2 to 8% risk of dialysis compared with a general

population risk of 2% for CIN[32,33]. These risks categories correspond to the Kidney Disease Outcome Quality Initiative (KDOQI) stages of chronic kidney disease (Table 2).

Figure 1: Formula to estimate eGFR or eCCr from serum creatinine (mg/dL)

MDRD: 4-variable equation

$$eGFR\,(mL/min/1.73m^2) = 186 \times SCr(mg/dL)^{-1.154} \times Age^{-0.203} \times [1.210 \text{ if African American}] \times [0.742 \text{ if Female}]$$

Cockcroft-Gault equation

$${}_eC_{Cr}\,(mL/min) = \frac{(140 - Age) \times Mass\,(kg) \times [0.85 \text{ if Female}]}{72 \times Serum\ Creatinine\,(mg/dL)}$$

Table 2: KDOQI Stages of Chronic Kidney Disease[24]

Stage	Description	eGFR(mL/min/1.73m^2)
1	Kidney damage with normal/increased GFR	>90
2	Kidney damage with mild decrease in GFR	60–89
3	Kidney damage with moderate decrease in GFR	30–59
4	Kidney damage with severe decrease in GFR	15–29
5	Kidney failure	<15

There is greater uncertainty with sub-stratification of risk when the eGFR is between 30 and 60, and currently it is difficult to make confident evidence-based recommendations in this group[31]. Currently, most define this category as ‘‘at risk.’’ The threshold of eGFR <60 for defining risk, however, is controversial and likely includes many patients with a mildly reduced eGFR that are truly at relatively low risk[32].

A publication by Thomsen et al of a pooled analysis of two studies of IV administration of contrast for CT, found that only 0.6% of patients

(1/170) with eGFR >40 mL/min met the definition of CIN[34]. Their recommendation was to take precautions in patients before IV contrast administration when eGFR is less than 40 mL/min, and before IA administration when eGFR is less than 60 mL/min. Analysis of the literature by Katzberg et al has suggested analogous conclusions for stratification of IV administration thresholds; these conclusions were based on subgroup analysis of multiple prospective studies of patients who underwent IV administration of contrast for CTA[19]. Higher presumed risks associated with IA administration of contrast media explain the differences in the threshold recommendations[18]. Although not currently accepted by any consensus panel, these recommendations appear to be based on reasonable evidence and may help guide the interventionist regarding sub-stratification of this risk group. It is still prudent to take basic, well-accepted precautions such as IV hydration in those undergoing IV contrast administration with any eGFR <60 until evidence has been more solidified[24].

❖ VOLUME OF IODINATED CONTRAST AND ITS RELATION TO CIN

It is generally accepted that the risk of developing CIN is related to the dose of contrast administered[29]. This notion is based primarily on evidence derived from cohort studies. Various publications, particularly in the interventional cardiology literature, have attempted to identify threshold doses of contrast that predict CIN or dialysis.

A study by Cigarroa et al suggested that in patients undergoing percutaneous coronary intervention (PCI), exceeding a volume of contrast greater than 5-mL/kg of body weight divided by serum creatinine (mg/dL) strongly predicts nephropathy that requires dialysis[35]. These

findings have been retrospectively validated in the PCI population by a larger study by Freeman et al reviewing 16,592 PCI procedures. In fact, Freeman et al found that exceeding the maximal dose calculated by this formula was the strongest independent predictor of nephropathy requiring dialysis[36].

A recent study by Laskey et al demonstrated that patients undergoing PCI who received a ratio of contrast dose in mL to calculated creatinine clearance (mL/min) of less than 3.7 had a low rate of CIN compared with those exceeding that dose[37]. These equations (Figure 2) can be used to calculate a theoretical maximum threshold dose for a given procedure to minimize CIN. Although validated for patients undergoing PCI, these data can be extrapolated for use in patients undergoing other interventional procedures.

Figure 2: ‘‘Threshold’’ dose for ICM to minimize CIN[24]

$$\text{Low risk of CIN}: \frac{\text{Contrast volume (mL)}}{\text{Creatinine Clearance (mL/min)}} \quad 3.7^{\dagger}$$

$$\text{Maximum contrast dose} = \frac{5 \text{ mL} \quad \text{Body weight (kg)}^{*}}{\text{Serum Cr (mg/dL)}} \ddagger$$

*Numerator should not exceed 300

❖ ADMINISTRATION ROUTE

Intraarterial administration of contrast is generally thought to result in greater incidence of CIN than IV administration, which may be due to several factors. Intrarenal concentration of contrast media is higher after IA administration at or above the renal arteries than during IV administration, where a dilution effect may be somewhat protective. Arterial procedures may also produce additional injury to the kidney such as atheroemboli[24].

❖ STRATEGIES FOR RENAL PROTECTION

Despite extensive study of a variety of agents for renal protection, use of low or iso-osmolar contrast agents and IV hydration with normal saline or sodium bicarbonate are the only strategies that have been shown to be effective in the reduction of CIN in those at risk. Although popular, use of NAC remains unproven. Historically, gadolinium agents were used in patients at higher risk for CIN to minimize the load of iodinated contrast. These strategies are now limited by the recognition of nephrogenic systemic fibrosis (NSF). Instead of angiography with iodinated contrast media alternative methods without contrast administration may be utilized, such as endovascular ultrasound, duplex-guided interventions, and carbon dioxide (CO2) injection[24].

❖ CO2 DIGITAL SUBTRACTION ANGIOGRAPHY (CO2 DSA)

The use of carbon dioxide (CO2) as a contrast agent goes back to 1920s when the gas was used to visualize retroperitoneal structures. In the 1950s and early 1960s, CO2 was injected intravenously to delineate the right atrium for the detection of pericardial effusion[38,39]. This imaging technique developed from animal and clinical studies, which demonstrated that CO2 was safe and well tolerated with venous injections[40]. With the advent of digital subtraction technique in 1980s, CO2 has evolved into a safe and useful contrast agent for vascular imaging[41].

CO2 is the only proven safe contrast agent in patients with renal failure and hypersensitivity to iodinated contrast medium. Now CO2 is used widely as an intravascular contrast agent in both the arterial and venous circulations for various indications. Because of the potential neurotoxicity and cardiac arrhythmia, CO2 should not be used in the

thoracic aorta, the coronary artery and the cerebral circulation. When injected into an artery or vein, CO2 displaces blood whereas contrast medium mixes with blood. Despite the difference in the physical property between the gaseous CO2 and liquid contrast medium (Table 3)[42], CO2 arteriograms are quite comparable to contrast arteriograms, providing much of the vascular information that can be derived from contrast medium angiography with less risk and at lower cost. With the availability of high-resolution DSA and a reliable gas delivery system, CO2 can be easy to inject and image for diagnostic angiography and endovascular intervention[42]. For years the development of each of these vascular diagnostic and endovascular applications has demonstrated the unique benefits of CO2 as a contrast agent[43].

❖ PROPERTIES OF CO2

Performance, imaging and interpretation of CO2 angiograms and CO2-guided vascular intervention are dependent upon the knowledge of CO2 properties. CO2 constitutes 0.03% of air and is treated as if its partial pressure were zero. The density and atomic weight of the substance determine whether it will be more or less dense than the body tissues, and accordingly is classified as a positive or a negative contrast medium. Because of the low atomic number and density, CO2 is a negative contrast agent, and absorbs therefore x-ray to a lesser extent than the surrounding blood and vessel wall. Therefore, CO2 imaging requires the DSA technique with good contrast resolution. When injected into a vein, CO2 is carried to the lungs, where the gas is eliminated in a single pass[44].

Table 3: Comparison of CO2 and Iodinated Contrast Media[43]

	Carbon dioxide	**Iodinated Contrast Medium**
Property	Gas	Liquid
Radio-opacity	Negative	Positive
Source	By-product	Chemical compound
Solubility	High	Poor
Viscosity	Low	High
Buoyancy	Yes	No
Compressibility	Yes	No
Hypersensitivity	No	Yes
Nephrotoxicity	No	Yes
Thoracic aorta	Do not use	Yes
Dose Limitation	No	Yes
Cost	Inexpensive	Expensive

1) *Solubility*

CO2 is 28 times more soluble than oxygen and 54 times more soluble than nitrogen. This high solubility of CO2 allows its injection into the arteries below the diaphragm and veins without clinically significant gas embolism. The solubility of CO2 and air can be assessed by DSA or fluoroscopy of the gas trapped in the right atrium in the left lateral

decubitus position (right-side up position). Five mL of CO2 trapped in the right atrium will dissolve within 45 seconds. Larger volumes of CO2 will take a longer time to dissolve[45]. With the patient in the supine position the CO2 bubble in the pulmonary outflow tract following an intravenous injection will disappear in 15 seconds. The same amount of air trapped in the right atrium or pulmonary outflow tract will take much longer time to dissolve. When performing CO2 aortography in the patient with abdominal aortic aneurysm (AAA), lateral fluoroscopy of the aneurysm should be done following the injection. If trapped CO2 is seen in the ventral portion of the AAA, the body position should be changed from the side to the side to wash out the gas[44].

2) *Viscosity*

The viscosity of a fluid or a gas is a measure of its resistance to flow. CO2 is 400 times less viscous than contrast medium. Therefore, CO2 in diagnostic quantities (15-30 mL) can be injected through a 3-Fr catheter; small bore needles (22-25 gauge), an end-hole catheter, between the guide wire and the catheter using a Touhy-Borst fitting (y-connector), and through the side ports of the introducer sheath and stent delivery system. The low viscosity of CO2 allows for detection of bleeding (traumatic and gastrointestinal bleeding), Type-2 endoleak, portal vein visualization with a wedged hepatic vein injection, central vein visualization with a peripheral vein injection, demonstration of tumor vessels, and visualization of collateral vessels in both arterial and venous occlusive disease. Because CO2 does not mix with blood; the gas bubbles remain undiluted, better visualizing peripheral vessels through collaterals[44].

3) *Buoyancy*

When CO2 is submerged in a fluid, the gas bubble rises very quickly because the upward force exerted by the fluid is much stronger than the weight of CO2. This property is called buoyancy that means floating on blood. The buoyancy of CO2 may not be apparent on the antero-posterior (AP) projection but can be seen on the cross-table lateral projection of large diameter vessels, such as the aorta, the inferior vena cava and the AAA. With selective injection and reflux technique, CO2 can visualize visceral arteries, such as the celiac, splenic, hepatic and superior mesenteric arteries[44].

Using a circulatory system model, Song et al[46] evaluated the gas dispersion patterns from different angiographic catheters, gas flow dynamics, and the effect of the vessel size and inclination on luminal gas filling. Regardless of the vessel size, the CO2 bubble shows a parabolic flow profile along the anterior (nondependent) part of the vessel with incomplete fluid displacement along its posterior (dependent) portion. The thickness of the fluid in the dependent part depends upon vessel diameter, increasing in width with an increase in the vessel size. In the 15.9mm diameter vessel, its luminal filling with CO2 was 65%, which increased to 85% at the 15-degree incline[44]. The buoyancy of CO2 results in better imaging of the vessels coursing anterior to the injection site, such as the celiac and superior mesenteric arteries. Therefore, CO2 is preferable to iodinated contrast medium when performing stent placement of the celiac and superior mesenteric arteries. Cross-table lateral fluoroscopy and DSA demonstrate their origins in profile that can help stent positioning. The buoyancy of CO2 is disadvantageous for renal angiography since the renal artery courses in the dependent position in relation to the aortic injection site.

Because of the buoyancy and low viscosity, CO2 is preferable to contrast medium in upper extremity venography. The central veins, such as the axillary, subclavian and innominate veins fill well with peripheral CO2 injection. The buoyancy is not a problem with CO2 arteriography of the lower extremity. Elevation of the feet, intra-arterial injection of nitroglycerin, and distal injection with gas reflux can improve the image quality of CO2 DSA of lower extremity arteries[44].

4) *Compressibility*

Another property of CO2 that plays a significant role in CO2 angiography is compressibility and explosive delivery of CO2. The volume of a given amount of gas at constant temperature is inversely proportional to the pressure. The density of CO2 increases as the injection exerts a force on the gas, resulting in decrease in its volume but increase its pressure. When the compressed gas exits from the catheter, there will be expansion of the gas, known as "explosive delivery" that may cause discomfort and pain to the patient and poor image quality. Clearing the fluid or blood of the catheter with an injection of 3 to 5 mL of CO2 decreases gas compression and explosion[44].

5) *Invisibility*

Probably the most significant property of CO2 and the one that causes the most concern and discourages competent operators from using it is that it is invisible. Because it is invisible, contamination with more occlusive room air is a major concern of many operators. During the inception of intravascular use of CO2, Hawkins found that routine, reusable cylinders contained carbonic acid, rust, particulate matter and water[7]. He suggested research grade, which is more pure. Not only does this avoid inappropriate embolization but it also avoids pain for the

patient.

Contamination may also result when a syringe of CO2 is left open to room air. Because of partial pressure differences, room air will enter the syringe and replace the pure CO2 at the rate of 0.2 cc per minute. So a 20 cc open syringe will contain 12 cc of room air after an hour. Delivery systems, especially those that use a bag reservoir, should be purged three times to rid the system of residual room air. Delivery system connections should be secured, either with glue or luer lock. Loose connections can lead to the aspiration of room air[47].

❖ **CO2 Gas Delivery System**

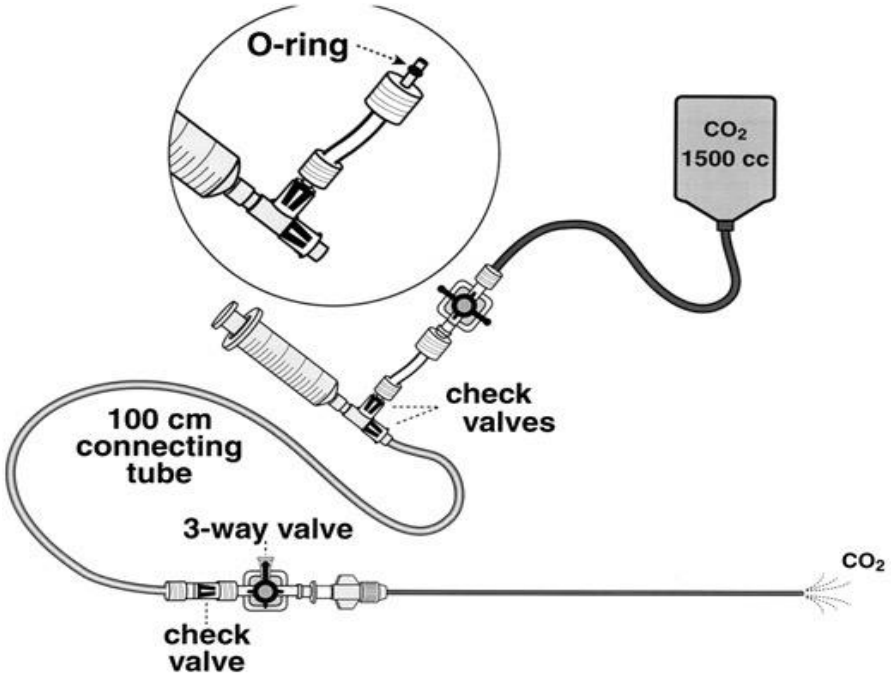
The primary disadvantage of CO2 angiography is learning how to employ a gas-based delivery system as opposed to iodinated contrast. CO2 is invisible, colorless, odorless, and cannot be seen or felt so the comfort level for use is much less than iodinated contrast. The operator must learn and feel confident in the type of delivery system.

Since the advent of intravascular CO2 delivery there have been a number of innovative methods of delivery developed[48-52]. Initial applications simply took a syringe of CO2 from the source and then delivered it into the catheter. The downside of this approach is that a compressed volume of CO2 is commonly within the syringe, which can result in the problems delineated above. Additionally, if the syringe is inadvertently left patent, over time, CO2 can be replaced with more occlusive room air. To circumvent this, CO2 delivery was initially performed with a typical liquid contrast injector. This set up had a number of weak links and to address this problem, the ‘Angioject’ dedicated CO2 injector was designed by Angiodynamics. The next tactic was to connect tubing from the source to the patient with a series of

stopcocks; but again the problem with this is human error.

To avoid the inadvertent overload of pressurized gas and the cumbersome presence of a large canister, Cho and James et al, introduced the use of a flaccid reservoir; a plastic bag[52,79] (Figure 3) with a series of one-way valves. This method used a converted fluid management system by Angiodynamics called the 'Angioflush-III' system. Regardless of the training and simplicity incorrect assembly can result in air embolus. Additionally, the bag must be filled and purged three times to remove residual room air.

Figure 3: Plastic bag CO2 gas delivery system[52,79].



The patient should never be connected directly to the cylinder. This has been modified recently by the development of a K-valve stopcock that precludes the possibility of CO2 passing directly from the canister to the patient. The next generation of delivery systems employs a compact

regulator that uses a small 10,000-cc canister of pharmaceutical-grade CO2. The system does not require assembly and is extremely user friendly. Set-up for use takes approximately 1 minute[53].

