



Augmentation Index in Connective Tissue Diseases

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Atherosclerosis and its complications are often reported in patients with connective tissue diseases (CTDs) showing chronic inflammation. Traditional cardiovascular risk factors do not account for accelerated atherosclerosis in patients with CTDs. Inflammation, although non-traditional, is considered one of the risk factors for endothelial dysfunction, atrial stiffness, and atherosclerosis. Therefore, it is essential to evaluate other risk factors for cardiovascular disease (CVD) in patients with CTDs. The interest in pulse wave analysis (PWA) is growing because of its predictive value for CVD. The arterial pressure waveform is a composite of an incidental wave produced by a ventricular contraction and a reflected wave. The wave reflection can be quantified using the augmentation index (AIx); it is defined as the difference between the inflection and peak systolic pressure, and expressed as a percentage of the pulse pressure. The PWA is represented by AIx. Risk score systems, such as the Framingham scoring system, were correlated with AIx. Many studies have analyzed the ability of the AIx to predict the CAD severity in the general population. In patients with CTDs, the AIx was found to increase compared to a healthy control group. The AIx was related to the activity of CTDs. The treatment for inflammation appeared to improve the AIx in some CTDs. Although more studies will be needed to obtain conclusive evidence, AIx is expected to be a prognostic factor or a risk factor for CVD in patients with CTDs. (**J Rheum Dis 2017;24:185-191**)

Key Words. Pulse wave analysis, Connective tissue diseases, Atherosclerosis

INTRODUCTION

In cardiology, the traditional risk factors for atherosclerosis are age, hypertension, diabetes, obesity, hyperlipidemia, smoking, and family history [1]. The development of atherosclerosis starts with endothelial dysfunction; the classic causes are shear stress or mechanical fatigue by cyclic strain. These aggravate arterial stiffness, elevate blood pressure, and cause endothelial dysfunction [2]. Inflammatory conditions can also cause endothelial dysfunction, atrial stiffness, and atherosclerosis [3,4]. Thus, it is not surprising that atherosclerosis and its complications are often reported in patients with connective tissue diseases (CTDs) showing chronic inflammation. The Framingham risk factors as well as nontraditional, inflammatory conditions, have been implicated in atherosclerosis and its complications underlying CTDs [5].

Therefore, it is necessary to evaluate other risk factors of cardiovascular disease (CVD). Arterial stiffness, common carotid artery intima-media thickness (CCA-IMT), pulse wave velocity (PWV), pulse wave analysis (PWA) of central aortic pressure, and brachial arterial flow-mediated vasodilation have recently been regarded as risk factors and prognostic factors of CVD [6]. Among these, PWV is introduced as an asymptomatic organ damaging factor in the European Hypertension Guidelines [7]. PWV is the velocity at which the arterial pulse propagates through the circulatory system. Recently, PWA of central aortic pressure has gained attention because of its predictive value for CVD and the differential effects of anti-hypertensive drugs, compared with brachial pressure [8,9]. The arterial pressure waveform is a composite of the incidental wave created by ventricular contraction and a reflected wave. The phenomenon of wave reflection can

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be quantified through the augmentation index (AIx), which is defined as the difference between the inflection and peak systolic pressures, and is expressed as a percentage of the pulse pressure. Hence, PWA is represented by AIx [10]. In CTDs, the evaluation and explanation of the augmentation index are rarely done. Therefore, we aimed to determine the AIx in CTDs, which is predicted to increase arterial stiffness, and determine its clinical applications.

MAIN SUBJECTS

Cardiovascular diseases in connective tissue diseases

Systemic lupus erythematosus (SLE), which occurs mainly in young women, is a chronic inflammatory disease. However, several patients with SLE have atherosclerosis and, as a result, have increased morbidity and mortality due to CVD [11]. In general, CVD does not occur in young women. However, the incidence of myocardial infarction (MI) is 5 times higher in patients with SLE as in the general population, and the age-specific incidence in young women with SLE is increased to as much as 50 times [12]. Two large cross-sectional cohort studies of patients with systemic sclerosis (SSC) demonstrated that they had a higher risk of coronary artery diseases (CAD) than the general population. The Australian Scleroderma Cohort Study investigated the prevalence of CAD, including acute myocardial infarction (AMI), percutaneous coronary intervention, coronary artery bypass grafting, and cardiovascular (CV) risk factors in a wide cohort of patients with SSC. The prevalence of CAD increased by approximately 3 times in the SSC group as compared to the control group after adjusting for diabetes mellitus, obesity, and hypercholesterolemia [13]. A more recent study provided similar evidence that SSC is associated with an increased risk of developing MI, stroke, and peripheral vascular disease. The incidence of MI, stroke, and peripheral vascular disease in patients with SSC were 1.8, 2.6, and 4.4 times, respectively, as compared to control group individuals, after adjustment for CV risk factors, including body mass index (BMI), smoking, hypertension, diabetes, hyperlipidemia, and nonsteroidal anti-inflammatory drug and oral glucocorticoid use. Youssef et al. [14] showed that the prevalence of peripheral macrovascular disease increased by approximately 6 times in patients with limited SSC as compared to control group individuals. In patients with rheumatoid arthritis (RA),

