“ASYMPTOMATIC RENAL ARTERY DISEASES IN ISCHAEMIC HEART DISEASE PATIENTS WITH NORMAL RENAL FUNCTIONS UNDERGOING CORONARY ANGIOGRAPHY IN A TERTIARY CARE HOSPITAL”

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ENDORSEMENT

This is to certify that the dissertation entitled **"ASYMPTOMATIC RENAL ARTERY DISEASES IN ISCHAEMIC HEART DISEASE PATIENTS WITH NORMAL RENAL FUNCTIONS UNDERGOING CORONARY ANGIOGRAPHY IN A TERTIARY CARE HOSPITAL"** is a bonafide research work done by **CANDIDATE REG NO. BG0113001**.

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LIST OF ABBREVIATIONS USED

ΔP	-	Pressure difference
3D	-	3-dimensional
AHA	-	American Heart Association
ARAS	-	Atherosclerotic renal artery stenosis
BP	-	Blood pressure
CAD	-	Coronary artery disease
cm/s	-	Centimeters per second
CT	-	Computed tomography
CTA	-	Computed tomographic arteriography
CVA	-	Cerebrovascular accident
DUS	-	Duplex ultrasonography
e.g.,	-	For example,
ESRD	-	End-stage renal disease
FMD	-	Fibromuscular dysplasia
GFR	-	Glomerular filtration rate
HDL	-	High density lipoprotein
i.e.,	-	That is,
Kg/m^2	-	Kilograms per square meter
LDL	-	Low density lipoprotein
m/s	-	Meters per second
mg	-	Milligrams
mg/dL	-	Milligram per deciliter
min	-	Minutes
mL	-	Milliliters

mL/ min/100g	-	Milliliters per minute per hundred grams
mm Hg	-	Millimeters of mercury
MR	-	Magnetic resonance
MRA	-	Magnetic resonance arteriography
n	-	Total number
p	-	Probability
PTRA	-	Percutaneous transluminal renal angioplasty
Q	-	Blood flow
R	-	Vascular resistance
RAS	-	Renal artery stenosis
RBS	-	Random blood sugar
RRI	-	Renal resistive index
s	-	Seconds
SD	-	Standard deviation
US	-	United States

ABSTRACT

Background and objectives

Atherosclerotic renal artery stenosis (RAS) and coronary artery disease (CAD) arise from the same multiple risk factors. This study was designed to determine the frequency of asymptomatic renal artery disease with normal renal functions in patients who had coronary artery disease.

Methodology

This one year cross-sectional study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2014 to December 2014. Data was gathered from a total of 480 patients who underwent coronary angiography with normal renal functions were evaluated for the presence of asymptomatic renal artery disease with internal blockage of ≥70%.

Results

Majority of the patients were males (74.19%) and male to female ratio was 2.96:1. The most common age group was 41 to 60 years (50.21%) and the mean age was 57.59 ± 10.56 years. Most of the patients (49.15%) had single coronary artery disease. Involvement of renal artery was noted in 47.71% of the patients. Bilateral involvement was noted in 48.48% of the patients. The incidence of significant renal artery disease was noted as 8.33%. 25 off the 108 patients with triple vessel disease had significant renal artery disease (23.15%) ($p<0.001$). The most common risk factor was low HDL (79.17%). Renal artery disease with not associated with sex, age and traditional risk factors.

Conclusion and interpretation

The incidence of asymptomatic significant renal artery disease (≥ 70%) is high in patients suspected to have coronary artery disease (8.33%) and patients having triple vessel disease are at risk of developing renal artery disease.

Keywords

Coronary angiography; Coronary artery disease; Renal artery disease;

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INTRODUCTION

Renal artery stenosis (RAS) is characterized by a heterogeneous group of pathophysiologic entities, of which fibromuscular dysplasia and atherosclerotic RAS (ARAS) are the most common.[1] Renal artery stenosis, narrowing of the renal arteries, is caused by a heterogeneous group of conditions, including atherosclerosis, fibromuscular dysplasia (FMD), vasculitis, neurofibromatosis, congenital bands, and extrinsic compression, and radiation.[2] Atherosclerosis accounts for approximately 90% of the lesions that obstruct blood flow to the renal arteries. Atherosclerotic renal artery stenosis (ARAS) typically involves the ostium and/or proximal one-third of the renal artery and often the adjacent aorta.[3] However, segmental and diffuse intrarenal atherosclerosis may also be observed, especially in advanced cases.[4]

Renal artery stenosis (RAS) is a frequently overlooked clinical entity that can cause uncontrolled hypertension and can lead to a progressive deterioration of renal function. The two major types are atherosclerosis and fibromuscular dysplasia. Fibromuscular dysplasia is a rare entity that can cause secondary hypertension. Revascularization can lead to cure of hypertension or a significant improvement in blood pressure control in most affected patients.[5]

On the contrary, atherosclerotic RAS is a common disease particularly in association with the presence of atherosclerosis elsewhere. Distinguishing between RAS and renovascular hypertension is important because the former does not always result in hypertension or hypertension may not be related to RAS.[5]

With an aging population, the incidence of atherosclerotic RAS has been increasing and was found in 6.8% of all individuals aged over >65 years in one US study.[6] Prior analysis of the US Medicare population has reported an incidence rate of 3.7 per 1000 patient-years.[7] It is well described that the prevalence of atherosclerotic RAS is even higher in patients with established coronary or peripheral artery atherosclerosis, with prevalence rates ranging from 20 to 30% in retrospective series, and up to 50–70% in several necropsy series.[8]

Renovascular hypertension, ischemic nephropathy resulting in ESRD and cardiac destabilization syndromes are the potential clinical consequences of atherosclerotic RAS.[9] The complex relationship between RAS severity and the impact on renal function remains poorly understood. The interplay of renal blood flow, neurohormonal activation, and the renal macro- and micro-vasculature have resulted in disappointing long-term results of renal artery interventions, despite excellent acute procedural results.[8]

Furthermore, due to low prevalence and invasive nature of investigations, many of the patients, who could be benefited from revascularization procedure, could not be diagnosed. For the same reasons, no true study of prevalence of renal artery stenosis has been performed in an unselected population.[10]

Understanding the epidemiology is an important aspect in improving the outcomes. Despite the data on atherosclerotic renal artery disease is scant in the literature and to date very few studies have reported the incidence of renal artery disease in India. Hence the this study was planned to determine the incidence of asymptomatic renal artery disease with normal renal functions in patients who had

coronary artery disease and to find the association between renal artery disease and other clinical variables including sex, age, hypertension, history of smoking and diabetes mellitus.

OBJECTIVES

The objectives of this study were to determine the frequency of asymptomatic renal artery disease with normal renal functions in patients who had coronary artery disease.

REVIEW OF LITERATURE

Historical note on renal artery disease

Bright reported (1836) the first potential association between hypertension and renal disease.[11] Tigerstedt and Bergman of Sweden discovered renin (1898), a substance exctracted from rabbit kidneys which caused hypertension when injected into healthy rabbits.[12] Goldblatt showed the relation between occlusion of renal arteries and hypertension (1934) and that renovascular hypertension could be treated by nephrectomy.[13]

The first patient successfully treated for renovascular hypertension by nephrectomy (1938) was a 5-year old child with severe hypertension and an ischemic kidney.[14] Treatment changed with introduction of renal artery revascularization by surgery (1954) and by balloon angioplasty (1978).[15,16]

Basic hemodynamic studies by Mann (1938) showed that the lumen-area of the carotid artery may be reduced by 50% without any change in blood flow, and by as much as 90% before a 50% reduction in blood flow occurs.[17] "Critical stenosis" was defined (1963) as the degree of stenosis when flow and pressure is beginning to be affected, further relatively small increase in the degree of stenosis cause significant reductions in flow and pressure. The presence of "critical stenosis" has been confirmed by experimental, mathematical and clinical studies.[18-20]

Normal kidney function

Normally the two kidneys are supplied by one artery each but anomalies common with accessory renal arteries reported in 20-30% of the patients in angiography or autopsy studies.[21]

The two kidneys together contain about 24,00,000 nephrons, and each single nephron is capable of forming urine by itself. The nephron is basically composed of a glomerulus where fluid is filtered from blood to Bowmans capsule and a long tubule in which the fluid is converted into urine on its way to the pelvis of the kidney.[22]

The function of the kidneys is to clean blood from waste products (mainly creatinine from protein metabolism), regulating salt and water balance within a narrow range which is essential for all the body functions, release erythropoietin which stimulates production of oxygen carrying red blood cells and control renal auto- regulation as well as the central blood pressure by release of renin. These functions require a high basal blood flow estimated to 20% (range 13-30%) of cardiac output or 400ml/min/100g tissue (equaled only by maximum coronary flow rate).[22] Variations in renal blood flow are related to for example intake of protein.[23,24]

Renal blood flow

Blood flow (Q) through a vessel is determined by two factors:

1. The pressure difference between the two ends (ΔP) and
2. The vascular resistance (R).

Blood flow can be described by Equation Q= P/R

Vascular resistance is the impediment to blood flow in a vessel. It increases when blood flow changes from laminar to turbulent flow, by obstructions reducing the vessel lumen and by constricting distal arterioles. Increased velocity of the passing blood will compensate for a mild-moderate stenosis. Beyond a certain degree of stenosis the increased velocity can no longer compensate for the reduction of radius of the artery (flow changes from laminar- to turbulent flow). At that point the transport of blood is physically limited by the stenosis.[25]

Autoregulation

Renal blood flow is autoregulated, normally for blood pressures ranging from 70-160 mmHg, by a myogenic response of the afferent arteriole and by the tubuloglomerular feedback of the "juxtaglomerular apparatus" affecting both the afferent and efferent arteriole. The myogenic response acts directly on changes in the perfusion pressure of the glomerulus.

The "juxta glomerular apparatus" is located at the junction of the distal tubule, the afferent and the efferent arterioles of the same nephron. This location is optimal for a tubuloglomerular feedback system. Alterations in the flow rate or ion composition of the distal tubule are detected and a signal is sent to the arterioles. They respond by vasodilatation of the incoming (afferent) arteriole and constriction of the outgoing (efferent) arteriole or the opposite, so as to regulate the glomerular filtration rate. The concentration of chloride ions in the distal tubule is one important signal for this feedback system. The complex process of tubuloglomerular feedback involves release of renin with activation of angiotensin II, complemented by a

variety of hormones and vasoactive substances such as norepinephrine, dopamine, endothelin, prostaglandins, thromboxane A2, histamine, platelet derived growth factor, leukotrienes and others.[26]

Hypertension induced by the kidney through the renin-angiotensin system serves to increase the renal perfusion pressure when autoregulation fails.

