

Sains Malaysiana 47(10)(2018): 2455–2461  
<http://dx.doi.org/10.17576/jsm-2018-4710-22>

## Association between Pulse Wave Velocity with Other Vascular Markers and Inflammation among Young Adults: An Evidence-Based Review

(Perkaitan antara Halaju Gelombang Nadi dengan Penanda Vaskular Lain dan Inflamasi dalam Kalangan Orang Muda: Satu Penilaian Berasaskan Bukti)

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### ABSTRACT

*Studies evaluating the association between pulse wave velocity (PWV), a gold standard measurement of aortic stiffness and established markers of cardiovascular disease (CVD), with other established vascular markers or inflammation among young adult is still scarce. A systematic review of the literature was conducted to identify relevant studies on the association between PWV with other vascular markers or inflammation. Relevant articles from Ovid Medline, Science Direct and Scopus databases were explored between 2009 and March 2018. Original articles published in English measuring any correlation between carotid-femoral PWV (PWVcf) with either augmentation index (AIx), carotid intima media thickness (CIMT) or C-reactive protein (CRP) on young adult with age range between 18 and 45 years old were included. The literature search identified 21 potential articles to be reviewed, which meet all the inclusion criteria. Four articles investigated the correlation between PWVcf with CRP, however only two studies gave significant but weak correlations. As for CIMT, a single relevant article was found and the correlation was not significant. In conclusion, lack of association between PWV and other vascular markers and inflammation may suggest that these vascular markers have their own property in assessing vascular status. Thus, these markers should be measured independently for comprehensive assessment of future CVD risk.*

*Keywords: Carotid-femoral pulse wave velocity; inflammation; vascular stiffness; young adults*

### ABSTRAK

*Halaju gelombang nadi (PWV) merupakan satu pengukuran piawai kekakuan aorta dan merupakan penanda terkenal penyakit kardiovaskular (CVD). Namun, kajian yang menilai hubungan antara PWV dengan penanda vaskular terkenal yang lain dan inflamasi masih terhad. Sorotan kajian yang sistematik telah dijalankan bagi mengenal pasti kajian yang mengukur hubungan antara PWV dengan penanda vaskular lain atau inflamasi. Pangkalan data Ovid Medline, Science Direct dan Scopus digunakan untuk mencari makalah berkaitan yang diterbitkan dari tahun 2009 sehingga Mac 2018. Hanya makalah asal yang diterbitkan dalam bahasa Inggeris dan mengukur sebarang korelasi antara PWV karotid-femoral (PWVcf) dengan indeks augmentasi (AIx), ketebalan intima media arteri karotid (CIMT) atau protein C-reaktif (CRP) ke atas populasi muda dengan julat umur 18 hingga 45 tahun diterima. Terdapat 21 makalah yang memenuhi semua kriteria kemasukan dan layak untuk dikaji dan dinilai. Empat makalah mengkaji hubungan antara PWVcf dengan CRP, namun hanya dua kajian menunjukkan hubungan yang signifikan namun lemah. Untuk CIMT, satu kajian yang berkaitan telah didapati dan hubungannya dengan PWV adalah tidak signifikan. Kesimpulannya, kekurangan hubungan antara PWV dengan penanda vaskular lain dan inflamasi mungkin menunjukkan setiap penanda vaskular mempunyai sifat tersendiri dalam menilai status vaskular. Sehubungan itu, penanda vaskular tersebut perlu diukur secara berasingan bagi menilai risiko CVD akan datang secara menyeluruh.*

*Kata kunci: Halaju gelombang nadi karotid-femoral; inflamasi; kekakuan vaskular; orang muda*

### INTRODUCTION

Cardiovascular diseases (CVD) remain the most important cause of mortality worldwide. As reported by World Health Organization (2017), more than three-quarters of heart disease and stroke-related death occur in low- and middle-income countries. As CVD have a prolonged asymptomatic period, it provides an opportunity for early preventive interventions. Assessment of future cardiovascular disease (CVD) risk using vascular markers has been extensively

studied. Measurement of arterial stiffness (AS) becomes one of the promising method in assessing cardiovascular risk as it is one of the earliest detectable manifestation of adverse structural and functional changes within the vessel wall (Stoner et al. 2012). Generally, AS will lead to thicker vessel and lesser inner diameter, which eventually reduce vessel compliance (Zahedi et al. 2007).

