

Sudan University of Science and Technology
College of Graduate Studies

**Assessment of haemodynamic changes of
intrarenal arteries in Sudanese diabetic patients**
**تقييم تغيرات حركة الدم في الشرايين الكلوية الداخلية لمرضى
السكر السودانين**

A thesis submitted for fulfillment of the requirement of Ph.D. degree In
Medical Ultrasound

By:

Ayman Hamza ElJack Abdalgadir

Supervisor:

Prof. Dr. Moatasim Ahmed Alseid

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Dedication

to;

my parents...

my wife...

and my daughters...

Acknowledgment

First of all, I thank Allah the Almighty for helping me complete this project. I thank Prof. Dr. Moatasim Ahmed Alseid, my supervisor, for his help and guidance.

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Abstract

Diabetes is worldwide in distribution and the incidence of both types of primary diabetes is rising due to genetic and environmental factors. Diabetes may cause life-threatening metabolic complications associated with permanent and irreversible functional and structural cells changes. Diagnostic ultrasound has become one of the most important investigations used in the assessment of vascular disease as it provides accurate information on the flow of blood in the arteries and veins. This study aimed to evaluate hemodynamic changes of the intra-renal arteries resistivity indices (RI) related to diabetes mellitus (DM) using 2D B-mode and Doppler ultrasonography. This study was carried out at diabetic referring clinics of Omdurman teaching Hospital for 100 patients with known diabetes with and without hypertension as sample and 50 normal individuals as controls. The females were 64 representing 64% and males were 36 representing 36%, their ages ranged between 34-65 years and the disease duration was in the range of 1-30 years. Controls were 18 males representing 36% and 32 females representing 64%, their ages ranged between 39-71 years. All patients and controls were underwent ultrasonography assessment of renal size, cortical echogenicity and the intra-renal arteries resistive index (RI) for upper, middle and lower poles and their clinical history were registered. The body mass index (BMI) and diabetic duration were assessed. The study results showed that there were changes in the renal size and cortical echogenicity. The Intra-renal arterial resistive index (RI) of the Sudanese diabetic patients was higher than that of the controls and this increment was statistically significant. The increment of Intra-renal arterial resistive index (RI) of diabetics is positively correlated with age and duration of disease. The (BMI) was inversely related to the intra-renal arterial (RI). There was insignificant difference in intra-renal arterial (RI) between hypertensive diabetics and non-hypertensive diabetics. Sudanese females are more affected by diabetes than Sudanese males.

المستخلص

مرض السكري منتشر في جميع أنحاء العالم والإصابة بكلا النوعين من مرض السكري في ارتفاع بسبب عوامل وراثية وبيئية. مرض السكري قد يهدد الحياة و يسبب مضاعفات الأيض المرتبطة بتغيرات وظيفية وتركيبية للخلايا بصورة دائمة لا رجعة فيها. أصبح التشخيص بالموجات فوق الصوتية واحد من أهم الفحوصات المستخدمة في تقييم أمراض الأوعية الدموية، حيث أنه يوفر معلومات دقيقة عن تدفق الدم في الشرايين والأوردة. هذه الدراسة تهدف إلى تقييم تغيرات الدورة الدموية في الشرايين عبر مؤشرات المقاومة داخل الشريان الكلوي للمرضى المصابين بداء السكري باستخدام صور الموجات فوق الصوتية والدوبلر. أجريت هذه الدراسة في عيادة السكري المحولة في مستشفى أم درمان التعليمي لعدد 100 مريض من مرضى السكري المعروفين بارتفاع ضغط الدم وبدون ارتفاع ضغط الدم بالإضافة إلي 50 شخص من الأصحاء. وكانت نسبة الإناث 64% والذكور يمثلون 36%، وتراوحت أعمارهم بين 34-65 سنة، وكانت مدة المرض في العينة من 1-30 سنوات. بالنسبة للأصحاء كانت نسبة الذكور 36% ونسبة الإناث تمثل 64%، وتراوحت أعمارهم بين 39-71 عاماً. جميع المرضى والأصحاء تم تقييمهم بالموجات فوق الصوتية فيما يختص بحجم الكلى، الخواص السطحية ومؤشر المقاومة الشرياني لشريان الكلى الداخلي لقطبي الكلية الأعلى والأسفل إضافة إلي الأوسط مع الأخذ في الاعتبار تاريخهم السريري. تم تقييم مؤشر كتلة الجسم ومدة السكري. أظهرت نتائج الدراسة أن هناك تغيرات في حجم الكلى والخواص السطحية للقشرة الكلوية. ومؤشر مقاومة الشرايين البينية الكلوية في مرضى السكري السودانيين كان أعلى من الأصحاء وكانت هذه الزيادة ذات دلالة إحصائية. وترتبط الزيادة في مؤشر المقاومة الشرياني الكلوي لدي مرضى السكري بشكل إيجابي مع تقدم العمر ومدة المرض. وعكسياً مع مؤشر كتلة الجسم. كان هناك اختلاف غير معنوي لمؤشر المقاومة الشرياني الكلوي بين مرضى السكري مع ارتفاع ضغط الدم والسكري فقط. والإناث السودانيات أكثر إصابة بمرض السكري من الذكور.

List of abbreviation

A/D	:	analog-to-digital
ave	:	average flow during the cycle
BMT	:	basement membrane thickness
CD	:	collecting duct
CHD	:	coronary heart disease
c-PAN	:	Classic polyarteritisnodosa
CrCl	:	creatinine clearance
DCT	:	distal convoluted tubule
DM	:	Diabetes mellitus
dP/dt	:	change of pressure/change of time
ECG	:	electrocardiography
ECM	:	extracellular matrix
EDV	:	end-diastolic volume
EM	:	electron microscopic
FFT	:	fast Fourier transform
GDM	:	gestational diabetes mellitus

GFR	:	glomerular filtration rate
HDL	:	high density lipoproteins
IDDM	:	insulin- dependent diabetes mellitus
IGT	:	impaired glucose tolerance
LDL	:	low-density lipoprotein
max	:	peak systolic velocities
MDGs:		Millennium Development Goals
MI	:	myocardial infarction
min	:	minimum diastolic velocities
mmol/L	:	milimol/liter
ms	:	millisecond
NaCl	:	sodium chloride
NCDs	:	non-communicable diseases
NIDDM	:	non- insulin-dependent diabetes mellitus
NO	:	nitric oxide
OGTT	:	oral glucose tolerance test
PI	:	pulsatility index
PKC	:	protein kinase C
PRF	:	pulse repetition frequency
PRP	:	pulse repetition period
PVD	:	peripheral vascular disease
RBF	:	renal blood flow
RI	:	resistivity index
RPF	:	renal plasma flow
T1DM	:	Type1 diabetes
TAL	:	thick ascending limb
U/S	:	ultrasound
UAE	:	urinary albumin excretion
UNGA	:	United Nations General Assembly

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Chapter one

Introduction

Diabetes mellitus (DM) is a clinical syndrome characterized by hyperglycemia due to absolute or relative insulin deficiency or resistance or both (Frier et al, 1999 and Parvein and Micheal, 1999). This can arise in many different ways. Most cases of diabetes are primary and relatively few are secondary to identifiable causes. Primary diabetes is subdivided on clinical grounds into insulin-dependent and non- insulin-dependent diabetes mellitus (IDDM and NIDDM). The critical difference between these primary types is the degree of insulin deficiency, which is so profound in IDDM that even the low insulin concentration which is normally prevent lipolysis and ketogenesis cannot be sustained without insulin replacement, IDDM patients become ketotic and die. By contrast, NIDDM patients have enough endogenous insulin to prevent ketosis and will survive without insulin therapy. Diabetes is worldwide in distribution and the incidence of both types of primary diabetes is rising. The prevalence of both varies considerably in different parts of the world and this is probably due to difference in genetic and environmental factors. The great majority of cases seen worldwide have primary diabetes and in Europe and North America the ratio of type 2: type 1 is approximately 7:3 (Frier et al, 1999). Diabetes may cause life-threatening metabolic complications and is the seventh leading cause of death in the U.S., -contributing to roughly 160.000death per year. Complications of diabetes are frequently associated with preeminent and irreversible functional and structural change in the cells of the body, which characteristically affect the eye, the kidney and the nervous system (Frier et al, 1999 and American Diabetes Association, 1996). The chronic tissue complications of diabetes are the single greatest anxiety for most diabetic people. There is a strong association between the overall degree of duration and of

hyperglycaemia and the development and severity of the complications (P.Johnet al, 1993). Chronic diabetic complications are included macovascular disease such as atherosclerosis and microvasculardisease, which is essential a component of retinopathy and nephropathy and are characteristic of, and specific to diabetes the role in neuropathy is not certain. Microvascular lesions in IDDM and NIDDM are identical suggesting that hyperglycaemia or some other metabolic disturbance of diabetes is responsible. Epidemiological evidence indicates that microvascular complications are commoner in poorly controlled and rarer in well- controlled diabetic patients (R.L Souhami and J. Maxham, 1998).

Diabetics have a substantially greater risk of occlusive atherosclerotic vascular disease in many organs (Emanuel, 2000) In the UK, diabetic nephropathy accounts for 25% of patients with end-stage renal failure. It is the commonest cause of premature death in IDDM (Vininc, 1995).

Polymorphic leukocyte and the lymphocyte functions are impaired in diabetes. Defenses against bacterial infection and tissue reparative processes are further retarded by the poor tissue perfusion secondary to vascular disease. Pulmonary and urinary tract infections occur more commonly and osteomyelitis may complicate deep skin ulceration (Vininc, 1995).

Diagnostic ultrasound is recognized as an important adjunct to clinical examination in the care of patients with many common illnesses (P.E.S Palmer, 1995) and it is noninvasive, informative and cost effective tool. It has become one of the most important investigations used in the assessment of vascular disease. This is because it provides accurate information on the flow of blood in the arteries and veins, but it is painless and risk free. Ultrasound has been used safely for years to assess babies in the womb. Colour flow ultrasound provides accurate information on the most arteries. It can assess the flow of blood and whether there is any impairment of flow caused by hardening of the arteries (WWW,Vascular.co.nz).

Gray scale ultrasound has greatly increased the morphological detail that displayed within the kidney. Further the addition of pulsed Doppler allowed arterial and venous perfusion to be assessed both qualitatively and quantitatively (Satish, 2003).

1-1 Problem of the study:

Diabetes mellitus is a growing health problem, particularly in developed countries. Complications of diabetes are frequently associated with preeminent and irreversible functional and structural change in the cells of the body, which characteristically affect the eye, the kidney and the nervous system. The chronic tissue complications of diabetes are the single greatest anxiety for most diabetic people. There is a strong association between the overall degree of duration and of hyperglycaemia and the development and severity of the complications. There is a lack of information about Doppler finding related to diabetes in Sudan.

1-2 Importance of the study:

Early detection of the haemodynamic changes aids in management and prevention complications of diabetes because the prevention is the best treatment for complications.

1-3 Objectives of this study:

1-3-1 general objective:

This study is designed to evaluate haemodynamic changes of the intrarenal arteries related to diabetes mellitus (DM) using 2D B-mode and Doppler ultrasonography.

1-3-2 the specific objectives of this study are:

- To measure the intrarenal resistive index of the diabetic patients and the healthy volunteers.
- To compare these measurements of the diabetic patients and the healthy volunteers.
- To correlate these measurements with the duration of diabetes, age, sex and body mass index.

1.4 Thesis outlines:

The thesis consists of five chapters. Chapter one is dealing with introduction, problems of the study, importance of the study, objectives and thesis outline. Chapter two shows the literature review and previous studies. Chapter three dealing with subjects and methodology. Chapter four shows the results. Chapter five dealing with discussion, conclusion and recommendations.

Literature Review

Theoretical Background

2.1 Diabetes:

The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs. Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. In its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment, death. Often symptoms are not severe, or may be absent, and consequently hyperglycaemia sufficient to cause pathological and functional changes may be present for a long time before the diagnosis is made. The long-term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/ or neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease. Several pathogenetic processes

are involved in the development of diabetes. These include processes which destroy the beta cells of the pancreas with consequent insulin deficiency, and others that result in resistance to insulin action. The abnormalities of carbohydrate, fat and protein metabolism are due to deficient action of insulin on target tissues resulting from insensitivity or lack of insulin (*World Health Organization, 2014*).

Diabetes mellitus is a growing health problem, particularly in developed countries. Global projections of diabetes estimate that by 2010 the total number of individuals with diabetes will be 239.3 million worldwide, with 23.7 million people with type 1 diabetes and 215.6 million with type 2. This is double the number estimated in 1994. Excess mortality in diabetics is approximately twice that of non-diabetics in Australia - similar to figures from the United Kingdom and Denmark (McCarty DJ et al, 1996). It is the seventh leading cause of death in the United States. It affects approximately 26.9% of U.S. residents aged 65 years and older. 1.9 million are diagnosed with diabetes every year, and an additional 7.0 million go undiagnosed and untreated. More than 1 in 5 health care dollars in the U.S. goes to the care of people with diagnosed diabetes, costing \$245 billion dollars annually (American Diabetes Association, 2012). On 13 May 2010, the United Nations General Assembly (UNGA) passed a resolution A/RES/64/265 on non-communicable diseases (NCDs). This step is of historic significance in global health and development, as the resolution recognizes the enormous human suffering, premature death and the seriously negative socioeconomic impact caused by NCDs (United Nations General Assembly, 2010).

These diseases, mainly diabetes, cardiovascular diseases, cancers and chronic lung diseases are emerging as a major threat to global development. Their magnitude is rapidly increasing, because of

population ageing, unplanned urbanization and globalization of trade and marketing. These preventable problems, largely caused by unhealthy diet, physical inactivity, being overweight and obese, tobacco use and the harmful use of alcohol, are now causing an estimated 36 million deaths every year, including 9 million people dying prematurely before the age of 60 years (World Health Organization, 2004).

Diabetes and other NCDs, which share the same risk factors, are a development issue because of the loss of household income from unhealthy behavior, from loss of productivity due to disease, disability and premature death, and from the high cost of health care which drives families below the poverty line. Additionally, the level of exposure of people in developing countries to unhealthy diets, physical inactivity, tobacco use and the harmful use of alcohol is higher than in high-income countries where a higher proportion of the population tends to be protected by comprehensive interventions aiming to promote healthier behavior. Also, affordable and accessible primary health care services for early detection, effective treatment and prevention of complications are often inadequate in developing countries (World Health Organization, 2009)

NCDs and their risk factors are also closely related to poverty, and contribute to poverty at the household level. Studies in developing countries demonstrate how health care for a family member with diabetes can consume a considerable proportion of household income, and how treatment of heart disease and other cardiovascular

complications greatly increases the likelihood of falling into poverty in developing countries, and due to “catastrophic” out of pocket expenditure and loss of income from ill-health (United Nations General Assembly, 2010). NCDs are reported by the World Economic Forum to be a leading macroeconomic risk at a global level (World Economic Forum, 2010).

There are three main types of diabetes - type 1 diabetes (known also as insulin-dependent diabetes mellitus); type 2 diabetes (known also as non-insulin-dependent diabetes mellitus); and gestational diabetes mellitus (GDM). Type 1 diabetes is predominantly a childhood disease and is more common in developed countries. It is also known as 'juvenile onset' diabetes. Management principally involves the injection of insulin into the body, as the cells of the pancreas cannot produce enough insulin (World Health Organization, 1999). Type 1 diabetes (T1DM) is relatively rare in sub-Saharan Africans, especially in young children - the peak age of onset is about a decade older than in white Europeans. Although data are limited, available information indicates that the prognosis in T1DM is poor in Africa, as a result of both acute and long-term complications. Diabetic nephropathy appears to be particularly frequent in diabetic Africans and is a major cause of morbidity and mortality, perhaps more so than in comparable populations of European extraction; no comparative data have been published ([W.J. Kalk](#), 2010). It is incompletely understood as to how this form of diabetes

is initiated, but it is believed that an auto-immune response that destroys the insulin-secreting cells of the pancreas (known as beta cells) may be triggered by a viral infection or by a physico-chemical agent. An individual may also be genetically predisposed to this development. Injections are necessary to provide insulin to cells. The onset of type 1 diabetes is rapid and includes symptoms of increased thirst and hunger, excessive urination, dramatic weight loss, and overwhelming tiredness. There is also a range of minor symptoms (*O'Dea, 1992*).

Type 2 diabetes on the other-hand, is a 'late onset' diabetes, and develops more commonly in people over 40 years of age. It is primarily managed through diet and exercise (*Rodolfo, 2010*). Type 2 Diabetes Mellitus (DM) is rapidly rising as a global health care problem that is threatening to reach pandemic levels by 2030. In 2003, an estimated 194 million adults had diabetes worldwide (5.1%) ([Sicree et al, 2003](#)). This prevalence increased to 6.0% in 2007, and is predicted to increase to 7.3% by 2025. People (380 million) are expected to have diabetes in 2025 (*Sicree et al, 2006*). The presence of hypertension in diabetic patients has dramatically increased the rate of complication (*Canadian Diabetes, 2003*). Individuals with type 2 diabetes are not usually dependent on insulin injections. This is because impaired insulin secretion and cell resistance to insulin cause the condition - it is not caused by insulin shortage (*Hovind et al, 2003*). Type 2 diabetes is often the result of an individual being

overweight for many years. This leads to cells becoming insulin-resistant, as a result of increased levels of sugar being stored as fat and processed. Consequently, the function of the beta cells deteriorates, and this signals the progression of disease from a state of insulin resistance to clinical diabetes. Prolonged and continued beta cell exhaustion can result in reliance on insulin injections. Complications are usually common in individuals with type 2 diabetes, largely because of the longer latent period of disease prior to diagnosis. The disease can go undetected for a number of years, during which time mild symptoms develop - these may become life-threatening (*The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1998*)).

Gestational diabetes mellitus (GDM) is less common than the other two forms. It is first diagnosed during pregnancy, and is primarily a temporary intolerance to carbohydrate, which returns to normal after the birth. More than 40% of women with GDM develop type 1 or type 2 diabetes in the following 10 years (*De Courten M et al, 1998*). As well as having a greater risk of birth defects, babies of women with GDM are more likely to develop obesity and impaired glucose intolerance and/or diabetes in later life. Diabetic women who become pregnant are not included in this category (*Commonwealth State Diabetes Forum, 1999*).

Other types of diabetes include those associated with certain conditions or syndromes, such as malnutrition-related diabetes mellitus, pancreatic disease, diseases of

hormonal aetiology, drug-induced or chemical-induced conditions, abnormalities of insulin or its receptors, genetic, and miscellaneous conditions (McCarty et al, 1996).

The diagnostic criterion for diabetes mellitus is a fasting blood sugar level of greater than 7.8 mmol/L. An individual must exhibit this level on at least two tests. Random blood sugar levels of greater than 11.1 mmol/L are also suggestive of the diabetic state. Fasting blood sugar levels of between 6.4 and 7.8 mmol/L indicate impaired glucose tolerance (IGT), which is often the precursor to diabetes. The detection of IGT is a primary signal that diabetes may develop if good health management is not attained. For most people with IGT, this involves following a low-fat diet and maintaining a healthy body weight (World Health Organization 1999).

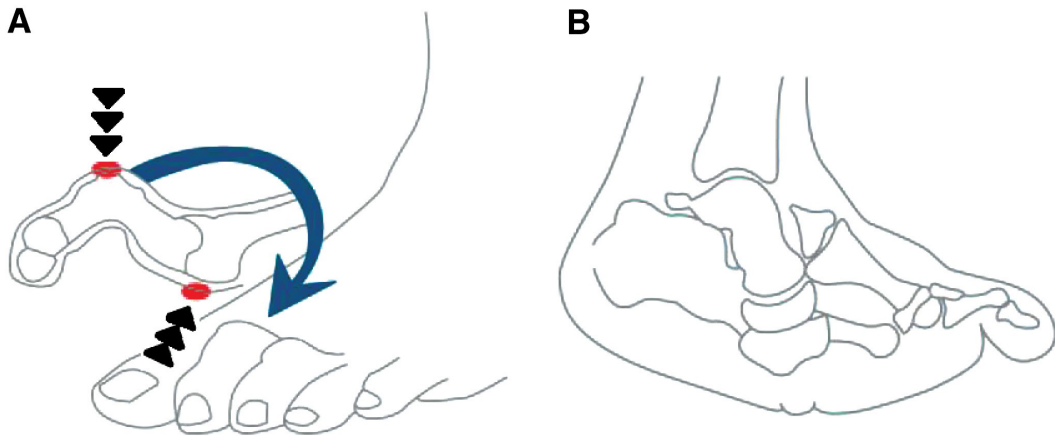
The duration of diabetes is associated with the progressive development of all complications. Complications can become life-threatening, in which case surgery may be necessary (for example, kidney transplantation and lower limb amputations). People with diabetes who develop complications of the disease are at increased risk of premature death (McCarty et al, 1996).

Macrovascular complications are primarily those affecting the circulatory system. Individuals with diabetes have increased rates of coronary heart disease (CHD; known also as ischaemic heart disease), stroke (cerebrovascular disease), and peripheral vascular disease (PVD), and are

two to three times more likely to develop cardiovascular disease than the general population (Commonwealth Department of Health and Aged Care, 1999). These risks are increased if an individual smokes, has high cholesterol, and high blood pressure (Jarrett, 1989).

Diabetes is considered to be an independent risk factor for CHD, and macrovascular diseases are responsible for over half of all diabetic deaths. Macrovascular complications usually lead to microvascular complications, such as nerve damage. Nerve damage is a major cause of morbidity among people with diabetes, primarily because of the loss of sensation in lower limbs (46). For example, trauma to the foot may go unnoticed due to foot numbness, increasing the severity of chronic foot ulcers and infections, sometimes leading to gangrene and amputations. In westernised societies, lower extremity amputations are 15 times more common among people with diabetes, accounting for approximately half of all amputations (*Nutbeam, 1993*). Diabetic foot problems are, in fact, a combination of macrovascular (PVD) and microvascular (neuropathy) complications, as well as increased susceptibility to bacterial infections. As a result of PVD, blood supply is decreased to the foot, with consequent necrosis (death) of foot tissues. Other factors – such as poor hygiene, ill-fitting footwear, orthopaedic problems, presence of calluses and pressure areas, and poor glycaemic control – contribute to diabetic foot problems. Dietary deficiencies (particularly of zinc, protein

and vitamins A and C) may also play a part by impeding healing, thus compounding foot problems(Knuiman, 1986). Nerve damage (primarily autonomic neuropathy) can also be responsible for the development of impotence and gastrointestinal problems, and can lead also to severe limb pain, loss of muscle strength and lack of bladder and bowel control. Studies conducted in Western Australia and South Australia have found that 14% to 20% of people with diabetes developed neuropathy (Commonwealth Department of Health and Aged Care, 1999).



F complications: A) claw toe deformity (increased pressure is placed on the dorsal and plantar aspects of the deformity as indicated by the triple arrows); and B) Charcot arthropathy (the rocker-bottom deformity leads to increased pressure on the plantar mid foot) (Knuiman, 1986).

Diabetic retinopathy, like nephropathy, is also caused by damage to the small blood vessels – in this case, to small vessels in the retina of the eye. In Australia, it is the most common cause of visual loss in adult Australians under the age of 60 year (Commonwealth Department of Health and Aged Care, 1999). Diabetic retinopathy is more common in people who have poor blood sugar control and has been associated with insulin and oral hypoglycaemic treatment, duration of diabetes and microalbuminuria . It is readily treatable by laser therapy if identified early. Other eye disorders associated with diabetes that can lead to loss of vision include glaucoma and cataracts (Phillipov, 1995).

Diabetic nephropathy is one of the most serious complications of diabetes and the most common cause of end-stage renal failure in the Western world. At present, diabetic kidney disease affects about 15 to 25% of type 1 diabetic patients (Hovind, 2003) and 30 to 40% of patients with type 2 diabetes (Yokoyama, 2000). Diabetic

nephropathy is characterized by specific renal morphological and functional alterations. Features of early diabetic renal changes are glomerular hyperfiltration, glomerular and renal hypertrophy, increased urinary albumin excretion (UAE), increased basement membrane thickness (BMT), and mesangial expansion with the accumulation of extracellular matrix (ECM) proteins such as collagen, fibronectin, and laminin. Advanced diabetic nephropathy is characterized by proteinuria, a decline in renal function, decreasing creatinine clearance (CrCl), glomerulosclerosis and interstitial fibrosis (Bieke et al, 2004).

Diabetes affects almost every system in the body - due to the metabolic nature of the disease. As a result of the development of complications, people with type 2 diabetes have higher hospitalisation and health service use than the general population - for treatment of infections, amputations, kidney dialysis and transplants, laser therapy for retinopathy, and other specialist care. Premature death is the most serious result of diabetes, usually caused ature death is the most serious result of diabetes, usually caused of the associated complications(McCarty et al, 1996).