Natural history of renal artery disease

FMD and atherosclerosis are progressive disorder and FMD can cause dissection and thrombosis. Among patients with ARAS, progression was reported in 51% of renal arteries over five years after diagnosis, including 18% of initially normal vessels.[27]

Progression to occlusion is rare. The risk of renal artery disease progression is highest among individuals with elevated systolic blood pressure, diabetes mellitus and preexisting high-grade stenosis in either renal artery.[28]

Prevalence

The most common cause of secondary hypertension is RAS with a reported prevalence ranging from 1% to 5% in a general hypertensive population.[6]

The prevalence of RAS increases with age, smoking and occlusive atherosclerotic disease in other parts of the body. A prevalence of 20% was reported in a group of patients with refractory hypertension referred for coronary angiography[29] and 41% in a study of patients ≥45 years of age starting dialysis for end- stage renal disease.[30]

Untreated RAS is a progressive disease, with several retrospective series confirming progression of the disease over time.[4] Four retrospective studies of 202 patients with RAS have demonstrated progression in 36–71% of patients.[31-34]

In a pooled review of five arteriography trials, 49% of the renal arteries demonstrated progression.[35] In this study, 14% progressed to total occlusion. In another retrospective series of 85 patients followed for a mean of 52 months, progression occurred in 44%, with 16% demonstrating total occlusion.[33] The more severe the baseline stenosis, the more likely the vessel will progress to total occlusion, with 39% of cases with a baseline stenosis of 75% progressing to total occlusion. Of those vessels with <50% stenosis, 69% showed no progression. Deterioration in serum creatinine occurred in 54% of patients with progressive stenosis compared with 25% in those without progression, and renal size deteriorated in 70% compared with only 27% ($p < 0.002$ and $p < 0.001$, respectively).[8]

Over a 3-year period, Zierler et al.[36] found that 48% of patients had progression of RAS from less than 60%, to 60% or greater diameter stenosis. The renal arteries that progressed to occlusion were characterized by a baseline diameter stenosis of 60% or greater. Progression of RAS occurred at an average rate of approximately 7% per year.

In a second prospective study[37] of 35 patients, progression occurred in 29%, with total occlusion occurring in 11%. In this article, Dean et al.[37] also reported on the rate of progression in 41 patients with RAS treated medically with control of hypertension and other comorbidities, with 40% developing an increase in serum

creatinine and 37% demonstrating a decline in renal mass.

In a prospective renal artery duplex ultrasound-based progression study,[36] 84 patients with 139 renal arteries with stenosis were followed for a mean of 13 months. Progression of RAS occurred in 42% at 2 years, with occlusion occurring in 11%.

Finally, Caps et al.[38] followed 122 patients and 204 kidneys prospectively for a mean of 33 months with duplex ultrasound and demonstrated that untreated bilateral severe RAS results in renal atrophy, with a 2-year cumulative renal atrophy incidence of 5.5, 11.7 and 20.8% in kidneys with a baseline artery classification of normal, less than 60% stenosis and greater than 60% stenosis, respectively.

In another duplex ultrasound-based study, Caps et al.[39] monitored 295 kidneys in 170 patients for a mean of 33 months. Disease progression was 35% at 3 years and 51% at 5 years. Nine renal artery occlusions (3%) occurred over the course of the study. All occlusions developed in patients with greater than 60% stenosis on the study that preceded the occlusion. Occlusion occurred most often in patients with diabetes, high-grade stenoses and severe hypertension.

The prevalence of RAS depends upon the population examined. Screening renal duplex ultrasonography (DUS) studies demonstrated RAS (>60% stenosis) in 6.8% of individuals in a Medicare population (mean age 77 years).[6] RAS was present in almost twice as many men as women (9.1% versus 5.5%, $P = 0.053$), but no differences were noted in the prevalence of RAS between white and African American individuals (6.9% versus 6.7%, $P = 0.933$).

An autopsy series found RAS (≥50% stensosis) in 27% of patients older than

50 years, and the proportion rose to 53% in those with a history of diastolic hypertension (>100 mmHg).[40]

RAS is the cause of end-stage renal disease in 10–15% of patients commencing kidney dialysis, and approximately 25% of elderly patients with renal insufficiency have undiagnosed renal artery stenosis. In the general hypertensive population, RAS is the most common (2–5%) secondary cause of hypertension.[41]

In the adult population, RAS is predominantly the result of atherosclerosis, although fibromuscular dysplasia commonly found in young women is the next most common cause of RAS. The presence of atherosclerosis in another circulatory bed (i.e. cerebral, coronary, or peripheral vascular) increases the likelihood of RAS being present. In patients undergoing cardiac catheterization for suspected coronary artery disease, RAS is found in up to a third of patients. RAS is present in 30–40% of patients with peripheral artery disease or abdominal aortic aneurysm.[41]

In a multivariable analysis, Weber-Mzell et al.[42] demonstrated that RAS was more prevalent in patients with extensive coronary artery disease (i.e. multivessel coronary disease) than in patients with single-vessel disease.

Prevalence of renal artery stenosis at the time of cardiac catheterization

Study	Number of patients (*n*)	Any RAS (%)	RAS > 50% (%)	Bilateral RAS (%)
Jean *et al*. (1994)[43]	196	33	18	NR
Weber-Mzell et al. (2002)[42]	177	25	11	8
Harding *et al*. (1992)[44]	1,302	30	15	36
Rihal *et al*. (2002)[45]	297	34	19	4
Vetrovec *et al*. (1989)[46]	116	29	23	29
Aqel *et al*. (2003)[47]	90	NR	28	10

Overall	NA	30.2	19.0	17.4

Pathophysiology of renal artery stenosis

RAS is the result of an abnormal process in the arterial wall but it is seldom of hemodynamically significance until the lumen diameter is reduced by ≥50%.

Symptoms of renal artery disease

RAS may cause hypertension, recurrent pulmonary edema and impaired renal function (including end- stage renal disease requiring dialysis or renal trans-plantation). Research based on Tigerstedt-Bergman and Goldblatt´s evidence has led to our present understanding of the renin-angiotensin-aldosterone system.[12,13]

Renovascular hypertension

It is important to distinguish between morphological RAS and renovascular hypertension. Severe RAS has been reported in normotensive patients at autopsy studies[40] and angiographic studies.[48]

In its early phase hypertension is dependent on the renin-angiotensin-aldosterone system. As the kidneys accumulate sodium and water, the extra-cellular fluid volume will expand and in a later "chronic phase" hypertension is volume dependent and renin release is suppressed.[4]

Treatment of renovascular hyper- tension with angiotensin II inhibitors or angiotensin receptor blockers is possible in the early phase but less effectively in the chronic phase. Revascularization or nephrectomy will result in natriuresis (excretion of Na+ and water) and lowered blood pressure in both phases.

Renovascular azotemia (ischemic nephropathy)

Decrease in number of functional nephrons will lead to Azotemia. It may be caused or worsened by RAS. Other causes include glomerulonephritis, pyelonephritis, microembolisation of cholesterol or thrombi, obstruction of urine excretion, traumatic loss of kidney tissue, congenital absence of kidney tissue, malignancies, polycystic kidney disease and urinary tract obstructions.

Occlusive vascular disease could affect either the main renal artery as in RAS or the small, distal renal arterioles as seen in nephrosclerosis. Nephrosclerosis is a progressive occlusion of end arterioles with resulting permanent loss of nephrons. Hypertension accelerates the process of nephrosclerosis. Severe nephrosclerosis will reduce renal blood flow by increasing the peripheral resistance. This may be seen as a flattened arterial pulse curve. Flow studies by duplex US will show increased RI values.

Azotemia may be induced by RAS by reducing blood flow in the ischemic kidney and accelerated nephrosclerosis due to hypertension in the contra-lateral kidney. Nephrosclerosis is recognized on angiography as thin or missing small arteries in the cortical vasculature of the kidney. Older people often have a combination of ARAS and other renal disease. The above combination may explain the poor clinical improvement in spite of technically successful revascularization.

Estimating the renal function may be done for individual renal GFR by combining plasma-clearance with scintigraphic renography. An alternative method is to estimate the total value of GFR by plasma clearance. GFR can be estimated by the

Cockcroft-Gault Equation using serum creatinine, bodyweight and age.[49]

Using only serum creatinine as a measure of renal function is a crude but simple, cheap and commonly used technique. Serum creatinine is affected by the individual´s muscle mass, muscular injury, meat intake and renal function. When GFR is reduced to ≤40% of normal, serum creatinine will be increased.

Flash pulmonary edema and unstable angina

Severe RAS affecting all nephrons (Illustrated by Goldblatt´s one-kidney-one-clip and two-kidney-two-clip models) with accumulation of water and sodium may induce unstable angina and acute pulmonary edema with or without renal failure. It has an acute onset, may be difficult to treat and may be recurrent.

Examples of RAS

The degree of RAS and the number of functioning nephrons will determine the patient's symptoms and signs.

1. Normal renal artery and unobstructed renal blood flow.

2. RAS but unobstructed renal blood flow. Nonsignificant RAS.

3. RAS with reduced blood flow but compensated by autoregulation and thus normal renal perfusion. Neither reduced GFR nor hypertension will be induced. Experiments have shown the canine perfusion pressure to be adequate as long as the acutely reduced systolic BP is above 70 mmHg.[50] The effect of chronic hypoperfusion on the autoregulatory function has not been studied.

4. RAS reducing the perfusion pressure to some nephrons, which will activate the Renin-angio- tensin system and cause hypertension. Due to the renal functional overcapacity, dysfunction will not be seen until more than half of all nephrons are affected.

If >60% of nephrons are under-perfused, azotemia will be the result. This is the case in bilateral severe RAS or in patients with single functioning kidney and severe RAS. In case of accumulation of total body water, flash pulmonary edema may be added to the symptoms.

Microembolization to the kidneys from atherosclerotic plaques induces azotemia. Stenosis of the smaller arteries in the cortex or medulla of the kidneys are seen in nephrosclerosis.

Diagnostic Imaging Modalities to Identify Atherosclerotic Renal Artery Disease

A number of imaging modalities exist to diagnose RAS, ranging from invasive diagnostic arteriography to noninvasive duplex ultrasonography, magnetic resonance arteriography (MRA), computed tomographic arteriography (CTA) and captopril renography. The following table summarizes the advantages and disadvantages.