Quantification of AS using pulse wave velocity (PWV) has been considered the most validated non-invasive

method. PWV is calculated by measuring the speed of pulse transit of the forward pressure waveforms from aorta to the vascular tree (Qawqzeh et al. 2011). The pulse transit from carotid to femoral, known as carotid-femoral PWV (PWVcf) becomes a gold standard for AS for its simplicity, reproducibility and give strong prediction of the adverse outcome (Stoner et al. 2012). PWVcf reflects the estimation of arterial PWV through the entire aorta (Laurent et al. 2006). A compliant and distensible blood vessel will conduct slower pulse wave compared to a stiffer blood vessel (Oliver & Webb 2003). Thus, PWV inversely correlates to vascular compliance whereby any increment in PWV is linked to cardiovascular risk factors and eventually predicts future cardiovascular events and all-cause mortality (Vlachopoulos et al. 2010).

Other than PWV, there are other cardiovascular disease markers that have been used to predict primary cardiovascular event, namely: Augmentation Index (AIx); carotid intima-media thickness (CIMT) and; C-Reactive Protein (CRP) (Greenland et al. 2010; Polak et al. 2011; Roberfroid et al. 2013). AIx is another measurement of AS, which represents a wave reflection that arrives back to the aorta after the forward wave, hits the peripheral artery (Laurent et al. 2007). CIMT measures the thickness of two arterial walls, namely tunica media and tunica intima. It has been used as a marker of early arterial wall alteration in detecting early to late stages of subclinical atherosclerosis (Pignoli et al. 1986). CRP is an established inflammatory marker for CVD which plays an important role in atherosclerotic process (Nilsson 2005).

A great number of studies have been conducted in order to assess AS by measuring PWV and other cardiovascular risk markers. However, evaluation on the association between PWVcf and other cardiovascular risk markers is still scarce, especially in young population. As CVD have a prolonged asymptomatic period and AS is a good predictor for future cardiovascular event, study involving young population is strongly needed. Therefore, the aim of this review was to study the existing association between pulse wave velocity with other vascular markers and inflammation among young adults.

## MATERIALS AND METHODS

### LITERATURE REVIEW

A systematic review of the literature was performed to identify the relevant previous studies focusing on the association between pulse wave velocity with other vascular markers and inflammation in young adults. A comprehensive search in Ovid Medline, Science Direct and Scopus databases (published between 2009 and March 2018) was conducted. The search strategy involved a combination of three (3) keywords: 'pulse wave velocity' OR 'aortic stiffness'; 'carotid intima media thickness' OR 'augmentation index' OR ('inflammation' OR 'c-reactive protein'); AND 'young adult\*.

### SELECTION OF RESEARCH ARTICLES

Articles selected were limited to English language publications. Review articles, supplementary issues, proceedings, poster presentations, books, bibliography, consensus/statement/guidelines, case reports, subject/keyword index, letters to editor and commentary were excluded from the review. For this review, only studies reported the association of pulse wave velocity with: other vascular markers or inflammation in young adults were included.

### INCLUSION AND EXCLUSION CRITERIA

For the purpose of this review, only studies that reported direct association between PWV with at least one of the selected vascular marker, or C-reactive protein in young adults were included. The measurement of pulse wave velocity includes carotid-femoral PWV (PWVcf). Studies included must measure at least one of these cardiovascular risk markers: augmentation index (AIx); carotid intima-media thickness (CIMT) or C-reactive protein (CRP). In term of young adults, only studies involving subjects with age range of 18 - 45 years old were included in this review.

### DATA EXTRACTION AND MANAGEMENT

Prior to review, selected articles were screened in three (3) phases. In the first phase, any articles that did not meet up the inclusion based solely on title and keywords criteria were excluded. Second phase involved screening the abstract of remaining articles and further exclusion if the articles did not fulfill the inclusion criteria. The final phase is the critical part where thorough reading by two (2) independent reviewers was done to exclude any articles that did not meet the inclusion criteria. Final selection of articles is based on mutual agreement by all reviewers on the inclusion criteria before any data extraction was conducted. Any difference of opinion between reviewers was resolved through discussion. A data extraction form was designed to obtain a standardized data collection comprising these data: population and sample size; mean age; age range; male percentage; distance of PWV measured; and association of PWVcf with selected vascular markers or inflammation. Data extraction process was conducted independently using the standardized form.