Another recently developed type of delivery is the 'Angiodroid' CO2 injector (Img-5), which utilizes digital versus hand injection. Carbon dioxide can be delivered and has been delivered without filtration for arteriography. However, the use of a filter (0.2 micrometer pore size) can effectively remove particulate contamination and bacteria (0.5 to 5.0 micrometer)[47].

Cherian et al reported a novel technique of CO2 angiogram with indigenous 'home made' delivery system created with blood bag as reservoir, syringes, three way stop-cock and catheter assembly system. The 44 cases evaluated with this system, obtained diagnostic quality angiograms in 42 (95.5%) cases. The system was easy to use and required minimal manpower and expertise to maintain and setup. There was no system malfunction at any time and no complications were encountered[49].

If the buoyancy of CO2 overcomes the kinetic force of blood flow, a transient vapor-lock phenomenon may result, producing fragmented CO2 images especially in distal and low-flow arteries. To solve those problems, Chang et al[54] developed a bubble-creating CO2 DSA technique by premixing the CO2 gas. The serum proteins act as natural foaming agents and create a fine bubble mixture. This alteration of CO2's properties toward a foam-like biological CO2 contrast agent produces a CO2 DSA that is more evenly distributed without fragmentation, resembling a traditional iodine-contrast angiogram[54].

❖ CONTRAINDICATIONS OF CO2 ANGIOGRAPHY

Absolute contraindications to the use of CO2 as a contrast agent include thoracic aortography, coronary arteriography and cerebral arteriography. Clinically, seizures and loss of consciousness have been encountered when CO2 refluxed into the thoracic aorta and cerebral circulation following an injection of CO2 into the brachial artery[55]. CO2 should not be injected into the abdominal aorta in the prone position since the buoyant gas may fill the spinal and lumbar arteries, and cause spinal cord ischemia. Similarly CO2 should not be injected into the abdominal aorta with the patient's head in an elevated position since the gas can flow in the opposite direction of blood flow, especially in a hypoplastic aorta in children[44].

In the patient undergoing nitrous oxide anesthesia, concurrent use of CO2 should be avoided since the nitrous oxide can diffuse into the CO2 bubble, increasing the CO2 volume significantly. Relative contraindications to the intravenous use of CO2 include pulmonary hypertension and chronic obstructive pulmonary disease. CO2 should be used cautiously in patients with patent foramen ovale (PFO) or atrial septal defect[44].

❖ CO2 ANGIOGRAPHY IMAGE QUALITY

Hawkins published his landmark paper of intra-arterial use of CO2 gas for angiography in 1982, after initial experiments for one decade on animal models. His initial experience with CO2 angiography involved 20 patients in which he observed diagnostic arterial images were slightly less dense than ICM[41].

A number of studies were published since the early 90's in an attempt to study the quality and accuracy of CO2 angiography as an

alternate to conventional iodinated angiography in routine endovascular interventions. In this process CO2 image quality improved with time as a result of the advent of digital fluoroscopy with subtraction and advance software capabilities. Weaver et al[56] observed 58% satisfactory CO2 images in 33 patients with PAD but he was able to performed PTA in only 21% of cases with CO2 gas being used as a sole contrast agent[56]. In contrast Seeger and co-workers[57] achieved a 91% excellent quality CO2 angiogram with 95% diagnostic agreement when compared with standard iodinated contrast angiograms[57].

The first systemic, randomized evaluation to compare CO2 DSA with standard ICM DSA in lower limb arterial occlusive disease was published by Bettmann et al[58] in 1994. He randomized 22 patients and observed that CO2 angiogram images were diagnostically adequate and consistent with clinical and non-invasive findings in all patients[58]. These two investigative methods were compared by analysis of the nine arterial territories in the entire group of 40 patients with a total number of 360 evaluated segments by Scalise and co-workers[59]. Considering ICM DSA as the gold standard, an overall diagnostic accuracy of 96.9% for CO2 DSA was observed. The diagnostic accuracy was 97.1% in the above the knee level and 96.7% in the below the knee district[59].

The quality of CO2 angiogram images also varies with the arterial segments being imaged and corresponding vessel diameters. In a retrospective study by Rolland et al[60] in 1998, which involved analysis of CO2 DSA versus ICM DSA by four different observers; he concluded that both techniques were equivalent for imaging of iliac, femoral and popliteal arteries but poor quality CO2 DSA in infrapopliteal vessels[60]. Recently published series by Madhusudhan[61] as well as by Almeida Mendes[50] also consolidated the fact that Ilio-femoral segments

visualization with CO2 gas is equivalent to conventional angiograms.

A constant observation in most of the studies published in last 3 decades is the inferior quality images with CO2 DSA in infrapopliteal segments. Rolland et al[60] noted that the CO2 DSA quality compared to ICM DSA in infrapopliteal segments was only in 50% of cases, which was statistically significant compared to iliac arteries ($P < 0.001$)[60]. Similarly Almeida et al concluded with a poor inter observer image quality concordance with respect to infrageniculate arteries imaged with CO2 DSA in his prospective randomized study for patients underwent femoropopliteal revascularization[50].

Kerns and Hawkins[62] describes this poor CO2 DSA qualities as a result of CO2 gas dissolution, slow flow in small vessels and collaterals, and gas fragmentations. Other significant factors also includes insufficient filling of vessels distant from point of CO2 injection, long segment occlusions of distal vessels and leg movement during CO2 DSA due to discomfort felt by the patients[60,63]. In view of discomfort and the gas fragmentation phenomenon in below-the-knee regions, Ho et al[64] concluded that CO2 couldn't replace ICM DSA as a routine diagnostic tool for PAD EVT[64]. In similar study by Diaz et al[63] noted that the limitation lies in the high proportion of uncompleted studies and CO2 images that cannot be read, particularly in the distal arterial segments because of poor patient tolerance to the procedure, small movements by patients that spoil CO2 images more readily than when iodinated contrast images, or insufficient filling of vessels distant from the point of injection[63].

Poor CO2 DSA quality in distal segments leads to the use of additional iodinated contrast material to complete diagnostic or

therapeutic endovascular interventions. In 1997, Frankhouse et al[65] performed intervention in 25 patients of PAOD with 68% of them requiring small amounts of iodinated contrast agents to complete the procedures. Similarly Eschelman et al[66] required ICM in 47% of interventions performed for lower limb revascularization in addition to CO2 gas. The need of additional ICM has decreased over time as a result of improved CO2 imaging techniques, its delivery system and development of imaging hardware and software. Kessel et al[67] noted that the only 12% of procedures required ICM additional to CO2 with modern equipment and stacking technology. He also noted ICM doses were significantly reduced in CO2 guided interventions[67].

An Indian author Madhusudhan and co-workers[61] compared the role of CO2 DSA using a novel 'home made' delivery system with ICM DSA in the evaluation of PAD of lower limbs. CO2 gas was opacified in 86.2% of major arteries and depicted stenosis adequately in 84.5% of arterial segments. A good or acceptable image quality of CO2 DSA was obtained in over 95% of patients. Infrapopliteal arteries were inadequately visualized. Inter-observer agreement was good ($k > 0.75$) at 70% of the segments[61]. Intravascular ultrasound (IVUS) guided EVT to supplement CO2 was studied by Kawasaki et al[68] for the treatment of 50 patients with CKD. All of the CO2 arteriograms were good or acceptable imaging quality, assessed by 2 independent observers[68].

Learning curves for CO2 angiography could obviously differ substantially between trainees and experienced operators. In a retrospective study[69], 21 patients who underwent peripheral arterial procedures with carbon dioxide angiography were systematically collected. Comparison according to phase of the learning curve (i.e. distinguishing the initial 10 cases from the 11 following ones) showed

that the overall number of ICM injections per procedure decreased over time (from 2.5±2.1 to 0.6±2.1, p=0.005). A similar trend was found also for the number of injections of ICM required for lower limb procedures (from 0.7 to 0, p=0.024). Accordingly, in the second phase of learning curve, iodinated contrast media were avoided altogether in 10 (91%) cases, in comparison to 2 (20%) procedures performed in the beginning[69] (p=0.002).

Recently in 2015, Fujihara et al[1] published a prospective multicenter study for CO2 angiography guided intervention in PVD patients. This study included 98 patients with 109 lesions. Good or fair quality CO2 angiogram were obtained in 98.4%; 83.9% and 56.2% of patients in the SFA, Aorto-Iliac (AI) and Renal artery stenting (RAS) groups respectively. The main reason for observing the highest percentage of good CO2 angiogram among patients in the SFA group is the absence of the interference provided by bowel loops and gas (seen more frequently in patients undergoing AI and RAS procedures), suggesting that CO2 angiogram can effectively replace traditional iodinated contrast in selected cases. Fujihara et al also obtained good images of CTO lesions with CO2 angiography, because CO2 spreading more rapidly than iodinated contrast media from the distal edge of CTO through the collateral circulation which was contradictory to previous observations[61-63].

❖ CO2 ANGIOGRAPHY COMPLICATIONS

Minor and transient complications related to intravascular CO2 injection include transient nausea, abdominal pain, paresthesia, tenesmus, vapor lock, and injection site discomfort. Major complications are extremely rare[70]. In a review of 800 cases, Hawkins et al[71] found only one

major complication related to CO2 angiography, in which the patient had watery diarrhea related to transient ischemia of the left colon[71].

Madhusudhan et al[61] noted one (5%) patient complained of severe pain in the affected limb during initial injection of the gas while CO2 DSA was performed. This was postulated due to explosive gas delivery. He also reported 28.6% patients complained of mild pain during both CO2 and ICM DSA studies. However, their procedure was not affected[61]. Other many studies also showed low incidence of complications attributable to CO2 DSA[50,56,60,72,73].

Rolland et al[60] noted that the CO2 was less tolerated ($P<0.01$) than iodine contrast in his comparative study between CO2 and ICM. Fifty-three percent of patients reported CO2 was equally well tolerated, 40% reported more discomfort than with iodine[60]. Diaz and coworkers[63] also reported 48% of the patients had discomfort during the CO2 examinations and 18% of the procedures had to be discontinued as a result. When problems relating to poor image quality were included, only 36% of the arteriograms obtained with use of CO2 were complete. Evaluation was possible in only 25% of CO2 studies of the feet. On average, the overall quality of the arteriograms obtained with use of CO2 was insufficient for diagnosis[63].

Seeger et al[57] experienced complications in only two (1.6%) of the 128 patients they studied with CO2 gas; one patient with abdominal aortic aneurysm had watery diarrhea and the other patient had septicemia and abdominal pain due to mesenteric artery ischemia. Spinosa et al[73] described a case of transient mesenteric ischemia, which occurred as a complication of intra-arterial CO2 DSA. Fujihara et al[1] noted CO2 angiography-related complications as high as 17.3% in which two cases

(2%) developed severe, fatal, non-occlusive mesenteric ischemia (NOMI).

With the advancements in interventional techniques and imaging technology; we are conducting a study to evaluate the feasibility, quality and safety profile of CO2 angiography-guided EVT and to clarify the therapeutic role of a CO2 angiography for EVT in CLI and CKD patients.

Aims and Objectives

AIM AND OBJECTIVES

- **Primary:** Qualitative assessment of Carbon Dioxide as a contrast agent for infra-inguinal arterial endovascular procedures in patients with critical limb ischemia in patients with renal dysfunction.
- **Secondary:**

    I. Immediate post procedure hemodynamic success (with non invasive technique like ABI/TBI and PVR).

    II. Freedom from adverse renal events (by monitoring eGFR) and CO2 angiography related complications

Materials & methods

MATERIAL AND METHODS

❖ Study site

All patients presenting to Jain Institute of Vascular Sciences (JIVAS), Bangalore, from June 2015 to December 2016 and undergoing CO2 angiogram in infra-inguinal therapeutic and diagnostic endovascular procedure for Critical limb Ischemia (CLI) were enrolled and evaluated prospectively.

❖ Study population

During this study period, 178 patients with CLI were admitted at JIVAS for infra-inguinal endovascular treatment. Among these patients, total 47 patients; whose eGFR <60 ml/min/1.73m^2 were underwent infra-inguinal endovascular treatment with CO2 angiogram.

❖ Study Design

A single centre, prospective, observational, open-ended, longitudinal study.

❖ Sample size calculation

Based on the published literate[63,64] interobserver agreement was 0.86. In a test for agreement between two raters using the *Kappa* statistic, a sample size of 40 subjects achieves 91% power to detect a true *Kappa* value of 0.86 in a test of H0: *Kappa* = 0.50 vs. H1: *Kappa* <>0.50 when there are 3 categories with frequencies equal to 0.20, 0.30, and 0.50. This power calculation is based on a significance level of 0.050**.** Sample size was estimated using PASS software and below equation.

$$n = \frac{n^\star}{1 + n^\star/N}, \text{ where } n^\star = \frac{1}{r^2(p_a - p_e)^2}$$

Relative error r and the difference $p_a - p_e$ between the overall agreement probability p_a and the chance-agreement probability p_e. N is the number of subjects in the entire population.

❖ **Time frame for study**

Patients were prospectively enrolled from June 2015 to December 2016 and were followed till one month post-procedure according to study protocol.

❖ **Inclusion criteria**

- Patients of age of 18 years or more.
- Having critical limb ischemia with infra-inguinal disease (Rutherford category 4 to 6)
- Chronic kidney disease (eGFR<60 ml/min/1.73m^2)
- Any patient with contraindications to iodinated contrast (such as allergy)
- Who gave consent for procedure

❖ **Exclusion criteria**

- Atrial/ventricular septum defect
- Known case of Pulmonary AV malformation
- Respiratory insufficiency
- Patients on Renal replacement therapy
- Who had hybrid procedure and simultaneous aorto-iliac intervention

❖ Methodology

1. Patient enrollment

Demographic data of patients were recorded with history and physical examination findings preoperatively in form of chief complaints, personal history of smoking, tobacco and alcohol use if any. They were assessed for medical risk factors like diabetes mellitus, hypertension, coronary artery disease (CAD), chronic kidney disease (CKD) and cerebro-vascular disease (CVD).

In all patients general, local examinations were carried out with careful documentation of vascular status of both lower limbs along with ankle brachial index (ABI) and pulse volume recording (PVR). Preoperative imaging was based on clinical findings and was performed in form of arterial Duplex. Patients with high levels of creatinine or diagnosed as chronic kidney disease but not on hemodialysis, MRI with Time of Flight (TOF) sequences were performed. In selected patients where aorto, iliac and femoral arterial diseases were excluded by clinical examinations, PVR, arterial duplex were directly considered for digital subtraction angiography with CO2 and endovascular therapy.

2. Laboratory analysis

Along with routine blood investigations including hematocrit, coagulation profile, and renal function tests were recorded in all patients after enrollment in study.

24 hours before the intervention, early morning sample was drawn with clean venipuncture from an antecubital vein using a 21-gauge x 3/4' needle (BD Vacutainer® Safety-LokTM Blood Collection Sets with Pre-Attached Holder). To avoid procedural

deviations, all blood samples were taken by the same physician applying a light tourniquet, which was immediately released. A 3cc of blood was drawn into a light green top vacutainer (BD Vacutainer ®) for serum creatinine (SCr) analysis. Serum Creatinine was analysed with modified Jaffe's kinetic method with fully automated clinical chemistry analyser (BA400-'Biosystems'), eGFR was calculated with help of MDRD[74] (Modification of Diet in Renal Disease) formula. MDRD calculator application availabe online from QxMD software desiners.

After 48 hours of endovascular procedure; serum creatinine was repeated and eGFR was calculated with MDRD calculator. In the perioperative period of 30 days SCr (eGFR) was done as and when required but not for all cases.

3. Pharmacological interventions

Patients planned for endovascular treatment received 6–12 hours of 0.9% normal saline pre-hydration intravenously at a rate of 1 ml/kg body weight per hour (0.5 ml/kg for patients with left ventricular ejection fraction <40%) with sodium bicarbonate and oral N-acetyl cysteine (NAC) at 1.2 g bid dosage for two days prior to procedure[74,75]. Infusion of sodium bicarbonate as a bolus of 3 mL/kg/hour for 1 hour before the administration of contrast, followed by 1 mL/kg/hour during and after the procedure for 6 hours[36]. All DM patients who were on oral hypoglycemic agents were switched to regular insulin and strict glycemic control was ensured perioperatively. Administration of non-steroidal anti-inflammatory drugs (NSAIDs) restricted for 2 days before the procedure[75].

Postoperatively, hydration was continued for 6 hours and N-acetyl cysteine for next 48 hours. All patients were started on aspirin 150mg OD and if the patient was already on double antiplatelets, they were continued. Medication for diabetes, hypertension and cardiac conditions were continued as per physician's advice. The antibiotics, analgesics prescribed as per patient and procedure requirements. NSAIDs restricted till 1month post-procedure and alternate form of analgesics were prescribed.

4. Endovascular intervention – Infrainguinal

Most of the procedures were carried out under local anesthesia with monitored anesthesia care (MAC) unless patient opted for general anesthesia. In later part of our study we carried procedures under regional anesthesia[76,77,78] (Femoral and popliteal nerve blocks) to decrease patients leg pain and movements. Consultant anesthetic according to standard protocol gave all regional nerve blocks with ultrasound guidance. Consultant vascular surgeons did all cases with more than 10 years experience in EVT. In most cases access obtained through ipsilateral antegrade common femoral artery (CFA). In cases of proximal SFA lesion contralateral retrograde CFA access was obtained.