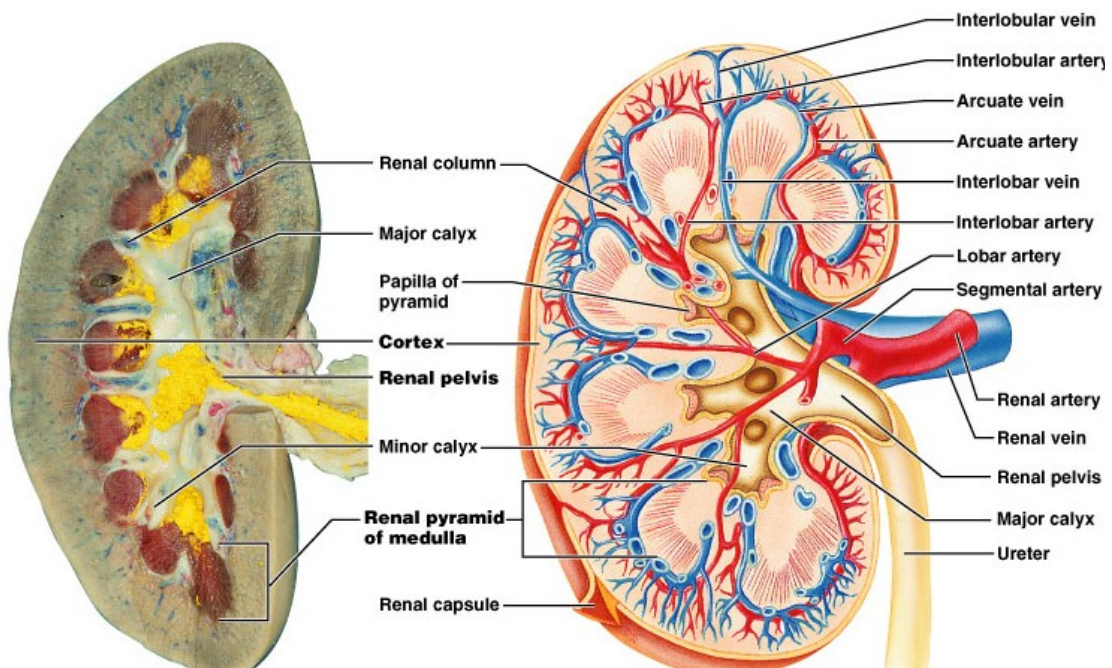
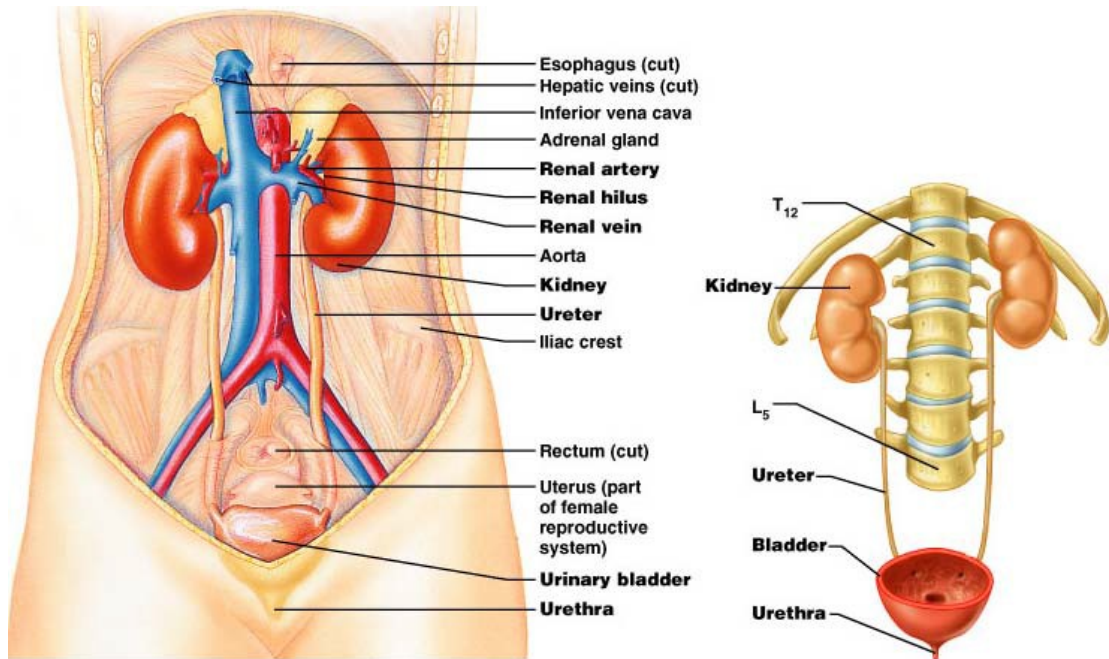
2-2 Anatomy:

2-2-1Anatomy of the kidney:

The renal system is comprised of the Kidneys and those structures including the ureters, bladder and urethra that form the urinary system. The formation of urine is the function of the kidneys, and the rest of the system is responsible for eliminating the urine. The main functions of the kidney are to regulate extracellular fluid volume, Extracellular fluid electrolyte composition, total body water volume, the body's acid-base balance and arterial blood pressure also it produce the active form of vitamin D (1, 25 dihydroxycholecalciferol), renin, erythropoietin, glucose. Kidney excrete endogenous waste products; for example, urea, creatinine, uric acid, and bilirubin and exogenous waste products; for example,

drugs and drug metabolites. Renal dysfunction can negatively impact on all of these roles. The process of urine formation, therefore, helps maintain the normal composition, volume, and pH of both blood and tissue fluid by removing those substances that would upset the normal constancy and balance of these extracellular fluids (Matthew and Jennifer, 2012).

The kidneys are situated in the retroperitoneum located between T12 and L3 on each side of the vertebral column behind the peritoneum (retroperitoneal). The upper portions of the kidneys rest on the lower surface of the diaphragm and are enclosed and protected by the lower rib cage. The kidneys are embedded in adipose tissue that acts as a cushion and is in turn covered by a fibrous connective tissue membrane called the renal fascia, which helps hold the kidneys in place. Each kidney has an indentation called the hilus on its medial side. At the hilus, the renal artery enters the kidney, and the renal vein and ureter emerge. The renal artery is a branch of the abdominal aorta, and the renal vein returns blood to the inferior vena cava. The ureter carries urine from the kidney to the urinary bladder (Valerie, 2007).



Malpighian body and the tubule. The Malpighian body is located in the renal cortex and consists of a tuft of capillaries (glomerulus) surrounded by a double-walled capsule (Bowman's capsule). The primary urine accumulates in the capsular space between its two layers. Blood enters the glomerulus by an afferent arteriole (vas afferens) and exits via an efferent arteriole (vas efferens) from which the peritubular capillary network arises. The glomerular filter separates the blood side from the Bowman's capsular space. The

glomerular filter comprises the fenestrated endothelium of the glomerular capillaries (50–100 nm pore size) followed by the basal membrane as the second layer and the visceral membrane of Bowman's capsule on the urine side. The latter is formed by podocytes with numerous interdigitating foot like processes (pedicels). The slit-like spaces between them are covered by the slit membrane, the pores of which are about 5 nm in diameter. They are shaped by the protein nephrine, which is anchored to the cytoskeleton of the podocytes. The proximal tubule is the longest part of a nephron (ca. 10 mm). Its twisted initial segment (proximal convoluted tubule) merges into a straight part. The loop of Henle consists of a thick descending limb that extends into the renal medulla, a thin descending limb, a thin ascending limb (only in juxtamedullary nephrons which have long loops), and a thick ascending limb, TAL. It contains the macula densa, a group of specialized cells that closely communicate with the glomerulus of the respective nephron. Only about 20% of all Henle's loops (those of the deep juxtamedullary nephrons) are long enough to penetrate into the inner medulla. Cortical nephrons have shorter loops. The distal tubule has an initially straight part (= TAL of Henle's loop) that merges with a convoluted part (distal convoluted tubule, DCT). The DCT merges with a connecting tubule. Many of them lead into a collecting duct, CD which extends through the renal cortex (cortical CD) and medulla (medullary CD). At the renal papilla the collecting ducts opens in the renal pelvis. From there, the urine (propelled by peristaltic contractions) passes via the ureter into the urinary bladder and, finally, into the urethra, through which the urine exits the body (*Agamemnon, 2003*).

2-2-2 Arteries:

Arteries are efferent vessels that transport blood away from the heart to the capillary beds. The two major arteries that arise from the right and left ventricles of the heart are the pulmonary trunk and the aorta, respectively. The pulmonary trunk branches, shortly

after exiting the heart, into right and left pulmonary arteries that enter the lungs for distribution. The right and left coronary arteries, which supply the heart muscle, arise from the aorta as it exits the left ventricle (Gartner and Hiatt, 2010).

The aorta, upon leaving the heart, course in an oblique posterior arch to descend in the thoracic cavity, where it sends branches to the body wall and the viscera; it then enters the abdominal cavity, the abdominal aorta terminates by bifurcating into the right and left common iliac arteries in the pelvis (Gartner and Hiatt, 2010).

2-2-2-1 General structure of blood vessels:

Most blood vessels have several features that are structurally similar, although dissimilarities exist and are the bases for classifying the vessels into different identifiable groups. For example, the walls of high pressure vessels (e.g., subclavian arteries) are thicker than vessels conducting blood at low pressure (e.g., subclavian veins). However, arterial diameters continue to decrease at each branching, whereas vein diameters increase at each convergence, thus altering the respective layers of the walls of the vessels. Therefore, the descriptions used as distinguishing characteristics for a particular type of artery or vein are not always absolute. Indeed, the walls of the capillaries and venules are completely modified and less complex compared with those in larger vessels. Generally, arteries have thicker walls and are smaller in diameter than are the corresponding veins. Moreover, in histological sections, arteries are round and usually have no blood in their lumina (Gartner and Hiatt, 2010).

Three separate concentric layers of tissues, or tunicas, make up the wall of the typical blood vessel as shown in Figure 2.4. The inner most layer, the tunica intima, is composed of single layer of flattened, squamous endothelial cells, which form a tube lining the lumen of the vessel, and the underlying subendothelial connective tissue. The intermediate layer, the tunica media, is composed mostly of smooth muscle cells oriented concentrically around the

lumen. The outermost layer, the tunica adventitia, is composed mainly of fibroelastic connective tissue arranged longitudinally. The tunica intima houses in its outermost layer the internal elastic lamina, a thin band of elastic fibres that is well developed in medium sized arteries. The outermost layer of elastic fibers is the external elastic lamina, which is not distinguishable in all arteries (Gartner and Hiatt, 2010).

Tunica intima:

The endothelial cells, simple squamous epithelium lining the lumen of the blood vessel rest on the basal lamina. These flattened cells are elongated into a sheet such that their long axis of the vessel, which nearly permits each endothelial cell to surround the lumen of a small caliber vessel. In larger bore vessels, several too many individual endothelial cells are required to line the circumference of the lumen. A subendothelial layer lies immediately beneath the endothelial cells. It is composed of loose connective tissue and a few scattered smooth muscle cells, both arranged longitudinally. Beneath the subendothelial layer is an internal elastic lamina that is especially well developed in muscular arteries. Separating elastic lamina is composed of elastin, which is a fenestrated sheet that permits the diffusion of substances into the deeper regions of the arterial wall to nourish the cells there (Gartner and Hiatt, 2010).

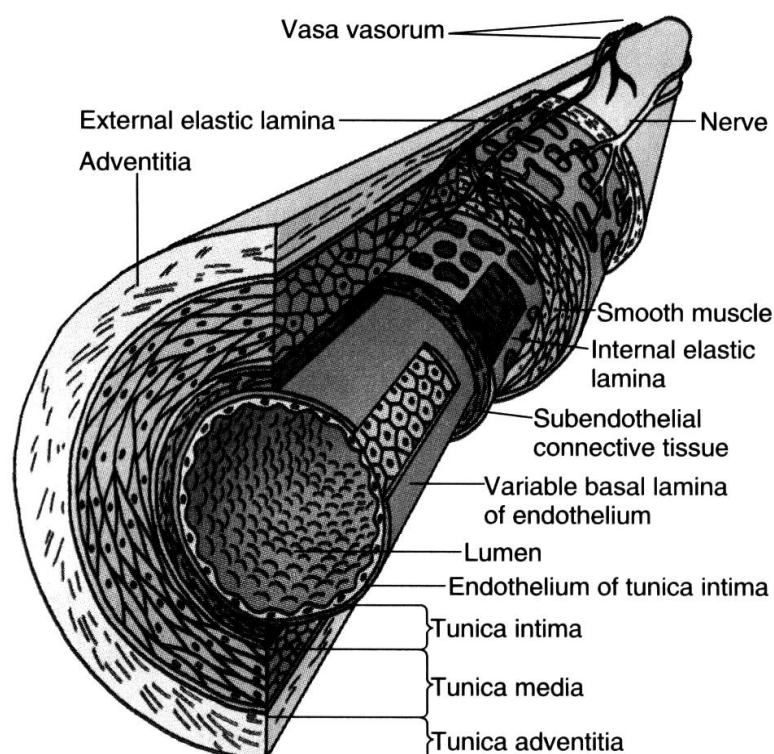


Figure 2-4 demonstrates diagram of a typical artery (Gartner and Hiatt, 2010).

Tunica media:

The tunica media is the thickest layer of the vessel. The concentric cell layer forming the tunica media comprise mostly helically arranged smooth muscle cells. Interspersed within the layers of smooth muscle are some elastic fibres, type III collagen, and proteoglycans. The fibrous elements form lamellae within the ground substance secreted by smooth muscle cells. Larger muscular arteries have an external elastic lamina, which is more delicate than the internal elastic lamina and separates the tunica media from the overlying tunica adventitia (Gartner and Hiatt, 2010).

Tunica Adventitia:

Covering the vessel on their outside surface is the tunica adventitia, composed mostly of fibroblasts, type I collagen fibers, and longitudinally oriented elastic fibres. This layer becomes continuous with the connective tissue elements surrounding the vessel (Gartner and Hiatt, 2010).

2-3 Cardiac Cycle

The cardiac cycle is the sequence of events in one heartbeat. In its simplest form, the cardiac cycle is the simultaneous contraction of the two atria, followed a fraction of a second later by the simultaneous contraction of the two ventricles. Systole is another term for contraction. The term for relaxation is diastole. In cardiac cycle, we can say that atrial systole is followed by ventricular systole (Valerie, 2007).

The resting heart rate is 60–80 beats per minute. A cardiac cycle therefore takes roughly 1 s. It can be divided into four distinct phases: (I) contraction phase and (II) ejection phase, both occurring in *systole*; (III) relaxation phase and filling phase (IV), both occurring in *diastole*. At the end of phase IV, the atria contract (phase IVc). Electrical excitation of the atria and ventricles precedes their

contraction. The cardiac valves determine the direction of blood flow within the heart, e.g., from the atria to the ventricles (phase IV) or from the ventricles to the aorta or pulmonary artery (phase II). All cardiac valves are closed during phases I and III. Opening and closing of the valves is controlled by the pressures exerted on the two sides of the valves (Agamemnon, 2003).

Cardiac cycle. Near the end of ventricular diastole, the sinoatrial (SA) node emits an electrical impulse, marking the beginning of the P wave of the ECG (phase IVc). This results in *atrial contraction* and is followed by *ventricular excitation* (QRS complex of the ECG). The ventricular pressure then starts to rise until it exceeds the atrial pressure, causing the atrioventricular valves (mitral and tricuspid valves) to close. This marks the *end of diastole*. The mean *end-diastolic volume* (EDV) in the ventricle is now about 120mL or, more precisely, 70mL/m² body surface area.

The isovolumetric contraction phase now begins (phase I, 50 ms). With all valves closed, the ventricles now contract, producing the first heart sound, and the ventricular pressure increases rapidly. The slope of this ascending pressure curve indicates the maximum rate of pressure developed (maximum dP/dt). The semilunar valves (aortic and pulmonary valves) now open because the pressure in the left ventricle exceeds that in the aorta at about 80 mm Hg, and the pressure in the right ventricle exceeds that in the pulmonary artery at about 10mmHg (Agamemnon, 2003).

The ejection phase (now begins phase II; 210 ms at rest). During this period, the pressure in the left ventricle and aorta reaches a maximum of ca. 120mmHg (systolic pressure). In the early phase of ejection (IIa or *rapid ejection* phase), a large portion of the stroke volume (SV) is rapidly expelled and the blood flow rate reaches a maximum. Myocardial excitation subsequently decreases (T wave of the ECG) and ventricular pressure decreases (the remaining SV fraction is slowly ejected, phase IIb) until it falls below that of the aorta or pulmonary artery, respectively. This leads to closing of the

semilunar valves, producing the second heart sound. The mean SV at rest is about 80mL or, more precisely, 47mL/m² body surface area. The corresponding mean ejection fraction (SV/ EDV) at rest is about 0.67. The end systolic volume (ESV) remaining in the ventricles at this point is about 40mL (Agamemnon, 2003).

The first phase of ventricular diastole or isovolumetric relaxation now begins (phase III; ca. 60 ms). The atria have meanwhile refilled, mainly due to the suction effect created by the lowering of the valve plane during ejection. As a result, the central venous pressure (CVP) decreases. The ventricular pressure now drops rapidly, causing the atrioventricular valves to open again when it falls short of atrial pressure (Agamemnon, 2003).

The filling phase now begins (phase IV; ca. 500ms at rest). The blood passes rapidly from the atria into the ventricles, resulting in a drop in CVP. Since the ventricles are 80% full by the first quarter of diastole, this is referred to as rapid ventricular filling (phase IVa). Ventricular filling slows down (phase IVb), and the atrial systole (phase IVc) and the wave of CVP follows. At a normal heart rate, the atrial contraction contributes about 15% to ventricular filling. When the heart rate increases, the duration of the cardiac cycle decreases mainly at the expense of diastole, and the contribution of atrial contraction to ventricular filling increases.

The heart beats produce a pulse wave (pressure wave) that travels through the arteries at a specific pulse wave velocity (PWV): the PWV of the aorta is 3-5 m/s, and that of the radial artery is 5-12 m/s. PWV is much higher than the blood flow velocity (V.), which peaks at 1 m/s in the aorta and increases proportionally to (a) decreases in the compliance of aortic and arterial walls and (b) increases in blood pressure (Agamemnon, 2003).

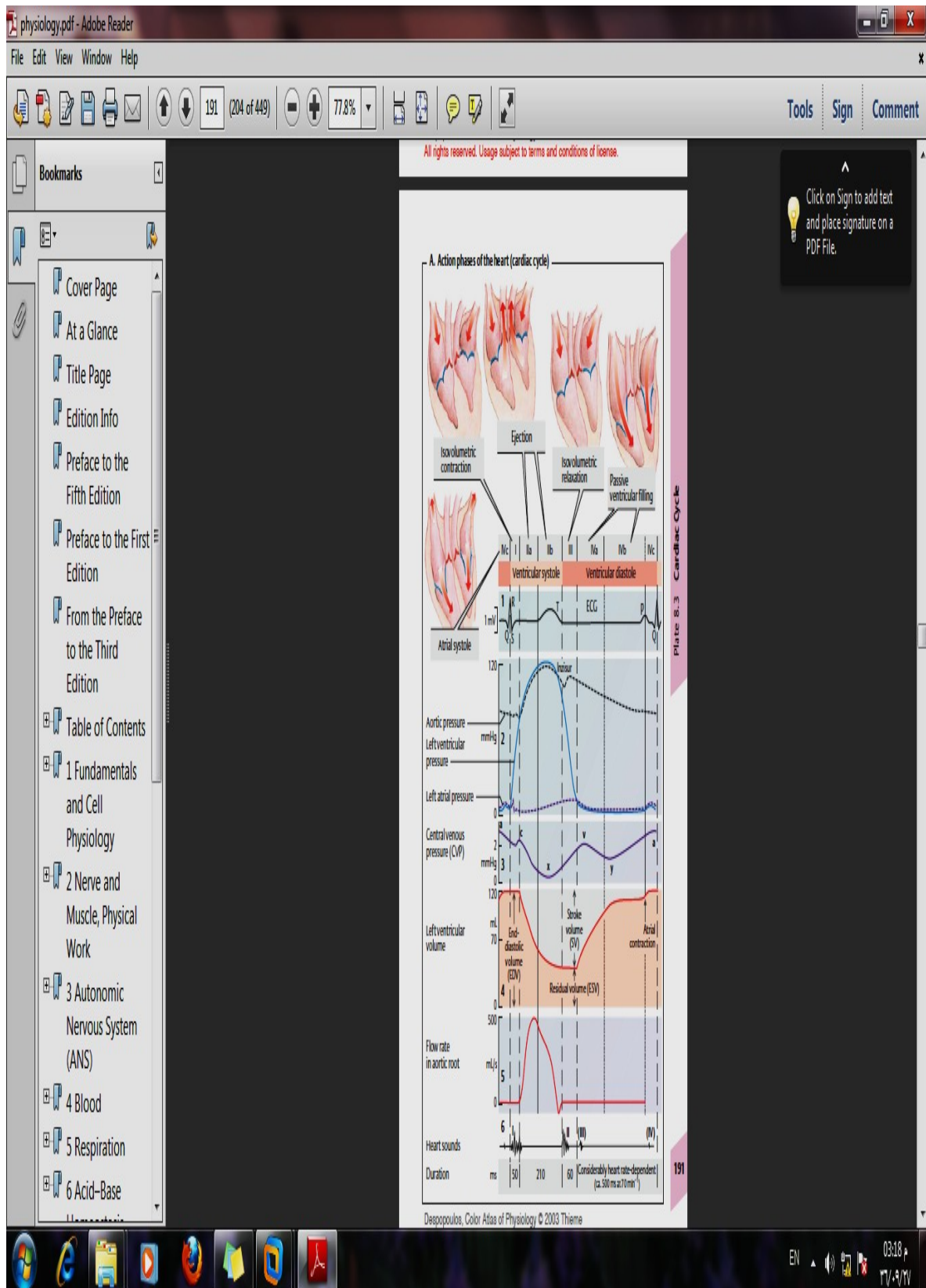


Figure 2-5 Action phases of the heart (cardiac cycle), (Despopoulos, Color Atlas of Physiology © 2003 Thieme)

Heart rate

A healthy adult has a resting heart rate (pulse) of 60 to 80 beats per minute, which is the rate of depolarization of the SA node. (The SA node actually has a slightly faster rate, closer to 100 beats per minute, but is slowed by parasympathetic nerve impulses to what we consider a normal resting rate.) A rate less than 60 (except for athletes) is called bradycardia; a prolonged or consistent rate greater than 100 beats per minute is called tachycardia. A child's normal heart rate may be as high as 100 beats per minute, that of an infant as high as 120, and that of a near-term fetus as high as 140 beats per minute. These higher rates are not related to age, but rather to size: the smaller the individual, the higher the metabolic rate and the faster the heart rate. Parallels may be found among animals of different sizes; the heart rate of a mouse is about 200 beats per minute and that of an elephant about 30 beats per minute. Let us return to the adult heart rate and consider

The person who is in excellent physical condition. As you may know, well-conditioned athletes have low resting pulse rates. Those of basketball players are often around 50 beats per minute, and the pulse of a marathon runner often ranges from 35 to 40 beats per minute. To understand why this is so, remember that the heart is a muscle. When our skeletal muscles are exercised, they become stronger and more efficient. The same is true for the heart; consistent exercise makes it a more efficient pump, as you will see in the next section (Valerie, 2007).

Cardiac output

Cardiac output is the amount of blood pumped by a ventricle in 1 minute. A certain level of cardiac output is needed at all times to transport oxygen to tissues and to remove waste products. During exercise, cardiac output must increase to meet the body's need for more oxygen. We will return to exercise after first considering resting cardiac output. To calculate cardiac output, we must know the pulse rate and how much blood is pumped per beat. Stroke volume is the term for the amount of blood pumped by a ventricle

per beat; an average resting stroke volume is 60 to 80 mL per beat. A simple formula then enables us to determine cardiac output: Cardiac output = stroke volume X pulse (heart rate) Let us put into this formula an average resting stroke volume, 70 mL, and an average resting pulse, 70 beats per minute (bpm):

$$\text{Cardiac output} = 70 \text{ ml} \times 70 \text{ bpm}$$

$$\text{Cardiac output} = 4900 \text{ ml per minute}$$

Approximately 5 liters

Naturally, cardiac output varies with the size of the person, but the average resting cardiac output is 5 to 6 liters per minute. Notice that this amount is just about the same as a person's average volume of blood. At rest, the heart pumps all of the blood in the body within about a minute. Changes are possible, depending on circumstances and extent of physical activity (Valerie, 2001).

If we now reconsider the athlete, you will be able to see precisely why the athlete has a low resting pulse. In our formula, we will use an average resting cardiac output (5 liters) and an athlete's pulse rate (50):

$$\text{Cardiac output} = \text{stroke volume} \times \text{pulse}$$

$$5000 \text{ ml} = \text{stroke volume} \times 50 \text{ bpm}$$

$$5000/50 = \text{stroke volume}$$

$$100 \text{ mL} = \text{stroke volume}$$

Notice that the athlete's resting stroke volume is significantly higher than the average. The athlete's more efficient heart pumps more blood with each beat and so can maintain a normal resting cardiac output with fewer beats.

Now let us see how the heart responds to exercise. Heart rate (pulse) increases during exercise, and so does stroke volume. The increase in stroke volume is the result of Starling's law of the heart, which states that the more the cardiac muscle fibers are stretched, the more forcefully they contract. During exercise, more blood returns to the heart; this is called venous return. Increased venous return stretches the myocardium of the ventricles, which contract

more forcefully and pump more blood, thereby increasing stroke volume. Therefore, during exercise, our formula might be the following:

Cardiac output = stroke volume X pulse

Cardiac output = 100 mL x 100 bpm

Cardiac output = 10,000 mL (10 liters)

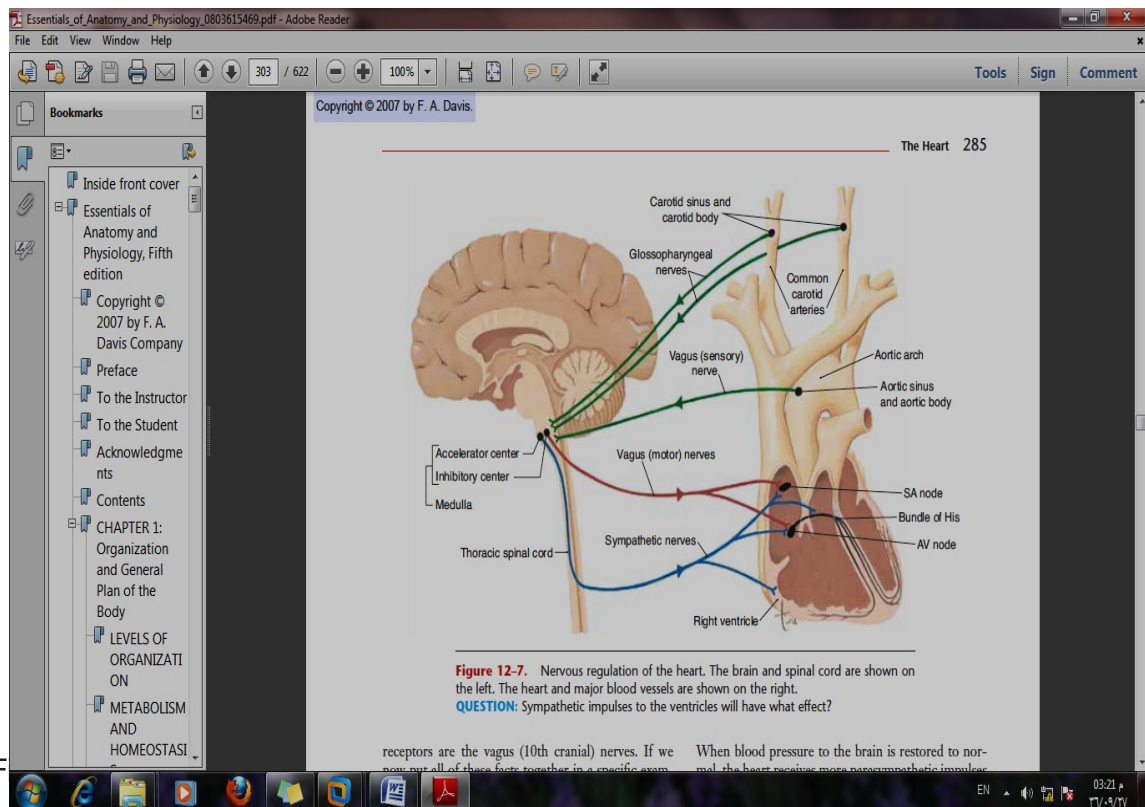
This exercise cardiac output is twice the resting cardiac output we first calculated, which should not be considered unusual. The cardiac output of a healthy young person may increase up to four times the resting level during strenuous exercise. This difference is the cardiac reserve, the extra volume the heart can pump when necessary. If resting cardiac output is 5 liters and exercise cardiac output is 20 liters, the cardiac reserve is 15 liters. The marathon runner's cardiac output may increase six times or more compared to the resting level and cardiac reserve is even greater than for the average young person; this is the result of the marathoner's extremely efficient heart. Because of Starling's law, it is almost impossible to overwork a healthy heart. No matter how much the volume of venous return increases, the ventricles simply pump more forcefully and increase the stroke volume and cardiac output (Valerie, 2007). Also related to cardiac output, and another measure of the health of the heart, is the ejection fraction. This is the percent of the blood in a ventricle that is pumped during systole. A ventricle does not empty completely when it contracts, but should pump out 60% to 70% of the blood within it. A lower percentage would indicate that the ventricle is weakening (Valerie, 2007).