### SEARCH RESULTS

The literature searches in three (3) databases identified 903 potential relevant articles. Initial independent screening by two reviewers excluded 488 articles that did not meet the inclusion criteria, based on the title and abstract. 327 articles were further excluded because they were not related to PWVcf or aPWV, or no measurement of association with other vascular markers or inflammation of interest and not involving young adults. From the remaining 88 articles, 26 were further excluded due to duplication. After thorough reading by both reviewers, 21 from 62 articles were valid for further assessment and data extraction for this review.

Any difference of opinion between reviewers was resolved through discussion. Flow of article selection and exclusion was showed in Figure 1.

#### STUDY CHARACTERISTICS

The summary of the characteristics of all studies is shown in Table 1. All studies were published between the year 2009 and March 2018. 21 studies were thoroughly reviewed. Method of PWV measurement includes tonometry, oscillometry and Doppler. However, in this review, we only include PWV measurement using tonometry or oscillometry method. Among them, five studies focus on direct association of PWVcf with other vascular markers or inflammation. Only study conducted by Kerkhof et al. (2012) measures the association with CIMT. However, the correlation is not significant in apparently healthy young adults. The other remaining studies measure the association of PWVcf with CRP or hsCRP, a marker of inflammation. The subjects recruited in the studies vary which include healthy young men, normotensive overweight and obese subjects,

inflammatory bowel disease, juvenile idiopathic arthritis and non-alcoholic fatty liver disease patients. Merely two studies showed significant correlation (Cooper et al. 2012; Ozturk et al. 2015a), however the correlations were weak.

#### RESULTS AND DISCUSSION

PWV is used as a measurement of arterial stiffness. The pulse wave travels along the arteries and the velocity depends on the mechanical properties of the arterial walls. It provides insight on the elastic properties of arterial system. The elasticity of the vessels decreased from the large arteries to the peripheral muscular arteries, resulting in higher PWV as it travels away from the heart. Besides, other factors involved in pathological processes also influence the value of PWV (Wilmer et al. 2005). In general, higher PWV is associated with lower vessel distensibility and compliance and consequently higher AS.

Shear stress imposed on the vessel walls and local disruption of elastic properties of the vessels can generate AS. This condition will affect the functional