Screening noninvasive diagnostic modalities to diagnose renal artery stenosis

Modality	Sensitivity (%)	Specificity (%)	Advantages	Disadvantages
Duplex ultrasound	84–98	62–98	Inexpensive; No radiation; Functional and anatomic data; Useful post revascularization	Body habitus limits imaging; Bowel gas limits imaging; Breath holding; Operator dependent; Learning curve; Difficulty detecting polar accessory arteries
CT angiography	89–100	82–100	Rapid; Volumetric acquisition allowing 3D reconstruction; Can detect polar vessels	Motion artifact/breath holding; Radiation exposure; Contrast nephrotoxicity; Timing artifacts; Calcification obstructs luminal interrogation
MR angiography	90–100	76–94	Rapid; No radiation; Can detect polar vessels	Motion artifact/breath holding; Nephrogenic systemic fibrosis with gadolinium exposure in CKD patients; Metallic objects precluding scanning; Resolution artifacts; Susceptibility artifacts; Timing artifacts; Claustrophobia
Captopril nuclear renogram	85–90	93–98	Functional assessment of severity of RAS	High false-positive and -negative rates; Radionuclide exposure; Unsuitable in advanced CKD; False negative in bilateral RAS cases

Duplex ultrasonography is the most commonly available and least expensive or invasive of all the modalities. It provides useful information about the degree of the stenosis, renal size and other associated diseases. It has been shown to have an excellent sensitivity and specificity when performed by experienced operators (up to 97 and 98%, respectively). Significant RAS (>60% diameter stenosis) exists when the peak systolic velocity is greater than 2.0 m/s or the ratio comparing the peak systolic velocity in the renal artery and aorta ratio exceeds 3.5.[8]

Duplex ultrasonography provides an excellent measure to of patients after revascularization by either endovascular or surgical techniques. A recent prospective trial of 100 patients undergoing stenting demonstrated the value of duplex in diagnosing in-stent restenosis with a concordance of 86.6% with contrast angiography.[41] Unlike MRA, which is affected by artifact or scatter produced by the stent, ultrasound transmission is not a problem.[8]

Magnetic resonance arteriography provides an excellent imaging of the abdominal vasculature and anatomy. Gadolinium-enhanced MRA has been shown to be superior to non enhanced studies. It has demonstrated a sensitivity of 90–100% and a specificity of 76–94% for the diagnosis of RAS. However, it is not useful in patients with metallic implants, and the imaging quality outside the research centers has never reproduced the high degrees of sensitivity and specificity initially reported.[42] Its use has further declined due to concerns over gadolinium administration in patients with renal dysfunction.[8]

Computed tomographic arteriography can be performed safely and rapidly with excellent resolution and its use has increased with the decline in MRA imaging. It has several advantages over conventional angiography – less invasive, better visualization of surrounding structures and better 3D resolution, permitting assessment of the anatomy and lesion from multiple angles and planes. However, it does involve radiation exposure and contrast use in patients with potential renal dysfunction. The sensitivity of CTA for detecting RAS ranges from 89–100% and 82–100%.[8]

Captopril nuclear renography is a noninvasive and safe tool for evaluation of renal blood flow and excretory function. In this test, the patient is injected with a technecium-radiolabelled compound usually secreted in the proximal convoluted tubule, such as diethylenetriamine penta-acetic or iodohippurate, and a baseline scintigram and time-activity curve are performed. Three hours later the patient is administered either 25 or 50 mg of captopril and a repeat scintigram and time–activity curve is performed 1 h after this. In most cases of unilateral RAS, the GFR of the stenotic kidney decreases by approximately 30% after administration of captopril. The contralateral kidney tends to increase its GFR. It has a sensitivity of 85–90% and a specificity of 93–98%. Patients with normal renal function and unilateral disease are the ideal candidates for this imaging modality. Its accuracy declines markedly in bilateral disease or advanced renal failure.[8]

Finally, angiography is still considered the gold standard for the diagnosis of RAS, although it is now largely surpassed by noninvasive testing modalities. The performance of angiography now occurs mainly in the setting of patients considered candidates for renal artery percutaneous intervention.[8]

Etiology of renal artery stenosis

The two main causes of RAS are atherosclerosis and FMD. Most common is atherosclerosis (90%), often seen in patients over the age of 50. It usually affects the proximal part of the main renal artery or the aortorenal orifice.

FMD (<10%) is a common expression for several diseases affecting the intima, media or adventitia of the vessel wall. It is primarily seen in females 15- 50 years old, affecting the distal main renal artery or the segmental branches with a

typically beaded, aneurysmal appearance on angiography.[4]

Rare causes are thromboembolic disease, arterial dissection, inflammatory processes in the artery wall (Takayasu disease, polyarteritis nodosa, post radiation), external compression from tumors adjacent to the renal artery (neurofibromatosis, lymphoma), retroperitoneal fibrosis, primary arterial tumor (sarcoma or myxoma) and iatrogenic (restenosis after vascular surgery or angioplasty, vessel injury during nonvascular surgery).

Atherosclerotic Renal Artery Stenosis

Atherosclerosis accounts for approximately 90% of the lesions that obstruct blood flow to the renal arteries. Atherosclerotic renal artery stenosis (ARAS) typically involves the ostium and/or proximal one-third of the renal artery and often the adjacent aorta. However, segmental and diffuse intrarenal atherosclerosis may also be observed, especially in advanced cases.[51]

The prevalence of atherosclerotic RAS is even higher in patients with established coronary or peripheral artery atherosclerosis, with prevalence rates ranging from 20 to 30% in retrospective series, and up to 50–70% in several necropsy series.[8]

In 319 patients from six studies with documented atherosclerosis in other arterial beds, 44% had bilateral RAS. In several studies of aorto–iliac or aortic aneursymal disease, the prevalence of significant (>50% diameter stenosis) RAS has been reported in 15–59% of patients, with 11–45% having bilateral disease.[52,53]

In a study from Duke University, 3987 patients underwent abdominal

aortography at the time of coronary arteriography to screen for RAS.[54] Of this cohort, 191 (4.8%) had stenosis of at least 75% or greater and 0.8% had bilateral disease.

In another series from the Mayo Clinic, RAS of greater than 50% diameter angiographically was described in 19.2% of hypertensive patients undergoing cardiac catheterization, with severe (>70%) disease found in 7%, and bilateral RAS in 3.7%.[45]

In addition, RAS is a marker of more extensive vascular disease. A study of 346 patients with abdominal aortic aneurysms or lower extremity peripheral artery disease found that 28% had significant RAS at autopsy.[55]

Of those with RAS, 58% had clinically overt coronary artery disease, while in those without RAS the incidence of coronary disease was only 39%. In another study, the presence of RAS was associated with increasing severity of coronary disease, from one-vessel to three-vessel disease, with three-vessel disease present in 39% of patients with RAS compared with 10.7% of patients without RAS.[8]

Renal artery stenosis is also prevalent in patients with chronic kidney disease, where it is reported in the US Medicare population to be 5.5% compared with 0.5% of the overall population. The burden of atherosclerotic vascular disease in this group, the cohort of patients with RAS and chronic kidney disease had a mortality rate 2.6-times greater than the general population.[8]

Other series have estimated the prevalence of unsuspected significant RAS in patients with renal insufficiency up to 25%.[56] Of the population beginning dialysis, there has been an increase in the proportion of end-stage renal disease (ESRD)

patients with prior RAS from 7.1% in 1996 to 11.2% in 2001.

This is further supported by Scoble et al.,[57] where 14% of new dialysis referrals for ESRD were due to underlying RAS in this prospective series.

It is also known that atherosclerotic RAS, if untreated, can progress to occlusion and renal atrophy can occur in the setting of severe stenotic disease without arterial occlusion. In several series, progression of severe stenosis to occlusion occurs in 10–40%.[8]

Global vascular risk factor modification and appropriate medical therapy with antiplatelet therapy, statin medications and antihypertensive agents remain the first line of management of atherosclerotic renal artery disease, although a study proving this concept has never been performed. Renovascular hypertension, ischemic nephropathy resulting in ESRD and cardiac destabilization syndromes are the potential clinical consequences of atherosclerotic RAS.[8]

It is demonstrated that the ability of percutaneous renal revascularization to improve blood pressure control and preserve or delay deterioration in renal function, recent randomized prospective trials have been negative, leading to the current dilemma regarding the optimal management of RAS.[8]

In addition, while renal arteriograghy is the accepted gold standard for diagnosing renal artery disease, it is well established that percentage angiographic diameter stenosis is an insensitive marker to identify patients who will ultimately benefit from revascularization. Prior work has established that, based on angiographic stenosis alone, up to 30–40% of patients will not demonstrate a benefit from revascularization, and this may be partly responsible, along with study design,

for the negative results seen in the randomized studies.[8]

The complex relationship between RAS severity and the impact on renal function remains poorly understood. The interplay of renal blood flow, neurohormonal activation, and the renal macro- and micro-vasculature have resulted in disappointing long-term results of renal artery interventions, despite excellent acute procedural results.[8]

The prevalence of ARAS increases with advancing age and with the presence of cardiovascular risk factors. Among patients with hypertension, ARAS is observed in only 1% to 6%, whereas the incidence of ARAS is more than 30% in patients undergoing cardiac catheterization and more than 50% in elderly patients with known atherosclerotic disease.[51]

In a study[28] of 170 patients with ARAS who were followed up with serial duplex scans, the cumulative incidence of disease progression was 51% 5 years after diagnosis.

In a pooled review of 5 trials using serial arteriography, 49% of all renal arteries examined demonstrated progression of stenosis during follow-up ranging from 6 to 180 months.[35]

Atherosclerotic renal artery stenosis results in a progressive loss of renal mass and function over time. In a subgroup of patients with renovascular hypertension and 60% obstruction, renal atrophy occurred in 21%.[51]

Historical data suggest that up to 27% of patients with ARAS will develop chronic renal failure within 6 years.[51]

A prospective angiographic study[44] revealed that ARAS was the cause of end-stage renal disease in 14% of patients in whom dialysis was newly initiated; thus, early detection and appropriate treatment of ARAS could have important economic consequences.

The presence of ARAS is known to predict adverse coronary events. In the Cardiovascular Health Study, patients diagnosed as having ARAS had a higher incidence of hospitalization for angina, myocardial infarction, and coronary revascularization.[51]

In a cohort of patients with ARAS detected at the time of coronary angiography, the 4-year survival rate was 65% for those with vs 86% for those without ARAS.[58]

Pathophysiology

The pathophysiology of hypertension in patients with RAS due to FMD was well-described in the seminal work on animal models of hypertension by Goldblatt[13] in the 1930s. This model describes renin-dependent hypertension in patients with FMD, but it does not adequately describe the etiology of hypertension in patients with ARAS, in whom the mechanisms of hypertension are more complex.[51]

Well-established animal studies have clearly shown that decreased renal artery perfusion leads to a cascade of events, starting with the production of renin. Renin promotes conversion of angiotensinogen to angiotensin I, which is converted to angiotensin II by angiotensin I converting enzyme, which also inactivates kinins that promote hypotension. The largest store of angiotensin I converting enzyme is found in the pulmonary vasculature, where it plays an important role in the

regulation of systemic blood pressure.[51]

In addition to causing hypertension by being directly vasoconstrictive, angiotensin II promotes hypertension by increasing total blood volume through its effect on aldosterone and by potentiating the vasoconstrictor response to circulating norepinephrine.[51]

Goldblatt's[13] work has been expounded on to suggest 3 phases of renovascular hypertension as demonstrated in animal models. In stage I (acute occlusion) and stage II (occlusion for days/weeks), the blood pressure and plasma renin/angiotensin II levels are elevated, and elimination of the obstruction leads to normalization of both blood pressure and plasma renin/angiotensin II levels. In stage III, the occlusion is prolonged for months, plasma renin/angiotensin levels are *no longer elevated*, and elimination of the obstruction does *not* lead to normalization of blood pressure.[51]

Although these stages were described in animal models, stage III may reflect hypertension seen in patients with ARAS who do not appear to have strict renin-dependence. Patients with ARAS and low renin/angiotensin II levels may have improvement in hypertension after renal revascularization, but the results are unreliable. In summary, activation of the sympathetic and central nervous systems, increasing total blood volume via aldosterone, and the direct pressor effects of angiotensin II in the setting of ARAS are thought to contribute to hypertension.[51]

It is suggested that ARAS results in cardiac morbidity that is disproportionate to the degree of hypertension. Multiple pathways account for this because angiotensin II has been associated with a range of proinflammatory and

toxic cardiovascular effects, including myocardial fibrosis, arterial medial hypertrophy, smooth muscle cell proliferation, endothelial cell dysfunction, and plaque rupture. Renin has been associated with vasculotoxic and nephrotoxic effects. Oxidative stress has been implicated in the ischemic and hypertensive parenchymal renal injury related to ARAS.[51]

