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Sudan University of Science and Technology
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Assessment of Carotid Arteries in Yemenis Khat Chewers Using Ultrasonography

تقييم الشرايين السباتية في ماضغي القات اليمنيين باستخدام الموجات فوق الصوتية

A thesis submitted for fulfillment the requirements of Ph.D. by Research in Medical Diagnostic Ultrasound

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الآية

قال تعالى:

﴿شَهِدَ اللَّهُ أَنَّهُ لَا إِلَٰهَ إِلَّا هُوَ وَالْمَلَائِكَةُ وَأُولُوا الْعِلْمِ قَائِمًا بِالْقِسْطِ لَا إِلَٰهَ إِلَّا هُوَ الْعَزِيزُ الْحَكِيمُ﴾

﴿سورة آل عمران الآية ١٨﴾

DEDICATION

This work is dedicated to all these Candles that glowed up to Lighten my way

To my parents souls

To my sisters

To my brothers

To my beloved wife and my kids Jowan, Yaman and Kenan

To my friends

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Abstract

Chewing Khat is considered as a major deep-rooted sociocultural habit in Yemen. it has been established to cause various health problems. The main objective of this study was to assess the changes of carotid arteries intima media thickness, flow velocities, and Doppler indices of in Yemenis Khat chewers using medical duplex ultrasound.

This prospective cross sectional study was achieved from July 2017 to July 2018 with 205 Subjects 108 (52.7%) as chewers and 97(47.3%) non-chewers, 10 subjects are excluded according to restricted sampling criteria. The mean age in two groups was 28.29 ± 7.0 years. In all cases, the carotid duplex ultrasound scanning protocol, based on the standard of American institute of ultrasound in medicine, was performed to get measurement of intima media thickness, peak systolic velocity, end diastolic velocity, resistivity index, and pulsatility index. The Khat chewing information of participants were obtained by standardized questionnaire. The SPSS was used for results analysis and p-value ≥ 0.05 was considered significant.

There was no statistically significant difference in the mean values of RT CCA-IMT and LT CCA-IMT between khat chewers and non-khat chewers. The CCA-MIT was significantly higher among male khat chewers compared to male non-chewers (P = 0.004). However, there was no statistically significant difference between khat chewers and non-chewers with respect to the age of 20 years or older (P = 0.301) and BMI of 18.5 kg/m2 or higher (P = 0.888). Age showed a significant positive correlation with RT CCA-IMT (r = 0.380; P < 0.001) and LT CCA-IMT (r = 0.458; P < 0.001) in Khat chewers. In contrast, age showed a significant positive correlation with LT CCA-IMT only in non-khat chewers (r = 0.236; P = 0.024). On the other hand, BMI showed a significant positive

correlation with LT CCA-IMT (r = 0.254; P = 0.010) among khat chewers, but no significant correlation was found in CCA-IMT of both sides among non-khat chewers. Among khat chewers, there was a significant positive correlation with RT CCA-IMT (r = 0.273; P = 0.005) and LT CCA-IMT(r = 0.194; P = 0.049).

This study showed the differences between Khat and non-Khat chewers regarding Doppler parameters. A significantly decreased RI and PI was observed in all CAs of the Khat chewers' group compared to those of the non-Khat chewers, except for bilateral ICA (p = .701, and .178) for RT and LT respectively. A decreased PSV was also observed in all bilateral CAs of the Khat chewers' group compared to those of the non-Khat chewers, but these were statistically significant only in the RT CCA ($p < 0.001$) and RT ICA ($p = 0.042$).

In the Khat chewers group, the PSV had a significantly negative correlation with the period of chewing only in the RT CCA ($p = 0.01$), left CCA (LT CCA) ($p < 0.001$) and ECA ($p = 0.005$). There was no significant difference in Doppler parameters between genders in the Khat Chewers group. Moreover, higher carotid flow velocities in males compared to females were observed in the control non-Khat chewers group. But this trend did not reach statistical significance except that of RT CCA PSV ($p < 0.001$).

Doppler indices had a significantly negative correlation with the period of chewing in the bilateral CAs, except in the RT ICA RI (p = .117) and LT CCA PI (p = .055), in the Khat chewers' group.

Therefore, the study concluded that chronic Khat chewing may slightly affect the CCA-IMT. And the age has a significant positive correlation with CCA-IMT in khat chewers and LT CCA-IMT in non-khat chewers, which could help to determine the contribution of different predisposing factors to atherosclerosis. And this study may provide an interpretation of high prevalence and mechanism of hemorrhagic stroke among Yemeni population in their middle age, and the correlation of chronic chewing Khat to this type of stroke more than ischemic one. More studies are recommended to confirm this finding using the transcranial Doppler technique.

المستخلص:

يعتبر مضغ القات عادة اجتماعية وثقافية عميقة الجذور في اليمن. وقد ثبت أن لها مشاكل صحية مختلفة. كان الهدف الرئيسي من هذه الدراسة هو تقييم التغيرات في سماكة الطبقتين الجدارية البطانية والمتوسطة، وسرعات التدفق، ومؤشرات دوبلر للشرايين السباتية في ماضغي القات اليمنيين باستخدام الموجات الصوتية الطبية (نظامي السطوع ودوبلر).

تم إجراء هذه الدراسة المستعرضة من يوليو 2017 إلى يوليو 2018 على 205 مشاركاً، 108 (52.7٪) منهم كماضغين للقات و 97 (47.3٪) غير ماضغين للقات، وتم استبعاد 10مشاركين لعدم التطابق التام مع معايير اختيار العينة. كان متوسط العمرفي المجموعتين 28.29 ± 7.0 سنوات. تم إجراء فحص الموجات الصوتية في كلا المجموعتين تبعاً لبروتوكول الفحص بالموجات الصوتية للشرايين السباتية، بناءً على معيار المعهد الأمريكي للموجات الصوتية في الطب، للحصول على قياس سماكة الطبقتين الجدارية البطانية والمتوسطة، وسرعة الانقباض القصوى، وسرعة الانبساط النهائي، ومؤشر المقاومة، ومؤشر النبض. تم الحصول على معلومات المشاركين حول مضغ القات من خلال استبيان موحد. تم استخدام برنامج الحزم الاحصائية للدراسات الاجتماعية (SPSS) لتحليل النتائج واعتبرت القيمة (p=0.05) دالة احصائياً.

لم يكن هنالك فرق معتد به إحصائياً في القيم المتوسطة لسماكة الطبقتين الجدارية البطانية والمتوسطة للشرايين السباتية الرئيسية الأيمن RT CCA-IMT والأيسر LT CCA-IMT، بين ماضغي القات مقارنة مع غير الماضغين. وكان معدل السماكة للطبقتين الجدارية CCA-IMT أعلى في الذكور الماضغين للقات مقارنة بالذكور غير الماضغين للقات (P = 0.004). ومع ذلك، لم يكن هناك فرق معتد به إحصائياً بين ماضغي القات وغير الماضغين للقات فيما يتعلق بعمر 20 سنة أو أكثر (P = 0.301) ومؤشر كتلة الجسم 18.5 كجم / م 2 أو أعلى (P = 0.888). أظهر العمر ارتباطًا إيجابيًا مع سماكة الطبقتين الجدارية للشريان السباتي الرئيسي الأيمن RT CCA-IMT.

(r = 0.380) ؛ P <0.001)، والأيسر LT CCA-IMT (r = 0.458) ؛ P <0.001) في ماضغي القات. في المقابل، أظهر العمر ارتباطًا إيجابيًا فقط مع سماكة الطبقتين الجدارية

للشريان السباتي الرئيسي الأيسر LT CCA-IMT في غير الماضعين للقات (r = 0.236 ؛ P = 0.024). من ناحية أخرى، أظهر مؤشر كتلة الجسم ارتباطًا إيجابيًا مع سماكة الطبقتين الجدارية للشريان السباتي الرئيسي الأيسر LT CCA-IMT (r = 0.254) ؛ (P = 0.010) بين ماضعي القات، ولكن لم يتم العثور على ارتباط ذي دلالة احصائية في كلا الجانبين الأيمن والأيسر بين غير الماضغين للقات. بين ماضغي القات، كان هناك ارتباط إيجابي بين فترة مضغ القات و سماكة الطبقتين الجدارية للشرايين السباتية الرئيسية، الأيمن RT CCA-IMT (r = 0.273 ؛ P = 0.005)، و الأيسر LT CCA-IMT (r = 0.194 ؛ P = 0.049).

أوضحت هذه الدراسة فروق بين ماضعي القات وغير الماضغين للقات فيما يتعلق بعوامل دوبلر، فقد لوحظ انخفاض مهم في مؤشري دوبلر للمقاومة والنبض RI ، PI في جميع الشرايين السباتية CAs لمجموعة ماضغي القات مقارنة مع غير الماضغين، باستثناء الشريان السباتي الداخلي ICA في الجانبين الأيمن RT والأيسر LT (p = .701 ، و 178.) على التوالي. كما لوحظ انخفاض سرعة الانقباض القصوى PSV في الشرايين السباتية CAs في مجموعة ماضعي القات مقارنة مع غير الماضغين، ولكن بدلالة إحصائية فقط في الشريان السباتي الرئيسي الأيمن RT CCA (p <0.001) و السباتي الداخلي الأيمن RT ICA (p = 0.042).

في مجموعة ماضغي القات، كان لسرعة الانقباض القصوى PSV علاقة سلبية مع فترة المضغ فقط في الشرايين الرئيسية الأيمن RT CCA (p = 0.01) و الأيسر LT CCA-IMT (p < 0.001) والسباتي الخارجي الأيسر ECA (p = 0.005).

لم يكن هناك فرق في معاملات دوبلر بين الجنسين في مجموعة ماضغي القات. علاوة على ذلك، لوحظ ارتفاع سرعات تدفق الدم للشرايين السباتية عند الذكور مقارنة بالإناث في الضابطة (غير الماضغين للقات)، لكن لم يصل إلى دلالة إحصائية سوى في الشريان الرئيسي الأيمن RT CCA PSV (p <0.001).

كان لمؤشرات دوبلر في الشرايين السباتية CAs إرتباط سلبي مع فترة مضغ القات باستثناء الشريان الداخلي الأيمن RT ICA RI ((p = .117)) والرئيسي الأيسر LT CCA PI (p = .055)، في مجموعة ماضغي القات.

لذلك، خلصت الدراسة إلى أن مضغ القات المزمن قد يؤثر بشكل طفيف على سماكة الطبقتين الجدارية البطانية والمتوسطة في الشرايين السباتية الرئيسية CCA-IMT، بينما أظهر العمر ارتباطاً إيجابياً مع في كلا الجانبين عند ماضغي القات، وفي الأيسر فقط LT CCA-MIT عند مجموعة غيرالماضغين للقات، مما قد يساعد في تحديد مساهمة العوامل المؤهبة المختلفة لتصلب الشرايين. علاوةً على ذلك تقدم هذه الدراسة تفسيراً لارتفاع معدل انتشار وآلية السكتة الدماغية النزفية بين السكان اليمنيين في منتصف أعمارهم، وعلاقة مضغ القات المزمن بهذا النوع من السكتات الدماغية. وتوصى الدراسة بإجراء مزيد من الأبحاث لتأكيد هذه النتيجة باستخدام تقنية الدوبلر عبر الجمجمة.

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List of Abbreviation:

CAs	Carotid Arteries
CCAs	Common Carotid Arteries
IMT	Intima Media Thickness
BMI	Body mass index
HTN	Hypertension
DM	Diabetes Mellitus
RI	Resistive Index
PI	Pulsatility Index
PSV	Peak Systolic Velocity
EDV	End Diastolic Velocity
PRF	Pulse Repetition Frequency

Chapter one

Introduction

CHAPTER ONE: INTRODUCTION

1.1 Introduction

Khat (qat, kat) is an evergreen shrub belong to the family of Celastraceae that was named by a botanist, Peter Forsskal and in Yemen, it is considered a deep-rooted sociocultural custom. (Numan, 2012).

Earlier, the clinical observation concluded that Khat had amphetamine-like properties. Then in subsequent chemical analysis, it was suggested that the fresh Khat leaves contain a number of compounds, including phenylalkylamine compounds (alkaloids) such as norpseudoephedrine (cathine) and alpha aminopropiophenone (cathinone) (N. Hassan, Gunaid, & Murray Lyon, 2007). The latter is the main active ingredient in fresh Khat leaves (Kalix, 1990) which is pharmacologically similar and structurally related to amphetamine (N. Hassan et al., 2007).

Chewing Khat is considered as risk factor for cardiovascular disease with cigarette smoking (Berhane, Bonita, & Wall, 2008; Tesfaye, Byass, Wall, Berhane, & Bonita, 2008). Because it is, evidently, causes a significant increase of pulse rate and arterial blood pressure in systolic and diastolic phases. (N. Hassan et al., 2007; N. A. Hassan, Gunaid, El-Khally, Al-Noami, & Murray-Lyon, 2005; YEHIA, 2015).

When the chronic Khat chewing is associated with increasing diastolic blood pressure, this may lead to sustained effect on the cardiovascular system which could contribute to rise the blood pressure at the population level (Andualem, Hassen, & Yemane, 2002; Ayana, Sherief, & Tekli, 2002; Getahun, Gedif, & Tesfaye, 2010; Tesfaye et al., 2008); Moreover, the increased risk of acute myocardial infarction was associated with regular chewing of Khat(Al-Motarreb et al., 2005), in addition to stroke as cerebrovascular complication. (Kassa, Loha, & Esaiyas, 2017; Kulkarni, Mughani, Onbol, & Kempegowda, 2012).

The correlation between Khat and strokes was suggested (Kassa et al., 2017; Kulkarni et al., 2012; Vanwalleghem, Vanwalleghem, & De Bleecker, 2006), and the correlation between the atherosclerosis and stroke has been discussed (Parish et al., 2019; van den Oord et al., 2013; Wang, He, & Zhang, 2018).

However, the correlation between chronic Khat chewing and atherosclerosis has not been established, although it may characterize suggested causal linking between the Khat chewing and stroke.

Moreover, the flow velocities were increased and the Doppler indices were decreased when assessing the immediate effect of Khat chewing on Doppler hemodynamics of common carotid arteries (Ibrahim, Gameraddin, & Malik, 2017).

Because the regular Khat chewing is associated with the increased diastolic blood pressure resulting from the effect of Cathinone as a peripheral vasoconstrictor, the sustained effect on the cardiovascular system may occur that can contribute, as mentioned above, to the elevation of blood pressure at the population level (Getahun et al., 2010); (Ayana et al., 2002).

The ultrasound investigation of carotid arteries (CAs) is crucial in assessment of subclinical atherosclerosis which offer significant improvement in cardiovascular risk prediction (Lee & Park, 2014) and chronic Khat chewing effects on the cerebrovascular systems. (Kassa et al., 2017). Additionally, carotid intima media thickness (CIMT) is strong parameter to detect the early development of atherosclerosis, (Lee & Park, 2014; Rashid & Mahmud, 2015; Simova, 2015) and it became important predictor of morbidity and mortality of cardiovascular system (Lee & Park, 2014; Mahmoud, 2013).

B-Mode high resolution ultrasonography is most useful non-invasive modality to caliper the Common Carotid Arteries'(CCAs) intima media thickness (IMT) with reliability to detect sub clinical atherosclerosis (Lee & Park, 2014; Mahmoud, 2013; Roxana et al., 2012), and several studies have used this technique, to publish normative CAs IMT and to study the effects of different factors such as Body mass index (BMI), Hypertension (HTN), diabetes mellitus (DM), and age on it, which concluded that age, obesity, HTN, DM, high serum cholesterol and triglyceride levels were found to have an impact on CAs IMT. (Rashid & Mahmud, 2015).

Moreover, with using the same B-mode ultrasound technique, Previous study has performed to characterize the CCAs IMT in regular Khat chewers, and it revealed that the carotid IMT was significantly increased in regular khat chewer than in conrol (P-value=0.016), with the higher values in smokers more than non-smoker among khat chewers themselves (0.6710±0.20687 vs 0.5789±0.16859mm). and a significant correlations existed between the duration of chewing Khat and age with the presence of the plaques (p=0.13 and .002, for the right (RT) and left (LT) respectively) (Gameraddin, Abdalmalik, Ibrahim, Mahmoud, & Alshoabi, 2019).

Doppler ultrasonography scan is non-invasive and appropriate for the bedside examination. With the measuring of flow volumes in the carotid arteries (CAs), this technique has been used to detect extra cerebral blood flow among healthy populations. Doppler's indices; resistive index (RI) and pulsatility index (PI) are common parameters for characterizing the waveform to translate the vascular resistance (Ibrahim, Gameraddin, et al., 2017).

Originally, Pourcelot (1976) introduced RI to assess peripheral vascular diseases. The RI and PI have become important parameters in studying the effect of many diseases on vascularity in different organs, then, according to Ibrahim et al. (2017), they are used to assess the effects of Khat chewing on CAs hemodynamics.

Nevertheless, to our knowledge, no study has been investigated the cumulative effects of chronic Khat chewing on CCAs IMT separately from other confounding factors like smoking. Additionally, no study has been investigated the accumulative effects of chronic Khat chewing on CAs hemodynamics. Therefore, using duplex ultrasound scanning (B-mode and Doppler), the present study aimed to determine that effects in order to estimate the complications of this habit on carotid atherosclerosis. And to determine the effect of chronic Khat chewing on the Doppler flow velocities and indices of CAs in order to estimate its effect on the vascular system and cerebral perfusion.

1.2 Problem of the Study

In Yemen, khat chewing is widespread with a deep-rooted sociocultural tradition, with high prevalence of chronic khat chewing for the entire population. And literature demonstrates that this habit associated with several health problems including cardiovascular disorders.

The duplex ultrasound is useful non-invasive modality to estimate sub clinical changes of cardiovascular system .

Therefore, this study will try to accept the following hypothesis:

1. Ultrasound Can be able to evaluate carotid arteries intima media thickness and blood hemodynamic in chronic Khat chewers.
2. There are carotid arteries changes in Yemeni population related to chronic Khat chewing.
3. There is consistency in the relationship between cardiovascular disorders in Yemeni population and chronic Khat chewing.

1.3 Study Objectives:

1.3.1 Main objective

The overall objective of this study is to evaluate carotid arteries changes in healthy Yemenis Khat chewers using medical duplex ultrasound in order to estimate khat chewing effects on cardiovascular system.

1.3.2 Specific objectives

- To measure carotid intima media thickness (IMT) in Yemenis population.
- To assess carotid intima media thickness (IMT) changes in Yemenis population in relation to chronic Khat chewing.
- To measure carotid blood hemodynamic, (Peak systolic velocity- PSV, End Diastolic Velocity- EDV) and Doppler indices (Pulsatility Index- PI, Resistive Index - RI) in Yemenis population.
- To assess the changes in carotid blood hemodynamic, (Peak systolic velocity- PSV, End Diastolic Velocity- EDV) and Doppler indices (Pulsatility Index- PI, Resistive Index - RI) in Yemenis population as association with chronic Khat chewing.
- To differentiate between the carotid duplex ultrasound measurements in Yemenis Khat chewers as compared to Non-Khat chewers.
- To estimate the extent of carotid changes in Yemeni population according to chronic Khat chewing period in years.
- To compare the results of this study with the previous findings

Chapter two

Literature Review

CHAPTER TWO: LITERATURE REVIEW

2.1 Anatomy

2.1.1 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 divided 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 & Hiatt, 2007).

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 viscera, it then enters the abdominal iliac arteries in the pelvic. Three major arterial trunks, the right brachiocephalic artery, the left common carotid artery and the left subclavian artery, arise from the arch of the aorta to supply the superior extremities, the head and neck continued branching of all these arteries into large numbers of smaller and smaller arteries continues until the vessel walls contain a single layer of endothelial cells. The resulting vessels, called capillaries, are the smallest functional vascular elements of the cardiovascular system(Gartner & Hiatt, 2007).

2.1.1.1 Classification of arteries

Arteries are classified into three major types based on their relative size, morphological characteristics, or both as shown in table 2-1 and figure 2-1. From largest to smallest, they are elastic (conducting) arteries, muscular (distributing) and arterioles.

Table 2-1. The characteristics of various types of arteries, (Gartner & Hiatt, 2007).

Artery	Tunica intima	Tunica media	Tunica adventitia
Elastic artery (con-ducting) (e.g., aorta)	Endothelium with Weibel-palade bodies, basal lamina, subendothelial layer, incomplete internal elastic lamina.	40-70 fenestrated elastic membranes, smooth muscle cells interspersed between elastic membranes, thin external elastic lamina vasa vasorum in outer half.	The layer of fibroelastic connective tissue, vas vasorum, lymphatic vessels, nerve fibers.
Muscle artery (distributing) (e.g.,femoral artery)	Endothelium with Weibel-palade bodies, basal lamina, subendothelial layer not very prominent, some elastic fibers instead of a defined internal elastic lamina	One or two layers of smooth muscle cells	Loose connective tissue, fibers.
Metarteriole	Endothelium, basal lamina	Smooth muscle cells form precapillary sphincter	Sparse, loose connective tissue

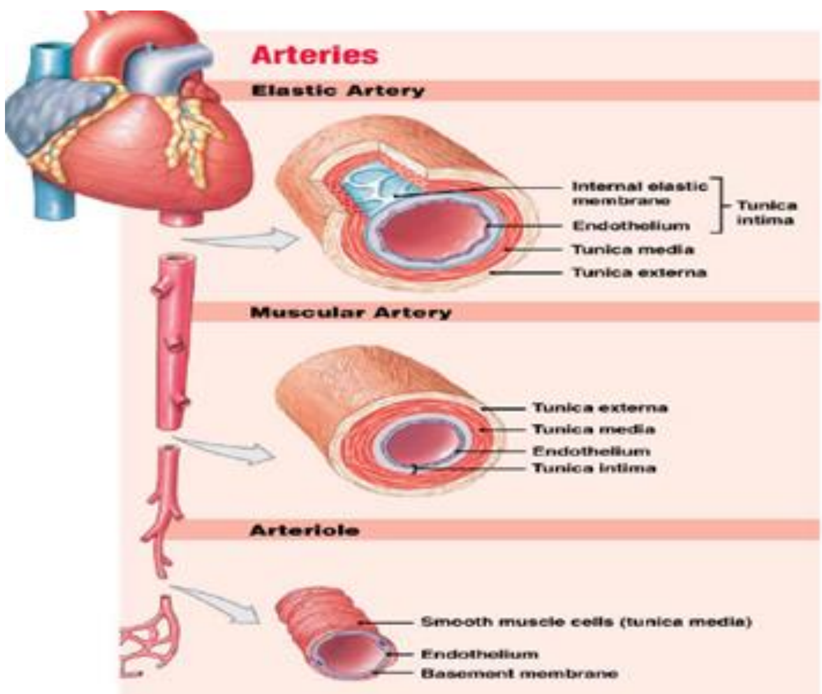


Figure 2-1. Types of arteries, (Bioscience Notes, 2019).

2.1.2 Tissues of the vascular wall

As illustrated in figure 2-2, walls of all blood vessels except capillaries contain smooth muscle and connective tissue in addition to the endothelial lining. These tissues in vessels have amount and arrangement, which influenced primarily by blood pressure, mechanical and metabolic factors. The endothelium acts as a semipermeable barrier between blood plasma and interstitial tissue fluids. The cells of vascular endothelial are squamous, polygonal, and elongated with the long axis in the blood flow direction. Endothelium with its basal lamina is markedly differentiated to mediate exchange of molecules by simple and active diffusion, receptor mediated endocytosis, and transcytosis(Mescher, 2013).

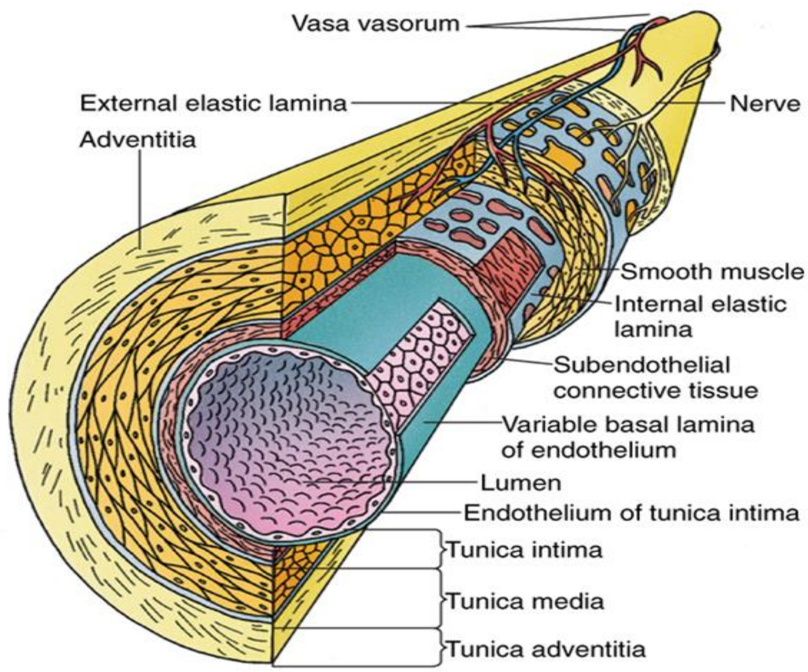


Figure 2-2. Wall of typical artery, (Gartner & Hiatt, 2007).

Smooth muscle fibres in the walls of vessels, except the capillaries arranged helically in layers. In small arteries and arterioles, the smooth muscle cells are connected by many gap junctions, and then permit vasoconstriction and vasodilation, which are the key in regulating of blood pressure (Mescher, 2013).

Connective tissuecomponents are present in vascular walls in different amounts and proportions based on the requirements of local functions. Collagen fibers are found in the subendothelial layer, between the smooth muscle layers, and in the outer covering. Elastic fibers provide the resiliency required for the vascular wall expansion under pressure. Elastin is a major component in the large arteries, which forms parallel lamellae, and regularly distributed between the layers of arteries muscles. Variations in the composition and amount of base substance components such as proteoglycans and hyaluronate also contribute to the physical and metabolic properties of the different vessels wall, especially affecting their permeability. The walls of all blood vessels larger than the microvasculature have different many components in common and similar organization. Vessels branching helps produce their size reduction, which are associated by gradual changes in the composition of the vascular wall. Transitions like those from "small arteries" to "arterioles" are not clear-cut. However, all of these larger vessels have three concentric layers walls, or tunics (L. tunica, coat) (Mescher, 2013).

The innermost layer (tunica intima) composes of the endothelium and a thin subendothelial layer of loose connective tissue sometimes with smooth muscle fibers. In arteries and large veins, the intima includes the internal elastic lamina, a prominent limiting layer, composed of elastin, with holes to allow better substances diffusion from blood deeper into the wall(Mescher, 2013).

The tunica media, the middle layer, consists mainly of concentric layers of smooth muscle cells that helically arranged. Variable amounts of elastic fibers and elastic lamellae, reticular fibers, and proteoglycans interposes among the muscle fibers, and all of which are produced by the smooth muscle cells. In arteries, the media layer may have a thin elastic lamina externally, separating it from the outermost tunic (Mescher, 2013).

The outer adventitia, or tunica externa, composes of type I collagen and elastic fibers principally. The adventitia is continuous with and bound to the organ stromal connective tissue through blood vessel runs (Mescher, 2013).

Just like the heart wall which is supplied by its own coronary vasculature for O2 and nutrients, large vessels also have vasa vasorum (vessels of the vessel) arterioles, capillaries, and venules in the adventitia and outer part of the media. The vasa vasorumis important to provide metabolites to cells of tunics in larger vessels because their thicker wall, then to be nourished solely by diffusion from the blood in the lumen. Luminal blood alone does provide the needs of cells in the intima. The large veins have more vasa vasorum compared to arteries because they carry deoxygenated blood (Mescher, 2013).

The larger vessels adventitia also contains an unmyelinated autonomic nerve fibers network, called the vasomotor nerves, that release the vasoconstrictor norepinephrine, with greater density of this innervation in arteries than in veins (Mescher, 2013).

Carotid artery is one of several arteries that supply the head and neck by oxygenated blood. There are two common carotid arteries extend headword on each side of the neck(Britannica, 2010).

The right common carotid artery arises from a bifurcation of the brachiocephalic trunk (the other branch is the right subclavian artery). This bifurcation occurs roughly at the level of the right sternoclavicular joint (Britannica, 2010).

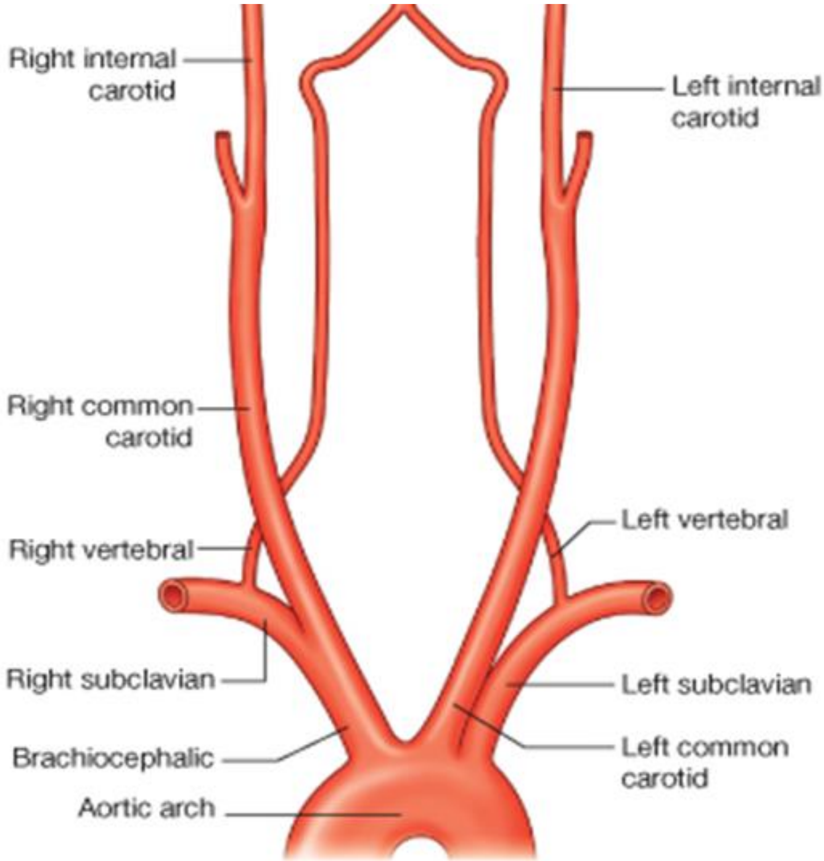


Figure 2-3. Origins of carotid arteries, (Drake, Vogl, Mitchell, & Gray, 2009)**.**

The left common carotid artery branches directly from the arch of aorta (Figure 2-3). The left and right common carotid arteries ascend up the neck, lateral to the trachea and the esophagus. They do not give off any branches in the neck. At the level of the superior margin of the thyroid cartilage (C4), the carotid arteries split into the external and internal carotid arteries(Britannica, 2010).

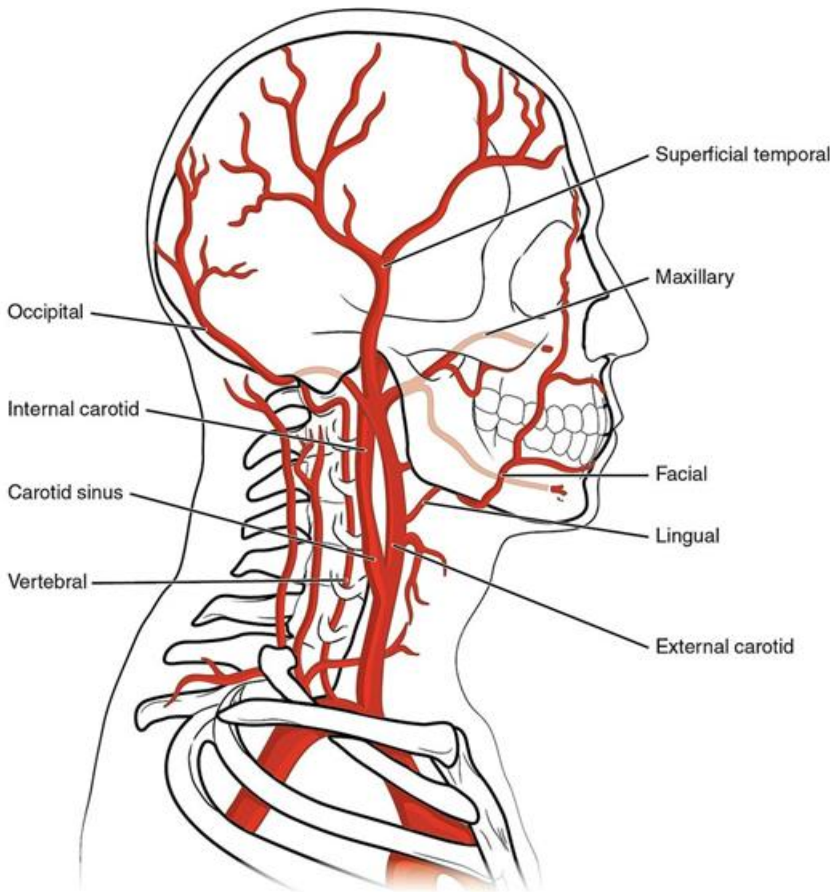


Figure 2-4. The carotid and vertebral arteries, (www.radiopaedia.org).

This bifurcation occurs in an anatomical area known as the carotid triangle. The common carotid and internal carotid are slightly dilated here, this area is known as the carotid sinus, and is important in detecting and regulating blood pressure (Oliver Jones, 2017).

2.1.3 Anatomical Relations within the Lower Neck

Relationships of the common carotid artery in the neck can be important in clinical practice. Both common Carotid arteries are separated within the lower aspect of the neck by trachea, larynx, pharynx, thyroid gland more superiorly. Each common carotid artery ascends anterior to the vagus nerve and medial to the internal jugular vein and within the carotid sheath. Inferior to the omohyoid muscle, the common carotid artery is covered by the skin, superficial fascia, deep cervical fascia, platysma, sternohyoid, sternothyroid, and sternocleidomastoid muscles. In addition, the intermediate tendon of the omohyoid muscle is crossed by the artery anterolaterally. Then, the artery ascends more superficially and is covered by the skin only, fascia layers, the platysma and the sternocleidomastoid, at the level of the cricoid cartilage. While at superior to the omohyoid muscle, the artery is crossed by the sternocleidomastoid and branch of the superior thyroid artery. The ancacervicalis, is superficial to the common carotid artery. Superficially, there are three veins cross the common carotid artery. At the upper side of the thyroid cartilage, the superior thyroid vein crosses the artery, whilst the middle thyroid vein crosses it at the cricoid cartilage level. Finally, the anterior jugular crosses the artery above the clavicle level (Figure 2-4) (Bengochea, 2018).

