Angiology: Open Access
ISSN: 2329-9495

Sun et al., Angiol 2016, 4:1
DOI: 10.4172/2329-9495.1000173

Research Article Open Access

Invasive Aortic Augmentation Index Could Predict the Adverse Events in Patients without Established Coronary Heart Disease

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Received date: February 18, 2016; **Accepted date:** March 16, 2016; **Published date:** March 18, 2016

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Abstract

Background: Previous studies had shown that an association between the arterial stiffness and cardiovascular events. Due to the invasive nature, fewer studies focus on invasive arterial stiffness in predicting adverse outcome. We examined the invasive predictive roles of pulsatile variables in patients without established coronary heart disease.

Method: Ascending aortic and radial artery waveforms were obtained during the angiography in 325 without severe coronary stenosis (<50%) from January, 2012 to October 2013 in An Zhen Hospital. These patients were followed for the cardiovascular adverse events during a median 2 years (inter-quartile range=0.6-3.2).

Results: During the followup, adverse events occurred in 36 (11%), after the adjustment of confounders, aortic augmentation index @75 remain the independent risks in predicting the clinical events. In Kaplan-Meier curve analysis, a 2 year cardiovascular event rate was 14% in patients with central aortic augmentation index @75 ≥ 0.15 vs. 4% in those with central aortic augmentation index @75<0.15 (Log Rank=0.045). The aortic augmentation index @75 (AUC 0.75) demonstrated a significant better predictive power compared with radial AIx@75 (AUC 0.54, P=0.01) and radial PP (AUC 0.52, P=0.006) but not for aortic PP (AUC 0.68, P=0.16).

Conclusion: Arterial stiffness assessed by the invasive catheter is associated with increasing risk for the adverse events. The central pulsatile parameter appeared to be a more efficient predictor than the peripheral arterial stiffness in patients without known artery heart disease.

Keywords: Arterial stiffness; Invasive; Adverse outcomes

Introduction

It had been established that arterial stiffness was an independently predictor for the development of cardiovascular (CV) events and all-cause mortality [1,2]. Many cross-sectional studies had established that central hemodynamics indices, markers of arterial stiffness, could predict cardiovascular disease better than peripheral arteries, mainly due to its more accurate representation of loading conditions on the heart and coronary and cerebral vessels [3-6]. Central aortic pressure waveforms are believed now to be accurately estimated through a mathematical transformation of the radial waveforms obtained by the noninvasive applanation tonometry [7]. However, a variety of multiple factors influence the circulation, which must be taken into account when applying the results of noninvasive testing utilizing these methods as a quantitative indicator of aortic stiffness [8], the accuracy of this noninvasive approach in determining the arterial stiffness has been also dispute [9], measuring central aortic pressure and related parameters could become an interesting important part of the routine clinical assessment of cardiovascular risk and related treatment effects [10]. Far fewer reports focused on the invasive pressure waveforms and its impact on adverse prognosis in clinical setting.

The purpose of this study was to examine whether the arterial stiffness of different segment, as detected by the invasive catheter during the angiography, may play different a role in predicting the adverse events in patients without angiographically established lumen stenosis.

Methods

Subjects

732 consecutive symptomatic inpatients (312 female) were screened with unexplained chest pain undergoing a diagnostic coronary artery angiogram via radial approach between January, 2005 and October 2013 in AnZhen Hospital. 12 patients were excluded by recent significant head trauma, intracranial bleeding, pheochromocytoma, severe liver and kidney disease, myocarditis hypertrophic cardiomyopathy, 304 patients with angiography-established lumen stenosis (>50% in diameter) undergoing percutaneous transluminal intervention (PCI) and coronary artery bypass graft surgery (CABG) were also excluded, 32 refused to participate in and 59 patients lost followup. We enrolled 325 patients in the study (Figure 1). The baseline characteristics of enrolled patients are detailed in Table 1. All the procedure received approval from the institution ethics committee, and participants provided informed consent.

Pressure waveforms acquisition

The invasive blood waveforms were recorded invasively via the 5F fluid-filled catheter positioned in the ascending aorta (fluoroscopically confirmed) and via the peripheral radial sheath. Only waveforms that

were technically adequate on visual inspection were included in the analysis; waveform analysis was performed manually. The merging point of the incident and the reflected wave (inflection point) was identified on the aortic and radial pressure waveform. The first and second systolic peaks (P1 and P2) of the aortic pressure waveform were analyzed. When the inflection point could not be identified (occurred in 31% of cases in the present study), an augmentation pressure of zero was assigned [11]. AP was calculated as the difference between the second and first systolic peaks (P2–P1). AIx was defined as AP expressed as a percentage of PP. In order to eliminate the heart rate effect, we translated the AIx at a given heart rate into an AIx@75 according to study previously described [12].