Clinical evaluation and screening

Clinical clues to the presence of ARAS are listed in Table.[59]

1. Onset of hypertension before age 30 y or severe hypertension after age 55 y
2. Accelerated, resistant, or malignant hypertension
3. Development of new azotemia or worsening renal function after administration of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker
4. Unexplained atrophic kidney or size discrepancy >1.5 cm between kidneys
5. Sudden, unexplained pulmonary edema
6. Unexplained renal dysfunction, including patients starting renal replacement treatment
7. Multivessel coronary artery disease or peripheral arterial disease
8. Unexplained congestive heart failure or refractory angina

On the basis of the American Heart Association (AHA) guidelines, screening and revascularization should be considered in patients who present in the setting of

the clinical scenarios outlined.[9,60]

The Joint National Committee stated that more extensive testing in patients with identifiable causes of ARAS is typically not necessary unless blood pressure control is not achieved while the patient is receiving maximal antihypertensive therapy.[61]

American Heart Association Recommendations for Revascularization of Atherosclerotic Renal Artery Stenosis (ARAS)[9]

Asymptomatic stenosis

- Percutaneous revascularization can be considered for treatment of an asymptomatic bilateral or solitary viable kidney with hemodynamically significant ARAS
- Usefulness of percutaneous revascularization of asymptomatic unilateral hemodynamically significant ARAS in a viable kidney is not well established and is currently clinically unproved

Hypertension

- Percutaneous revascularization is reasonable for patients with hemodynamically significant ARAS and accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with unexplained unilateral small kidney, and hypertension with intolerance to drug treatment

Preservation of renal function

- Percutaneous revascularization is reasonable for patients with ARAS and

progressive chronic kidney disease with bilateral ARAS or ARAS of a solitary functioning kidney

- Percutaneous revascularization can be considered for patients with ARAS and chronic renal insufficiency with unilateral ARAS

Effect of ARAS on congestive heart failure and unstable angina

- Percutaneous revascularization is indicated for patients with hemodynamically significant ARAS and recurrent, unexplained congestive heart failure or sudden, unexplained pulmonary edema

- Percutaneous revascularization is reasonable for patients with hemodynamically significant ARAS and unstable angina

Diagnosis

Magnetic resonance angiography (MRA), helical computed tomographic angiography (CTA), Doppler ultrasonography, renal scintigraphy (ie, captopril scan), invasive angiography, peripheral renin levels, and renal vein renin sampling have all been used as screening tests to detect ARAS. Renal vein renin sampling, peripheral renin levels, and renal scintigraphy are not generally recommended for ARAS screening because of their low sensitivity and low specifity.[51]

For an imaging study to be considered optimal, the following 4 objectives must be met: (1) ARAS must be detected and characterized on the basis of anatomic and hemodynamic severity; (2) anatomic consequences of ARAS on the artery itself and on the kidney must be assessed (eg, severe ARAS can result in poststenotic dilatation of the artery, which can be detected by CTA and MRA, and also in

shrinkage of the renal parenchyma, with the kidney being <8 cm); (3) functional and cellular consequences of ARAS on the kidney must be evaluated (eg, functional data can be obtained via the abnormal intrarenal transit of gadolinium during magnetic resonance imaging with use of captopril, future studies are assessing the ability of diffusion-weighted magnetic resonance imaging to determine the cellular viability of renal parenchyma tissue in patients with chronic kidney disease; and (4) criteria associated with renal impairment related to renovascular disease must be identified).[51]

Ultrasonography

Ultrasonography is widely available, safe, and inexpensive and consequently is typically the first imaging study used to detect ARAS. However, results are operator dependent, with accuracy ranging from 60% to 90%; the entire length of the renal artery or an accessory renal artery can be overlooked, and thus the stenotic lesion will be missed.[51]

Information on size of the kidneys, renal functional reserve, and renal resistive index (RRI [defined as peak systolic velocity – end-diastolic velocity/peak systolic velocity]) can be obtained with ultrasonography.[51] A high renal artery end-diastolic velocity (>90 cm/s) and low RRI (<75-80) indicate no microvascular disease or increased resistance.[51]

Spectral broadening and increased velocity on ultrasonography are markers of hemodynamically significant stenoses. For example, a renoaortic velocity ratio (defined as the renal artery peak systolic velocity/aortic peak systolic velocity) greater than 3.5 has been correlated to 60% stenosis, whereas a renal artery peak

systolic velocity greater than 150 cm/s correlates to 50% stenosis, and a velocity greater than 180 cm/s correlates to 60% stenosis.[51]

Severe stenoses can produce tardus-parvus spectral changes on Doppler ultrasonography, revealed as a slowed systolic acceleration with a decreased resistive index. Quantitative criteria proposed for the diagnosis of distal stenoses include blunting of early systolic peak acceleration (<3 m/s^2), an acceleration index greater than 4 m/s^2, increase in time to systolic peak (>0.07 s), or greater than 5% difference in RRI between kidneys. However, because of the difficulty in interpretating these complex waveforms, these criteria are seldom used.[51]

Computed Tomographic Angiography

The possibility of 3-dimensional reconstructions has made CTA an important tool in the diagnosis of ARAS. Because CTA involves use of ionizing radiation and iodinated contrast medium, it is contraindicated in patients with contrast allergy. Patients with impaired renal function can develop contrast-induced nephropathy if iodinated contrast is used, but generous fluid hydration before contrast administration can effectively prevent this complication. For detection of ARAS, the sensitivity of CTA is 94%; the specificity varies between 60% and 90%.[51]

Compared to MRA, CTA can detect small accessory renal arteries because of its high spatial resolution. It is also preferred for patients who have implanted devices, for patients with limited breath-hold capacity (requiring shorter acquisition times), and for patients with claustrophobia. However, CTA has less specificity than MRA for detecting hemodynamically significant ARAS; it cannot be used safely in patients with borderline renal dysfunction because of the necessity of iodinated

contrast agents; images obtained with CTA are difficult to interpret in heavily calcified arteries, and CTA requires use of ionizing radiation.[51]

Magnetic Resonance Angiography

Magnetic resonance angiography has a reported sensitivity and specificity of 90% to 100% and does not require use of iodinated contrast or radiation. Gadolinium-based contrast medium should be avoided in patients with moderate to end-stage renal failure because of the risk of nephrogenic systemic fibrosis. Additionally, MRA should not be used in patients with certain implanted devices (ie, pacemakers, defibrillators, cochlear implants, and spinal cord stimulators) or in claustrophobic patients. Unlike CTA, MRA has no calcification artifact, neither iodinated contrast medium nor radiation is used, and contrast reaction rates are lower.[51]

Angiography

Invasive renal arteriography is helpful in evaluating ARAS. In addition to assessing the severity of ARAS, angiography can detect intrarenal vascular abnormalities and anatomic abnormalities of the kidneys, renal arteries, and aorta. Digital subtraction angiography improves contrast resolution and may decrease the volume of contrast needed to as little as 15 mL. However, because renal angiography is invasive, there are risks associated with arterial puncture and manipulation of the catheter/wire, which can result in arterial trauma, spasm, or thromboembolic phenomenon. In patients with renal impairment or contrast allergy, carbon dioxide can be used as a nonnephrotoxic contrast agent.[51]

The early work by White et al.[62] established that there is substantial intra-

and interobserver variability in the visual estimation of coronary stenoses, which likely also applies to the visual estimation of ARAS. Therefore, relying solely on angiography to visually estimate the severity of ARAS is suboptimal, and adjunctive tools should be used to determine whether renal ischemia is present.

Translesional pressure gradients can be measured across areas of stenosis to determine hemodynamic significance (if there is doubt) before performing therapeutic procedures such as percutaneous transluminal renal angioplasty (PTRA) or stenting.[51]

In a small case series, Mangiacapra et al.[63] measured translesional pressure gradients using papaverine and dopamine to induce renal hyperemia in 53 consecutive patients before PTRA. They found that patients with the most substantial improvement in hypertension were those with a translesional gradient greater than 20 mm Hg (corresponding to a distal-proximal pressure ratio of 0.79 as the optimal cutoff).

Diagnostic Dilemmas

The cutoff point beyond which revascularization is advised has been a matter of concern and not even conventional angiography (gold standard) is able to accurately help decision making regarding revascularization. In general more than 50% luminal narrowing is taken significant stenosis warranting treatment, but stenosis is hemodynamically important only if the diameter is reduced by more than 60% or by more than 70%. There is no correlation is found between the BP response to treatment and the severity of RAS at base line. Reduction of renal blood flow sufficient to reduce kidney size and stimulate renin release may develop despite

preserving normal overall levels of both cortical and medullary tissue oxygenation. This is because kidney overall receives more blood than needed strictly for its metabolic activity. Anatomically and physiologically significant RAS is defined as >70-80% of cross-sectional area stenosis of either renal arteries and >15-25 mmHg gradient across the lesion, respectively measured with a less than or equal to 5 Fr catheter or pressure wire. Hence it is suggested that, renal angiography along with coronary angiography particularly in high risk patients with above clinical conditions.[64]

METHODOLOGY

The present study was done in the Department of cardiology and Nephrology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Study design

The study design was a one year cross sectional study.

Study period and duration

This study was conducted for the period of one year from January 2014 to December 2014.

Source of Data

Patients presenting with coronary artery disease and undergoing coronary angiography at Department of Cardiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the study period were enrolled in the study.

Sample size

A total of 480 patients suspected to have coronary artery disease fulfilling the selection criteria were selected for the study.

Sampling procedure

The sample size was calculated using the following formula.

$n = z\alpha^2 p\ q / d^2$

Where, $z\alpha = 1.96$

P = Prevalence of the disease

q = (100-p)

d = Absolute error which was considered as 4.

Therefore,

$n = 1.96 \times 13^{65} \times 87 / 4^2$

n= 275

Hence a minimum sample size of 275 patients undergoing coronary angiography was considered. However, during the study period, 480 patients satisfied the selection criteria hence were enrolled.

Selection criteria

Inclusion

- Patients who are undergoing coronary angiography.
- Asymptomatic regarding kidney disease with serum creatinine less than 1.5 mg/dl

Exclusion

- Symptomatic renal dysfunction or patients whose serum creatinine is >1.5 mg/dL.
- Patients who had undergone nephrectomy in the past.
- Patients who were known cases of renal artery stenosis.

Ethical clearance

Prior to the commencement, the ethical clearance was obtained from Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

The patients willing to participate in the study were enrolled after obtaining a written informed consent (Annexure I).

Method of collection of data

Demographic data such as age, sex were noted. Patients were interviewed and history of smoking, diabetes, hypertension, hypercholesterolemia, serum urea and serum creatinine were recorded. Physical examination was conducted for anthropometry, vitals (pulse rate, blood pressure and respiratory rate) and clinical signs followed by systemic examination. These findings were recorded on a predesigned and pretested proforma (Annexure II).

Investigations

The patients were evaluation for following laboratory markers.