The inferior thyroid artery branches, the sympathetic trunk and the ascending cervical, lie posterior to the common carotid artery, while the longuscolli, longuscapitis and scalenus anterior muscles situated deeper to these arteries and attached to the transverse processes of C4-6. At the level below C6, the CCA is located in between the scalenus anterior and longuscolli muscles(Bengochea, 2018).

The internal and external carotid arteries are main supplying vessels of the head and neck, which arise from the common carotid artery in bifurcation at the neck after originating from the aortic arch. Moreover, there is anastomotic connections between the internal and external carotid arteries (Schünke, Schulte, Ross, Lamperti, & Schumacher, 2007).

Mainly - but not exclusively, the internal carotid artery supplies the intracranial structures, while the external carotid artery supplies the neck and head.

The common carotid artery and the external carotid artery give smaller branches in the neck region, while branches of the subclavian artery supply the areas near the thorax. Carotid bifurcation is the situation of the carotid body. It detects hypoxia and PH changes; therefore, it is important for the breathing regulation(Schünke et al., 2007).

2.1.4 The common carotid artery branches

No branch usually is given of from the common carotid before its bifurcation, when it divided into ICA and ECA (Figure 2-5), but occasionally it gives origin to the superior thyroid or its laryngeal branch, the inferior thyroid, the ascending pharyngeal, or rarely, the vertebral artery(Drake et al., 2009).

2.1.4.1 A Common and external carotid arteries and their branches in the neck

Each side of the neck is traversed by two major arteries, at left lateral view, which provide “thoroughfares” function to carry blood from the aortic arch to the head and brain: the common carotid artery (and it’s branch the internal carotid artery) and the vertebral artery. The right common carotid artery arises from the brachiocephalic trunk, while the left common carotid artery arises directly from the aortic arch. The bifurcation of common carotid artery into the internal and external carotid arteries occurs at approximately the level of the C4 vertebral body. Then the internal carotid artery directly ascends to the skull base and enters the cranial cavity, without giving of any branches in the neck. The external carotid artery gives a numerous branches in the head and neck. Mainly, the cervical part of this artery supplies anterior structures in the neck, such as the cervical viscera. Bilateral common carotid arteries are enclosed in the carotid sheath, a brous expansion of the cervical fascia (Schünke et al., 2007).

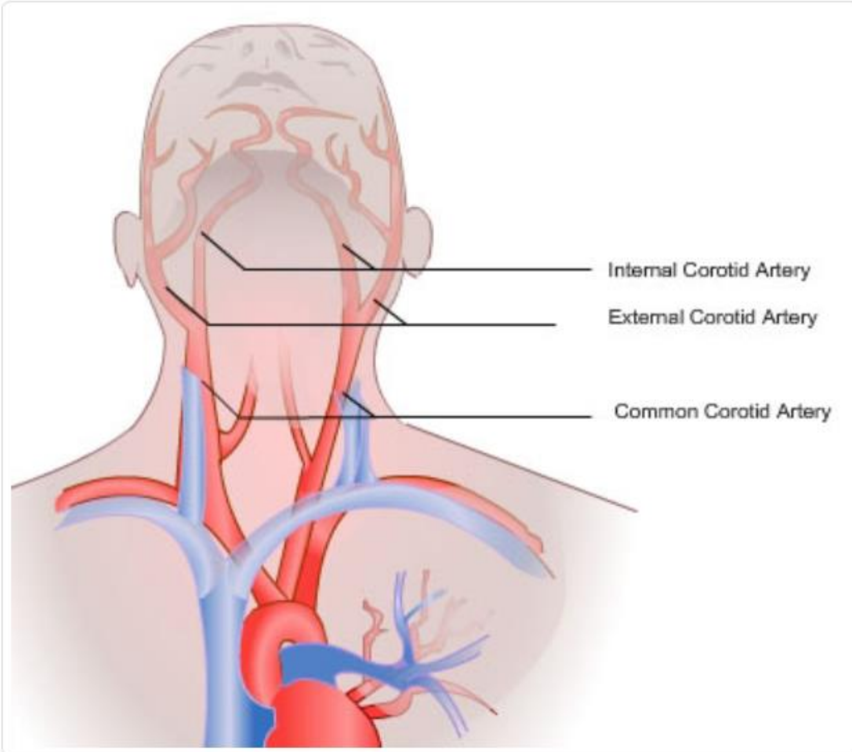


Figure 2-5. The common carotid artery and its branches, (www.VascularConcept, 2017).

2.1.4.2 Collateral circulation

The collateral circulation can be established perfectly after ligature of the common carotid, by the free communication between the bilateral carotid arteries, both without and within the cranium, and by the branches of the subclavian artery enlargement on the side corresponding to that on which the vessel has been tied. The communication between the superior and inferior thyroid arteries is considered the chief one outside the skull, in addition to the profundacervicis and ramus descends of the occipital. The vertebral takes the place of the internal carotid within the cranium (Drake et al., 2009).

2.1.5 The external carotid artery

The external carotid artery starts in opposition to the upper border of the thyroid cartilage, and passes with a slightly curved course upward, forward and then inclines posteriorly to the space behind the mandible neck, in which its division into the superficial temporal and internal maxillary arteries occur. It rapidly decreased in size in its course up the neck, owing to given off the numbers of large size of the branches as shown in Figure 2-7. In the childhood, it is smaller than the internal carotid, whereas in the adulthood, they are of nearly equal size. This artery, at its origin, is more superficial, situated nearer the middle line than the internal carotid, and is contained inside the carotid triangle (Drake et al., 2009).

2.1.5.1 The external carotid artery relations

The skin, superficial fascia, platysma, deep fascia and anterior margin of the Sternocleidomastoideus cover the external carotid artery. Moreover, ECA is crossed by the hypoglossal nerve, by the lingual, ranine, common facial and superior thyroid veins and by the digastricus and stylohyoideus. In higher location, it passes deeply within the parotid gland substance, and in which it lies deeper than the facial nerve and junction between the temporal and internal maxillary veins. The hyoid bone is Medial to EAC, as well as the wall of the pharynx, the superior laryngeal nerve, and a portion of the parotid gland. While the internal carotid artery is located lateral to it, in the lower of the course. Near its origin, the superior laryngeal nerve is placed Posterior to it, and higher up, the styloglossus and stylopharyngeus, the glossopharyngeal nerve, the pharyngeal branch of the vagus, and part of the parotid gland separate it from the internal carotid (Figure 2-6) (Drake et al., 2009).

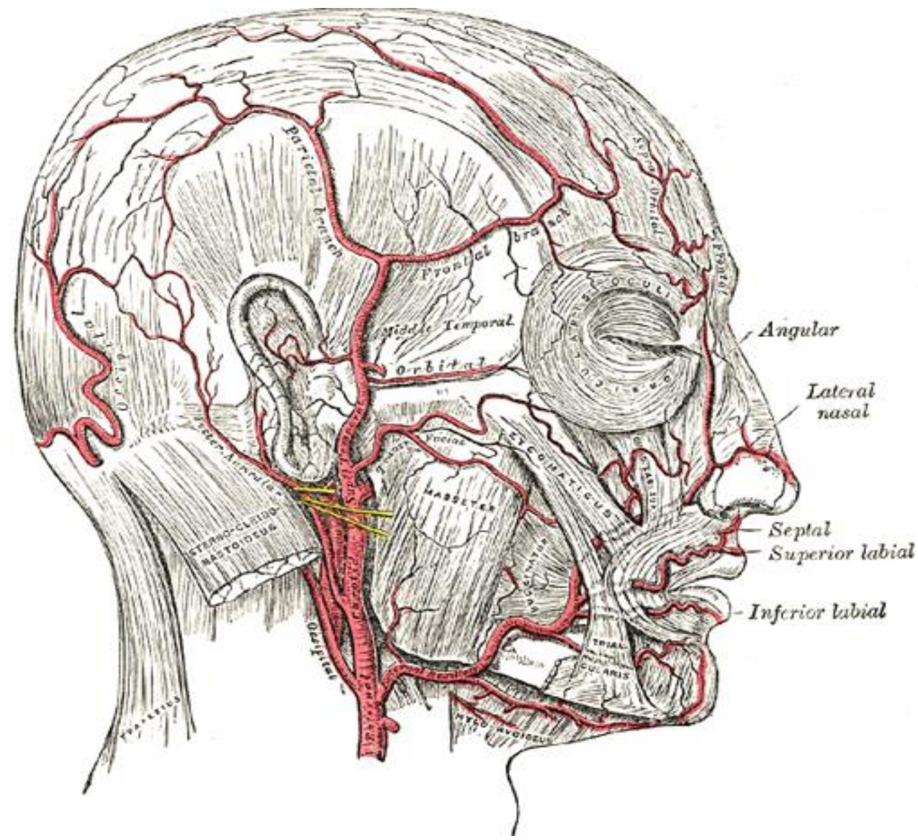


Figure 2-6. The external carotid artery relations, (www.theodora.com).

2.1.5.2 Branches of the external carotid artery

The external carotid artery branches can be divided into four sets. The superior thyroid artery, lingual artery and external maxillary artery are considered as the anterior set, while, the occipital artery and posterior auricular artery are posterior set, the ascending pharyngeal artery is The ascending set, finally, includes the superficial temporal artery and the internal maxillary artery The terminal set (Drake et al., 2009).

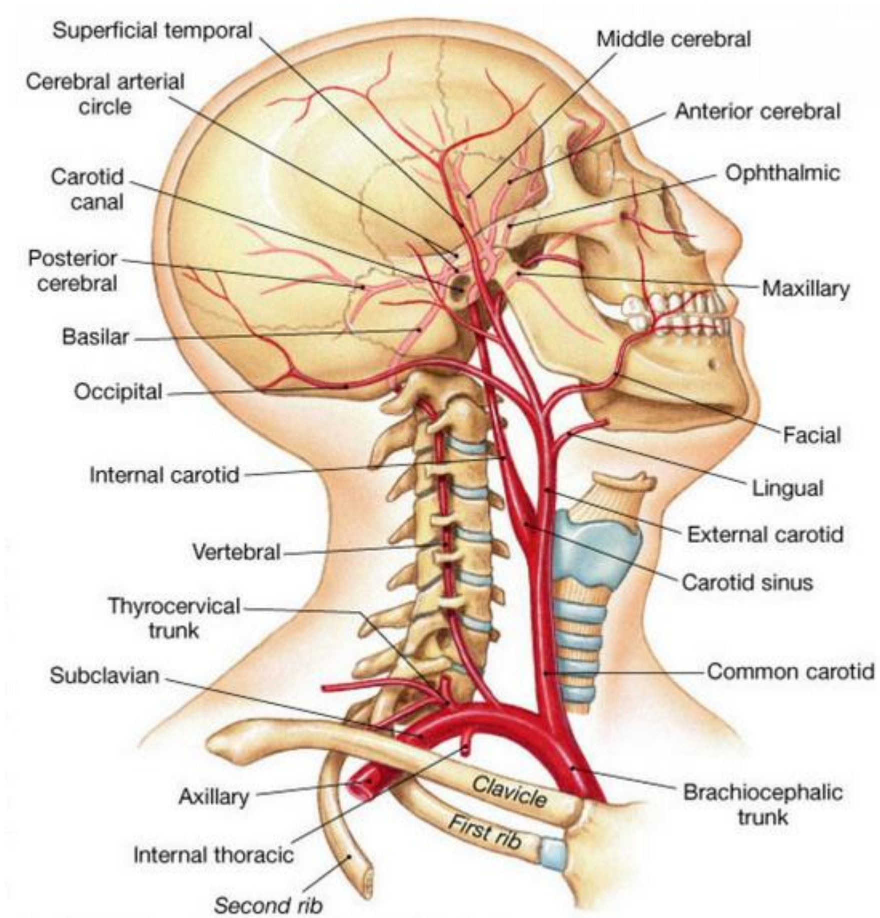


Figure 2-7. Branches of external carotid artery, (www.Anatomy-medicine.com).

Subdivision of the external carotid artery branches; the facial artery is an important anterior branch of the external carotid artery, which is palpable at the anterior border of the masseter muscle insertion on the mandibular ramus. This artery gives branches in the neck and face, the superior and inferior labial arteries combine to build an arterial circle around the mouth, whereas the terminal branch is the angular artery, which anastomoses with the dorsal nasal artery. The ascending palatine artery is the principal cervical branch; therefore, because of extensive arterial anastomoses, facial injuries have a tendency to bleed profusely but also tend to heal quickly and well owing to the copious blood supply. The principal branches of the posterior auricular artery include the posterior tympanic artery and the parotid artery (Figure 2-7) (Schünke et al., 2007).

2.1.6 The internal carotid artery

The internal carotid artery gives supply to the anterior part of the brain, the eye and its appendages, and sends branches to the forehead and nose. This artery is equal to that of the external carotid in the adult, though, it is larger in the child. Moreover, the number of the curvatures in different parts of its course are remarkable. Near the base of the skull, it occasionally has one or two flexures, while it resembles the italic letter "S" in its passage through the carotid canal and long the side of the body of the sphenoid bone because of its double curvature (Figure 2-8) (Drake et al., 2009).

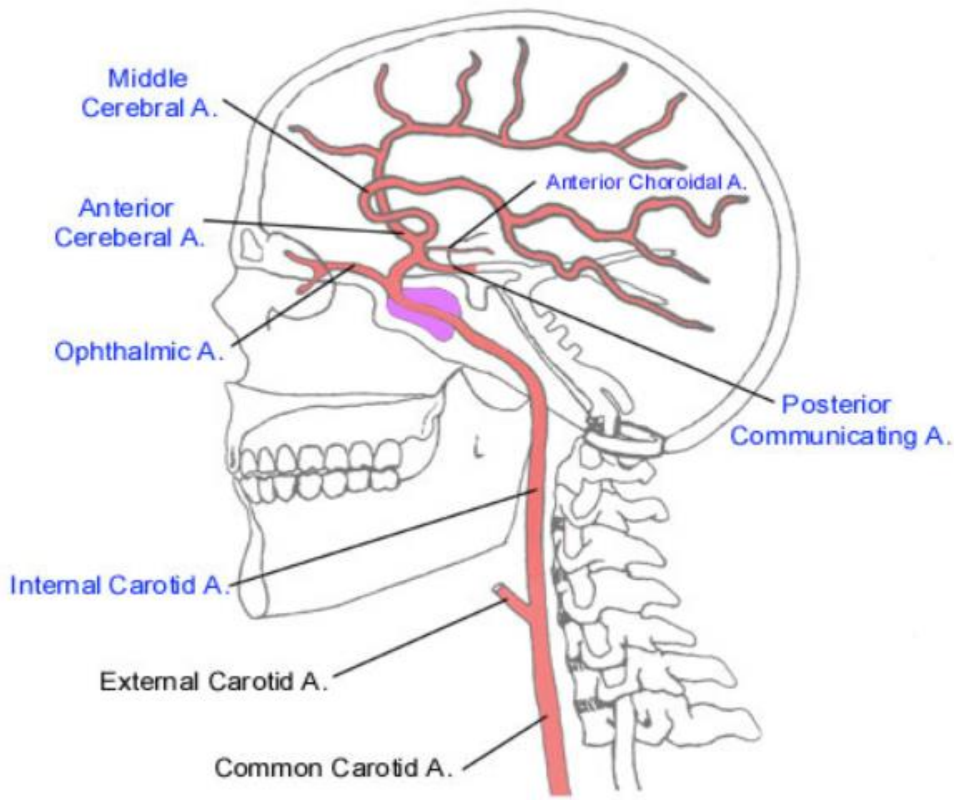


Figure 2-8. The internal carotid branches, (www.meddean.luc.edu).

2.1.6.1 The internal carotid artery course and relations:

Cervical, petrous, cavernous and cerebral portions are the portions of the internal carotid course and relations as describe below (Drake et al., 2009).

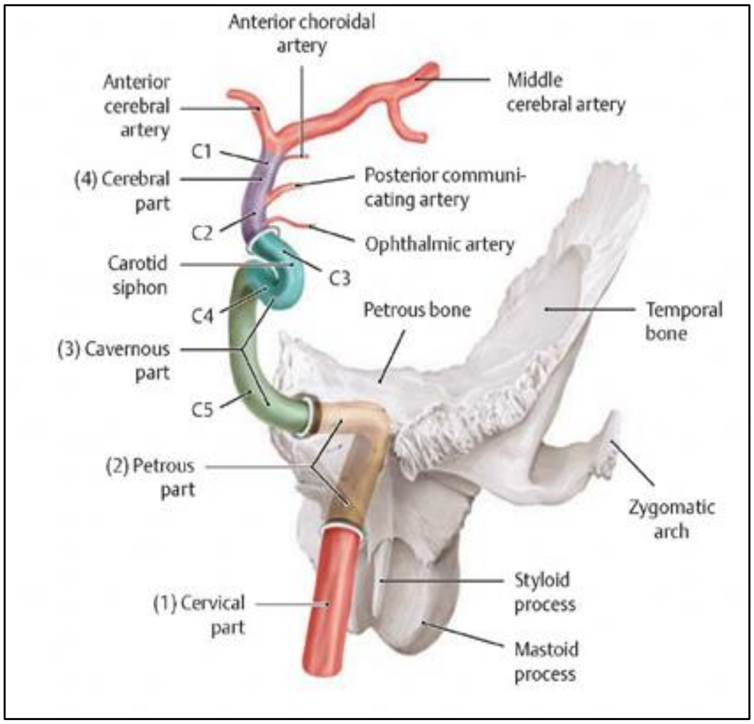


Figure 2-9. The four anatomical segments of the internal carotid artery, (Schünke et al., 2007).

2.1.6.1.1 Cervical part:

The bifurcation of the common carotid is considered as beginning of this portion that is opposite the upper border of the thyroid cartilage, and then it runs upward perpendicularly in front of the transverse processes of the first, second and third cervical vertebrae, to the carotid canal in the petrous portion of the temporal bone. Its commencement is superficial, where it is contained in the carotid triangle and lies behind and lateral to the external carotid. It is overlapped by the Sternocleidomastoids, and covered by the deep fascia, platysma and integument, and then passes beneath the parotid gland, and crossed by the hypoglossal nerve, the Digastricus and Stylohyoideus and the occipital and posterior auricular arteries. Superiorly, it is separated from the external carotid by the Styoglossus and

Stylopharyngeus, the tip of the styloid process and the stylohyoid ligament, the glossopharyngeal nerve and pharyngeal branch of the vagus. It is in relation behind with the Longuscapitis, the superior cervical ganglion of the sympathetic trunk, and the superior laryngeal nerve, laterally with the internal jugular vein and vagus nerve. At the base of the skull the glossopharyngeal, vagus, accessory and hypoglossal nerves lie between the artery and the internal jugular vein (Figure 2-9) (Drake et al., 2009).

2.1.6.1.2 Petrous part:

In the petrous portion of the temporal bone, and as the ICA enters to the carotid canal, firstly it ascends a short distance, before it's curves forward and medial ward then, again ascends to leave the canal and enter the cavity of the skull between the lingual and petrosal process of the sphenoid. The artery lies at first in front of the cochlea and tympanic cavity; it is separated by a thin bony lamella from the latter cavity, which is cribriform in the young subject, and often partly absorbed in old age. Further forward it is separated from the semilunar ganglion by a thin plate of bone, which forms the floor of the fossa for the ganglion and the roof of the horizontal portion of the canal. Frequently this bony plate is more or less deficient and then the ganglion is separated from the artery by fibrous membrane. The artery is separated from the bony wall of the carotid canal by a prolongation of dura mater and is surrounded by a number of small veins and by filaments of the carotid plexus derived from the ascending branch of the superior cervical ganglion of the sympathetic trunk (Figure 2-9) (Drake et al., 2009).

2.1.6.1.3 Cavernous part

The artery is placed between the dura mater layers, forming the cavernous sinus, and covered by the lining membrane of the sinus in this portion in its course. Firstly, it ascends toward the posterior clinoid process, then runs forward in the side of the sphenoid bone body. Secondly, it moves again upward on the medial aspect of the anterior clinoid process and perforates the dura mater forming the roof of the sinus. In this part, the filaments of the sympathetic nerve surround the artery on its lateral side (Figure 2-9) (Drake et al., 2009).

2.1.6.1.4 Cerebral part

After it's perforation to the dura mater on the medial aspect of the anterior clinoid process, and between the optic and oculomotor nerves, The internal carotid passes to the anterior perforated substance at the medial extremity of the lateral cerebral fissure, where it gives off its cerebral branches (Figure 2-9) (Drake et al., 2009).

2.1.6.1.5 Extracerebral branches of internal carotid artery

Chiefly, the internal carotid artery is distributed to supply the brain but also has subdivisions supply extracerebral regions of the head. The additional small arteries that supply local structures and are usually named from the areas they supply. Such as ophthalmic artery, which arises from the cerebral part of the internal carotid artery, supplies blood to the eyeball itself and to orbital structures. Some of its terminal branches are distributed to the eyelid and portions of the forehead, while the others (anterior and posterior ethmoidal arteries) contribute to the supply of the nasal septum. The Branches of the lateral palpebral artery and supraorbital artery may build an anastomosis with the frontal branch of the superficial temporal artery (territory of the external carotid artery), in atherosclerosis of the internal carotid artery, this anastomosis may become an important alternative stream for blood to the brain (Figure 2-9) (Schünke et al., 2007).

2.1.7 The brain arteries

Due to the considerable number of the pathologies that may occur in the brain and since the distribution mode of the brain vessels has an important bearing upon those pathologies, little more in detail the manner in which the vessels are distributed is considered important. The cerebral arteries are derived from the internal carotid and vertebral, which they form a remarkable anastomosis known as the arterial circle Willis at the base of the brain. In front it is formed by branches of the internal carotid which are connected together by the anterior communicating give the anterior cerebral arteries, behind by the two branches of the basilar which are connected on either side with internal carotid by the posterior communicating and give posterior cerebral arteries Figure 2-10, 2-11 and 2-12. The lamina terminalis, the optic chiasma, the infundibulum, the tuber cinereum, the corpora mammillaria and the posterior perforated substance are the parts of the brain including within this arterial circle (Drake et al., 2009).

From this arterial circle of Willis, three trunks arise, to supply together each cerebral hemisphere. The two anterior cerebrals proceed from its anterior part and the middle cerebrals from its antero-lateral parts, whereas the posterior cerebrals from its posterior part. Two different systems of secondary vessels are given off from each of these principal arteries. One of these is named the ganglionic system supplies the thalami and corpora striata. the other is the cortical system, and its vessels supply the cortex and subjacent brain substance where they ramify in the pia mater. There is no communication between two systems at any point of the their peripheral distribution, and they are entirely independent of each other and there is a borderland of diminished nutritive activity between the parts supplies by the two systems, where it is softening is especially liable to occur in the brains of old people (Drake et al., 2009).

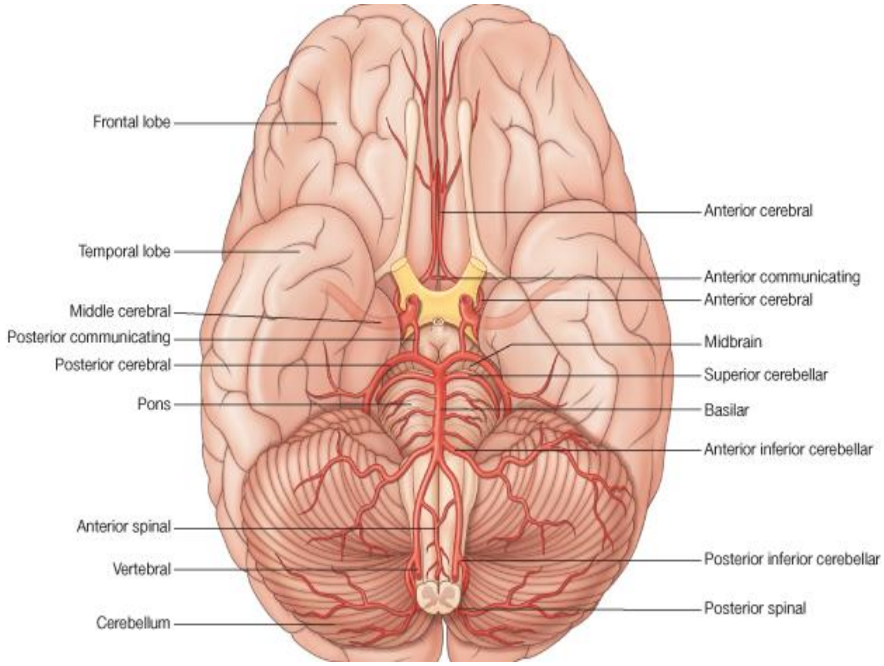


Figure 2-10. Arteries on the base of the brain, (Drake et al., 2009).

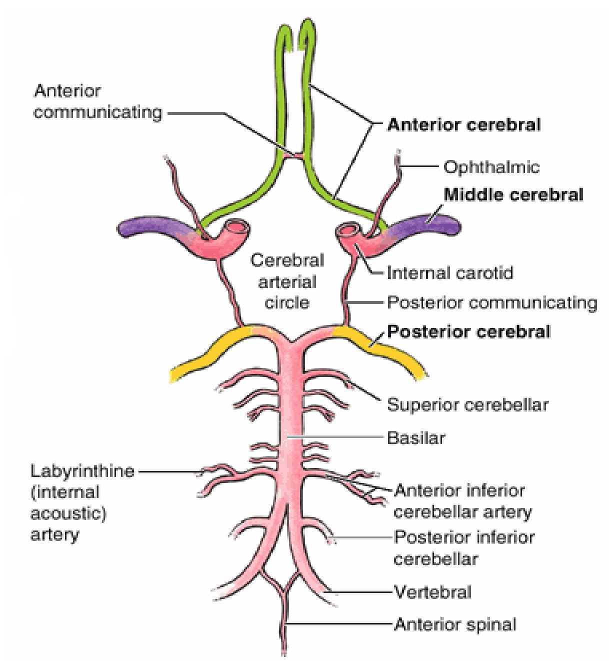


Figure 2-11. The Circle of Willis, (Moore & Dalley, 2018).

2.1.8 The ganglionic system:

All the vessels of this system are derived from the arterial circle of Willis or the vessels close to it. This system form six principal groups, from the anterior cerebrals and anterior communicating, the antero-medial forms. While, the posterior-medial group forms from the posterior cerebrals and posterior communicating, and the right and left antero-lateral groups, derived from the middle cerebrals and the right and left postero-lateral groups, derived from the posterior cerebrals after having wound around the cerebrals peduncles. The ganglionic system characterizes by vessels which larger than those of the cortical system. These vessels neither supply nor receive any anastomotic branch from their origin to their termination, so only a limited area of the thalamus or corpus striatum can be injected through any one of these vessels, and the injection cannot be reached beyond the area of the part supplied by the particular vessel, which is the subject of the experiment (Drake et al., 2009).

2.1.9 The cortical system:

The terminal branches of the anterior, middle and posterior cerebral arteries form the vessels of this system, which they divide and ramify in the substance of the pia mater, and their branches penetrate the brain cortex in perpendicular manner. These branches are divisible into two a long and short classes. The long medullary arteries run through the gray substance penetrating the subject white substance to the depth 3 or 4 cm, without intercommunicating but by fine capillaries, which constitute so many independent small systems. While the short class vessels confine to the cortex, where they build a compact network in the middle zone of the gray substance with long vessels. Sparingly, The outer and inner zones being supplied with blood.

The vessels of the cortical arterial system are not strictly terminal compared to those of the ganglionic system, but they approach very closely, so that the injection of one area from the vessel of another area is frequently very difficult, and only through vessels of small caliber are effected. Therefore, the obstruction of one of the main branches or its small portions may produce softening in a limited area of the cortex (Drake et al., 2009).

2.1.10 Arterial Sensory Structures

Carotid sinuses are slight dilations in each internal carotid artery, at their branching from the common carotid arteries; these sinuses act as baroreceptors to monitor arterial blood pressure. In addition, to permit a more distension in these sinuses when blood pressure increases, because of thin their media layer, moreover, there are many sensory nerve endings from cranial nerve IX, the glossopharyngeal nerve, contained in the adventitia layer. Therefore, vasomotor centres in the brain process these afferent impulses and make adjustment in vasoconstriction to maintain normal blood pressure. Similar function receptor is found in the body of aorta(Mescher, 2013).

For monitoring blood levels of CO2, O2, and its hydrogen ion concentration (pH) as well, chemoreceptors that are more complex are found in the bodies of carotid and aorta, placed in the carotid sinuses walls and aortic arch, respectively. These structures are called paraganglia, considered as parts of the autonomic nervous system with rich networks of capillaries. These capillaries are closely circled by multiple, large, neural crest-derived glomus (type I) cells filled with dense-core vesicles containing dopamine, acetylcholine, and other neurotransmitters, which are supported by smaller satellite (type II) cells, through activation of release process of neurotransmitters, appropriate channels of ion in the glomus cell membranes respond to stimuli in the arterial blood, particularly hypercapnia (excess CO_2), hypoxia (low O_2), or acidosis. Then, to correct the condition, Sensory fibres branching from the glossopharyngeal nerve form synapses supported by the glomus cells and signal brain centres perform respiratory and cardiovascular systems adjustments (Mescher, 2013).

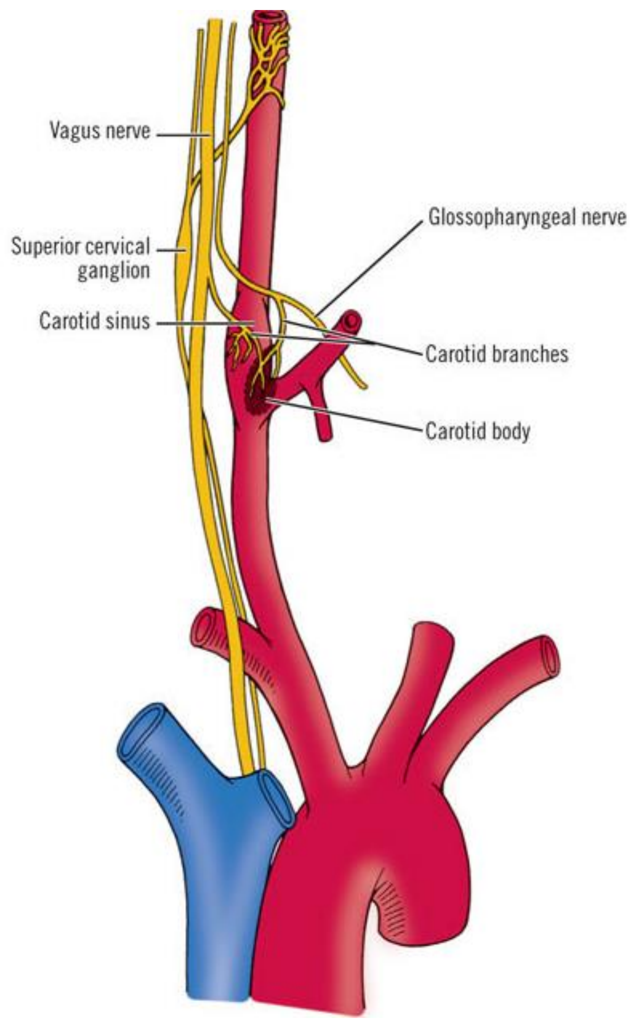


Figure 2-12. Carotid sinus, carotid body, and their innervations, (Skandalakis, Colborn, Skandalakis, & Weidman, 2004).

2.2 Physiology:

The circulatory system transports oxygen (O2) from lungs and substance absorbed from the gastrointestinal tract to the tissues, returns carbon dioxide (CO2) to the lungs and other waste products to the kidneys. Regulation of the body temperature and distribution of hormones and other agents that regulate cell function depend also on the circulatory system. The blood is pumped through a closed system of blood vessels from the left ventricle to the arteries, arterioles, and capillaries (Ganong, 2005).

The function of circulation is to meet the needs of the tissues for nutrients, waste product, and hormonal transport, in order to maintain an appropriate homeostasis and internal environment in the tissue fluids of the body for optimal survival and function of the cells (Guyton & Hall, 2006).

2.2.1 Mechanical events of the cardiac cycle

The cardiac events that occur from the beginning of one heartbeat to the beginning of the next are called the cardiac cycle (Guyton & Hall, 2006). The frequency of the cardiac cycle is the heart rate. Thus, a cardiac cycle consists of systole and diastole of the atria plus systole and diastole of the ventricles. In each cardiac cycle, the atria and ventricles alternately contract and relax, forcing blood from areas of higher pressure to areas of lower pressure (Tortora & Derrickson, 2012). The events follow a regular sequence of five phases. First, late diastole which is when semilunar valves close, the atrioventricular (AV) valves open and the whole heart is relaxed . Second, atrial systole, when atria are contracting, AV valves still open and blood is forced to flow from atria to the ventricles. Third, isovolumetric ventricular contraction, it is when the ventricles begin to contract, AV valves close as well as the semilunar (SL) valves and there is no change in volume. Fourth, ventricular ejection, blood is ejected to aorta and pulmonary artery, and ventricles are empty, they are still contracting and the semilunar valves are open. The fifth phase is isovolumetric ventricular relaxation, pressure drops, no blood is entering the ventricles then ventricles stop contracting and begins to relax; the semilunar are shut. The cardiac cycle is coordinated by a series of electrical signals that are generated by specialized heart cells found within the sinoatrial and the atrioventricular node (Guyton & Hall, 2006).

2.2.1.1 Events in the late diastole

As the ventricles continue to relax, the ventricular pressure falls quickly, AV valves open, and SL valves close. Blood flows into the heart throughout diastole, filling the atria and ventricles. The rate of filling declines as the ventricles become distended. At the end of the relaxation period, the ventricles are about three-quarters full. The cusps of the AV valves drift towards the closed position as shown in figure 2-13 below, and the pressure in the ventricles remains low (Ganong, 2005).

