CHAPTER 3

REVIEW OF SCIENTIFIC LITERATURE

3. REVIEW OF SCIENTIFIC LITERATURE

3.1 BACKGROUND

The arterial pulse is one of the fundamental life signals in medicine which is generated at heart and is detected at arteries (Fan, Zhang, & Liao, 1997). The arterial pulse as it travels from the heart along the arterial tree is influenced by various factors such as resistance to blood flow, elasticity of the arteries, viscosity of the blood and reflections from multiple levels of blood vessels which has a direct impact on pulse shape and parameters. The arterial pulse provides significant information about cardiovascular state which can be deduced from the pulse shape and parameters and in the paper “Characteristics of the dicrotic notch of the arterial pulse wave in coronary heart disease”, Tomas classified the pulse wave into four categories based on the dicrotic notch (Dawber, Thomas, & Mcnamara, 1973) as shown in Fig 3.1.

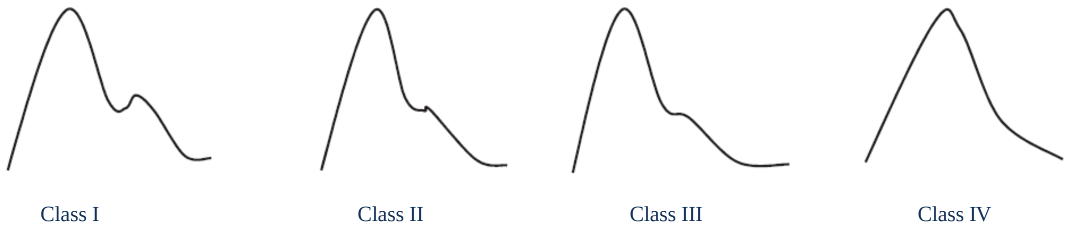

Fig 3.1. Pulse Classification Based on Dicrotic Notch

Class I – A distinct incisura is inscribed on the downward slope of the pulse wave

Class II – No incisura develops but the line of descent becomes horizontal

Class III – No notch is present but a well defined change in the angle of descent is observed

Class 1V -- No evidence of a notch is seen

In similar lines, Bates has classified the pulse waves based on shape of the pulse as shown in Fig 3.2 and explained the physiological cause and possible disease for each of the shape as shown in Table 3.1 (Fan et al., 1997).

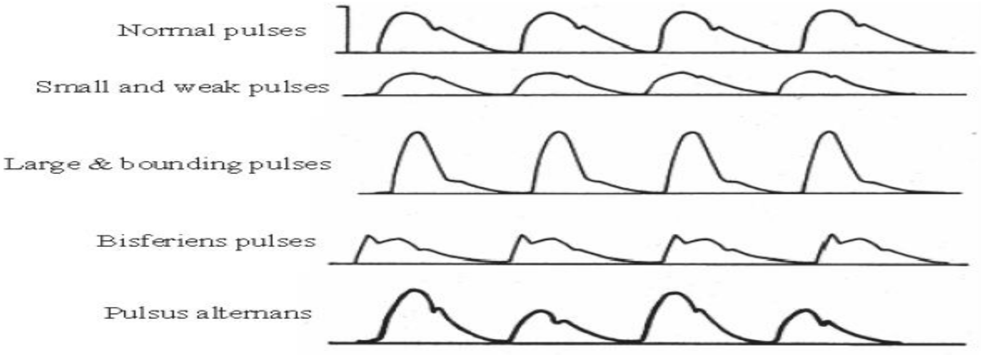

Fig 3.2 Pulse Classification Based on Pulse Shape

Pulse Type	**Physiological Cause**	**Possible Disease**
small & weak	decreased stroke volume increased peripheral resistance	heart failure, hypovolemia, severe aortic stenosis
large & bounding	increased stroke volume, decreased peripheral resistance decreased compliance	fever, anemia, hyperthyroidism, aortic regurgitation, bradycardia, heart block, atherosclerosis
bisferiens	increased arterial pulse with double systolic peak	aortic regurgitation, aortic stenosis and regurgitation, hypertropic cardiomyopathy
pulsus alternans	Pulse amplitude varies from peak to peak rhythm basically regular	left ventricular failure

Table 3.1 Pulse Type and Possible Disease

The pulse shape provides an initial assessment of cardiovascular system but it does not give sufficient information to predict the cardiovascular risk. Framingham risk score (Kannel, McGee, & Gordon, 1976) and European Society of Cardiology (ESC) risk score (Conroy et al., 2003) are more popular in cardiovascular risk assessment and these risk scores are based on the established risk factors such as age, gender, systolic blood pressure, cholesterol and glycemic status. In the recent past arterial stiffness has gained significant research interest as a surrogate biomarker for cardiovascular risk assessment and the additive value of pulse wave velocity, a measure of arterial stiffness, above and beyond ESC and Framingham risk scores has been quantified in number of studies (Mancia et al., 2013). The aim of the current review is to study the arterial stiffness and its significance as an independent predictor of cardiovascular disease. In this review, basics of arterial stiffness and various methods and techniques to measure the arterial stiffness were discussed. The longitudinal studies highlighting the significance of arterial stiffness were reviewed and the association of arterial stiffness with diabetes and obesity were studied.