Usually 6Fr sheath was deployed for arterial access. Systemic heparinisation was done as soon an access was obtained, 80U/kg body weight and then 1000units IV for every passing hour. After access and sheath placement index limb angiogram performed with CO2. Femoro-popliteal and infrapopliteal segments were evaluated respectively. For infrapopliteal segment end hole diagnostic catheter was used and tip was kept as distal

possible in popliteal artery to obtain CO2 angiogram. All CO2 DSA were analyzed and graded as ‘good’, ‘fair’ or ‘poor’ by two individual observers[1], one who is doing procedure himself and other was consultant intervention radiologist blinded to procedure. All patient undergoing CO2 angiography were monitored with ECG, Pulse Oximetry, Blood pressure, and respiratory rate. Capnography (ETCO2) was obtained if patient is intubated[47].

The CO2 delivery system was filled with 99.99% laboratory grade CO2 from disposable cylinder. Cylinder is supplied with Angioset CO2 delivery system (Figure 4,6), pressure reduction valve (Figure 5), CO2 aseptic filter, pressure-gauge (Angioset®, Opti-Med, Germany).

Figure 4: Angioset CO2 gas delivery system

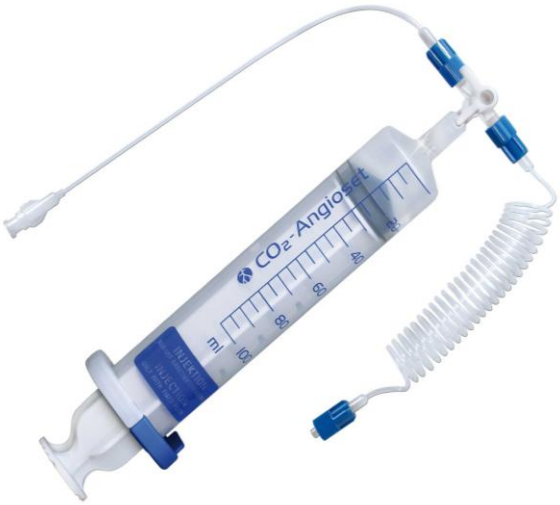
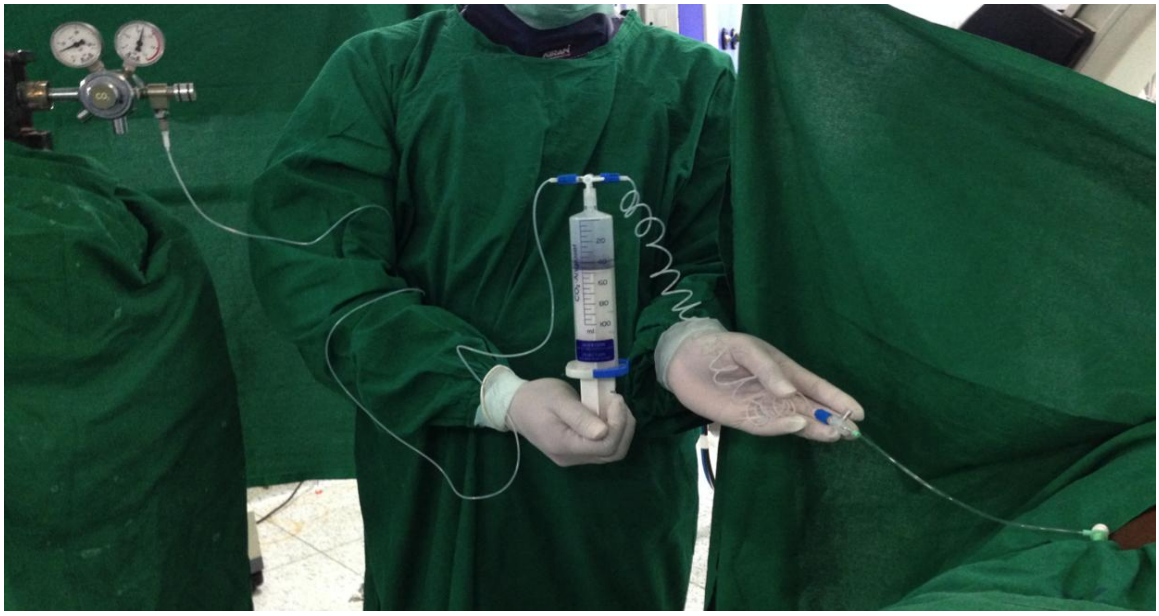


Figure 5: CO2 cylinder pressure control valve

Figure 6: A closed system of Angioset connected to cylinder pressure valve on left side and to sheath on right side



The Opti-Med® CO2-Angioset delivery system (100 ml syringe: dose chamber/adjustable setting in 20 ml steps) was be used. Injection rate of CO2 15 to 20 ml/sec and volume 40ml with fixed gas pressure of 1.3 bars[61]. All CO2 DSA were done with Innova IGS 530 image guided system with optimal panel size (30 x 30) with GE® Innova software's (GEIGS 530) or GE® OEC-9900 elite mobile C-arm. Rapid exposures (7.5 or 8 frames/sec) were obtained in anterior-posterior projection. While filming the infrapopliteal segments; the X-ray beam was perpendicular to the interosseous membrane to splay the arterial trifurcation[64]. Elevation of targeted vessels 15-20^0 above the level of angiographic table for same. Intra-arterial administration of 100-150 microgram of nitroglycerin used to improve filling of CO2 in peripheral arteries particularly in infrapopliteal vessels[4,73,79].

The standard wire and catheter technique used to cross the lesion and the diseased segments were treated with angioplasty

PTA balloons. In case of flow limiting dissection or residual stenosis, stent was placed in Femoro-popliteal segments, but stenting was avoided in infrapopliteal vessels. Nonionic iodine contrast media Iohexol 300mg I/ml (omnipaque™®) was used for imaging in patients whose CO2 angiograms were suboptimal to complete endovascular treatment. After the procedure, the sheath was removed when the ACT was dropped to less than 180 seconds. Closure device or the manual compression was applied for 10 minutes or till there was no bleeding with continuous hemodynamic monitoring in the recovery room. The post procedure arterial pulse/doppler signals status was noted and the PVR/ABI noted within 48 hours post-procedure.

Any other significant perioperative events in form of morbidity (ACS, CIN, etc…) and mortality were also recorded.

5. Secondary procedures

Patients with infected ulcers or gangrene underwent wound debridement and/or toe amputation 48 hours prior to endovascular treatment or following it depends on type of wound/gangrene. Depending upon the type of wound, they were either dressed with hydrocolloids or vacuum assisted device were used.

All patients were counseled about the life style modification regarding the foot ware and foot care and were regularly followed for a month. All enrolled patients had thorough clinical examination; PVR/ABI surveillance at 1 month and Renal function test (eGFR) was done as and when indicated but not in all patients.

❖ Statistical analysis

Statistical analysis was performed using SPSS, version 17.0 (SPSS, Chicago, IL). Descriptive statistics were evaluated in terms of frequencies, percentages, or means ± standard deviations. Categorical variables were evaluated by Fisher's exact test and continuous variables were assessed by the t-test. Data before and after procedures, unpaired t-tests were applied to compare repeated measures for continuous variables. P-values of <0.05 was considered significant. Cohen's kappa was used to assess the two observers agreement on ratings for diagnostic accuracy and image quality. This statistical approach documents point-by-point agreement and stringent in determining observer agreement (or reliability).

❖ Ethic committee and scientific committee

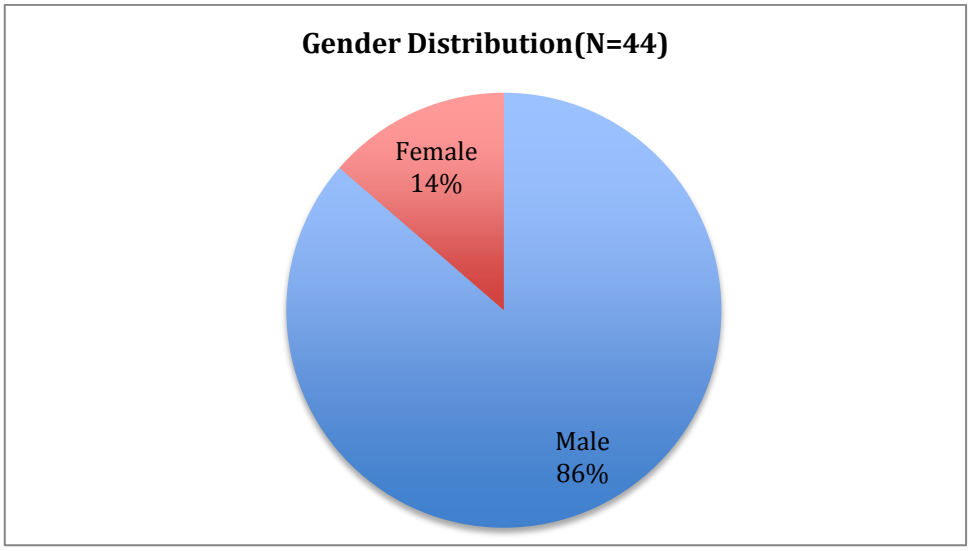
Present study design is approve by ethic and scientific committee of Bhagwan Mahaveer Jain Hospital, Bangalore (annexure V and VI).

Results

RESULTS

Total of 178 patients underwent isolated infra-inguinal endovascular revascularization for critical limb ischemia at Jain Institute of Vascular Sciences (JIVAS), Bangalore, from June 2015 to December 2016. Among 131 patients were excluded, as their eGFR was ≥60ml/min/1.73m^2. Out of 47 patients whose eGFR was <60 ml/min/1.73m^2, underwent CO2 angiography guided endovascular intervention. Three patients, who underwent hybrid procedures with CO2 angiography, were excluded. So total 44 patients (44 limbs) were included in the study, of which 38(86%) were male and 6(14%) female, predominately male population (Figure 7).

Figure 7: Gender Distribution



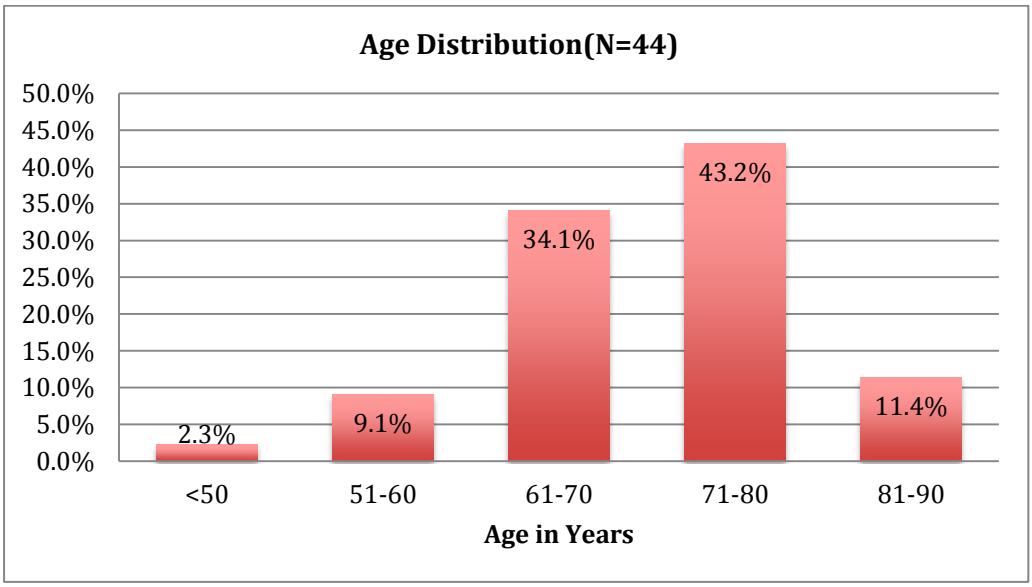
❖ **Age Distribution:**

The mean age of study population was 70.36 ± 8.44 years with 77% of them between 61-80 years and 12% more than 80 years of age. (Table 4 and Figure 8)

Table 4: Age Distribution

Age in Years	Number of Patients	%
<50	1	2
51-60	4	9
61-70	15	34
71-80	19	43
81-90	5	12
Mean Age: 70.36 ± 8.44		

Figure 8: Age Distribution



❖ Co-morbidities:

On analyzing the comorbidities, all (44) were diabetics, 93% hypertensive, 57% had history of CAD, 16% had dyslipidemia. Thirty two (83%) patients had no history of smoking and 12(17%) were smoker among them 2(5%) were current smoker and 10(23%) Ex-smoker. (Table 5 & 6 and Figure 9 & 4) All patients classify as per KDOQI stages[24] of chronic kidney disease, 61% were stage 3, 32% and 7% were stage 4 and 5 respectively. Two patients were post-renal transplant with low eGFR (Table 2b, Figure 3b).

Table 5: Co-morbidities

Co-morbidities	Number of patients (N=44)	%
DM	44	100
HTN	41	93
Dyslipidemia	7	16
CAD	25	57
Smoker (current)	2	5
Smoker (Ex)	10	23

Table 6: KDOQI Stages of Chronic Kidney Disease

CKD Stage	Number of Patients (N=44)	%
3	27	61
4	14	32
5	3	7

Figure 9: Co-morbidities

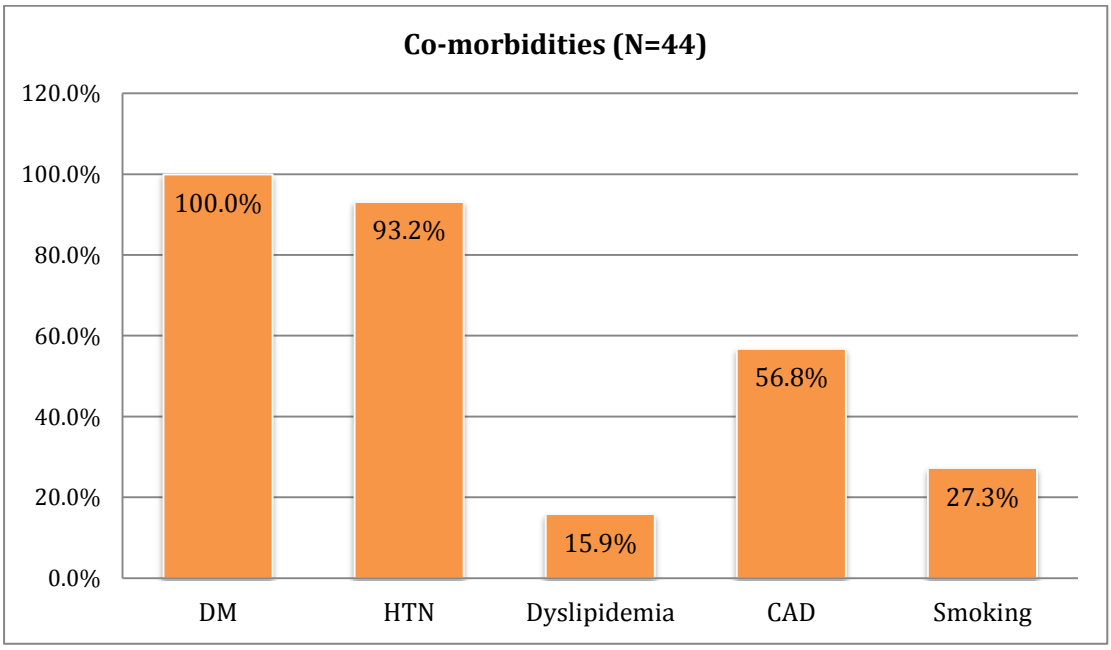


Figure 10: Smoking Habit

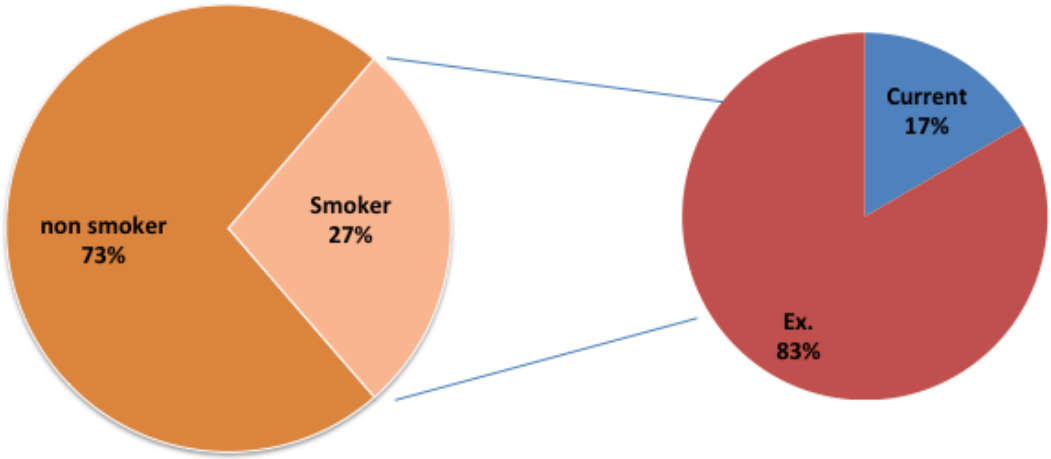
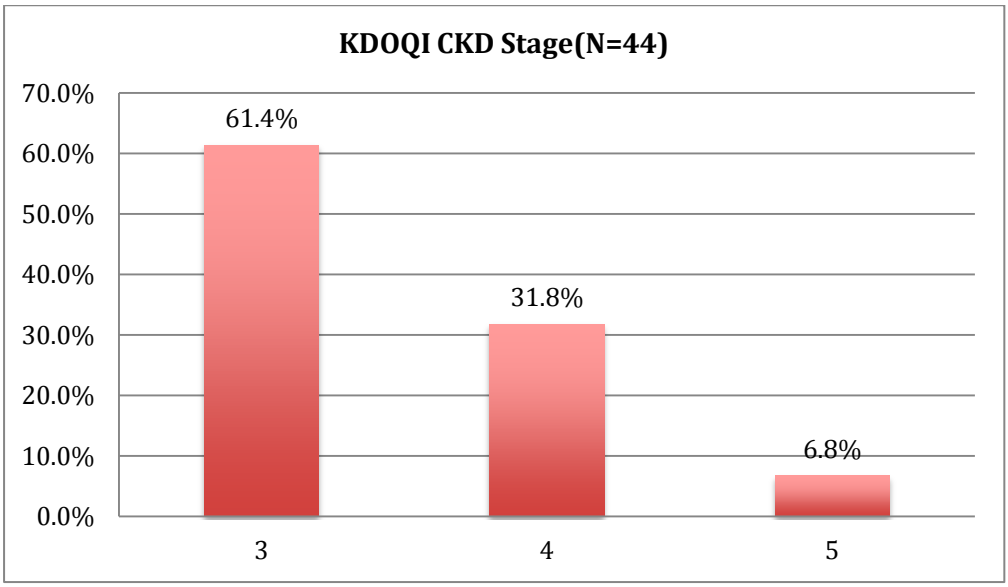


Figure 11: KDOQI Stages of Chronic Kidney Disease



❖ **Clinical and Wound Classification:**

Patients were categorized according to Rutherford-Becker[80] classification for chronic limb ischemia (Table 7) and wounds were categorized according to wound characteristic staging from WIFi classification[81] (Wound, Ischemia and Foot infection) (Table 8).