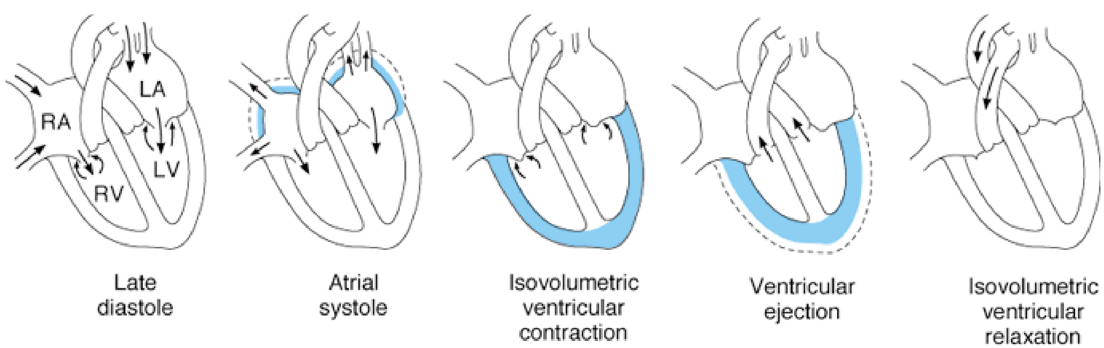


Figure 2-13. Blood flow in the heart and great vessels during the cardiac cycle, the portions of the heart contracting in each phase are indicated in color, (Ganong, 2005).

2.2.1.2 Atrial systole:

During atrial systole, which lasts about 0.1 sec, the atria are contracting. At the same time, the ventricles are relaxed (Tortora & Derrickson, 2012). Contraction of the atria pushes some additional blood into the ventricles, but about 70% of the ventricular filling occurs passively during diastole. Contraction of the atrial muscle that surrounds the orifices of the superior and inferior vena cava and pulmonary veins narrows their orifices, and the inertia of the blood moving toward the heart tends to keep blood in it; however, there is some regurgitation of blood into the veins during atrial systole (Ganong, 2005).

2.2.1.3 Ventricular systole:

At the start of ventricular systole, the AV valves close. Ventricular muscle initially shortens relatively little, but intraventricular pressure rises sharply as the myocardium presses on the blood in the ventricle (Figure 2-14). This period of isovolumetric ventricular contraction lasts about 0.05 second, until the pressures in the left and right ventricles exceed the pressures in the aorta (80 mm Hg) and pulmonary artery (10 mm Hg) and the SL valves open (Ganong, 2005).

The phase of ventricular ejection begins when the SL valves open. Ejection is rapid at first, then slowing down as systole progresses. The intraventricular pressure rises to a maximum and then declines before ventricular systole ends. Peak left ventricular pressure is about 120 mm Hg, and peak right ventricular pressure is 25 mm Hg or less (Ganong, 2005).

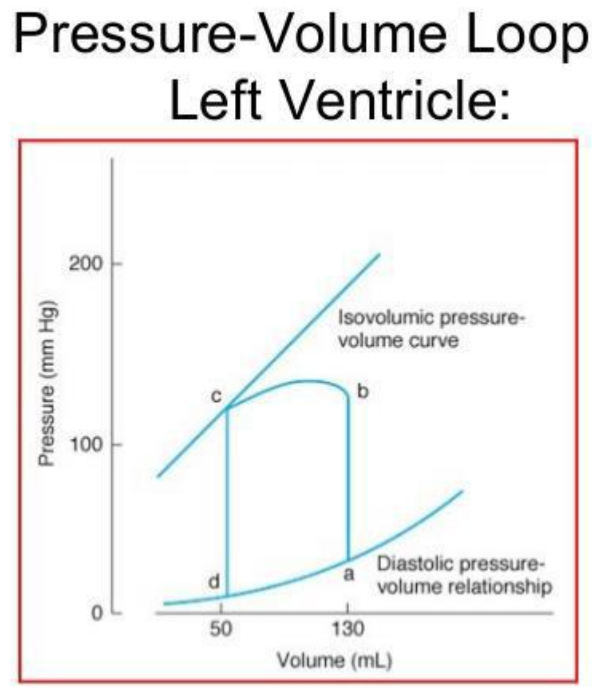


Figure 2-14. Pressure–volume loop of the left ventricle.

During diastole, the ventricle fills and pressure increases from d to a. Pressure then rises sharply from a to b during isovolumetric contraction and from b to c during ventricular ejection. At c, the aortic valves close and pressure falls during isovolumetric relaxation from c back to d (Ganong, 2005).

Atrial systole contributes a final 25 mL of blood to the volume already in each ventricle (about 105 mL). The end of atrial systole is also the end of ventricular diastole (relaxation). Thus, each ventricle contains about 130 mL at the end of its relaxation period (diastole). This blood volume is called the end-diastolic volume (Tortora & Derrickson, 2012).

2.2.1.4 Early diastole:

At the end of systole, ventricular relaxation begins suddenly, allowing both the right and left intraventricular pressures to decrease rapidly (Guyton & Hall, 2006).

This is the period of protodiastole. It lasts about 0.04 second. It ends when the momentum of the ejected blood is overcome and the SL valves close. After closing the valves, pressure continues to drop rapidly during the period of isovolumetric ventricular relaxation. Isovolumetric relaxation ends when the ventricular pressure falls below the atrial pressure and AV valves open, then drop and slowly rises again until the next atrial systole (Ganong, 2005).

2.2.1.5 Regulation of Heart Pumping

When a person is at rest, the heart pumps only 4 to 6 liters of blood each minute. During severe exercise, the heart may be required to pump four to seven times this amount. This intrinsic ability of the heart to adapt to increasing volumes of inflowing blood is called the Frank-Starling mechanism of the heart. Basically, the Frank-Starling mechanism means that the greater the heart muscle is stretched during filling, the greater is the force of contraction and the greater the quantity of blood pumped into the aorta (Guyton & Hall, 2006).

2.2.2 Control of the Heart by the Sympathetic and Parasympathetic Nerves

The pumping effectiveness of the heart also is controlled by the sympathetic and parasympathetic (vagus) nerves, which abundantly supply the heart. For given levels of input atrial pressure, the amount of blood pumped each minute (cardiac output) often can be increased more than 100 per cent by sympathetic stimulation. By contrast, the output can be decreased to as low as zero or almost zero by vagal (parasympathetic) stimulation. Strong sympathetic stimulation can increase the heart rate in young adult humans from the normal rate of 70 beats per minute up to

180 to 200 and, rarely, even 250 beats per minute. Also, sympathetic stimulation increases the force of heart contraction to as much as double normal, thereby increasing the volume of blood pumped and increasing the ejection pressure (Guyton & Hall, 2006).

On the other hand, strong vagal stimulation of the heart can stop the heartbeat for a few seconds, but then the heart usually "escapes" and beats at a rate of 20 to 40 beats per minute as long as the parasympathetic stimulation continues. In addition, strong vagal stimulation can decrease the strength of heart muscle contraction by 20 to 30 per cent. The vagal fibers are distributed mainly to the atria and not much to the ventricles. This explains the effect of vagal stimulation mainly to decrease heart rate rather than to decrease the strength of heart contraction. Nevertheless, the great decrease in heart rate combined with a slight decrease in heart contraction strength can decrease ventricular pumping 50 per cent or more (Guyton & Hall, 2006).

2.2.2.1 Length of systole and diastole:

Cardiac muscle has the unique property of contracting and repolarizing faster when the heart rate is high and the duration of systole decreases from 0.27 seconds at a heart rate of 65 to 0.16 seconds at a rate of 200 beats per minutes see Table 2-2. However, the duration of systole is much more fixed than that of diastole and when the heart rate is increased diastole is shortened to a much greater degree. For example, at a heart rate of 65, the duration of diastole is 0.62 seconds, whereas at a heart rate of 200, it is only 0.14 seconds. At heart rates up to 180, filling is adequate as long as there is ample venous return and cardiac output per minutes is increase in rate. However at every high heart rates, filling may be compromised to such a degree that cardiac output per minutes falls and symptoms of heart failure develop. The cardiac muscle cannot be tetanized like skeletal muscle due to its prolonged action potential. In its refractory period it will not contract in response to a second stimulus until near the end of initial contraction, see Figure 2-15 below (Ganong, 2005).

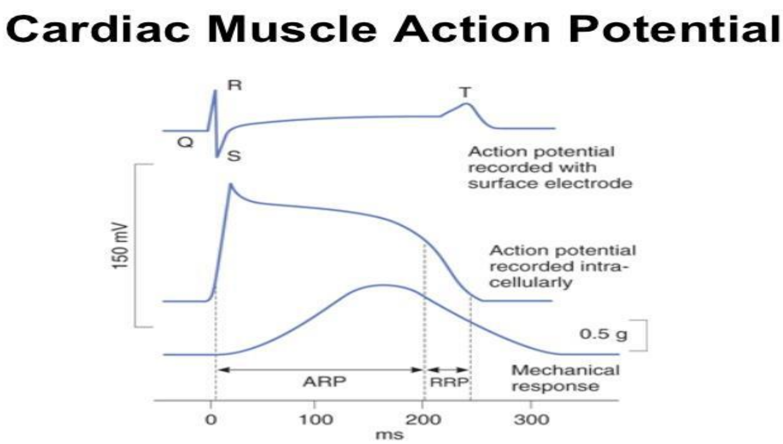


Figure 2-15. Action potentials and contractile response of mammalian cardiac muscle fiber plotted on the time axis where ARP, absolute refractory period, refractory period, (Ganong, 2005).

Table 2-2. The variation in length of action potential and associated phenomena with cardiac rate, all values are in seconds, (Ganong, 2005).

Duration	Heart rate 75/min	Heart rate 200/min	Skeletal Muscle
Duration each cardiac cycle	0.80	0.30	
Duration of systole	0.27	0.16	
Duration of action potential	0.25	0.15	0.007
Duration of absolute refractory period	0.20	0.13	0.004
Duration of relative refractory period	0.05	0.02	0.003
Duration of diastole	0.53	0.14	

2.2.3 Cardiac function curve

The relationship between right arterial pressure (x-axis) and cardiac output (y-axis) is illustrated by a graph called the cardiac function curve. Superimposition of the cardiac function curve and venous return curve is used in one hemodynamic model (Brengelmann, 2003).

Low filling pressure is showed as a steep line, while plateau is used where further stretch is not possible and so increases in pressure have little effect on output. The pressures where there is a steep relationship lie within the normal range of the right atrial pressure (RAP) found in the healthy individuals. This range is about -1 to +2 mmHg. The higher pressures occur only in disease conditions such as heart failure (Brengelmann, 2003).

Increase in sympathetic activity or decrease in vagal tone cause the heart to beat more frequently and more forcefully, and cause the cardiac function curve to be shifted upwards. This allows the heart to cope with the required cardiac output at a relatively low right atrial pressure (Brengelmann, 2003).

2.2.3.1 Mechanisms of blood flow control:

Local blood flow control can be divided into two phases: (1) acute control and (2) long-term control. Acute control is achieved by rapid changes in local vasodilation or vasoconstriction of the arterioles, metarterioles, and precapillary sphincters, occurring within seconds to minutes to provide very rapid maintenance of appropriate local tissue blood flow (Guyton & Hall, 2006).

Long-term control, however, means slow, controlled changes in flow over a period of days, weeks, or even months. In general, these long-term changes provide even better control of the flow in proportion to the needs of the tissues. These changes come about as a result of an increase or decrease in the physical sizes and numbers of actual blood vessels supplying the tissues (Guyton & Hall, 2006).

The main resistance of the circulation lies in the small arteries and arterioles, these vessels are controlled by the local action of the chemical or physical factors, hormones circulating in the blood or by the autonomic nerves supply, through changing calibers of blood vessels. Blood flow to any tissue is normally regulated by local factors to serve the needs of that tissue but it may be subordinated to supply the needs of the entire body by hormonal or nervous factors (Emslie-Smith, Paterson, Scratcherd, & Read, 1988).

In any tissue of the body, an acute increase in arterial pressure causes immediate rise in blood flow. But, within less than a minute, the blood flow in most tissues returns almost to the normal level, even though the arterial pressure is kept elevated. This return of flow toward normal is called "autoregulation of blood flow" (Guyton & Hall, 2006).

2.2.3.2 Local control, effect of metabolism:

After temporary occlusion of blood flow in the limb and release of the occlusion, the blood flow is raised well above the resting level and then gradually returns towards the resting level as shown in figure 2-16 (Emslie-Smith et al., 1988).

The increase in blood flow after occlusion is known as reactive hyperemia. Reactive hyperemia is caused by a local mechanism since it is confined to those tissues whose circulation has been reduced. It is not mediated by the influence of the autonomic nerves (Emslie-Smith et al., 1988). After short periods of vascular occlusion, the extra blood flow during the reactive hyperemia phase lasts long enough to repay almost exactly the tissue oxygen deficit that has accrued during the period of occlusion (Emslie-Smith et al., 1988).

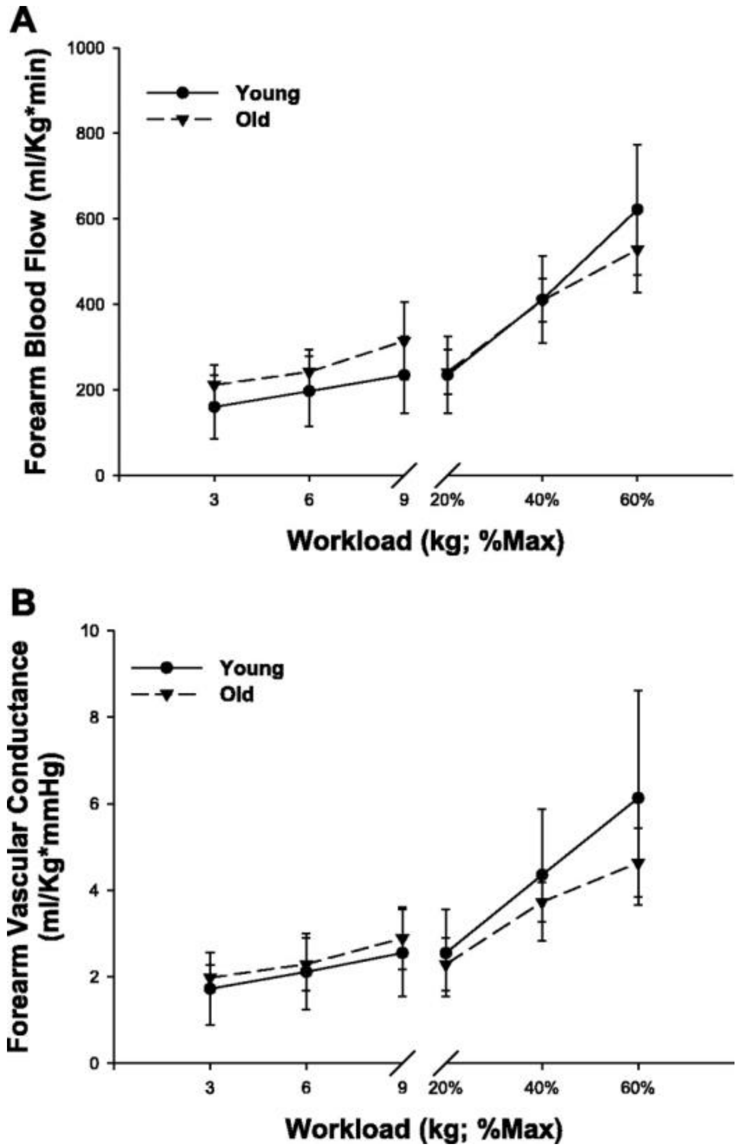


Figure 2-16. Change in forearm blood flow and exercise of the forearm muscles, (Emslie-Smith et al., 1988).

A similar increase in blood flow is seen following highly active period of a tissue, which is called active hyperemia. When any tissue becomes highly active, such as an exercising muscle, a gastrointestinal gland during a hypersecretoryperiod, or even the brain during rapid mental activity, the rate of blood flow through the tissue increases. Here again, the increase in local metabolism causes the cells to devour tissue fluid nutrients extremely rapidly and also to release large quantities of vasodilator substances. The result is to dilate the local blood vessels and, therefore, to increase local blood flow. In this way, the active tissue receives the additional nutrients required to sustain its new level of function. Active hyperemia in skeletal muscle can increase local muscle blood flow as much as 20-fold during intense exercise (Guyton & Hall, 2006).

Active hyperemia is confined to the exercising tissues and still occurs after section of the autonomic nerves to the tissue. The intensity of the exercise hyperemia is related to the severity and duration of the exercise. When the circulation is re-established, the increased blood flow through the dilated vessels washed away the metabolites in an exponential manner until their concentration in the tissues returns to normal levels. When the raised blood flow has cleared the excess of metabolites the blood flow returns to normal. So. it is the local control of resistance blood vessels by metabolites that precisely regulates and ensures the exact amount of blood flow to each tissues (Emslie-Smith et al., 1988; Guyton & Hall, 2006).

The occurrence of metabolic hyperemia is most evident in tissues such as muscle and liver where blood flow is mainly determined by metabolic needs. In tissues such as skin and kidney, where blood flow is related to functions other than metabolism, metabolic hyperemia is less evident (Emslie-Smith et al., 1988).

2.2.3.3 Local control, effect of local temperature:

If the hand or foot is put into water at 45°C the blood flow through the part increases several fold. The increase is restricted to the part that is immersed, and is independent of the autonomic nerve supply. This vasodilatation serves to protect the extremity from the damaging effect of heat. If the extremity is immersed in water at 45C with the circulation occluded, it becomes painful as the tissue temperature rises. The vasodilatation that normally occurs tends to keep the tissues relatively cool by increasing their perfusion with blood at central body temperature. The immersion of an extremity in moderately cold water normally causes vasoconstriction, which reduces the loss of the heat from the blood to the environment. In an extremity exposed to near freezing temperature, for example 0°C to 4°C, the local blood flow falls to about zero initially and the part becomes painful. Blood flow then starts to rise rapidly to a value well above resting level (figure 2-17) (Emslie-Smith et al., 1988).

2.2.3.4 Local control, effect of transmural pressure:

Transmural pressure is the pressure difference across the wall of a blood vessel. It is measured by subtracting the external tissue pressure from the intravascular pressure. The transmural pressure causes local changes in the arterioles. As the transmural pressure in the vessels rises, one would expect the arterioles to dilate due to distension and the blood flow to increase. However, this expectation is not fulfilled. If the arterial pressure is raised above the normal value of about 100 mmHg., blood flow rises only very slowly but at a high critical pressure it rises sharply. In fact, flow does not change very much when the pressure is elicits an increase in vascular resistance. If the pressure is lowered below normal levels, the blood flow at first does not fall proportionately. However, at very low perfusion pressures the flow stops even while there is still a positive perfusion pressure. This closure of vessels below a certain limit of transmural pressure is known as critical closure (figure 2-17) (Emslie-Smith et al., 1988).

2.2.3.5 Local control, effect of oxygen partial pressure in pulmonary alveoli:

Oxygen lack is thought to be one of the factors responsible for vasodilatation in active tissues. However, when the pressure of oxygen in the alveoli of one part of the lungs falls, vasoconstriction occurs in the blood vessels perfusing that part. In this condition hypoxia acts as a vasoconstrictor agent. This response guarantees that blood is not sent to poorly ventilated alveoli and so helps to maintain the normal ventilation to perfusion ratio in the lungs (figure 2-17) (Emslie-Smith et al., 1988).

2.2.4 Nervous control:

Vasoconstrictor nerves: stimulation of these nerves causes blood vessels to contract. Impulses reaching their terminals release noradrenalin, which excites the smooth muscle in the walls of the blood vessel. Nerve fibers are originated from vasomotor center in the medulla. Afferent impulses to blood vessels are constantly reaching the vasomotor center from all parts of the body, especially from the pressor receptor in the carotid sinus and aortic arch and from the cardiac and respiratory centers in the medulla itself, efferent impulses are thus initiated or modified and appropriate adjustment made in the circulatory system via the sympathetic nervous system The vasoconstrictor impulses pass down from the medulla into the spinal cord and leave through the anterior spinal roots of the thoracic and upper lumber segments of the cord. The fibers pass by way of the white rami communicants to the sympathetic ganglia (preganglionic fibers) where new fibers (postganglionic fibers) arise (figure 2-18) (Emslie-Smith et al., 1988).

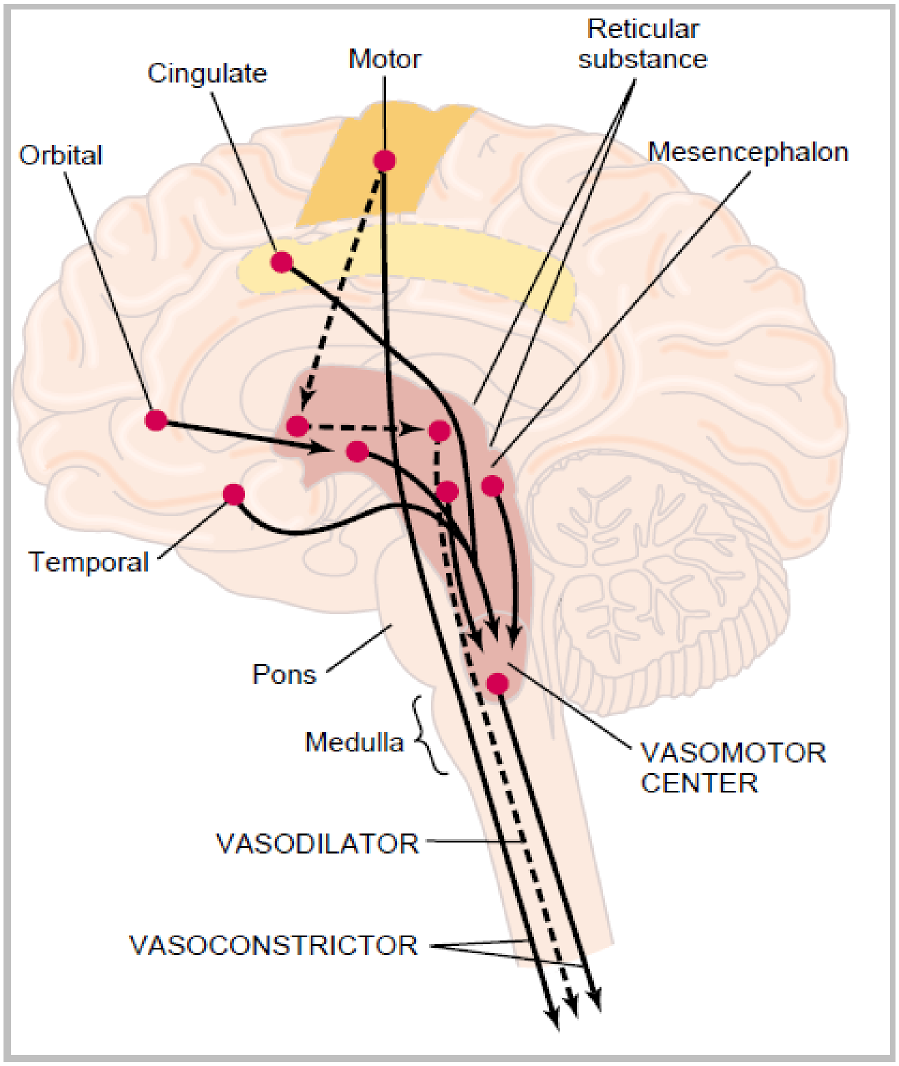


Figure 2-17. Brain areas that play important roles in the nervous regulation of the circulation. The dashed lines represent inhibitory pathways, (Guyton & Hall, 2006).

The frequency of impulses in vasoconstrictor nerves is usually quite low compared with that in somatic motor fibers. It has been shown that almost complete vasoconstriction is produced when vasoconstrictor nerves are stimulated at rates of about 8 impulses per second. In somatic fibers, maximum contractions of skeletal muscle are achieved with impulse frequency of about 50 per second. The resting level of vasoconstrictor tone could be reached at about one impulse per second (Emslie-Smith et al., 1988).

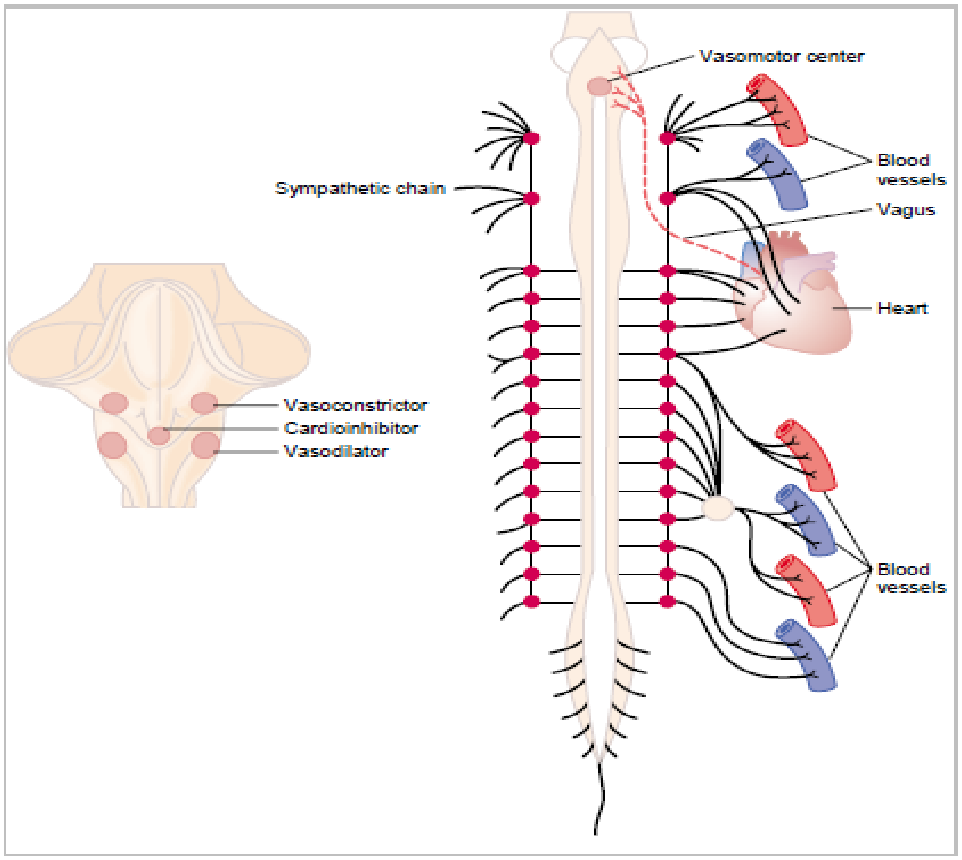


Figure 2-18. Anatomy of sympathetic nervous control of the circulation, red dashed line is a vagus nerve that carries parasympathetic signals to the heart, (Guyton & Hall, 2006).

Vasodilator nerves: these are nerves which, when stimulated cause dilatation of the blood vessels. They are thought to do this by releasing a vasodilator substance such as acetylcholine at their nerve endings. Vasodilator nerve fibers are found in both sympathetic and parasympathetic systems (figure 2-18) (Emslie-Smith et al., 1988).

2.2.5 Vasomotor reflexes:

Thermoregulatory reflexes: when hands are immersed in warm water, the blood flow to hands increases. This reflex is mediated by release of sympathetic vasoconstrictor tone. A similar release of vasoconstrictor tone occurs in other extremities, such as the ears, nose and lips. Vasodilatation also occurs in the skin of other parts of the body, but this is the result of activity in the sympathetic cholinergic nerves. The dilation may be secondary to the release of bradykinin-forming enzyme by active sweat glands, which have sympathetic cholinergic innervations. Reflex vasodilatation in response to body heating is not seen in vascular beds such as in muscles, which lie deep to the skin (Emslie-Smith et al., 1988).

If the body becomes cold, a reflex increase in vasoconstrictor tone occurs in most of the skin areas of the body. The vasoconstrictor, by decreasing skin temperature and therefore prevents losing body temperature. The coordinating centers for these reflexes are thought to lie in the hypothalamus (Emslie-Smith et al., 1988).

Blood shift reflexes: many stimuli, which have the effect of shifting blood towards or away from the chest, can produce reflex alterations in vasoconstrictor tone. These reflex changes are most evident in the blood vessels of muscles and also can be observed in skin. Tilting a person into the foot down position, the application of negative pressure to the lower part of the body, breathing at positive pressure, all tend to shift blood away from the chest towards the feet. These stimuli are associated with a reflex increases in vasoconstrictor tone in blood vessels of muscles. Titling a person into the foot up position, the application of positive pressure to the lower limbs and squatting all tend to move blood towards the chest and result in reflex vasodilatation in chest (Emslie-Smith et al., 1988).

Chemoreceptor reflexes: primarily, the effect of carbon dioxide on the blood vessels is to dilate them. Nevertheless, when carbon dioxide is breathed in high concentration a reflex increases the peripheral vascular resistance in the muscles. This is mediated through sympathetic vasoconstrictor fibers. If these fibers are blocked peripheral vasodilatation occurs when high concentrations of CO_2 are breathed. Carbon dioxide is thought to act on the vasomotor center in the medulla but it also probably acts on the peripheral chemoreceptor (Emslie-Smith et al., 1988).

Exercise reflexes: during muscle exercise, strong local vasodilatation is brought about by metabolites in the active muscle. However, in other tissues, such as the muscles that are not taking part in the exercise, there is a reflex vasoconstriction.

For instant, during leg exercise, there is a reflex increase in the peripheral vascular resistance in the forearm. The efferent limb of the reflex consists of sympathetic vasoconstrictor fibers but the nature and location of the receptors on the afferent limb and reflex center are not known. If all the sympathetic vasoconstrictor fibers are blocked pharmacologically, exercise cannot be sustained for long (Emslie-Smith et al., 1988).

Emotional Fainting or Vasovagal Syncope: a particularly interesting vasodilatory reaction occurs in people who experience intense emotional disturbances that cause fainting. In this case, the muscle vasodilator system becomes activated, and at the same time, the vagal cardioinhibitory center transmits strong signals to the heart to slow the heart rate markedly. The arterial pressure falls rapidly, which reduces blood flow to the brain and causes loss of consciousness. This overall effect is called vasovagal syncope. Emotional fainting begins in the cerebral cortex. The pathway probably then goes to the vasodilatory center of the anterior hypothalamus next to the vagal centers of the medulla, to the heart through the vagus nerves, and also through the spinal cord to the sympathetic vasodilator nerves of the muscles(Guyton & Hall, 2006).

Baroreceptor Arterial Pressure Control System or Baroreceptor Reflexes: by far the best known of the nervous mechanisms for arterial pressure control is the baroreceptor reflex. Basically, this reflex is initiated by stretch receptors, called either baroreceptors or pressoreceptors, located at specific points in the walls of several large arteries. A rise in arterial pressure stretches the baroreceptors and causes them to transmit signals into the central nervous system. "Feedback" signals are then sent back through the autonomic nervous system to the circulation to reduce arterial pressure downward toward the normal level(Guyton & Hall, 2006).

Lung inflation reflexes: taking a deep breath causes a reflex vasoconstriction in the skin of the peripheral parts in body. It does not occur if the sympathetic fibers have been activated. In fact, a large number of relatively trivial stimuli, such as sudden noise, a pinch or the inflation of a cuff on arm can cause well marked reflex vasoconstrictor in the hand. The muscles of blood vessels are not involved in these responses. Some of these responses form part of the altering reaction in human being but their physiological significance are not obvious (Emslie-Smith et al., 1988).

2.2.6 Humoral Control of the Circulation

Humoral control of the circulation means control by substances secreted or absorbed into the body fluids - such as hormones and ions. Some of these substances are formed by special glands and transported in the blood throughout the entire body. Others are formed in local tissue areas and cause only local circulatory effects. Among the most important of the humoral factors that affect circulatory function are the following.

2.2.6.1 Vasoconstrictor Agents:

They include norepinephrine& epinephrine, Angiotensin II, and vasopressin. Norepinephrine is an especially powerful vasoconstrictor hormone; epinephrine is less so and in some tissues even causes mild vasodilation (a special example of vasodilation caused by epinephrine occurs to dilate the coronary arteries during increased heart activity). When the sympathetic nervous system is stimulated in most or all parts of the body during stress or exercise, the sympathetic nerve endings in the individual tissues release norepinephrine, which excites the heart and contracts the veins and arterioles. In addition, the sympathetic nerves to the adrenal medullae cause these glands to secrete both norepinephrine and epinephrine into the blood. These hormones then circulate to all areas of the body and cause almost the same effects on the circulation as direct sympathetic stimulation.

a) Angiotensin II is another powerful vasoconstrictor substance. The effect of angiotensin II is to constrict powerfully the small arterioles. If this occurs in an isolated tissue area, the blood flow to that area can be severely depressed. However, the real importance of angiotensin II is that it normally acts on many of the arterioles of the body at the same time to increase the total peripheral resistance, thereby increasing the arterial pressure. Thus, this hormone plays an integral role in the regulation of arterial pressure(Guyton & Hall, 2006).

b) Vasopressin also called antidiuretic hormone, is even more powerful than angiotensin II as a vasoconstrictor, thus making it one of the body's most potent vascular constrictor substances. It is formed in nerve cells in the hypothalamusthen transported downward by nerve axons to the posterior pituitary gland, where it is finally secreted into the blood(Guyton & Hall, 2006).

It is clear that vasopressin could have enormous effects on circulatory function. Yet, normally, only minute amounts of vasopressin are secreted. . However, experiments have shown that the concentration of circulating blood vasopressin after severe hemorrhage can rise high enough to increase the arterial pressure as much as 60 mm Hg. In many instances, this can, by itself, bring the arterial pressure almost back up to normal. Vasopressin has a major function to increase greatly water reabsorption from the renal tubules back into the blood, and therefore to help control body fluid volume. That is why this hormone is also called antidiuretic hormone(Guyton & Hall, 2006).

c) Endothelinis a powerful vasoconstrictor in damaged blood vessels. Endothelin still another vasoconstrictor substance that ranks along with angiotensin and vasopressin in its vasoconstrictor capability. This substance is present in the endothelial cells of most blood vessels. The usual stimulus for release is damage to the endothelium, such as that caused by crushing the tissues or injecting a traumatizing chemical into the blood vessel (Guyton & Hall, 2006).

2.2.6.2 Vasodilator Hormonal Agents:

They include bradykinin, and histamine. Kinins cause powerful vasodilation when formed in the blood and tissue fluids of some organs. The kinins are small polypeptides that are split away by proteolytic enzymes from alpha2-globulins in the plasma or tissue fluids. These substances become activated by maceration of the blood, by tissue inflammation, or by other similar chemical or physical effects on the blood or tissues to produce the bradykinin. Bradykinin causes both powerful arteriolar dilation and increased capillary permeability.

Histamine. Histamine is released in essentially every tissue of the body if the tissue becomes damaged or inflamed or is the subject of an allergic reaction. Most of the histamine is derived from mast cells in the damaged tissues and from basophils in the blood.

a) Histamine: has a powerful vasodilator effect on the arterioles and, like bradykinin, has the ability to increase greatly capillary porosity, allowing leakage of both fluid and plasma protein into the tissues. In many pathological conditions, the intense arteriolar dilation and increased capillary porosity produced by histamine cause tremendous quantities of fluid to leak out of the circulation into the tissues, inducing edema. The local vasodilatory and edema-producing effects of histamine are especially prominent during allergic reactions (Guyton & Hall, 2006).