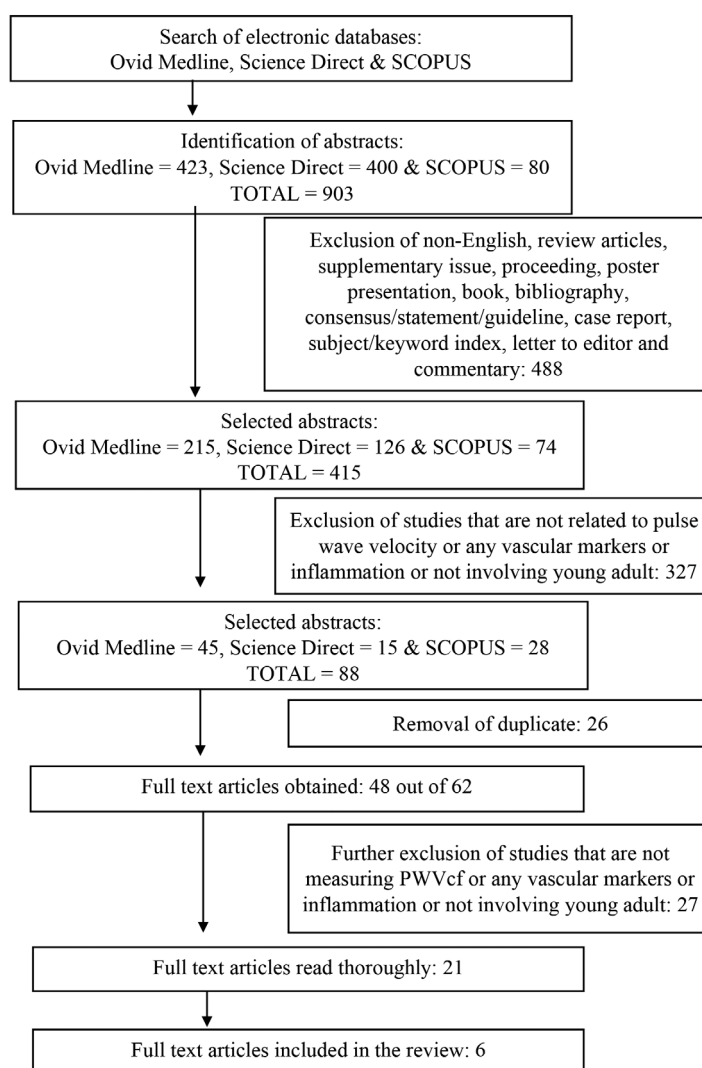


FIGURE 1. Flowchart of the selection process

TABLE 1. Summary of study included

Author (year)	Population (n)	Mean age (year)	Age range (year)	Male (%)	Distance of PWV (instrument)	Association of pulse wave velocity with other cardiovascular markers		
						Aix	CIMT	CRP
Aulie et al. (2014)	Juvenile idiopathic arthritis patients (87)	38.4	not mentioned	23	Carotid-Femoral (SphygmoCor)	not measured	not measured	$\beta=0.001^{\#}$ , $p=0.877$ during 29 years of disease activity (not significant)
Cooper et al. (2012)	Normotensive obese & overweight subjects (344)	37.9	20-45	23	Carotid-Femoral & Heart-Femoral (VP2000)	not measured	not measured	$R^2=0.14^*$ ; $p<0.02$ (significant correlation)
Ozturk et al. (2015a)	Non-alcoholic fatty liver disease patient (102)	not mentioned	20-40	100	Carotid-Femoral (Arteriograph)	not measured	not measured	$r = 0.279^{\ddagger}$ ; $p=0.016$ (significant correlation)
Ozturk et al. (2015b)	Inflammatory bowel disease patients (162)	not mentioned	20-40	100	Carotid-Femoral (Arteriograph)	not measured	not measured	$r = 0.014^{\ddagger}$ ; $p=0.857$ (not significant)
Kerkhof et al. (2012)	Healthy subjects (406)	$20.8 \pm 1.7$	18-24	43.1	Carotid-Femoral (SphygmoCor)	not measured	$\beta=-0.62$ , adj. $R^2=0.172$ , $p=0.259$ (not significant)	not measured

<sup>#</sup>CRP is measured by area under the curve, <sup>\*</sup>both CRP and PWVhrf are log transformed, <sup>‡</sup>correlation with hs-CRP

properties of large arteries and marks the early stage of atherosclerosis. PWVcf, a gold-standard marker of AS, has been established as an independent and important predictor of future cardiovascular events in patients with diabetes, renal failure and hypertension (Blacher et al. 1999; Cruickshank et al. 2002; Laurent et al. 2001). Additionally, it also applies to the general population and apparently healthy subjects (Mattace-Raso et al. 2006; Willum-Hansen et al. 2006).

The literature search found that only one study reported the correlation between PWVcf and CIMT (Kerkhof et al. 2012). However, the correlation is not significant. The scarceness of this association might be due to our narrow focus on young population between 18-45 years old. In older population, various study showed significant association between both markers. For instance, a study conducted on 320 subjects, mean age  $57.11 \pm 15.47$  years, with various degrees of abnormality in cardiac structure and function showed a significant correlation between PWVcf with CIMT and AIX (Yu et al. 2008). In older hypertensive patients, aortic PWV (aPWV) significantly associated with CIMT and age, signifies the role of aging in AS (Geraci et al. 2016). It has been shown that aging triggers the gradual replacement of the degenerated elastic fibres with collagenous fibres. This leads to structural change of the vessel and increases AS and eventually increases PWV. Besides that, any structural changes that occur at an early stage may develop slowly and might show a non-significant association (Aminuddin et al. 2014).