3.2 REVIEW OF ARTERIAL STIFFNESS BASED STUDIES

The blood flows faster in aorta compared to peripheral network and the speed varies from meters per second in aorta to mm per second in peripheral network. The velocity of the blood flow termed as pulse wave velocity (PWV) normally ranges from 5 to 15 meters per second and studies have confirmed that increased PWV is associated to arterial stiffening. The arteries stiffen due to age and atherosclerosis and recently the arterial stiffness measured from pulse wave velocity (PWV) has gained significant research importance as it is considered to be strong predictor of cardio-vascular events

(Vlachopoulos, Aznaouridis, & Stefanadis, 2010; Zoungas & Asmar, 2007) and Alberto et al have discussed in detail the role of arterial pulse wave analysis in cardiovascular risk assessment (Avolio, Butlin, & Walsh, 2010). A longitudinal study by Boutouyrie provides the first direct evidence that the aortic stiffness is an independent predictor of primary coronary events in hypertensive patients (Boutouyrie et al., 2002) and in another independent study by Laurent, the aortic stiffness is confirmed to be in an independent predictor of all cause and cardiovascular mortality in hypertensive patients (S Laurent et al., 2001). In similar lines the increased arterial stiffness has shown independent predictive value in patients with end stage renal disease (ESRD) (Jacques Blacher et al., 1999). The study on subjects above 70 years has shown that the aortic stiffness is an independent marker of cardiovascular risk which needs to be validated with interventional studies (Meaume, Benetos, Henry, Rudnichi, & Safar, 2001). The results of these studies demonstrate the significance of arterial stiffness especially aortic stiffness in predicting the cardiovascular risk but the populations involved in these studies were different and the size of the populations were also different. To confirm the robustness of the predictive value of arterial stiffness in predicting cardiovascular events and all cause mortality, Vlachopoulos (Vlachopoulos et al., 2010) has conducted a systematic review and meta-analysis of longitudinal studies and confirmed that the aortic stiffness is strong predictor of cardiovascular risk. The meta-analysis included 17 original articles assessing the predictive values of aortic stiffness and in total 15,877 subjects were analyzed as part of the meta-analysis. The populations with diabetes, ESRD, hypertensive, coronary artery disease and subjects from general population were included in the study. It is quite evident from the literature survey that arterial stiffness is a potential indicator of cardiovascular risk but the predictive value of arterial stiffness largely depends on the measurement techniques and the site of artery used for measurement. The regional and local arterial stiffness measurements directly measure the arterial stiffness from various sites of the arteries and are more popular when compared to systemic arterial stiffness measurement based on models of circulation such as Windkessel model. The longitudinal studies based on systemic arterial stiffness measurement have not shown independent predictive values in predicting the cardiovascular disease whereas longitudinal studies based on regional and local arterial stiffness measurements proved that the arterial stiffness is a independent predictor of cardiovascular disease (Stephane Laurent et al., 2007). The aorta is considered to be significant artery for regional measurements of arterial stiffness when compared to various other arteries such as brachial, ankle and radial arteries. The pulse wave velocity measured from peripheral arteries especially brachial and femorotibial arteries have not shown any prognostic values in ESRD patients whereas the predictive value of arterial stiffness measured from peripheral arteries is yet to be established in general population (Pannier, Guérin, Marchais, Safar, & London, 2005). The local arterial stiffness is measured using ultrasound devices and the diameter of the artery at diastole and stroke changes in diameter are used for measuring the arterial stiffness and Blacher reported that carotid arterial stiffness measured using ultrasound is a strong predictor of cardiovascular disease in patients with end stage renal disease (J. Blacher et al., 1998). The advantage with local arterial stiffness measurement is that it is a direct measurement of arterial stiffness but it requires high degree of technical expertise and takes longer time compared to regional arterial stiffness. Hence the ultrasound based arterial stiffness measurement is not used in epidemiological studies and is limited to clinical studies. The carotid stiffness measured using ultrasound and the pulse wave velocity based aortic stiffness have shown similar effect on aging of large artery in normal healthy subjects but aortic stiffness is higher when compared to carotid stiffness in patients with hypertension and Type 2 diabetes (Paini et al., 2006). The longitudinal studies on aortic and carotid stiffness in predicting the cardio-vascular disease are listed in **Table 3.2** as taken from Expert Consensus Document On Arterial Stiffness (Stephane Laurent et al., 2006).