2.3 Pathology of Carotid Arteries

2.3.1 Carotid Artery Disease - Atherosclerosis

Carotid artery disease is also referred as carotid artery stenosis, which means narrowing of the carotid arteries. This narrowing is usually caused by the accumulation of fatty substances and cholesterol deposits, called plaque. Atherosclerosis may develop in carotid arteries. Complete carotid artery blockage refers to occlusion (WebMD, 2017).

Atherosclerosis, from Greek root words for "gruel" and "hardening," underlies the pathogenesis of coronary, aortic, carotid, cerebral and peripheral vascular disease, and causes more morbidity and mortality (roughly half of all deaths) in the Western world than any other disorder (Kumar, Abbas, & Aster, 2015).

The risk factors for atherosclerotic disease include aging, smoking, hypertension, hyperlipidemia and hypercholesterolemia, insulin resistance and diabetes, obesity, sedentary lifestyle, and family history of atherosclerosis. Men younger than age 75 are in a greater risk than women in the same age group. On the contrary, women older than age 75 have a greater risk than men older than age 75. There is an association between coronary artery disease and carotid artery disease. Typically, the carotid arteries become diseased a few years later than the coronary arteries. The symptoms of atherosclerotic disease are not apparent until a significant narrowing builds-up to cause a transient ischemic attack (TIA) or a stroke. Manifestations of a stroke may include vision impairment, numbness; weakness; or even paralysis in on or both sides of the body, sudden dizziness and/or confusion, lack of movement coordination and loss of balance, speech difficulty, swallowing difficulty, and memory impairment (WebMD, 2017).

2.3.1.1 Pathogenesis of Atherosclerosis:

The contemporary view of atherogenesis integrates the risk factors previously discussed and is called the "response to injury" hypothesis. This model views atherosclerosis as a chronic inflammatory and healing response of the arterial wall to endothelial injury. Lesion progression occurs through interaction of modified lipoproteins, macrophages, and T lymphocytes with endothelial cells and smooth muscle cells of the arterial wall. Atherosclerosis progresses in the following sequence (Kumar et al., 2015)

Endothelial injury and dysfunction, causing (among other things) increased vascular permeability, leukocyte adhesion, and thrombosis. Endothelial cell injury is the cornerstone of the response-to-injury hypothesis. The two most important causes of endothelial dysfunction are hemodynamic disturbances and hypercholesterolemia.

- Accumulation of lipoproteins (mainly LDL and its oxidized forms) in the vessel wall.

- Monocyte adhesion to the endothelium, followed by migration into the intima and transformation into macrophages and foam cells.
- Platelet adhesion.
- Factor released from activated platelets, macrophages, and vascular wall cells, inducing smooth muscle cell recruitment, either from the media or from circulating precursors.
- Smooth muscle cell proliferation, extracellular matrix production, and recruitment of T-cells.
- Lipid accumulation both extracellularly and within cells (macrophages and smooth muscle cell).

2.3.1.2 Pathologic features of atherosclerosis

Two types of atherosclerotic lesions were initially described: the fatty streak and the atheromatous plaque. The fatty streak is considered a precursor lesion to the advanced atheromatous plaque. It is less elevated and not prone to thrombosis. It consists of smooth muscle cells, lipid-rich macrophages, and lymphocytes within a proteoglycan-collagenous matrix. The atheromatous plaque is a raised lesion having a lipidrich necrotic core with cholesterol and cholesterol esters, and overlapped by a fibrous cap. The atheromatous plaque, unlike the fatty streak, is prone to complications as calcification, ulceration, thrombosis and hemorrhage (Virmani, Ladich, Burke, &Kolodgie, 2006).

For technical reasons, it is hard to correlate carotid, aortic and cerebrovascular plaques morphology at autopsy. Therefore, the mechanisms by which carotid atherosclerosis results in cerebrovascular symptoms are less understood than those linking coronary disease and myocardial symptoms. Previous studies of surgically excised carotid plaques denoted that plaque rupture and consequence occlusive thrombus is relatively uncommon in the carotid arteries (Golledge, Mitchell, Greenhalgh, & Davies, 2000; Spagnoli et al., 2004).

Unlike the myocardial circulation, ischemic damage in the brain is likely to be related more to embolization than static occlusion of the artery (Virmani, Burke, Ladich, & Kolodgie, 2007).

2.3.1.3 Effect of high flow on carotid plaque formation

It has been observed that the atherosclerotic plaques tend to occur at ostia of vessels, branch points, bifurcations, and bends, suggesting that flow dynamics play an important role in its induction (Kumar et al., 2015; Masawa, Glagov, & Zarins, 1994). The intimal thickness is the least on the flow divider side at the junction of the internal and external carotid arteries where wall stress is the highest (Masawa, Glagov, & Zarins, 1988).

High flow rates and the shear forces caused by the bifurcation of the common carotid artery into the internal and external carotids result in unique features of carotid plaque morphology as compared to that of coronary. Most importantly, the ulcerated plaque, which is uncommon in the coronary artery, is relatively common in the carotid and other elastic arteries. Ulcerated plaque is a term used when the thrombus and a portion of the plaque have embolized, leaving an excavation in the remaining lesion. Another feature of carotid atherosclerosis is the infrequency of total occlusion comparing to the coronary artery. Occlusive carotid disease is reported in 3% of patients with posterior cerebral circulation infarcts, 14% in those with partial anterior cerebral circulation infarcts and 29% in patients with total anterior cerebral circulation infarcts; however, in coronary circulation the incidence of chronic total occlusion in patients dying suddenly is 40% (Golledge, Greenhalgh, & Davies, 2000). The explanation for the low rate of complete occlusions in carotid plaques is most likely related to high-flow rates that limit thrombotic occlusions (Virmani, Ladich, Burke, & Kolodgie, 2006)

2.3.2 Takayasu Arteritis

This is a granulomatous vasculitis of medium and larger arteries characterized principally by ocular disturbances and marked weakening of the pulses in the upper extremities (hence the name pulseless disease). Takayasu arteritis manifests with transmural fibrous thickening of the aorta - particularly the aortic arch and its branching vessels - with severe luminal narrowing of the major branch vessels. On the contrary of giant cell arteritis, which affects patients older than 50, Takayasu arteritis affects patients younger than 50 years old. Takayasu arteritis classically involves the aortic arch. In a third of patients, it also affects the remainder of the aorta and its branches, with pulmonary artery involvement in half the cases; coronary and renal arteries may be similarly affected. There is irregular thickening of the vessel wall with intimal hyperplasia; when the aortic arch is involved, the great vessel lumina can be markedly narrowed or even obliterated. Histologically, the changes range from adventitial mononuclear infiltrates with perivascular cuffing of the vasa vasorum, to intense mononuclear inflammation in the media, to granulomatous inflammation, replete with giant cells and patchy medial necrosis. As the disease progresses, collagenous scarring, with admixed chronic inflammatory infiltrates, occurs in all three layers of the vessel wall. Occasionally, aortic root involvement causes dilation and aortic valve insufficiency (Kumar et al., 2015).

The initial symptoms are usually nonspecific, including fatigue, weight loss, and fever. With progression, vascular symptoms appear and dominate the clinical picture, including reduced blood pressure and weak pulses in the carotids and the upper extremities; ocular disturbances, including visual defects, retinal haemorrhage, and total blindness; and neurologic deficits. Involvement of the more distal aorta may lead to claudication of the legs; pulmonary artery involvement can cause pulmonary hypertension. Narrowing of the coronary ostia may lead to myocardial infarction, and involvement of the renal arteries leads to systemic hypertension in roughly half of patients. The prognosis is variable. In some there is rapid progression, while others enter a quiescent stage after 1 to 2 years, permitting long-term survival, albeit with visual or neurologic deficits (Kumar et al., 2015).

2.3.3 PolyarteritisNodosa

Polyarteritisnodosa (PAN) is a systemic vasculitis of small- or medium-sized muscular arteries, typically involving renal and visceral vessels but sparing the pulmonary circulation. There is no association with antineutrophil cytoplasmic antibodies (ANCA), but about 30% of patients with PAN have chronic hepatitis B and deposits containing HBsAg-HBsAb complexes in affected vessels. The cause remains unknown in the remaining cases.

Classic PAN is characterized by segmental transmural necrotizing inflammation of small- to medium-sized arteries. Vessels of the kidneys, heart, liver, and gastrointestinal tract are involved in descending order of frequency. Lesions usually involve only part of the vessel circumference with a predilection for branch points. The inflammatory process weakens the arterial wall and can lead to aneurysms or even rupture. Impaired perfusion with ulcerations, infarcts, ischemic atrophy, or haemorrhages may be the first sign of disease.

During the acute phase, there is transmural inflammation of the arterial wall with a mixed infiltrate of neutrophils, eosinophils, and mononuclear cells, frequently accompanied by fibrinoid necrosis. Luminal thrombosis can occur. Later, the acute inflammatory infiltrate is replaced by fibrous (occasionally nodular) thickening of the vessel wall that can extend into the adventitia.

Characteristically, all stages of activity (from early to late) may coexist in different vessels or even within the same vessel, suggesting ongoing and recurrent insults(Kumar et al., 2015).

Although typically a disease of young adults, PAN can also occur in pediatric and geriatric populations. Clinical manifestations result from ischemia and infarction of affected tissues and organs. The course is frequently remitting and episodic, with long symptom-free intervals. Because the vascular involvement is widely scattered, the clinical signs and symptoms of PAN can be quite variable. A "classic" presentation can involve some combination of rapidly accelerating hypertension due to renal artery involvement; abdominal pain and bloody stools caused by vascular gastrointestinal lesions; diffuse myalgias; and peripheral neuritis, predominantly affecting motor nerves. Renal involvement is often prominent and a major cause of mortality. Untreated, PAN is typically fatal; however, immunosuppression can yield remissions or cures in 90% of cases.

2.3.4 Pathology of Vascular Intervention

The morphologic changes that occur in vessels following therapeutic intervention (e.g., stenting, endarterectomy, or bypass surgery) largely recapitulate the changes that occur in the setting of any vascular insult. Local trauma or thrombosis (e.g., due to a stent or endarterectomy), all induce the same stereotypical healing responses. Analogous to the various insults that drive atherosclerosis, any therapeutic intervention that injures the endothelium also tends to induce intimal thickening by recruiting smooth muscle cells and promoting extracellular matrix deposition (Kumar et al., 2015).

2.4 Ultrasound studies

the second most popular imaging modality in medicine is ultrasonography ranked under x-ray.Over 25% of all medical imaging procedure is estimated to be with ultrasound. Ultrasonic imaging is complementaryof the other imaging modalities, i.e. x-rays and magnetic resonance (MR) imaging etc.(Hughes, 2001).

2.4.1 B-mode ultrasound

The B-mode is a two-dimensional (2D) image of the area that is simultaneously scanned by a linear array of 100–300 piezoelectric elements rather than a single one as in A-mode . The amplitude of the echo from a series of A-scans is converted into dots of different brightness in B-mode imaging. The horizontal and vertical directions represent real distances in tissue, whereas the intensity of the grayscale indicates echo strength. B-mode can provide an image of a cross section through the area of interest(Xu, 2020).

2.4.2 Doppler ultrasound

Doppler is animportant major component of ultrasonography especially in the investigation of cardiovascular system disease. Doppler system in recent and modern machines are accuratein providing good information with high accuracyregarding the effects of disorders on blood hemodynamics. These accurate blood hemodynamics information is helpful in estimation the effects of these certain disease on system and organ physiology and can provide physician help in the treatment of patients(Corbett, 2005).

2.4.2.1 Doppler Principles

In modern scanning systems at recent years, the imaging of flow using ultrasonography have enormously increased capabilities. For example, the recent color flow imaging is now facilities and common place using ‘power’ or ‘energy’ as new approach of flow imaging. With such multipurpose technique, it is employ the useful approach for more demanding applications and increasingly to estimate subtle changes in circulations in obstetrical scanning. And in order to prevent wrong demonstration of results, however, it is essential for the Doppler ultrasound operators should be aware of the factors setting that affect the signal in Doppler interrogation(Bowman et al., 2003).

The following describes how these components contribute to the quality of Doppler ultrasound images. Guidelines are given on how to obtain good images in all flow imaging modes. Competent use of Doppler ultrasound techniques requires an understanding of three key components: The capabilities and limitations of Doppler ultrasound; The different parameters which contribute to the flow display;

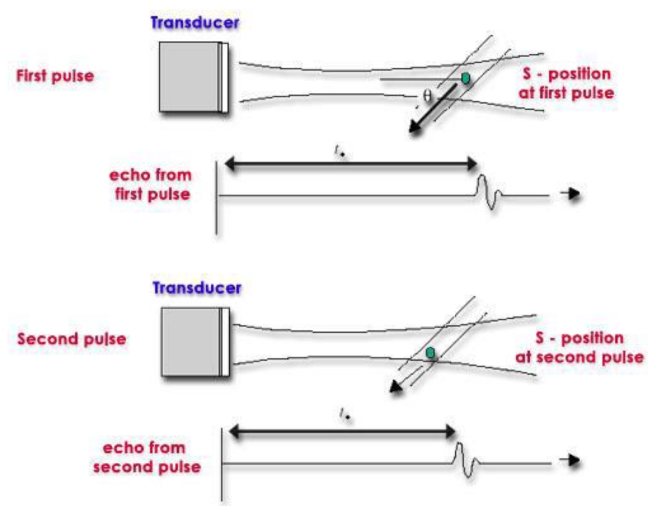


Figure 2-19. Ultrasound velocity measurement. (Bowman et al., 2003)

2.4.2.1.1 Basic Principles

Blood flow sonograms, whether color Doppler or spectral one, are obtained essentially from movement estimation. In ultrasound machines, a pulses series are transmitted for blood movement detection. Echoes reflected from stationary objects are the same from pulse to pulse. While reflected echoes from moving objects demonstrate slight differences in the time for the signal to be returned to the probe (Figure 2-19). the measurement of these differences is a direct time difference or in terms of a phase shift from which the 'Doppler signal' is obtained (Figure 2-19). after processing, They are then produce either a color coding presentation or a Doppler diagram.

Figures 2-19 and 2-20, revealed motion in beam direction; but if there is perpendicular relationship between the flow and the beam, no relative motion from pulse to pulse would be obtained. Therefore, the size of the Doppler signal is dependent on:

(1) flow velocity of blood: as velocity increases, so does the Doppler frequency;

(2) Ultrasound frequency: higher frequencies give more Doppler frequency. Like in B-mode, lower sonic frequencies provide better penetration.

(3) The choice of frequency is a compromise between better blood flow sensitivity or better penetration;

(4) The angle of insonation: the Doppler frequency increases when the sonic beam of Doppler becomes more aligned to the direction of blood flow, i.e. smaller angle q between the Doppler ultrasound beam and the flow direction. This setting is the most important during Doppler ultrasound scanning. As schematically illustrated in Figure 2-21.

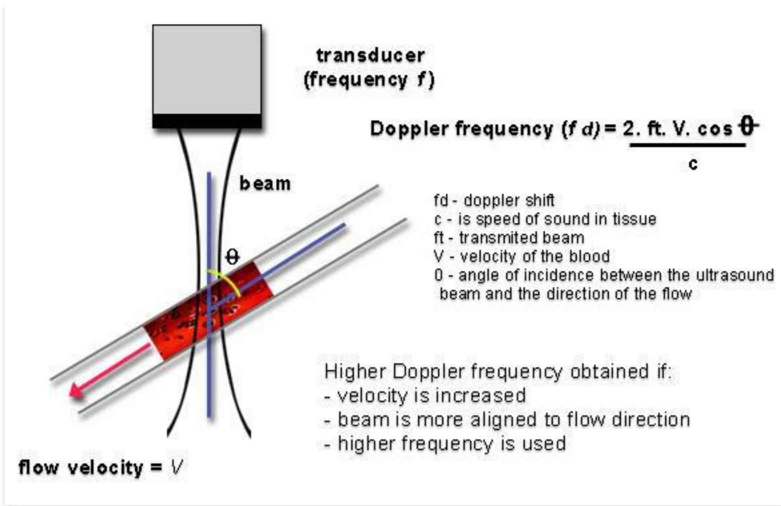


Figure 2-20. Doppler ultrasound of the scatterers movement. (Carrol MR, 2005)

Machines of Doppler ultrasound employ filters, in different Doppler types, provides capability of cutting out the high amplitude, and also low signal as result of tissue movement, for instance due to motion of vessel wall. Usually, the Doppler Operator can alter this Filter frequency, for example, to exclude frequencies below 100 or 150 Hz. Therefore, the Doppler frequency filter limits the lowest velocities of blood flow that can be estimated(Carrol MR, 2005).

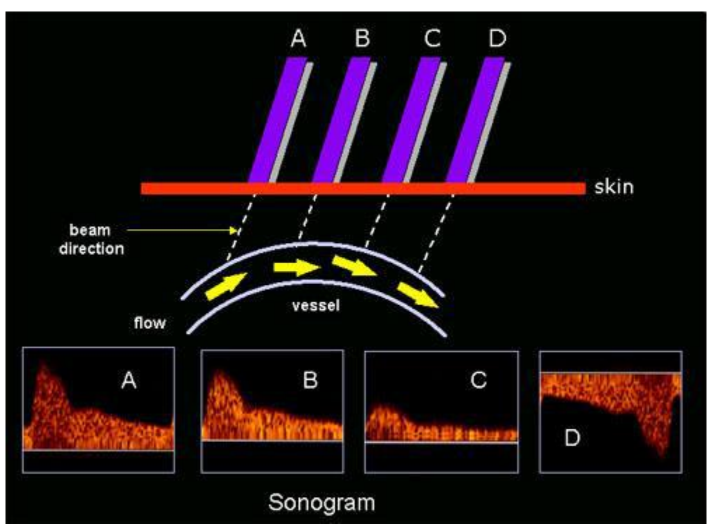


Figure 2-21. Effect of the Doppler angle in the sonogram (A) beam is aligned more to the direction of flow than (B), while (C) is almost 90° leads to very poor Doppler signal, in (D) is away from the beam leads to negative signal. (Carrol MR, 2005).

2.4.2.1.2 Continuous wave and pulse wave

continuous wave scanners use continuous transmission and reception of ultrasound as its name suggests. Subsequently, Doppler frequencies can be obtained from all blood flow in the path of the ultrasound beam (even with more attenuated beam arise from deeper tissues)(Bluth, 2004).

However, continuous wave Doppler has no ability to determine the specific region of flow velocities within the ultrasound beam and cannot be used to produce color flow sonograms. Available Doppler ultrasound systems employ continuous wave transducers giving Doppler output, but without providing B-mode sonograms which are relatively inexpensive. Investigation of the high blood velocities in the aorta in adult cardiac scanners can be obtained using continuous wave (figure 2-22) (Bluth, 2004).

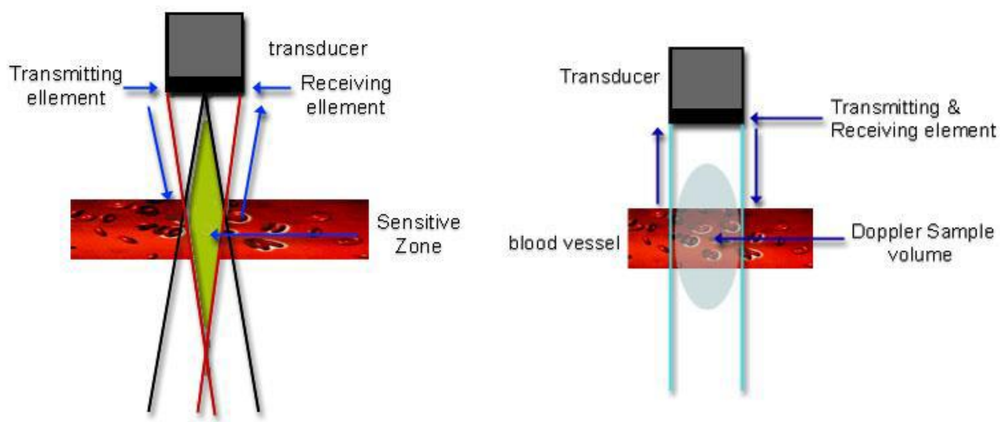


Figure 2-22. Doppler transducers according to the type of wave production, a) Continuous-wave Doppler transducer, b) Pulsed-wave Doppler transducer. (Bluth, 2004)

In general and obstetrical ultrasound systems, Doppler imaging performed using pulsed wave technique that allows measurement of specific flow site in the specific depth (or range). Additionally, sample volume gate (sample size) can be adjusted. Doppler sonograms and color flow presentation can be provided using this type of wave (pulse wave ultrasound) (figure 2-22) (Bluth, 2004).

2.4.2.1.3 Aliasing

There is a fundamental restriction faces pulsed wave scanners. When pulses are transmitted at specific pulse repetition frequency(a given sampling frequency), the maximum Doppler frequency fd that can be measured obviously is equal half the pulse repetition frequency. In the vessels with high flow velocity that measured in combination with the beam/flow angle to give a value of fd greater than half of the pulse repetition frequency, the Doppler signal will be ambiguous. This ambiguity is known as aliasing. A similar feature is seen in movie where wagon wheels can appear to be going backwards due to the low frame rate using in movie show causing misinterpretation of the spokes wheel movement (Bluth, 2004).

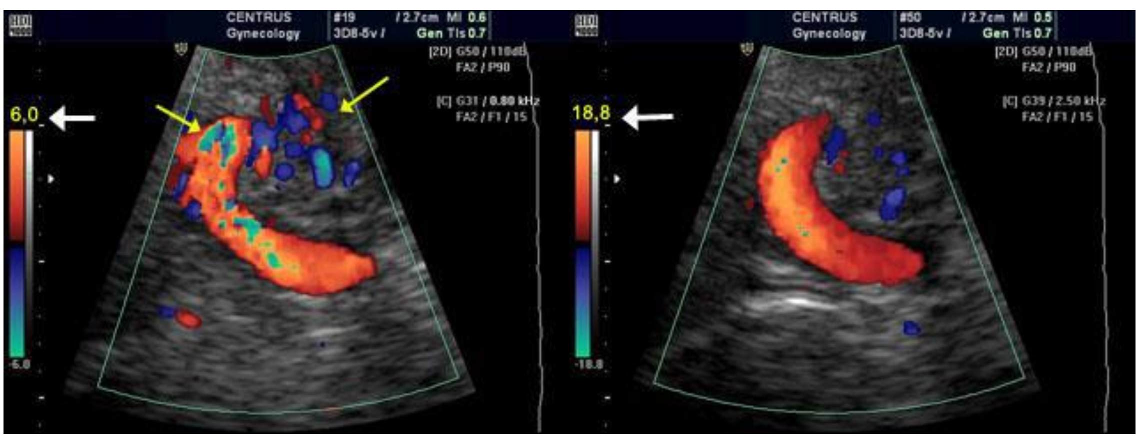


Figure 2-23. Aliasing artifact in Doppler color imaging. Right image, aliased flow (yellow arrows). Left image, correction by Reduce color gain and increase pulse repetition frequency.

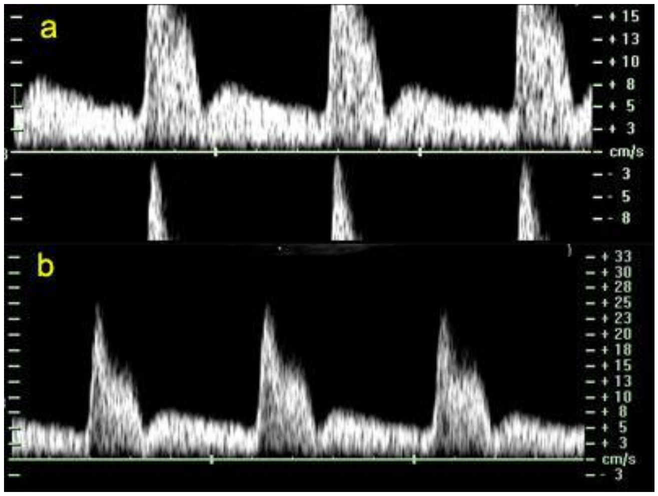


Figure 2-24. Example of aliasing and its correction (a) Waveforms with aliasing, (b) Correction: increased the pulse repetition frequency and adjust baseline.(Bluth, 2004)

The pulse repetition frequency is constrained itself by the range of the sample volume. The time interval between pulses from sampling must be adequate for a pulse journey from the probe to the reflector and return back. If a next pulse is sent before the receiving of the first one, the receiver cannot discriminate between the reflected signal from both pulses making ambiguity in the range of the sample volume. As the depth of vessel to be investigated increases, the time of the pulse journey to and from the reflector is increased that lead to reduce the pulse repetition frequency for unambiguous ranging. Therefore, the maximum measurable **fd** decreases with depth (Bluth, 2004).

Low pulse repetition frequencies are employed to examine venous flow that considered low velocities. The longer time interval between the pulse and next pulse gives the Doppler instrument a better chance to identify slow flow. Aliasing occurs if high blood velocities is measured using low pulse repetition frequencies (short velocity scales) (Figure 23, 24 and 25). Conversely, if a high pulse repetition frequency is used to estimate high velocities; low velocities may not be identified.

Figure 2-25. Color flow imaging: effects of pulse repetition frequency (PRF), (**right) The PRF is set low (yellow arrow), (b)The PRF is set appropriately (left).**(Bluth, 2004)

2.4.2.2 Ultrasound modes of flow

As color Doppler ultrasound provides just average information on the large volume of tissue using color box, while more details should take by other type of Doppler imaging from the a specific small region within the interrogated vessel using sample gate of spectral Doppler, the operator, in practice, should use two Doppler modes as complementary as such.

Color Doppler imaging should be used to determine vessels requiring Doppler study, and to identify firstly the presence of flow and then its direction, in order to focus on gross circulation anomalies, throughout the large region as interrogated by adjustment of color box, and finally to provide correct beam/vessel angle in order to get accurate measurements of Doppler flow velocities and indices.

Spectral Pulsed Doppler is suitable to do more analysis of the blood flow at center of the vessel being investigated. When using both Doppler modes, in addition to the B-mode, the color flow/B-mode image (duplex mode) is frozen while the spectral Doppler is activated. Recently, a triplex ultrasound imaging have produces by high technology manufacturers showing concurrent color flow imaging and pulsed wave Doppler simultaneously (Ahmed & Noori, 2011).

When these techniques are used, that leads to decreased performance of each mode. As result of decreased frame rate that results to reduce the color flow and box and available pulse repetition frequency causing finally increased susceptibility to aliasing artifact.

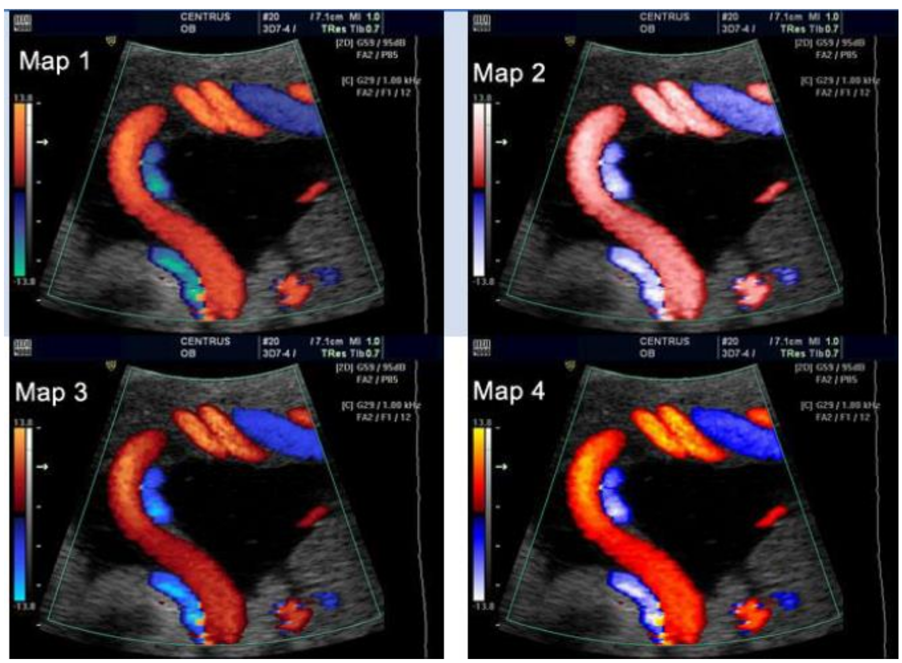
Other type of Doppler imaging called Power Doppler (also referred to amplitude Doppler, energy Doppler, and Doppler angiography). In which the magnitude of the color flow results is displayed rather than signal of Doppler frequency. This type of flow imaging does not display the direction or details of flow velocities. However, It is often to detect small weak flow because of its high sensitivity that results from its conjunction with frame averaging. Some manufacturers complement these Hybrid two color modes (Table 2-3) incorporating power and velocity data. These can also have improved sensitivity to low blood flow. There are many factors influencing the displaying every Doppler mode that is given in a brief summary in following sections. Although the operator should usually adjust many of these factors control during the blood flow study to optimize the image, some of these factors are set up for a particular application such as fetal scan.

Table 2-3. blood Flow Doppler modes.

pulsed Spectral Doppler
• Examines blood flow at specific site • Analyse blood flow distribution in details • Allows estimation of flow velocities and indices • Provides good temporal resolution – efficient study of flow waveform
Color Doppler imaging

- Has a colour flow map
- Provides Overview on blood flow in a region
- Provides general information about blood flow
- Has a Limited blood flow information
- Has a Poor temporal resolution/ in hemodynamic (deep interrogation can be associated with low frame rate)
- Can estimates a turbulent flows
- Provides information about flow direction in such mode
- And no directional information in other (power mode)
- Susceptible to noise

COLOR FLOW MAPS (DIRECTIONAL)



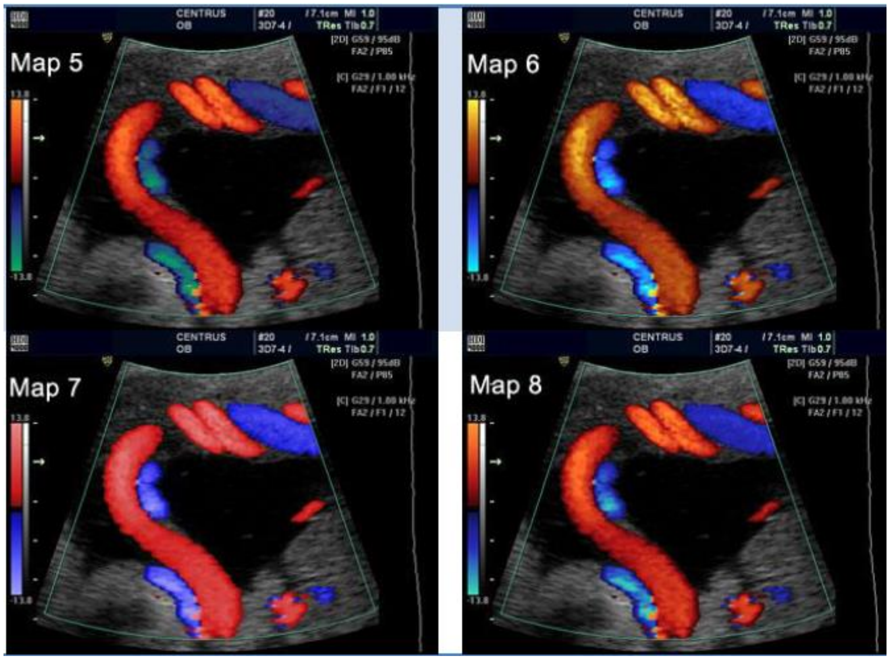


Figure 2-26. show Power/energy/amplitude flow sensitive to low flows.

(Ahmed & Noori, 2011)

Although pulsed wave ultrasound is used in color Doppler imaging uses, the processing of this type differs from that used in providing the Doppler ultrasound image. A several thousand color points may have produced in Color Doppler imaging as flow information in each frame overlapped with the B-mode sonogram. In color mode imaging, ultrasound scanner uses fewer, and shorter waves along every scan line of color image giving a mean of variance in measurement at each specific region, (mean Doppler shift). This Doppler (frequency shift) is displayed as a color pixel. This process then repeats in scanner for several lines building up the color sonogram, onto the B-mode one. Simultaneous duplex image produced by switching rapidly between B-mode and color flow imaging in transducer elements to give an impression that is just one sonogram. color Doppler imaging used for flow imaging three to four times longer pulses than those used for the B-mode scan, with a corresponding decreased an axial resolution (Ahmed & Noori, 2011).

Demonstration of frequency shifts color is usually based on flow direction (for example, red for shifts towards the ultrasound probe and blue for shifts away from it) and magnitude (different degree, lighter color saturation for higher Doppler shifts). The image of color Doppler depends on Several general Doppler factors, specially, setting a perfect angle of beam/flow. a radiating pattern of sonic will be produced from a Curvilinear and phased array probes that can lead to complex color images production, based on the orientation of the blood vessel. Practically, the skillful operator adjusts the approach of scanning to obtain a perfect angles of Doppler interrogation so as to take unambiguous flow sonograms. Table 2-3 summarizes The controls that affect the appearance of the color flow image. The main factors include:

(1) **Selection of Frequency**: different scanner/probe combinations allow frequency changes. High frequencies give better sensitivity to estimate low flow and have better spatial resolution. Low frequencies have better penetration (Figure 2-24) and are less susceptible to aliasing at high velocities.

(2) **Power and gain**: intensity power of Color flow is higher than that of B-mode. Therefore, Attention should be paid to mechanical and thermal safety indices. Power and gain should be set to obtain good signal for flow and to minimize the signals from surrounding tissues (figure 2-26, (figure 2-27).

(3) **Velocity scale/pulse repetition frequency**: in estimation of low velocities, Low pulse repetition frequencies should be used but aliasing may occur if high velocities are encountered (Figure 2-25 a,b).

(4) **Field of view**: blood flow examination needs more pulses than for the B-mode image, reduction in the width and maximum depth of the color flow in area

being examined will usually improve frame rate and may allow a higher color scan line density with improved spatial resolution (Figure 2-28).

(5) **Ultrasound Focus***:* level of the area of interest should be coincided to focus. This technique can achieve a significant difference to the appearance and color image accuracy (Figure 2-28).