Different property of vessel measurement might contribute to the absence of significant correlation between PWVcf and CIMT. PWV is related to vessel function while CIMT signify the vessel structural change. AS, measured by PWV, occurs when there is imbalance of collagen and elastin in the arterial wall. This imbalance leads to overproduction of abnormal collagen and diminished quantities of normal elastin, which contribute to vascular stiffness. In addition, change in elastin production and molecular repair mechanisms further promote the loss of vascular elasticity. Formation of advanced glycation end products collagen (AGES-link collagen) also stimulates stress signaling and inflammatory responses. In turn, matrix metalloproteases (MMPs) will be activated and cause elastin and collagen breakdown. This will eventually lead to vascular stiffness (Wallace et al. 2005; Ziemann et al. 2005). On the other hand, CIMT evaluates the thickness of tunica media and intima layer of arterial wall. Mainly, vessel walls are composed of tunica intima, media and adventitia. Damage on the intima surface due to hyperlipidemia attracts migration of smooth muscle cells (SMCs) into the intima layer. Excessive proliferation of SMCs and apoptosis suppression resulting in arterial wall fibrosis and thickens the luminal stenosis via synthesis of extracellular matrix and lipid deposition (Ross & Glomset 1973). Thickening of this intima-media layer of carotid artery may reflect early stage of atherosclerosis (Nafikudin et al. 2003).

AIX is a measurement of wave reflection to the aortic waveform. It typically refers to the ratio or percentage of pressure variations in the vascular bed (Sohani et al. 2012). The value of AIX depends on PWV and reflected pressure wave magnitude and site. This will provide a valuation of large artery (systemic) stiffness (Safar & London 2000). In contrast, the reflected waveform timing provides aPWV estimation and thus aortic stiffness (Marchais et al. 1993; Murgu et al. 1980). Due to various factors affecting AIX such as peripheral vasodilation, height and heart rate (Laurent et al. 2007), the association between PWV and AIX may not be straightforward and their use in determining the vascular stiffness may have different outcome. For example, some studies showed both PWV and AIX increased in subjects with risk factors (Ghiadoni et al. 2008; Pietri et al. 2006), while some studies observed an increased in PWV but not AIX (Aminuddin et al. 2013; Vyssoulis et al. 2010). This review showed that there was limited study carried out to determine the association between PWV and AIX in the young subjects. Future studies should be conducted to address this issue.

In term of association with inflammation, we selected CRP or hsCRP as our marker of inflammation. CRP has been found as an independent predictor both in CVD patients (Liuzzo et al. 1994; Nuruddin et al. 2016; Ridker et al. 1998) and healthy individuals (Hamidon et al. 2004; Ridker et al. 2002, 1997). From this investigation, five studies showed correlation between PWVcf and CRP or hsCRP, but only two gave significant correlations (Aulie et al. 2014; Cooper et al. 2012; Ozturk et al. 2015a, 2015b). CRP has direct pro-inflammatory effects on human endothelial cells and can induce endothelial dysfunction (Venugopal et al. 2002). Study by McEniery et al. (2004) demonstrates a positive correlation between aPWV and CRP in healthy individuals with age range of 16 to 83 years old. High level of CRP may increase AS via several mechanisms: Inflammation promotes endothelial dysfunction (Jadhav & Kadam 2005; Kharbanda et al. 2002); inflammation increases MMPs level and cause elastin and collagen breakdown (Wallace et al. 2005; Ziemann et al. 2005); and in relation to insulin resistance, inflammation increases the production of AGES-link collagen in the arterial wall which is stiffer than normal collagen (Festa et al. 2000; Ramasamy et al. 2010). In the young, PWV is weakly related to CRP, which may be due to young age, where vascular structure is still intact and any vascular alteration may take longer time to change.

## CONCLUSION

Lack and weak association between PWV and other vascular markers and inflammation may suggest that these vascular markers have their own property in assessing vascular status. Thus, these markers should be measured independently for comprehensive assessment of future CVD risk. However, this conclusion is based on limited number of papers and future studies should be conducted to address these issues.

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Received: 30 March 2018

Accepted: 20 June 2018