Regulation of heart rate

Although the heart generates and maintains its own beat, the rate of contraction can be changed to adapt to different situations. The nervous system can and does bring about necessary changes in heart rate as well as in force of contraction. The medulla of the brain contains the two cardiac centers, the accelerator center and the inhibitory center. These centers send impulses to the heart along

autonomic nerves. The autonomic nervous system has two divisions: sympathetic and parasympathetic. Sympathetic impulses from the accelerator center along sympathetic nerves increase heart rate and force of contraction during exercise and stressful situations. Parasympathetic impulses from the inhibitory center along the vagus nerves decrease the heart rate. At rest these impulses slow down the depolarization of the SA node to what we consider a normal resting rate, and they also slow the heart after exercise is over (Valerie, 2007).

Blood contains oxygen, which all tissues must receive continuously. Therefore, changes in blood pressure and oxygen level of the blood are stimuli for changes in heart rate(Valerie, 2007). Pressoreceptors and chemoreceptors are located in the carotid arteries and aortic arch. Pressoreceptors in the carotid sinuses and aortic sinus detect changes in blood pressure. Chemoreceptors in the carotid bodies and aortic body detect changes in the oxygen content of the blood. The sensory nerves for the carotid receptors are the glossopharyngeal (9th cranial) nerves; the sensory nerves for the aortic arch receptors are the vagus (10 th cranial) nerves. If we now put all of these facts together in a specific example, you will see that the regulation of heart rate is a reflex (Valerie, 2007).



F

Tina Sanders. 2007).

A person who stands up suddenly from a lying position may feel light-headed or dizzy for a few moments, because blood pressure to the brain has decreased abruptly. The drop in blood pressure is detected by pressoreceptors in the carotid sinuses-notice that they are “on the way” to the brain, a very strategic location. The drop in blood pressure causes fewer impulses to be generated by the pressoreceptors. These impulses travel along the glossopharyngeal nerves to the medulla, and the decrease in the frequency of impulses stimulates the accelerator center. The accelerator center generates impulses that are carried by sympathetic nerves to the SA node, AV node, and ventricular myocardium. As heart rate and force increase, blood pressure to the brain is raised to normal, and the sensation of light headedness passes. When blood pressure to the brain is restored to normal, the heart receives more parasympathetic impulses from the inhibitory center along the vagus nerves to the SA node and AV node. These parasympathetic impulses slow the heart rate to a normal resting pace (Valerie, 2007).

The heart will also be the effector in a reflex stimulated by a decrease in the oxygen content of the blood. The aortic receptors are strategically located so as to detect such an important change as soon as blood leaves the heart. The reflex arc in this situation would be aortic chemoreceptors, vagus nerves (sensory), accelerator center in the medulla, sympathetic nerves and the heart muscle, which will increase its rate and force of contraction to circulate more oxygen to correct the hypoxia. The hormone epinephrine is secreted by the adrenal medulla in stressful situations. One of the many functions of epinephrine is to increase heart rate and force of contraction. This will help supply more blood to tissues in need of more oxygen (Valerie, 2007).

The heart muscle becomes less efficient with age, and there is a decrease in both maximum cardiac output and heart rate, although resting levels may be more than adequate. The health of the myocardium depends on its blood supply, and with age there is greater likelihood that atherosclerosis will narrow the coronary arteries. Atherosclerosis is the deposition of cholesterol on and in the walls of the arteries, which decreases blood flow and forms rough surfaces that may cause intravascular clot formation.

High blood pressure (hypertension) causes the left ventricle to work harder; it may enlarge and outgrow its blood supply, thus becoming weaker. A weak ventricle is not an efficient pump, and such weakness may progress to congestive heart failure; such a progression may be slow, or may be rapid. The heart valves may become thickened by fibrosis, leading to heart murmurs and less efficient pumping. Arrhythmias are also more common with age, as the cells of the conduction pathway become less efficient (Valerie, 2007).

2-4 Renal Circulation

Each kidney receives its blood via the renal artery, a direct branch of the abdominal aorta (usually a single vessel but in around a quarter of individuals there are two renal arteries on each side).

Venous drainage is usually via a single renal vein into the inferior vena cava (IVC). These vessels, (along with the ureter) enter the kidney via an indentation in its medial surface called the hilum. Due to the location of each kidney relative to the aorta and the IVC, the right kidney has a longer renal artery, whilst the left kidney has a longer renal vein. Once the renal artery has entered the hilum of the kidney it divides into numerous interlobar arteries which radiate out towards the cortex. The interlobar arteries divide into arcuate arteries which arc around, following the line of the corticomedullary junction. The arcuate arteries pass between the renal cortex and medulla. They branch towards the cortex into the interlobular arteries from which the afferent arterioles (or vasa afferentia) arise. Unlike other organs, the kidney has two successive capillary networks that are connected with each other by an efferent arteriole (or vas efferens). Pressure in the first network of glomerular capillaries is a relatively high and is regulated by adjusting the width of interlobular artery, the afferent and/or efferent arterioles. The second network of peritubular capillaries winds around the cortical tubules. It supplies the tubule cells with blood, but it also contributes to the exchange of substances with the tubule lumen (reabsorption). The renal blood flow (RBF) is relatively high, 1.2 L/min, equivalent to 20–25% of the cardiac output. This is required to maintain a high glomerular filtration rate (GFR) and results in a very low arteriovenous O_2 difference (15 mL/L of blood). In the renal cortex O_2 is consumed (18 mL/min) for oxidative metabolism of fatty acids, etc. Most of the ATP produced in the process is used to fuel active transport. In the renal medulla, metabolism is mainly anaerobic. Around 90% of the renal blood supply goes to the cortex. Per gram of tissue, approximately 5, 1.75 and 0.5 mL/min of blood pass through the cortex, external medulla, and internal medulla, respectively. The latter value is still higher than in most organs. The kidney contains two types of nephrons that differ with respect to the features of their second network of capillaries. Cortical nephrons are

supplied by peritubular capillaries and have short loops of Henle. Juxtamedullary nephrons are located near the cortex-medulla junction. Their efferent arterioles give rise to relatively long (40 mm), straight arterioles (vasa recta) that descend into the renal medulla. The vasa recta supply the renal medulla and can accompany long loops of Henle of juxtamedullary nephrons as far as the tip of the renal papilla. Their hairpin shape is important for the concentration of urine. Any change in blood distribution to these two types of nephrons affects NaCl excretion. Antidiuretic hormone (ADH) increases the GFR of the juxtamedullary nephrons as far as the tip of the renal papilla. Their hairpin shape is important for the concentration of urine. Any change in blood distribution to these two types of nephrons affects NaCl excretion. Antidiuretic hormone (ADH) increases the GFR of the juxtamedullary nephrons. Due to autoregulation of renal blood flow, only slight changes in renal plasma flow (RPF) and glomerular filtration rate (GFR) occur (even in a denervated kidney) when the systemic blood pressure fluctuates between 80 and about 180mmHg. Resistance in the interlobular arteries and afferent arterioles located upstream to the cortical glomeruli is automatically adjusted when the mean blood pressure changes. If the blood pressure falls below about 80mmHg, however, renal circulation and filtration will ultimately fail. RBF and GFR can also be regulated independently by making isolated changes in the (serial) resistances of the afferent and efferent arterioles (*Agamemnon, 2003*).

2-5 Pathology:

Disorder of arteries:

In recent years, the dominance of chronic diseases as major contributors to total global mortality has emerged and has been previously described in detail elsewhere (WHO, 2008b). By 2005, the total number of cardiovascular disease (CVD) deaths (mainly coronary heart disease, stroke, and rheumatic heart disease) had increased globally to 17.5 million from 14.4 million in 1990. Of

these, 7.6 million were attributed to coronary heart disease and 5.7 million to stroke. More than 80 percent of the deaths occurred in low and middle income countries (WHO, 2009e). The World Health Organization (WHO) estimates there will be about 20 million CVD deaths in 2015, accounting for 30 percent of all deaths worldwide (WHO, 2005).

Around the world, diabetes is growing increasingly common and is a significant contributor to [CVD](#) risk. People with diabetes have a more than two-fold greater risk of fatal and nonfatal CVD compared to non-diabetics, with some indication that diabetes mellitus may confer an equivalent risk of having had a cardiovascular event (Cohort Studies Collaboration, 2003). In fact, CVD is the leading cause of morbidity and mortality in people with diabetes (Booth et al., 2006).

The magnitude of the risk of [CVD](#) associated with diabetes is even greater in women and younger individuals. Indeed, there is substantial evidence that diabetes mellitus may erase, or substantially attenuate, the “female advantage” in the risk of CVD observed in non-diabetics, and that having diabetes may be equivalent to aging by at least 15 years with regard to the clinical manifestations of CVD (Huxley et al, 2006). Diabetes is emerging as a particular concern in Asia, where more than 110 million individuals were living with diabetes in 2007, a large proportion of whom were young and middle aged. Asians tend to develop diabetes at a relatively young age and low [BMI](#), and by 2025 the number of individuals with diabetes in the region is expected to rise to almost 180 million, of which approximately 70 million will be in India and almost 60 million in China. The reasons for this increased risk are still being fully elucidated; however, “normal weight” Asians often exhibit features of abdominal or central obesity, which is particularly detrimental to insulin resistance and glucose metabolism. Moreover, the increased risk of gestational diabetes combined with exposure to poor nutrition in utero and overnutrition in later life may

contribute to increased diabetes, resulting in a situation of “diabetes begetting diabetes” (Chan et al, 2009).

The balance of risks and benefits associated with intensive glucose control has been assessed in recent clinical trials, which have convincingly demonstrated beneficial microvascular outcomes of diabetes. By contrast, these trials have individually failed to show such an effect on cardiovascular outcomes. However, the extension of the follow-up of the Diabetes Control and Complications Trial in type 1 diabetes and the United Kingdom Prospective Diabetes Study in type 2 diabetes have shown that intensive glucose control substantially lowered the risk of cardiovascular outcomes, suggesting a legacy effect with still unexplained underlying mechanisms (Holman et al, 2008). Recently conducted meta-analyses of relevant trials in people with type 2 diabetes have also consistently shown that intensive glucose control reduces the risk of major cardiovascular events by approximately 10 percent, primarily driven by a 10 to 15 percent reduction in the risk of [CHD](#), compared with standard treatment in people with diabetes. Interestingly, this benefit appeared to be independent of concurring cardiovascular risk factors (Kelly et al., 2009).

In sum, as with the escalating obesity epidemic, the prevalence of diabetes has increased dramatically worldwide. It is associated with

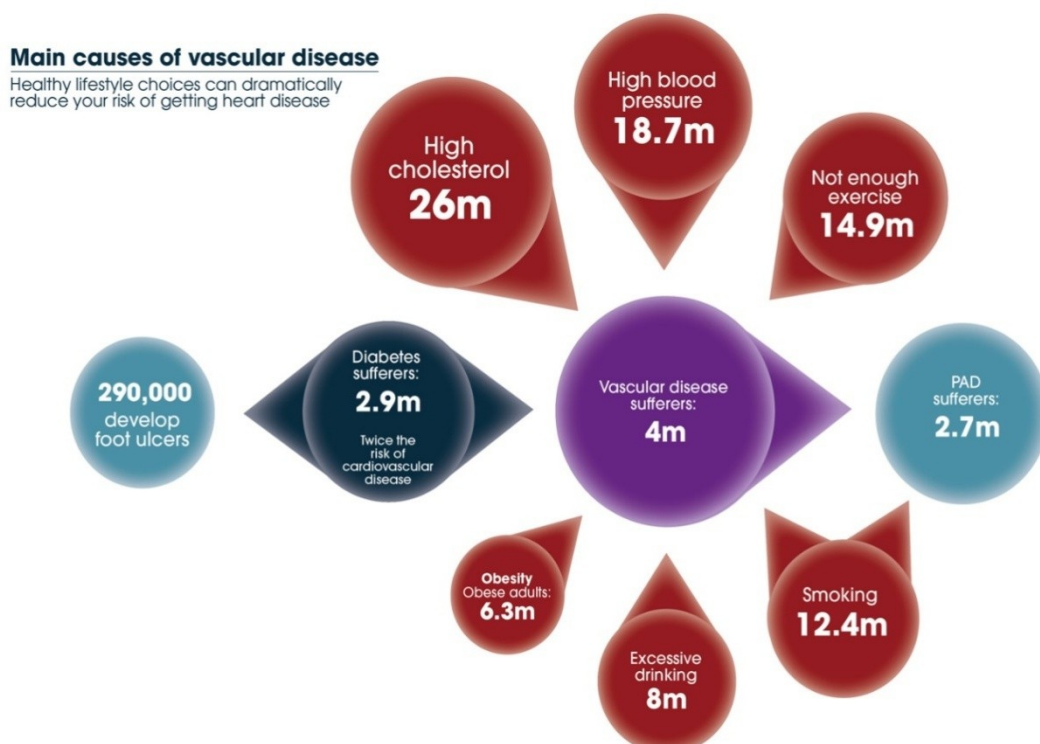


Figure 2.7 shows the main causes of vascular disease

2-5-1 Atherosclerosis:

Atherosclerosis is a common disorder and a leading cause of morbidity and mortality worldwide. In many cases, individuals are asymptomatic and the disease is therefore not recognized until an acute thrombotic manifestation like myocardial infarction (MI), stroke or sudden death occurs. Moreover, the prevalence of atherosclerotic disease and its related costs are expected to increase not only in the industrialized but also in developing countries. It remains a huge challenge to solve this global clinical problem (*Anders et al, 2015*).

Atherosclerosis has been a human disease for 3,500 years; it occurred in Egyptian mummies and showed the same pathologic features that are observed in modern times. Several risk factors may intensify or provoke atherosclerosis through their effects on low-density lipoprotein (LDL) particles and inflammation. These risk factors most frequently include hypertension, tobacco smoking, diabetes mellitus, obesity, and genetic predisposition; the molecular details of how they work are not yet known (*William Insult 2008*).

Arteries, which are blood vessels that carry blood from the heart out to all the tissues of the body, are formed by a remarkable interaction between lining cells - endothelial cells - and arterial wall cells - smooth muscle cells. The faster blood flows through an artery, the larger it will grow. We can take advantage of this fact by

using exercise to create rapid blood flow through the coronary arteries. Exercise seems to strongly prevent coronary atherosclerosis, and a key mechanism may be the production of nitric oxide by endothelial cells exposed to rapidly flowing blood. The intima - the innermost layer - of the artery is the place where atherosclerosis develops. Atherosclerosis is a disease in which cholesterol builds up in the intima and damages the inner lining of the artery. This disease is so dangerous to human life that it causes about one-third of all deaths in modern, industrialized countries of the world (<http://www.yatesville.net/healthsmart/cad/70.html>).

The arterial intima is a connective tissue. However, unlike almost all other connective tissues in the body, the intima has no lymphatic vessels to drain away excess proteins that leak across the endothelial lining. Because of the lack of lymphatics, the concentration of low density lipoproteins (LDL, sometimes called "bad cholesterol") in the arterial intima is 10 times higher than it is in any other connective tissue in the body. This sets the stage for atherosclerosis. The concentration of LDL in the intima is about equal to LDL concentration in blood. The LDL concentration in blood is a strong risk factor for atherosclerosis. Other factors that raise the risk for atherosclerosis include tobacco use, high blood pressure, diabetes, male sex, and low levels of high density lipoproteins (HDL, or "good cholesterol").

(<http://www.yatesville.net/healthsmart/cad/70.html>).

In addition to endothelial cells and smooth muscle cells, inflammatory cells enter the arterial wall from the blood in atherosclerosis. The high concentration of LDL in the intima seems to be a major reason for the entry of inflammatory cells. C-reactive protein in the blood is a marker for inflammatory stimulation in the body, and C-reactive protein is also a very strong risk factor for atherosclerosis. The earliest lesions (abnormal spots) of atherosclerosis are fatty streaks, which contain inflammatory cells loaded with cholesterol, called foam cells. As time passes, some

fatty streaks develop another kind of cholesterol deposition outside of cells in the deep intimal layer. These cholesterol deposits become the lipid-rich core of the atherosclerotic plaque. The plaque grows by fibroproliferation to become a thickened area in the inner artery wall. The deep lipid-rich core also expands, and it may undermine and erode the living artery wall tissue all the way up to the inner surface of the artery wall. If this happens, the inner surface can break or rupture. Weakening of the arterial tissue seems to be caused by a combination of cholesterol and inflammation. When flowing blood comes into contact with the lipid-rich core of a ruptured plaque, the blood can clot within one to a few minutes (<http://www.yatesville.net/healthsmart/cad/70.html>).

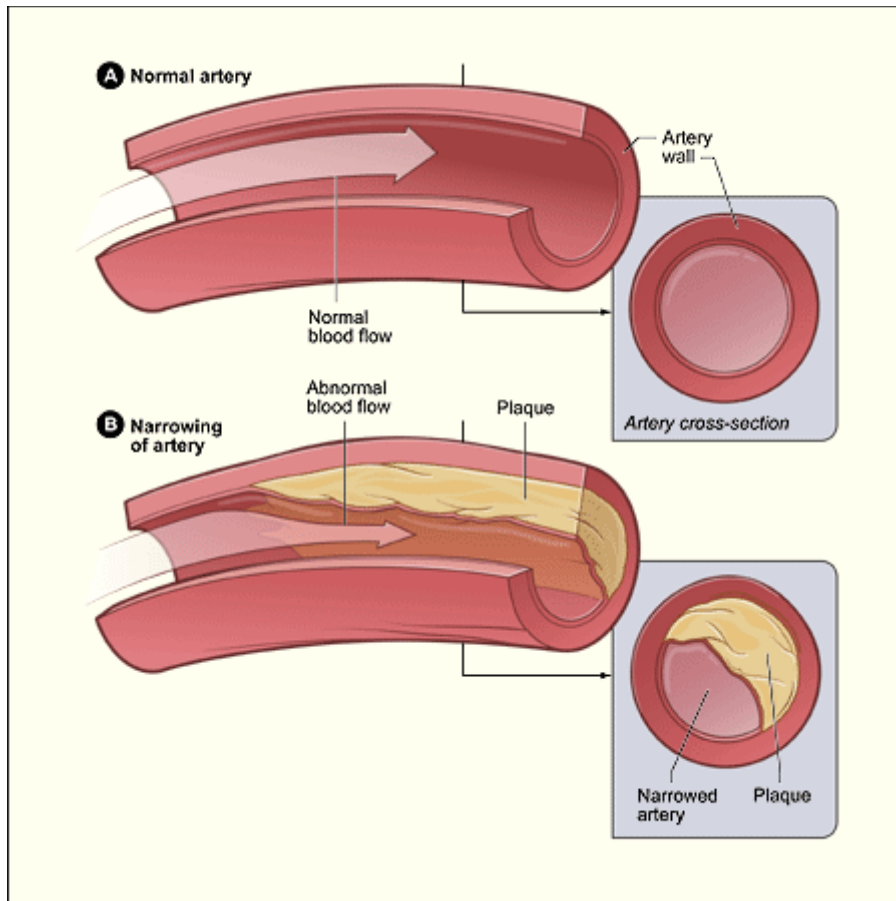


Figure 2-8 (A) shows a normal artery. The inset image shows a cross-section of a normal artery. Figure 2-8 (B) shows an artery with plaque buildup. The inset image shows a cross-section of an artery with plaque buildup.

LDL are lipoproteins that carry cholesterol into the artery wall. HDL are lipoproteins that can pick up cholesterol from the artery wall and direct the cholesterol back to the liver. This is consistent with the fact that people with high levels of HDL have fewer heart attacks and stroke. The final event in the history of some atherosclerotic plaques is the blood clot that forms over the ruptured plaque. If the clot blocks enough blood flow to the heart or brain, then a fatal heart attack or stroke can happen. Certain medications, including aspirin, can help to prevent the formation of clots and thus help to prevent heart attacks and strokes (<http://www.yatesville.net/healthsmart/cad/70.html>).

Reversal or regression of atherosclerosis is a goal often sought by patients. Sometimes regression cannot be achieved. When it does occur, it is difficult and slow. Widening of the narrowed channel for

blood flow, called angiographic regression, could happen in one of two ways. Either the plaque shrinks, or the whole arterial wall relaxes and expands. Most angiographic regression probably results from relaxation and expansion of the whole arterial wall. If only one cholesterol-modifying drug is used, angiographic regression is not achieved in most patients, but combinations of drugs can achieve regression. Two trials of diet and lifestyle have also achieved regression. Significant arterial narrowing are usually narrow the channel by 70% or more. When angiographic regression is seen, the average extent of the regression is one to a few percent. This is not enough to replace the need for coronary bypass operations and heart catheterization balloon and stent procedures (<http://www.yatesville.net/healthsmart/cad/70.html>).

While bypass operations and balloon-stent procedures effectively relieve anginal chest pain, they usually do not reduce the risk of heart attacks very much. One of the discoveries of the 1990s is that giving drugs such as statins to lower LDL can reduce the risk of heart attacks and strokes by 25% to 40%. Early evidence also suggests that risk can be reduced further by using drugs that raise HDL. These discoveries have led to a new idea that vulnerable atherosclerotic plaques – that is, plaques prone to rupture because of a large lipid-rich core can be stabilized to prevent rupture. A recent research study using magnetic resonance imaging brings up the possibility that most of the cholesterol in an atherosclerotic plaque might be removed by using drugs that lower LDL and raise HDL. This could lead to stabilization of the vulnerable plaque (<http://www.yatesville.net/healthsmart/cad/70.html>).

Calcium is deposited in the lipid-rich core of early atherosclerotic plaques, and late atherosclerotic plaques sometimes become heavily calcified. This fact is useful in detecting coronary atherosclerosis at an early stage and in measuring the extent of coronary atherosclerosis. Special techniques of CT scanning (computed tomographic scanning) are needed to detect and

measure coronary calcium deposits
(<http://www.yatesville.net/healthsmart/cad/70.html>).

2-5-2 Hypertension:

Hypertension is high blood pressure, that is, a resting systemic pressure consistently above the normal range (90 to 120/60 to 80 mmHg). Clinicians now consider 125 to 139/85 to 89 mmHg to be prehypertension. A systolic reading of 140 to 159 mmHg or a diastolic reading of 90 to 99 mmHg may be called stage 1 hypertension, and a systolic reading above 160 mmHg or a diastolic reading above 100 mmHg may be called stage 2 hypertension. The term “essential hypertension” means that no specific cause can be determined; most cases are in this category. For some people, however, an over- production of renin by the kidneys is the cause of their hypertension. Excess renin increases the production of angiotensin II, which raises blood pressure. Although hypertension often produces no symptoms, the long-term consequences may be very serious. Chronic hypertension has its greatest effects on the arteries and on the heart. Although the walls of arteries are strong, hypertension weakens them and contributes to arteriosclerosis. Such weakened arteries may rupture or develop aneurysms, which may in turn lead to a CVA or kidney damage. Hypertension affects the heart because the left ventricle must now pump blood against the higher arterial pressure. The left ventricle works harder and, like any other muscle, enlarges as more work is demanded; this is called left ventricular hypertrophy. This abnormal growth of the myocardium, however, is not accompanied by a corresponding growth in coronary capillaries, and the blood supply of the left ventricle may not be adequate for all situations. Exercise, for example, puts further demands on the heart, and the person may experience angina due to a lack of oxygen or a myocardial infarction if there is a severe oxygen deficiency. Although several different kinds of medications (diuretics, vasodilators) are used to treat hypertension, people with moderate hypertension may limit their

dependence on medications by following certain guidelines: Don't smoke, because nicotine stimulates vasoconstriction, which raises BP. Smoking also damages arteries, contributing to arteriosclerosis. Lose weight if overweight. A weight loss of as little as 10 pounds can lower BP. A diet high in fruits and vegetables may, for some people, contribute to lower BP. Cut salt intake in half. Although salt consumption may not be the cause of hypertension, reducing salt intake may help lower blood pressure by decreasing blood volume. Exercise on a regular basis. A moderate amount of aerobic exercise (such as a half hour walk every day) is beneficial for the entire cardiovascular system and may also contribute to weight loss (George L. Brengelmann. , 2003).