Pujades-Rodriguez et al. [15] showed a 1.4~2.3 times increase in the risk of MI and cardiac death after adjustment for CV risk factors. Interestingly, Aviña-Zubieta et al. [16] suggested that glucocorticoid use is not associated with an increased risk of cerebrovascular accidents in RA. Many studies have shown that gout, another major form of arthritis, is associated with traditional CV risk factors such as obesity, diabetes, and hypertension [17-19]. In recent studies, both hyperuricemia and gout have been shown to be independent risk factors for cardiovascular disease [20,21]. In a recent case-control study of 2,277 AMI patients and 4,849 matched controls, allopurinol use was associated with a 20% decreased risk of AMI after adjustment for traditional risk factors [22]. According to a meta-analysis of the major types of arthritis and AMI, AMI was significantly increased in RA, gout, psoriatic arthritis, and osteoarthritis after adjustment for age and sex. Traditional CV risk factors were more prevalent in all types of arthritis. However, interestingly, the risk of AMI still increased in RA, gout, and psoriatic arthritis after adjustment for traditional CV risk factors [23].

Inflammation and cardiovascular disease in connective tissue diseases

The traditional cardiovascular risk factors do not account for accelerated atherosclerosis in SLE [17]. Additionally, the increased risk of CV events in SSC may depend on both atherosclerosis and non-atherosclerotic factors, such as vasospasm, vasculitis, and thrombosis [24]. These findings have raised questions regarding the role of chronic inflammation or other risk factors. In particular, it has been noted that inflammation associated with CTDs can exacerbate atherosclerosis. Recently, a part of the pathogenesis in endothelial dysfunction, atrial stiffness, and atherosclerosis have been explained by inflammation in the general population [3,4]. Endothelial dysfunction is described as oxidative stress resulting in reactive oxygen species (ROS) production. ROS oxidizes low-density lipoprotein (LDL), and the subsequent consumption of oxidized LDL by monocytes is what leads to the formation of atherogenic foam cells [25,26]. Although foam cells have not been studied in CTDs, circulating ox-LDL/ β 2-glycoprotein 1 complexes and anti-ox-LDL antibodies may be elevated in CTDs [27]. SSC patients also have higher levels of atherogenic pro-inflammatory high-density lipoprotein and lipoprotein (a) [24,28]. Uric acid also generates ROS species, leads to inflammation, and promotes endothelial dysfunction and proliferation

[29]. Therefore, it is unreasonable to be able to predict atherosclerosis and CVD in CTDs, which are presented as chronic inflammatory conditions according to traditional risk factors. The study of new risk factors and early detection of atherosclerosis are very important.

Pulse wave analysis

The central pulse wave is composed of an early incident wave caused by a left ventricular ejection and a reflected wave from the periphery (Figure 1). As arterial stiffness increases, the velocity of the early incident wave and late reflected wave increase. If the reflected wave arrives at the central aorta early, the central aortic systolic blood pressure (SBP) rises. This increased pressure is called augment pressure and its percentage of the pulse pressure is called the AIx. AIx is influenced by heart rates. Thus, the AIx@75 (expressed as the AIx corrected for a heart rate of 75 bpm) is defined as the standard value [10]. AIx by an invasive study presents technical problems because the selection of inflection point is not easy. In principle, the time of peak flow is the time of inflection point, because the inflection point indicates the beginning upstroke of the reflected wave. Clinically, it is very difficult and expensive to measure flow and pressure simultaneously (Figure 2). Recently, SphygmoCor (Atcor Medical,