Among 44 patients 4(9%) were Rutherford category-V and 40(91%) of them category-VI. According to WIFi classification 18% and 82% of patients belongs to stage 3 and 4 respectively. Sixty one percent of patients had left lower limb as index limb and 39% with right (Table 9).

Table 7: Rutherford-Becker Classification

Rutherford Category	Number of Patients (N=44 limbs)	%
V	4	9
VI	40	91

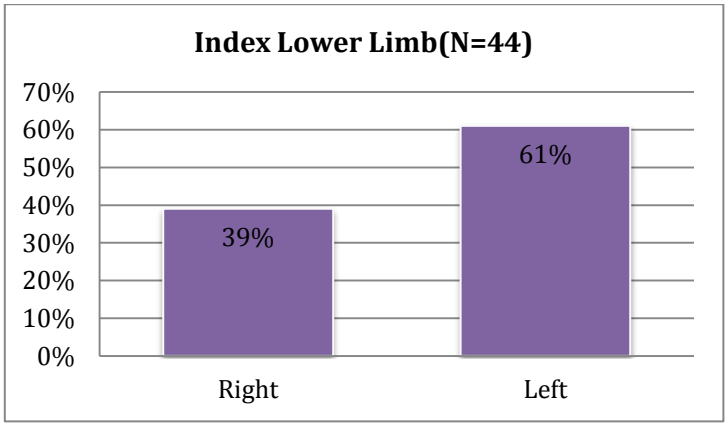
Table 8: WIFi Classification

WIFi Stage	Number of Patients (N=44 limbs)	%
3	8	18
4	36	82

Table 9: Index Limb

Index limb	Number of Patients (N=44 limbs)	%
Right	17	39
Left	27	61

Figure 12: Index Lower Limb



❖ **Distribution of Lesions:**

Operative intervention was infrainguinal EVT with CO2 angiography consisting of angioplasty and selective stenting as needed. Left lower limb involved in 61% of cases (Figure 12). Distribution of lesions divided in two segments, femoropopliteal and infrapopliteal segments respectively (Table 10, Figure 13). In 39(87%) patients we took ipsilateral antegrade CFA access and in 5(13%) contralateral retrograde CFA access was obtained (Table 11, Figure 15). Predominant revascularization required in infrapopliteal segments of 25(57%) of patients, only 5(11%) required femoropopliteal correction and rest 12(27%) required multilevel corrections. Out of total 17 cases of femoropopliteal intervention 2 required stenting. The distributions in infrapopliteal lesions were 25- ATA, 5- TPT, 12-PTA, 9-Peroneal artery. Technical success was achieved in 78% of interventions. In Two cases during intervention, lesions were not crossed hence only CO2 DSA was performed (Table 10, Figure 14).

Table 10: Arterial lesions Distribution

Lesions Distribution	**Number of Cases (44)**
Femoropopliteal vessels	5 (11%)
Angioplasty Alone	4
Angioplasty with Stenting	1
Infrapopliteal vessels (Angioplasty)	25 (57%)
ATA	12
TPT	0
PTA	3
Peroneal	1
Multi-Vessels	9
Multi-Level	12 (27%)
Femoropopliteal + Infrapopliteal angioplasty	11
Femoropopliteal Angioplasty and stenting + Infrapopliteal angioplasty	1
Only DSA	2 (5%)

Figure 13: Level of Revascularization

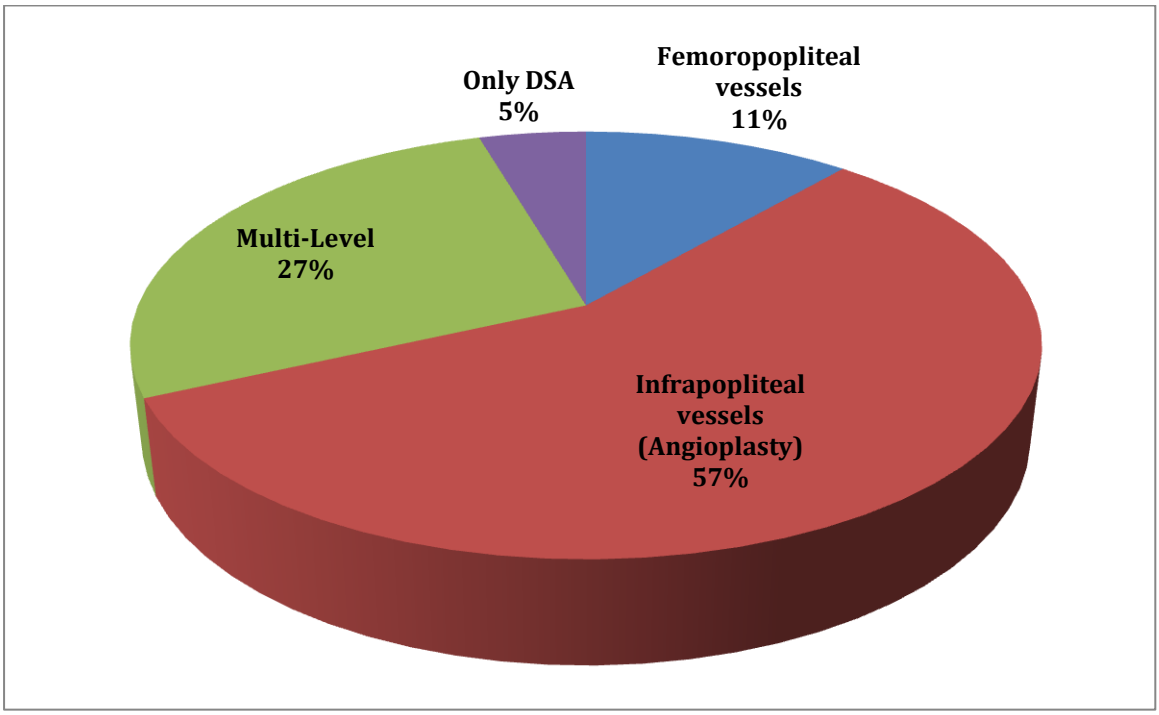


Figure 14: Distribution of Arterial Lesions

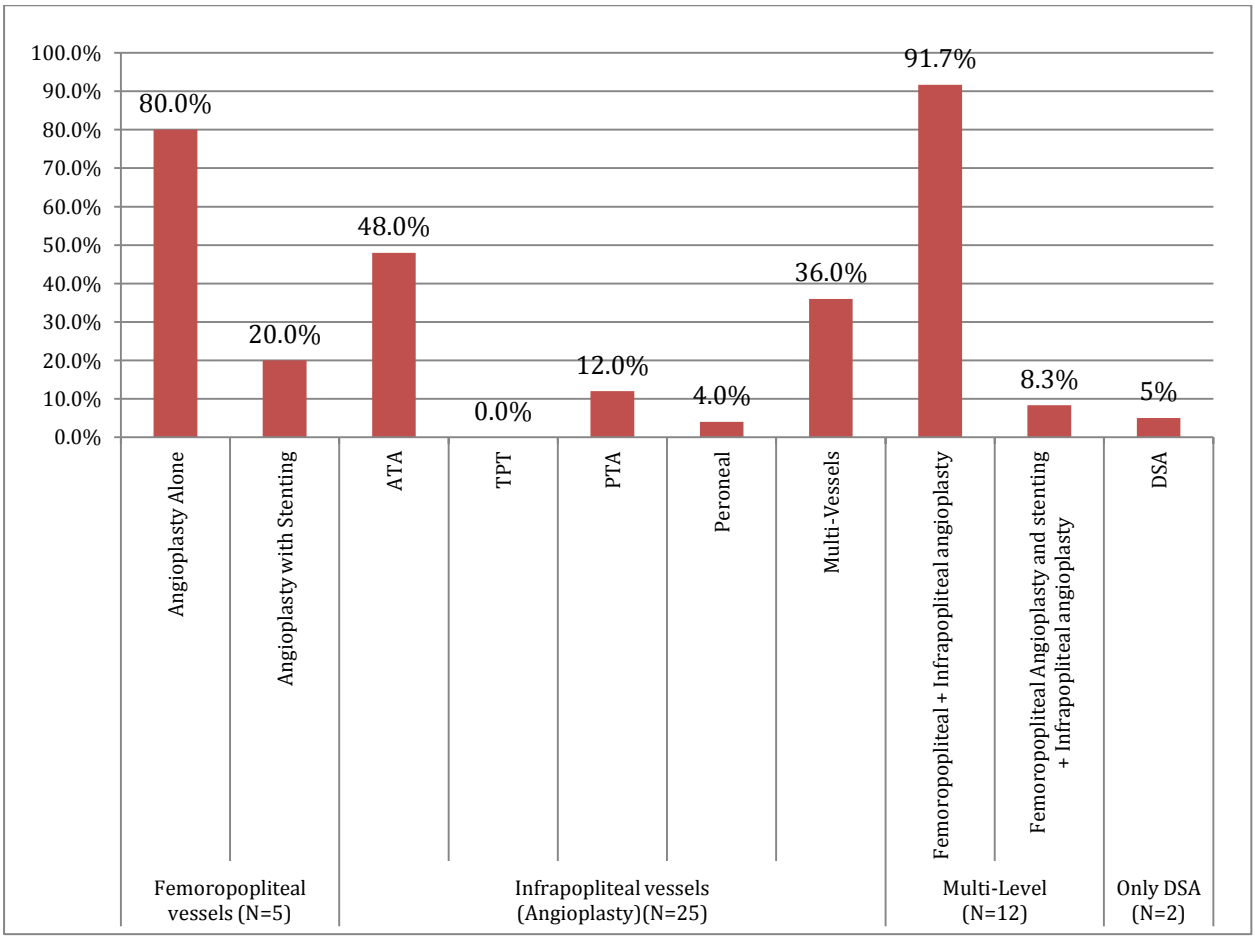


Table 11: Arterial Access

Access	Number of Patients (N=44)	%
Antegrade	39	87
Contralateral Retrograde	5	13

Figure 15: Arterial Access

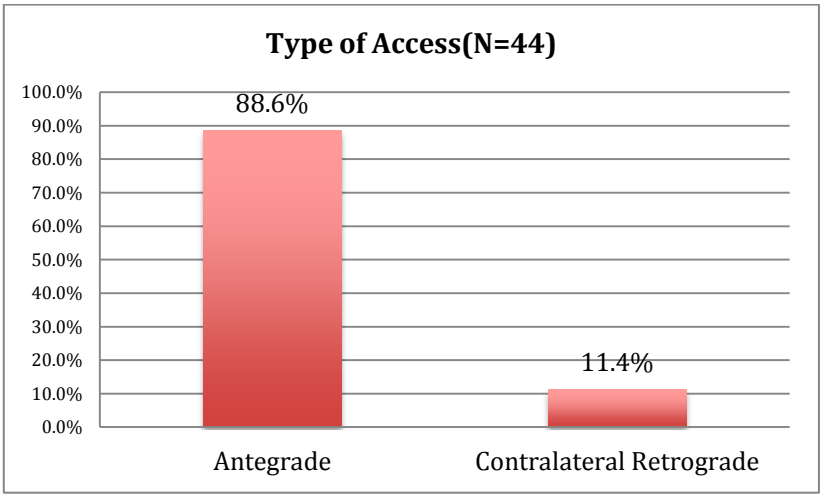
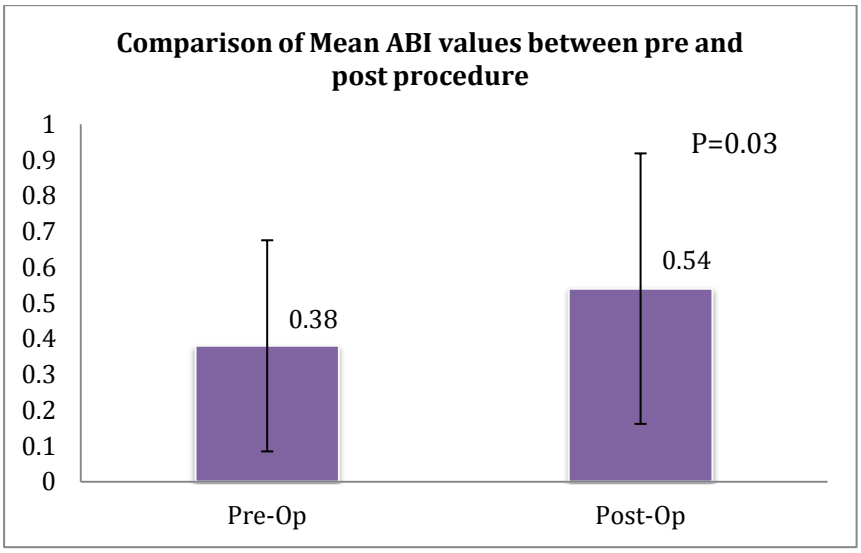


Figure 16: Pre and Post-operative mean ABI



The mean pre procedure ABI was 0.38 ± 0.30 and post procedure it was 0.54 ± 0.38 (Figure 16) with technical success rate of 77.3% (Table 12, Figure 19). The mean Preprocedure serum creatinine (Figure 17) and eGFR(Figure 18) were 2.16 ± 0.7 mg/dl and 34.59 ± 10.93

ml/min/1.73m^2 and post procedure 2.03 ± 0.65 mg/dl and 36.98 ± 11.58 ml/min/1.73m^2 respectively. In 12(27%) cases endovascular procedure were completed with help of only CO2 gas, rest 32(73%) cases use of ICM was necessary to complete the procedure. During procedure average CO2 consumption was 481.81 ± 130.46 ml (range 280-800 ml) and average dose of iodine contrast media was 10.14 ± 8.77 ml (range 0-30ml). Exact procedure duration was not recorded but examination time was always longer with use of CO2 than with use of contrast medium.