Table 2-4. Factors affecting color flow image

Main factors
• Gain: represents main sensitivity to flow signals. • Power: transmitted power into region of interest. • Frequency: effects penetration for resolution and sensitivity. • Pulse repetition scale: low pulse repetition frequency to study slow velocities, high pulse repetition frequency to reduce aliasing artifact. • Area of investigation: the area inversely proportion to frame rate. • Focus: to optimize color flow image at specific region.
Other factors
• Pre-processing: trades resolution versus frame rate. • Filter: more signal filtration get out more noisy signal, may reach to cut out more signal. • Triplex color: demand of B-mode/spectral Doppler reduces frame rate and pulse repetition scale. • Post-processing assigns color map/variance • Persistence: smoother image is obtained by high persistence but the latter reduces temporal resolution. • Settings appropriate for specific examinations assigned by set-up/application keys

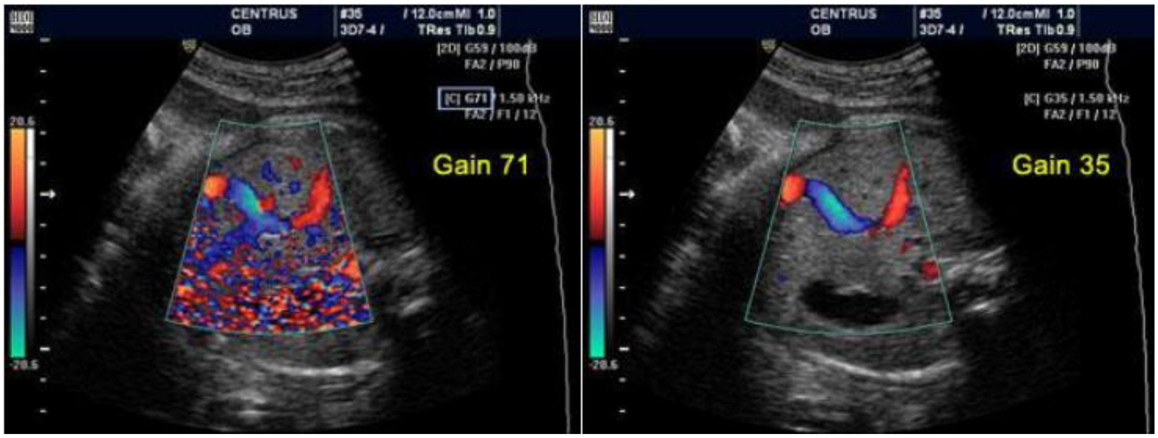


Figure 2-27. Setting the color gain to minimize the signals (artifacts) from surrounding tissue, on left color gain = 71, then on right decreasing gain to 35.

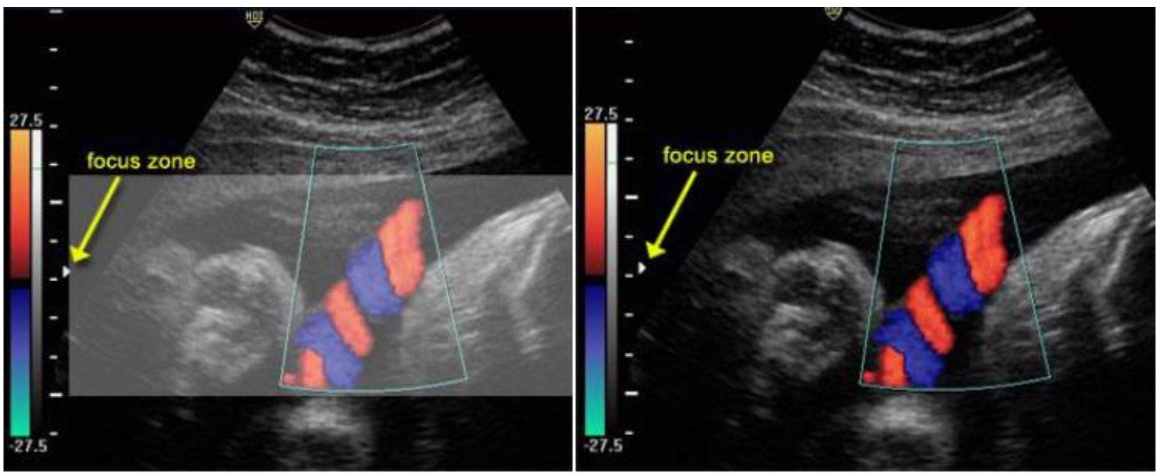


Figure 2-28. Set the focus at the region of interest, and also could use more than one focal zone.(Ahmed & Noori, 2011)

the operator should make many changes, in clinical practice, to the key controls and use different approach or probe positions to optimize the color sonogram. Practical guidelines are illustrated in Table 2-5.

Table 2-5. Color flow imaging: practical guidelines

Color Doppler guidelines
(1) Selection of the appropriate techniques/ using set-up key, to obtain parameters optimization in specific scanning.

(2) Setting of the color flow region as small as appropriate. Because smaller color box leads to good frame rate therefore better color sensitivity and resolution.

(3) Using different scanning approach with beam steering will obtain better beam/vessel angle.

(4) Adjustment of pulse repetition scale will suit the flow conditions. Operator should mention that Low PRF has higher sensitivity to low flow velocities but leads to aliasing artifact, While the High PRF has vice versa technical effects.

(5) In fetal study, power should be within limits. Adjustment of color gain should be performed. And focusing should be used with caution at the region of interest to optimize color signal

2.4.2.3 Spectral or pulsed wave Doppler

Pulsed wave Doppler ultrasound is appropriate to provide a sonogram of the blood vessel being examined (Figure 2-29), with providing detailed a measurement of the flow velocity during different events of cardiac cycle and follow the velocities distribution in the sample volume (Figure 2-30 & 2-31). Using the accurate angle lead to accurately absolute velocities measurements. Freezing of B-mode and color images allows all the time to be employed for spectral mode of Doppler and therefore lead to obtained best spectral sonogram resolution. While the concurrent imaging techniques, triplex mode, will compromise the temporal resolution of the sonogram (Ahmed & Noori, 2011).

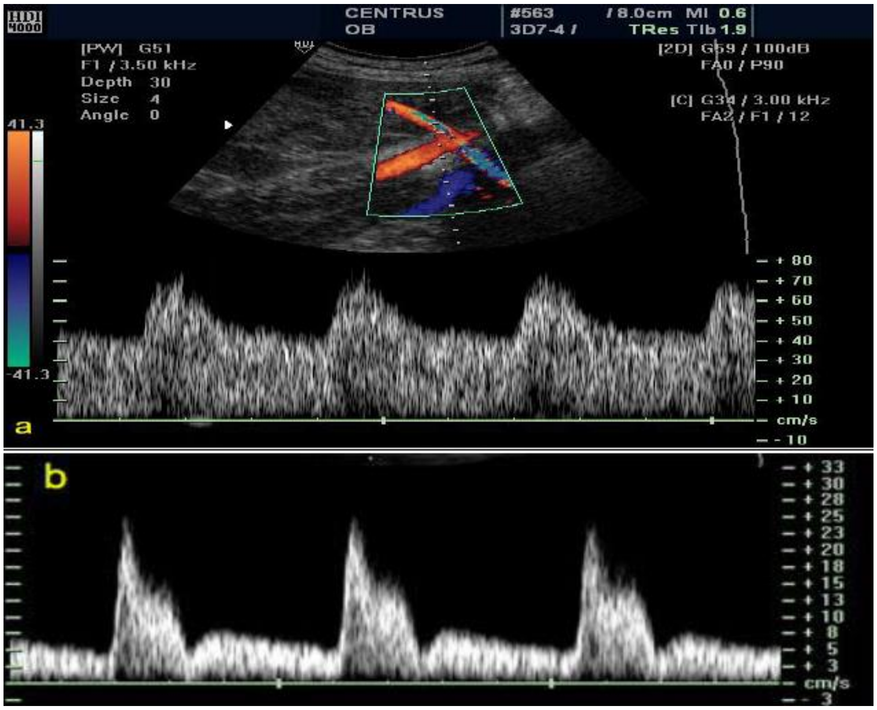


Figure 2-29. Doppler spectra of uterine artery flow, **(a) high velocities indicating low distal resistance. (b) low diastolic velocities indicating high distal resistance.**

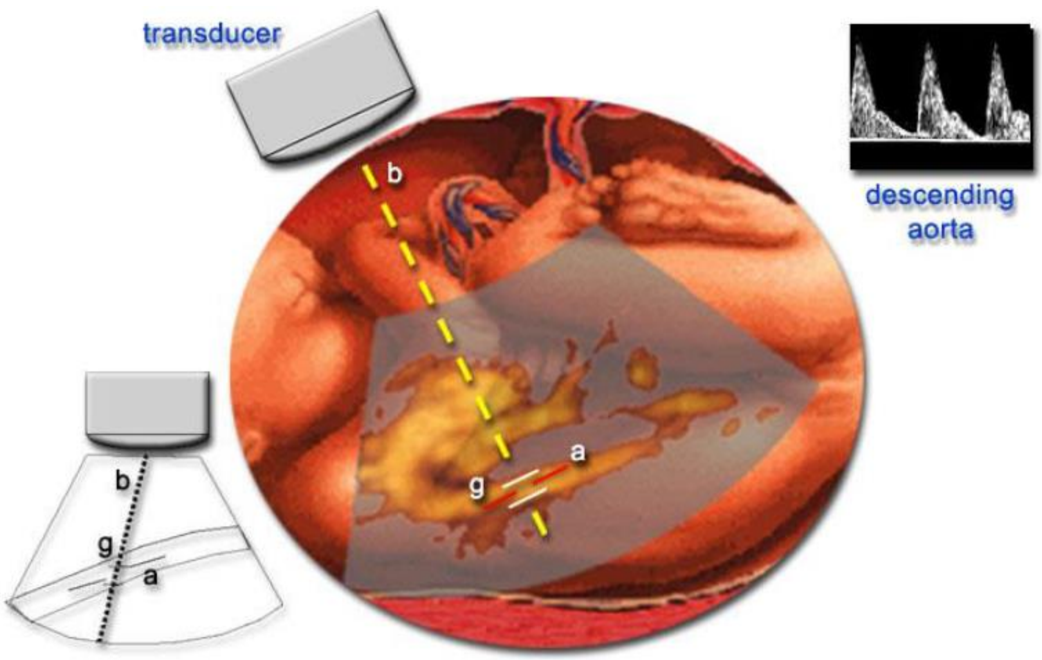


Figure 2-30. Setting up the sample volume in descending aorta. (b) - direction of the Doppler beam (g) gate or sample volume (a) angle correction (Ahmed & Noori, 2011).

The controls that affect the spectral sonogram appearance are summarized in Table 2-6. The main factors include:

(1) **volume size:** when the flow measurements are being attempted, the region within blood vessel should be interrogated.

(2) **Power and gain***:* higher power intensity will be used in spectral Doppler compare to that of B-mode ultrasound. Therefore, in fetal spectral scanning, operator should take attention to safety indices at the screen. Using appropriate gain and acoustic Power should be done to obtain a clear signals.

(3) **Velocity scale:** using of Low pulse repetition frequencies should be set to increase sensitivity seeking after slow blood flow, however, aliasing may occur in encountering high velocities flow.

Table 2-6. Factors affecting the spectral Doppler image

Main factors
• Gain: represents main sensitivity to flow signals. • Power: transmitted power into region of interest. • Frequency: effects penetration for resolution and sensitivity. • Gate size. • Beam steering that allows beam/flow angle adjustment to obtain accurate velocity calculation. • Associated Real time duplex ultrasound (B-mode and colour) with spectral imaging with lead to resolution constraining.
Other factors
• Gate: effects resolution sharpness. • Filter: more signal filtration get out more noisy signal, may reach to cut out more signal

- Post-processing: assigns brightness to output
- Settings appropriate for specific examinations assigned by set-up/application keys

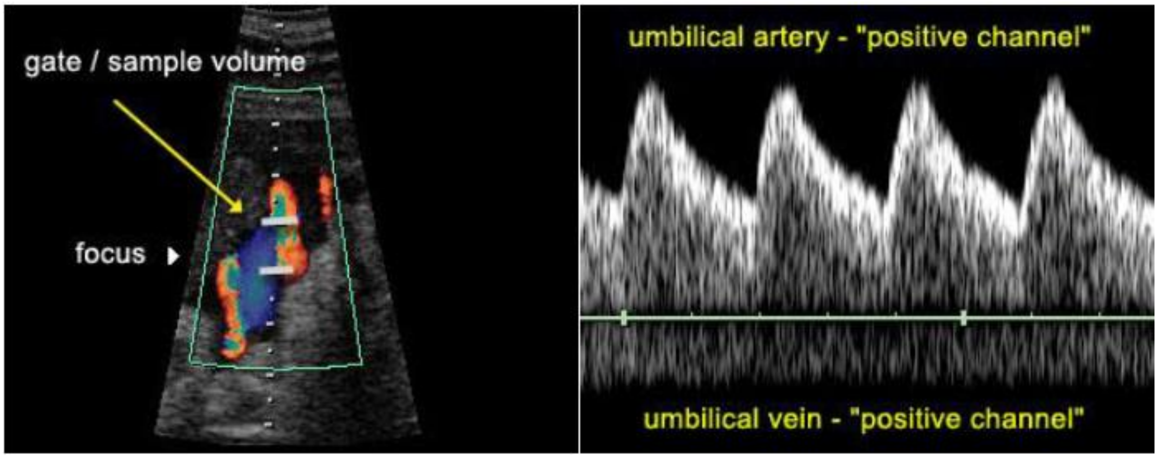


Figure 2-31. Umbilical cord displaying umbilical artery and vein, sample volume include both, (left). Sonogram of the umbilical artery and vein (right).(Ahmed & Noori, 2011).

Guidelines for a practical approach to obtain good-quality spectral images are given in Table 2-7.

Table 2-7. Spectral Doppler imaging: practical guidelines.

Spectral guidelines
(1) Positioning of volume gate cursor of spectral Doppler should be in middle of vessel being investigated
(2) Adjustment of gain should be lead to clearly visible sonogram free of noise.
(3) Adjustment of velocity scale and baseline should be suited according to flow conditions, so that aliasing would be prevented.
(4) Using of good scanning approaches with good beam steering should performed, because the perpendicular insonation angles will give ambiguous/unclear values. And the solution is setting of angle 60° or less

during velocity measurement.

(5) Setting of power should be within limits in fetal scanning

2.4.2.4 Blood Flow Measurements

Velocity Measurement: As stated in the Doppler equation, once the beam/flow angle is known, blood flow velocities can be calculated from the Doppler spectrum theoretically. but, the errors in the velocity measurement may still encountered. These errors can be established broadly from three categories:

(1) Errors arising during Doppler spectrum formation due to using of multiple elements in array probes; or Non-uniform insonation of the vessel lumen; or interrogation of more than one vessel; as well as use of filters removing low-velocity components.

(2) Errors arising in relation to measurement of insonation angle, use of angles more than (60°) may lead to error caused by comparatively large changes in the cosine of the angle which occur with small changes of angle (Figure 2-32). In this circumstance the velocity vector may not be in the direction of the vessel axis.

(3) Errors arising during the packages calculation provided by the manufacturers for analysis of the Doppler spectrum (for instance, of intensity weighted mean velocity).

Therefore, Extra efforts should be made to minimize errors, such as repeat velocity measurements that is good practice, as well as if possible using a different beam approach, to gain a feel for the variability of measurements in a particular application.

The applied effort in producing accurate velocity estimation should be balanced against the importance of absolute velocity estimation for such investigation, when the subtle changes in velocity estimation are often of more clinical relevance and effects the diagnosis. While in other cases, absolute velocity values may not be required.

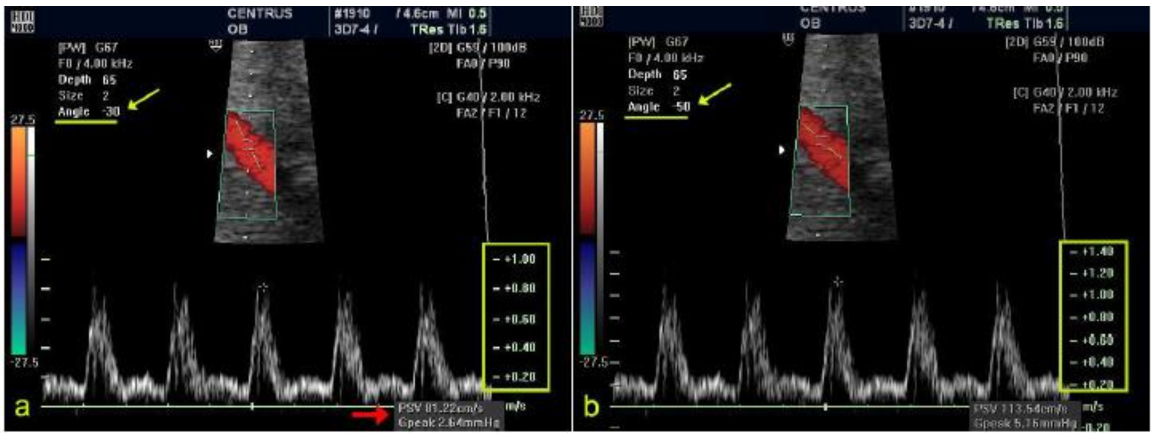


Figure 2-32. Effect of high vessel/beam angles, (a) and (b), Beam/flow angles should be 60° or less. A huge discrepancy is observed when use inappropriate angles.

(Rothwell, Villagra, Gibson, Donders, & Warlow, 2000)

Absolute flow calculation: the flow measurement with absolute value using Doppler ultrasound is faced such difficulties, even under ideal technical setting. The Errors may arise from:

1- Inaccurate measurement of vessel cross-sectional area. Particularly, the cross-sectional area of arteries which pulsate during the cardiac cycle.

2- Derivation of velocity.

These errors become particularly large when the flow velocity will be calculated in small vessels; errors in diameter measurement are magnified when the diameter is used to derive cross-sectional area. Therefore, it is prudent for operator to be aware of possible errors and to conduct repeatability tests (Rothwell et al., 2000).

Analysis of Flow wave form: this analysis of the flow waveform shape and spectrum is non-dimensional, so it has proved to be a useful parameter in the study of many vascular beds, because of its advantage that derived indices independently of the beam/flow angle.

The investigation of both proximal disease such as in the peripheral arterial circulation for adult cases and distal changes like in the and uterine arteries or fetal circulation can be performed using the changes in the shape of flow waveform. While the breadth of possible uses shows the technique to be versatile, it also serves as a reminder of the range of factors which cause changes to the local Doppler spectrum. If waveform analysis is to be used to observe changes in one component of the proximal or distal vasculature, consideration must be given to what effects other components may have on the waveform (Rothwell et al., 2000).

Flow wave form shape: Many different indices of measurement have been used in describing the shape of flow waveforms. These indices are generally a compromise between simplicity and the amount of information obtained. Techniques range from simple indices of systolic to diastolic flow to feature extraction methods such as principal component analysis (e.g. form of arterial velocity, figure 2-33). All are designed to describe the waveform in a quantitative way, usually as a guide to some kind of classification.

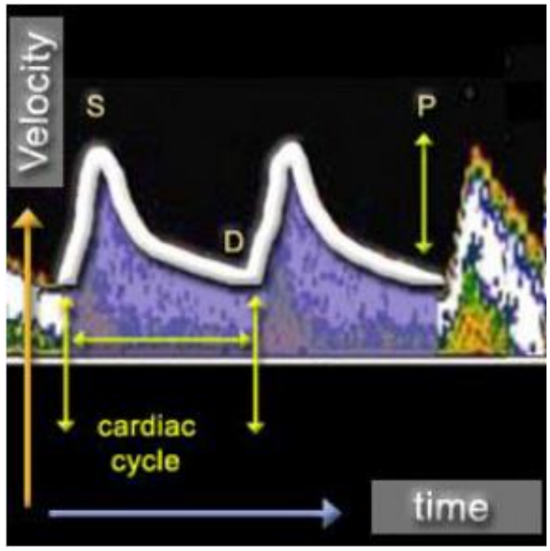


Figure 2-33. Arterial velocity sonogram (waveform). (Rothwell et al., 2000).

Commonly used indices available on most ultrasound scanners are:

(1) Resistive index (RI) or Pourcelot's index (also called Resistance index);

(2) Systolic/diastolic (S/D) ratio, sometimes called the A/B ratio;

(3) Pulsatility index (PI).

These indices are all based on the maximum Doppler shift waveform and their calculation is described in Figure 2-34, The PI takes slightly longer to calculate than the RI or S/D ratio because of the need to measure the mean height of the waveform. It does, however, give a broader range of values, for instance in describing a range of waveform shapes when there is no end-diastolic flow.

In addition to these indices, the flow waveform may be described or categorized by the presence or absence of a particular feature, for example the absence of end-diastolic flow and the presence of a post-systolic notch(Rothwell et al., 2000).

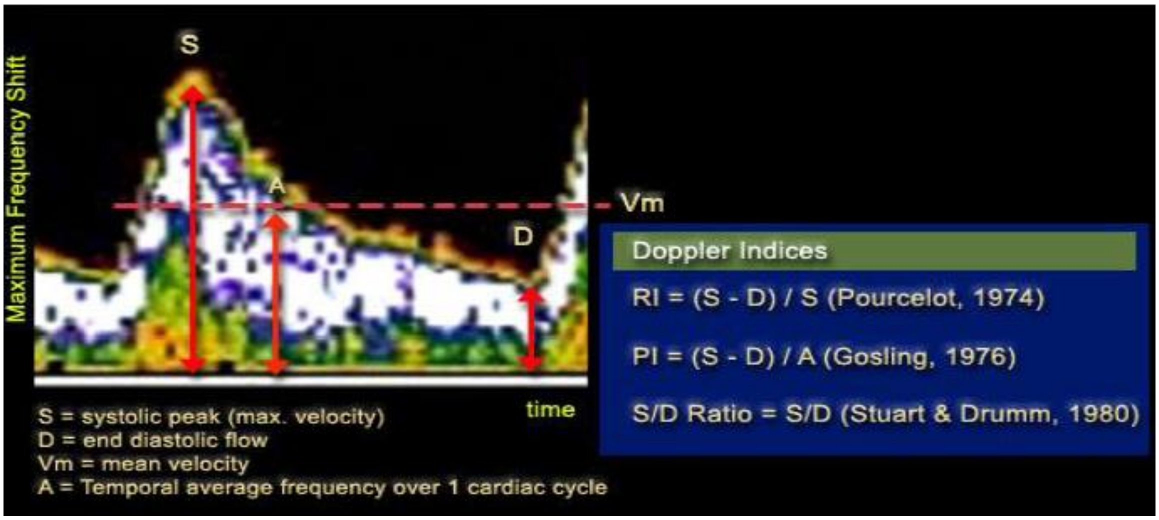


Figure 2-34. The Flow velocity indices. (Rothwell et al., 2000).

Generally, a low pulsatility waveform is indicative of low distal resistance and high pulsatility waveforms occur in high-resistance vascular beds (Figure 2-34), although the presence of proximal stenosis, vascular steal or arteriovenous fistulas can modify waveform shape. Care should be taken when trying to interpret indices as absolute measurements of either upstream or downstream factors. For example, alterations in heart rate can alter the flow waveform shape and cause significant changes in the value of indices.

2.4.3 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 2-31&2-35). The cursor position is controlled by the operator. Many duplex instruments allow the operator to indicate the direction of low 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-share" 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 the 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 determine the exact location of the sample volume during a Doppler study, an important consideration especially for smaller vessels (Zagzebski, 1996).

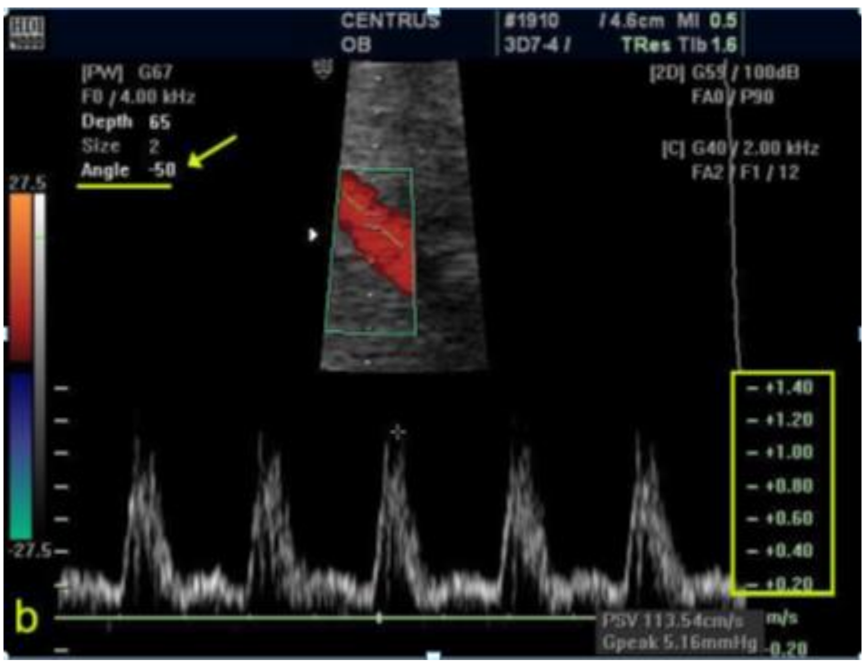


Figure 2-35. sonogram of a Doppler phantom, vertical scale of the spectral Doppler indicates velocity in meters per second (m/s), (Zagzebski, 1996).

2.4.3.1 Transducer 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 time B-mode. Because there are no moving parts in the transducer assembly the array scanning instrument can quickly 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).

2.5 Previous Studies

Previous Studies

About the issue of Khat chewing effects generally in the cardiovascular system and particularly common carotid arteries, many researchers and ultrasound practitioners have wrote bout. They agree that there are obvious effect in the cardiovascular system such as increased heart rate and blood pressure, and risk of myocardial infarction. In general the influence of chewing Khat on the cardiovascular system has been cited by many authors, however the influence of common carotid arteries with chewing Khat which is under focus in this research which also has been considered by many researchers to highlight it is response to chewing Khat in different aspects as follows:

(Moawia Gameraddin, 2019) performed the study to evalute the effect of chewing Khat on the intima media thickness (IMT) of the common cartid arteries, a total of 50 participants of chronic khat chewers were investigated using B mode ultrasound with 7- 10 MHz linear transducer and the IMT was measured and the presence of plaques was assessed. The result of study showed that the carotid IMT was significantly increased in regular khat chewer than in conrol (P-value=0.016), the common carotid IMT increased in smokers more than non smoker among khat chewers (0.6710±0.20687 vs 0.5789±0.16859mm). significant correlations existed between the duration of chewing khat and age with the presence of the plaques(p-value=0.13 and 0.002, respectively). They concluded that there is significant corrlation between the carotid plaque and long khat chewing and the khat is contibutary factor for increasing carotid intima media thickness and formation of carotid plaques and combination between the khat chewing and smoking produce more thickening of carotid intima-media.

(Ibrahim, Gameraddin, et al., 2017)carried out study to explore the Effects of Chewing Khat On hemodynamic of the common Carotid Arteries, a total of 200 of healthy non-Khat volunteers were investigated in this study with gray scale and Doppler sonography. The CCAs hemodynamics, diameters and intima media thickness were assessed. The heart rate and blood pressure were taken on the left arm and measured at 3-5 min interval. The blood flow in CCAs was assessed using the Doppler parameters, peak systolic velocity, end-diastolic velocity, pulsatility index and resistive index. The Doppler parameters were measured before and after chewing Khat. They found that chewing Khat had significantly raised the heart rate and blood pressure (p-value = 0.00 and 0.001, respectively). The blood resistivity and pulsatility of the common carotid arteries were significantly decreased after chewing Khat. The peak systolic velocity and maximum end-diastolic velocity were significantly increased after chewing Khat (p-values = 0.001 and 0.00, respectively). The diameters and intima media thickness of each CCA were not affected with Khat chewing. They concluded that Chewing Khat has significant impact on the hemodynamics of the common carotid arteries, probably as a consequence of vasoconstrictor effect of Khat on the blood vessels and This may affect the cerebral perfusion. (Ibrahim, Gameraddin, et al., 2017).

(N. Hassan et al., 2007) provided evidence that the khat chewing induced a significant rise of arterial systolic and diastolic blood pressure and pulse rate in comparison with the baseline values in healthy Yemeni adult volunteers. The effect reaches the peak on the arterial blood pressure and pulse rate was reached 3 hours after starting to chew, followed by a decline 1 hour after spitting the leaves out. These changes run parallel with changes in plasma cathinone levels during and after khat chewing. (N. Hassan et al., 2007)

(N. A. Hassan et al., 2005) achieved a randomized controlled clinical trial study of alpha1 and selective 1 adrenoceptor blockade on adult Yemeni volunteers to get more insight into the pharmacological effects of khat chewing. Sixty-three male volunteers chewed khat for 3 hours on 3 separate occasions, 1 or 2 weeks apart. Fifty age and weight matched male controls did not chew. The khat chewers received in a double blind 3-arm crossover design either indoramin 25mg, atenolol 50mg or placebo one hour before starting to chew. The non-chewing controls received atenolol 50mg on a separate occasion. Pulse and blood pressure were measured at regular intervals before, during and after the chewing period. The conclusion of this study showed that the effect of khat chewing on systolic blood pressure and pulse rate is blocked by atenolol but not by indoramin. Beta-1 adrenoreceptors are probably important in mediating the cardiovascular effects of khat in man. (N. A. Hassan et al., 2005)

(Getahun et al., 2010)carried out the study to compare systolic and diastolic blood pressure of adults 35-65 years of age who reported regular chewing of Khat during the preceding five years to those who never chewed Khat during the same period. Study participants were recruited from purposively selected urban and rural villages of Butajira District in Ethiopia. The comparative groups, chewers (334) and non-chewers (330), were identified from among the general population. They concluded that chewing of Khat regularly is associated with increased mean diastolic blood pressure, which is consistent with the peripheral vasoconstrictor as effect of Cathinone. Regular Khat chewing may have sustained effects on the cardiovascular system that can contribute to elevated blood pressure at the population level. (Getahun et al., 2010).

(Mega & Dabe, 2017)accomplished systemic review and meta-analysis to synthesize the best available evidence for the effect of khat on the cardiovascular system. Databases searched were PubMed, Cochrane database of systematic reviews, CINAHL, poplin, LILACS, MedNar and Scopus. All papers included in the review were subjected to rigorous appraisal using the Joanna Briggs Institute (JBI) standardized critical appraisal tool. Review Manager Software (Revman 5.3) was used for meta-analysis and effect size and the 95% confidence interval (CI) was calculated. Data was extracted from 10 articles. study meta-analysis included 9,207 subjects, (2123 chewers and 7084 non-chewers, respectively). Finally, the study showed that khat chewing could significantly affect the cardiovascular system through its effect on heart rate and blood pressure. Therefore, health promotion should be aimed to encourage quitting khat chewing.

(Manal Abdulwahed AlKherbash, 2004) fulfilled thesis to study the uterine and umbilical blood flow in Yemeni pregnant khat chewers using Doppler sonography, It was found that 35 of pregnant women consumed Khat during pregnancy, the magnitude of the problem is great especially if it has an adverse effect on the fetus. This study showed that there was significant decrease of fetal weight and Apgar score in the daily Khat consumers group. Also there was significant increase of Doppler indices among the daily Khat consumers group which indicates reductions in the utero-placental blood flow. Doppler indices showed significant correlation with the birth weight and Apgar score. (Manal Abdulwahed AlKherbash, 2004).

Chapter three

Methodology

CHAPTER THREE: MATERIAL AND METHODS

3.1 Materials

3.1.1 Study design

This study is cross sectional Prospective study, where the Yemeni participants conveniently selected and categorized into two groups, healthy khat chewers, and non-khat chewers.

3.1.2 Study population

The study conducted for 205 participants including 108 (52.7%) Khat chewers and 97 (47.3%) non-Khat chewers.

3.1.3 Study area and duration

Participants were scanned in the Radiology Department of University of Science and Technology Hospital (USTH), Sana'a, Yemen, from August 2017 to August 2018.

3.1.4 Study sample

A convenient sampling was conducted for 205 participants, with inclusion criteria include current and former Yemenis khat chewers who chew fresh khat leaves regularly for a period (not less than three years) beside healthy Yemenis non khat chewers. The included subject must be non-hypertensive, non- diabetic, non-cigarettes smoker, non- affected with coronary artery disease, high blood cholesterol level, obesity, and cardiopulmonary disorders, so to avoid significant influence in the extra cranial blood velocities. Therefore, 10 subjects are excluded according to these restricted sampling criteria.

3.2 Methods

3.2.1 Ultrasound technique

Carotid arteries were scanned to determine intima media thickness (IMT), peak systolic velocity (PSV), and end diastolic velocity (EDV), pulsatility index (PI), and resistivity index (RI) in the supine position with supported knee, and the operator seated on the right of the patient's head. The enhancement of neck scanning was performed by tilting and rotating the head away from the side being examined, with possible appropriate adjustment for the head and neck position during the examination. Several positions of transducer were used in this research to investigate the carotid arteries in the longitudinal planes. The short-axis (transverse) view of the carotid arteries was obtained from different an anterior and lateral or posterolateral approach, depending on which best views of the vessels. An initial sweeping of carotid arteries Doppler was performed to determine the values of Doppler parameters using the manual and automatic calculation software. While the beam angle of Doppler was maintained ≤60 degrees at all times. All measurements in spectral Doppler were obtained with a small sample volume ≤ 2mm and in the center stream of the flow at the area of greatest velocity shift.

3.2.2 Equipment used

High-resolution ultrasound system (model: TUS-Aplio 400 / Toshiba-MEC-US) equipped with a linear high frequency probe.

3.2.3 Data collection

The demographic data were obtained from participants including age, governorate, occupation, and BMI. Then the information of their chewing Khat habit were collected including the daily duration of chewing in hours and the period of chewing in years using a standardized questionnaire and data collection sheet.

3.2.4 Statistical analysis:

All statistical analysis was achieved by SPSS version 21.0 (SPSS Inc, Chicago, IL, USA). Data then presented in tables and figures. Quantitative variables were expressed as mean±standard deviation. The independent sample t test is used to compare continuous variables between groups (Khat chewers and Non-Khat chewers) A p-value<0.05 was considered as statistically significant. Pearson's correlation is also used to study the relationships between different variables.

3.2.5 Ethical consideration

Prior to samples scanning, a formal approval is obtained from Ethics and Scientific Committee of University of Science and Technology. And after the nature of the procedure was fully explained, informed consent is obtained from both the consecutively enrolled patients and the ultrasound department.

Chapter four

Results

CHAPTER FOUR: RESULTS

Results

This chapter will deal with entire results related to Carotid Characterization in Yemenis Khat Chewers.