2-5-3 Polyarteritis Nodosa:

Classic [polyarteritis nodosa](#) (PAN or c-PAN) is a systemic vasculitis characterized by necrotizing inflammatory lesions that affect medium-sized and small muscular arteries, preferentially at vessel bifurcations, resulting in microaneurysm formation, aneurysmal rupture with hemorrhage, thrombosis, and, consequently, organ ischemia or infarction. Kussmaul and Maier first described PAN in 1866. The autopsy of a patient with fever, weight loss, abdominal pain, and polyneuropathy revealed areas of focal inflammatory exudations that gave rise to palpable nodules along the course of medium-sized arteries. PAN, like other vasculitides, affects multiple systems and has protean manifestations, although it most commonly affects skin (see the image below), joints, peripheral nerves, the gut, and the kidney. The lungs are usually spared with PAN. A typical PAN patient might present with fever, night sweats, weight loss, skin ulcerations or tender nodules, and severe muscle and joint pains developing over weeks or months (Pettigrew HD, 2007).

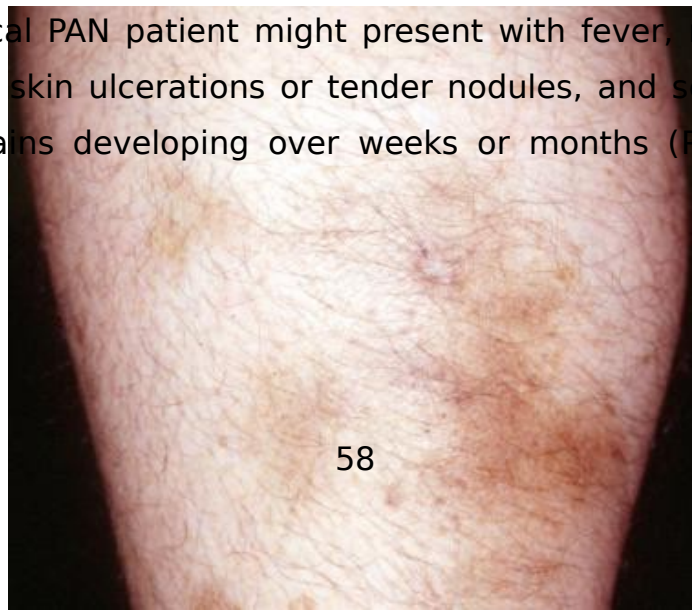


Figure: 2-9 Nonspecific, firm, tender subcutaneous nodules without livedoreticularis and/or systemic involvement may be the first sign of polyarteritis nodosa (Pettigrew HD, 2007).

This was the first vasculitis, originally described in 1866. The term polyarteritis nodosa (PAN) was adopted in 1992 (6). In 1994 PAN was separated into two subtypes according to the size of vessel involved in adults: classical PAN - medium-sized vessels. and microscopic polyangiitis (MPA) - small vessels (Pettigrew HD, 2007).

A less severe form called cutaneous polyarteritis nodosa (CPAN) has also been described. Its features include tender subcutaneous nodules, [livedoreticularis](#), cutaneous ulcers and necrosis. It is often associated with streptococcal infection. Although progress to classical PAN at a later stage has been reported, generally it is thought to be unlikely (Nakamura T et al, 2008).

Epidemiology

Polyarteritis nodosa (PAN) affects approximately 3.1 and microscopic polyangiitis (MPA) 9.4 per 100,000 people per year (Mohammad AJ et al, 2007). It is seen in all ethnic groups and appears to be present throughout the world, although the incidence is higher in areas where [hepatitis B](#) is endemic. It can occur from childhood with a peak incidence at around 10 years. In adults, the most commonly affected age group is between the ages of 40 and 50 ([Ozen S](#), 2004).

In adults, men are more commonly affected than women, but children are equally affected. Some authors state that the incidence is falling, others that it is rising but this may be due to increased recognition (Lane SE et al, 2000).

PAN is divided into subacute, acute, and chronic stages. In the subacute stage, infiltration of mononuclear cells becomes more prominent, while in the acute stage, polymorphonuclear neutrophils infiltrate all layers of the vessel wall. In the chronic stage, fibrinoid necrosis of the vessels causes thrombosis and tissue infarction. Aneurysmal dilatations of the involved arteries, as large as 1 cm in size, are characteristic findings of PAN. Kidney lesions show predominant arteritis without glomerulonephritis; however, in patients with severe hypertension, glomerulosclerosis may be superimposed with glomerulonephritis. Pulmonary arteries are not involved, and bronchial artery involvement is uncommon (Jennette JC et al, 1994).

Presentation

Diagnosis is not easy as it often presents in a vague manner and many different areas can be affected. Patients may suffer weakness, weight loss and malaise. Symptoms and signs are attributable to the inflammation and ischaemia of the affected organs. Any organ may be affected, with the exception of the lungs. [Peripheral neuropathy](#), gastrointestinal, osteoarticular and renal artery pathologies are the most common ([Colmegna I and Maldonado-Cocco JA](#), 2005). Peripheral neuropathy is usually asymmetric, distal mononeuropathy. Gastrointestinal symptoms occur in 14-65% of patients and postprandial abdominal pain from ischaemia is the most common symptom. Bowel necrosis and perforation are associated with a poor prognosis. Myalgia is reported in 72% of childhood patients.

Renal involvement may be in the glomeruli or renal vasculature and may cause [acute kidney injury](#) and [hypertension](#). The typical presentation in children is one- or two-organ involvement, with

constitutional symptoms, and the diagnosis is often based on pathology. Without treatment, hypertension-induced glomerulonephritis is a cause of great morbidity and mortality ([Ozen S, 2004](#)).

Almost half will die within three months of diagnosis if untreated, usually secondary to [chronic kidney disease](#). Poor prognostic features include: older age group, renal and CNS or cardiac involvement(Bourgarit A et al, 2005).



Figure 2-10 Skin involvements occur most often on the legs and is very painful (Bourgarit A et al, 2005).

2-5-4 Takayasu arteritis

Takayasu arteritis, also known as pulseless disease, occlusive thromboaropathy, and Martorell syndrome, is a chronic inflammatory arteritis affecting large vessels, predominantly the aorta and its main branches. Vessel inflammation leads to wall thickening, fibrosis, stenosis, and thrombus formation. Symptoms reflect end organ ischaemia. More acute inflammation can destroy the arterial media and lead to aneurysm formation. Early reports suggested that the disease was confined to females from Eastern Asia, but it has now been recognized worldwide in both sexes, although disease manifestations vary between populations. The female to male ratio appears to decline from Eastern Asia towards the West ([Johnston](#) et al, 2002).

Published descriptions of this arteritis date back as far as 1830. Yamamoto described the case of a 45 year old man with persistent fever who developed impalpable upper limb and carotid pulses associated with weight loss and dyspnea. In 1905 Takayasu, professor of ophthalmology at Kanazawa University Japan, presented the case of a 21 year old woman with characteristic fundal arteriovenous anastomoses. In the same year, Onishi and Kagosha each described similar cases associated with absent radial pulses). In 1920, the first postmortem case of a 25 year old woman demonstrated panarteritis and suggested that the fundal appearances resulted from retinal ischaemia. In 1951, Shimizu and Sano summarised the clinical features of this “pulseless disease” ([Johnston](#) et al, 2002).

Takayasu arteritis is rare, but most commonly seen in Japan, South East Asia, India, and Mexico. In 1990, it was included in the list of intractable diseases maintained by the Japanese government and to date 5000 patients have been registered. A study of North American patients by Hall et al found the incidence to be 2.6/million/year.⁶ The UK incidence is unknown ([Johnston](#) et al, 2002).

Clinical features:

The clinical features have been well documented by cohort studies of over 570 patients from different countries. Manifestations range from asymptomatic disease found as a result of impalpable pulses or bruits, to catastrophic neurological impairment. A two stage process has been suggested with a “pre-pulseless” phase characterised by non-specific inflammatory features, followed by a chronic phase with the development of vascular insufficiency, in some cases accompanied by intermittent flares, although not all patients conform to this pattern “As the inflammation progresses and stenosis develop, the more characteristic features become apparent, influenced by the development of collateral circulation”. The disease commonly presents in the 2nd or 3rd decade of life, often with a delay in diagnosis from the onset of first symptoms of months to years. In one of the largest cohorts (n = 107) 80% of patients were between 11 and 30 years, 77% had disease onset between the ages of 10 and 20 years, with time from onset of symptoms to diagnosis of two to 11 years in 78%.¹ A study of 88 patients from India⁹ gave a mean (SD) age at symptom onset of 24.0 (8.8) years and mean (SD) age at diagnosis of 28.3 (9.9) years. The National Institute of Health study by Kerr et al suggested that the delay in diagnosis was longer in juveniles, being up to four times that of adult patients.¹⁰ However, data from India¹² looking at patients aged under 18 years demonstrated a delay of only 2.5 to 5.5 months. This discrepancy presumably relates to the difference in disease incidence between the two populations, which results in differences in awareness. The clinical features and progress of young patients with Takayasu arteritis appear to be very similar to those of adults ([Johnston](#) et al, 2002).

Non-specific features include fever, night sweats, malaise, weight loss, arthralgia, myalgia, and mild anaemia. As the inflammation progresses and stenoses develop, the more characteristic features become apparent, influenced by the development of collateral circulation. Stenotic lesions predominate and tend to be bilateral.

Nearly all patients with aneurysms also have stenoses and most have extensive vascular lesions ([Johnston](#) et al, 2002).

Characteristic features:

Diminished or absent pulses in 84–96% of patients associated with limb claudication and blood pressure discrepancies. Vascular bruits in 80–94% of patients, often multiple, and particularly affecting the carotids, subclavian, and abdominal vessels. Hypertension in 33–83% of patients, generally reflecting renal artery stenosis, which is seen in 28–75% of patients. Takayasu retinopathy in up to 37% of patients. Aortic regurgitation resulting from dilatation of the ascending aorta, separation of the valve leaflets, and valve thickening in 20–24%. Congestive cardiac failure associated with hypertension, aortic regurgitation, and dilated cardiomyopathy. Neurological features secondary to hypertension and/or ischaemia, including postural dizziness, seizures, and amaurosis. Pulmonary artery involvement in 14–100% of patients, depending on the method used to assess pulmonary vasculature. Oligaemic lung fields on plain chest x ray correlate with pulmonary vasculopathy in approximately a third of cases.¹⁴ Pulmonary artery disease shows little correlation with the systemic pattern of arterial involvement,^{7,14} but can be useful in the differential diagnosis by helping to confirm Takayasuarteritis. Other symptoms include dyspnoea, headaches, carotodynia, myocardial ischaemia, chest wall pain, and erythema nodosum([Johnston](#) et al, 2002).

Variable disease presentation between different populations is well illustrated by Moriwaki et al in their study of Indian and Japanese patients. The Japanese patients (n = 80) were predominantly female (96%), presenting with dizziness, vertigo, pulselessness, more prolonged and severe inflammation, and more aortic regurgitation, reflecting involvement of the aortic arch and its main branches. This contrasted with the Indian patients (n = 102), 37% of whom were male. They tended to present with headache, hypertension, and left ventricular hypertrophy as a result of vasculitis affecting the

abdominal aorta and renal vessels. However, most patients in both countries had diffuse disease ([S L Johnston](#) et al, 2002).

Diagnosis:

From the more typical features of Takayasu's arteritis, the American College of Rheumatology (ACR) defined specific diagnostic criteria for this disorder in 1990. Angiography remains the gold standard for diagnosis. Assessment of pulmonary vasculature by angiography is not universally recommended, being reserved for patients with symptoms of pulmonary hypertension. Doppler ultrasound is a useful non-invasive procedure for the assessment of vessel wall inflammation. In view of the vessels involved, histological diagnosis is usually impractical and histological assessment is limited to those cases undergoing revascularisation procedures ([Johnston](#) et al, 2002).

2-5-5 Thromboangiitis obliterans

Thromboangiitis obliterans is a segmental nonatherosclerotic inflammatory disorder that involves primarily the small and medium arteries, veins, and nerves of the extremities. Von Winiwarter provided the first description of a patient with thromboangiitis obliterans in 1879. Thromboangiitis obliterans is also known as Buerger's disease, named after Leo Buerger who published a detailed description of the pathological findings of amputated limbs in patients with the disease in 1908 (*Jeffrey and Olin, 2001*).

The annual incidence of thromboangiitis obliterans is reported to be 12.6 per 100 000 in the United States. Although it is observed worldwide, thromboangiitis obliterans is more prevalent in the Middle East and Far East. The disease typically presents in patients 45 years of age. Young men are more frequently affected, but thromboangiitis obliterans also occurs in women (*Jeffrey and Olin, 2001*).

Risk factors

Exposure to tobacco is central to the initiation, maintenance, and progression of thromboangiitis obliterans. Although smoking tobacco

is by far the most common risk factor, thromboangiitis obliterans may also develop as a result of chewing tobacco or marijuana use. Nearly two-thirds of patients with thromboangiitis obliterans have severe periodontal disease, and chronic anaerobic periodontal infection may represent an additional risk factor for the development of the disease. Polymerase chain reaction analysis demonstrated DNA fragments from anaerobic bacteria in both arterial lesions and oral cavities of patients with thromboangiitis obliterans but not in arterial samples from healthy control subjects (Jeffrey and Olin, 2001).

Pathophysiology:

Thromboangiitis obliterans is a vasculitis characterized by a highly cellular inflammatory thrombus with relative sparing of the vessel wall. Although acute-phase reactants such as erythrocyte sedimentation rate and C-reactive protein and commonly measured autoantibodies are typically normal, abnormalities in immunoreactivity are believed to drive the inflammatory process. Patients with thromboangiitis obliterans have been shown to have increased cellular immunity to types I and III collagen with those who have atherosclerosis. In addition, high titers of anti-endothelial cell antibodies have been detected in patients with this disorder. Prothrombotic and hemorheologic factors may also play a role in the pathophysiology of thromboangiitis obliterans. The prothrombin gene mutation 20210 and the presence of anticardiolipin antibodies are associated with an increased risk of the disease. Thromboangiitis obliterans patients with high anticardiolipin antibody titers tend to have a younger age of onset and an increased rate of major amputation compared with patients who do not have detectable antibodies. Hemorheologic parameters such as hematocrit, red blood cell rigidity, and blood viscosity are increased in patients with thromboangiitis obliterans compared with those with atherosclerosis. Thromboangiitis obliterans involves 3 phases: acute, subacute, and chronic. The acute phase is composed of an

occlusive, highly cellular inflammatory thrombus. Polymorphonuclear neutrophils, microabscesses and multinucleated giant cells are often present. The chronic phase is characterized by organized thrombus and vascular fibrosis that may mimic atherosclerotic disease. However, thromboangiitis obliterans in any stage is distinguished from atherosclerosis and other vasculitides by the preservation of the internal elastic lamina (*Jeffrey and Olin, 2001*).

Clinical Presentation

Patients with thromboangiitis obliterans typically present with ischemic symptoms caused by stenosis or occlusion of the distal small arteries and veins. Involvement of both the upper and lower extremities and the size and location of affected vessels help distinguish it from atherosclerosis. Although symptoms may begin in the peripheral portion of a single limb, thromboangiitis frequently progresses proximally and involves multiple extremities. Arterial occlusive disease resulting from thromboangiitis obliterans often presents as intermittent claudication of the feet, legs, hands, or arms. Symptoms and signs of critical limb ischemia, including rest pain, ulcerations and digital gangrene, occur with more advanced disease. Raynaud's phenomenon is present in 40% of patients with thromboangiitis obliterans and may be asymmetrical. Although most common in the extremities, thromboangiitis obliterans may also involve the cerebral, coronary, renal, mesenteric and pulmonary arteries. Superficial thrombophlebitis differentiates thromboangiitis obliterans from other vasculitides and atherosclerosis, although it may also be observed in Behcet's disease. Superficial thrombophlebitis may predate the onset of ischemic symptoms caused by arterial occlusive disease and frequently parallel disease activity. Patients may describe a migratory pattern of tender nodules that follow a venous distribution. The physical examination of a patient with suspected thromboangiitis obliterans includes a detailed vascular examination with palpation of peripheral pulses,

auscultation for arterial bruits, and measurement of ankle: brachial indices. The extremities should be inspected for superficial venous nodules and cords and the feet and hands should be examined for evidence of ischemia. Although nonspecific, a positive Allen test in a young smoker with digital ischemia is strongly suggestive of the disease. Neurological examination may document peripheral nerve involvement, with sensory findings in up to 70% of patients (*Jeffrey and Olin, 2001*).

Diagnosis

Thromboangiitis obliterans is a clinical diagnosis that requires a compatible history, supportive physical findings, and diagnostic vascular abnormalities on imaging studies. Several criteria have been proposed for the diagnosis of thromboangiitis obliterans. Common clinical criteria include age 45 years; current or recent history of tobacco use distal extremity ischemia confirmed by noninvasive testing; exclusion of thrombophilia, autoimmune disease, diabetes and a proximal source of emboli; and consistent angiographic findings (*Jeffrey and Olin, 2001*).

Laboratory testing in patients with suspected thromboangiitis obliterans is used to exclude alternative diagnoses. Initial laboratory studies should include a complete blood count, metabolic panel, liver function tests, fasting blood glucose, inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein, cold agglutinins, and cryoglobulins. In addition, serological markers of autoimmune disease, including antinuclear antibody, anticentromere antibody, and anti-SCL-70 antibody, should be obtained and are typically negative in thromboangiitis obliterans. Lupus anticoagulant and anticardiolipin antibodies are detected in some patients with thromboangiitis obliterans but may also indicate an isolated thrombophilia. Echocardiography may be indicated in certain cases when acute arterial occlusion caused by thromboembolism is suspected to detect a cardiac source of embolism (*Jeffrey and Olin, 2001*).

Computed tomographic, magnetic resonance, or invasive contrast angiography may be performed to exclude a proximal arterial source of embolism and to define the anatomy and extent of disease. Although advances in computed tomographic and magnetic resonance angiography show promise for imaging distal vessels, most patients require invasive contrast angiography to provide the spatial resolution necessary to detect small-artery pathology. Distal small- to medium-artery involvement, segmental occlusions, and “corkscrew”- shaped collaterals around areas of occlusion are typical angiographic findings in thromboangiitis obliterans. Proximal arteries should be normal without evidence of atherosclerosis. Biopsy is rarely indicated but is most likely to be diagnostic in a vein with superficial thrombophlebitis during the acute phase of the disease (*Jeffrey and Olin, 2001*).

Prognosis

The prognosis for patients with thromboangiitis obliterans depends largely on the ability to discontinue tobacco use. In a retrospective series of 110 patients with thromboangiitis obliterans, 43% of patients underwent 108 amputation procedures. Among those who continued smoking, 19% required a major amputation. None of those who stopped smoking underwent amputation. A substantial proportion (85%) of patients with thromboangiitis obliterans who underwent major amputation lost their jobs (*Jeffrey and Olin, 2001*).

2-6 Doppler:

The diagnosis of extent and nature of blood flow abnormality in diabetic nephropathy is important in the evaluation and management of diabetic patients. In kidney diseases, ultrasonography is used as a first-line imaging technique. Ultrasound is now both competitive and complementary to angiography for many arterial investigations even when the circulation is seriously compromised. Doppler ultrasound is a relatively inexpensive, noninvasive imaging technique. Doppler is a

major component of ultrasound imaging especially in the investigation of cardiac and peripheral vascular diseases.

2-6-1 Nature of the Doppler shift:

2-6-1-1 Doppler shift for audible sounds:

Whenever there is relative motion between a sound source and a listener, the frequency heard by the listener differs from that produced by the source. The perceived frequency is either greater or less than that transmitted by the source, depending on whether the source and the listener are moving toward or away from one another. This change in the perceived frequency relative to the transmitted frequency is called Doppler shift. In general, a Doppler shift can occur for a moving source and stationary listener, a moving listener and stationary source, or a moving source and moving listener ((Zagzebski, 1996).

Most of researchers are familiar with the Doppler effects occurring when an automobile, truck, or other motor vehicle sounds its horn as it passes us. If the horn is sounding continuously, its pitch seems to drop abruptly just as the vehicle passes and as the vehicle approaches the listener, the Doppler shift results in the perceived pitch of the horn being higher than that actually transmitted. Similarly, the perceived frequency is lower than that transmitted as the vehicle recedes. The very noticeable drop in pitch as the vehicle passes is just the transition between the two conditions. Another way to experience a Doppler shift is to be a listener travelling towards or away from a stationary source. A listener moving towards a stationary sound source hears a higher frequency, while a listener moving away hears a lower frequency than the transmitted frequency (Zagzebski, 1996).

2-6-1-2 Doppler shift in medical ultrasound:

In medical ultrasound we get Doppler shifts when echo signals are picked up from moving reflectors. In Figure 2.11 a stationary transducer is sending sound waves to the right and receiving echoes from a reflector. The emerging echo pattern from the reflector

varies, depending on whether the reflector is stationary or moving. Slightly higher frequencies are received from a reflector moving towards the transducer than from a stationary reflector, while the opposite is true for a reflector moving away from the transducer. The Doppler effect is actually manifested twice in the production of an echo from a moving reflector. First the reflector plays the role of a moving "listener" as it travels towards or away from the ultrasound transducer. The ultrasound waves the reflector encounters are thus initially Doppler shifted. The reflector subsequently acts as a moving "source" as it sends echoes back towards the transducer. This results in an additional shift in the frequency of the waves compared to the transmitted frequency. The Doppler frequency is the difference between the frequency of the incident ultrasound beam and that of the received echoes (Zagzebski, 1996).

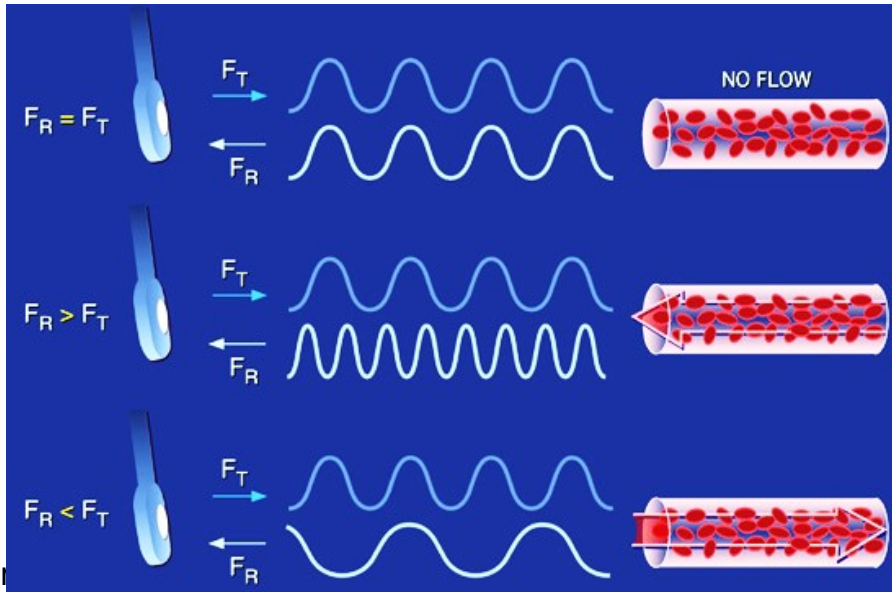


Figure 2-11 Doppler shift in reflection on ultrasound frequency. The motion of an object alters the frequency of a reflected ultrasound signal. A: The reflected echoes from a stationary target are of the same frequency as the transmitted signal. B: Objects such as red blood cells moving toward the transducer compress the sound signal, and the reflected frequency is increased. C: When red cells travel away for the transducer, the frequency of the reflected echoes is decreased. These modulations in the frequency of the reflected ultrasound are used to detect blood flow.

2-6-2 The Doppler equation:

Doppler equipment is commonly used for detecting and evaluating blood flow in arteries and veins.

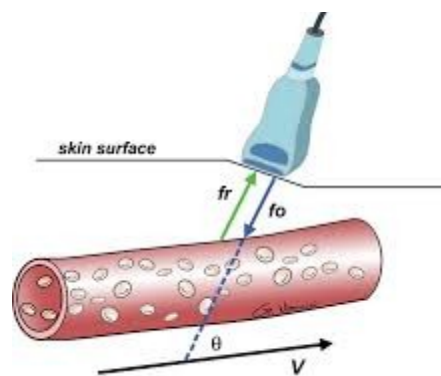


Figure 2-12 arrangement for detecting Doppler signals from and within a vessel, where θ is the Doppler angle (Zagzebski, 1996).

A typical arrangement is shown in Figure 2.12 above. The ultrasonic transducer is placed in contact with the external skin surface and the ultrasound beam directed toward the vessels. The beam is at an

angle θ with respect to the axis of the vessel. Red blood cells flowing in the vessel scatter ultrasound waves, giving rise to echo signals. In most instruments the echo signals are detected by the same transducer used to produce the incident beam. Because the scatters are moving, the frequency of the return echo signals is Doppler shifted. The Doppler frequency is given by equation 2.1:

$$F_D = \frac{2F_o V \cos\theta}{C} \quad 2.1$$

Where: F_o is the transmitted ultrasound frequency, V is the reflector velocity, C is the speed of sound, and $\cos\theta$ is the cosine of the angle between the transmitted beam and the reflector patch (Zagzebski, 1996).

In many situations we use Doppler equipment to estimate reflector velocities. As equation 2.1 indicates the Doppler frequency which is in turn in a direct proportional to the reflector velocities. When the reflector velocity doubles, the Doppler frequency doubles; when it halves, the Doppler frequency halves. Equation 2.1 also indicates that the Doppler frequency depends on the frequency of the incident ultrasound beam. The Doppler frequency obtained from the red blood cells within a vessel when using a 10 MHz beam is twice that obtained when a 5-MHz beam is used for the same vessel and geometry. A 2.5-MHz beam yields a Doppler frequency that is half to that obtained with a 5-MHz beam (Zagzebski, 1996).