Figure 17: Pre and Post-operative mean Creatinine Level

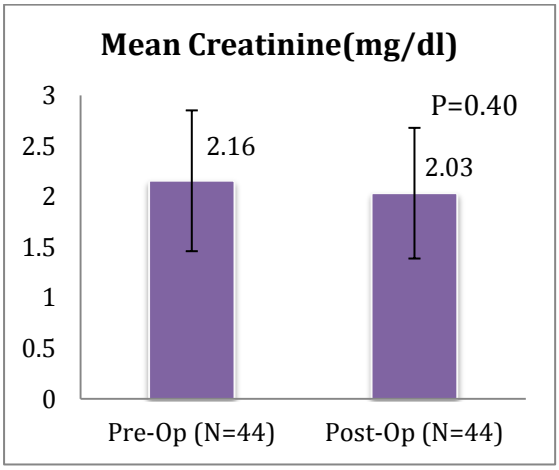


Figure 18: Pre and Post-Operative mean eGFR

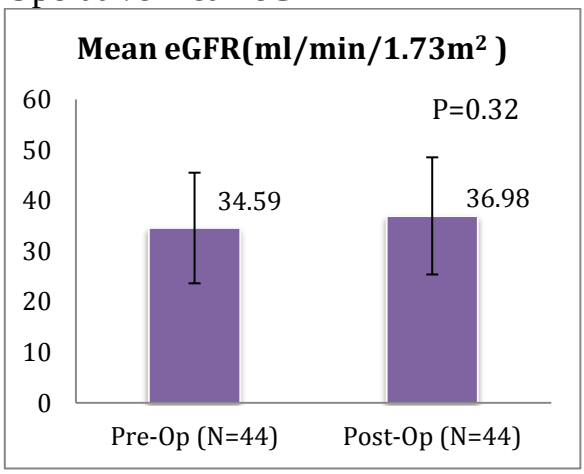
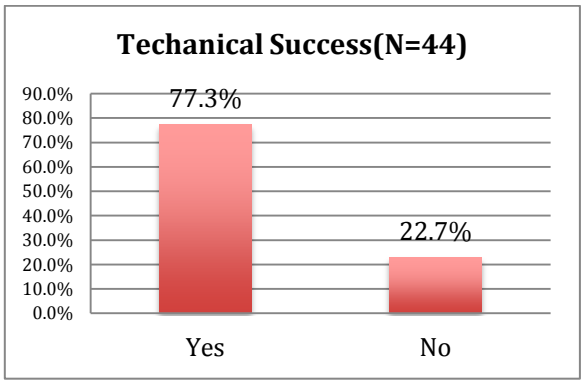


Table 12: Technical Success

Technical Success	Number of Patients (N=44)	%
Yes	34	78
No	10	22

Figure 19: Technical Success



❖ **The Quality Evaluation of CO2 Angiogram**

The 'Good' quality CO2 angiograms were obtained in 35 (79.54%) of patients in femoropopliteal segment (Table 13, Figure 20). The 'Poor' quality angiograms most commonly observed with infrapopliteal segment in 29 (65.90%) patients (Table 14, Figure 21). The 'Fair' quality angiograms were seen in 3 (6.81%) in both femoropopliteal and infrapopliteal segments respectively. The interobserver agreement in femoropopliteal and infrapopliteal segments was good (86.36%) with Cohen's kappa were 0.61 and 0.71 respectively. In infrapopliteal segment only in 14% of cases seen 'Good' quality angiogram.

Table 13: CO2A Image Quality of Femoropopliteal segment

Image Quality	'Good'	'Fair'	'Poor'
Observer-1	37(84%)	7(16%)	0
Observer-2	35(80%)	5(11%)	4(9%)
IOR=86.36%			
Kappa= 0.61 – GOOD Inter observer Agreement			

IOR= Interobserver Reliability

Figure 20: Inter observer Agreement for Femoropopliteal segment

	A	B	C	Total
A	35	0	0	35
B	0	3	2	5
C	0	4	0	4
Total	35	7	2	44

Number of observed agreements: 38 (86.36% of the observations)
Number of agreements expected by chance: 28.8 (65.50% of the observations)

Kappa= 0.605
SE of kappa = 0.093
95% confidence interval: From 0.423 to 0.787
The strength of agreement is considered to be 'good'.

Table 14: CO2A Image Quality of Infrapopliteal segment

Image Quality	'Good'	'Fair'	'Poor'
Observer-1	6(14%)	9(20%)	29(66%)
Observer-2	6(14%)	5(11%)	33(75%)
IOR= 86.36%			
Kappa= 0.71- GOOD Inter observer Agreement			

Figure 21: Inter observer Agreement for Infrapopliteal segment

	A	B	C	Total
A	6	2	0	8
B	0	3	0	3
C	2	2	29	33
Total	8	7	29	44

Number of observed agreements: 38 (86.36% of the observations)
Number of agreements expected by chance: 23.7 (53.82% of the observations)

Kappa= 0.705
SE of kappa = 0.103
95% confidence interval: From 0.502 to 0.907
The strength of agreement is considered to be 'good'.

❖ **Type of Anesthesia And CO2 Angiography**

The commonest anesthesia used for CO2A was local anesthesia (LA) in 21(48%) of cases, followed by regional anesthesia (RA) in 12(27%) and general anesthesia (GA) in 11(25%) cases (Table 15). In initial 12 months of the study period, we observed that one of the reason for 'Poor' quality infrapopliteal angiogram was due to patient's leg pain and movement during injection of CO2 gas among other reasons. Based on above observations we started using regional nerve blocks to control patient's leg pain and movement during CO2 angiogram apart from

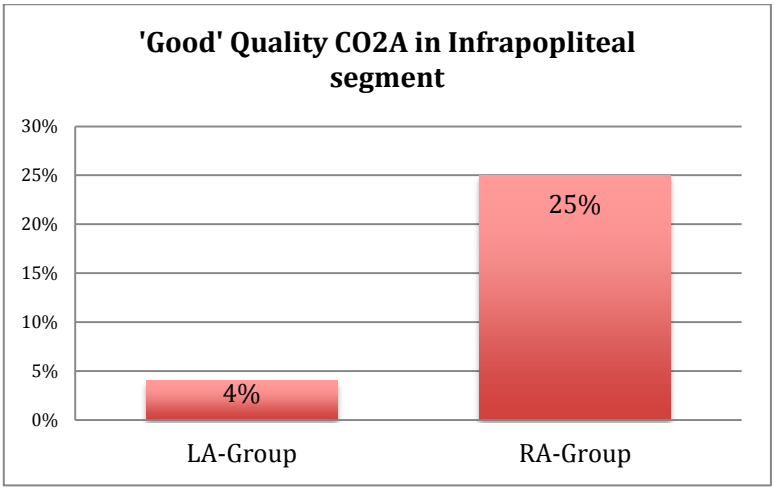
general anesthesia. In sub analysis of our study we divide this cohort in LA-group (LA/GA) and RA-group (RA/GA).

Table 15: Type of Anesthesia

Anesthesia Type	Number of Patients (N=44)	%
GA	11	25
LA	21	48
RA	12	27

A group-LA was had 24 patients in time duration from April 2015 to June 2016 who received LA or GA. RA-group had 20 patients in time duration from July 2016 to December 2016 who received RA or GA. Analysis between this groups showed that no difference in 'Good' quality angiogram (80%) in femoropopliteal segments with inter observer agreement of 87.5% and 85% for LA-group and RA-group respectively. In infrapopliteal segment, we observed only 1(4%) 'Good quality angiogram from LA-group but 5(25%) 'Good' quality angiogram from RA-group (Figure 22), which is statistically significant between two observers (P=0.045). Inter observer agreement for infrapopliteal segment between LA-group and RA-group was 83.3% and 90% respectively.

Figure 22: 'Good' quality CO2 angiogram in infrapopliteal segment



The mean iodine contrast volume (Table 16, Figure 23) used in LA-group was 14.25 ± 8.87ml (range 0-30ml) and in RA-group much low 5.33 ± 5.6 ml (range 0-20ml, P=0.0003). The mean CO2 gas volume (Figure 24) used for LA-group and RA-group was 445 ± 107ml (range 280-640ml) and 526 ± 144 ml (range 280-800ml)[p=0.044]

The mean use of iodine contrast volume for isolated infrapopliteal (N=25), isolated femoropopliteal (N=5) and multilevel (N=12) endovascular treatment was 13.72ml, 1.4ml(P=0.0036) and 6.33ml(P=0.0121) respectively. (Table-17)

Table 16: Mean ICM Volume

	LA-Group (N=24)	**RA-Group (N=20)**
ICM Vol. (ml)	14.25 ± 8.87 **P= 0.0003**	5.33 ± 5.6 ml

Figure 23: ICM Volume

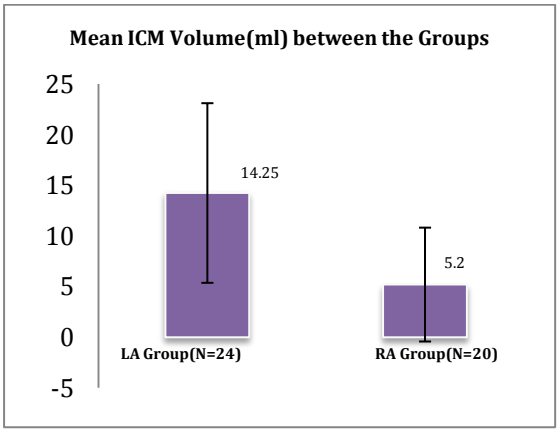


Figure 24: CO2 volume

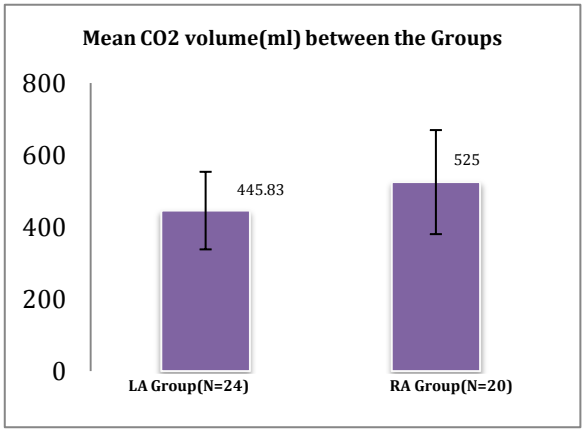


Table-17 ICM volume in different arterial segment

Level	**ICM vol. (mean)**	**P value**
Infra-popliteal (N-25)	13.72	0.0036
Femoro-popliteal (N-5)	1.4	
Fem-pop & distal (N-12)	6.33	0.0121

❖ **Complications**

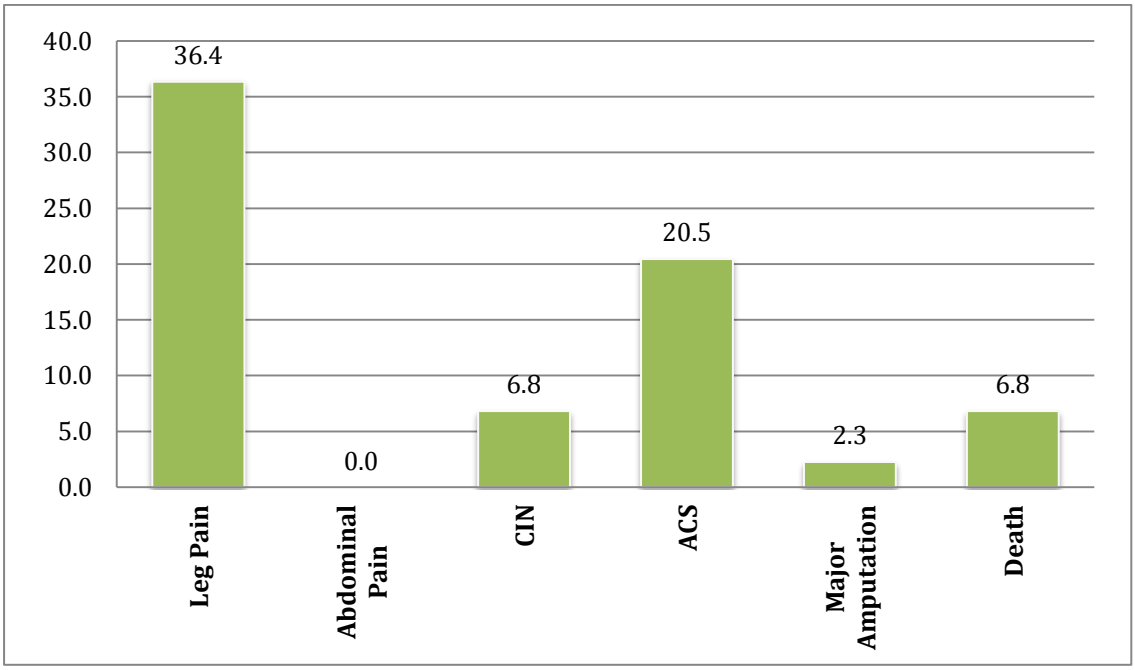
1. CO2 angiography related:

Among the 44 patients, in 16 (36.36%) cases had CO2-related minor complications. Respiratory and neurological abnormalities were not observed in perioperative period. Transient leg pain was noted in all 16 cases during procedure. No patients complained of abdominal pain during or after the procedure. No major complications like bowel ischemia or CO2-related death was occur (Table 18, Figure 25).

Table 18: Complications

Complication	Number of Patients (N=44)	%
CO2-Related		
Leg Pain	16	36.36
Abdominal Pain	0	0
CIN	3	6.82
General		
ACS	9	20.45
Major Amputation	1	2.27
Death	3	6.82

Figure 25: Complications



2. Contrast induced nephropathy:

The incidence of CIN was 6.82%(3/44) in patients who had ICM. Two patients eventually recovered with medical management only. One patient required dialysis and subsequently the patient died due to acute coronary syndrome (ACS) in spite of intensive treatment.

3. General complications:

Out of 44 patients, 9(20.45%) had acute coronary syndrome (ACS), 3(6.8%) died, 2 due to ACS and another one due to CIN and ACS. One patient underwent below knee amputation out of 44 in perioperative period.

Discussion

DISCUSSION

The high nephrotoxicity and antigenicity of iodinated contrasts, has restricted the use of this agent in patients with renal impairment or iodine-related hypersensitivity. There is a continual increase in the number of CIN cases because of the increase in the number of interventional procedures requiring contrast administration in aged patients with CKD. The most effective preventive strategy for CIN is to reduce the volume of iodinated contrast media. The other well-known preventive methods include the administration of N-acetyl cysteine, ascorbic acid, sodium bicarbonate, and alternate form of contrast agent like CO2 gas, gadolinium or IVUS[1].

CO2 possesses several attractive properties as an intravascular contrast agent. It is non-allergic, eliminating the possibility of fatal hypersensitivity reactions. It is rapidly diffused and has no effect on plasma osmolality. In addition, there is no evidence in either clinical experience or animal studies to suggest that C02 is nephrotoxic. These properties obviate the need for pre-arteriography hydration in patients, in whom cardiac and renal dysfunction coexists[65]. Therefore, CO2 has been increasingly used in surgical practice, especially in individuals with renal impairment.

The CO2 angiography has now been used for decades in these settings; however, it has not gained popularity as an aid to endovascular interventions. There are three primary reasons. First, there may be insufficient high-quality digital subtraction angiography systems available. Second, the use of a gas rather than a liquid contrast agent may be unfamiliar to most vascular interventionists. Third, there may be some concern about bowel ischemia due to the trapping of CO2 gas in celiac, superior and/or inferior mesenteric arteries[1].

Carbon Dioxide is most reliable for examination of peripheral vascular disease of the lower extremity, since the images are not degraded by bowel gas motion. There are many literatures and publications in lower extremity CO2 angiography in last 3 decades after Hawkins pioneered its intra-arterial application. Comprehensive literature is available regarding comparative studies between CO2 and ICM image quality[49,50,58-61,63,63,72], however, limited data are available on EVT and CO2 as a contrast agent in patients with symptomatic PAD[1,65-67,69,73,82]. In this study, we examined CO2 DSA images from 44 CLI patients and the subjective experience of patients during angiography to assess the potential of CO2 as an alternative contrast material for angiography. Concomitant use of iodinated contrast to improve visualization of vascular anatomy was done to complete procedure when required.

Table 19: Comparing our study with previous study

Demography	**Our Study**	**Fujihara[1]**	**Scalise[59]**	**Giordano[69]**	**Mendes[50]**
Total Cases	N=44	N=98	N=40	N=21	N=19
Age (Years)	70.4±8.4	75.6±7.9	71.7±7.2	67.9±10	65
Male (Gender)	38(86%)	73(74.4%)	24(60%)	12(57%)	13
DM	44(100%)	49(50%)	24(60%)	9(43%)	9(47%)
HT	41(93%)	93(95%)	23(58%)	18(86%)	16(85%)
CAD	25 (57%)	65(66%)	9(23%)	4(19%)	NA
CKD(>stage 3)	44 (100%)	98(100%)	11(28%)	5(24%)	NA
Smoking Habit	12(28%)	NA	17(43%)	4(19%)	15(79%)
Dyslipidemia	7(16%)	62(63%)	28(70%)	6(29%)	7(37%)
Limb Ischemia	RB-Cat. 5/6 4/40	RB-Cat 2/3/4/5 11/35/5/12	RB-Cat 1/2/3/4/5 8/9/13/8/12	Fontaine 2/3/4/NA 9/0/2/10	-
Technical Success	78%	98.4%(SFA)	NA	NA	-
ICM Vol. (ml)	10.14±8.77	15±18.10	NA	NA	31.29
CO2 Vol. (ml)	482±130	281±156	NA	NA	70.7
Leg Pain	16(36%)	8(8.1%)	3(%)	NA	NA
Abdominal pain	No	6(6.1%)	NA	NA	NA
Major Complications	No	2(2%) NOMI	No	NA	No
CIN	3(6.82%)	5(5.1%)	No	NA	No

Comparing our demographic data to the studies published after the year 2010 (Table 19) on CO2 angiography showed that all of them had predominant male population, as in our study (86%). In the present study 77% of the patients were in age between 61 and 80 years with mean age of 70.4±8.4 years. In present study youngest patient was 49 years old and eldest was of 85 years.