- Serum urea
- Serum creatinine
- Fasting lipid profile
- Urine routine
- CoronaryAngiography
- Renal angiogram

Outcome variables

Body mass index

A thorough clinical examination was conducted. Height and weight was recorded and body mass index was calculated based on formula;

$$\text{Body Mass Index} = \frac{\text{Weight (Kg)}}{\text{Height}^2 \text{ (m)}}$$

Body mass index was classified according to Overweight and obesity by BMI in adult Asians as below.[66]

Classification	BMI (Kg/m^2)	Risk of co-morbidities
Underweight	< 18.5	Low (But increased risk of other clinical problems
Normal range	18.5 to 22.9	Average
Overweight	≥ 23	
At risk	23.0 to 24.9	Increased
Obese I	25.0 to 29.9	Moderate
Obese II	≥ 30.0	Severe

Coronary artery disease

Patients were evaluated for the presence of coronary artery disease and number of vessels involved.

Renal artery disease

Selective Renal angiography was done in patients who underwent coronary angiography. Severity of lesion was graded according to visual estimation of extent of luminal diameter narrowing. An angiographically significant renal artery disease was defined as >70% luminal diameter narrowing of a major renal artery.

In patients with renal artery disease, they were evaluated for the laterality, percentage of block and the presence of risk factors.

Statistical analysis

The data obtained was coded and entered into Microsoft Excel Worksheet. The data was analysed using SPSS version 20.0 statistical software. The categorical data was expressed in terms of rates, ratios and proportions and comparison was done using chi-square test. The continuous data was expressed as mean ± standard deviation (SD). A probability value (‘p’ value) of less than or equal to 0.05 was considered as statistically significant.

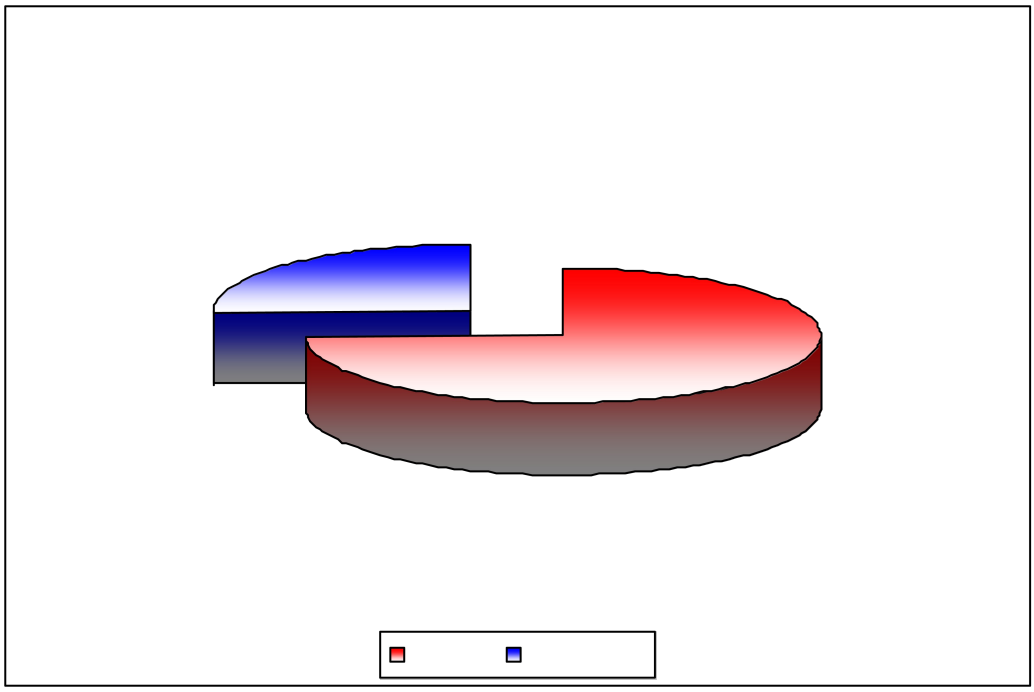
RESULTS

One year cross-sectional study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2014 to December 2014. A total of 480 patients who underwent coronary angiography with normal renal functions in the Department of Cardiology were evaluated for the renal artery disease.

The data obtained was analysed and final results and observations were tabulated as below.

Table 1. Sex distribution of the study population

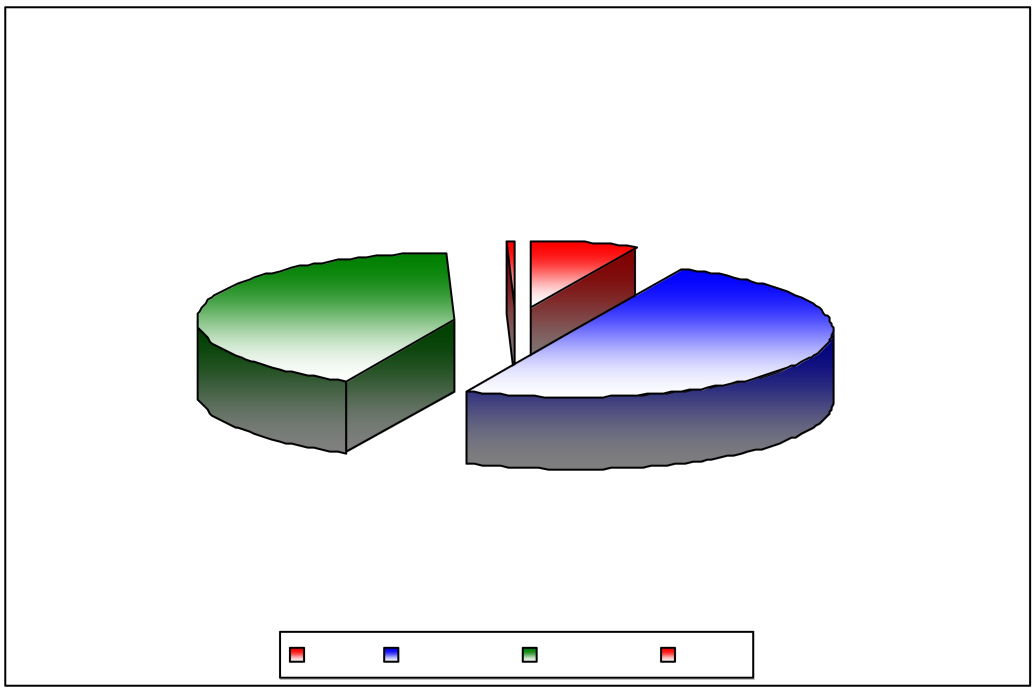
Sex	Distribution (n=480)	
	Number	**Percentage**
Males	359	74.79
Females	121	25.21
Total	**480**	**100.00**



In the present study 74.79% of the patients were males and 25.21% were females. The male to female ratio was 2.96:1.

Table 2. Age distribution of the study population

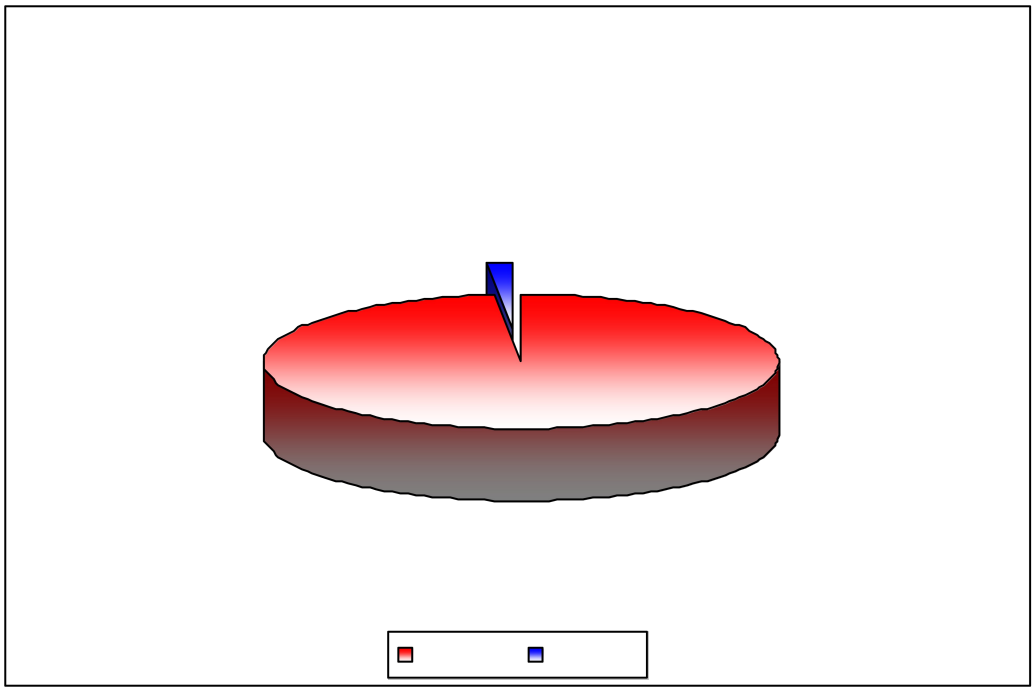
Age group (Years)	Distribution (n=480)	
	Number	**Percentage**
≤ 40	32	6.67
41 to 60	241	50.21
61 to 80	205	42.71
> 80	2	0.42
Total	**480**	**100.00**



In the present study 50.21% of the patients were aged 41 to 60 years and 42.71% were aged 61 to 80.

Table 3. Distribution of patients with coronary artery disease

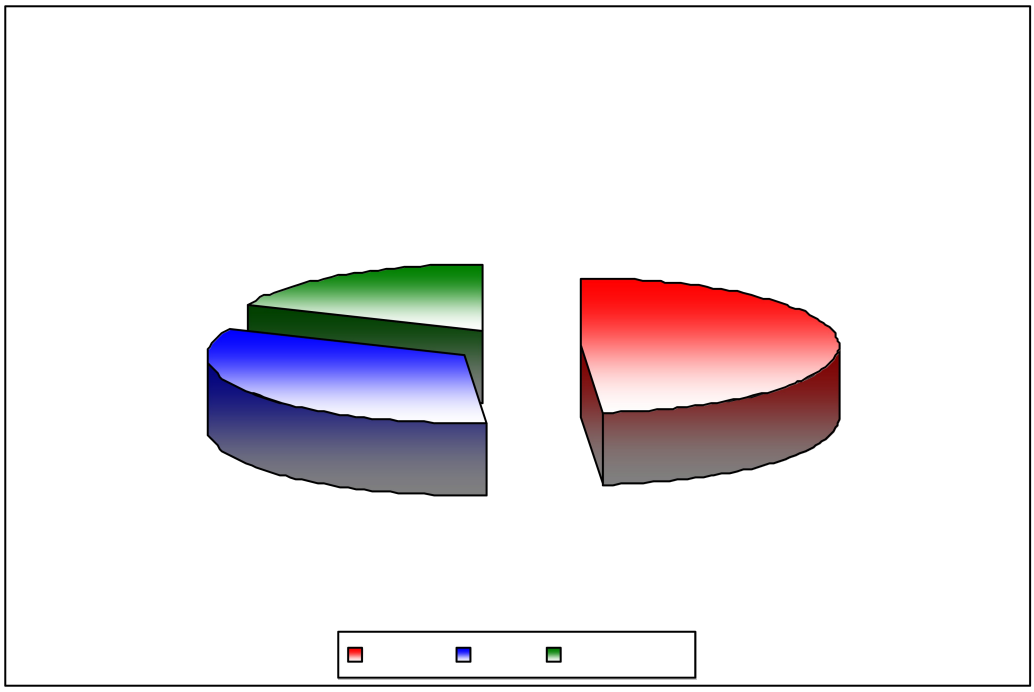
Coronary artery disease	Distribution (n=480)	
	Number	**Percentage**
Present	472	98.33
Absent	8	1.67
Total	**480**	**100.00**



In the present study of 480 patients enrolled coronary artery disease was present in 472 (98.33%) of the patients. The rest 8 patients had NSTEMI and hence included.