2-6-2-1 The Doppler angle:

In description of the Doppler angle, the angle θ in Figure 2.13 is called the Doppler angle. With Doppler equipment, the Doppler frequency is proportional to the reflector velocity but also to the cosine of the angle. The cosine function is plotted in Figure 2.14. The cosine varies from 1 at 0 degrees to -1 at 180 degrees (Zagzebski, 1996).

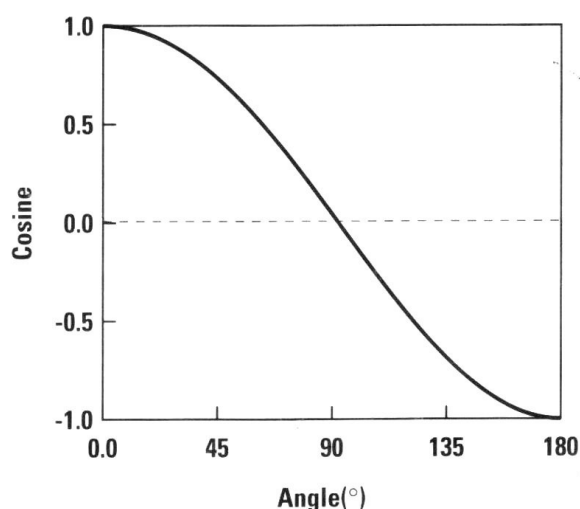


Figure 2-13 shows the changes according to cosine function for angles from 0 up to 180 degrees (Zagzebski, 1996).

Looking closely at Figure 2.13, a 0-degree Doppler angle corresponds to reflectors moving directly towards the transducer, while a 180-degree Doppler angle means the reflectors are moving directly away from the transducer. If the Doppler angle is 90 degrees, reflectors are moving perpendicular to the ultrasound beam (Zagzebski, 1996).

The effect of Doppler angle on the Doppler frequency for a given reflector velocity will describe in Figure 2.14 where the given example assumes that the reflectors are moving at a speed of 1 m/s and that the ultrasound frequency is 5-MHz, Doppler frequencies for different Doppler angles, determined by the location of the ultrasound transducer, are presented (Zagzebski, 1996).

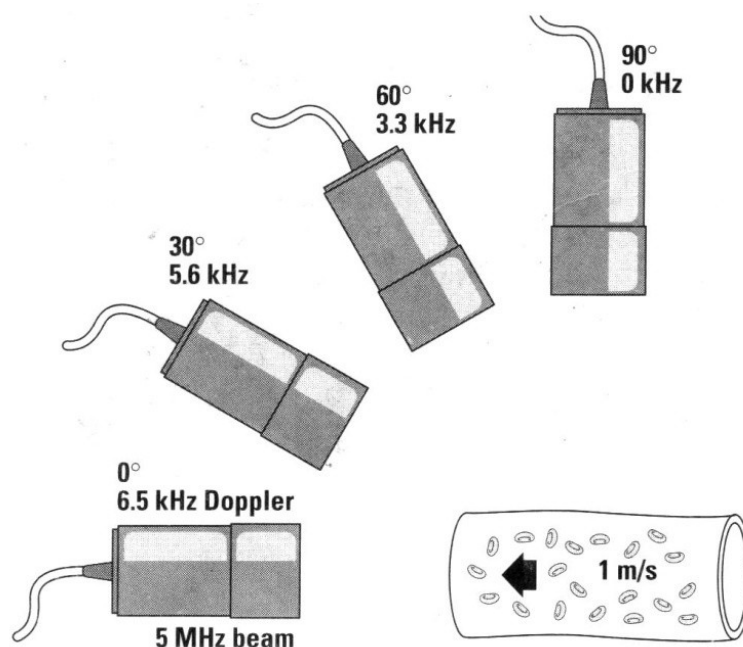


Figure 2-14 illustrate Doppler frequencies from reflectors moving at a velocity of 1 m/s versus the Doppler angle, ultrasound transducer frequency is assumed to be 5 MHz at 0 degrees these conditions yield a Doppler frequency of 6.5 kHz, at 30 degrees 5.6 kHz, at 60 degrees only 3.3 kHz for this reflector velocity and no Doppler frequency shift is detected when the Doppler angle is 90 degrees ((Zagzebski, 1996).).

For a Doppler angle 0 degree, the Doppler signal frequency is 6.49-KHz, this frequency would detected if it were possible to “interrogate” the flow at a 0-degree angle, for other angles, the Doppler frequency is lower. Applying the cosine θ term for the angles illustrated, we see that the Doppler frequency decreases to 5.6-KHz for a 30-degree angle and to just 3.3-KHz for a 60-degree angle. Finally, at 90-degrees, when the ultrasound beam is perpendicular to the reflector direction, the detected frequency is 0-Hz because there is no Doppler shift (Zagzebski, 1996).

If the incident beam angle is greater than 90-degrees to the flow, the cosine of the angle is negative, this corresponds to the flow directed away from the transducer; the frequency of echo signals

from moving reflectors is now lower than F_0 , the transmitted frequency. Most equipment detects the magnitude of Doppler frequency, so the Doppler signals sound the same as for signals from flow directed towards the transducer. Notice, the transducer beam orientation that provides the best B-mode image detail of a vessel wall, that is, perpendicular beam incidence, results in the least favorable Doppler signals from within the lumen of the vessel.

In practice the transducer beam is usually oriented to make a 30- to 60-degree angle with the lumen of the vessel when the vessel runs nearly parallel to the skin surface. If the Doppler angle is greater than 60-degree, Doppler shift signals can usually be detected; however, it becomes difficult to quantify the Doppler velocity from the Doppler signal frequency because of errors in estimating the Doppler angle introduce large uncertainties in the reflector velocities as the Doppler angle approaches 90 degrees and also transducer related spectral broadening results in uncertainties in the peak Doppler frequencies (Zagzebski, 1996).

2-6-3 Continuous wave Doppler instruments:

Continuous wave Doppler system description:

Continuous wave (CW) Doppler instruments are the simplest and often the least expensive Doppler devices available. A simplified block diagram is presented in Figure 2.15. A CW transmitter continuously excites the ultrasonic transducer with a sinusoidal electrical signal. This produces a sound wave of frequency

(Zagzebski, 1996). F_c .

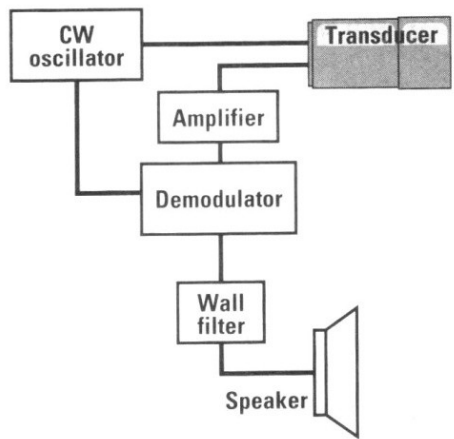


Figure 2-15 schematic showing parts of a CW (continuous-wave) Doppler instrument (Zagzebski, 1996)..

Echo signals resulting from reflection and scattering return to the transducer, creating an electrical signal that is applied to the receiver amplifier. The signal is boosted in strength and then applied to the demodulator. Here the echo signal is multiplied with a

reference signal derived from the transmitter, producing a complicated product shown in Figure 2.16. The product contains a mixture of signals, one whose frequency is equal to the sum of the reference frequency and the return echo signal frequency and another that is equal to the difference between the reference frequency and the return frequency. The “difference frequency” signal is the Doppler signal that we are after. It is isolated by electronically filtering away all of the high frequencies in the complicated product. The result is that only low frequency Doppler shift signals emerge in the output (Zagzebski, 1996).

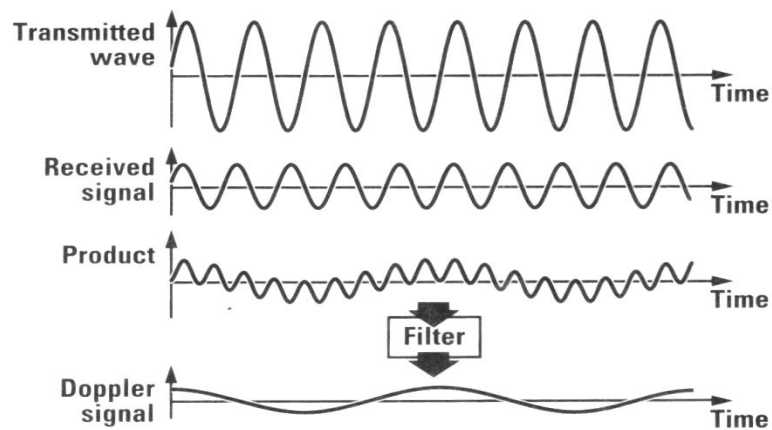


Figure 2-16 shows simple Doppler signal processing. The top trace represents the wave transmitted into the tissue; the second trace represents echo signals from a reflector moving towards the transducer, with the signal frequency slightly higher than the transmitted frequency. The Doppler signal is derived by multiplying the received signal by a signal derived from the transmitter, then filtering out all the ultrasound frequencies and higher. It is shown on the bottom (Zagzebski, 1996).

High frequency signals are removed in the demodulator. Further filtering is applied after this stage to remove the very low frequency Doppler signals originating from slowly moving reflectors, such as vessels walls. This filter is usually called a wall filter and is adjusted by the operator. The wall filters available on most Doppler instruments preferentially remove low frequency Doppler signals from the display. This is illustrated in Figure 2.17. As the wall filter setting or the “filter” setting is adjusted upward, more of the

Doppler signal from the baseline is lost. The filtered output Doppler signal may be applied to a loudspeaker or headphones for interpretation. The signals also can be recorded on audio tape or applied to a spectral analysis system (Zagzebski, 1996).

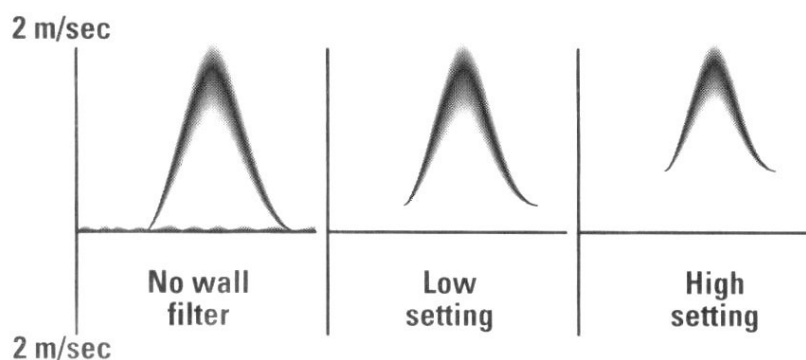


Figure 2-17 illustrates effect of variations in the wall filter setting of a Doppler instrument increasing the setting cuts off a larger range of the lower frequency Doppler signals (Zagzebski, 1996).

Continuous wave Doppler instruments range in complexity from simple, pocket-type instruments to units that are part of large, “duplex” scanners. Operator controls available on a continuous wave Doppler instrument vary with the degree of complexity of the unit. Typically the following are available: transmit power control; this varies the electrical power applied to the ultrasound transducer and, hence, varies the amplitude of the transmitted beam. Higher power output settings result in larger amplitude echo signals picked up by the transducer. Of course, they also result in greater acoustic exposure to patients. Receiver sensitivity or gain control; this adjusts the amount of amplification or gain of the receiver amplifier. Loudness or volume control; this allows adjustments of the gain of the audio amplifier section of the instrument. Wall filter control; adjusts the low frequency cutoff of the output Doppler signals. Signals whose frequencies are lower than this cutoff are eliminated from the display. Some combination of the first three controls generally is available to allow the operator to vary the sensitivity of

the Doppler instrument. Most Doppler units have a wall filter adjust (Zagzebski, 1996).

Continuous wave Doppler transducers:

Most continuous wave Doppler instruments employ separate transducer elements for transmitting and receiving. The reason for this is that since the transducer transmits sound waves continuously, weak echo signals picked up by the transducer would be overwhelmed by the transmit signal if the same element were used for both transmitting and receiving. Thus one element is used for continuous transmitting while the other is used for receiving. This could be done using separate elements in the array of a duplex scanner. More commonly, stand -alone transducers are used in continuous wave Doppler (Zagzebski, 1996).

The stand-alone transducer design for continuous wave Doppler is illustrated in Figure 2.18. The beam patterns of the transmitting and receiving transducer are thus made to cross. The region of beam overlap is the most sensitive area of this type of transducer, and scatterers that happen to be within this region yield the largest amplitude Doppler signals. Transducers may be designed to emphasize signals from any depth by appropriate choice of beam overlap or beam focal distance. Since a continuous wave Doppler transducer does not produce short duration pulse, steps taken to dampen the ringing of the element that are common to pulsed transducers do not need to be taken. It may be advantageous, however, to add quarter-wave matching layers to improve the sensitivity of the probe (Zagzebski, 1996).

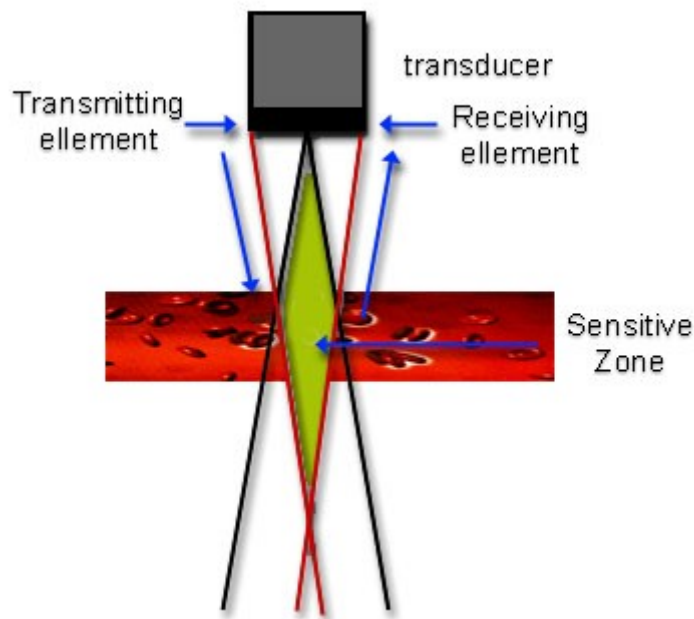


Figure 2-18 shows CW Doppler transducer containing two piezoelectric elements. One element continuously transmits ultrasound waves and the other continuously detects echoes (Zagzebski, 1996).

Choice of Doppler ultrasound frequency:

Choice of operating frequency for a modality was the result of a trade-off between the desire to obtain high resolution (which improves with increasing frequency) and the need to obtain adequate penetration of the ultrasound beam (which decrease with increasing frequency). These trade-offs also are factors in determining the best frequency for specific applications of Doppler instruments. However, factors in addition to attenuation play a role in the signal strength in Doppler ultrasound. Since the source of Doppler ultrasound signals is blood; the scatterers are small, Rayleigh scatterers. The intensity of scattered signals for Rayleigh scatterers increases with the frequency raised to the fourth power. It would thus seem reasonable to use a high ultrasound frequency to increase the intensity of echo signals scattered from blood (Zagzebski, 1996).

As the frequency increases, however, the rate of beam attenuation also increases. In selecting the optimal frequency for detecting blood flow these competing processes must be balanced, and the choice is related to the depth of the vessel of interest. For small, superficial vessels, where attenuation from overlying tissues is not significant, Doppler probes operating in the 8- to 10-MHz frequency range are common. Frequencies as low as 2-MHz is sometimes used where significant ranges and large amounts of attenuation are present. In instruments that provide combined B-mode imaging and Doppler operating modes, it is not unusual to have different ultrasound frequencies applied for each mode. For example, a 7.5-MHz B-mode image might be combined with Doppler processing done at 5-MHz to optimize the detect ability of the Doppler signals from all depth of interest. The echoes originating from stationary structures displayed in B-mode are of significant greater amplitude than those from blood, so greater amounts of beam attenuation can be tolerated for their detection than for detection of signals from blood (Zagzebski, 1996).

2-6-4 Directional Doppler:

In a simple, “nondirectional” Doppler instrument, the output Doppler signals are identical for reflectors moving at a fixed speed; say 50 cm/s, towards the transducer or away from the transducer. In other words, a nondirectional Doppler instrument cannot distinguish whether the Doppler shift in the returning echoes is positive or negative. In some applications only the presence of flow or the relative speed of reflectors needs to be detected, and simple processing without this directional information will do. However, in many situations the direction of flow also is important, requiring directional Doppler circuitry (Zagzebski, 1996).

Special signal processing is required in an instrument that displays the direction of flow. Ordinarily this is done in two stages: Doppler signals are generated that have the directional information encoded and then the directional information is displayed using

loudspeakers, spectral analyzers, or velocity waveform circuits (Zagzebski, 1996).

A commonly used signal processing method in directional Doppler instruments is known as quadrature detection as shown in Figure 2.19. After the received signal is amplified it branches into two separate demodulator circuits. In each circuit the signal is mixed with a reference signal derived from the transmitter, similar to nondirectional processing outlined earlier. Filtering out the high frequency signals, leaving only the audible Doppler signals for each branch, yields two nearly identical Doppler signals, V_a and V_b from the separate demodulators. Processing in the two demodulators is the same except for a slight difference signals. These differ in phase by exactly one fourth the period of the reference frequency, hence the term quadrature detectors. It turns out that the output Doppler signals, V_a and V_b , also differ in phase. Their relative phase depends on whether the received echo signal frequency is greater or less than the transmitted signal frequency (Zagzebski, 1996).

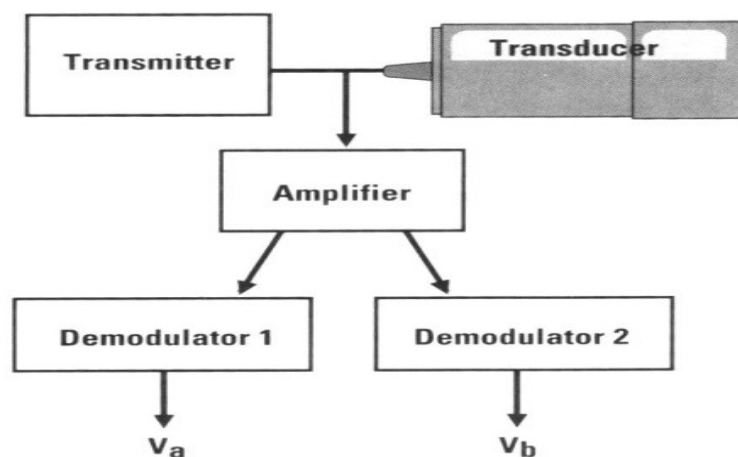


Figure 2-19 illustrate quadrature detection to determine flow direction, echo signals are sent to two demodulators, producing two Doppler signals, V_a and V_b , the phase relationship between these two signals can use by the instrument to determine whether the Doppler shift is positive or negative (Zagzebski, 1996).

Hence the phase relationship of the output quadrature signals depends on whether the scatterers are moving toward or away from the transducer as shown in Figure 2.20. This can be used to

determine the flow direction. The two quadrature signals sound identical when applied individually to loudspeakers. They are processed further to derive directional information (Zagzebski, 1996).

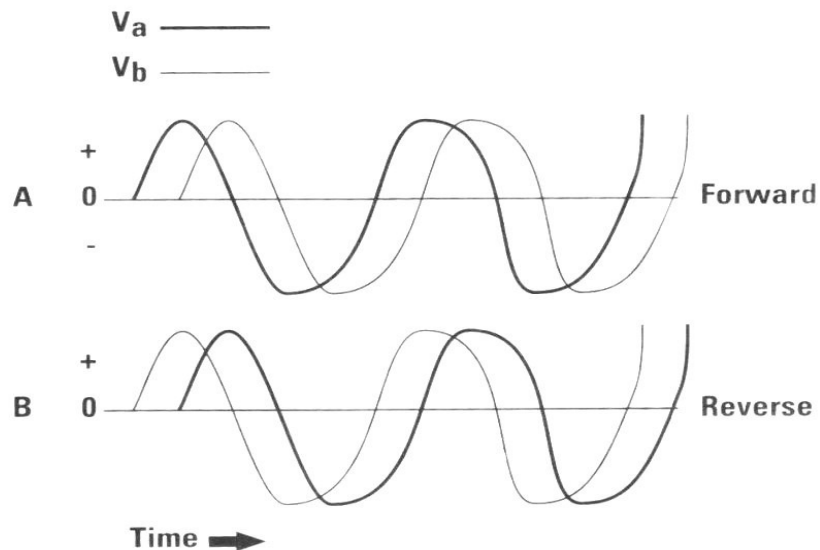


Figure 2-20 shows the two output Doppler signals, V_a and V_b following quadrature demodulation, their relative timing, or phase, depends on whether flow is towards the transducer or away from the transducer an additional processing within the instrument takes advantage of this phase relationship in the two channels to determine reflector direction (Zagzebski, 1996)..

2-6-5 Pulsed Doppler:

With continuous wave Doppler instruments, reflectors and scatters anywhere in the beam of the transducer can contribute to the Doppler signal. Pulsed Doppler provides the ability to select Doppler signals from specific depths. The region from which the signals are selected is called the sample volume. When combined with steerable Doppler beams on duplex scanners, pulsed Doppler enables the precise selection of the depth and angle of the sample volume (Zagzebski, 1996).

Pulsed Doppler circuitry:

Pulsed Doppler is somewhat like pulse echo ultrasound in that sounds pulses are produced by the transducer at regular intervals. A transmitter as shown in Figure 2.21 applies a transmit pulse to the

transducer; this pulse has a well-defined frequency. Some pulsed Doppler instruments allow the operator to vary the pulse duration, that is, the number of cycles in the pulse, in order to vary the sensitivity. More cycles in the pulse results in improve sensitivity and better performance of the Doppler circuitry. This is done at the expense of somewhat greater acoustic exposure to the patient and poorer axial resolution (Zagzebski, 1996).

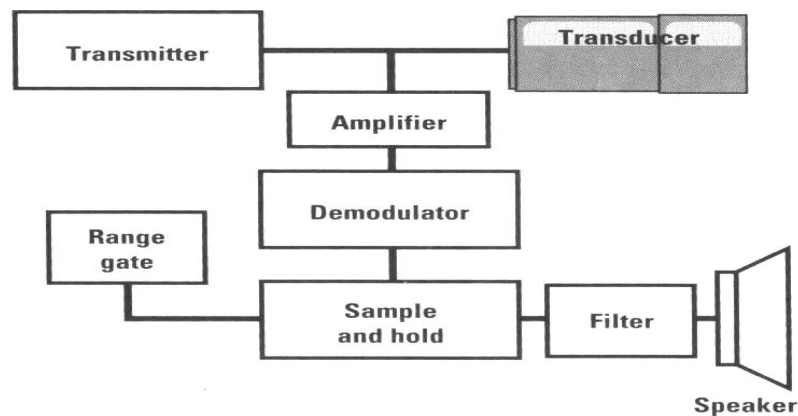


Figure 2-21 shows pulsed Doppler instrument. Following each transmit pulse, echoes are amplified and Doppler processed in the demodulator, so the signal depends both on the echo amplitude and the phase a segment of the signal from a fixed depth is selected by the range gate/sample and hold system (Zagzebski, 1996).

Amplification and demodulation of the echo signals occur, analogous to continuous wave Doppler. The output of a Doppler demodulator depends not only on the amplitude of echoes from reflectors, but also on the precise phase of the echo signals. An operator adjusted “range gate” isolates signal from the desired depth. These are stored temporarily in the sample and hold unit. Awaiting the outcome of another transmit pulse. If reflectors within the gated volume are moving, echoes collected during the subsequent pulse echo sequence are of slightly different phase. This difference will show up during Doppler processing in the Doppler signal from the gated volume is built up gradually in the sample and hold unit (Zagzebski, 1996).

Pulsed Doppler controls:

Operator controls on pulsed Doppler instruments, in addition to those already mentioned for continuous wave Doppler units, include the following: range gate position; the operator can place the range gate at various depths, gate or sample volume size; increasing the range gate accepts Doppler signals from a longer axial region, pulse duration which appear on some instruments as flow angle cursor; for duplex instruments; the angle cursor is positioned by the operator so that it follows the perceived direction of flow. The instrument then makes an angle correction to the velocity display (Zagzebski, 1996).

A more detailed view of the build-up of the pulsed Doppler signal is obtained with the help of Figure 2.22. In this sketch, we are assuming a signal reflector is moving towards the transducer. The amplified echo signal shows only the signal from the reflector; four waveforms corresponding to four successive pulse echo sequences are shown (Zagzebski, 1996).

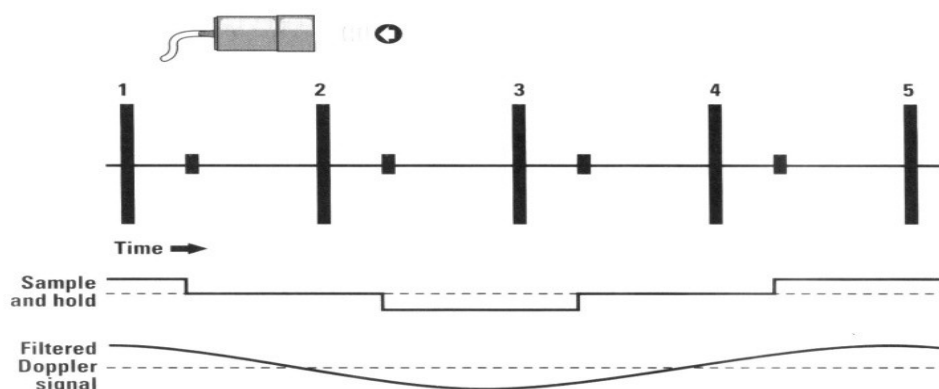


Figure 2.22 shows the build-up of the pulsed Doppler signal. Amplified echo signals from the moving reflector are shown for four successive pulse-echo sequences (a fifth pulse has been launched, but the echo does not show up in this diagram) also shown is the output of the sample and hold device; this signal varies because the phase of the echo from the reflector changes as it moves. The bottom trace is a filtered (smoothed) version of this signal, which is the Doppler signal (Zagzebski, 1996).

Because of the motion of the reflector, the time for the echo to return shortens from one pulse to the next. The gated output of the demodulator depends on the phase of the amplified echo signal compared to that of the transmit oscillator. It is highest when the

phase are the same and lowest when they differ by 180 degrees. Because the echo signal phase varies between pulses, the gated demodulator output also varies. The sample and hold unit retains the demodulator output between pulse echo sequences. The filtered version of this retained signal is the Doppler signal (Zagzebski, 1996).