In the present study, diabetic population is 100%, which is the highest compared to previous studies. In previous studies it contributed to 40-60% of the total study population. In all previously mentioned studies co-morbidities like hypertension, CAD, CKD has much varied distribution. In the present study, the prevalence of hypertension, CAD, CKD is 93%, 57% and 100% respectively. In our study all patients are CKD stage 3 or more as per our inclusion criteria. Fujihara et al[1] noted CKD stage 3/4/5=60/36/4%, which was comparable to CKD population 61/32/7% in our study. Prevalence of dyslipidemia is also variable in all studies (Table 19). In present study it was in 7/44 (16%) patients.

Smoking is an established risk factor for atherosclerosis and its influence on endovascular treatment outcomes. In the present study, 12 (27%) were smokers. Previously mentioned studies included patients from Rutherford categories 2 to 5 or Fontaine II to IV. In the present study all the patients included belongs to Rutherford categories 5 or 6 and this is a major difference compared to other studies in terms of foot infection and wound burden. Sepsis also affects kidney function and can add on to causality of CIN[24].

- **Quality evaluation of CO2 Angiography**

A ‘Good’ or ‘Fair’ quality CO2 angiogram could be of sufficient high quality to be used as an adequate alternative to iodinated contrast[1]. In our study femoropopliteal segment ‘Good’, ‘Fair’ or ‘Poor’ quality

CO2 angiograms were obtained in 37(84%), 7(16%) and 0 by observer-1 while observer-2 noted 35(79.5%), 5(11%) and 4(9%) respectively. Combining the results of both the observers, we found that over 85% of the CO2 arteriograms were of 'Good' or 'Fair' quality with interobserver agreement of 86.36% and Cohen's *kappa*-0.61 (good agreement).

Recent study by Fujihara et al[1] noted that CO2 angiogram quality in SFA was 'Good', 'Fair' or 'Poor', in 62.9%, 22% and 1% respectively, which is lower than our study. The main reason Fujihara noted for observing a high percentage of 'Good' quality CO2A among these patients in his study was the absence of the interference provided by bowel loops and gas. In a large study by Rolland et al[60] ICM images were judged to be superior in 35% patients, image quality was identical in 61% and CO2 angiography was superior only in 4%. In the series by Seeger et al[57] 91% of the angiograms were judged to be of 'Good' or 'Excellent' quality by the two blinded observers and only one CO2 angiogram was found to be inadequate. Hawkins and Caridi[7] obtained 92% diagnostic angiograms using CO2, rated to be good or excellent when compared with ICM arteriogram. However, in the study by Diaz et al[63], 17 (24.3%) of 70 CO2 angiograms were similar to or better than ICM studies as assessed by reader 1 while reader 2 considered 8(11.4%) CO2 studies to be as good as the ICM DSA.

Various techniques are available for the injection of intravascular CO2. These include hand injection[7,56], Leveen pressure inflator[83] and dedicated delivery system by Coject (Angiodynamics, Glens Falls, NY, USA)[62,72,84]. The latter equipment is expensive, but reported to be safer[63,72]. Kerns et al[62] reported that a lower limit to the volume and rate of injection exists below which the bolus breaks up in the area of the imaging. We used an injection rate of CO2 15 to 20 ml/sec and volume

40ml with fixed gas pressure of 1.3 bars with Angioset (Opti-Med, Germany) closed CO2 delivery system.

In a recent report by Almaida et al[50], noted that all 19 cases CO2 angiograms of the supragenicular arteries were graded as 'Good' or 'Fair' by both observers with high interobserver image quality concordance. Similarly, for infrageniculate arteries only 2 images were graded as 'Poor' quality. Suboptimal efficiency of CO2 in evaluating infrapopliteal arteries is well documented in literature. In a study by Rolland et al[60], the imaging quality of CO_2 DSA was comparable to ICM DSA at the pelvis in 93% and at the thigh in 74% of 120 arteries studied. Infrapopliteally the same quality was achieved in only half of the cases.

Carbon dioxide inadequately opacified the infrapopliteal vessels in many cases of our study, which forced us to use a small amount of ICM. The 'Good', 'Fair' or 'Poor' quality CO2 angiograms in infrapopliteal segment were rated in 6(14%), 9(20%) and 29(66%) by observer-1 while observer-2 rated 6(14%), 5(11%) and 33(75%) respectively. Combining the results of both the observers, we found that over 66% of the CO2 arteriograms were of 'Poor' quality and only 14% of 'Good' quality, with interobserver agreement of 86.36% and Cohen's *kappa*-0.71 (good agreement). A study from an Indian author Madhusudhan[61] noted 95% 'Good' or 'Acceptable' quality CO2 angiogram compared to ICM but 'Poor' quality for infrapopliteal vessels diagnosis. Oliva et al[72] found no significant differences in the mean stenosis values obtained with CO2 or ICM in any segment for any of the observers. Hawkins[7] also noted good or excellent quality angiogram in 117 cases (91%) with only in 7 cases diagnostic insufficiencies were due to inadequate visualization of infrapopliteal arteries.

Infrapopliteal disease is different from other vascular tree in aspect

of small caliber vessels, calcification, diffuse and long segment disease, involvement of multiple vessels. Focal lesions and good distal vessel runoff will be present in only 20% of cases[85]. The reason for inadequate opacification of the arteries and collaterals by CO_2 in our study could be that most patients had complete occlusion of the proximal vessels, which caused slow distal flow and inadequately opacified collateral vessels. Although it has been described that CO2 due to its low viscosity would show collaterals better than ICM, we did not observe this[7,57]. Weaver et al[56] also found inadequate imaging of the collaterals and the arterial tree distal to severe lower extremity occlusive disease by CO2, which forced them to use ICM[56].

Poor patient tolerance to intra-arterial injection of CO2 is a problem when attempting to standardize test procedures but this difficulty was particularly significant and limiting in the present study for infrapopliteal segment. Although some authors have reported discomfort in fewer than 10% of cases[52,79], most authors[1,61,63] have regularly reported higher levels of discomfort when using CO2 than when using iodinated contrast agents.

Diaz et al noted that the limitation lies in the high proportion of uncompleted studies and CO2 images that cannot be read, particularly in the distal arterial segments because of poor patient tolerance to the procedure, small movements by patients that spoil CO2 images more readily or insufficient filling of vessels distant from the point of injection. He was forced to discontinue 18% of the examinations on account of patient discomfort and was only able to complete 36% of the procedures using CO2.

We do not consider this as an impediment to the technique, because of gain of experience with the use of CO2 permitted us to understand that the injection of CO2 through catheters positioned more distally in the arteries, closer to the target lesion, allows acquisition of superior-quality images. Considering that we have performed all the procedures in a highly equipped hybrid angiography suite with integrated software for advance CO2 angiography including image inversion from negative to positive, seems its effect on image quality is negligible in present study.

In our study we observed 36.3%(16/44) patients had leg pain and movement during CO2 injection, which was one of the reasons for 'Poor' quality infrapopliteal CO2 angiogram. It is known that general anesthesia increases postoperative complications, and central neuraxial blocks may cause serious sympathetic block and hemodynamic side effects in high-risk patients. For these reasons, peripheral regional anesthesia is generally preferred in high-risk patients. In the initial part of our study period we performed CO2A under LA/GA in 55%(21/3), among them 12/21(57%) cases had leg pain and movement during procedure. In the later part of our study we had performed CO2A under RA/GA in 45% (12/8) of cases. We observed only 4%(1) 'Good' quality angiogram with CO2 in infrapopliteal segment in LA group while 25%(5) 'Good' quality angiogram in RA group (P=0.045). In femoropopliteal segment around 80% 'Good' quality angiograms were observed in both the groups. The reason to obtain high percentage of 'Good' quality angiogram in RA group was absent of leg movement and pain.

In our study, in 12(27%) cases the endovascular procedures were completed with help of only CO2 gas, rest 32(73%) cases required ICM to complete the procedure, which is comparable to Frankhouse et al[65],

who was able to performed 25%(5/20) infrainguinal procedure with CO2 only. Eschelman[66] also reported 27%(7/26) of procedure performed only with CO2. However, Rolland et al[60] reported a 50% success rate for completing an entire lower extremity angiographic study with CO2. In a small series published by Giordano et al[69] completed 57%(12/21) procedure without ICM. Our technical success rate was 77.3% in infrainguinal EVT with CO2A which is low as compared to Fujihara et al[1], but they have considered only SFA, not infrapopliteal segment EVT for technical success. In literature technical success of EVT with CO2 was noted between 74% to as high as 98% but for all kind of procedures and not for only infrainguinal revascularization [1,65,66].

❖ **CO2-Related Complications**

No major CO2-related complications occurred in our study. In 36%(16/44) cases had leg pain and discomfort during CO2 injection. No patients complained of abdominal pain. The leg pain could have been due to explosive gas delivery. However, none of our procedures needed to abandon due to patient's discomfort. Seeger et al[57] experienced complications in only two (1.6%) of the 128 patients they studied; one patient with abdominal aortic aneurysm had watery diarrhea and the other patient had septicemia and abdominal pain due to mesenteric artery ischemia. Other studies also showed similar low incidence of complications attributable to CO_2 DSA[56,60,72]. Spinosa et al[73] described a case of transient mesenteric ischemia, which occurred as a complication of intra-arterial CO_2 DSA. Madhusudhan et al[61] noted 28.6% patients complained of mild pain during both CO_2 and ICM DSA studies and 1/21 patient had severe leg pain. Fujihara[1] described 2% of patients had non-occlusive mesenteric ischemia and died. In his study he noted abdominal and leg pain in 6.1 and 8.1% of cases. In a study of 21

patients, Giordano et al[69] described that none of the patients experienced referred pain or discomfort.

In literature abdominal pain was noted predominately while performing aorto iliac angiography with CO2[1,44,47]. We performed 11.4%(5/44) procedures from contralateral retrograde access, no patients complained of abdominal pain. Contamination of an open syringe filled with pure CO2 with room air occurs at a rate of 0.02–0.2 mL/sec[86]. With a closed system, which was used in our study, the chances of contamination with room air were presumed to be negligible. We did not encounter any complications related to air embolism in our study.

❖ **Contrast Induced Nephropathy (CIN)**

During procedure mean volume of CO2 used was 481.81 ± 130.46 ml (range 280-800 ml) and average dose of ICM was 10.14 ± 8.77 ml (range 0-30ml) in present study. Post procedure no significant decline in mean eGFR as compared to preprocedure. We have used more volume of CO2 gas as compared to previously published study[1,50,69,82] but we have not observed any hypercarbia or CO2 embolism during procedures.

In the study by Fujihara et al[1], average ICM volume used to supplement CO2A was 15 ± 18.1ml and mean CO2 injection volume used was 281.4±156ml with rate of CIN was 5.1%(5/98). No CIN was noted in few studies for CO2A supplemented with ICM[7,50,69]. Eschelman et al[66] noted 14.3%(3/21) CIN but none of the patients required dialysis. Frankhouse[65] described rate of CIN 8%(2/26) with mean volume of ICM used was 39ml. Spinosa et al[73] reported CIN as high as 40% in patients group who were supplemented with ICM additional to CO2 and 5% CIN with gadolinium contrast. In the present study 3(6.82%) patients showed decline in eGFR 48 hours after procedure which is very low as compared

to recently published report of 12.8% CIN in symptomatic PAD patients[8]. Two patients recovered with conservative management and the other patient who had extensive comorbidities and CKD stage-4, underwent maintenance hemodialysis but finally succumbed to ACS.

We also noted that high average ICM volume of 13.72ml used in isolated infrapopliteal angioplasty as compared to femoropopliteal or multilevel revascularization, which was 1.4ml(P=0.036) and 6.33ml(P=0.012) respectively. The reason for more volume of ICM used in infrapopliteal segment as compare to femoral or multilevel segment was poor visualization of arterial anatomy and collaterals with CO2A. In femoropopliteal revascularization we used ICM for visualization of dissection or taking decision on residual stenosis for stent placement. The mean used ICM volume of 14.35ml and 5.33ml in LA and RA group (P=0.0003) respectively but on contrary to it, in LA group 4%(1/24) had CIN and 10%(2/20) in RA group.

The independent risk factors for CIN in symptomatic PAD are anemia, CLI, and pre-procedural eGFR, described by Sigterman et al[8] in recent publication. Other comorbidities that increases the risk are hypotension, DM, age>75 and large contrast volume used. Comparing with above factors in over study all patients were DM, 51% population >70 years, 57% population had CAD, all patients low preprocedure eGFR but not used very large volume of ICM. However, there is an ongoing debate with regard to the causality of contrast induced acute kidney injury, which increases risk of cardiovascular events and mortality. It is currently unclear whether CIN is the cause of increased cardiovascular events and death, or that patients at increased risk of cardiovascular events and death are more prone to develop acute kidney injury, owing to their comorbidities. Nevertheless, physicians should be more aware when

patients develop acute kidney injury following contrast administration.

With CO2 angiography development of renal dysfunction or aggravation of existing renal insufficiency was lessened, suggesting this technique should be used for procedures in which iodinated contrast nephrotoxicity is a concern.

Conclusion

CONCLUSION

Though recent technical improvements in CO2 injection, image acquisition and post processing, CO2 angiography cannot replace iodinated contrast angiography as a routine diagnostic tool in CLI patients. In our experience, this is reflected by the lower tolerance to CO2 and the limited diagnostic information provided by CO2 images when visualizing the infrapopliteal arterial segments.

On the other hand, we consider CO2 useful as a vascular contrast agent capable of adequately imaging vascular lesions in femoropopliteal segment and we have been able to reduce ICM load in impaired renal function patients. The visualization of tibial vessels with CO2 angiography can be improved with 15-20° leg elevation, catheter position near to arterial lesion, local nerve block to reduce discomfort and movement for better image acquisition. The CO2 angiography can be used as an adjunct to ICM for diagnosis and therapeutic lower limb endovascular therapy in patients with impaired renal function.

Summary

SUMMARY

A prospective, non-randomized, single center study was conducted at Jain Institute vascular Sciences (JIVAS) Bangalore with aim to analyze quality of CO2 angiogram for infra-inguinal diagnostic and therapeutic endovascular procedure in critical limb ischemia.

To summarize we enrolled 44 patients according to our inclusion criteria, all patients were diabetic and renal impairment (eGFR<60 ml/min/1.73m^2). We were able to perform 27% the endovascular procedure with help of only CO2 gas, rest 73% cases required ICM to complete the procedure. The 'Good' quality CO2 angiogram was obtained in 79.54% of femoropopliteal segment and only in 14% of infrapopliteal segment. The 'Poor' quality angiograms most commonly observed with infrapopliteal segment in 29 (65.90%) patients. The 'Fair' quality angiograms were seen in 3 (6.81%) in both femoropopliteal and infrapopliteal segments respectively. The interobserver agreement in femoropopliteal and infrapopliteal segments was good (86.36%) with Cohen's *Kappa* were 0.61 and 0.71 respectively.

A poor patient tolerance to intra-arterial injection of CO2 is a problem when attempting to standardize test procedures but this difficulty was particularly significant and limiting in the present study for infrapopliteal segment. In our study we observed 36.3%(16/44) patients had leg pain and movement during CO2 injection, which was one of the reasons for 'Poor' quality infrapopliteal CO2 angiography. In the initial 12 months our study, we performed CO2A under LA/GA in 55% (LA group), among them 57% cases had leg pain and movement during procedure. In the later part of our study we performed CO2A under RA/GA in 45% of cases (RA group). We observed only 4% 'Good' quality angiogram with CO2 in infrapopliteal segment in LA group while 25% 'Good' quality angiogram in RA group (P=0.045). In femoro-

popliteal segment around 80% ‘Good’ quality angiograms were observed in both the groups. The reason to obtain high percentage of ‘Good’ quality angiogram in RA group was absent leg movement and pain.

In our study mean volume of CO2 gas used was 481.81 ± 130.46 ml and mean dose of ICM was 10.14 ± 8.77 ml. The difficulty in visualization of arterial anatomy in infrapopliteal segment leads us to use more amount of ICM (13.7ml) as compared to femoropopliteal segment (1.4ml) or multilevel correction (6.33ml). The incidence of CIN was 6.82%, leg pain in 36.36%. In Perioperative period we observed 20.45% acute coronary syndrome (ACS) and 6.8% mortality rate in our study.

Thus we conclude that even with recent technical improvements in CO2 injection, image acquisition and post processing, CO2 angiography cannot replace iodinated contrast angiography as a routine diagnostic tool in CLI patients. In our experience, this is reflected by the lower tolerance to CO2 and the limited diagnostic information provided by CO2 images when visualizing the infrapopliteal arterial segments.

On the other hand, we consider CO2 useful as a vascular contrast agent capable of adequately imaging vascular lesions in femoropopliteal segment and we have been able to reduce ICM load in impaired renal function patients. The visualization of tibial vessels with CO2 angiography can be improved with 15-20° leg elevation, catheter position near to arterial lesion, local nerve block to reduce discomfort and movement for better image acquisition. The CO2 angiography can be used as an adjunct to ICM for diagnosis and therapeutic lower limb endovascular therapy in patients with impaired renal function.