Table 4-1. Distribution of study sample according to Participant's Gender with comparison of gender age.

Gender	Frequency	Percent %	Age Mean±Std. Deviation	t-test Sig.(2-tailed)
Male	179	91.8	27.93±6.76	.33
Female	16	8.2	26.18±6.60	
Total	195	100%		

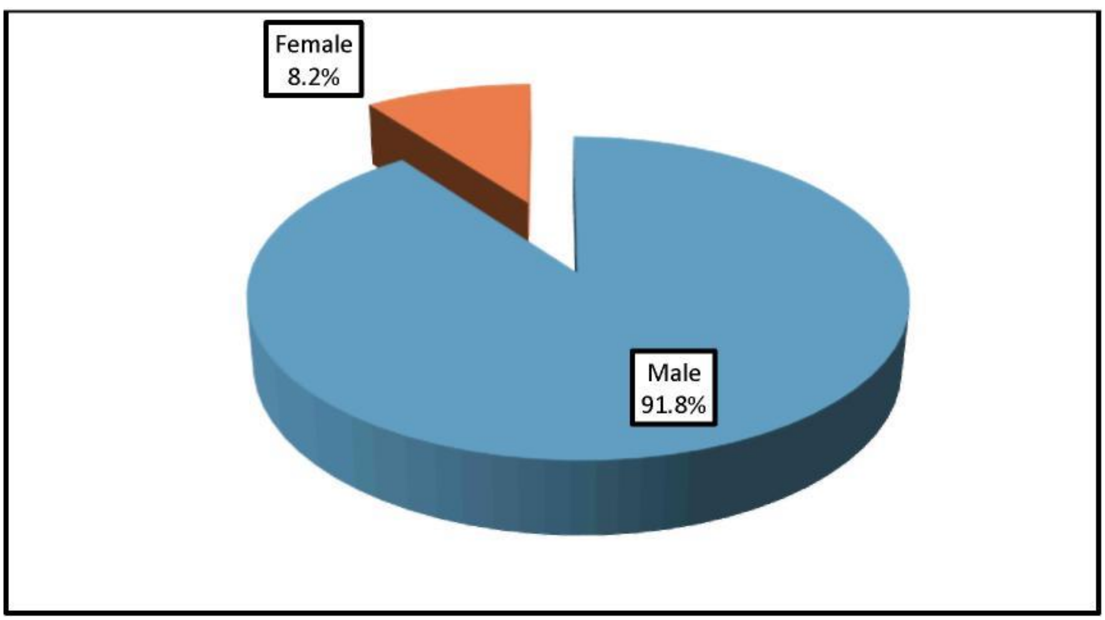


Figure 4-1. Distribution of study sample according to Participant's gender.

Table 4-2. Distribution of study sample according to Participant's age group.

Age categories (Yrs.)	Frequency	Percent %
16-20	15	7.7
20-30	113	57.9
31-40	56	28.7
more than 40	11	5.6
Total	195	100%

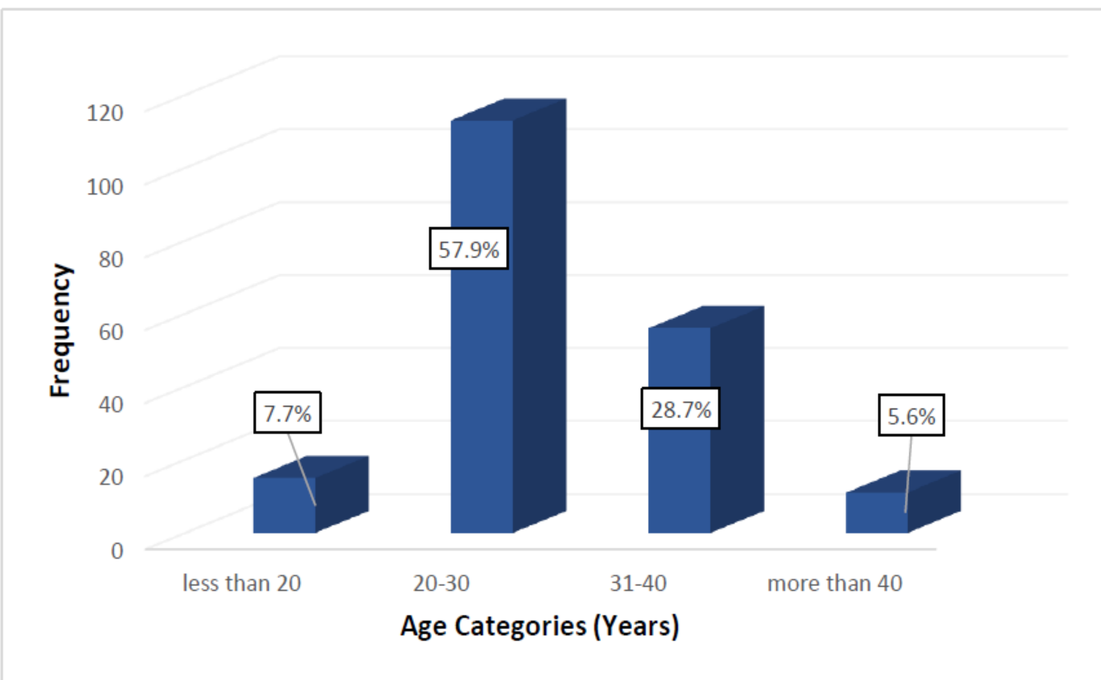


Figure 4-2. Distribution of study sample according to Participant's age group.

Table 4-3. Distribution of study sample according to Participant's Governorate.

Governorate	Frequency	Percent %	Governorate	Frequency	Percent %
Sana'a	19	9.7	**Raimah**	12	6.2
Ha jab	17	8.7	**Al-hlldaidah**	8	4.1
Taiz	50	25.6	**A maran**	12	6.2
ALmahweet	17	8.7	**Lahj**	1	.5
D ha mar	27	13.8	**Al-baidha**	2	1.0
Abyaii	1	.5	**Aden**	3	1.5
Ibb	21	10.8	**Hadhramout**	5	2.6
			Total	195	100%

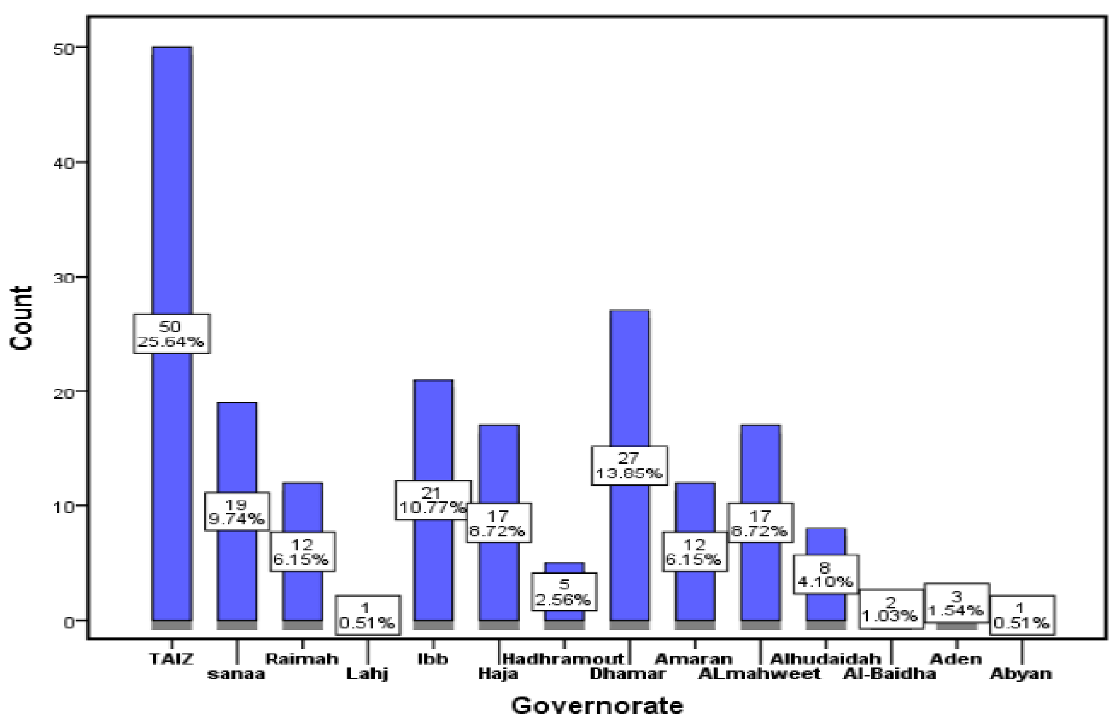


Figure 4-3. Distribution of study sample according to Participant's Governorate.

Table 4-4. Distribution of study sample according to Participant's Occupation.

Occupation	Frequency	Percent %	Occupation	Frequency	Percent %
Cleaner	47	24.1	rad. tech	9	4.6
Nurse	8	4.1	cooker	2	1.0
Security	20	10.3	g. manager	1	.5
correspondent	1	.5	soldier	3	1.5
Sonographer	2	1.0	police man	2	1.0
Accountant	9	4.6	pharmacist	2	1.0
Farmer	7	3.6	teacher	1	.5
Engineer	10	5.1	worker	19	9.7
Student	35	17.9	physician	3	1.5
Secretary	4	2.1	driver	2	1.0
Waiter	7	3.6	Total	195	100%

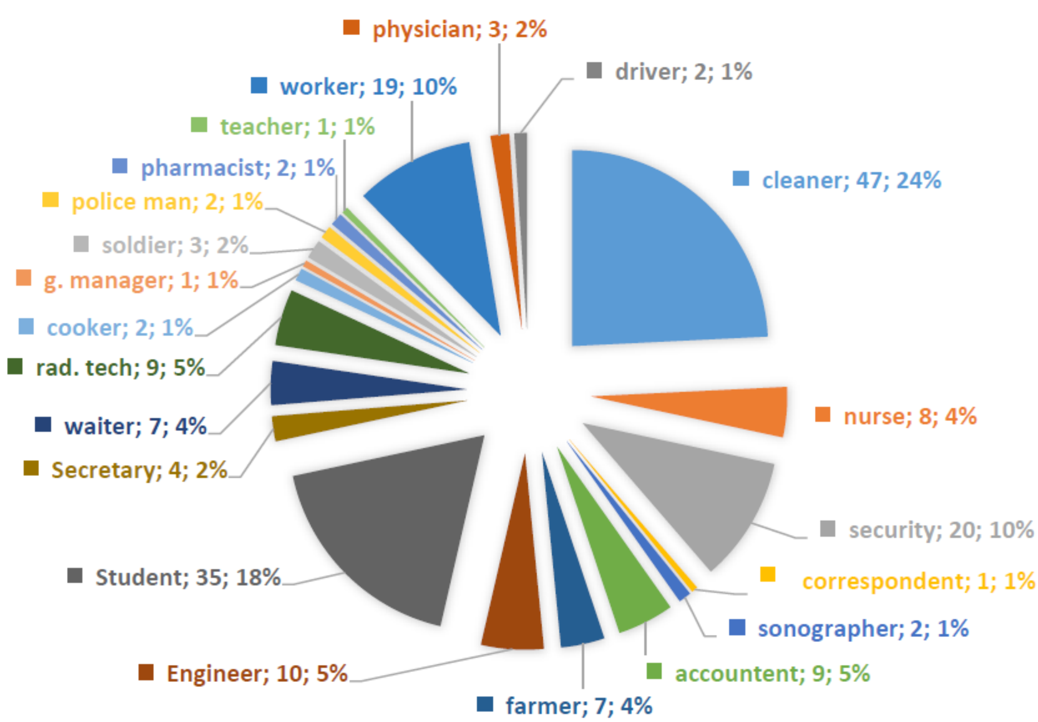


Figure 4-4. Distribution of study sample according to Participant's Occupation.

Table 4-5. Distribution of study sample according to Participant's Marital Status.

Marital Status	Frequency	Percent %
Married	107	54.9
Single	88	45.1
Total	195	100%

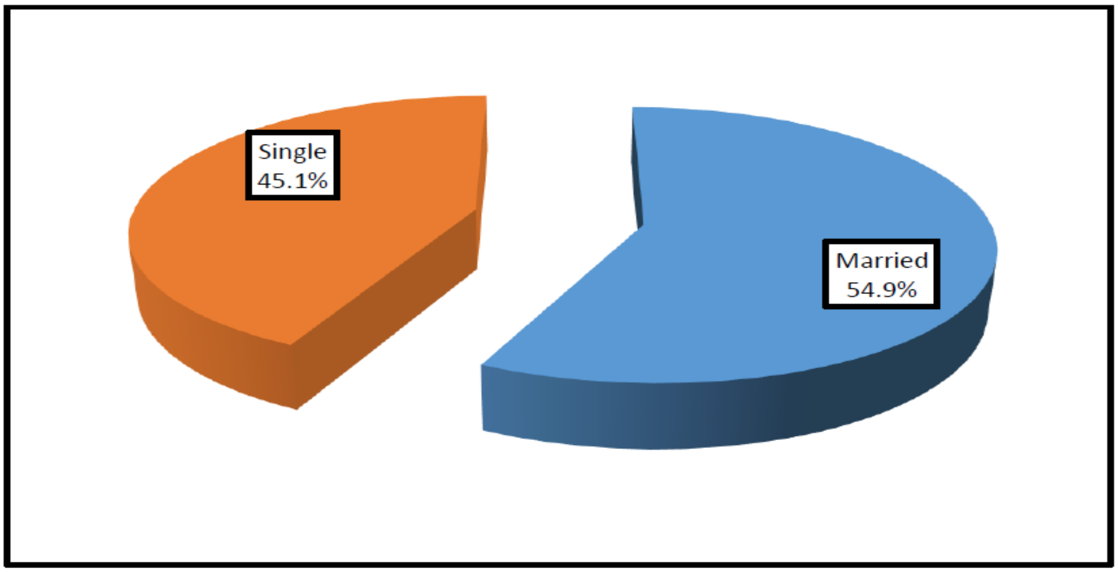


Figure 4-5. Distribution of study sample according to Participant's Marital Status.

Table 4-6. Distribution of study sample according to Participant's Chewing Status with compare of age.

Chewing Status	Frequency	Percent %	Age Mean±Std. Deviation	t-test Sig. (2-tailed)
Khat chewer	103	52.8	29.2±7.45	0.002
Non- Khat chewer	92	47.2	26.1±5.67	
Total	195	100%		

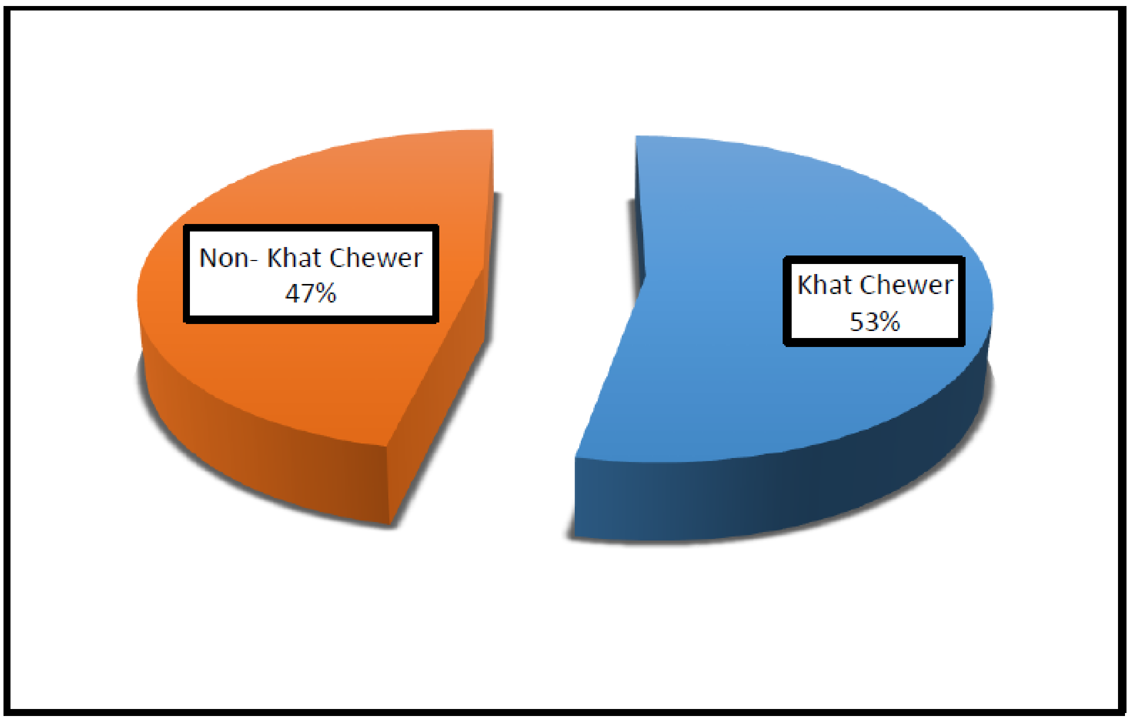


Figure 4-6. Distribution of study sample according to Participant's Chewing Status.

Table 4-7. Distribution of CCAs IMT among the age categories in Non-Khat chewers.

Age categories (Yrs.)	Frequency	Percent %	RT CCA IMT	LT CCA IMT
16-20	24	23.3	0.700±.0333	0.667±.0236
20-30	40	38.8	0.695±.0104	0.707±.0097
31-40	27	26.2	0.705±.0291	0.705±.0291
more than 40	12	11.7	0.733±.133	0.733±.0881

Table 4-8. Comparison between RT and LT CCA IMT among Khat and Non-Khat Chewers.

Chewing Status	B-Mode Parameter	N	Mean	Std. Deviation	t-test Sig. (2-tailed)
Khat chewer	**RT CCA IMT**	103	.7019	.12444	.000
	LT CCA IMT	103	.7126	.13910	
Non- Khat chewer	**RT CCA IMT**	92	.6957	.09366	.000
	LT CCA IMT	92	.7011	.08832	

Table 4-9. Comparison between CCA IMT according to the gender's participant.

Chewing Status	B-Mode Parameter	N	Mean	Std. Deviation	t-test Sig. (2-tailed)
RT CCA IMT	Male	179	.6922	.10885	.004
	Female	16	.7750	.10646	
LT CCA IMT	Male	179	.7011	.11755	.016
	Female	16	.7750	.10000	

Table 4-10. Correlation of CCA IMT with BMI in Khat and Non Khat Chewers.

KhatChewing Status	B-Mode Parameter	BMI	
Khat Chewers	RT CCA IMT	Pearson Correlation	.037
		Sig. (2-tailed)	.710
		N	103
	LT CCA IMT	Pearson Correlation	.254**
		Sig. (2-tailed)	.010
		N	103
Non-Khat Chewers	RT CCA IMT	Pearson Correlation	-.020
		Sig. (2-tailed)	.849
		N	92
	LT CCA IMT	Pearson Correlation	.122
		Sig. (2-tailed)	.247
		N	92

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Table 4-11. Correlation between the CCAs IMT with age among both groups.

KhatChewing Status	B-Mode Parameter	Age	
Khat Chewers	RT CCA IMT	Pearson Correlation	.380**
		Sig. (2-tailed)	.000
		N	103
	LT CCA IMT	Pearson Correlation	.458**
		Sig. (2-tailed)	.000
		N	103
Non-Khat Chewers	RT CCA IMT	Pearson Correlation	.084
		Sig. (2-tailed)	.427
		N	92
	LT CCA IMT	Pearson Correlation	.236*
		Sig. (2-tailed)	.024
		N	92

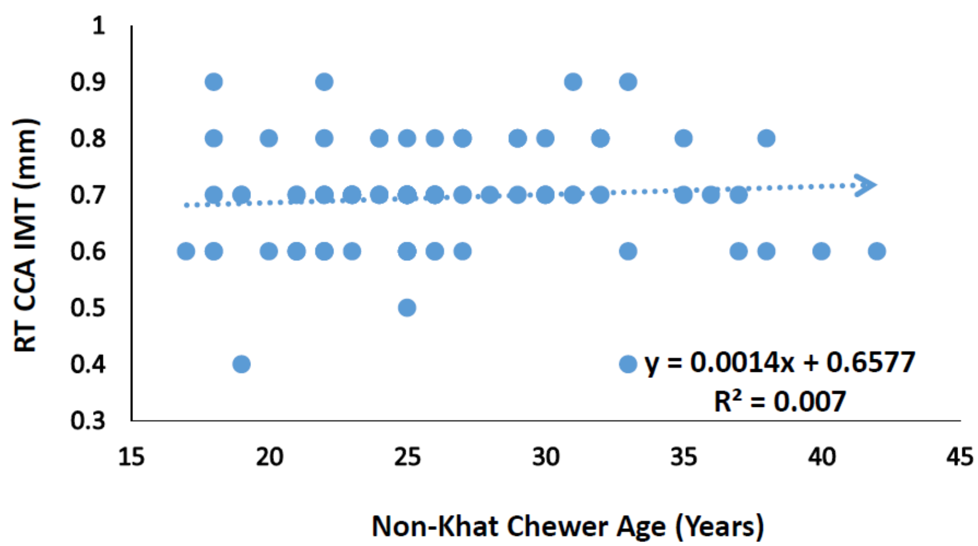


Figure 4-7. correlation between RT CCA IMT and age among healthy Non-chewer.

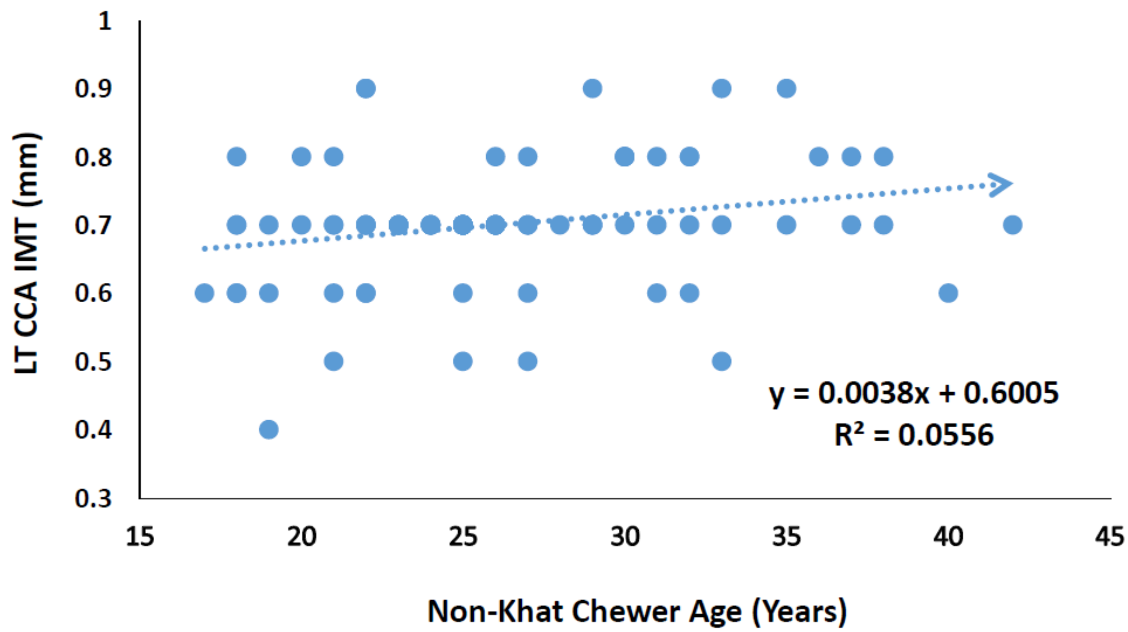


Figure 4-8. correlation between LT CCA IMT and age among healthy Non-chewer.

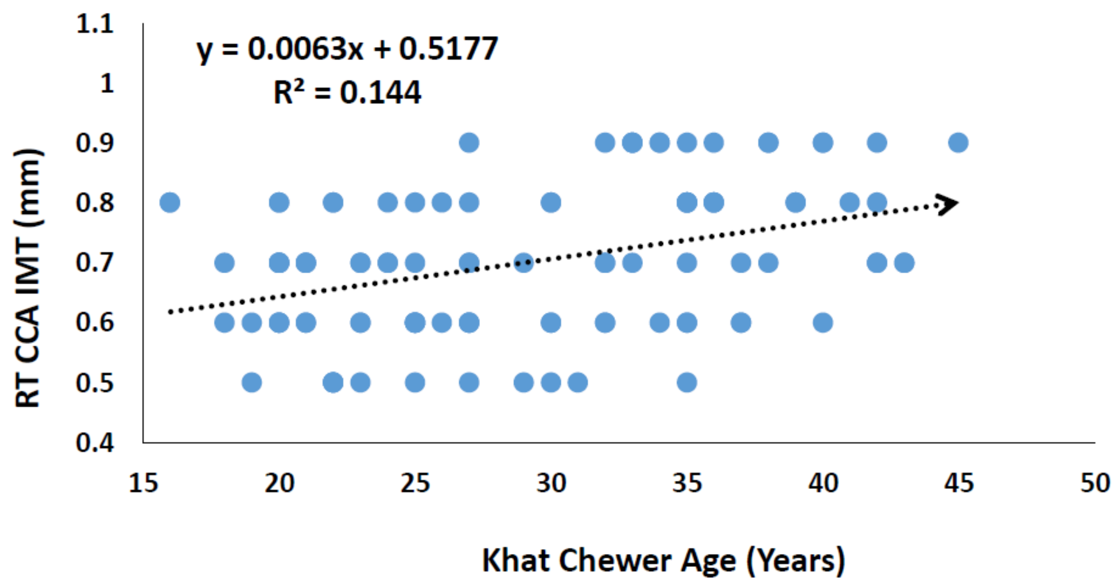


Figure 4-9. correlation between RT CCA IMT and age among Khat chewer.

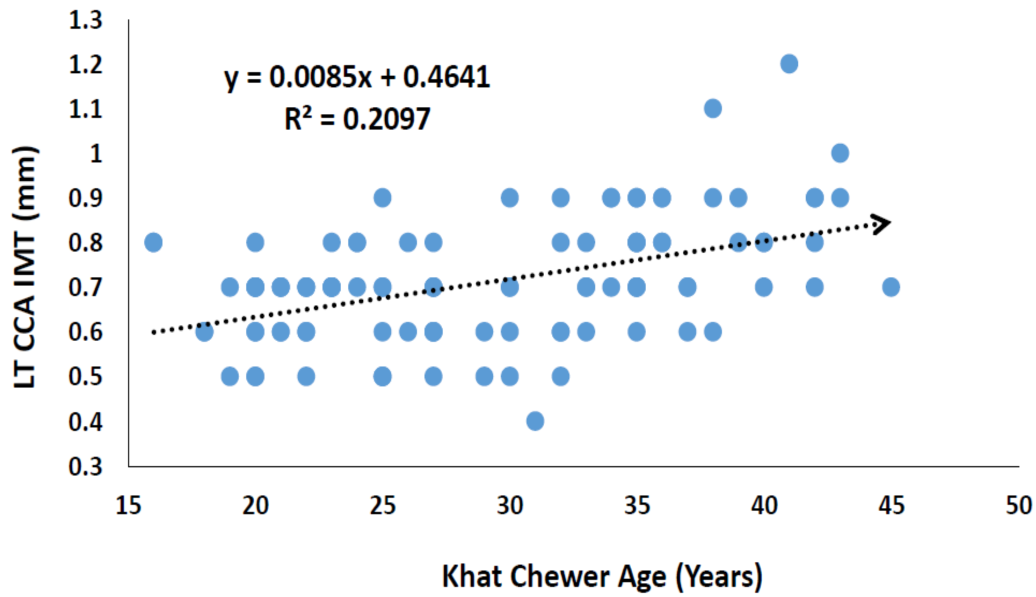


Figure 4-10. correlation between the LT CCA IMT and age among Khat Chewer.

Table 4-12. Comparison of CCAs IMT between Khat and non-Khat chewers.

B-Mode Parameter	Chewing Status	N	Mean	Std. Deviation	t-test Sig. (2-tailed)
RT CCA IMT	Chewer	104	.7038	.12535	.761
	Non-chewer	94	.6989	.09782	
LT CCA IMT	Chewer	104	.7154	.14126	.475
	Non-chewer	94	.7032	.08975	

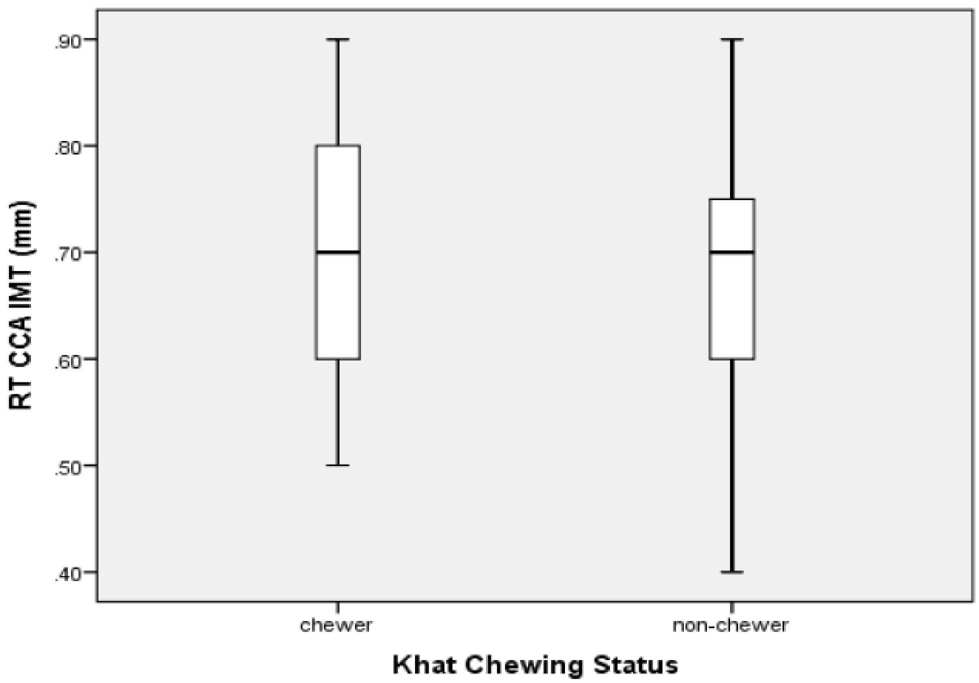


Figure 4-11. Comparison of RT CCA IMT between Khat and Non Khat Chewer.

Table 4-13. Correlation between the CCA IMT and age with Period of Khat Chewing.

B-Mode Parameter and age	Period of Khat chewing	
RT CCA IMT	Pearson Correlation	.342
	Sig. (2-tailed)	.000
	N	103
LT CCA IMT	Pearson Correlation	.235
	Sig. (2-tailed)	.017
	N	103
Age	Pearson Correlation	.623
	Sig. (2-tailed)	.000
	N	103

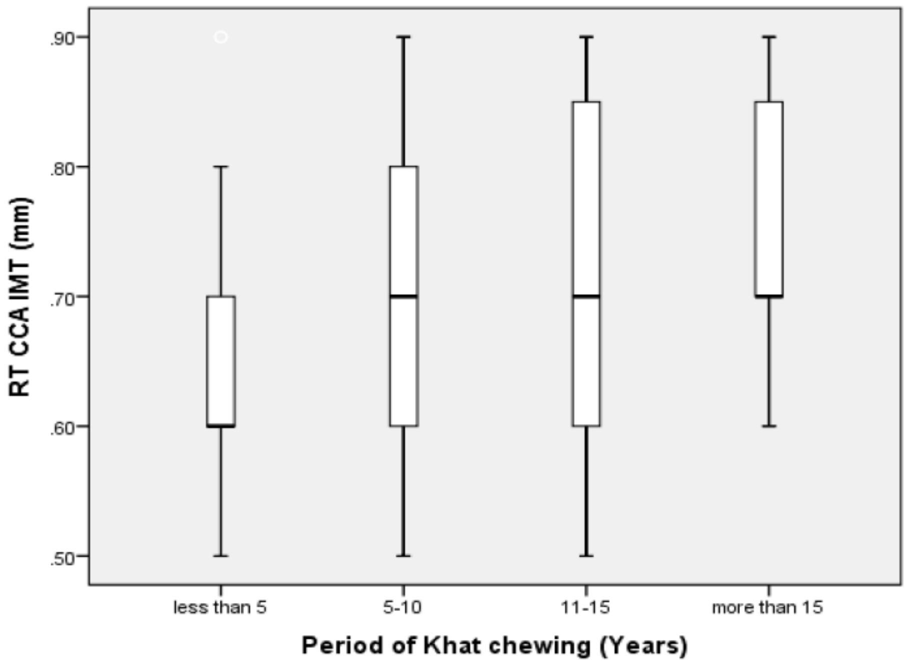


Figure 4-12. Correlation of RT CCA IMT with period of Khat chewing.

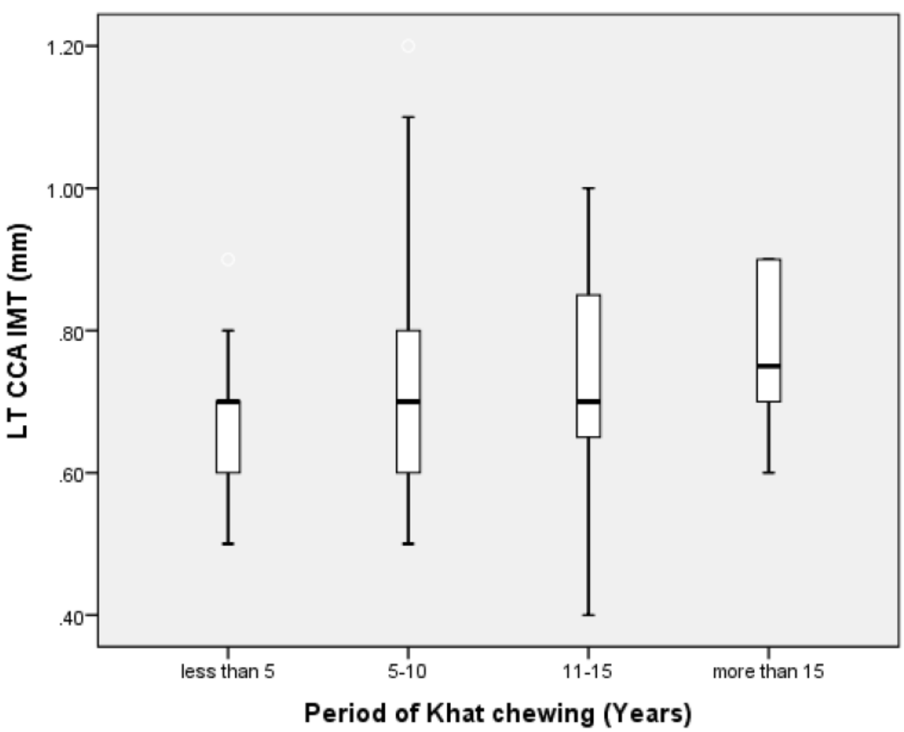


Figure 4-13. Correlation of left CCA IMT with period of Khat chewing.