Size of the pulsed Doppler sample volume:

The sample volume size, indicated in Figure 2.23, is determined by two factors. The ultrasound beam width, both in the scan plane and perpendicular to the scan plane, determines the cross sectional area of the sample volume. Thus a more tightly focused ultrasound beam results in a smaller beam area and narrower sample volume (Zagzebski, 1996).

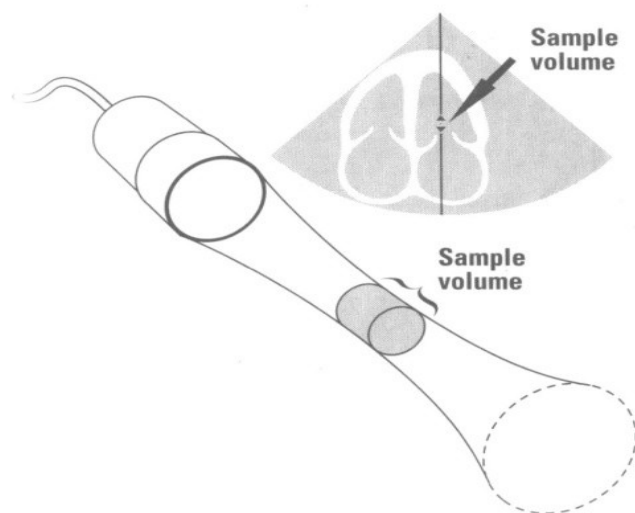


Figure 2-23 illustrates pulsed Doppler sample volume where the beam width, both in the scan plane and perpendicular to the scan plane, determines the sample volume cross-sectional area where the gate size and pulsed duration determine the axial extent of the sample volume (Zagzebski, 1996).

The axial length of the sample volume is determined by the pulse duration and by the sample gate size. Most instruments provide a control so that the operator can adjust the gate size (Zagzebski, 1996).

Increase the gate size; increase the volume from which Doppler signals are picked up. This is easily demonstrated using a flow phantom as shown in Figure 2.24. When a narrow gate is used figure 2.24, A, and is centered in the middle of the vessel, a very narrow range of velocities is picked up, as shown by the velocity traces on the bottom. When a larger gate is used Figure 2.24, B, and a larger range of velocities is picked up (Zagzebski, 1996).

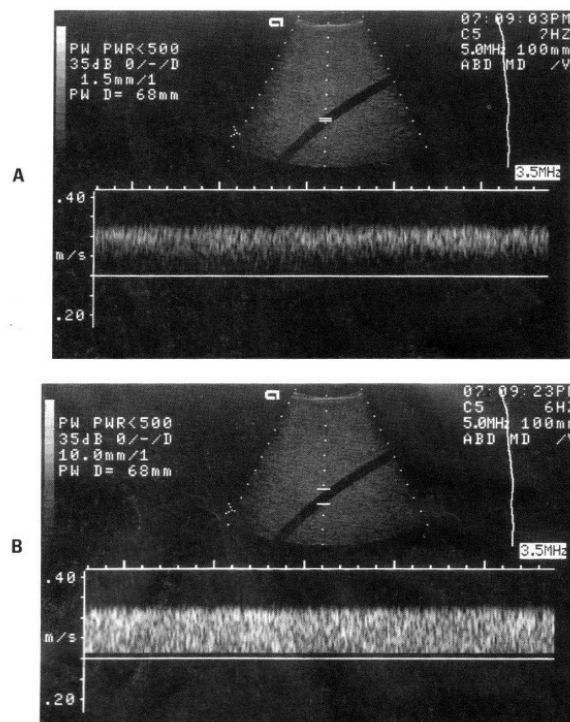


Figure 2-24 (A) shows control of sample volume size by varying the gate size of a pulsed Doppler instrument in this flow phantom, the velocities are highest in the middle of the vessel and slowest near the edges. When a narrow gate is used and is centered in the middle of the vessel, a very narrow range of velocities is picked up, as shown by the velocity trace on the bottom of Figure 2.24 (B) when a larger gate is used, a large range of velocities is picked up while spectral velocity trace is filled in from approximately 0 m/s all the way up to the maximum velocity in the vessel, about 25 m/s (Zagzebski, 1996).

2-6-6 **Duplex Instruments:**

A pulse echo scanner and a Doppler instrument provide complementary information in that the scanner can best outline anatomical details whereas a Doppler instrument yields information regarding flow and movement patterns. "Duplex" ultrasound instruments are real-time B-mode scanners image obtained with a duplex scanner is used to localize areas where flow will be examined using Doppler. The area to be studied in pulsed Doppler mode is selected on the B-mode image with a "sample volume" or "sample gate" indicator, Figure 2.25. The cursor position is controlled by the operator. Many duplex instruments allow the operator to indicate the direction of flow with respect to the ultrasound beam direction by adjusting an angle cursor. This is necessary to estimate the reflector velocity from the frequency of the Doppler signal. During duplex scanning, the ultrasound transducer assembly and the instrument "time-shares" between pulse echo and Doppler mode. The extent of this time sharing is often under operator control directly or indirectly. Thus some instruments allow the operator to specify the rate at which the B-mode image is update while in Doppler mode. This may range from 7 to 10 times per seconds to no updating at all of course, the more frequently the B-mode image is update, the more certain the operator is of the exact location of the sample volume during a Doppler study, an important consideration especially for smaller vessels (Zagzebski, 1996).

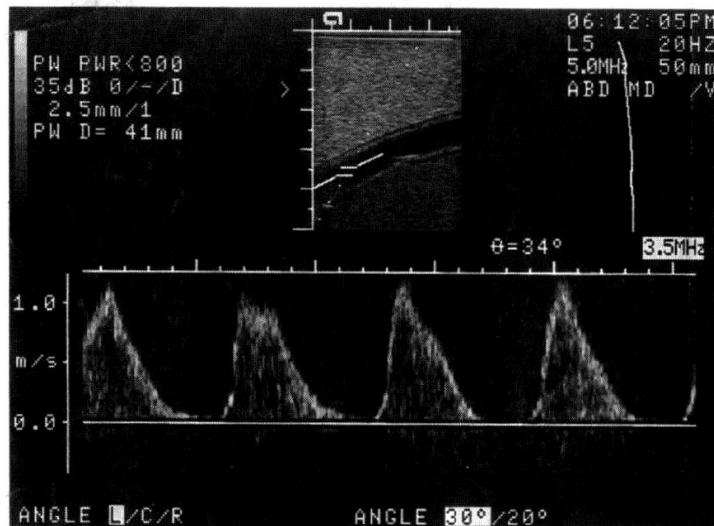


Figure 2-25 shows ultrasound B-mode image of a Doppler phantom (top) a-long with a spectral Doppler trace (bottom) where the vertical scale in the spectral Doppler trace indicates velocity in meters per second (m/s), operator positioned angle cursor is located in the middle of the gated region. The cursor is aligned along the assumed axis of the vessels (Zagzebski, 1996).

Transducers for duplex:

Both mechanical scanners and array transducer assemblies are used as duplex scanners. Mechanical sector scanners provides the ability to incorporate annular array transducer for an improve slice thickness over the image. However, phased linear and curvilinear arrays offer other advantages for duplex scanning, especially in the flexibility in switching between Doppler and real tie B-mode. Because there are no moving parts in the transducer assembly the array scanning instrument can quickly and automatically shift between steering the beam toward the sample volume in Doppler mode and then back to B-mode to build up part of the B-mode image, then back to Doppler mode, and so on. Thus B-mode image updating may be more rapid when studies are done in a combined B-mode scan and pulsed Doppler mode (Zagzebski, 1996).

2-6-7-Doppler spectral analysis:

Characteristics of flow in vessels:

Doppler signals from flowing blood may be complicated because of the nature of the flow patterns encountered by the sound beam. Sometimes the flow is parabolic or laminar. As shown in A of Figure 2.26. Blood cells move fastest along the axis of the vessel; the velocity drops to zero at the vessel wall. Laminar flow is often considered an ideal condition that slow to moderately fast flow reaches if there are no abrupt discontinuities in the aorta, the flow may take on a more blunt profile. Here the flow profile is nearly constant across the vessel; near the wall the flow decreases to zero again. Finally, a turbulent flow pattern as might be caused by a blockage or narrowing is shown in C of Figure 2.26. The actual velocity profile across any vessel depends on a number of factors, including the diameter of the vessel, the mechanical properties of blood, the flow velocity, and the time. If echo signals are detected simultaneously from across the vessel, a range of Doppler frequencies is present in the signal. The number of different frequencies depends on the distribution of velocities present, the transducer beam width, and the size of the Doppler sample volume if pulsed Doppler is employed. A quantitative analysis showing the distribution of frequencies is done by spectral analysis (Zagzebski, 1996).

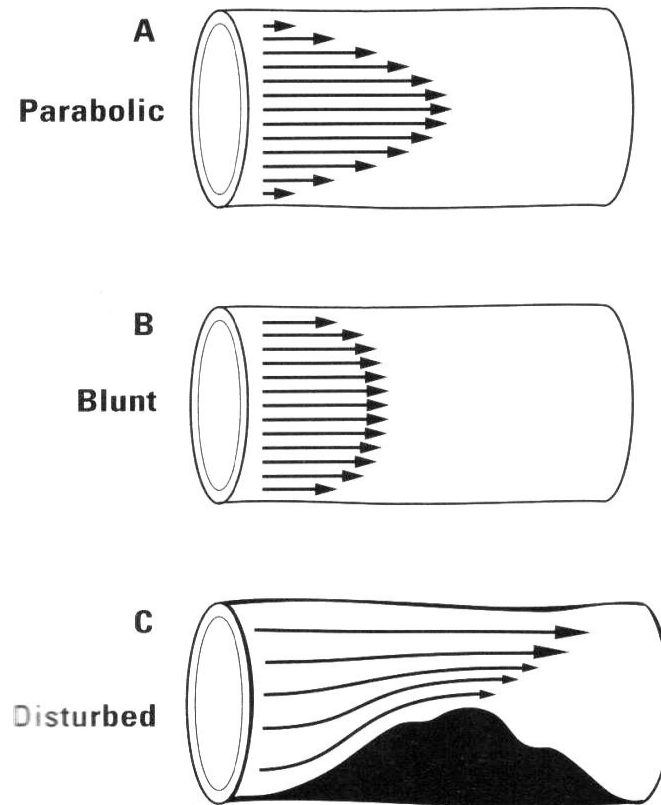


Figure 2-26 illustrate laminar, blunt, and turbulent flow patterns (Zagzebski, 1996).

Spectral analysis:

Spectral analysis is a process by which a complex signal is broken down or analyzed into simple frequency components. In physics and engineering the most common way to do spectral analysis is to use a process called Fourier analysis. A commonly used device that performs the spectral analysis in ultrasound instruments is a fast Fourier transform (FFT) analyzer. The FFT instrument, along with a display screen, allows the amount of Doppler signal present at different frequencies to be displayed as a function of time. The FFT analyzer, Figure 2.27 operates serially on small, 1- to 5-ms, segments of the Doppler signal. The signal segment is converted to digital format “digitized” in an analog-to-digital (A/D) converter and is then sent to the spectral analyzer. The analyzer produces a record showing the relative amount of signal with each of several discrete

frequency bins. It then operates on another signal segment, and so on, producing a continuous display (Zagzebski, 1996).

The result of the FFT's operation is illustrated schematically in Figure 2.27. In this figure the horizontal axis represents time and is broken into small intervals to correspond to the signal segments. The vertical axis represents Doppler frequency, or reflector velocity, and is divided into discrete frequency bins where the higher the bin on the vertical scale, the greater the frequency. The FFT analyzer fills each frequency bin with a density or shade of gray that represent the amount of signal with that frequency during the segment. The amount of signal is related to the number of red blood cells and the Doppler frequency is proportional to their velocity; hence, we have the representation as illustrated. By operating on successive signal segments the analyzer produces a continuous spectral display (Zagzebski, 1996).

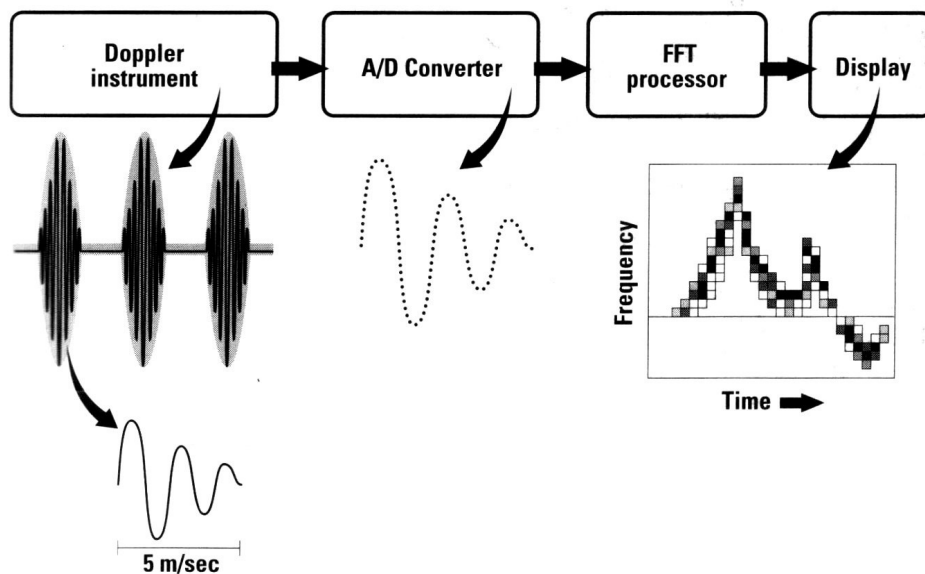


Figure 2-27 illustrate spectral analyzer, Doppler signal (left) is partitioned into small segments, and each chunk is analyzed to determine the amount of signal present at various frequencies. Each segment is represented as a column on the display, with the frequency (or velocity) appearing vertically and the amount of signal at each frequency (or velocity) indicated as a shade of gray (Zagzebski, 1996).

2-6-8 Information on the spectral display:

The Doppler spectral display provides a readout of the distribution of frequencies and hence, reflector velocities contributing to the signal. Velocity versus time flow patterns for arteries and many large veins have been established. Deviations of these patterns from normal are evaluated using spectral Doppler. The example in Figure 2.28 is for a normal carotid artery and one that has a stenosis, where the sample volume was placed at the distal margin of the stenotic region. Other important characteristics of flow pattern may also be gleaned from the spectral display. For example, with pulsed Doppler and a short sample gate positioned in the center of a vessel, a narrow band Doppler frequency spectral display is usually obtained (Zagzebski, 1996).

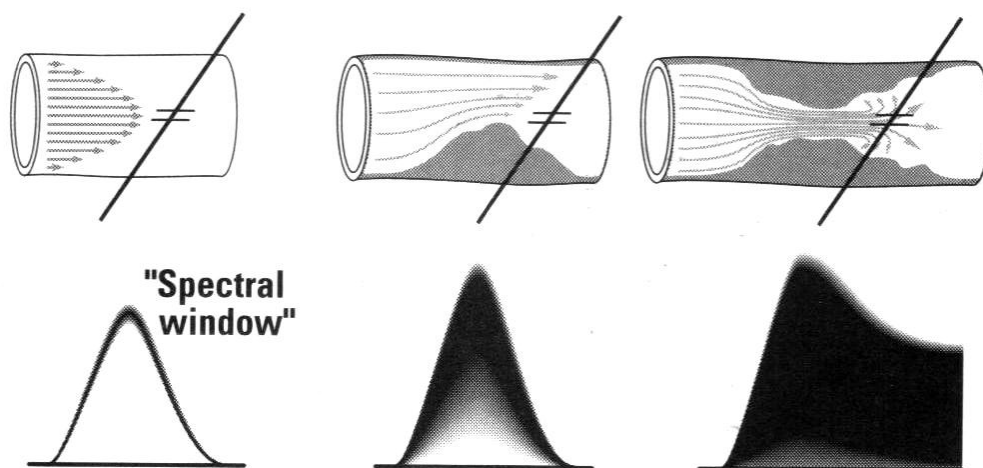


Figure 2-28 shows some characteristics of the Doppler signal spectral display for different flow conditions, left diagram presents a normal spectrum with the gate selecting a very narrow range of velocities that contribute to the signal, open region within the spectral envelope during peak flow is called the spectral window, partial or total fill in of the spectral window occurs with turbulence seen in the two panels on the (Zagzebski, 1996).

The area beneath the peak of the spectral trace is called the spectral window, partial or total fill-in of the spectral window can occur in the presence of turbulence. These disturbances in the Doppler spectrum are also called spectral broadening because they

are related to a wider range of Doppler frequencies from the sample volume. The presence of obstructions may sometimes be detected from the spectrum. If the vessel is large compared to the sample volume, a fairly narrow velocity range is sampled. This results in a narrow frequency band and the spectral window on the display. In presence of mild or several turbulence caused by obstruction, this spectral window is filled in partially or entirely Figure 2.28 (Zagzebski, 1996).

Some instruments display additional information related to the instantaneous distribution of velocities in the spectrum. The “mean” Figure 2.29 is the average value of all signals in the spectrum at any given time. An example is shown in Figure 2.29, where the mean frequency trace is superimposed on spectral trace from the carotid artery. The “mode” is the most likely velocity, or the value in the spectrum that is the whitest shade of gray; this correspond the most prevalent red blood cell velocity in the sample volume. The spectral “width” indicates the range of Doppler frequencies, and hence, reflector velocities contributing to the Doppler signal, and the “peak” is the top of the spectral envelope (Zagzebski, 1996).

Various parameters have been derived from the Doppler signal spectrum to quantify important properties of the flow. For example, the pulsatility index, PI, is defined by equation 2.2:

$$PI = \frac{\max - \min}{ave} \quad 2.2$$

Where max and min refer to the peak systolic and minimum diastolic velocities, respectively, during the cardiac cycle and ave is the average flow during the cycle (Zagzebski, 1996).

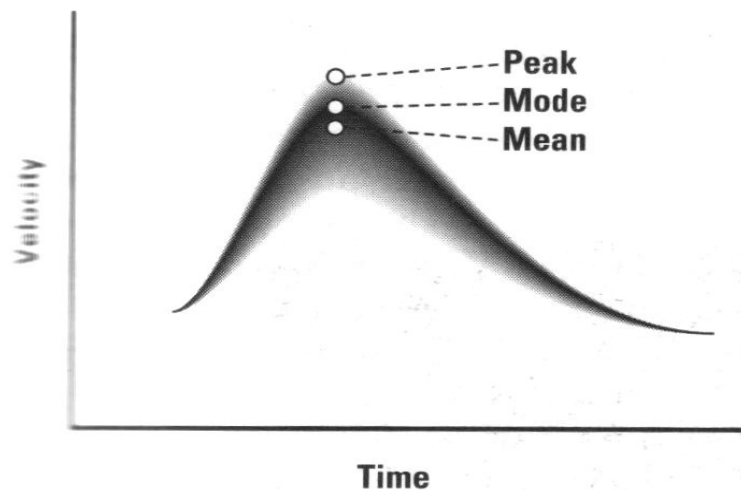


Figure 2-29 determine definition of the “peak,” “mode,” and “mean” frequencies (or velocities) on a Doppler spectral display (Zagzebski, 1996).

These quantities are obtained from the spectral display. The average value during the cardiac cycle either must be obtained by the operator tracing the mean spectral waveform, or, for some instruments, by algorithms in the instrument. A similar index, the resistivity index does not require estimates of the mean velocity during the cardiac cycle, but only maximum and minimum values. It is defined by the following equation 2.3:

$$RI = \frac{\text{max} - \text{min}}{\text{max}} \quad 2.3$$

An advantage of these parameters is that they provide data on the relative resistance to flow of the vascular bed; they do this without the need to quantify velocities and flow absolutely, where angle correction must provide. Angle correction may be impossible, especially in situations where the vessel lumen cannot be visualized, such as in the kidney (Zagzebski, 1996).

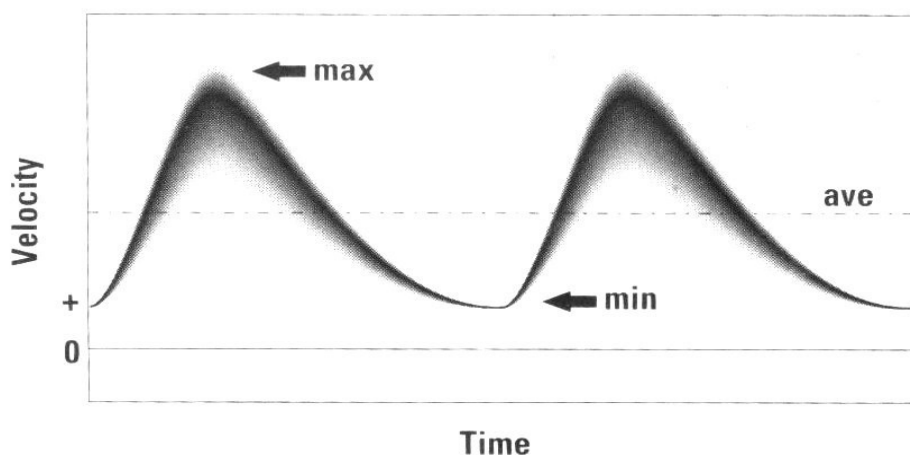


Figure 2-30 determine the parameters used to complete the pulsatility index, PI, and the resistivity index, RI (Zagzebski, 1996).

In general PI values greater than 1.2 are considered high and values below 0.8 are considered low also RI values greater than 0.7 are interpreted as high and values less than 0.4 are considered low (Zagzebski, 1996).

2-6-9 Aliasing and the Nyquist frequency:

Sampling the Doppler signal:

With a pulsed instrument the output Doppler signal is built up in discrete “pieces”, one piece being added each time a pulse is launched, and echo signals are detected from the sample volume. We say that the Doppler signal is “sampled” rather than recorded continuously. Sampling in this context is somewhat like a strobe light illuminating a dancer on stage. If the strobe frequency is high enough, the movements of the dancer may be followed easily, but if the strobe flashes are too slow, the audience only sees a jerky, discontinuous movement. In pulsed Doppler, each time a pulsed is launched by the transducer and an echo from moving reflectors detected, a sample of Doppler signal is stored in the sample and hold unit. The sampling frequency of a pulsed Doppler instrument is equal to the pulse repetition frequency (PRF) in Doppler mode (Zagzebski, 1996).

Aliasing:

Aliasing occurs with pulsed ultrasound and is most commonly encountered with color Doppler or pulse wave spectral Doppler. With pulsed ultrasound, there is an upper limit of the Doppler shift which can be displayed. This is known as the Nyquist limit and is defined as the pulse repetition frequency/2. With high velocity blood flow generating Doppler shifts above the Nyquist limit, aliasing occurs and is displayed as bright, turbulent appearing flow in color Doppler and in blood flow profiles which "wrap around" the displayed scale in pulse wave spectral Doppler (Zagzebski, 1996).

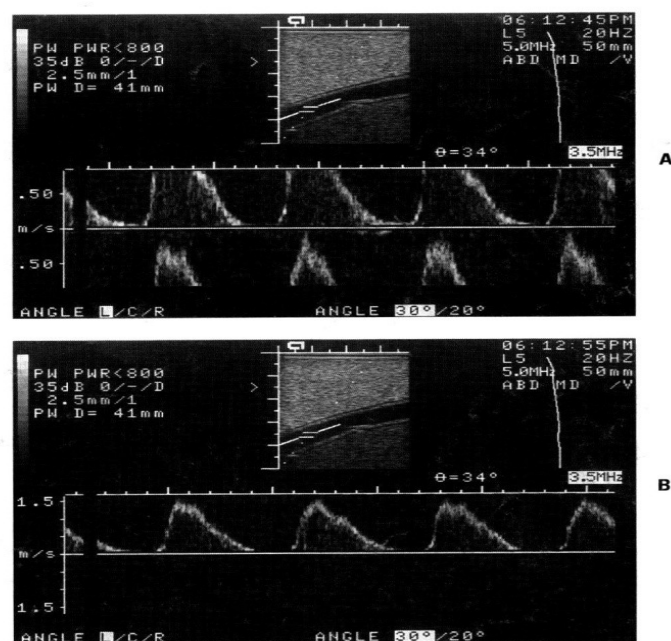


Figure 2-31 (A) spectral Doppler display the spectrum wraps around from the top to the bottom of the display, producing an apparent reversal of flow even though flow does not reverse itself the high frequencies are converted to low frequencies on the display where in figure 2-31 (B) the elimination of aliasing is by increasing the velocity scale and the Doppler instrument automatically increases the PRF when the operator changes the scale setting (Zagzebski, 1996).

Means of Eliminating Aliasing

Image at a Shallower Depth: Notice that the Nyquist limit is dependent on the PRF which in turn is the reciprocal of the pulse repetition period (PRP). If one images at a shallower depth, the listening time decreases and therefore the PRP decreases. A decrease in the PRP therefore leads to an increase in the PRF and therefore the Nyquist limit.

Increase Angle of Insonification: The Doppler shift is dependent on the cosine of the angle between the ultrasound beam and the direction of motion. When the beam and the object are parallel, the cosine of 0 degree is 1. However, if this shift results in aliasing, increasing the angle between the beam and the direction of motion of blood flow will decrease the Doppler shift (for example cosine of 30 degree is 0.8). This may eliminate aliasing and allow display of the flow, at the expense of underestimating the true velocity.

Use Low Frequency Transducer: Recall that the Doppler shift frequency is directly related to the fundamental frequency emitted by the transducer. Therefore, using a lower frequency transducer will generate a smaller Doppler shift for any given blood flow velocity and may eliminate aliasing.

Use Continuous Wave Imaging: With CW, there is one element always emitting ultrasound and another element always listening. Therefore, there is no "listening time" and no limitation on the Doppler shift which can be measured and displayed. This is why CW is used to measure all high velocity jets in echocardiography. This advantage of CW imaging unfortunately comes at the expense of range resolution.