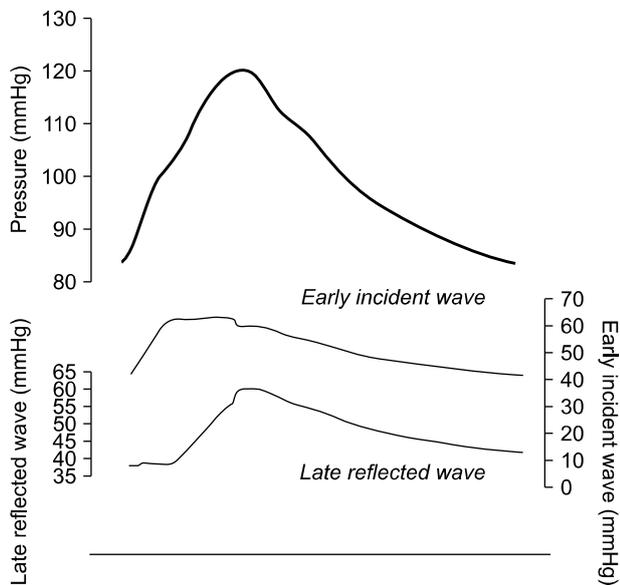


Figure 1. Central aortic pressure using SphygmoCor (Atcor Medical, Sydney, Australia) by applanating the left radial artery was separated into early incident wave and late reflected wave through the formula by central aortic flow using a Vivid 7 system (GE Vingmed, Horten, Norway) with a 3.5 MHz transducer.

Sydney, Australia) was used for AIx determination after applanation of the left radial artery. This device finds an inflection point mathematically and mechanically, following an analysis of the relationship between the time at which the second zero crosses the fourth derivative and the peak flow time, using the formula: $y=0.91+1.31x$; $R=0.75$, where x is the time at which the second zero crosses the fourth derivative, and y is the peak flow time. Therefore, PWA (including the AIx and related parameters) can be done easily, efficiently, and safely using this method [30].

Classically clinical implication of pulse wave analysis

Many studies have analyzed the ability of the AIx to predict CAD severity using PWA. Weber et al. [9] showed that patients with multi-vessel CAD had high AIx values. Choi et al. [31] presented that the AIx@75 seemed to reflect the clinical severity of CAD and was associated with revascularization of the coronary artery in patients, and that it was independent of a high Framingham risk score. Risk score systems, such as the Framingham scoring system, were developed to predict CVD in patients with atherosclerosis. Therefore, higher risk scores are correlated to more frequent atherosclerotic events. Thus, a correlation is expected between these risk score systems and PWA, as proven in many studies [9,32,33]. The relationship between cardiac ischemia and PWA can be explained as an increased AIx, resulting from an increased central SBP (increasing myocardial oxygen demand), and a decreased central diastolic blood pressure (disturbed coro-

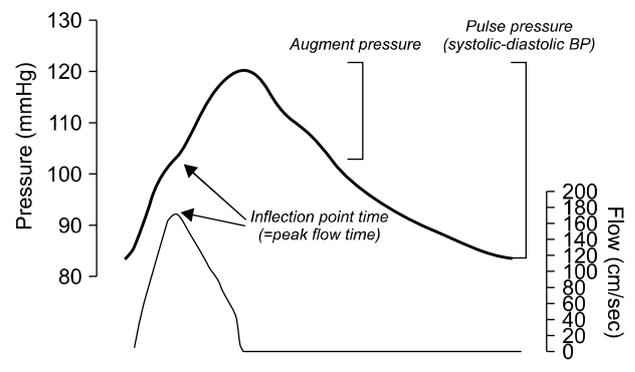


Figure 2. Augmentation index is defined as the ratio of augment pressure and pulse pressure and is usually expressed as a percentage. The inflection point indicates the beginning upstroke of the reflected wave. The inflection point time is equal to the peak flow time.

nary blood flow), contributing to an imbalance between oxygen demand and supply; these factors occur due to ischemia [10].

Augmentation index and markers of arterial stiffness in CTDs

Surrogate markers of arterial stiffness, atherosclerosis, and cardiovascular disease, such as AIx, PWV, and common carotid artery intima-media thickness (CCA-IMT), were found to be increased in patients with CTDs as compared with the control group individuals [34-38]. Unfortunately, there are few reports of these markers that predict CVD in the CTDs in literature. However, some studies that have investigated the relationship between arterial stiffness and CTDs.