Measurement Site	**Reference**	**Events**	**Follow Up (years)**	**Type of Patient**	**Mean Age**
Aortic PWV (Regional arterial stiffness)	(Jacques Blacher et al., 1999)	CV Mortality	6	End Stage Renal Disease	51
	(S Laurent et al., 2001)	CV Mortality	9.3	Hypertension	50
	(Meaume et al., 2001)	CV Mortality	2.5	Elderly (>70)	87
	(Shoji et al., 2001)	CV Mortality	5.2	End Stage Renal Disease	55
	(Boutouyrie et al., 2002)	CHD events	5.7	Hypertension	51
	(Cruickshank et al., 2002)	All cause mortality	10.7	Impaired Glucose Tolerance	51
	(Stéphane Laurent et al., 2003)	Fatal Strokes	7.9	Hypertension	51
	(Sutton-Tyrrell et al., 2005)	CV mortality	4.6	Elderly	74
	(Shokawa et al., 2005)	CV mortality	10	General Population	64
	(Hansen et al., 2006)	CV	9.4	General Population	55

		mortality			
	(Mattace-Raso et al., 2006)	CV mortality	4.1	Elderly	72
Ascending Aorta (invasive)	(Stefanadis et al., 2000)	Recurrent acute CHD	3	Recurrent acute Coronary Heart Disese	55
Carotid stiffness (local stiffness)	(J. Blacher et al., 1998)	All cause mortality	2.1	End Stage Renal Disease	58
	(Barenbrock et al., 2002)	CV events	7.9	End Stage Renal Disease	43

Table 3.2 Longitudinal studies on aortic and carotid stiffness

3.2.1 Studies On Diabetes And Obesity

Diabetes and obesity are considered to be cardiovascular risk factors but the association of arterial stiffness with diabetes and obesity is not yet established. The criteria for diagnosis and classification of diabetes defined by American Diabetes Association is well established clinical practice in diagnosing the diabetes (American Diabetes Association, 2004) and according to Expert Committee on Diagnosis and Classification of Diabetes the diagnosis of Type 2 diabetes is based on one of the following conditions.

- *Symptoms of diabetes and casual fasting plasma glucose ≤ 200 mg/dl*
- *Fasting plasma glucose (FPG) ≥ 126 mg/dl*
- *2h post load glucose ≥ 200 mg/dl*

The Expert Committee has recognized an intermediate group of patients whose FPG is between 100 and 126 mg/dl and similarly whose 2h post load glucose is ≥ 140 mg/dl are considered as pre diabetes. Later committee has introduced HbA1c as a better means for diagnosing diabetes which is considered to be more reliable than FPG and accordingly persons having HbA1c ≥ 6.5% are considered diabetic (Nathan et al., 2009). As the prevalence of diabetes is increasing globally and is estimated to be 334 million in 2030 when compared to 171 million in 2000 (Wild, 2004), there is a lot of interest to investigate whether arterial stiffness can be considered as a surrogate marker for Type 2 diabetes. The arterial stiffness is proven to be an independent marker of cardiovascular risk in hypertensive patients but still the association of arterial stiffness with Type 2 diabetes is yet to be established (Mansour et al., 2013). Bouchi et al in their study demonstrated that the aortic stiffness is an independent predictor of incident albuminuria and decline in renal function in patients with Type 2 diabetes (Bouchi et al., 2011). Sheen et al have seen similar results with arterial stiffness whereas they have used brachial ankle pulse wave velocity for measuring the arterial stiffness and earlier study was based on carotid femoral pulse wave velocity (Sheen, Lin, Li, Bau, & Sheu, 2013). Recent studies on patients with Type 2 diabetes have shown that arterial stiffness is closely associated to Cardiac Autonomic Neuropathy (CAN) (N. Wu et al., 2014) and Glaucoma (Shim et al., 2015). As the fasting plasma glucose and HbA1c are used in clinical practice to diagnose diabetes, the investigators have done some studies to understand the association of arterial stiffness with glucose levels including fasting plasma glucose and HbA1c. The studies have shown that the increased levels of arterial stiffness is associated with fasting plasma glucose in non diabetic subjects (Shin, Lee, & Lee, 2011) and is associated with HbA1c in diabetic patients (Kinouchi et al., 2014). The initial studies on arterial stiffness have shown mixed results with diabetes and there is a need to do extensive studies especially longitudinal studies are needed to establish the association of arterial stiffness with diabetes.

Increase in incidence of obesity is likely to have long term implication of cardiovascular disease and studies have shown that excess weight is associated with cardiovascular risk factors such as hypertension, dyslipidemia, Type 2 diabetes etc. Recent studies have shown close association of aortic stiffness with excess weight (Wildman, Mackey, Bostom, Thompson, & Sutton-Tyrrell, 2003)] and in another study the authors have reported that weight change is associated with change in arterial stiffness (Wildman et al., 2005)]. Initial studies have shown interesting results but similar to diabetes, it requires more extensive studies to establish the relationship between arterial stiffness and obesity.