Table 4. Distribution of patients according to the involvement of Right, Left and Bilateral Renal arteries.

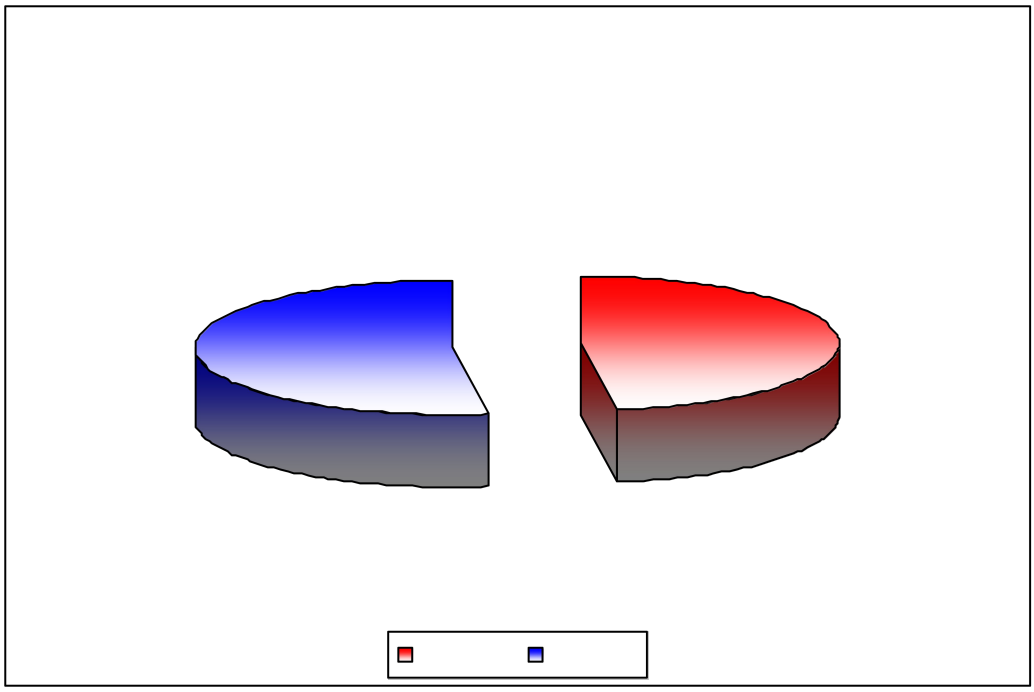
Side	Distribution (n=229)	
	Number	**Percentage**
Bilateral	111	48.48
Right	76	33.18
Left	42	18.34
Total	**480**	**100.00**



In our study 48.48% of patients had Bilateral Renal artery involvement. 33.18% had involvement of Right Renal artery and 18.34% patients had involvement of Left Renal artery.

Table 5. Frequency of patients with involvement of renal artery

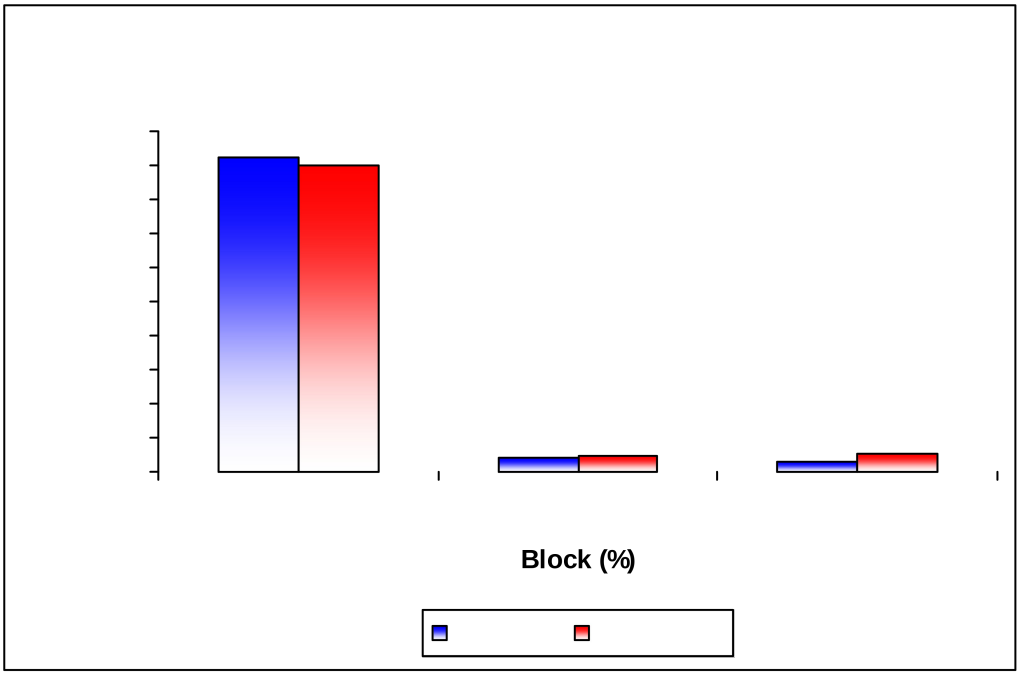
Involvement of renal artery	Distribution (n=480)	
	Number	**Percentage**
Present	229	47.71
Absent	251	52.29
Total	**480**	**100.00**



In the present study 47.71% of the patients had involvement of renal artery.

Table 6. Distribution of patients according to side and percentage block of Renal arteries on each side

Block (%)	Left side (n=480)		Right Side (n=480)	
	Number	**Percentage**	**Number**	**Percentage**
< 50	444	92.50	433	90.21
50 to 69	21	4.38	22	4.58
70 or more	15	3.13	25	5.21
Total	**480**	**100.00**	**480**	**100.00**

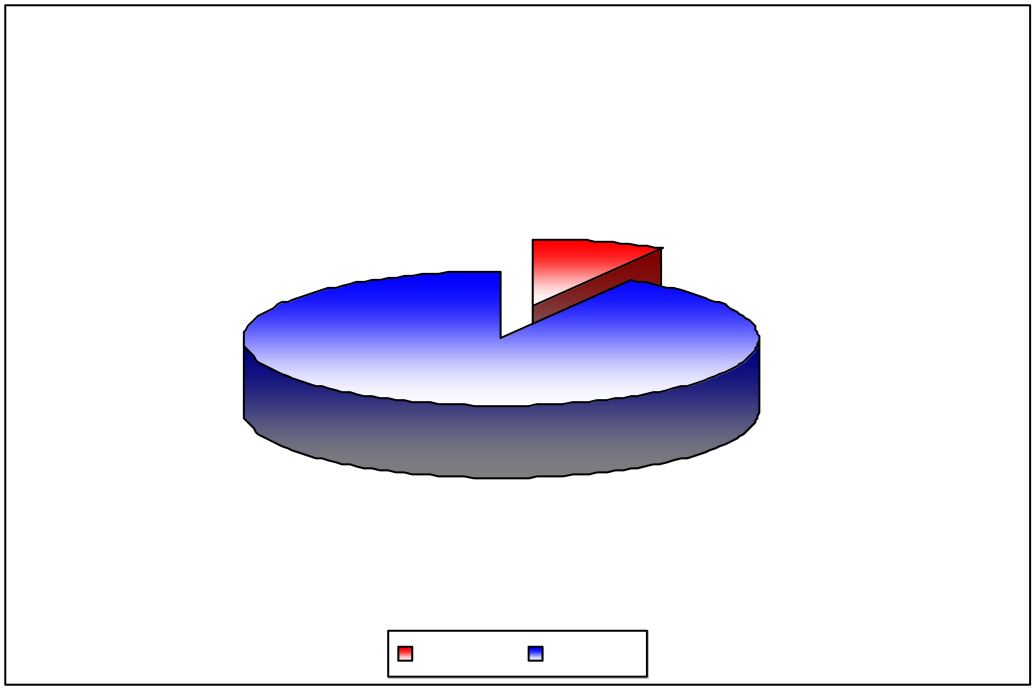


In this study majority of the most of the patients had <50% stenosis of right (92.5%) and left (90.21%) renal arteries while 4.38% of the patients with left renal artery stenosis had 50 to 69% block and 4.58% had right renal artery block. Left renal artery stenosis of >70% was noted in 3.13% of the patients and 5.21% of the patients had Right renal artery stenosis.

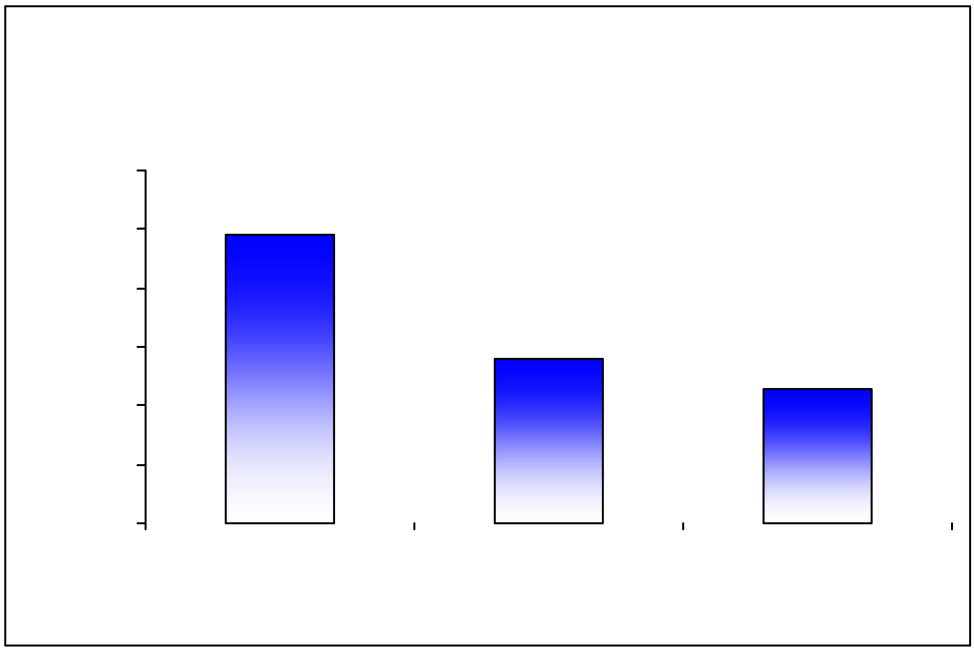
Table 7. Frequency of Significant renal artery disease (>70% stenosis)

Renal artery disease	Distribution (n=480)	
	Number	**Percentage**
Present	40	8.33

Absent	440	91.67
Total	**480**	**100.00**



In the present study incidence of significant Renal artery disease was noted as 8.33%.