Change the Scale: On rare occasion, the scale for color or spectral Doppler is set inappropriately low such that the color flow or spectral Doppler aliases even at a velocity which one would not expect it to. This is usually remedied by increasing the color scale. However, one can only increase the Doppler scale a relatively small amount.

Change the Display Baseline: This is not a true means of reducing aliasing because in both color and spectral Doppler the baseline can only be shifted so much and you are really only changing the how Doppler shift detected is displayed rather than changing the properties of the Doppler shift itself (<http://echocardiographer.org/index.html>).

2-6-10 Resistive index:

The Doppler-derived renal resistive index has been used for years in a variety of clinical settings such as the assessment of chronic renal allograft rejection, detection and management of renal artery stenosis, evaluation of progression risk in chronic kidney disease, differential diagnosis in acute and chronic obstructive renal disease, and more recently as a predictor of renal and global outcome in the critically ill patient. More recently, evidence has been accumulating showing that an increased renal resistive index not only reflects changes in intrarenal perfusion but is also related to systemic hemodynamics and the presence of subclinical atherosclerosis. The Doppler resistive index (RI) ($[\text{peak systolic velocity} - \text{end diastolic velocity}] / \text{peak systolic velocity}$) was advanced as a useful parameter for quantifying the alterations in renal blood flow that may occur with renal disease. The highest frequency probe that gives measurable waveforms should be used, supplemented by color or power Doppler sonography as necessary for vessel localization. Interlobar arteries (adjacent to medullary pyramids) are then insonated using a 2- to 4-mm Doppler gate. Waveforms should be optimized for measurement using the lowest pulse repetition frequency without aliasing (to maximize waveform size), the highest gain without obscuring background noise, and the lowest wall filter. Three to five reproducible waveforms from each kidney are obtained, and RIs from these waveforms are averaged to arrive at mean RI values for each kidney. In general, most sonographers now consider 0.70 to be the upper threshold of the normal RI in adults. Important exceptions to this threshold have been reported, however. In children, it is common for the mean RI to exceed 0.70 through the first year of life, and a mean RI greater than 0.70 can be seen through at least the first 4 years of life. In elderly patients without renal insufficiency, the normal RI can also exceed 0.70. It is uncertain whether this is a normal phenomenon, perhaps due to age-related changes in vascular compliance, or the consequence of

small vessel changes in the kidney due to aging (Mitchell E et al. 2003).

2-7 Previous studies:

Kin Hung Liu et al (2012) examined the association between intrarenal arterial RI and diabetic complications in Chinese type 2 diabetic subjects. Clinical and biochemical parameters, including diabetes-related microvascular complications (nephropathy, retinopathy and sensory neuropathy) were examined. Three hundred and eighty-seven Chinese type 2 diabetic patients underwent ultrasound examinations for the assessment of intrarenal arterial RI of both kidneys. The mean RI of patients with any microvascular complications (0.70 ± 0.09 versus 0.65 ± 0.06) such as nephropathy (0.71 ± 0.09 versus 0.66 ± 0.06), retinopathy (0.71 ± 0.08 versus 0.67 ± 0.08) and sensory neuropathy (0.75 ± 0.07 versus 0.68 ± 0.08) and with any macrovascular complications (0.71 ± 0.09 versus 0.68 ± 0.08) was higher than those without ($P < 0.05$) ($0.745 \pm .07$ versus 0.665 ± 0.0035).

Lin ZY et al (2003) investigated the influence of age on intrarenal arterial resistive index (RI) measurement in 135 normal subjects (71 male, 64 female; age range = 17-68 years, median age = 37 years). They found that although there is a statistically significant positive correlation between intrarenal RI and age, the correlation is weak. This suggests that the influence of age on RI measurement is small and may be of no clinical importance.

Spomenka Ljubia et al (2006) investigated the predictive variables for RI elevation in patients with type 2 diabetes. Forty-three patients (21 male and 22 female, age range 39-71 years, diabetes duration 0-25 years) were included in the study. The stepwise regression method was used to analyze the influence of predictor variables: patient age, diabetes duration, systolic and diastolic blood pressure, albumin excretion rate (AER), lipid values, glycated hemoglobin and creatinine clearance on RI elevation. A statistically significant correlation was found between RI and diabetes duration, systolic

blood pressure and AER. In the group of normoalbuminuric patients, RI elevation was observed in 8 patients. A statistically significant difference was found in diabetes duration between normoalbuminuric patients with $RI < 0.70$ and $RI \geq 0.70$ ($p < 0.05$), but not in systolic blood pressure ($p = 1.000$). RI elevation can be observed prior to the occurrence of microalbuminuria. The values of diabetes duration, systolic blood pressure and albumin excretion rate can explain the high percentage (53%) of RI variance.

[Ohta Y](#) et al (2005) evaluated the relationship between these indices and pulse wave velocity (PWV), a measure of arterial stiffness, which reflects atherosclerosis, and determined whether renal RI and PI differ depending on the underlying renal disease. A total of 245 inpatients with or without renal impairment who underwent ultrasonographic assessment of the renal artery were enrolled in the study. Patients with renal artery stenosis or severe renal failure (serum creatinine ≥ 6 mg/dl) were excluded from the study. They concluded that these results suggested that the increased RI of the renal arteries is associated with the severity of systemic atherosclerosis. Furthermore, the intrarenal vascular resistance differs depending on the underlying renal disease, and appears to increase to a greater extent in diabetic nephropathy.

[Richard J](#) et al (2006) studied 325 unselected clinic patients who had sufficient clinical and biochemical information to calculate an estimated glomerular filtration rate (eGFR) using the Modified Diet in Renal Disease six-variable formula, at least two estimations of urinary albumin excretion rates (AER), and a renal duplex scan to estimate the resistance index of the interlobar renal arteries. The resistance index, measured as part of a complications surveillance program, was compared in patients with an $eGFR < \text{or} \geq 60$ ml/min per 1.73 m^2 who were further stratified into normo- (AER < 20), micro- (20–200), or macroalbuminuria ($> 200 \mu\text{g}/\text{min}$) categories. Their results were Patients with an $eGFR < 60$ ml/min per 1.73 m^2 had a higher resistance index of the renal interlobar arteries

compared with patients with an eGFR ≥ 60 ml/min per 1.73 m². However, the resistance index was elevated to a similar extent in patients with an eGFR < 60 ml/min per 1.73 m² regardless of albuminuric status (normo- 0.74 ± 0.01 , micro- 0.73 ± 0.01 , and macroalbuminuria resistance index 0.75 ± 0.11). Multiple regression analysis revealed that increased age ($P < 0.0001$), elevated BMI ($P = 0.0001$), decreased eGFR ($P < 0.01$), and decreased diastolic blood pressure ($P < 0.01$), but not an increased AER, were independently associated with an elevated resistance index in patients with impaired renal function. They concluded that Subjects with type 2 diabetes and reduced glomerular filtration rate had similar degrees of intrarenal vascular disease, as measured by the intrarenal arterial resistance index, regardless of their AER status. The pathological mechanisms that determine the relationship between impaired renal function and AER status in subjects with type 2 diabetes remain to be elucidated.

Hans et al (1983) studied the effect of early aggressive antihypertensive treatment on kidney function in diabetic nephropathy. It carried out prospectively in ten insulin-dependent diabetics (mean age 29 years). During the mean pretreatment period of 29 (range 23-38) months the glomerular filtration rate (GFR) decreased significantly and the urinary albumin excretion rate and arterial blood pressure rose significantly. During the 39 month (range 28-48) period of antihypertensive treatment with metoprolol, hydralazine, and frusemide (furosemide) or thiazide, arterial blood pressure fell from 144/97 mm Hg (mean of all pretreatment values) to 128/84 mm Hg (mean of all post-treatment values), urinary albumin excretion from 977 $\mu\text{g}/\text{min}$ to 433 $\mu\text{g}/\text{min}$, and GFR from 80 to 62 ml/min/1.73 m². The rate of decline in GFR decreased from 0.91 ml/min/month before treatment to 0.39 ml/min/month (range 0.08 to 0.68 ml/min/month) during treatment.

[Doaa M Youssef and Faten M Fawzy \(2012\)](#) hypothesized that one of the markers that could be helpful in detecting functional alterations in

renal hemodynamics is assessment of the renal resistive index (RI) by using renal Doppler. They studied 25 patients with T1-DM (Group-A), which comprised of 15 females and 10 males, with a mean age of 10.8 ± 2.2 years and duration of diabetes of 5 ± 1.1 years. A control group (Group-B) comprising 20 healthy children, 12 females and eight males with mean age of 11.6 ± 2 years, was also studied. The following parameters were studied in the two groups: age, serum creatinine, albumin excretion rate (AER), glomerular filtration rate (GFR), glycosylated hemoglobin (HbA1c) and mean renal RI of both kidneys. They found an increase in the mean RI in diabetic patients versus healthy children. This increase in RI had a positive correlation with duration of the disease, GFR and HbA1c levels, but there was no correlation with serum creatinine or AER. They concluded that RI is increased early in T1-DM, and it can be a predictor of DN (129). (the mean RI in Group-A was 0.64 ± 0.055 while it was 0.58 ± 0.028 in Group-B ($P < 0.000$) versus $0.745 \pm .07$ versus 0.665 ± 0.0035 due to age and duration).

[Ishimura E](#) et al (1997) studied Intrarenal hemodynamics by duplex Doppler sonography in 112 in-patients with [type II diabetes mellitus](#) (DM; 65 males, 47 females, 58 ± 13 years old). Their results showed that multiple regression analysis revealed that RI values in DM patients were significantly affected by [creatinine](#) clearance, age, and duration of [diabetes](#) ($R^2 = 0.554$, $P < 0.0001$). These results demonstrate that intrarenal hemodynamic abnormalities are present in type II DM patients with [nephropathy](#), and that intrarenal hemodynamics are affected by decreased glomerular function and also probably by advanced [arteriosclerosis](#).

Tushar P Rauta et al (2012) studied the clinical profile of Diabetic nephropathy and the correlation of intrarenal resistivity index with parameters of renal dysfunction like Glomerular filtration rate, Serum Creatinine, micro and macroalbuminuria. This was a cross sectional observational study carried out over a period of 2 years. Patients of type 2 Diabetes as per WHO criteria who had

nephropathy were included. A Detailed history was taken and clinical examination was done. Urine routine and microscopic examination and biochemical investigations were done. Patients were subjected to ultrasound of kidneys and renal Doppler. A total of 160 patients of type 2 diabetes with diabetic nephropathy were studied. They were divided into two groups based on intrarenal resistivity index (IRI) by duplex ultrasonography as Group I: Patients with $IRI \leq 0.70$ (n = 72) and Group II: Patients with $IRI > 0.70$ (n = 88). Mean age in group I was 50.42 ± 4.89 and in group II was 60.34 ± 7.92 (P = 0.000). Mean duration of diabetes mellitus in group I was 4.57 ± 3.65 years and 11.25 ± 6.97 years in group II. Mean systolic BP in group II was 144.09 ± 16.79 mmHg whereas in group I it was 128.47 ± 13.07 mmHg, 80.55% in group I were in the early stage of nephropathy whereas 69.32% patients of group II were in established stage of nephropathy. On multivariate analysis, factors which independently affected IRI were age, Hypertension, Complications - Coronary artery disease and retinopathy, Macroalbuminuria, Decreased creatinine clearance. they concluded that Intrarenal resistivity index as assessed by duplex ultrasonography is a non-invasive parameter that can be correlated with the clinical profile and biochemical parameters of renal dysfunction type II diabetes mellitus with diabetic nephropathy.

Knowler WC et al (1981) examined the determinants of the incidence of non-insulin-dependent diabetes mellitus among blacks and whites from the NHANES I Epidemiologic Follow-up Study conducted from 197 to 1987. A total of 880 incident cases of diabetes mellitus developed among the 11,097 white and black participants who were between the ages of 25 and 70 years at baseline. This slide points out the striking differences in body mass index among the four race/sex groups. The mean body mass index was higher among black women, and the age adjusted slope of the BMINIDDM risk relation among blacks differed from that among whites. At nearly every level of obesity, blacks had a higher risk of

diabetes than whites, suggesting that other factors may contribute to risk. Among both the very lean (body mass index < 20) and the overweight (body mass index > 26), blacks experienced a greater age-adjusted risk of diabetes than whites. Among white women, there was essentially no excess risk compared with white men. Black women were 50 percent more likely to develop non-insulin-dependent diabetes mellitus (NIDDM) than black men, and they had twice the risk of white women.

Study of Adamu G Bakari (2006) was undertaken to determine whether BMI and casual blood sugar are related. In this study Three-hundred and seventeen subjects participated in the study. Mean age of subjects was 35.0 + 9.8 years (33.0 + 9.6 among females and 36.2 + 9.6 among males $p= 0.1007$). Their Results were female subjects had significantly higher BMI than their male counterparts, (26.6 + 7.2 kg/m² versus 24.0 + 5.4 kg/m² $p=0.0341$). Random blood sugar levels were, however, similar between males and females (85.2 + 27.0 mg/dl versus 85.9 + 14.7 mg/dl, $p=0.8868$). There was a positive but non-significant correlation between casual blood sugar and BMI among female subjects ($r= +0.1520$, $p>0.05$). In the males however, there was no correlation between these variables ($r= -0.0395$, $p>0.5$). He conclude that BMI is higher among females in this community and correlates with random blood glucose levels.

Hilary Jane Bambrick's (2005) study was designed to determine whether the body mass index (BMI) threshold defined for obesity (30kg/m²) adequately reflects risk in an Aboriginal community with a high rate of Type 2 diabetes. Their BMI \geq 30kg/m² and central obesity assessed by WC (women \geq 88cm; men \geq 102cm) were strongly and positively associated. Among women, central obesity was near universal, occurring at BMIs below the 'healthy' range of 20-25. WC was linearly associated with other diabetes risk factors. WC \geq 88cm was more sensitive but less specific than BMI \geq 30 in predicting elevated FG and hypertension among women, while

BMI \geq 25 among men tended to be both more sensitive and Specific than both BMI \geq 30 and WC \geq 102cm.

Study of H. E. Bays et al (2007) was designed to explore the relation between body mass index (BMI) and prevalence of diabetes mellitus, hypertension and dyslipidaemia; examine BMI distributions among patients with these conditions; and compare results from two national surveys. Their results were increased BMI was associated with increased prevalence of diabetes mellitus, hypertension and dyslipidaemia in both studies ($p < 0.001$). For each condition, more than 75% of patients had BMI ≥ 25 kg/m². Estimated prevalence of diabetes mellitus and hypertension was similar in both studies, while dyslipidaemia was substantially higher in NHANES than SHIELD. In both studies, prevalence of diabetes mellitus, hypertension and dyslipidaemia occurred across all ranges of BMI, but increased with higher BMI. However, not all overweight or obese patients had these metabolic diseases and not all with these conditions were overweight or obese. Except for dyslipidaemia prevalence, SHIELD was comparable with NHANES.

N. K. Mungreiphy et al (2011) designed their study to find the prevalence of overweight/obesity and hypertension, and to study the association between BMI, blood pressure, and age. Cross-sectional study was carried out among 257 Tangkhul Naga males of Northeast India, age ranging from 20–70 years. Their results were Mean systolic, and diastolic BP was higher among subjects with elevated BMI and among older subjects. Minimum BP was found among underweight and maximum among obese. BP was found lowest among the youngest age group and higher among the elderly subjects. BMI was also found to be associated with age independently. Although the magnitude of correlation differed, there was significant positive correlation among BMI, age, systolic and diastolic BP. Odd ratios showed overweight/obese subjects to be more likely to have hypertension than those with normal BMI.

Kumileo H et (2008) found that increased RI when defined as RI 0.72 (median) was significantly associated with age.

Gertraud Maskarinec et al (2009) found that for underweight participants, the prevalence tended to be as high, or higher, than in normal-weight subjects. Mean age of subjects was 35.03 ± 9.79 years (33.00 ± 9.64 among females and 36.18 ± 9.59 among males $p=0.1007$). The females had significantly higher BMI than their male counterparts (26.6 ± 7.2 versus 24.0 ± 5.4 , $p=0.0341$). Random blood sugar levels were, however, similar between males and females 85.2 ± 27.0 mg/dl versus 85.9 ± 14.7 mg/dl, $p=0.8868$. There was a positive but non statistically significant correlation between random blood sugar and BMI among female subjects ($r= +0.1520$, $p> 0.05$). However, there was no correlation between these variables ($r= -0.0395$, $p>0.05$) in male subjects.

In the study of Adamu G Bakari et al (2006), 317 subjects participated in the study. 267 (84.2%) were males and 50 (15.8%) females. Of these 43 (33 males and 10 females) were excluded from analysis; 5 for blood sugar in the diabetic range and the rest for age reasons. Mean age of subjects was 35.03 ± 9.79 years (33.00 ± 9.64 among females and 36.18 ± 9.59 among males $p=0.1007$). The females had significantly higher BMI than their male counterparts (26.6 ± 7.2 versus 24.0 ± 5.4 , $p=0.0341$). Random blood sugar levels were, however, similar between males and females 85.2 ± 27.0 mg/dl versus 85.9 ± 14.7 mg/dl, $p=0.8868$. There was a positive but none statistically significant correlation between random blood sugar and BMI among female subjects ($r= +0.1520$, $p> 0.05$). However, there was no correlation between these variables ($r= -0.0395$, $p>0.05$) in male subjects.

Study of [Mancini M](#) et al (2013) was designed to evaluate the renal volume and intrarenal hemodynamics with duplex sonography in a group of diabetic patients with normal renal function in comparison to nondiabetic controls. The renal volume and resistive index (RI) of

segmental arteries were assessed by duplex sonography in 88 diabetic patients (44 male and 44 female; median age, 58 years [range, 37-69 years]) and 73 nondiabetic control participants (48 male and 25 female; median age, 53 years [range, 27-75 years]) without renal artery stenosis. They found that both renal volume and RI values in the diabetic patients were significantly higher compared to the controls (mean volume \pm SD: diabetic patients, 197.3 ± 47.6 mL; controls, 162.5 ± 35.2 mL; $P < .0001$; RI: diabetic patients, 0.70 ± 0.05 ; controls, 0.59 ± 0.06 ; $P < .0001$). Renal hypertrophy was present even in diabetic patients without proteinuria (renal volume: patients without proteinuria, 198.3 ± 45.9 mL; controls, 162.5 ± 35.2 mL; $P < .005$). Patients with higher RI values had significantly greater proteinuria (RI < 0.75 , 15.9 mg/g [range, 4.2-1718.9 mg/g]; RI > 0.75 , 37.9 mg/g [range, 11.34-2087.0 mg/g]; $P < .02$). They concluded that changes in renal volume and hemodynamics are detectable on sonography in diabetic patients. Those changes are also present in patients without proteinuria or signs of renal atherosclerosis and with both normal and increased glomerular filtration rates. These results indicate a potential role of duplex sonography in the early identification of morphologic and hemodynamic renal changes in type 2 diabetic patients.

[Jörg Radermacher](#) et al (2002) prospectively tested the hypothesis that a high renal resistance index (≥ 80) predicts progression of renal disease in patients without renal artery stenosis. In 162 patients newly diagnosed with renal disease, the resistance index ($1 - [\text{end diastolic velocity} / \text{maximum systolic velocity}] * 100$) was measured in segmental arteries of both kidneys. Creatinine clearance was measured at baseline, at 3, 6, and 12 months, and then at yearly intervals thereafter (mean follow-up 3 ± 1.4 years). The combined endpoint was a decrease of creatinine clearance by $\geq 50\%$, end-stage renal disease with replacement therapy, or death. Twenty-five patients (15%) had a renal resistance index value ≥ 80 at baseline. Nineteen (76%) had a decline in renal function; 16

(64%) progressed to dialysis, and 6 (24%) died. In comparison, in patients with renal resistance index values <80 , 13 (9%) had a decline in renal function, only 7 (5%) became dialysis-dependent, and 2 (1%) died ($P<0.001$). In a multivariate regression analysis, only proteinuria and resistance index were independent predictors of declining renal function. A renal resistance index value of ≥ 80 reliably identifies patients at risk for progressive renal disease.

The study of [Brandt TD](#) et al (1982) confirmed the accuracy and reliability of sonographic assessment of renal dimensions when meticulous scanning techniques are employed. Sonographic renal dimensions are smaller than those obtained by radiography, since there is neither the geometric magnification nor the change in size related to an osmotic diuresis from iodinated contrast material. Sonographically, with patients in the prone position, the mean right renal length was 10.74 cm (± 1.35 SD) and the mean left renal length was 11.10 cm (± 1.15 SD). A prospective sample demonstrated the mean depth (ventral-dorsal dimension) to be approximately 4.5 cm when the transducer was angulated for the lie of the kidney.

[Mostbeck GH](#) (1991) evaluated the histopathologic changes influencing Doppler measurements of the resistive index (RI) in renal arteries in renal parenchymal diseases, 68 kidneys in 34 consecutive patients with various forms of renal parenchymal diseases were studied by duplex Doppler ultrasound (duplex US) immediately before percutaneous renal biopsy. The RI, renal length, and renal cortical echogenicity were correlated with the amount of glomerular, interstitial, and vascular changes graded on a scale from 0 to 100. The renal vascular resistance and therefore the RI are significantly correlated with the prevalence of arteriosclerosis, glomerular sclerosis, edema, and focal interstitial fibrosis. There was no significant difference of the RI in five groups of different renal parenchymal diseases. Of 34 patients, 24 presented with an RI less than 0.7, which was thought to be within the normal range so far.

Additionally, the RI increases as the patient's age increases, due to higher incidence of arteriosclerosis. Of our patients, 44% presented with normal cortical echogenicity. Quantitative duplex US using the RI does not reliably distinguish different types of renal medical disorders.

Mahmoud Fallah et al (2012) their study was designed to compare renal arterial RI in different stages of renal function according to glomerular filtration rate (GFR), serum creatinine level and proteinuria. In a cross-sectional study on 81 diabetic patients in three groups (Without albuminuria, with microalbuminuria, with macroalbuminuria), pulsatile Doppler ultrasonography was performed to measure intra-renal arterial resistance index and find the association of this parameter with features of diabetic nephropathy. Their results were serum creatinine, GFR and proteinuria were significantly different among three groups. RI was highest in the group with macroalbuminuria and the difference among three groups was statistically significant. (P value<0.001) RI was correlated with serum creatinine, GFR and proteinuria .they concluded that higher RI correlates with higher proteinuria in diabetic patients.

Chapter Three

Materials and Methods

3-1 Area of study:

This study was carried at diabetic referring clinic of Omdurman teaching hospital.

3-2 Population of study:

The data of this study was collected from patients of known diabetics which referring the diabetic clinic of Omdurman teaching hospital and normal individuals.

:sample size and selection 3-3

The sample of this study was selected randomly from the known diabetic patients referring the diabetic clinic of Omdurman teaching hospital. The size of the sample was 100 diabetic patients. 50 normal individuals were selected randomly as control group.

3-4 design of the study:

This is an analytical study of a case control type.

3-5 tools and equipment:

Ultrasound machine:

The applied Ultrasound unit was a General electric (GE) medical system, logic 5 expert.

Ultrasound transducer:

The applied Ultrasound transducer was a convex probe with a frequency of 3.5 MHz.

3-6 patient preparation:

The patients were examined early in the morning if at all possible after overnight fast to diminish the amount of bowel gas.

3-7 examination technique:

All patients and controls underwent duplex ultrasonography for estimation of renal size, cortical echogenicity and intrarenal arterial resistance index.

The patients were examined in supine, right decubitus and left decubitus positions. A low-frequency (3.5 MHz) was used.

Kidney length and cortex echogenicity were evaluated by using brightness mode (B-mode). Then, colour Doppler followed by pulse wave Doppler (PW) modes were applied for the spectral analysis and determination of intrarenal arterial (RI) value which obtained from upper, middle, and lower portions of both kidneys.

Chapter Four

Results

This chapter shows the all the results related to the sample of diabetic Sudanese patients, control group and the comparison of the results of the diabetics and controls as follows:

4-1 Data of controls:

Table 4-1-1 shows age of controls:

Age class	Frequency	Percentages%
34-39	12	24
40-45	9	18
46-51	7	14
52-57	12	24
58-63	7	14
64-69	3	6
total	50	100

Table 4-1-2 shows BMI of controls:

BMI	Frequency	Percentages%
<18.5	1	2
18.5 - 24.9	33	66
25 - 29.9	13	26
≥30	3	6
total	50	100

Table 4-1-3 shows gender of controls:

Gender	Frequency	Percentages%
Male	18	36
Female	32	64
Total	50	100

Table 4-1-4 shows Right kidney size of controls:

RT Kidney Size	Frequency	Percentages%
Normal	50	100
Increased	-	-
Decreased	-	-
Total	50	100

Table 4-1-5 shows Left kidney size of controls:

LT Kidney Size	Frequency	Percentages%
Normal	50	100
Increased	-	-
Decreased	-	-
Total	50	100

4-2 Data of diabetic patients:

Figure 4-2-1 shows age of patients

Figure 4-2-2 shows the BMI of the patients

Figure 4-2-3 shows gender of diabetic patients

Table 4-2-1 shows duration of diabetes:

Duration	Frequency	Percentages%
Dm≤10	79	79
Dm>10	21	21
Total	100	100

Table 4-2-2 shows distribution of hypertension among diabetics:

HPT	Frequency	Percentages%
With	18	18
Out	82	82
total	100	100

Table 4-2-3 shows Right kidney size:

Size	Frequency	Percentages%
Normal	95	95
Increased	5	5
Deceased	0	0
Total	100	100

Table 4-2-4 shows Left kidney size:

Size	Frequency	Percentages%
Normal	95	95
Increase	5	5
d Decease	0	0
d Total	100	100

Table 4-2-5 shows the symptomatic and asymptomatic patients:

	Frequency	Percentages%
Symptomatic	8	8
Asymptomatic	92	92
Total	100	100%

Table 4-2-6 shows the frequency of patients with and without complication:

	Frequency	Percentages%
With complication	3	3
Without complication	97	97
Total	100	100%

Table 4-2-7 shows echogenicity of the kidneys:

Echogenicity	Frequency	Percentages%
Increased	4	4
Normal	96	96
Total	100	100%

Table 4-2-8 shows distribution of HPT among diabetics

Diabetes	With HPT		Without HPT		Total	
	Frequency	percentage	Frequency	percentage	Frequency	percentage
Total	17	100%	83	100%	100	100%

Figure: 4-2-4 shows the relation between BMI and age of diabetic patients.