3.3 ARTERIAL STIFFNESS MEASUREMENT TECHNIQUES

As the sensor and semiconductor technologies have advanced further the pulse wave acquisition has become more sophisticated and various techniques are employed in measuring the arterial stiffness with ease and precision. In this section various arterial stiffness measurement techniques and devices used in cardiovascular studies are discussed. The arterial stiffness measurement techniques and the arteries used for measurement are listed in **Table 3.3**

Measurement Technique	**Measurement site**
Carotid femoral pulse wave velocity	Carotid and femoral arteries
Brachial ankle pulse wave velocity	Brachial and ankle arteries

Stiffness Index from radial artery	Radial artery
Ultrasound	Carotid and femoral arteries

Table 3.3 Arterial stiffness measurement sites and techniques

3.3.1 Carotid Femoral Pulse Wave Velocity (cfPWV)

The measurement of pulse wave velocity using carotid femoral pulse wave velocity is the standard technique and is considered to be non invasive, robust and reproducible method for assessing the arterial stiffness (Stephane Laurent et al., 2007). In cfPWV technique, pulse wave is obtained simultaneously at carotid and femoral arteries and the distance between these two arteries is recorded. The pulse wave velocity is computed as the ratio of distance between carotid and femoral arteries to the pulse transit time from carotid to femoral arteries as shown in Fig 3.3.

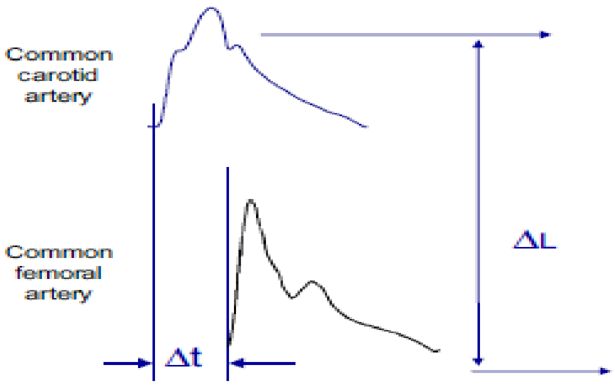

Fig 3.3 Carotid femoral pulse wave measurement (Δ*t – Pulse Transit Time;* Δ*L - Distance between carotid and femoral arteries)*

The pulse transit time (Δt) and measurement of distance between carotid and femoral arteries play a significant role in assessing pulse wave velocity and the accuracy of pulse wave velocity largely depends on the accuracy of pulse transit time and physical distance between the arteries. The pulse transit time Δt as shown in Fig 3.3 is measured using foot to foot method wherein foot of waveform is considered to be the end of the diastole. The pulse transit time is the time taken for the foot of the carotid wave to foot of the femoral wave and usually right carotid and right femoral arteries are used for measurement. The distance between carotid and femoral arteries ΔL is measured physically and is considered as an estimate of the distance traveled by the pulse wave. The precise distance measurement is very important as any inaccuracies in the measured distance may lead to errors in the absolute value of PWV. As the true distance travelled by the pulse is critical for PWV the investigators have recommended that the distance from carotid artery to sternal notch is subtracted either from the total distance between carotid and femoral arteries or from the distance between sterna notch to femoral artery (Stephane Laurent et al., 2006).

The carotid femoral pulse wave technique is considered as gold standard and number of epidemiological studies has demonstrated the predictive value of cfPWV technique in assessing arterial stiffness. The European Society of Hypertension and Eurpoean Society of Cardiology has suggested a threshold exceeding 12m/s as a conservative estimate of significant alterations in aortic function of hypertensive patients and later the threshold has been adjusted to 10m/s considering the true anatomical distance traveled by pulse wave (Mancia et al., 2013). The advantage with cfPWV is that it is gold standard; however, due to the difficulties in acquiring the femoral pulse from the patients with obesity, diabetes and periperal artery disease and inaccuracies in measuring the distance from the patients with abdominal obesity, it is not widely used in clinical setup and is limited to the research.

There are number of devices available today to measure the pulse wave velocity using cfPWV technique but Complior and SphygmoCor are widely used in PWV based studies and the way pulse transit time and distance between arteries are computed varies between these two devices (Stephane Laurent et al., 2007; Pereira, Correia, & Cardoso, 2015). The Complior (Artech-Medical, France) is based on pressure transducers and the pulse at carotid and femoral arteries is acquired simultaneously. The correlation algorithm is applied between the two simultaneous pulse recordings to determine the pulse transit time. The distance travelled by pulse is obtained by directly measuring the distance between carotid and femoral arteries. In the SphygmoCor system (Artcor, Sydney, Australia) high fidelity applanation tonometers are used for pulse acquisition and the pulse is acquired at carotid artery along with the ECG recording followed by femoral pulse acquisition with simultaneous ECG recording. The pulse transit time is computed by subtracting the time difference between R wave of ECG and carotid pulse peak from the time difference between R wave of ECG and femoral pulse peak. The distance traveled by the pulse is computed by subtracting the distance between sternal notch to carotid artery from the distance between sternal notch to femoral artery.