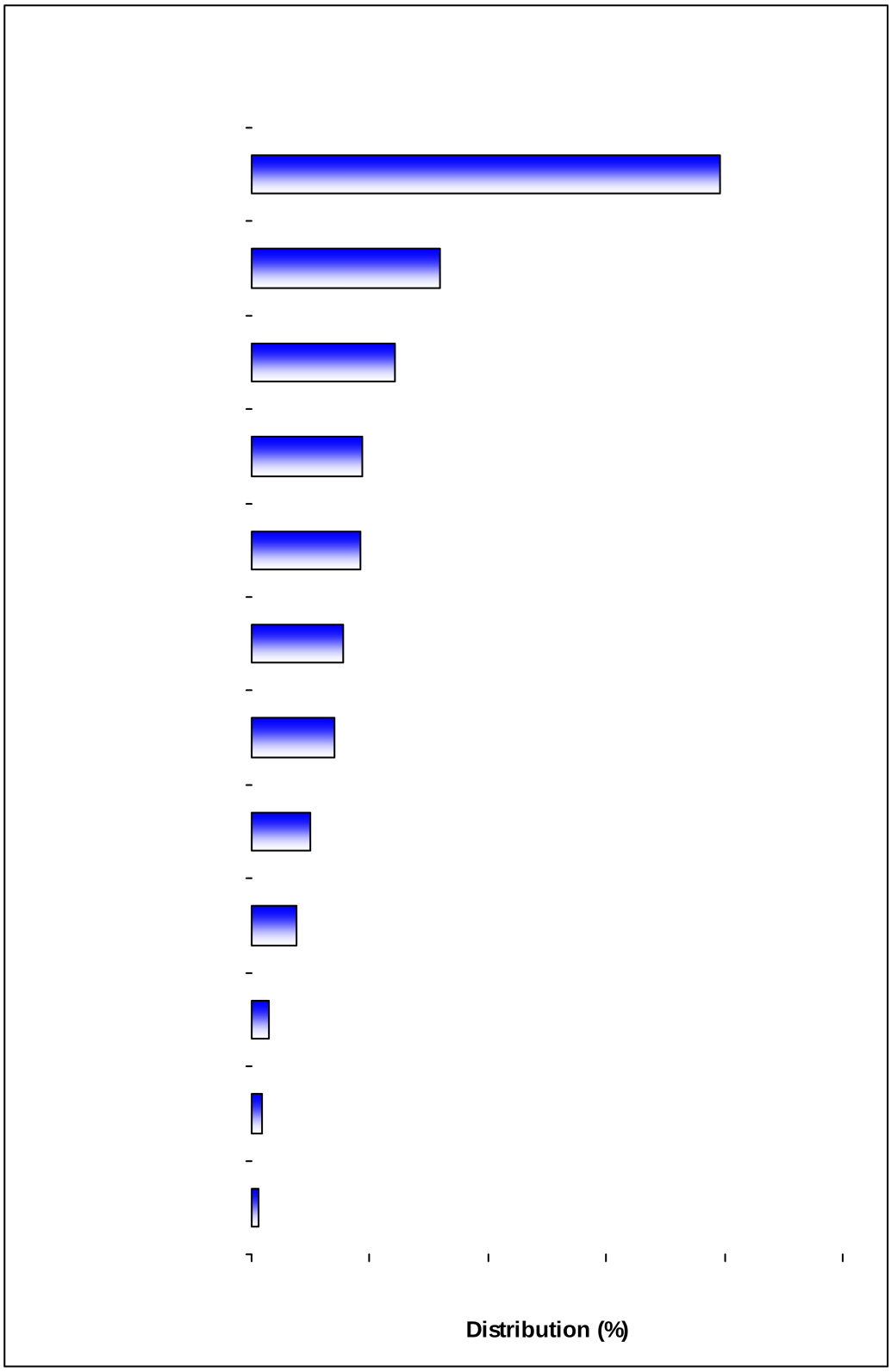


In this study 49.15% of the patients had single artery disease while double and triple artery disease was noted in 27.97% and 22.88% of the patients.

Table 8. Characteristics of the study population

Variable	Mean		Median	Range	
	Mean	SD		Minimum	Maximum
Age (Years)	57.59	10.56	57.5	22	85
Body mass index (Kg/m2)	23.60	1.48	23.53	14	32
Respiratory rate (/Minute)	15.20	1.33	15	6	20
Systolic BP (mm Hg)	131.43	16.71	130	100	170
Diastolic BP (mm Hg)	79.28	8.28	80	50	100
Total cholesterol (mg/dL)	168.38	26.44	170	79	281
LDL (mg/dL)	86.64	23.06	80	25	212
HDL (mg/dL)	34.97	6.43	36	10	48
Triglycerides (mg/dL)	135.72	26.20	136	51	352
RBS (mg/dL)	134.33	56.09	110	59	473

The clinical and lipid profile of the study population is as depicted in table 8.


Distribution (%)

The above table represents risk factor of all the study patients. In the present study the most common risk factor was low HDL which was noted in 79.17% of all the patients. The next common risk factors were history of hypertension (31.88%), diabetes mellitus (24.28%), smoking (18.75%), raised triglyceride levels (18.54%), Hyperglycemia (15.42%), overweight (13.96%) and raised cholesterol (10%). Few patients had higher LDL (2.8%), history of cerebrovascular accident (1.25%) and alcohol consumption (1.88%).

Table 9. Association of sex with significant asymptomatic renal artery disease

Sex	Total (n=480)	Renal artery disease (n=40)
Male	359	27 (7.52%)
Female	121	13 (10.74%)

p=0.267

In this study 74.19% of the patients were males and 25.21% were females. The male to female ratio was 2.96:1. The incidence of significant renal artery disease was 7.52% in males compared to 10.74% in females. However this difference was statistically not significant (p=0.267).

Table 10. Association of age with significant asymptomatic renal artery disease

Age group	Total (n=480)	Renal artery disease (n=40)
≤ 40	32	4 (12.5%)
41 to 60	241	19 (7.88%)
61 to 80	205	17 (8.29%)
> 80	2	0 (0%)
Total	**480**	**40 (8.33%)**

p=0.671

In the present study peak incidence of significant asymptomatic renal artery disease was in the age group of 61 to 80 years (8.29%) followed by 41 to 60 years (7.88%). However the incidence of significant renal artery disease in different age groups was almost comparable (p=0.671).

Table 11. Distribution of patients according to the number of coronary arteries involved and its association with renal artery disease

Number of arteries	Total (n=480)	Renal artery disease (n=40)
Single artery	232 (49.15%)	5 (2.76%)
Double arteries	132 (27.97%)	10 (7.57%)
Triple arteries	108 (22.88%)	25 (23.15%)
Absent	8 (1.67%)	0 (0%)

p<0.001

In this study it was observed that, significantly higher number of patients with triple artery disease had renal artery involvement (23.15%) (p<0.001).

Table 12. Association of traditional risk factors with significant asymptomatic renal artery disease

Number of arteries	Total (n=480)	Renal artery disease (n=40)	p value

HDL	380 (79.17)	29 (7.63%)	0.471
Hypertension	153 (31.88%)	16 (10.46%)	0.249
Diabetes mellitus	117 (24.28%)	10 (8.55%)	0.923
Smoking	90 (18.75%)	5 (5.56%)	0.290
Triglycerides	89 (18.54%)	10 (11.24%)	0.272
Hyperglycaemia	74 (15.42%)	8 (10.81%)	0.402
Overweight	67 (13.96)	5 (7.46%)	0.134
Total cholesterol	48 (10%)	6 (12.5%)	0.198
Dyslipidemia	37 (7.71%)	2 (5.41%)	0.385
LDL	10 (2.8%)	1 (10%)	0.585
CVA	6 (1.25%)	1 (16.67%)	0.408
Alcohol consumption	9 (1.88%)	0 (0%)	0.454

However none of the risk factors were associated with significant renal artery disease ($p>0.050$).

DISCUSSION

Atherosclerosis remains the major cause of death and disability. Moreover current predictions estimate that by the year 2020 cardiovascular diseases, notably atherosclerosis will become leading cause of total disease burden. An increased prevalence of renal arterial disease, including stenosis and calcification, has been noted in persons with coronary artery disease and systemic vascular disease. Among those without clinically apparent cardiovascular disease (CVD), coronary artery calcification (CAC), a marker of subclinical CVD, has been established as a risk factor for incident cardiovascular events and mortality.[67] This study was sought to determine the incidence of renal artery disease in patients who had coronary artery disease with normal renal functions and to find its association with other clinical variables.

The present one year cross-sectional study was carried out under the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 480 patients undergoing coronary angiography in the Department of Cardiology were ascertained for the asymptomatic renal artery disease from January 2014 to December 2014

In the present study out of 480 patients who underwent coronary angiography, majority of the patients (98.33%) had coronary artery disease, rest of the 8 eight patients had NSTEMI. Nearly half of the study population (49.15%) was affected with single artery involvement while double and triple arteries were involved in 27.97% and 22.88% of the patients respectively. The characteristics of

renal artery disease with renal artery involvement in this study 48.48% of patients had Bilateral Renal artery involvement. 33.18% had Right Renal artery and 18.34% Left Renal artery involvement.

Considering the significant blockage as ≥70%, the incidence of significant renal artery disease was 8.33%.

As reported, in Europe and America the prevalence of RAS(defined as stenosis ≥50%) has been reported to be 13.5 to 18% among all patients undergoing routine cardiac catheterization; where as other studies in Asian population reported a lower incidence of RAS as low as 3.1% to 7%.[68,69]

Most recent studies describe a prevalence of RAS of 14–29% in individuals with coronary artery stenosis and 10% in individuals with normal coronary arteries.[70] Atherosclerotic RAS is one aspect of a multiterritory (systemic) atherosclerotic disease.

In a seminal study, Harding et al.[44] found an 11% prevalence of RAS (defined as stenosis ≥50%) in an unselected cohort of 1,235 patients. Subsequent reports[42,43] derived from small series of clinically (rather than systematically) selected cohorts observed prevalence rates of 11% and 18%, respectively. These reports focused on the relationship between coronary disease burden and RAS prevalence but were limited by the absence of protocol-based patient selection and characterization.

Recently a study by Goel P. et al.[71] reported overall prevalence of RAS as 6.1% in population undergoing CAG and/or PAG for suspected CAD. Another study by Joshi H. et al.[72] in India reported incidence of 6.11%. The incidence of renal

artery disease observed in the present study was comparable with the studies by Goel P. et al.[71] and Joshi H. et al.[72] A similar study by Liang F. et al.[73] carried out diagnostic evaluations of coronary arteriography and renal artery angiography performed during the same procedure; the patients who were proposed for CABG in terms of CAD anatomy and clinical manifestation were enrolled. RAS was evaluated and a diameter stenosis of ≥50% was considered as significant RAS; significant RAS patients were divided into five groups. A total of 151 patients were enrolled, and RAS (≥50% stenosis in either or both renal arteries) was identified in 47.02% (71/151) patients. Unilateral RAS ≥50–70% was identified in 16.6% (25/151) patients, unilateral RAS ≥70% in 4.6% (7/151) patients, bilateral RAS ≥50–70% in 7.9% (12/151) patients, one-renal-artery stenosis ≥50–70% and contralateral RAS ≥70% in 7.9% (12/151) patients, and bilateral RAS ≥70% was in 9.9%(15/151) patients.