Figure 4-2-5 shows the relation between age and RI of the right kidney.

Figure: 4-2-6 shows the relation between age and RI of the left kidney:

Figure: 4-2-7 shows the relation between age and RI of lower pole of the right kidney and RI of lower pole the lefty kidney:

Figure: 4-2-8 shows the relation between age and RI of middle pole of the right kidney and RI of middle of pole the lefty kidney:

Figure: 4-2-9 shows the relation between age and RI of upper pole of the right kidney and RI of upper of pole the lefty kidney:

Figure: 4-2-10 shows the relation between duration of diabetes and age:

Figure: 4-2-11 shows the relation between duration of diabetes and RI of right kidney:

Figure: 4-2-12 shows the relation between duration of diabetes and RI of left kidney:

Figure: 4-2-13 shows the relation between duration of diabetes and RI of lower pole of the right kidney and RI of lower of pole the lefty kidney:

Figure: 4-2-14 shows the relation between duration of diabetes and RI of middle pole of the right kidney and RI of middle of pole the lefty kidney:

Figure: 4-2-15 shows the relation between duration of diabetes and RI of upper pole of the right kidney and RI of upper of pole the lefty kidney:

Figure: 4-2-16 shows the relation between BMI of diabetes and RI of the right kidney:

Figure: 4-2-17 shows the relation between BMI of diabetes and RI of the left kidney.

Figure: 4-2-18 shows the relation between BMI of diabetes and RI of the left kidney.

Figure: 4-2-19 shows the relation between BMI of diabetes and RI of middle pole of the right kidney and RI of middle of pole the lefty kidney:

Figure: 4-2-20 shows the relation between BMI of diabetes and RI of upper pole of the right kidney and RI of upper pole the lefty kidney:

4-3 Comparison between findings of diabetics and controls:

Table 4-3-1 shows Comparison of resistive index (RI) of right kidney between diabetics and controls:

RI	Diabetics	Controls
Mean±SD		
LP*	0.75±0.07	0.67±0.03
MP*	0.74±0.07	0.68±0.03
UP*	0.76±0.08	0.66±0.03

Table: 4-3-2 shows Comparison of resistive index (RI) of left kidney between diabetics and controls:

RI	Diabetics	Controls
Mean± SD		
LP*	0.77±0.07	0.64-0.9
MP*	0.7±0.06	0.56-0.87
UP*	0.75±0.07	0.54-0.89

Table: 4-3-3 shows Comparison of resistive index (RI) of RT kidney among diabetics according to the duration of diabetes:

RI	DM≤ 10	DM>10
Mean± SD	YEARS	YEARS
LP*	0.73±0.07	0.82±0.0
		5
MP*	0.72±0.05	0.82±0.0
		4
UP*	0.75±0.07	0.82±0.0
		8

Table: 4-3-4 shows Comparison of resistive index (RI) of LT kidney among diabetics and controls according to the duration of diabetes:

RI	DM≤ 10	DM>10
Mean±SD	YEARS	YEARS
LP*	0.76±0.07	0.82±0.06
MP*	0.68±0.05	0.76±0.07
UP*	0.73±0.07	0.82±0.05

Table: 4-3-5 shows Comparison of resistive index (RI) of RT kidney between diabetics with HPT and those without hypertension;

RI	Diabetics with HPT	Diabetics without HPT
Mean±SD		
LP*	0.76±0.08	0.75±0.07
MP*	0.75±0.08	0.74±0.06
UP*	0.79±0.09	0.76±0.08

Table: 4-3-6 shows Comparison of resistive index (RI) of LT kidney between diabetics with HPT and those without hypertension

RI	Diabetics with HPT	Diabetics without HPT
Mean±SD		
LP*	0.78±0.09	0.77±0.07
MP*	0.72±0.06	0.70±0.06
UP*	0.77±0.06	0.75±0.08

Table: 4-3-7 shows the t-test for RI-Rt-Kd-LP for diabetic versus control:

Independent Samples Test					
Group Statistics					T-test for Equality of Means
	Item	N	Mean	t	P-value
RI-	Diabeti			-7.736	
	c	10			
	Rt-Kd-	0	0.7516		1.47
	LP				
	Control	50	0.6676		

The two means are significantly different (At the level 0.05)

Table: 4-3-8 shows the t-test for RI-Rt-Kd-MP for diabetic versus control:

Independent Samples Test				
Group Statistics				T-test for Equality of Means
Item	N	Mean	t	P-value
Diabetic	10	0.7448	-6.64672	
RI- Rt-Kd-MP	0			5.38583
Control	50	0.6798		

The two means are significantly different (At the level 0.05)

Table 4-3-9 shows the t-test for RI-Rt-Kd-UP for diabetic versus control:

Independent Samples Test				
Group Statistics				T-test for Equality of Means
Item	N	Mean	t	P-value
Diabetic	10	0.7612	-8.70544	
RI- Rt-Kd-UP	0			5.7233
Control	50	0.6586		

The two means are significantly different (At the level 0.05)

Table 4-3-10 shows the t-test for RI-Lt-Kd-LP for diabetic versus controls:

Independent Samples Test					
Group Statistics				T-test for Equality of Means	
	Item	N	Mean	t	P-value
RI	Diabeti			-9.83218	
	c	10	0.7704		
	Lt-Kd-LP	0			7.20385
	Control	50	0.6654		

The two means are significantly different (At the level 0.05)

Table 4-3-11 shows the t-test for RI-Lt-Kd-MP for diabetic versus controls:

Independent Samples Test					
Group Statistics				T-test for Equality of Means	
	Item	N	Mean	t	P-value
RI	Diabeti			-5.09962	
	c	10	0.7022		
	Lt-Kd-MP	0			1.02624
	Control	50	0.00372		

The two means are significantly different (At the level 0.05)

Table 4-3-12 shows the t-test for RI-Lt-Kd-UP for diabetic versus controls:

Independent Samples Test				
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Group Statistics					T-test for Equality of Means
	Item	N	Mean	t	P-value
RI	Diabeti			-8.68318	
	c	10	0.7529		
	Lt-Kd-UP	0			6.51597
	Control	50	0.6562		

The two means are significantly different (At the level 0.05)

Table 4-3-13 shows the t-test for RI-Rt-Kd-LP for diabetics with duration > 10 years versus diabetics with duration ≤ 10 years:

Independent Samples Test					T-test for Equality of Means
Group Statistics					P-value
	Item	N	Mean	t	
RI	Diabeti			-8.68318	
	c	10	0.821		
	Rt-Kd-LP	0			4.97087
	Control	50	0.73425		

The two means are significantly different (At the level 0.05)

Table 4-3-14 shows the t-test for RI-Rt-Kd-MP for diabetics with duration > 10 years versus diabetics with duration ≤ 10 years:

Independent Samples Test					T-test for
Group Statistics					

					Equality of Means
					P-value
	Item	N	Mean	t	
	Diabetic			-7.59348	
	c	10	0.822		
RI	Rt-Kd- MP	0			1.8495
	Control	50	0.7236		
The two means are significantly different (At the level 0.05)					

Table 4-3-15 shows the t-test for RI-Rt-Kd-UP for diabetics with duration > 10 years versus diabetics with duration ≤ 10 years:

Independent Samples Test					
Group Statistics					T-test for Equality of Means
	Item	N	Mean	t	P-value
	Diabetic			-4.19525	
	c	10	0.822		
RI	Rt-Kd- UP	0			5.99136
	Control	50	0.74512		
The two means are significantly different (At the level 0.05)					

Table 4-3-16 shows the t-test for RI-Lt-Kd-LP for diabetics with duration > 10 years versus diabetics with duration ≤ 10 years:

Independent Samples Test					
Group Statistics				T-test for Equality of Means	
	Item	N	Mean	t	P-value
RI	Diabeti			-3.85939	
	c	10	0.821		
	LT-Kd- LP	0			2.03744
	Control	50	0.7575		

The two means are significantly different (At the level 0.05)

Table 4-3-17 shows the t-test for RI-Lt-Kd-MP for diabetics with duration > 10 years versus diabetics with duration ≤ 10 years:

Independent Samples Test					
Group Statistics				T-test for Equality of Means	
	Item	N	Mean	t	P-value
RI	Diabeti			-5.97258	
	c	10	0.763		
	LT-Kd- MP	0			3.75844
	Control	50	0.6846		

The two means are significantly different (At the level 0.05)

Table 4-3-18 shows the t-test for RI-Lt-Kd-UP for diabetics with duration > 10 years versus diabetics with duration ≤ 10 years:

Independent Samples Test				
Group Statistics				T-test for

					Equality of Means
					P-value
	Item	N	Mean	t	
	Diabeti			-5.47632	
	c	10			
RI	LT-Kd-	0	0.8235		3.35398E-7
	UP				
	Control	50	0.732		
The two means are significantly different (At the level 0.05)					

Table 4-3-19 shows the t-test for RI-Rt-Kd-LP for Hypertensive diabetics versus non- Hypertensive diabetics:

Independent Samples Test					
Group Statistics					T-test for Equality of Means
	Item	N	Mean	t	P-value
	Diabeti			0.26429	
	c	10			
RI	RT-Kd-	0	0.75072		0.79211
	LP				
	Control	50	0.75588		
The two means are NOT significantly different (At the level 0.05)					

Table 4-3-20 shows the t-test for RI-Rt-Kd-UP for Hypertensive diabetics versus non- Hypertensive diabetics

Independent Samples Test				
Group Statistics				T-test for Equality of Means P-value
Item	N	Mean	t	
Diabeti			1.47743	0.14277
c	10	0.7553		
RI RT-Kd- LP	0			
Control	50	0.78647		
The two means are NOT significantly different (At the level 0.05)				

Table 4-3-2 1 shows the t-test for RI-Lt-Kd-LP for Hypertensive diabetics versus non- Hypertensive diabetics:

Independent Samples Test				
Group Statistics				T-test for Equality of Means P-value
Item	N	Mean	t	
Diabeti			0.75034	0.45485
c	10	0.76904		
RI LT-Kd- LP	0			
Control	50	0.78353		
The two means are NOT significantly different (At the level 0.05)				

Table 4-3-22 shows the t-test for RI-Lt-Kd-UP for Hypertensive diabetics versus non- Hypertensive diabetics:

Independent Samples Test				
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Group Statistics				T-test for Equality of Means
	Item	N	Mean	P-value
	Diabetic			1.21112
	c	10		
RI	LT-Kd-UP	0	0.74614	0.22876
	Control	50	0.77059	

The two means are NOT significantly different (At the level 0.05)

Chapter five Discussion, conclusion and recommendation

5-1 Discussion

This study was carried out at diabetic referring clinics of Omdurman teaching Hospital for 100 patients with known diabetes as sample and 50 normal individual as controls. In our study, females were 64 representing 64% and males were 36 representing 36% (Figure: 4-2-3), their ages ranged between 34-65 years (figure: 4-2-1). The disease duration was in the range of 1-30 years. Controls were 32 female representing 64% and 18 male representing 36% (table: 4-1-3), their ages ranged between 34-69 years (table: 4-1-1). All controls were in good clinical condition. All patients and controls were underwent ultrasonographic assessment of renal size, cortical echogenicity and the intrarenal arteries resistive index for upper, middle and lower poles and their clinical history were registered.

In this study the t-test for intrarenal arterial RI of upper, mid and upper poles of RT and LT Kidneys of diabetic versus control revealed that the intrarenal arterial RI of diabetics was higher than that of the controls and this relation was statistically significant (tables: 4-3-7, 4-3-8, 4-3-9, 4-3-10, 4-3-11 and 4-3-12). [Doaa M Youssef and Faten M Fawzy \(2012\)](#) studied 25 patients with T1-DM (Group-A), which comprised of 15 females and 10 males, with a mean age of 10.8 ± 2.2 years and duration of diabetes of 5 ± 1.1 years. A control group (Group-B) comprising 20 healthy children, 12 females and eight males with mean age of 11.6 ± 2 years, was also studied. They found an increase in the mean RI in diabetic patients versus healthy children. [Ohta Y et al \(2005\)](#) concluded that the increased RI of the renal arteries is associated with the severity of systemic atherosclerosis. Furthermore, the intrarenal vascular resistance differs depending on the underlying renal disease, and appears to increase to a greater extent in diabetic nephropathy.

Regarding the percentage of the diabetic patients it reflects that the prevalence of diabetes in females is more than male in Sudan (Figure: 4-2-3). Study of [Gale EA](#) and [Gillespie KM](#) (2001) found that Type II diabetes showed a pronounced female excess in the first half of the last century but is now equally prevalent among men and women in most populations, with some evidence of male preponderance in early middle age. [Knowler WC et al \(1981\)](#) examined the determinants of the incidence of non-insulin-dependent diabetes mellitus among blacks and whites from the NHANES I Epidemiologic Follow-up Study conducted from 197 to 1987. He concluded that black women were 50 percent more likely to develop non-insulin-dependent diabetes mellitus (NIDDM) than black men, and they had twice the risk of white women. The difference between these studies may be due the difference in sample size, ethnicity and duration of the study.

In this study, patients were classified into 6 groups of age, the range of each age group is 6 years. The most frequent age groups were

(34-39) representing 24% and (52-57) representing 24% and the most little frequent group was (64-69) representing 6% (Figure 4-2-1). In this study, we found that the duration of diabetes increased with age (Figure: 4-2-10). The intrarenal arterial RI is increased with age (Figures: 4-2-5 and 4-2-6). This may be due to increased cholesterol deposits of atherosclerosis with advancing age. Previous studies have shown that age may alter intrarenal arterial RI and they found a considerable correlation between age and RI and maintain that age is an important variable in regarding normal RI values. Lin ZY et al (2003) investigated the influence of age on intrarenal arterial resistive RI measurement in 135 normal subjects (71 male, 64 female; age range between 17-68 years, median age was 37 years). They found that there is a statistically significant positive correlation between intrarenal RI and age. Kumileo H et al (2008) found that the intrarenal arterial RI increased significantly with age. Spomenka Ljubia et al (2006) investigated the predictive variables for RI elevation in patients with type 2 diabetes. The stepwise regression method was used to analyze the influence of predictor variables: patient age, diabetes duration, systolic and diastolic blood pressure, albumin excretion rate (AER), lipid values, glycated hemoglobin and creatinine clearance on RI elevation. A statistically significant correlation was found between RI and diabetes duration, systolic blood pressure and AER. [Ishimura E](#) et al (1997) studied Intrarenal hemodynamics by duplex Doppler sonography in 112 in-patients with [type II diabetes mellitus](#) (DM; 65 males, 47 females, 58 +/- 13 years old). Their results showed that multiple regression analysis revealed that RI values in DM patients were significantly affected by age, and duration of [diabetes](#) ($R^2 = 0.554$, $P < 0.0001$).

BMI is regarded as an important health characteristic that is as a risk factor to health. The importance of BMI, with regard to the negative burden of health from high BMI as well as the extent of the global obesity pandemic are documented in. Our study showed that

2% of diabetics were underweight, 66% were of normal weight, 26% were of overweight and 6% were obese (figure: 4-2-2). It also showed that BMI is inversely related to age (figures: 4-2-4) and the intrarenal arterial RI (figures: 4-2-16 and 4-2-17). Our findings disagree with Australian Bureau of Statistics (2010) and Sui, X et al (2007) who revealed that BMI has relation with age. N. K. Mungreiphy et al (2011) found that significant positive relation among BMI and age. Study of Adamu G Bakari (2006) was undertaken to determine whether BMI and casual blood sugar are related. There was a positive but non-significant correlation between casual blood sugar and BMI among female subjects ($r = +0.1520$, $p > 0.05$). In the males however, there was no correlation between these variables ($r = -0.0395$, $p > 0.5$). Gertraud Maskarinec et al (2009) found that There was a positive but none statistically significant correlation between random blood sugar and BMI among female subjects ($r = +0.1520$, $p > 0.05$). However, there was no correlation between these variables ($r = -0.0395$, $p > 0.5$) in male subjects also he found that for underweight participants, the prevalence tended to be as high, or higher, than in normal-weight subjects. Adamu G Bakari et al (2006) studied the relationship between random blood sugar and body mass index in an African Population. He found that There was a positive but none statistically significant correlation between random blood sugar and BMI among female subjects ($r = +0.1520$, $p > 0.05$). However, there was no correlation between these variables ($r = -0.0395$, $p > 0.5$) in male subjects Study of H. E. Bays et al (2007) was designed to explore the relation between body mass index (BMI) and prevalence of diabetes mellitus, hypertension and dyslipidaemia; examine BMI distributions among patients with these conditions; and compare results from two national surveys. Their results were increased BMI was associated with increased prevalence of diabetes mellitus, hypertension and dyslipidaemia in both studies ($p < 0.001$). For each condition, more than 75% of patients had $BMI \geq 25 \text{ kg/m}^2$.

Estimated prevalence of diabetes mellitus and hypertension was similar in both studies, while dyslipidaemia was substantially higher in NHANES than SHIELD. In both studies, prevalence of diabetes mellitus, hypertension and dyslipidaemia occurred across all ranges of BMI, but increased with higher BMI. However, not all overweight or obese patients had these metabolic diseases and not all with these conditions were overweight or obese. This difference may be due to the poor compliance to therapy or diet, and infections, particularly malaria and Infections related to diabetes in Sudan. The role of fruits, vegetables and important proteins in the Sudanese diet is minor due to their high cost and poverty also storage. It is also may be due environmental factors.

In our study distribution of HPT among diabetics were 18% compared to that of 82% without hypertension (Table 4-2-2). The t-test for intrarenal arterial RI for Hypertensive diabetics versus non-Hypertensive diabetics which was statistically insignificant (Table 4-3-22). Our findings disagree with various studies that revealing the correlation of hypertension and intrarenal arterial RI. According to Ishimura et al (1997), there was a significant correlation between blood pressure and intrarenal arterial RI .According to Amini et al (169) observed that with presence of hypertension there was a three times higher risk and faster progression of diabetic nephropathy. Thus hypertension has an impact on the intrarenal arterial RI especially through the effect of renin angiotensin system on the renal vascular resistance. Disagree of our findings and the previous studies; may due to the small sample size of our study also it may due to some antihypertensive drugs which were taken by the patients.

The mean right renal length is 10.74 ± 1.35 cm and the mean left renal length is 11.10 ± 1.15 cm, measured as the longest diameter with a lower limit of normality generally indicated as 9 cm. Renal length under 8 cm is definitely reduced and should be attributed to chronic renal failure (CRF), whereas a length between 8 and 9 cm

should always be correlated to the patient's phenotype, particularly the height (170). The study of [Brandt TD](#) et al (1982) confirmed the accuracy and reliability of sonographic assessment of renal dimensions when meticulous scanning techniques are employed. Our study showed that most of patients 95%; had normal kidneys size while 0% showed small kidneys and 5% showed increasing in the size on both sides (Tables 4-2-3 and 4-2-4). Study of [Mancini M](#) et al (2013) was designed to evaluate the renal volume and intrarenal hemodynamics with duplex sonography in a group of diabetic patients with normal renal function in comparison to nondiabetic controls. The renal volume and resistive index (RI) of segmental arteries were assessed by duplex sonography in 88 diabetic patients (44 male and 44 female; median age, 58 years [range, 37-69 years]) and 73 nondiabetic control participants (48 male and 25 female; median age, 53 years [range, 27-75 years]) without renal artery stenosis. They found that both renal volume and RI values in the diabetic patients were significantly higher compared to the controls. The pioneer work of Mogensen (1984) found that the high risk of microalbuminuria in diabetic patients with large kidneys has been reported frequently. Chong YB et al, 2012 studied the difference in the renal findings detected by US in type 2 diabetic patients with or without chronic renal failure nephropathy. They found that most of type 2 diabetic patients with chronic renal failure had small kidneys (<9 cm length).

In our study 8% of patients with increased intrarenal arterial RI were symptomatic and (92%) were asymptomatic patients (tables 4-2-5 and 4-2-6). This may be due to the progression of the stage of diabetic nephropathy. Our findings were similar to the study done by Milovanceva-Popovska et al (2007) who mentioned that most of the patients were asymptomatic in the early stage of nephropathy (176). According to Platt et al (1994), the patients were asymptomatic in the early stage of nephropathy characterized only by microalbuminuria whereas those with established nephropathy

have some clinical manifestations associated with development of macroalbuminuria. Tushar P Rauta et al (20012) studied the clinical profile of Diabetic nephropathy and the correlation of intrarenal resistivity index with parameters of renal dysfunction like Glomerular filtration rate, Serum Creatinine, micro and macroalbuminuria. Their result was factors which independently affected IRI were age, Hypertension, Complications and they concluded that Intrarenal resistivity index as assessed by duplex ultrasonography is a non-invasive parameter that can be correlated with the clinical profile and biochemical parameters of renal dysfunction type II diabetes mellitus with diabetic nephropathy. Kin Hung Liu et al (2012) examined the association between intrarenal arterial RI and diabetic complications in Chinese type 2 diabetic subjects. Clinical and biochemical parameters, including diabetes-related microvascular complications (nephropathy, retinopathy and sensory neuropathy) were examined. The mean RI of patients with any microvascular complications and with any macrovascular complications was higher than those without.

Our study showed that 5% of diabetics with increased cortical echogenicity and 95% with normal parenchymal echogenicity. [Mostbeck GH](#) (1991) evaluated the histopathologic changes influencing Doppler measurements of the resistive index (RI) of renal arteries in renal parenchymal diseases, 68 kidneys in 34 consecutive patients with various forms of renal parenchymal diseases were studied by duplex Doppler ultrasound (duplex US) immediately before percutaneous renal biopsy. The RI, renal length, and renal cortical echogenicity were correlated with the amount of glomerular, interstitial, and vascular changes graded on a scale from 0 to 100. The renal vascular resistance and therefore the RI are significantly correlated with the prevalence of arteriosclerosis, glomerular sclerosis, edema, and focal interstitial fibrosis. There was no significant difference of the RI in five groups of different renal parenchymal diseases. Of 34 patients, 24 presented with an RI less

than 0.7, which was thought to be within the normal range so far. Additionally, the RI increases as the patient's age increases, due to higher incidence of arteriosclerosis. Of our patients, 44% presented with normal cortical echogenicity. Quantitative duplex US using the RI does not reliably distinguish different types of renal medical disorders.

In our study, there was statically significant difference in intrarenal arterial RI between the diabetics with duration more than 10 years and that diabetics with duration less than 10 years (tables 4-3-13, 4-3-14, 4-3-15, 4-3-16, 4-3-17 and 4-3-18. Ishimura E et al revealed that the RI values in patients with DM were significantly affected by creatinine clearance, age and duration of type-2 diabetes.

5-2 Conclusion

Ultrasound is an easy, accurate, non-expensive and non-invasive test that can be used in diabetic patients to prove or exclude diabetic or non-diabetic nephropathy and also to diagnose associated renal diseases not related to DM e.g. renal cysts, stones or masses.

Sudanese females are more affected by diabetes than Sudanese male, while the most frequent age group of diabetics were (34-39) and (52-57) and the most little frequent group was (64-69).

Diabetics have higher values of RI compared to controls and this increment in intrarenal arterial RI of diabetics is proportional to the age and duration of DM.

BMI of diabetics is reversely related to their intrarenal arterial RI.

BMI of diabetics is reversely related to their age.

The difference in intrarenal arterial RI of the diabetics with hypertension and that without hypertension is statically insignificant.

5-3 Recommendation:

In respect to this study the researcher recommends the followings:

- To increase the number of the duplex ultrasound •
.machine at public hospital
- To increased diabetes care centersbecause •
diabetes mellitus is currently emergingas an
.important health problem in Sudan and worldwide
- To provide the appropriate training course for •
the staff to provide high quality medical services
.for patents
- To conduct more studies on a larger sample size •
.to confirm our findings

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Figure.A-1 RT. kidney coronal oblique (LI-lateral decubitus)



Figure A-2 .Lt. kidney coronal oblique (Rt. lateral decubitus)



Figure A-3 right Kidney - coronal (supine)



Figure A-4 LI.Kidney (B-mode)

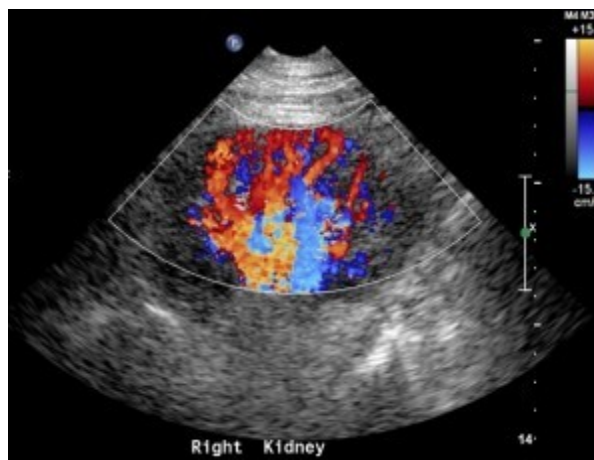


Figure A-5 RT.kidney (color flow)

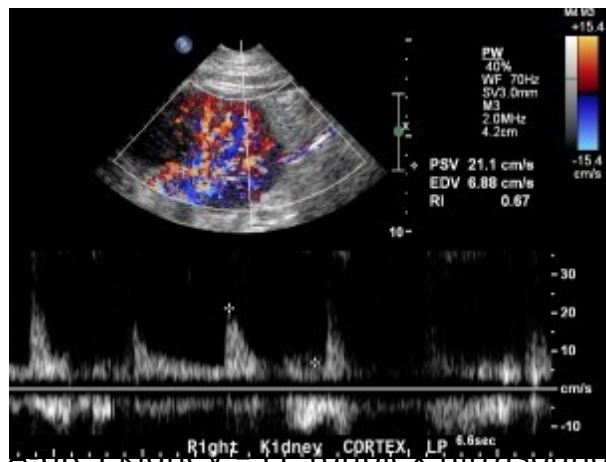


Figure 1. Color Doppler ultrasound image of the right kidney cortex showing a peak velocity of 21.1 cm/s (duplex ultrasound)