3.3.2 Brachial Ankle Pulse Wave Velocity (baPWV)

The brachial ankle pulse wave velocity (baPWV) is another technique introduced in Japan in 2000 to measure the pulse wave velocity from brachial and ankle arteries. The complexities involved in arterial stiffness measurement with cfPWV technique have been addressed in baPWV. The pulse wave velocity is measured in baPWV by connecting volume plethysmographic sensors to the cuffs connected to brachial and ankle as shown in Fig 3.4.

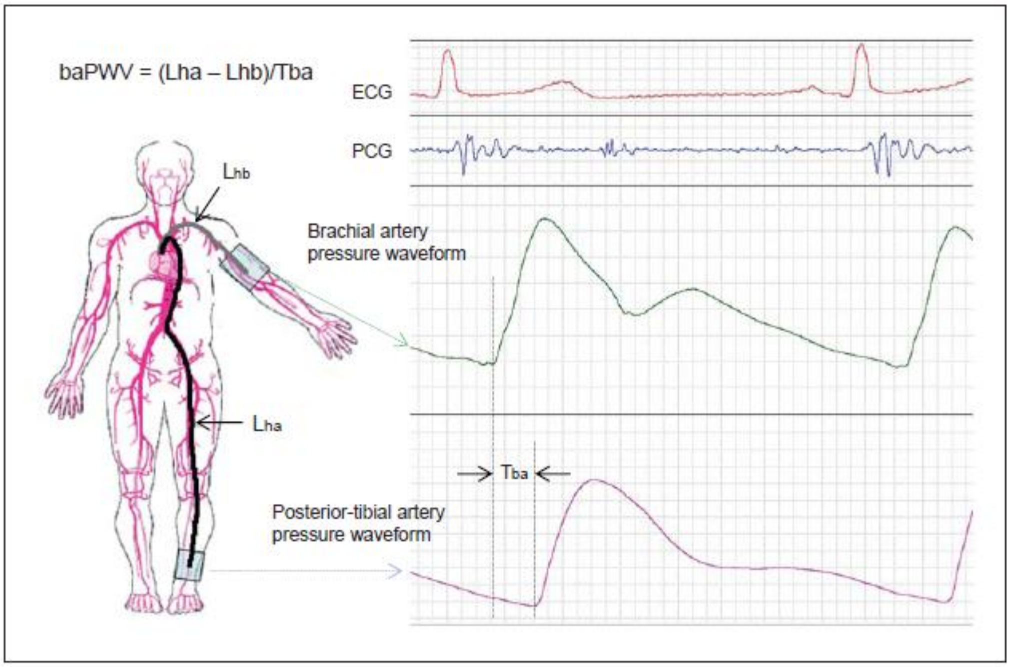

Fig 3.4 brachial ankle pulse wave measurement

The pulse transit time is the time difference between the pulse at brachial and ankle arteries and the distance is estimated based on the height of the person which eliminates the need for measuring the physical distance between the two arteries. The virtual arterial length is computed as shown below.

*Path length from heart to brachium (Lb) = 0.2195 * height of the person (cm) – 0.20734*

*Path length from heart to ankle (La) = 0.8129 * height of the person (cm) + 12.238*

Virtual arterial path length = La – Lb

The pulse wave velocity is computed as the ratio of virtual arterial length between these two arteries to the pulse transit time from brachial to ankle arteries. The pulse acquisition and physical distance measurement have been extremely simplified in baPWV due to which it has gained significant clinical interest but still it is not widely accepted in research communities as there are number of questions and concerns on the measurement of arterial stiffness using baPWV which Sugawara has addressed thoroughly in his review (Sugawara & Tanaka, 2015). The arterial site and the virtual arterial path length need to be investigated further to understand their significance in arterial stiffness measurement. The arterial stiffness measured using baPWV is undoubtedly gaining significant research and clinical interests but the investigators think that the arterial stiffness measurement using this technique is not appropriate as the pulse wave velocity is measured between the arteries which do not belong to the same arterial tree. In cfPWV the pulse wave velocity is measured between carotid and femoral arteries which again do not belong to the same arterial tree but this violation is acceptable and has been considered as gold standard. Hence the arteries belonging to different arterial tree should be acceptable for arterial stiffness measurement using baPWV. Secondly, the pulse wave velocity using baPWV is measured from peripheral arteries which may not be appropriate for arterial stiffness measurement when compared to central elastic arteries as the latter has more close association with cardiovascular risk compared to peripheral arteries. The studies have shown significant positive correlation between the pulse wave velocity measured using cfPWV and baPWV techniques. The results of aerobic interventional study confirmed that the reduction in baPWV was significantly associated to reduction in cfPWV which confirms that the baPWV can be used for risk assessment though it measures peripheral stiffness. There are some concerns on virtual arterial path length as the height based formula has been validated with Japanese population but its applicability to other racial and ethnic populations needs to be validated. The ratio of the distance from suprasternal notch to the ankle is strongly correlated with height irrespective of races and ethnicities (Jurgens, Aune, & Pieper, 1991) and in addition the ratios of upper arm length and height are comparable across Asians, Whites and African-Americans confirming that virtual arterial path is unbiased and can be used for arterial stiffness measurement. The height based estimation eliminates the need for measuring the physical distance between two arteries and thereby simplifies the arterial stiffness measurement when compared to cfPWV. The height based arterial path length computation grossly overestimates the actual path length resulting in overestimation of PWV values when compared with the arterial path length measured using MRI but height based path length can be converted to actual length with an adjustment factor as PWV measured from height based path length is linearly correlated to PWV measured from actual path length (Sugawara, Hayashi, & Tanaka, 2014). As the baPWV technique is simple to use and pulse wave velocity is strongly correlated to pulse wave velocity measured using cfPWV, it has gained much of clinical and research interest and number of studies are reported using this technique. Number of articles published has increased year by year as shown in **Fig 3.5** which signifies the importance of baPWV is assessing cardiovascular risk.