Table 4-14. Correlation of age, BMI and period of khat chewing with CCA-IMT among khat chewers and non-khat chewers

Variables	Khat chewers				Non-khat chewers			
	RT CCA-IMT		LT CCA-IMT		RT CCA-IMT		LT CCA-IMT	
	R	***P*-value**	***r***	***P*-value**	***r***	***P*-value**	***r***	***P*-value**
Age (years)	0.380	<0.001	0.458	<0.001	0.084	0.427	0.236	0.024
BMI (kg/m^2)	0.037	0.710	0.254	0.010	-0.02	0.846	0.122	0.247
Period of khat chewing (years)	0.273	0.005	0.194	0.049	-	-	-	-

Table 4-15. Comparison of internal carotids flow volume between Khat and non-Khat chewers.

Doppler Parameter	Chewing Status	N	Mean	Std. Deviation	t-test Sig. (2-tailed)
RT ICA flow volume (ml/min)	Chewer	49	433.0524	135.56262	0.044
	Non-chewer	49	378.3753	129.33580	
LT ICA flow volume (ml/min)	Chewer	49	491.1616	145.26714	0.060
	Non-chewer	49	438.6129	127.82918	

Table 4-16. Comparison of Doppler flow velocity between Khat and Non Khat Chewer.

B-Mode Parameter	Chewing Status	N	Mean	Std. Deviation	t-test Sig. (2-tailed)
RT CCA PSV	Chewer	103	108.9874	24.43629	.000
	Non-chewer	92	125.3907	27.65176	
RTICA PSV	Chewer	103	73.9130	16.90030	0.028
	Non-chewer	92	79.1870	20.97555	
LT CCA PSV	Chewer	103	103.4786	22.76351	.059
	Non-chewer	92	109.9033	24.46918	
LTICA PSV	Chewer	103	76.8612	17.75237	0.92
	Non-chewer	92	77.1293	17.70646	
RT CCA EDV	Chewer	103	23.6408	5.69269	.649
	Non-chewer	92	24.0277	6.17299	
LT CCA EDV	Chewer	103	23.4583	5.41848	.040
	Non-chewer	92	21.8435	5.48954	

Table 4-17. Correlation of Doppler flow velocities and period of Khat Chewing.

Doppler flow velocity	Period of Khat chewing	
RT CCA PSV	Pearson Correlation	-.228*
	Sig. (2-tailed(	.020
	N	103
LT CCA PSV	Pearson Correlation	-.359**
	Sig. (2-tailed(	.000
	N	103
RT CCA EDV	Pearson Correlation	.094
	Sig. (2-tailed(	.343
	N	103
LT CCA EDV	Pearson Correlation	-.068
	Sig. (2-tailed(	.497
	N	103

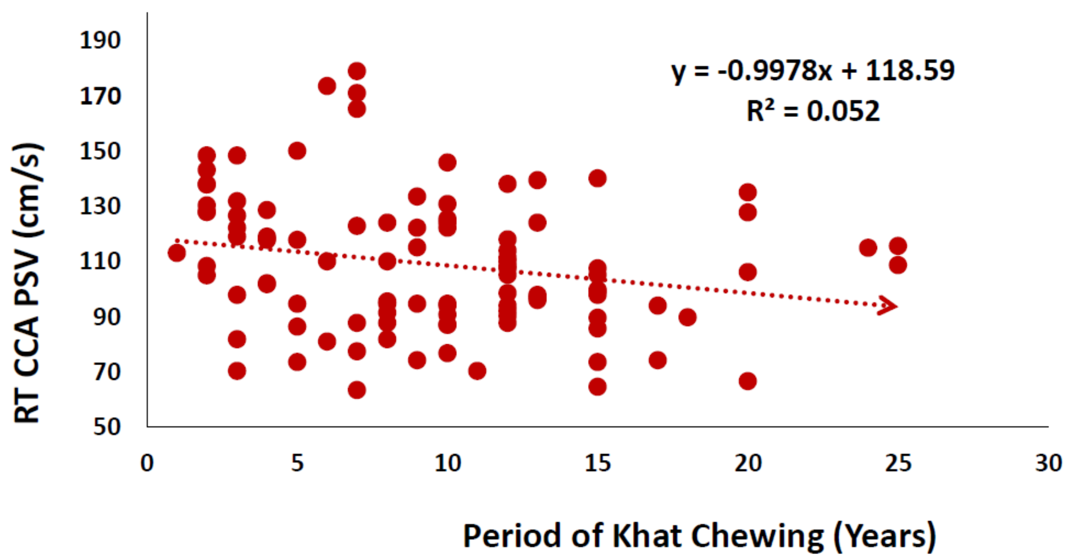


Figure 4-14. Correlation of RT CCA PSV with period of Khat Chewing.

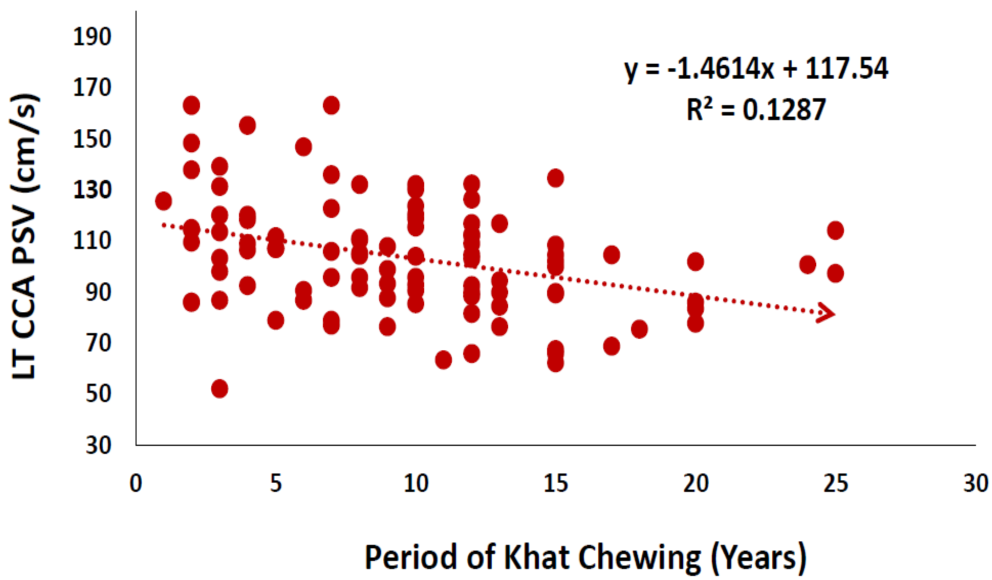


Figure 4-15. Correlation of LT CCA PSV with period of Khat Chewing.

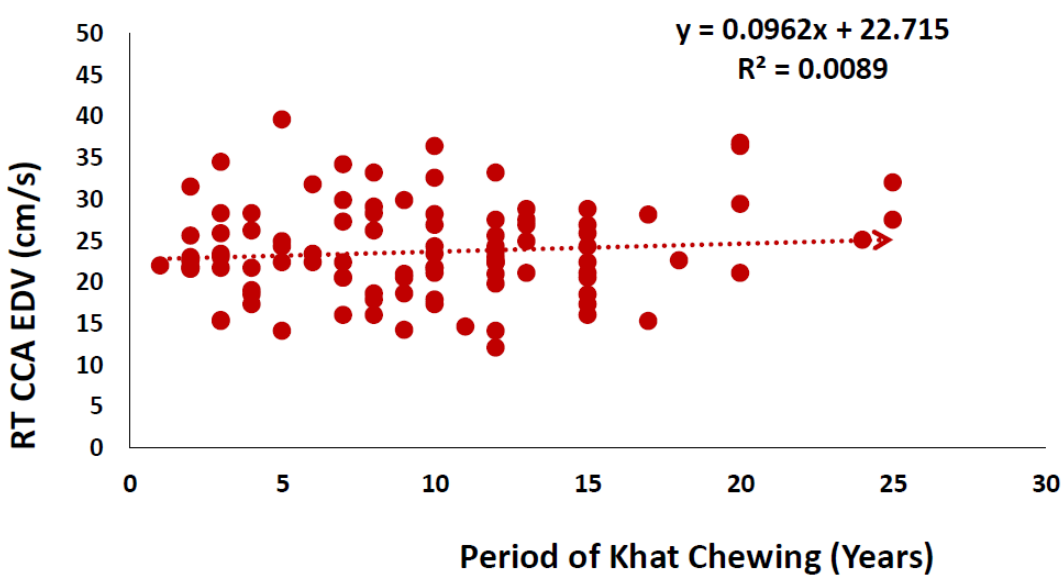


Figure4-16. Correlation of RT CCA EDV with period of Khat Chewing.

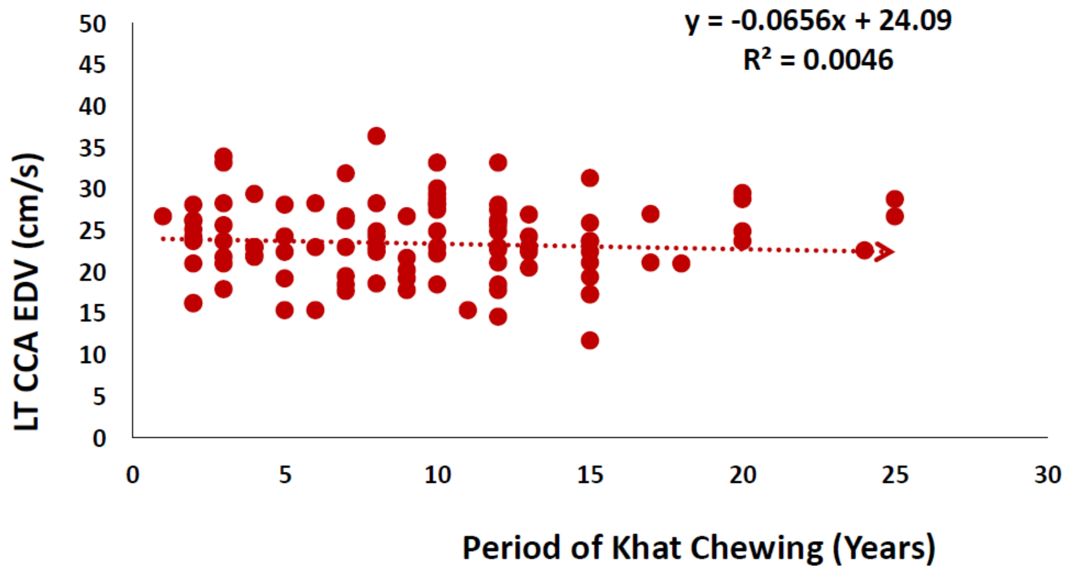


Figure 4-17. Correlation of LT CCA EDV with period of Khat Chewing.

Table 4-18. Comparison of carotids Doppler indices between Khat and non-Khat chewers.

Doppler index	Chewing Status	Mean	Std. Deviation	t-test Sig. (2-tailed)	Doppler index	Chewing Status	Mean	Std. Deviation	t-test Sig. (2-tailed)
RT CCA RI	Chewer	.7739	.04767	.026	**RT CCA PI**	Chewer	1.9072	.45763	.000
	non-chewer	.7884	.04401			Non-chewer	2.2053	.49456	
RT ICA RI	Chewer	.6143	.08511	.012	**RT ICA PI**	Chewer	1.0879	.36626	.000
	Non-chewer	.6457	.09150			Non-chewer	1.3101	.45799	
RT ECA RI	Chewer	.8190	.07414	.000	**RT ECA PI**	Chewer	2.3366	.81658	.000
	Non-chewer	.8625	.08737			Non-chewer	2.8952	1.05374	
LT CCA RI	Chewer	.7584	.04853	.000	**LT CCA PI**	Chewer	1.8256	.46958	.000
	Non-chewer	.7861	.05281			Non-chewer	2.1576	.54098	
LT ICA RI	Chewer	.6079	.08068	.701	**LT ICA PI**	Chewer	1.1028	.34266	.178
	Non-chewer	.6124	.08661			Non-chewer	1.1657	.32052	
LT ECA RI	Chewer	.8143	.07303	.001	**LT ECA PI**	Chewer	2.1790	.69968	.000
	Non-chewer	.8528	.08805			Non-chewer	2.8276	.86916	

Table 4-19. Correlation between Doppler indices of CAs and period of Khat chewing.

Dependent variable		**RI**						**PI**					
		RT CCA	RT ICA	RT ECA	LT CCA	LT ICA	LT ECA	RT CCA	RT ICA	RT ECA	LT CCA	LT ICA	LT ECA
Period of Khat chewing (yrs.)	Pearson Correlation	-.369**	.152	.319**	.319**	-.193*	.395**	-.264**	-.190*	-.318**	-.185	.285**	.322**
	Sig. (2-tailed(	.000	.117	.001	.001	.045	.000	.006	.049	.001	.055	.003	.001
	N	108	108	108	108	108	108	108	108	108	108	108	108

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

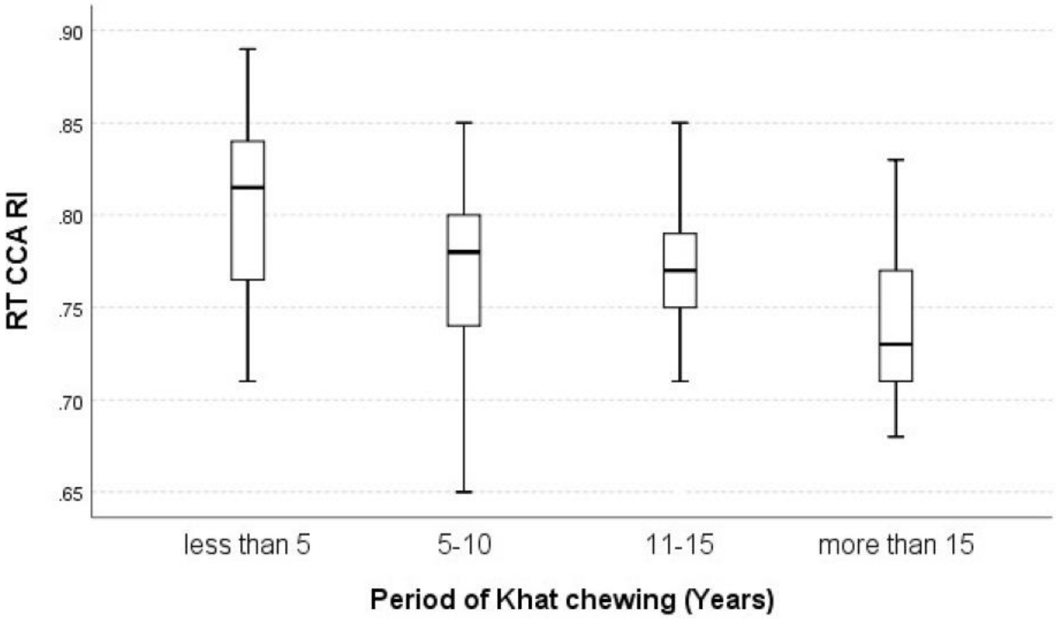


Figure 4-18. Correlation of right CCA RI with period of Khat chewing.

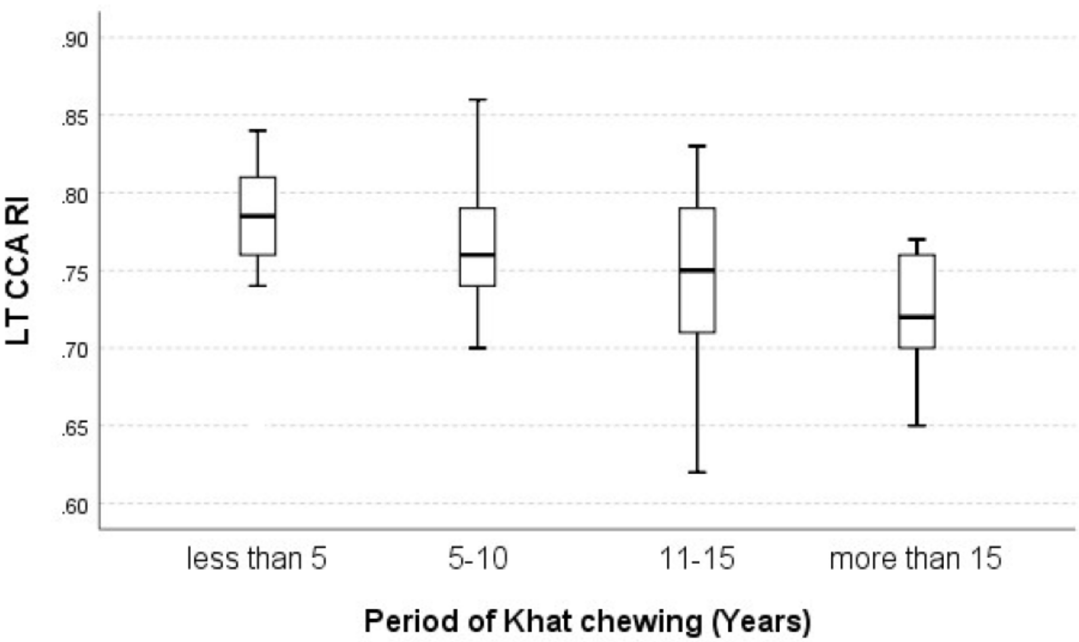


Figure 4-19. Correlation of LT CCA RI with period of Khat chewing.

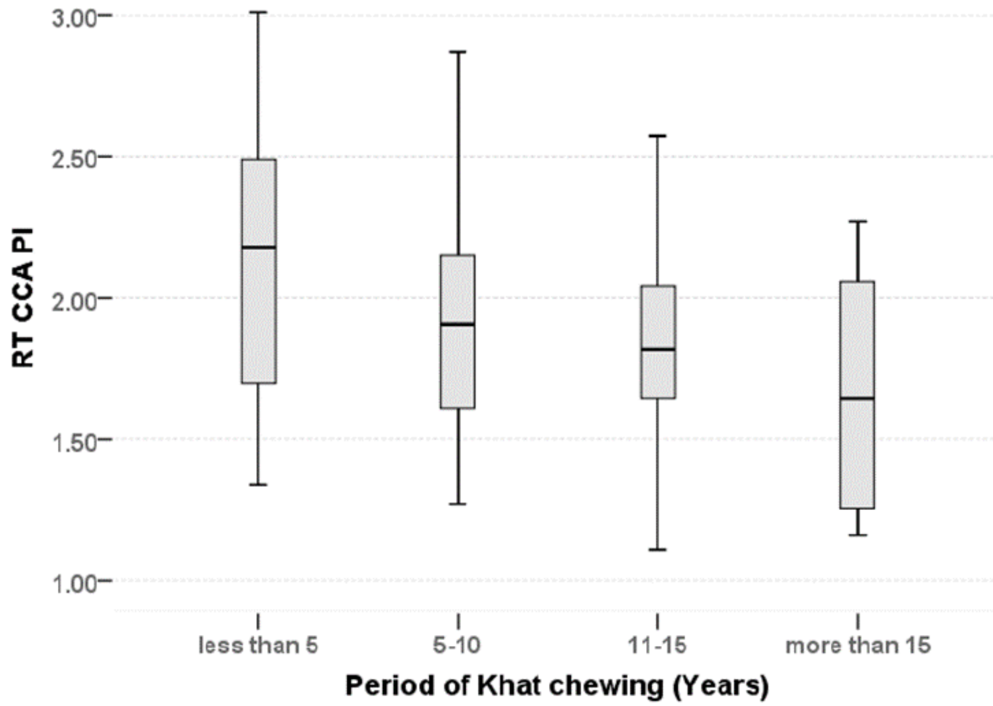


Figure 4-20. Correlation of RT CCA PI with period of Khat chewing.

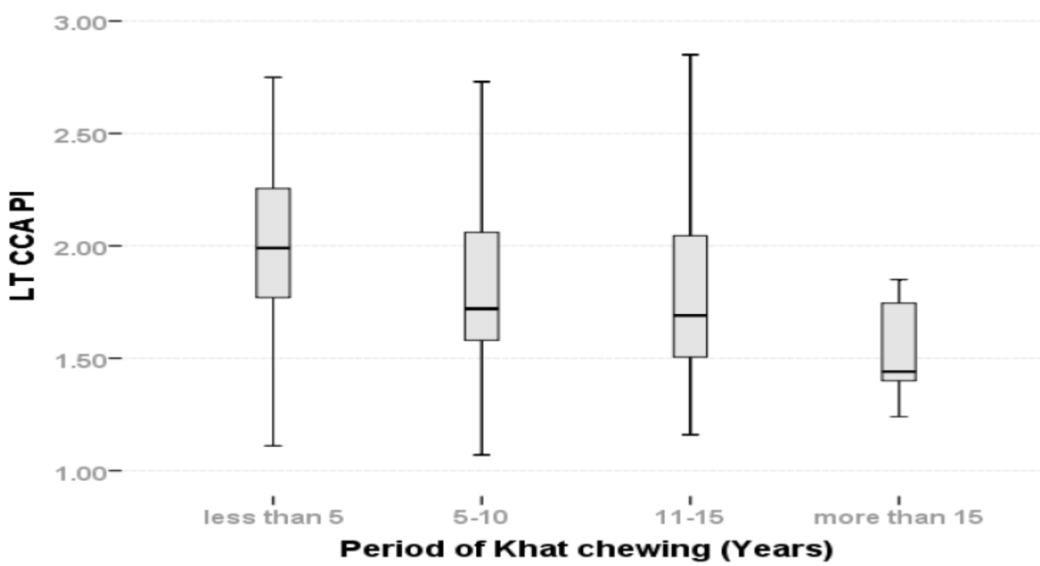


Figure 4-21. Correlation of LT CCA PI with period of Khat chewing.

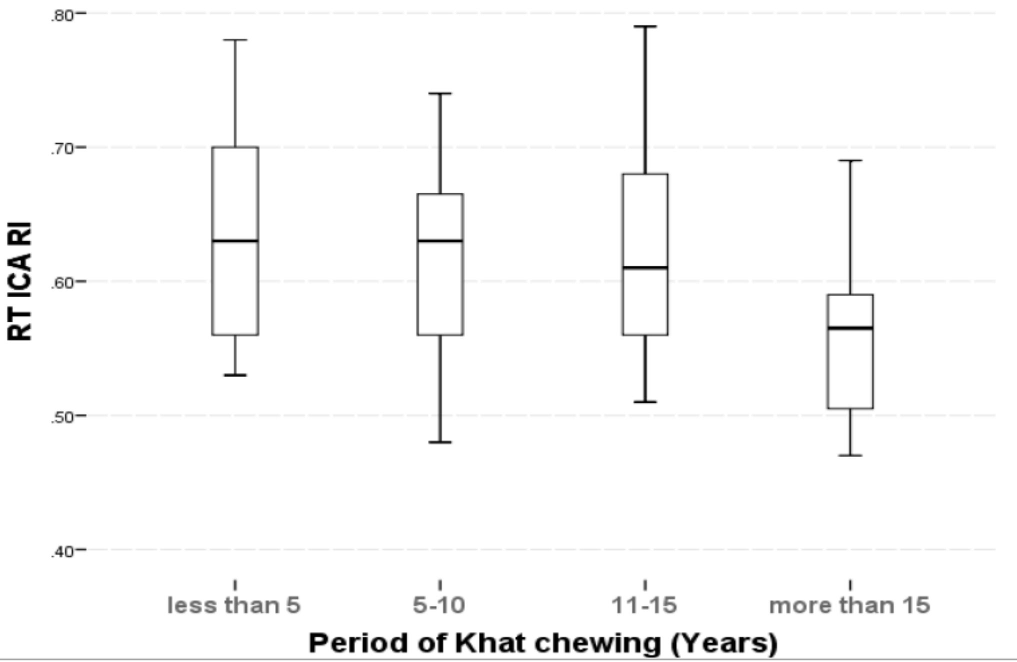


Figure 4-22. Correlation of RT ICA RI with period of Khat chewing.

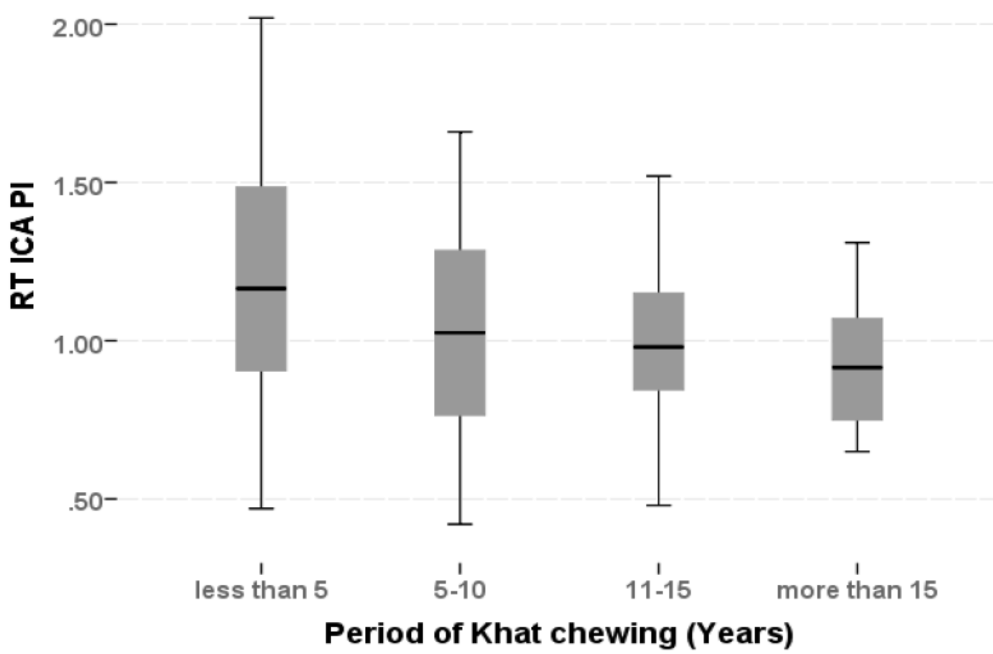


Figure 4-23. Correlation of RT ICA PI with period of Khat chewing.

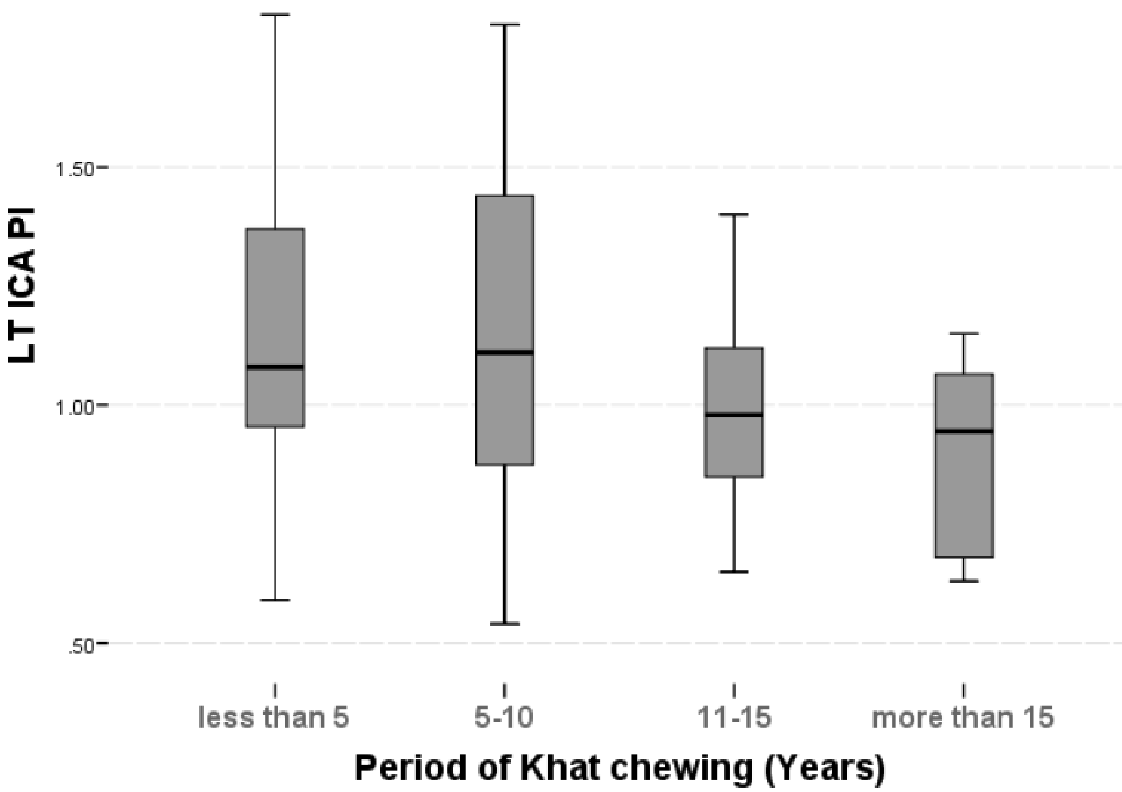


Figure 4-24. Correlation of LT ICA PI with period of Khat chewing.

Chapter Five

Discussion

Chapter Five: Discussion, Conclusion and Recommendation

In Yemen, the Khat (qat, kat) is considered as a major deep-rooted sociocultural phenomenon. and it is evergreen shrub belong to the family Celastraceae that was named by botanist Peter Forsskal who litanies the Arabic name khat to Catha (from the Catha edulistree) (Numan, 2012). This study has been perform to characterize bilateral carotid arteries in Yemenis Khat chewers using medical duplex ultrasonography, 195 Yemeni participants were examined, 16 (8.2%) females and 179 (91.8%) males, The mean age was 27.78 ± 6.74 ranging from 16 to 45 years, (Table 4-2).

5.1 Discussion

Khat chewer were 103 subjects representing 52.8%, with age from 16 to 45, mean and standard deviation 29.2±7.45105 years, and 92 subjects representing 47.2% were Non-Khat chewer with age from 17 to 43 and mean age and standard deviation (SD) was 26.1±5.67 years, and with significant age difference between two groups, p=.002.

Table 4-1 and figure 4-1 Show the distribution of sample according to the gender with 179 males, which represents 91.8% from the study sample and 16 females as 8.2%. the study samples were conveniently selected that may not reflect the percentage of Khat chewing according to gender, Furthermore, this difference in the percentage agree with World Bank document which attributed that to traditions and customs of society, so the social pressures take young women away from Khat. These social restrictions tend to lower once women are married, and this interprets the lowering of percentage in women’s Khat users (Bank, 2007).

Table 4-3 and figure 4-3 Show the sample distribution according to the governorate of the participants with the higher numbers of participants from Taiz governorate and that reflects the distribution of Yemeni population in which Taiz is actually the densest population governorate(center, 2014). Moreover, the most Khat chewers was from the northern governorate particularly the higher mountains regions where the Khat is cultivated from hundreds of Years (Bank, 2007).

Table 4-4 and figure 4-4 reveal the distribution of study sample according to the participant's occupation, which shows the higher percentage in security worker and hospital cleaner reflecting firstly the study as hospital based procedures. Furthermore, this also reflects the Chewer's believes in Khat that to get them able to work more with mental alertness, increased energy, and wakeful (al'Absi et al., 2013; Balint, Falkay, & Balint, 2009; Bank, 2007; Dachew, Bifftu, & Tiruneh, 2015).

Table 4-5 and figure 4-5 Show the distribution according to marital status, while the Table 4-6 and figure 4-6 demonstrate the distribution according to the Khat chewing status with increased percentage of married participants and chewers compare to single one and non-chewers, with significantly lower mean age of non-chewers that reflects presence of social restrictions which taken younger single member and women away from Khat chewing (Bank, 2007), and due to difficulties that we faced in founding non chewers meet the study inclusion criteria, because the high prevalence of Khat chewing (Bank, 2007)which is really deep major custom in Yemen (Numan, 2012).

Table 4-7 revealed that there is a difference between the IMT across the age categories in control group, and the equations derived from the correlation between the CCAs IMT and increasing age among this healthy population were $Y=0.02*X+0.1$ for RT And $Y=0.0167*X+0.15$ for LT. therefore the decade increment will be 0.4 and 0.167 for RT and LT respectively, which showed the higher value in compare to other study findings(Lee & Park, 2014). And the mean value of measurement across the entire control group were 0.695±0.094 for RT and 0.701± 0.088 for LT which was in the range of several studies finding in different population. (Alamin, 2016; Engelen et al., 2013; Mahmoud, 2013).

LT CCA IMT was significantly greater than that of RT in both Khat and non- Khat chewers (P<.001), (Table 4-8) consistent with other study findings which concluded this difference due to the anatomical fact where LT CCA is usually thicker as it is a main branch arises directly from Aortic Arch while the RT arises from brachiocephalic trunk(Vicenzini et al., 2007).

In this study, CCAs IMT was significantly higher in female than in male,(p=.004 and .016)for Right and Left respectively,(Table 4-9) which is in line of Sudanese findings, that possibly related to that women tend to weigh more than men (Alamin, 2016; Mahmoud, 2013).

In addition to the age, other CCAs IMT risk factors including smoking, blood pressure (BP), and blood fat, blood sugar, alcohol consumption, and lifestyle habits were reported (Qu & Qu, 2015; Sim et al., 2006).

Table 4-10 reveals that The CCAs IMT has positive correlation in this study with increasing body mass index among the healthy non-Khat chewer group but not reach a significance like in the findings of previous studies.(Asaleye, Braimoh, Oyinloye, Asaleye, & Omisore, 2019; Bae et al., 2013; Mahmoud, 2013; Youn et al., 2011).

Table 4-11, and figures 4-9,4-10 show the significant positive correlation of CCAs IMT with participant's age among Khat chewer (P<.001) and even in Non-Khat chewers p=.024, except for the RT CCA in Non-Khat chewer p=.427 (Table 4-11and figures 4-7, 4-8), these positive significant correlation consistent with that of several studies in systemic review literature(van den Munckhof et al., 2018).

Most of previous studies have not assessed chronic Khat effect on CCAs IMT as one of affecting risk factors, except the study performed among Somali chewers those use smoking concurrently(Gameraddin et al., 2019).

Therefore, there was no study demonstrated the cumulative effect of Chronic Khat chewing on CCAs IMT without interference of the other confounding factors.