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Annexure

Annexure-I

Definitions

Diabetes mellitus was defined as baseline fasting blood glucose levels of > 126mg/dl, HbA1c (>6.5%) or the need for glucose lowering treatment according to the World Health Organization Criteria[1].

Hypertension was defined as having high blood pressure (systolic blood pressure > 140mg Hg and /or diastolic blood pressure >90 mm Hg) and/or receiving antihypertensive treatment for at least 1 year before inclusion in study[2].

Coronary artery disease (CAD) was defined as a history of angina pectoris, myocardial infarction, congestive heart disease, or prior coronary artery revascularizations[3].

Cerebro-vascular disease (CVD) was defined as a history of stroke, transient ischemic attack, or carotid artery revascularization[4].

Chronic kidney disease (CKD) was defined as serum creatinine >1.5 mg/dL 24 hrs before surgery[5].

Smoking habit was defined as active smoker when the patient smoked at the time of the inclusion or gave up the habit in a period lower than 6 months.[6]

Technical success was defined in terms of procedural, hemodynamic and clinical success. Procedural success was defined as presence of antegrade flow through treated lesion in native vessel at end of procedure[7,8,9] or the presence of less than 25% to 30% residual stenosis, lack of flow limiting dissection by angiography at the termination of the procedure, flow to the pedal arch[10,11,12,13.] Hemodynamic success was defined as an ABI increase of at least 0.10 or improvement in plethysmographic tracing by at least 5 mm for patients with non-compressible vessels. Clinical success was defined as an improvement of at

least one clinical Rutherford classification category with demonstrable hemodynamic success for patients in category IV. [14,15.]

Major amputation was defined as limb loss below or above the knee level, while minor amputation was defined as a transmetatarsal or more distal level amputation of the lower extremity.[16.17]

Acute coronary syndrome (ACS) refers to group of clinical symptoms compatible with acute myocardial ischemia and includes unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI).[18]

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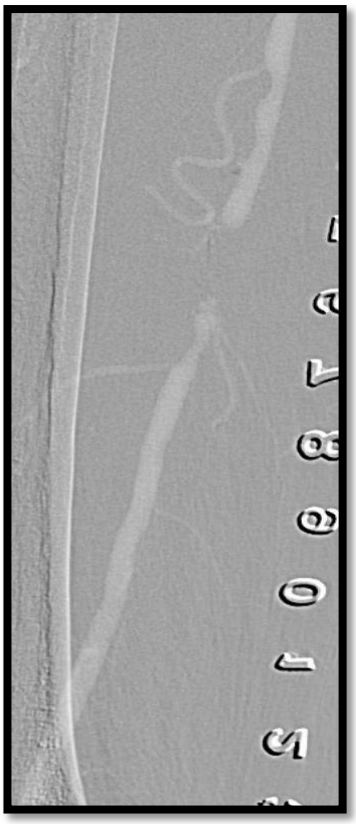
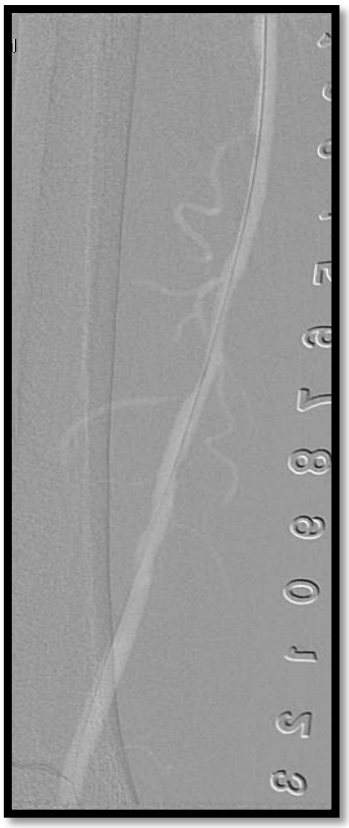
Annexure-II

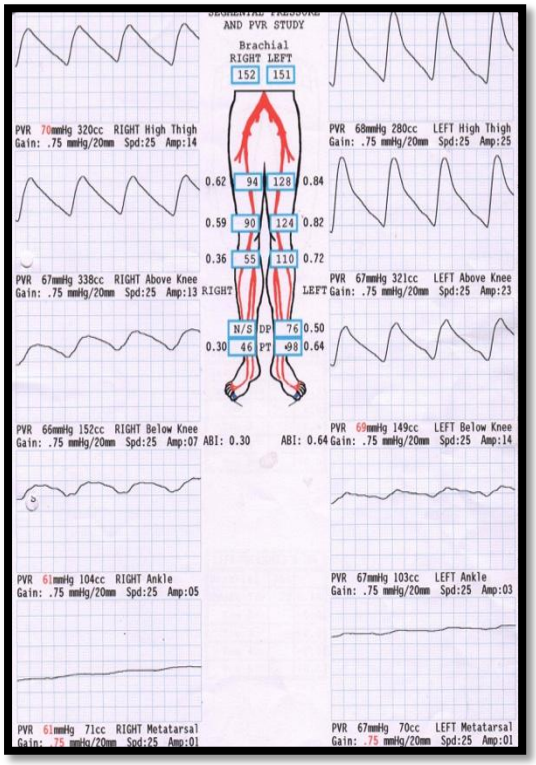
CO2 Angiography Images
Femoropopliteal Segment