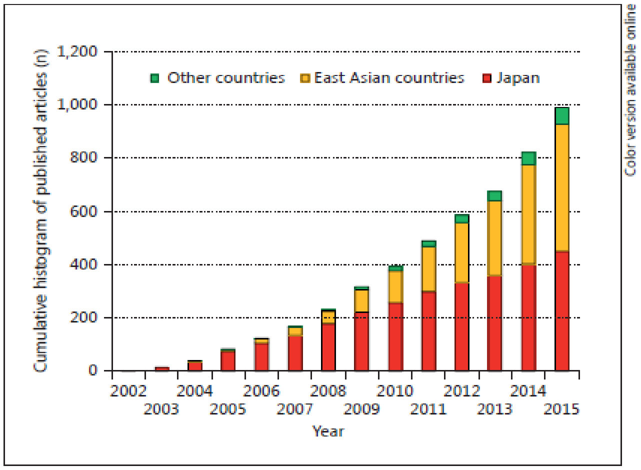

Fig 3.5 Number of articles published in 2002 – 2015

3.3.3 Local Arterial Stiffness Measurement

The local arterial stiffness is of interest in arteriosclerosis as there will be regional differences in mechanical properties of arteries (Rabben et al., 2004) and it is measured using ultrasound devices. The ultrasound devices are used primarily to measure the diameter at the diastole and change in the diameter during systole as shown in **Fig 3.6**.

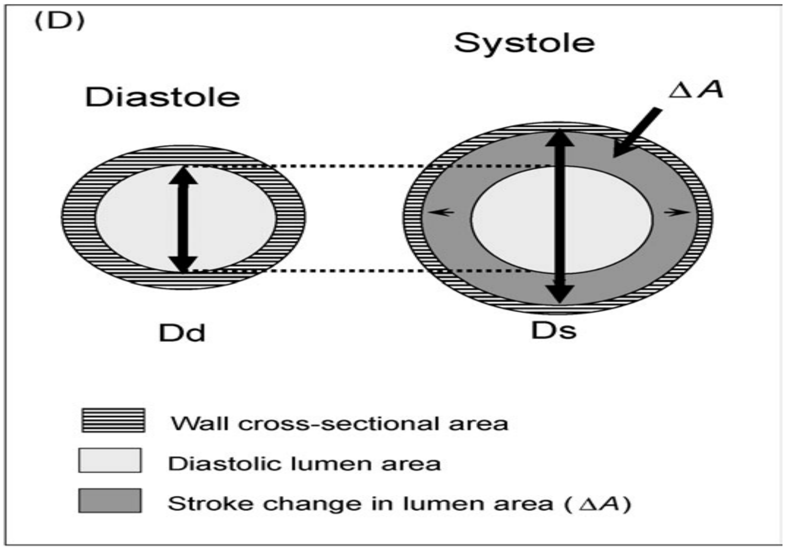

Fig 3.6 Change in cross sectional area of artery

The local pulse wave velocity is directly related to the distensibility coefficient (DC) of artery via Bramwell Hill equation as given below

PWV = $\sqrt{1/(\rho.DC)}$ where DC = $(\Delta A/A) / \Delta P$

- ρ = density of the blood ;
- ΔA = change in the cross sectional area from diastole to systole
- A = cross sectional area during diastole
- ΔP = local pulse pressure