In SLE, patients with higher inflammation levels had higher AIx [39]. Carotid AIx was correlated with disease activity after adjustment for age, BMI, and blood pressure [40]. PWV has been established as a reliable parameter of asymptomatic organ damage [41]. The study by Sacre et al. is interesting because it relied upon adjustments from the Framingham score. PWV was faster in SLE patients than in control individuals [36]. According to the meta-analysis, patients with SLE showed an increased prevalence of carotid plaques and a higher CCA-IMT than individuals in the control group [42].

In systemic sclerosis, AIx was higher in SSC than in the age- and pressure-matched control group. However, PWV was not different between the groups [43]. The patients who had pulmonary hypertension had higher AIx than those without pulmonary hypertension [38]. Pulmonary arterial hypertension is a poor prognosis factor for SSC. In some studies, PWV was correlated with anti-Scl-70 antibodies and anticentromere antibodies [44]. Choi et al. [45] showed that CCA-IMT was significantly thicker in SSC than in SLE after adjusting for risk factors. However, AIx values showed no difference in both groups.

In a meta-analysis for RA, AIx and PWV were increased in the patients with a more severe inflammatory status [35]. Tumor necrosis factor alpha (TNF- α) antagonists reduced the AIx, but this improvement was influenced by the clinical response and age. On the other hand, PWV independently improved after TNF- α [46].

Clinically, hyperuricemia or gout is often associated with hypertension and metabolic syndrome; notably, these are CVD risk factors. Therefore, hyperuricemia or gout is related to CVD [47]. Furthermore, gout therapy,

such as allopurinol, may be associated with a reduced risk of MI and a reduced AIx [22,48]. Therefore, AIx is expected to increase in patients with hyperuricemia or gout. In patients with hypertensive chronic kidney disease, uric acid level was associated with only AIx@75, but not with PWV [49]. However, in newly diagnosed and untreated hypertensive patients, uric acid level was associated with PWV but not with AIx [50,51]. This phenomenon was also observed in patients in the active phase of Adaman-tiades-Behçet's disease. This difference can be explained by the fact that inflammation in acute phase causes the peripheral vessel to dilate, thereby reducing the reflected waves in the central artery. This process also reduces AIx despite increased arterial stiffness [52]. In other words, AIx can be affected by the phases of CTDs.

Treatment to reduce augmentation index

The differential effect of antihypertensive medication on the AIx and clinical outcomes is well known in cardiology. Despite a similar effect on brachial BP, calcium channel blocker (CCB) \pm angiotensin-converting enzyme inhibitor (ACEi)-based therapy reduced AIx better than beta-blocker (BB) \pm diuretic-based therapy. CCB \pm ACEi-based therapy significantly reduced total coronary events, cardiovascular death, and stroke, compared with BB \pm diuretic-based therapy [53]. CCB reduced AIx the most, followed by diuretics and ACEi, in order. However, BB did not affect AIx [54]. Atorvastatin therapy also reduced AIx in patients with hypertension, hypercholesterolemia, and RA [55,56]. In SLE, there has been little research on treatment to reduce the AIx. N-acetylcysteine and atorvastatin reduced the stiffness index and reflection index, which are similar to the AIx [55]. Regular exercise did not reduce the AIx [57]. In SSC, oral endothelin-receptor antagonists improved AIx and pulmonary hypertension [58]. In RA, TNF- α antagonists reduced the AIx. However, the clinical response and age influenced this improvement [46]. In patients with hyperuricemia or gout, allopurinol reduced the AIx and PWV [48]. Interestingly, allopurinol improved PWV in chronic kidney disease after adjusting for risk factors and use of ACEi or angiotensin II receptor blockers [59]. One study suggested that allopurinol may reduce the risk of MI [22].

AIx is a parameter with many limitations. First, it is influenced by heart rate. Thus, AIx@75 is defined as the standard value [10]. Second, it is influenced by ventricular ejection patterns and vasodilatory agents [60]. Therefore, AIx can be considered a risk factor before my-

ocardial infarction, heart failure, and treatment of hypertension. Third, it is influenced by the height and leg length of the patient [61]. This means that sex can be a confounding factor. Thus, it is necessary to evaluate the normal value according to the sex and height.

CONCLUSION

CTDs were associated with CVD independent of traditional risk factors because of inflammation. Pulse wave analysis-related metrics such as AIx, can predict CVD in the general population. AIx was found to be increased in patients with CTDs as compared with that in healthy control group individuals. Additionally, AIx was related to the activity of CTDs. The treatment of inflammation seemed to improve the AIx in some CTDs. Therefore, although more studies are needed, AIx is expected to act as a prognostic factor or a risk factor for CVD in patients with CTDs.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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