In this study, which performed on Yemeni Khat chewers compared to Non-Khat chewers with exclusion of participants have smoking, high blood pressure, obesity, and history of cardio cerebrovascular diseases in both groups. The statistical difference of CCAs IMT was slightly higher in chewers compared to non-Khat chewers, Table 4-12 and figure 4-11. however, this trend of difference did not reach a significance, that consistent with a study evaluated the Khat effect on CCAs IMT before and After Chewing habitus(Ibrahim, Gameraddin, et al., 2017).

However, Table 4-13 and figures 4-12, 4-13 show that the CCAs IMT has significantly positive correlation with period of Khat chewing (P>001and =.017) for the RT and LT respectively. Therefore, the Khat chewing may could affect the IMT of CCAs as stated in previous study which reported that the Khat chewing may be predisposing factor to atherosclerosis accelerating and plaque formation. And that based on induced oxidative stress on the arterial wall caused by increased blood pressure besides other atherogenic stimuli (Alexander, 1995; Gameraddin et al., 2019).

Moreover, this impact of chronic Khat chewing on CCAs IMT was markedly lesser when compared to age effect that is demonstrated as strongest and the only significant variable in predicting the CCAs IMT in applying multivariate regression analysis in this study, table 4-14, in addition to significantly positive correlation between the age and period of Khat chewing. Therefore, chronic Khat chewing is less affecting CCAs IMT compared to other factors like age and cigarettes smoking. (al'Absi et al., 2013; Alhassen, 2010; Gameraddin et al., 2019).

in the control group, most of the CAs flow velocities in males were higher compared to females, which supports the previous findings in a healthy adults (Yazici, Erdogmus, & Tugay, 2005). Also there was no statistical significantly difference in Doppler parameters between genders in the Khat Chewers.

Khat chewing causes increased blood pressure and heart rate(N. Hassan et al., 2007; Ibrahim, Malik, & Gameraddin, 2017; YEHIA, 2015), therefore, it is considered a risk factor for cardiovascular complications(Al-Motarreb, Al-Habori, & Broadley, 2010; Al Suwaidi, Ali, & Aleryani, 2013; Balint et al., 2009).

The decreased PSVs in CAs of Khat chewers compared to those of non-Khat chewers in this study (Table 4-15) is consistent with the proven inverse relationship between the velocity and pressure according to physics laws controlling hemodynamics such as Bernoulli principle(Kirsch, Mathur, Johnson, Gowthaman, & Scoutt, 2013). This result agrees also with that of (Homma, Sloop, & Zieske, 2009)whom noticed that the PSV is lower in the hypertensive patient compared to healthy individuals.

These decreased PSVs in the CAs of Khat chewers compared to those of non-Khat chewers were statistically significant in the RT CCA and RT ICA (P>001, and 0.028) respectively. While the decreased PSVs in addition to the Doppler indices in CAs of Khat chewers was not statistically significant in the LT ICA, (Tables 4-15 and 4-17). This may be attributed, according to(Homma et al., 2009), to the probability of slower velocity in the ICA or the effect of anatomical variation in cerebral vessels on ICA, which are anatomically closer in distance to ICA than CCA.

Since(Agunloye & Owolabi, 2014)reported that the decreased PSVs were associated with stroke, the lower PSVs among Khat chewers in the current study may consolidate that Khat can be a cause of cerebral complications beside causing cardiovascular events(Al-Motarreb et al., 2010; Al Suwaidi et al., 2013; Balint et al., 2009; Kulkarni et al., 2012; Vanwalleghem et al., 2006). Moreover,(Ibrahim, Gameraddin, et al., 2017)indicated that the EDVs in CAs of Khat chewers were mostly increased, which is in line with the current study finding, (Table 4-15).

To confirm the aforementioned findings, the decrease in RI and PI (Table 4-16) is mathematically consistent with the decrease in PSVs and the increase in EDVs(Chow et al., 2013). Moreover, the decrease in RI and PI in CAs i.e. leading to low blood resistance in extracranial blood vessels agrees with an increased blood flow volume in bilateral ICAs, that statistically significant in the Right one (p=0.044), of the Khat chewers group compared to non-chewers (Table 4-15).

Moreover, these findings agree with the results of(Ibrahim, Gameraddin, et al., 2017) who revealed that cerebral perfusion may be affected and increased by Khat chewing.

Since the active gradient in Khat (cathinone) is pharmacologically similar and structurally related to amphetamine(Wabe, 2011), the decrease in Doppler indices and increased cerebral perfusion are also noticed as amphetamine impact on cerebral capillary(N. Hassan et al., 2007; Russo, Hall, Chi, Sinha, & Weiss, 1991), which may interpret the correlation of amphetamine abuse to hemorrhagic stroke(Westover, McBride, & Haley, 2007).

Consequently, a decreased Doppler indices and increased cerebral perfusion may interpret the desirable and acutely psychostimulant effects of Khat chewing including mental alertness, increased energy, wakeful, optimism feelings, increased flow of ideas during activity of studying and enhanced concentration(al'Absi et al., 2013; Balint et al., 2009; Dachew et al., 2015), and also interprets its side effects including intracranial swelling, edema and hemorrhage(Abdul-Mughni, El-Nahla, Hassan, & Dessouki, 2018).

The correlation between Khat and strokes was proven due to the effect of cathinone on the Central Nervous System (CNS), which finally leads to platelets aggregation(Kassa et al., 2017; Kulkarni et al., 2012; Vanwalleghem et al., 2006). Although this mechanism relates to the ischemic stroke and also confirmed the above aforementioned findings of this study regarding the lesser impact of chronic Khat chewing to CAs IMT in compared to aging and smoking that finally causing the atherosclerosis(Fernandes, Keerthiraj, Mahale, Kumar, & Dudekula, 2016), the mechanism related to the hemorrhagic one correlated with chronic Khat Chewing(Ali et al., 2011; Attafi, 2018; Benois et al., 2009), to the best of our knowledge, has not been established and no study has discussed the cause of increased hemorrhagic strokes among Khat chewers. Nevertheless, it was recommended for further studies(Makwana, Mistri, & Patel, 2017; Sallam, Al-Aghbari, & Awn, 2009).

Additionally, a study conducted in Sana'a city, Yemen revealed that hemorrhagic strokes are happened mostly (51.7%) among patients aged between 15-44 years, and 43.4% of the entire sample were Khat chewers(Sallam et al., 2009). However, another study conducted on Mukalla city, Yemen revealed that the mean age of stroke among the study sample is similar to that noticed in other Middle East countries(Bamekhlah, Bin-Nabhan, & Musaian, 2014), which was within the 6th and 7th decade with predominance of the ischemic over hemorrhagic type(El-Hajj, Salameh, Rachidi, & Hosseini, 2016). This controversial argument resulting from one country can be due to regional and cultural reasons. In Yemeni Northern mountainous areas, Khat is grown and cultivated from hundreds of years(Bank, 2007; Numan, 2012), while it is not cultivated in Southern coastal areas(Bank, 2007).

Therefore, Khat chewing could be one of the main causes of hemorrhagic stroke in Yemen, and it may become like untreated hypertension(Woo et al., 2004).

Accordingly, this is the first study that reveals and discusses the mechanism of hemorrhagic stroke based on the significantly decreased resistance of extracranial and cranial blood flow among Khat chewers, in addition to increased blood flow volume in ICAs.

When evaluating the Doppler parameters in CAs among the Khat chewers' group itself in our study, it was revealed that the RI, PI and most of the PSVs had a negatively significant correlation with the period of chewing indicating that these Doppler parameters decrease with the increasing period of chewing (Tables 4-16, 4-18 & figures 4-14 to 4-24), which confirmed and supported the previous findings in the comparison between Khat and non-Khat chewers' groups.

These results with the results of (Al-Motarreb et al., 2010; Al Suwaidi et al., 2013; Balint et al., 2009),who reported that chronic Khat chewing has obvious effects on cardiovascular system, may strengthen the previous suggested conclusion that Khat could be a risk factor of hemorrhagic stroke. They may also reinforce the interpretation of why the hemorrhagic stroke mostly occurs among younger population in Yemen while it mostly occurs among the elderly in the other

Middle East countries(El-Hajj et al., 2016; Kulkarni et al., 2012; Lahoud, Salameh, Saleh, & Hosseini, 2016; Sallam et al., 2009; Vanwalleghem et al., 2006).

Therefore, this study is important and can be a clinical guideline for physicians in preventing or at least decreasing the complications associated with cerebrovascular perfusion resulting from chronic Khat chewing, particularly among those with known cardiovascular disorders.

Further studies are recommended to address and confirm findings using transcranial Doppler ultrasound technique which can provide measurements of cerebral blood flow with higher temporal resolution(Markus, 2004).

5.2 Conclusion:

The present study concluded that duplex ultrasound is effective modality in evaluating carotid changes in chronic Khat chewers. chronic Khat chewing may slightly affect the CCA-IMT. the age has a significant positive correlation with CCA-IMT in khat chewers and LT CCA-IMT in non-khat chewers, which could help to determine the contribution of different predisposing factors to atherosclerosis. Moreover, chronic Khat chewing has significantly altered the carotid blood hemodynamics because the study showed that there were a differences in systolic velocities between Khat chewers and non-chewers with lower values for the chewers, and they were significant in the right common carotid artery and in the internal carotid artery. The carotid Doppler indices, except the right internal carotid artery, were significantly decreased, and the Right internal carotid artery blood flow volume was significantly increased among Khat chewers compared to that of non-chewers.

Moreover among Khat chewers Doppler indices and most of the peak systolic velocities had a significantly negative correlation with the Khat chewing period. Therefore, this study may provide an interpretation of high prevalence and mechanism of hemorrhagic stroke among Yemeni population in their middle age, and the correlation of chronic chewing Khat to this type of stroke more than ischemic one. More studies are recommended to confirm this finding using the transcranial Doppler technique.

5.3 Recommendations:

- Yemeni society should be aware from the effects of chronic Khat chewing using different broadcasting and social media.
- Governmental relative authorities in Khat cultivating countries, the first of which is Yemen should take action to reduce the prevalence of Khat cultivating and chewing in societies.
- The study findings should be taken as clinical guideline for physicians in preventing or at least decreasing the complications associated with cerebrovascular perfusion resulting from chronic Khat chewing, particularly among those with known cardiovascular disorders.
- Further studies are recommended to address and confirm this study findings using transcranial Doppler ultrasound technique that has higher temporal resolution.

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Appendix

University of Science & Technology
Faculty of Medicine & Health Sciences
Research Ethics Committee

For Committee Use Only
MECA NO.: (EAC/UST133)

MEDICAL ETHICAL COMMITTEE APPROVAL

This is to declare that the ethical committee of the medical research has reviewed the proposal titled:

Assessment of Common Carotid Arteries Changes in Yemenis Khat Chewers Using Medical Duplex Ultrasonography

Presented by: Amin Mohsen Amer

Faculty: Medicine and Health Sciences, UST

And found that it has fulfilled the guarantees and safeguards for the medical research ethics and that the proposal is in compliance with the policy of the committee.

Chair, Ethical Committee
Prof. Husni A. AL-Goshae

Sudan University of Science and Technology

College of Graduate studies

PhD research title: Assessment of Carotid Arteries Changes in Yemenis Khat Chewers Using Medical Duplex Ultrasonography

Data collection sheet

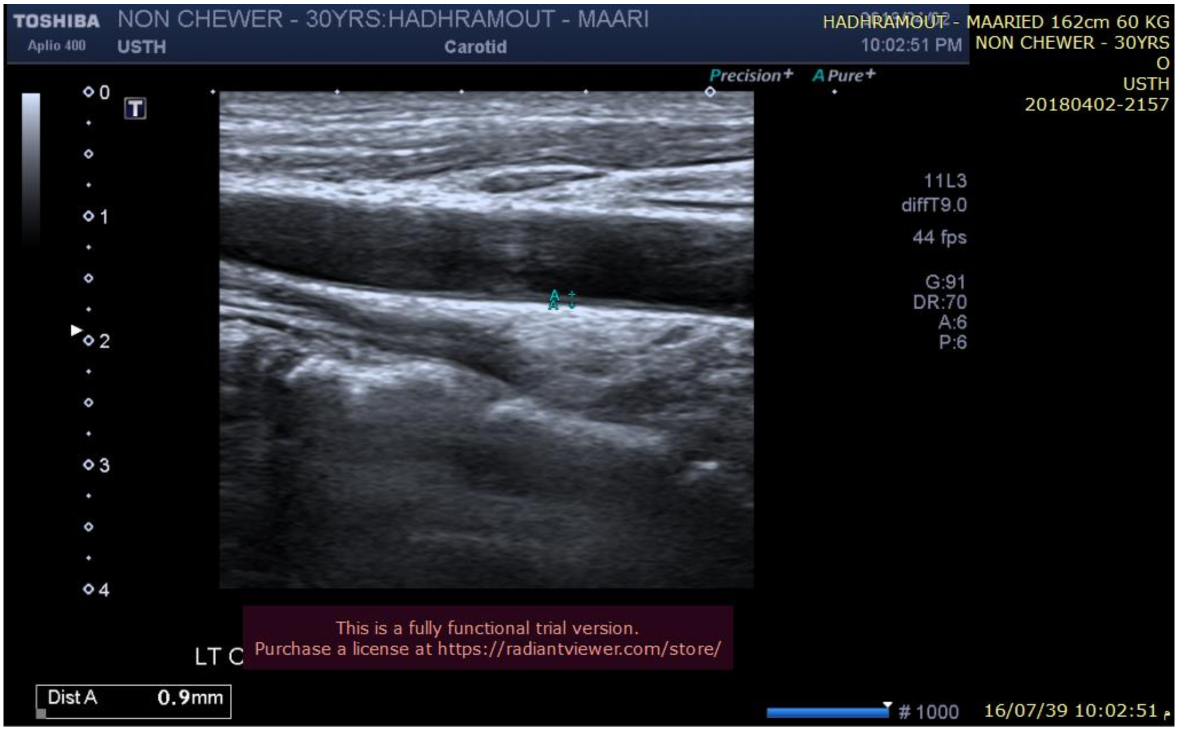
<u>Section one: Questionnaire</u>

- **Participant's personal Data:**
  - **Participant No. …………..**
  - **Gender: M ( ) or F ( ).**
  - **Age: ……………………..….Yrs.**
  - **Governorate: …………………**
  - **Occupation: …………………..**
  - **Marital status: Married ( ), Single ( ), or other ( ).**

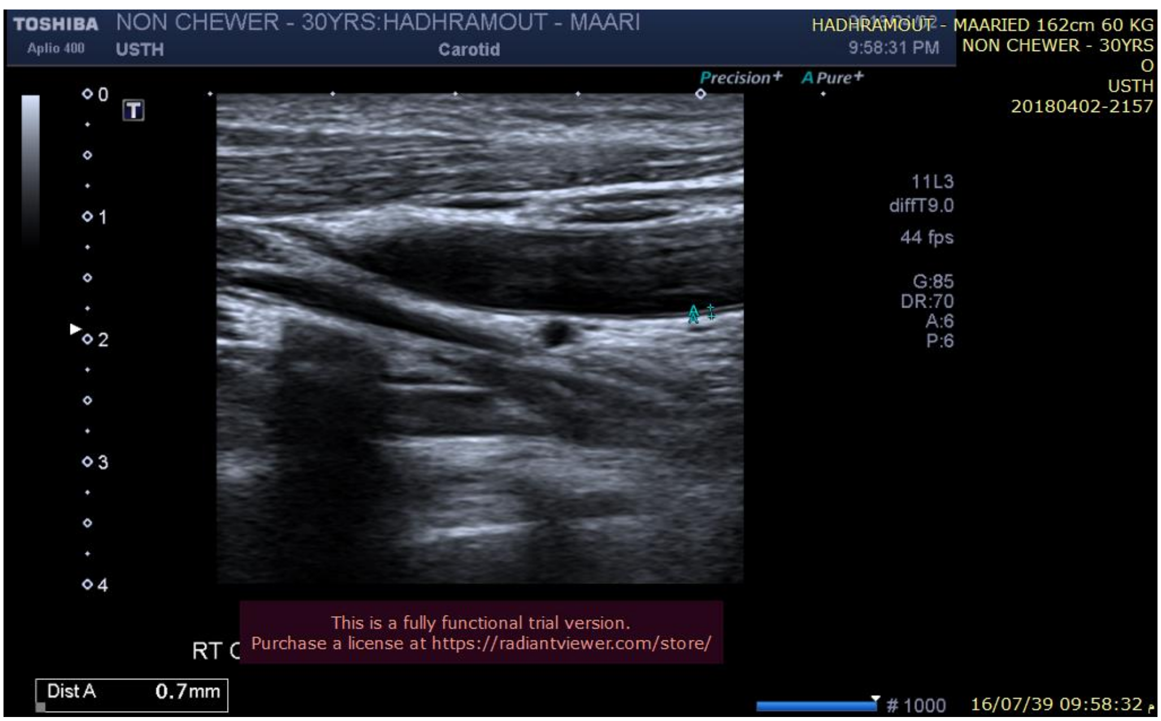
- **Participant's Khat chewing information:**
  - **Khat chewer ( ) or Non Khat Chewer ( ).**
  - **Are there other type of habits? Yes ( ) No ( ).If yes, what are these?........**
  - **If Khat chewer: Former ( ) or current ( ).**
- **Khat Chewing frequency: daily ( ) or not daily ( ). If daily,**
- **No. of Khat chewing sessions in day: one ( ) two ( ) three ( ).**
- **Duration of Khat chewing session/ sessions(in hours):**
  < 2 ( ) 2-4 ( ), 5-7 ( ), > 7( ).
- **Side of chewing: right ( ), Left ( ) or both ( ).**
- **Period of chewing (in years): <5 ( ),5-10( ),11-15( ),or > 15 ( ).**
- **If not daily, No. of chewing sessions in week.…………………………**

<u>Section two: Findings of CAs duplex ultrasonography</u>

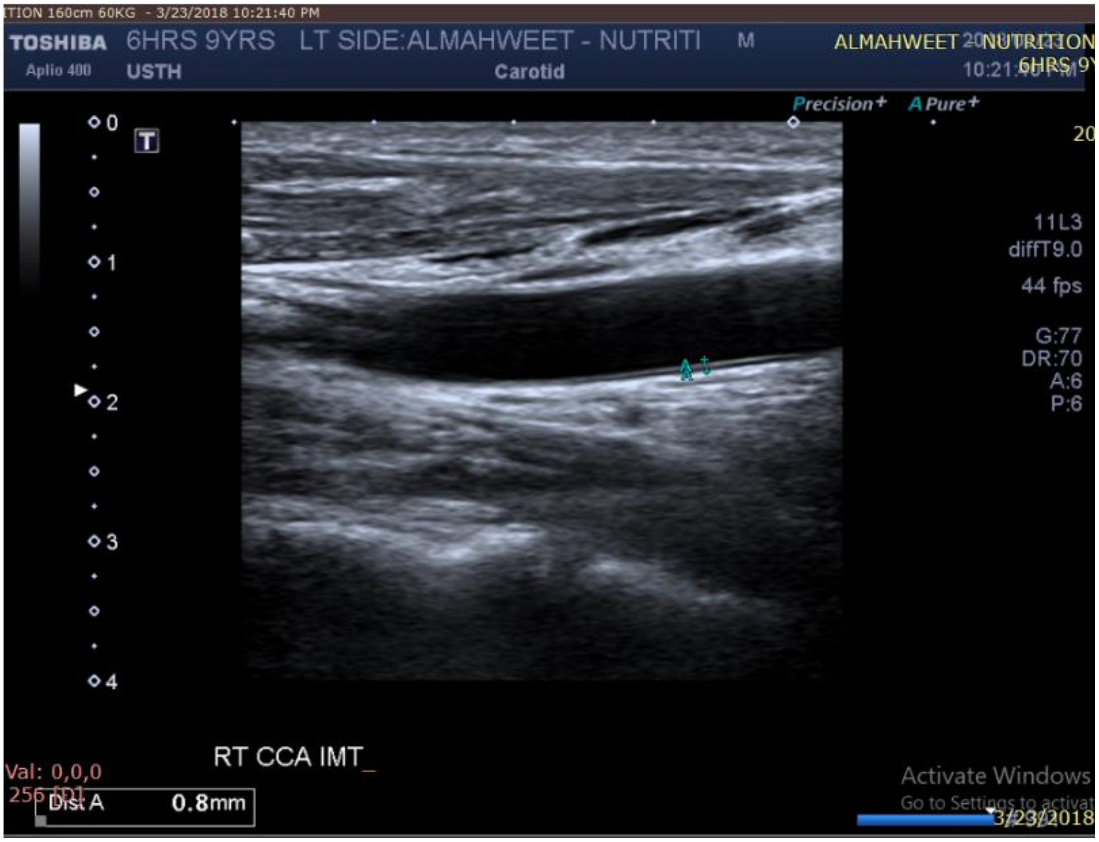
RT CCA		IMT (mm)			LT CCA		IMT (mm)	
PSV (cm/sec)		RI			PSV (cm/sec)		RI	
EDV(cm/sec)		PI			EDV(cm/sec)		PI	
RT ICA		RT ECA			LT ICA		LT ECA	
PSV (cm/sec)		PSV (cm/sec)			PSV (cm/sec)		PSV (cm/sec)	
EDV(cm/sec)		EDV(cm/sec)			EDV(cm/sec)		EDV(cm/sec)	
RI		RI			RI		RI	
PI		PI			PI		PI	



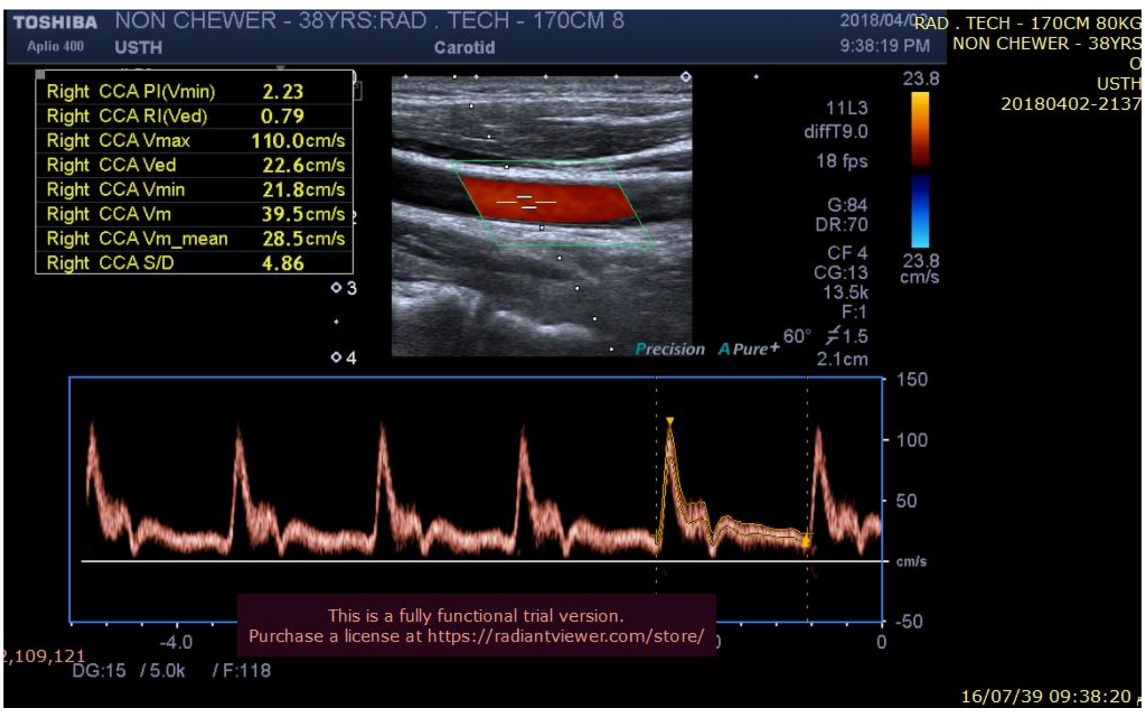
B-mode sonogram of measuring of LT CCA IMT for a Non-Khat chewer participant from Hadhramout governorate has a 30 years old.



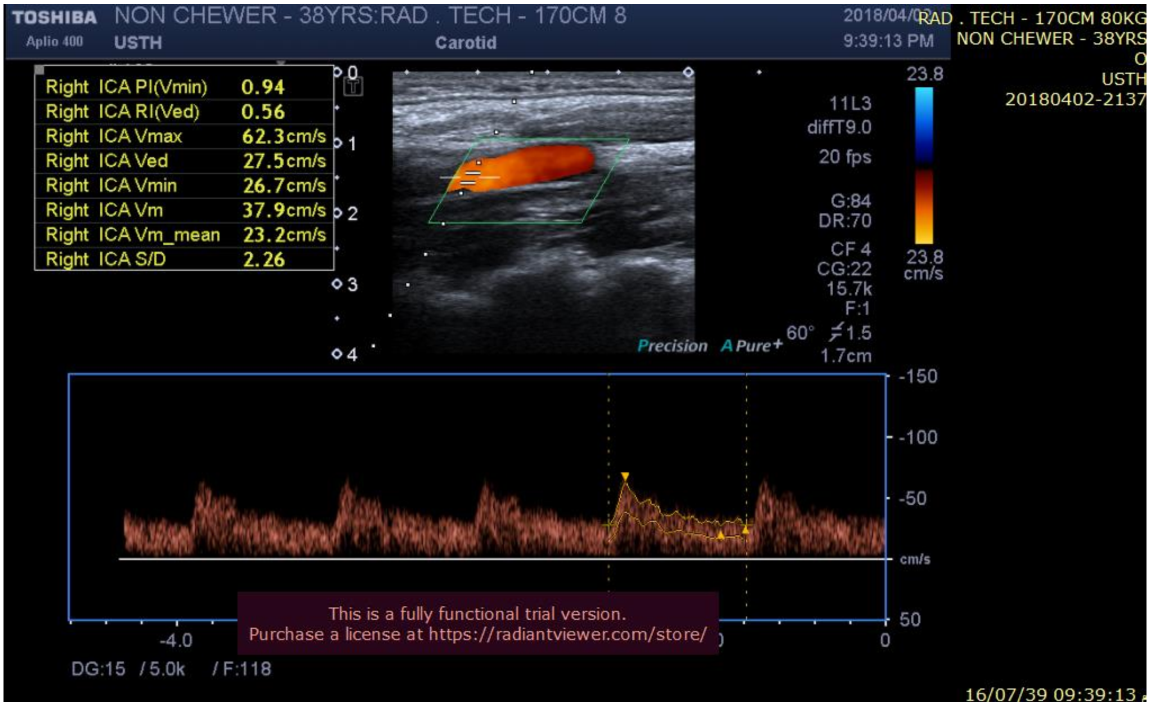
B-mode sonogram of measuring RT CCA IMT for a Non-Khat chewer participant from Hadhramout governorate has a 30 years old.



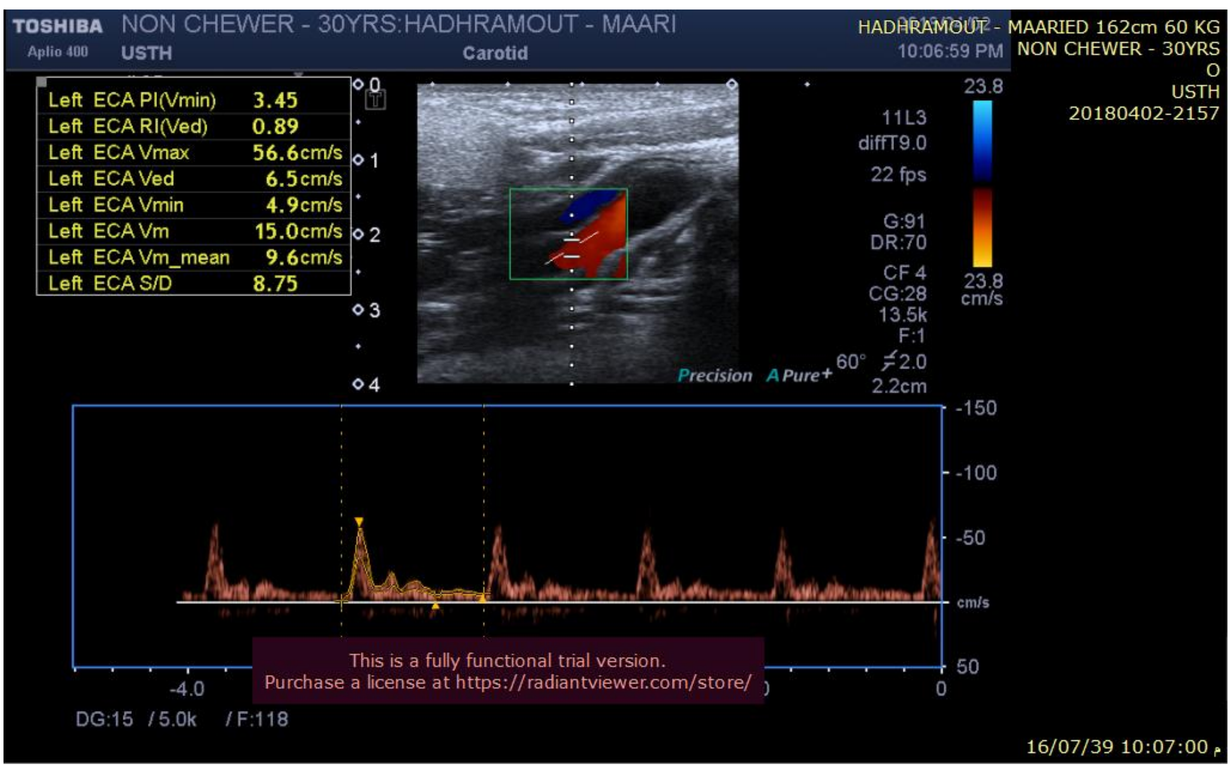
B-mode sonogram for measuring the RCCA IMT in Yemeni Khat chewer from Al-Mahweet governorate has 9 years period of chewing



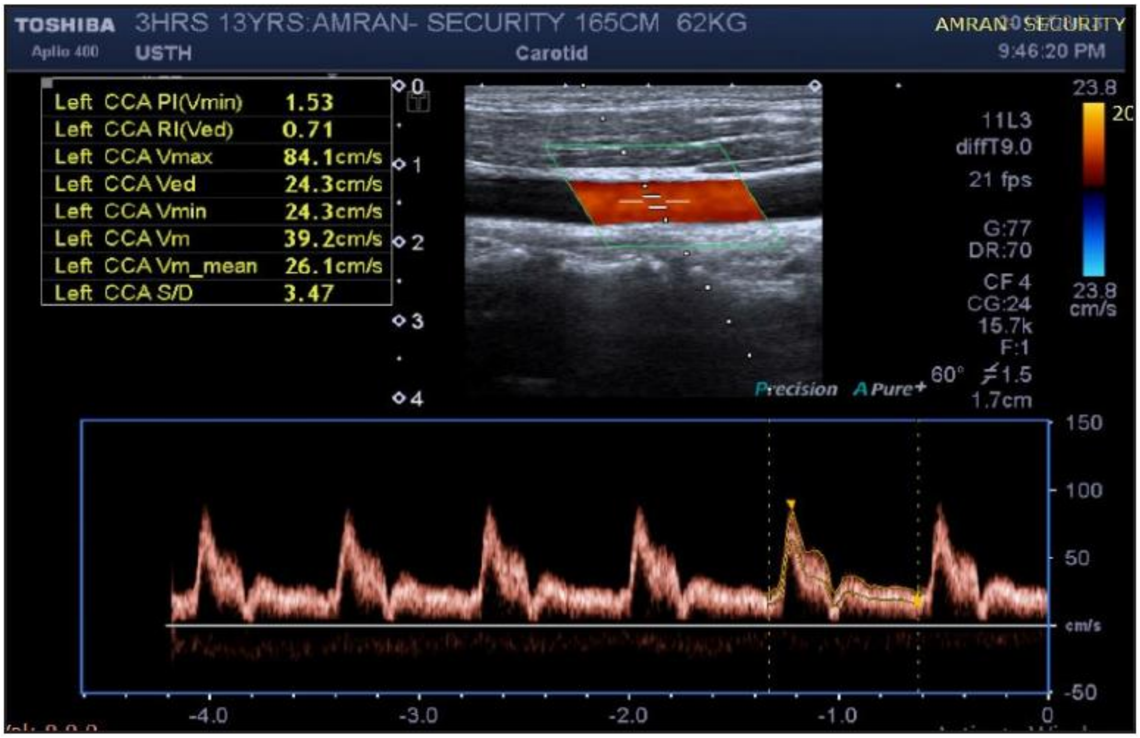
Doppler interrogation of RT CCA hemodynamic for a radio technologist Non-Khat chewer participant has a 38 years old.



Doppler interrogation of RT ICA hemodynamic for a radio technologist Non-Khat chewer participant has a 38 years old.



Doppler interrogation of LT ECA for a Non-Khat chewer participant from Hadhramout governorate has a 30 years old.



Doppler interrogation of Lt CCA hemodynamic for a Khat chewer participant has a 13 year period of Khat chewing from Amran governorate.

High-resolution ultrasound system (model: TUS-Aplio 400 / Toshiba-MEC-US)

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Short Communication

Impact of Chronic Khat Chewing on Carotid Doppler Flow Velocities and Indices in Yemeni Volunteers

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ABSTRACT

Chewing Khat is considered as a major deep-rooted sociocultural habit in Yemen. This custom has been causing various health problems. Using Doppler ultrasonography, this study assessed the changes that occurred in bilateral carotid arteries' flow velocities and Doppler indices in Yemenis who regularly chewed Khat for years. Convenient sampling was conducted from August 2017 to August 2018 for 384 participants of whom 179 were excluded and the sample size became 205 participants including 108 (52.7%) Khat chewers and 97 (47.3%) non-Khat chewers. The mean age of the sample was 28.29 ± 7.0 years. In all cases, the carotid Doppler ultrasound scanning protocol, based on the standards of American Institute of Ultrasound in Medicine, was performed to measure carotid Doppler velocities and indices, in addition to internal carotid flow volume. The Khat chewing information of participants was obtained by a standardized questionnaire, and SPSS was used for result analysis. There were differences in systolic velocities between Khat chewers and non-chewers with lower values for the chewers, and they were significant in the right common carotid artery and in the internal carotid artery. The carotid Doppler indices, except the right internal carotid artery, were significantly decreased, and the Right internal carotid artery blood flow volume was significantly increased among Khat chewers compared to that of non-chewers. Moreover among Khat chewers, Doppler indices and most of the peak systolic velocities had a significantly negative correlation with the Khat chewing period. Therefore, this study may provide

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