The pulse wave velocity is measured as the ratio of distance between two adjacent positions on the artery to the time delay between the adjacent diameter waveforms. Alternately in place of diameter, waveforms pressure or flow waveforms can be considered. The reliable identification of foot of the diameter waveform and measuring the precise time delay between the adjacent diameter waveforms require technical expertise. Brands et.al have introduced alternate way of measuring the pulse wave velocity which is based on temporal and longitudinal gradient of change in arterial diameter and the ratio of temporal and longitudinal gradients provide the estimate of local pulse wave velocity (Brands, Willigers, Ledoux, Reneman, & Hoeks, 1998). In another independent study by Calabia et al the pulse wave velocity has been computed by measuring the diameter waveform at carotid and femoral arteries synchronized to R wave of ECG and demonstrated that it is comparable to carotid femoral pulse wave velocity (Calabia et al., 2011). Rabben illustrated that the local pulse wave velocity measured as the ratio of change in flow to change in diameter is associated to pulse wave velocity estimated using Bramwell Hill equation (Rabben et al., 2004). In the recent past there is an increased interest in magnetic resonance imaging (MRI) based measurement of local pulse wave velocity due to the availability of faster and robust MRI sequences (Wentland, Grist, & Wieben, 2014) and the accurate measurements of arterial path length is the advantage with this technique. Echocardiograpy is widely used in evaluation of cardiac function and Jae has discussed its utility in evaluation of arterial stiffness. According to him it is still a research tool and requires large validation studies before using it for arterial stiffness based studies (Cho & Kim, 2016).

The ultrasound based arterial stiffness measurement is more accurate compared to the conventional pulse wave techniques but it requires very good technical expertise and is more time consuming and hence it is more used in clinical studies compared to epidemiological studies.

3.3.4 Stiffness Index Measured From Radial Artery

The pulse wave as it travels from heart gets reflected at multiple peripheral sites and typical pulse wave at radial artery is composed of both forward pulse and reflected pulse. The pulse wave measured from radial artery is similar to the digital volume pulse measured from PPG (Photoplethysmography) and is related by a transfer function (S C Millasseau et al., 2000). The pulse at radial artery exhibits systolic and diastolic peaks similar to that of digital volume pulse acquired from PPG as shown in **Fig 3.7**. A peak appears in the forward wave during systolic phase of the pulse and peak corresponding to reflected wave appears in diastolic phase of the pulse. The time taken for diastolic peak from the systolic peak depends on the stiffness of the arteries and height of the person. Arteries stiffen due to age and arteriosclerosis and as the arteries stiffen the reflected wave travels faster and the diastolic peak in stiffen arteries appears closer to the systolic peak when compared with elastic arteries. The time difference between systolic and diastolic peaks is considered as surrogate measure of pulse wave velocity which represents the arterial stiffness (S C Millasseau et al., 2000; Sandrine C Millasseau, Ritter, Takazawa, & Chowienczyk, 2006) and is well known as stiffness index (SI).

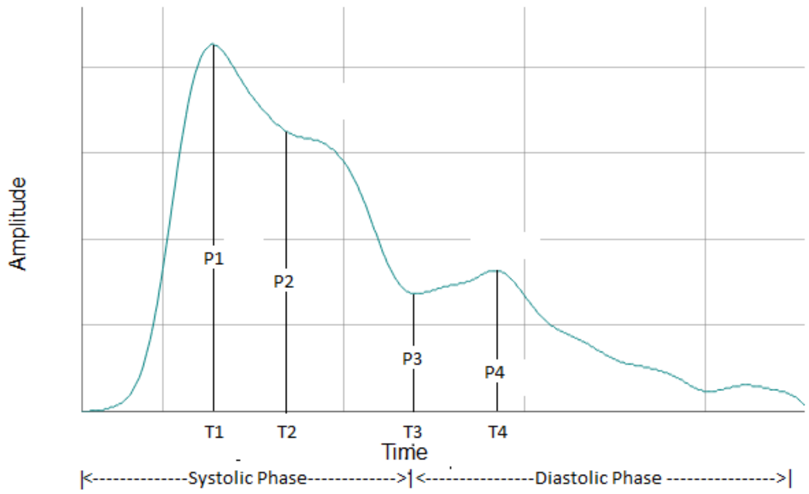

Fig 3.7 Pulse wave acquired using Nadi Tarangini

- *P1 = pulse amplitude at systolic peak; P2 = pulse amplitude at second systolic peak;*
- *P3 = pulse amplitude at dichrotic notch; P4 = pulse amplitude at Diastolic Peak;*
- *Time periods T1, T2, T3, T4 are measured from start of the systolic phase*
- *T1 = time period at systolic peak; T2 = time period at inflection point;*
- *T3 = time period at dichrotic notch; T4 = time period at diastolic peak*

The stiffness index from PPG has been extended to radial artery as the pulse wave from radial artery exhibits properties similar to PPG. The arterial stiffness is represented by stiffness index (SI) and is computed as the ratio of height of the person to the time difference between systolic and diastolic peaks.

- *SI = height of the person (cm) / (T4 – T1)*

The reflection index (RI) and augmentation index (AI) are the other two parameters which are of research significance. The augmentation index is a measure of enhancement of pulse pressure due to reflected wave and is more appropriate at aorta compared to peripheral arteries. The augmentation index is represented as given below

- *AI = (Systolic First Peak - Systolic Second Peak) / Total Pulse Height*

  = (H1 – H3) / H1 or (H3 / H1)

Reflection index is a measure of amount of reflected wave representing the endothelial function and is determined as the ratio of diastolic to systolic peak amplitudes as shown below

- *RI = Amplitude of Diastolic Peak / Amplitude of Systolic Peak*

  = H5 / H1

The second derivative of pulse as represented below also play key role in pulse wave analysis.