In this study maximum patients that is, 49.15% had single artery disease. Double and triple artery blockage was noted in 27.97% and 22.88% respectively. The incidence of renal artery disease was significantly high in patients with triple vessel disease (23.15%) compared to double (7.57%) and single (2.76%) artery involvement ($p<0.001$). These findings propose strong association between the extent of coronary arteries involved and risk of renal artery disease that is as the involvement of arteries increases chances of renal artery disease increase. Liang F. et al.[73] in 2012 also reported that, the frequency of ARAS increased in proportion with the number of stenotic coronary arteries; the incidence of ARAS was 10%, 15.8%, and 18.1% in patients with single-vessel, two-vessel, and three-vessel CHD, respectively. It infers that treatment of vascular risk factors would result in better

management of the widespread atherosclerotic disease in this high-risk population. Danesh et al,[74] reported that, two and 3-vessel coronary disease were reported as an independent predictor of significant RAS. In contrast a study by Goel P. et al.[71] India showed statistically insignificant relationship with three vessels CAD with RAS.

In this study majority of the patients (74.19%) were males and male to female ratio of 2.96:1. These findings suggest that, coronary artery disease is common in males. Further no statistically significant association was noted between sex and renal artery disease as almost equal number of males (7.52%) and females (10.74%) had renal artery disease (p=0.267). These findings suggest that, renal artery disease affects equal number of men and women.

The strong association of renal artery disease with CAD in female gender extends previous observations. Persistence of female gender in the multivariate model after adjustment for age and other factors is intriguing and remains unexplained. Moreover, data suggest a gender-specific distribution of atherosclerosis characterized by greater coronary disease burden among men, greater RAS burden among women, and similar rates of clinically evident carotid and peripheral arterial disease in both genders. Heart failure with preserved systolic function has also recently been shown to be strongly associated with female gender. The pathogenetic basis for this association, however, remains enigmatic.[70]

A study observed higher incidence of RAS in women compared with men, which we observed, with a consequently greater burden of systolic hypertension, ischemic renal dysfunction, LV and vascular hypertrophy, and sodium retention could account, at least partly, for this observation.[70]

It is reported that, older age is strongly and independently associated with RAS, implying delayed development or slower progression of atherosclerosis in renal compared with coronary and other peripheral vascular territories.[70] In the present study age ranged from 22 to 85 years. 50.21% of the patients were aged 41 to 60 years and 42.71% were aged 61 to 80. The mean age was 57.59 ± 10.56 years and median age was 57.5 years. In our study significant asymptomatic renal artery disease was more common in the age group of 61 to 80 years (8.29%) followed by 41 to 60 years (7.88%). These findings suggest that, coronary artery disease is widely prevalent in elderly individuals. However the incidence of renal artery disease in different age groups was almost comparable. These findings showed that, renal artery disease is independent of age as a risk factor which can be attributed to the higher incidence of elderly population in the present study. In contrast to our findings Liang F. et al.[73] on 151 patients reported that, the incidence of RAS was 29.03% (18/62) in patients aged ≤60 years, 60% (36/60) in patients aged >60 and ≤70 years, and 58.62% (17/29) in patients aged >70 years. The incidence of RAS was significantly higher in patients aged >60 - ≤70, and >70 years than patients aged ≤60 years (P = 0.001 and P = 0.007, respectively).

Another study[71] from India also reported age more than 64 years was significantly associated with RAS by bivariate analysis. But, logistic regression analysis failed to find any significant association between age and RAS. In a number of studies, this issue was addressed with different thresholds, in which it was more than 60 years at a minimum.[75,76]

In the present study the predominant risk factor in all of the study patiens was low HDL (79.17%). The other risk factors were history of hypertension

(31.88%), diabetes mellitus (24.28%), smoking (18.75%), raised triglyceride levels (18.54%), hyperglycaemia (15.42%), overweight (13.96%) and raised cholesterol (10%). Few patients had higher LDL (2.8%), history of cerebrovascular accident (1.25%) and alcohol consumption (1.88%) ($p>0.050$). Overall, our study showed no difference in patients with significant RAS compared to those without, with respect to major atherosclerotic risk factors. This may reflect that traditional risk factors have a limited potential for predicting RAS. Dzielińska et al.[77] and Wang et al[78] had reported similar results, but considerable variability was seen in many other studies. In contrast to our results, a study by Joshi H. et al.[72] reported that, main risk factors associated with RAS were advancing age (P=0.033), hypertension (P=0.0002), diabetes (P=0.0003), smoking (P=0.046) and dyslipidemia (P=0.002). Patients with CAD were higher in patients with RAS than those without, although the difference was not significant (P = 0.286). Another study by Liang F. et al.[73] showed a trend that the incidence of RAS in patients with hypertension [HTN, 50.40% (64/127)] was higher than those without HTN (29.17%, 7/24), with $P = 0.056$.

Overall the present study explored the incidence and risk profile of renal artery disease in patients undergoing coronary angiography. Considering ≥ 70% blockage as significant renal artery disease the present study showed higher incidence. Taking in account the current scenario, it may be suggested that identification of patients undergoing CAG for suspected CAD which will help in early diagnosis, enhancing optimized treatment strategy with better renal and health outcome.

CONCLUSION

The incidence of asymptomatic significant (>70% luminal blockade) renal artery disease among the patients suspected to have coronary artery disease undergoing routine cardiac angiography is 8.33%.

Furthermore, incidence of atherosclerotic renal artery disease is high in patients with triple vessel involvement, which is independent of traditional risk factors.

SUMMARY

Atherosclerotic renal artery stenosis (RAS) and coronary artery disease (CAD) arise from the same multiple risk factors. This study was designed to determine the frequency of asymptomatic renal artery disease with normal renal functions in patients who had coronary artery disease.

This one year cross-sectional study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2014 to December 2014. Data was gathered from a total of 480 patients who underwent coronary angiography with normal renal functions were evaluated for the presence of asymptomatic renal artery disease with internal blockage of ≥70%. The salient findings of the study are summarized below.

- Majority of the patients were males (74.19%) and male to female ratio was 2.96:1.

- The most common age group of study population was between 41 to 60 years(50.21%) and 61 to 80 years (42.71%) and the mean age was 57.59 ± 10.56 years.

- Most of the patients (49.15%) had single coronary artery disease while double and triple artery disease was noted in 27.97% and 22.88% respectively.

- Involvement of renal artery was noted in 47.71% of the patients.

Out of the patients who had renal artery disease, bilateral involvement was noted in 48.48% of the patients and right artery was involved in 33.18% of the patients while left involvement was noted in 18.34% of the patients.

- Incidence of significant renal artery disease was noted as 8.33%.

- 25 off the 108 patients with triple vessel disease had significant renal artery disease (23.15%) ($p<0.001$).

- The incidence of renal artery disease was 7.52% in males compared to 10.74% in females ($p=0.267$).

- The most common risk factor was low HDL (79.17%) followed by hypertension (31.88%), diabetes mellitus (24.28%), smoking (18.75%), raised triglyceride levels (18.54%), random blood sugar levels (15.42%), overweight (13.96%) and raised cholesterol (10%).

- None of the traditional risk factors were associated with renal artery disease ($p>0.050$).

- Limitations of the study is that a small number of patients have been involved in the study. Further studies are required for better conclusion.

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ANNEXURE I – CONSENT FORM

Title Of Research Study: "ASYMPTOMATIC RENAL ARTERY DISEASES IN ISCHAEMIC HEART DISEASE PATIENTS WITH NORMAL RENAL FUNCTIONS UNDERGOING CORONARY ANGIOGRAPHY IN A TERTIARY CARE HOSPITAL"

Principal Investigator

Dr. **** ******
Post Graduate Student,
Department Of General Medicine,
J. N. Medical College, Belgaum.

Introduction and Purpose

The study would be to determine the frequency of renal artery disease in patients who had CAD. Association between renal artery disease and other clinical variables will then be observed with respect to age, sex, hypertension, diabetes mellitus.

Procedure

If you agree to be part of the research study, you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood and urine samples for the necessary investigations. Angiogram is a procedure carried out to examine the blood vessels. A dye is injected into the catheter to visualize the arteries. Renal shoots are taken to visualize the renal artery.

Risk and Benefits

The only risk and possible discomfort you might get is while taking blood from my arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn. Allergic reaction to the dye, renal complications is a rare possibility. The kidney function may deteriorate, but is only temporary.

The benefit is that asymptomatic renal artery disease could be detected.

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study at any time. If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy

In case of any injury related to the study, treatment will be made available at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. There is no compensation or payment for such medical treatment by law.

Financial incentives for participation

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

Questions

In case of the queries during study or in future you may contact following persons:

1. Dr. ********** Investigator, PG in General Medicine, JNMC, Belgaum. Ph.no- **********.	2. Dr. **********, Professor, Dept of Nephrology, JNMC, Belgaum. ph.no- **********.
3. Dr. ********** Professor, Dept of cardiology, JNMC, Belgaum. Ph. No. **********.	4. Dr. **********, J.N.M.C Ethical Committee for Human Research, Ph.no-**********. Extn: ****.

Consent Statement

"ASYMPTOMATIC RENAL ARTERY DISEASES IN ISCHAEMIC HEART DISEASE PATIENTS WITH NORMAL RENAL FUNCTIONS UNDERGOING CORONARY ANGIOGRAPHY IN A TERTIARY CARE HOSPITAL"

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form, and have had all my questions answered.

Name of the Participant : _____Signature / Thumb print _____

Name of the Witness _____ Signature/ Thumb print _____

Investigator Name: _____Signature :_____

Date: Place:

ANNEXURE II – PROFORMA

“ASYMPTOMATIC RENAL ARTERY DISEASES IN ISCHAEMIC HEART DISEASE PATIENTS WITH NORMAL RENAL FUNCTIONS UNDERGOING CORONARY ANGIOGRAPHY IN A TERTIARY CARE HOSPITAL”

Case No:

NAME: AGE/SEX:

IP No. ADDRESS:

COMPLAINTS AT PRESENTATION: YES NO

PAST HISTORY:

PHYSICAL EXAMINATION:

GENERAL CONDITION:

Pallor:	Yes/No
Icterus:	Yes/No
Lymphadenopathy:	Yes/No
Cyanosis:	Yes/No
Clubbing:	Yes/No
Edema:	Yes/No

VITALS:

Temperature:

Pulse:

Respiratory rate:

Blood pressure:

Height:

Weight:

BMI:

SYSTEMIC EXAMINATION:

R. S.:

C.V.S.:

P.A.:

C.N.S.:

Serum urea:

Serum creatinine:

Urine Routine:

Coronary angiography finding:

Renal angiography finding:

ANNEXURE III – KEY TO MASTER CHART

-	-	Absent
+	-	Present
Cms	-	Centimeters
DVD	-	Double vessel disease
F	-	Female
G	-	Glucose
Kg/m^2	-	Kilograms per square meter
Kgs	-	Kilograms
M	-	Male
mg/dL	-	Milligrams per deciliter
mm Hg	-	Millimeters of mercury
N	-	Normal
S1	-	First heart sound
S2	-	Second hear sound
SVD	-	Single vessel disease
TVD	-	Triple vessel disease
VBS	-	Vesicular breaths sounds