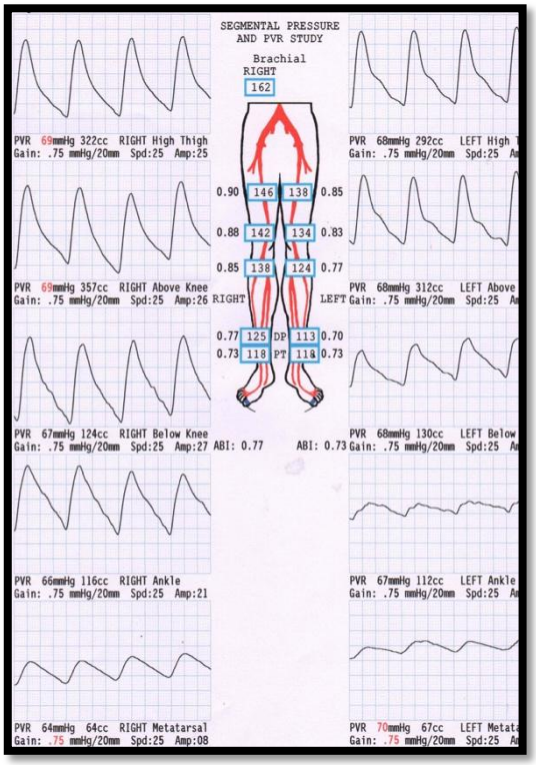
'Good' Quality CO2A
Pre-angioplasty



'Good' Quality CO2A
Post-angioplasty

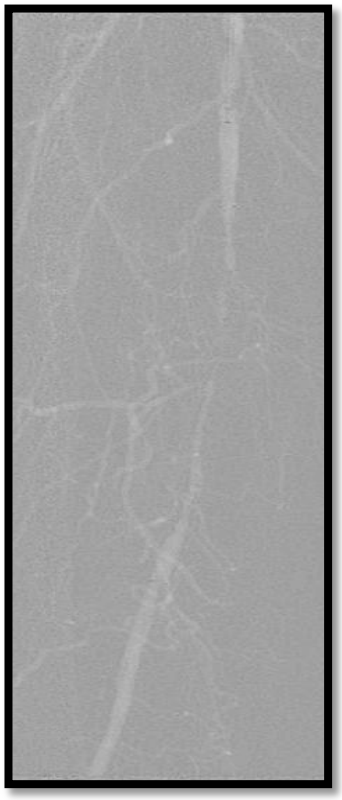


Pre-angioplasty PVR
Right Lower Limb

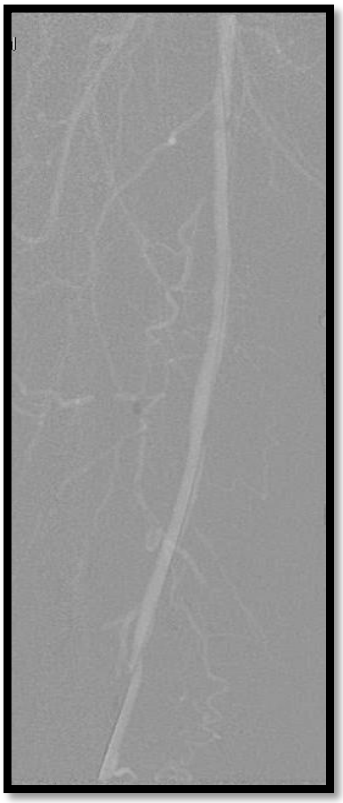


Post-angioplasty PVR
Right lower limb

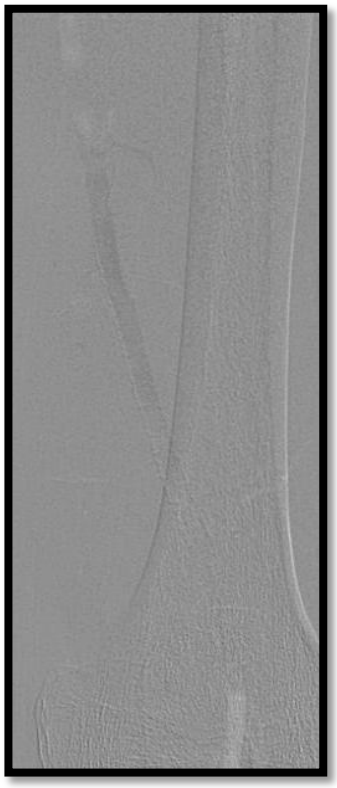
Femoropopliteal Segment CO2 Angiogram



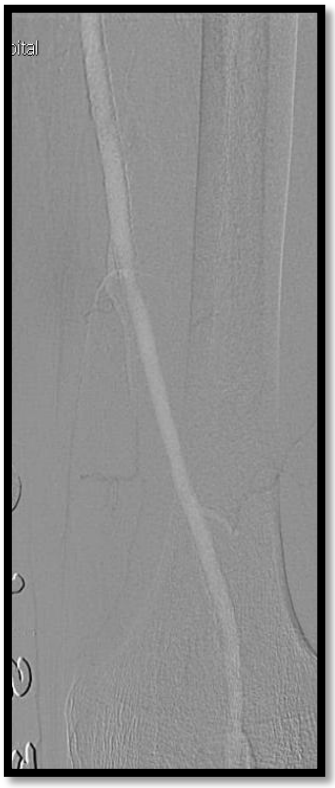
'Fair' Quality CO2A
Pre-Angioplasty



'Fair' Quality CO2A
Post-Angioplasty

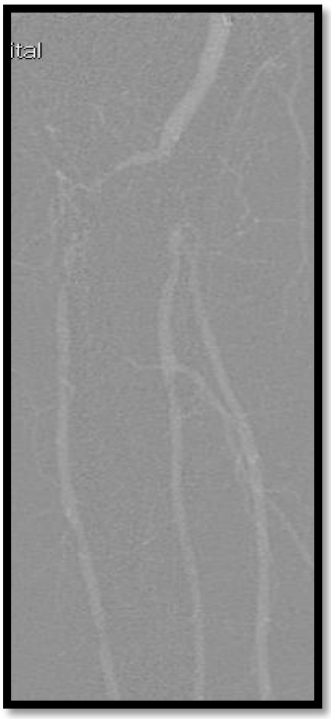


'Poor' Quality CO2A
Pre-Angioplasty

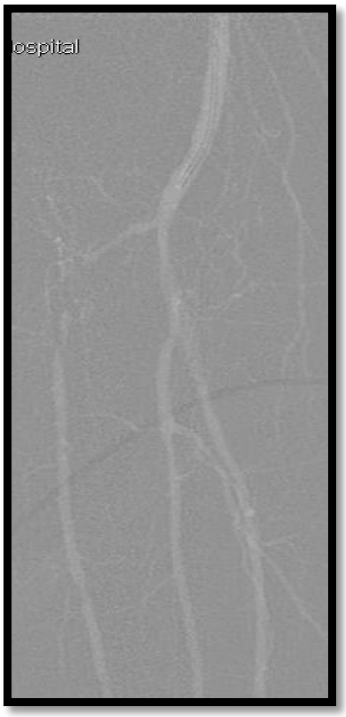


'Poor' Quality CO2A
Post-Angioplasty

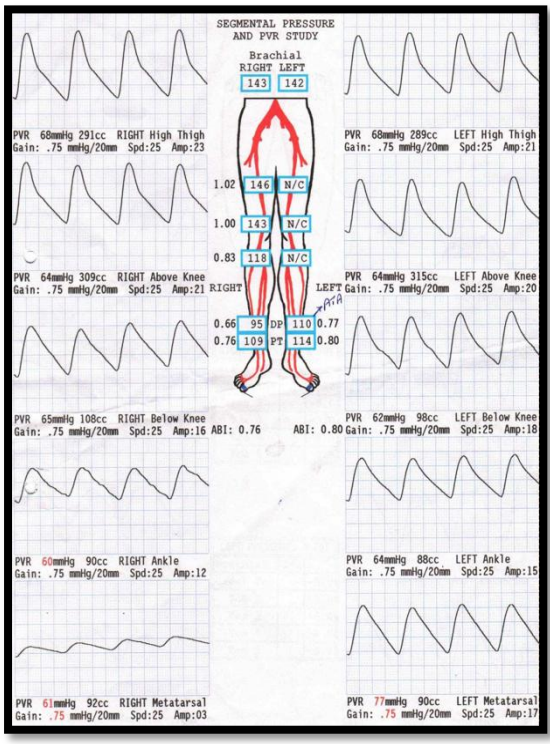
Infrapopliteal Segment CO2 Angiogram



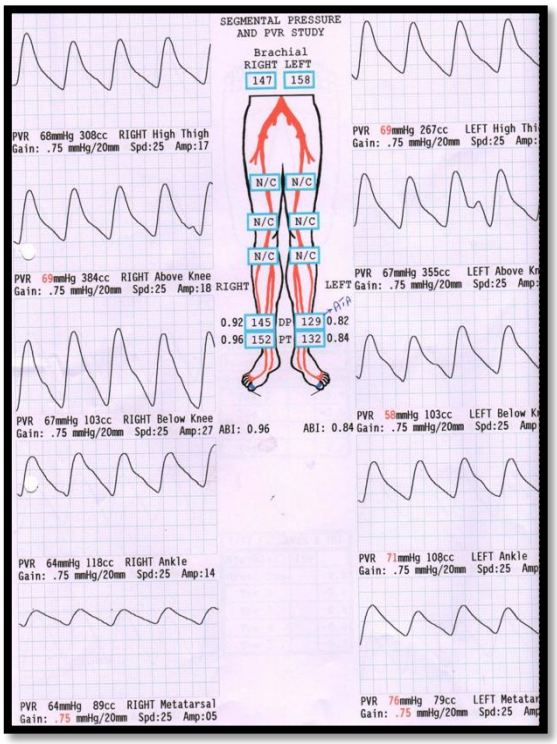
‘Good Quality CO2A
Pre-Angioplasty



‘Good Quality CO2A
Post-Angioplasty

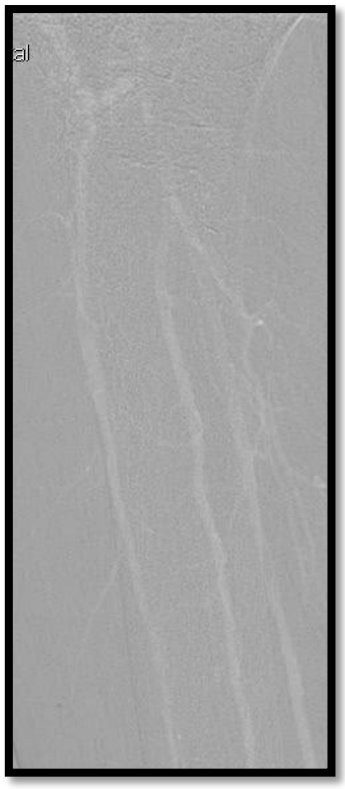


Pre-Angioplasty PVR
Right Lower Limb

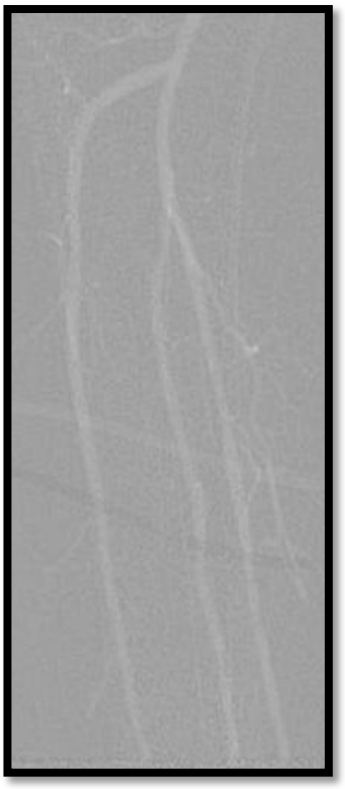


Post-Angioplasty PVR
Right Lower Limb

Infrapopliteal Segment CO2 Angiogram



'Fair' Quality CO2A
Pre-Angioplasty



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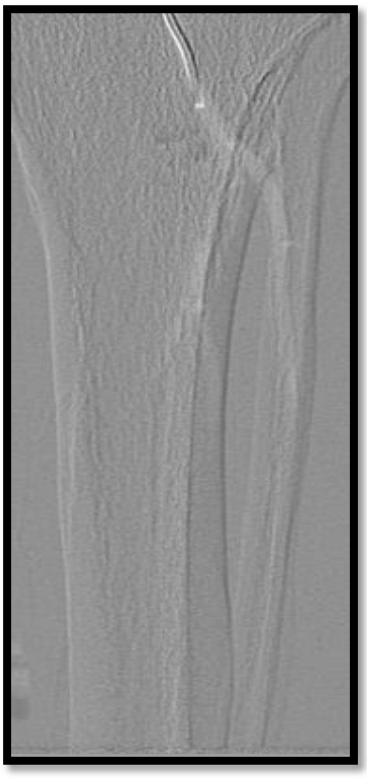
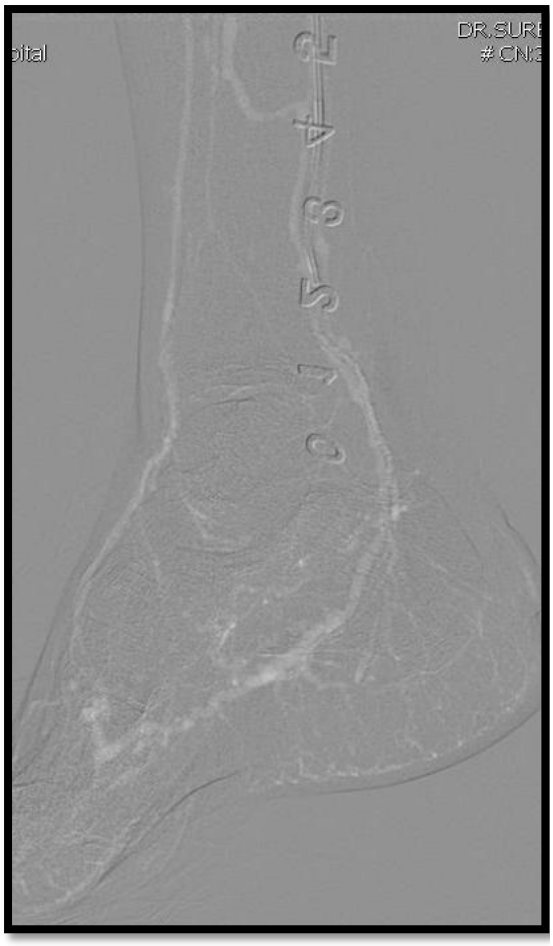
Post-Angioplasty



'Poor' Quality CO2A
Pre-Angioplasty

'Poor' Quality CO2A
Post-Angioplasty

Foot CO2 Angiogram



CO2A as A Negative contrast

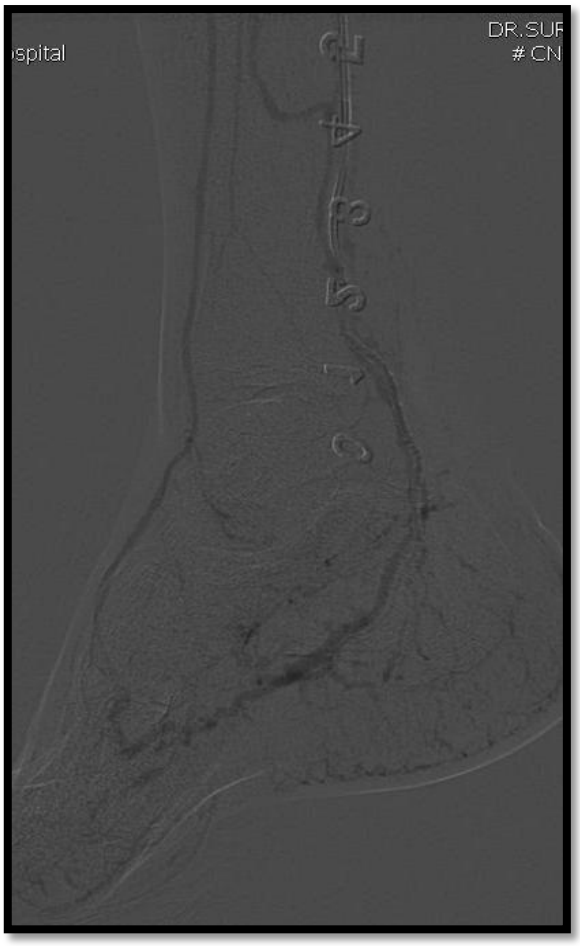


Image Inverted to Positive CO2A

Annexure-III

STUDY PROFORMA

DEMOGRAPHIC DATA

NAME: AGE/SEX:

HOSPITAL No. :

DATE OF ADMISSION: JIVAS No. :

OCCUPATION: TELEPHONE:

CHIEF COMPLAINTS –

1) Pain -

Yes ☐ No ☐

Site - ……

Type (onset) -……

Duration -……

Claudication distance-……

Rest Pain - ……..

Progression - ……..

Interferes with - Sleep ☐ Yes ☐ No

Work ☐ Yes ☐ No

Exercise ☐ Yes ☐ No

Other ☐ Yes ☐ No

	AGGRAVATION	**REDUCES**	**OTHERS**
Dependency			
Exercise			
Rest			
Heat			
Cold			
Pressure			
Position			
Activity			

DESCRIPTION:

2) Ulcer - Site -

Duration -

3) Discoloration - Toe/Finger ☐ Foot/Hand ☐ Others…….

Duration -

4) Associated Complaints: _____

5) Swelling - Site

Duration

PAST HISTORY –

Allergies -

Operation -

Injuries -

Phlebitis

Pregnancies

Cardiac	-		Duration
Angina	☐ No	☐ Yes	……
Arrhythmia	☐ No	☐ Yes	…….
CAD	☐ No	☐ Yes	……
MI	☐ No	☐ Yes	…….
DOE	☐ No	☐ Yes	……..
Orthoppnea	☐ No	☐ Yes	……...

Others

Respiratory

Diabetes - Duration

Yes ☐ No ☐ Treatment - OHA Insulin

Chronic kidney Disease - Duration

Yes ☐ No ☐ On Dialysis - Yes ☐ No ☐

Treatment

			Duration	On medication
Hypertension	☐ Yes	☐ No	☐	☐
Neurological	☐ Yes	☐ No	☐	☐
Arthritis	☐ Yes	☐ No	☐	☐
Collagen Vascular disease	☐ Yes	☐ No	☐	☐
Bleeding Tendencies	☐ Yes	☐ No	☐	☐
Hyper lipidemia	☐ Yes	☐ No	☐	☐
Others	☐ Yes	☐ No	☐	☐

Social History:

Tobacco: ☐ No ☐ Yes Duration ☐ Ex-smoker ☐

Alcohol ☐ No ☐ Yes Duration ☐

Education: ☐ Yes ☐ No Occupation

Others:

Family History			**Medication**
Same Condition	☐ Yes	☐ No	…..…….
Other Vascular Problems	☐ Yes	☐ No	……..
Diabetes	☐ Yes	☐ No	……..
Hypertension	☐ Yes	☐ No	……..
CVA	☐ Yes	☐ No	……..
Cardiac	☐ Yes	☐ No	……..
Clotting abnormalities	☐ Yes	☐ No	……

Examination

Pulse- BP Rt. Arm Lt. Arm

Pallor - ☐ Yes ☐ No

Lymphadenopathy ☐ Yes ☐ No

Neck -

RS -

CVS -

Abdomen -

EXTREMITIES:

EXTREMITIES		**UPPER**		**LOWER**	
		RIGHT	**LEFT**	**RIGHT**	**LEFT**
SKIN	WARM/COOL				
	ATROPHIED/THICKENED				
	CVANOSIS/MOTTLING				
	PALLOR/RUBOR				
	CAPILLARY FILLING				
	HAIR GROWTH				
	NAILS				
EDEMA	BRAWN/PITTING/SPONGY				
	DEGREE				
	EXTENT				
	SUBCUTANEOUS ATROPHY FIBROSIS				
	ULCERATION TISSUE LOSS				
	DISCOLORATION/PIGMENT ATION				
	ERYTHEMA/CELLULITIS				
	LYMPHANGITIS				
MUSCULO SKELETAL	SYMMETRY/ATROPHY				
	HYPERTROPHY				
	JOINT ENLARGEMENT/SWELLING				
	RANGE OF MOTION				
	REFLEXES				
	SENSORY				
	MOTOR				

DESCRIPTION OF ABOVE

ARTERIAL SURVEY

	Pulse		Bruit/Doppler		Aneurysm	
	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT
Carotid						
Brachial						
Radial						
Ulnar						
Aorta (Abdomen)						
Femoral						
Popliteal						
ATA						
PTA						
DPA						

DIAGNOSIS

PLAN:

Pre-operative:

Laboratory Investigations:

Urea	
Creatinine	
eGFR	

ABI /TBI (Index limb)	
PVR (wave forms)	
Arterial color Doppler (If any)	
MRI/CT Angiogram (If any)	

Check list:

- ☐ 6–12 hours of 0.9% normal saline pre-hydration intravenously at a rate of 1 mL/kg body weight per hour (0.5 mL/kg for patients with left ventricular ejection fraction <40%) with sodium bicarbonate.
- ☐ Oral N-acetyl cysteine (NAC) at 1.2 g bid for two days prior to procedure.
- ☐ Administration of Nonsteroidal anti-inflammatory drugs (NSAIDs) restricted for 2 days before the procedure.

Intra Operative:

Procedure performed:

Arterial access: Right Antegrade Left retrograde

CO2 volume (ml) –
Gas pressure (bar)-
CO2 Rate (ml/sec) -
Dye volume (ml) -
Frame rate (per sec.) -
Image Quality:
a) Femoro-popliteal segment:

Image Quality	Observer 1	Observer 2
Good		
Fair		
Poor		

b) Infra-popliteal segment:

Image Quality	Observer 1	Observer 2
Good		
Fair		
Poor		

Level of Revascularization:

SFA	
Angioplasty	
Angioplasty + stenting	
Infra-popliteal	
TPT	
ATA	
PTA	
Peroneal Artery	
Multi-vessel	
Multilevel	
SFA/PA angioplasty with infrapopliteal	
SFA/PA Angioplasty + stenting	

Technically Successful - Yes / No

Complication: if any-

Post procedure:

- ✓ Saline hydration would continue to about 6 hours post-procedure

Investigation	Postoperative (at 48 hours)
ABI/TBI (index-limb)	
PVR (wave forms)	
eGFR	

Annexure-IV

Endovascular Treatment with CO2 Angiogram for Critical Limb Ischemia

Patient Information

I have been explained in the language I understand, which is……..., about the study conducting at Jain Institute of Vascular sciences, a unit of Bhagwan Mahaveer Jain Hospital. Prior to the procedure, you will undergo a detailed clinical examination, Ankle-Brachial Index (ABI), Pulse volume record (PVR), and estimated Glomerular filtration rate (eGFR) will be calculate. Intra-operatively you will undergo carbon dioxide angiogram as a part of endovascular treatment. Postoperatively we will assess ABI, PVR and eGFR. All of the above procedures will be perform as per the standard protocol followed at our institute. You may refuse to participate or withdraw from the study at any time without this affecting in any way the treatment that you are receiving. Your participation in the study is voluntary, and study will not have untoward effects on your present health condition and treatment / surgery you will be receiving.

The data obtained from the study and your records will be used for research purpose only. The information concerning your participation in the study will be kept confidential to the full extent permitted by law and used only for medical purposes. Your name will not be used in any report or released in any way.

Declaration

I (the undersigned) have explained all the details of the endovascular procedures and the assessment of its outcome to the patient explicitly.

----------	----------	----------
Name of investigator	Signature of the investigator	Date

Informed Consent

I have been explained in detail about the procedure that I will be undergoing for my Critical Limb Ischemia and I agree to visit for regular follow up for assessing the outcome of the treatment that I have received. I hereby give consent regarding utilization of my hospital records and data for assessment regarding the same.

……	……
Name of patient	Name of witness
Date:	Date:
Signature	Signature

Annexure-V

Phone : 41100550 (30 Lines)
Fax : 080 - 2226 1153
E-mail : bmjainhospital@vsnl.net
Website : www.jainhospitalbangalore.com

BHAGWAN MAHAVEER JAIN HOSPITAL

A UNIT OF BHAGWAN MAHAVEER MEMORIAL JAIN TRUST
MILLERS' ROAD, VASANTHNAGAR, BENGALURU - 560 052.

Ref. Date : .....

SCIENTIFIC COMMITTEE

APPROVAL CERTIFICATE OF DISSERTATION FOR NBE

Approval has been granted by Scientific Committee of Bhagwan Mahaveer Jain Hospital for the following Dissertation as per NBE requirement to study titled **QUALITATIVE ASSESSMENT OF CARBON DIOXIDE AS A CONTRAST AGENT FOR INFRA-INGUINAL ARTERIAL DIAGNOSTIC AND THERAPEUTIC PROCEDURE IN CRITICAL LIMB ISCHEMIA** conducted by **Dr. DAVRA DHARMESHKUMAR BHIMJIBHAI** Department **VASCULAR** under the guidance of **DR. SUMANTH RAJ** approximate period of study from **JUNE 2015 TO JULY 2016.**

Scientific Committee meeting held on **27/05/2015.**

Date : 01/06/2015

Dr. Preethi Adoni
Chair Person
Scientific Committee

DEPUTY MEDICAL DIRECTOR
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MILLERS ROAD, VASANTHNAGAR, BENGALURU - 560 052.

Ref

Date : .....

01/06/2015

SCIENTIFIC COMMITTEE COMPOSITION

Sl. No.	Name	Designation
1.	Dr. Preethi Adoni	Chairman (Dy. Medical Director)
2	Dr. Prakash K Mehta	HOD, Dept. of OBG
3	Dr. K.R. Suresh	Director of JIVAS
4	Dr. C.R. Chhallani	HOD, Dept. of General Surgery
5	Dr. H.B. Chandrashekar	HOD, Dept of Respiratory Diseases
6	Dr. T.S. Ravindra	HOD, Dept of Medicine
7	Dr. Sudhakar Koppad	HOD, Dept of Anesthesia
8	Dr. Mahesh B.H.	Consultant, Spine Surgeon

Dr. (Wg Cdr) M.D.Marker
Member Secretary
BMJH Ethics Committee

Member Secretary of
Ethics Committee on Human Research
Bhagwan Mahaveer Jain Hospital
Miller's Road, Vasanthnagar
Bangalore-560 052

Annexure-VI

ETHICS COMMITTEE ON HUMAN RESEARCH
BHAGWAN MAHAVEER JAIN HOSPITAL
A UNIT OF BHAGWAN MAHAVEER MEMORIAL JAIN TRUST
Millers Road, Vasanthnagar, Bangalore - 560 052.
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ETHICS CLEARENCE CERTIFICATE

Approval has been granted by Ethics Committee of Bhagwan Mahaveer Jain Hospital for the following Dissertation as per NBE requirement **QUALITATIVE ASSESSMENT OF CARBON DIOXIDE AS A CONTRAST AGENT FOR INFRA- INGUINAL ARTERIAL DIAGNOSTIC AND THERAPEUTIC PROCEDURE IN CRITICAL LIMB ISCHEMIA** conducted by **Dr. DAVRA DHARMESHKUMAR BHIMJIBHAI** Department **VASCULAR** under the guidance of **DR. SUMANTH RAJ** approximate period of study from **JUNE 2015 TO JULY 2016.**

Ethics Committee meeting held on **01/06/2015.**

Dr. (Wg Cdr) M.D.Marker
Member Secretary
BMJH Ethics Committee

Member Secretary of
Ethics Committee on Human Research
Bhagwan Manaveer Jain Hospital
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Date : 01/06/2015

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Ref

Date : 01/06/2015

ETHICS COMMITTEE COMPOSITION

Sl. No.	NAME	DESIGNATION	APPOINTMENT	AFFILIATED INSTITUTION
1	Prof. H.P.Kincha	Scientist	Chairperson	IISc Bangalore
2	Sri. Phoolchand Jain	President BMJH	Non Scientific member	BMJH
3	Dr. M.D.Marker	Medical Director BMJH	Member Secretary	BMJH
4	Dr. H.J.Hrishikeshawan	Pharmacologist	Member	IISc Bangalore
5	Dr. Prakash K Mehta	Consultant OBGYN BMJH	Scientific Member	BMJH
6	Dr. G.R. Nagabhushan	CMO	Scientific Member	IISc B'lore
7	Sri. Prabhakar	Social Scientist	Non Scientific member	Nil
8	Sri. F.R Singhvi	Consumer Protection Activist	Non Scientific member	Nil
9	Dr. Preethi Adoni	Deputy Medical Director	Lady Member	BMJH
10	Dr. Sunanda Kulkarni	Consultant OBGYN	Scientific Member	Retired Prof
11	Sri V.Y Kumar	Advocate	Non scientific	Karnataka High Court

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Annexure-VII
Master chart