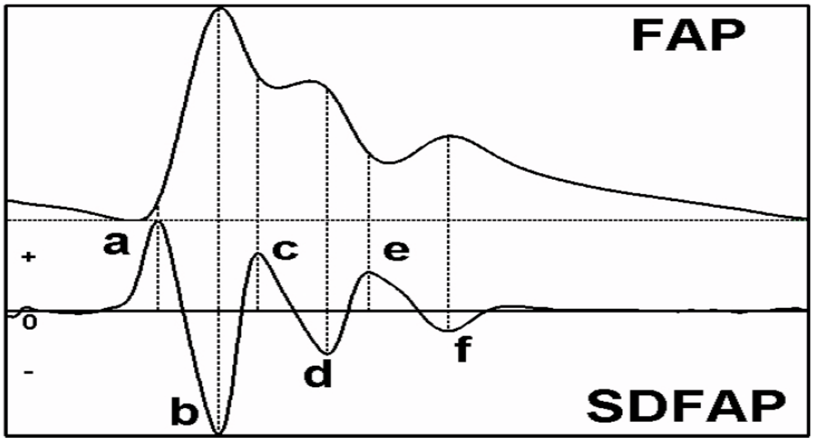

Fig 3.8. Second Derivative of Finger Arterial Pulse

- *A, B, C waves correspond to early systole*
- *D, E, F waves correspond to late systole*

- *Positive waves A, C, E represent the instant acceleration of blood pressure*
- *Negative waves B, D, F represent the deceleration waves*

- **Significant Second Derivative parameters in pulse analysis**
    - *The ratios B/A, C/A, D/A, E/A*
    - *Aging index (AGI) -- (B-C-D-E) / A*

The studies have shown that the stiffness index from PPG is positively correlated to the pulse wave velocity from the gold standard cfPWV technique (Fan et al., 1997) which emphasizes the potential of stiffness index in cardiovascular studies. Gunarathne et al have shown that SI measured from PPG is strongly associated to ESC risk score and it may aid in identifying the individuals with cardiovascular risk (Gunarathne, Patel, Hughes, & Lip, 2008). The second derivative parameters of pulse wave have shown significant results in the recent studies wherein the early systole indices B/A and C/A are able to discriminate the hypertensive patients from healthy controls (Šimek et al., 2005). In another study by Pilt et al, the aging index AGI, another second derivative parameter, has higher values in patients with diabetes when compared with healthy controls (Pilt et al., 2013). The stiffness index and second derivative parameters of digital volume pulse has shown significant results with hypertensives and diabetics which confirms the potential of these parameters in cardiovascular studies. The pulse wave from radial artery is similar to digital volume pulse from PPG but the studies are limited with pulse from radial artery. Kim et al have shown that arterial stiffness measured from radial artery was associated to left ventricular diastolic dysfunction but they have used radial augmentation index in their study but not SI and RI (Kim et al., 2016). Hsien-Tsai et al have studied the significance of SI and RI measured from radial artery in monitoring the progression of arterial stiffness and endothelial function of elderly persons with diabetes and in the same study, correlation between arterial stiffness measured using PPG and radial artery was established (H. T. Wu et al., 2011). The stiffness index from radial artery is also equally potential parameter which can throw light on cardiovascular state of the person similar to brachial and ankle arteries. The advantage with radial artery is that the pulse locations are convenient for pulse acquisition compared to carotid, femoral, brachial and ankle arteries and secondly, it eliminates the complex process of accessing the pulse from two locations and synchronizing with ECG as the arterial stiffness can be measured from the time difference between systolic and diastolic peaks. The arterial path length measurement is the challenge in other techniques and significant effort has gone in standardizing the measurements whereas in radial artery based measurement the arterial path length is approximated to the height of the person eliminating the need for path length measurements. The path length has been extremely simplified by considering the height of the person and there are no proper justifications for such consideration but studies have shown that the stiffness index measured as ratio of height of the person to the time difference between systolic and diastolic peaks is strongly correlated with carotid femoral pulse wave velocity which confirms the validity of the assumption. The pulse based diagnosis especially by sensing the pulse at radial artery is not new to medicine and *Āyurveda* has thousands of years of rich experience in pulse based diagnosis. There is a need for extensive studies with the pulse measured from radial artery to bring out the diagnostic values of pulse from radial artery.

CONCLUSION

The arterial stiffness is proven to be an independent predictor of cardiovascular disease and longitudinal studies have confirmed the same. There are multiple ways in which arterial stiffness can be measured and the available techniques for measuring the pulse wave velocity are reviewed in this chapter. Association of diabetes and obesity with pulse wave velocity has been discussed and reviewed. The significance of arterial stiffness measurement from radial artery and the need for radial artery based studies have been emphasized.