Variables	Values
Age, y (± SD)	55 ± 12
Gender (F, %)	45
Heart rate (bpm)	78 ± 15
Hypertension, %	70%
Diabetes mellitus	9%
AF/Af (%)	4%
Family history	12%
Current smoking, %	80
Hyperlipidemia, %	65%
Aortic PP (mm Hg)	56 ± 21
Aortic AIx @75%	21 ± 9
Radial PP (mm Hg)	69 ± 28
Radial AIx @75%	17 ± 10
Discharge medicine	
Aspirin, %	95
β-blocker, %	86
Statins, %	75
ACEI, %	56
Adverse outcome	36
Death (HF, sudden death & shock)	5
Rental failure	4
Stroke or TIA	15
Cardiac hospitalization	5
Onset AF/Af	7

Table 1: Baseline characteristics of 325 patients in the enrolled patients. ACEI: Angiotensin-converting Enzyme; AF/Af: Atrial Fibrillation/ Atrial Flutter; HF: Heart Failure. Invasive BP waveforms were collected supine from the ascending aortic artery when the angiograms were performed.

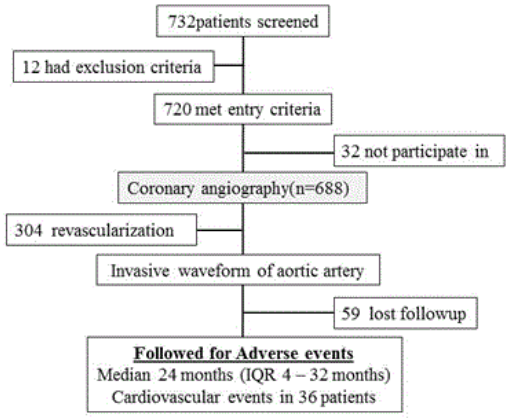


Figure 1: Study flow.

Assessment of clinical characteristics and follow up

The clinical data, including age, sex, symptom, stress triggers, concomitant diseases, discharged medicine and echocardiograms parameters were collected from the clinical system at AnZhen Hospital. Diabetes was defined as self-reported history of diabetes mellitus, diabetes medication use, or a fasting glucose level of 126 mg/dL or greater. Demographics, medical history, and anthropometric and laboratory data for the present study were taken from the first examination. Current smoking was defined as having smoked a cigarette in the last 30 days. Use of antihypertensive and other medications was based on review of prescribed medication containers. Resting blood pressure was measured 3 times in the seated position and the average of the second and third readings was recorded. Hypertension was defined as a systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or use of medication prescribed for hypertension. Body mass index was calculated as weight in kilograms divided by height in meters squared. Total cholesterol and high-density lipoprotein (HDL) cholesterol were measured from blood samples obtained after a 12-hour fast.

An analysis of the patient medical records was performed to detect the occurrence of any of the following adverse events (1) death from heart failure, arrest or shock; (2) renal failure; (3) stroke or TIA; (4) cardiac hospitalization; (5) onset AF/Af death. Death certificates were reviewed to verify the date and cause of deaths occurring during the follow-up period.

Statistical Analysis

Continuous variables were expressed as means and compared by use of the unpaired Student t test or Wilcoxon rank test as appropriate. Categorical variables were expressed as percentages and compared by use of the Fisher exact test or χ^2 tests as appropriate. Pulsatile hemodynamic variables that showed significant relation with events in multivariate Cox model were evaluated further. P-value was adjusted for the multiple tests performed to identify the optimal cutoff point. We also estimated the improvement, using the methods of Hanley and McNeil [13], in discrimination by comparing the area under the receiver operator characteristic curve (AUC) in different models. ROC curves were developed using a probability-weighted Cox model.

Cumulative probability curves were constructed by using Kaplan-Meier method with participants groups segregated according to the cut-off points. Stepwise forward selection was used to create the final model. All statistical tests were 2 sided. A value of P<0.05 was set a priori and considered statistically significant. All statistical analyses were performed with the Statistical Package for Social Sciences version 11.5 for Windows (SPSS, Chicago, IL).

Results

325 patients undergoing the angiogram according to the inclusion criteria in AnZhen Hospital were enrolled. The mean (SD) age was 55 ± 12 years. Of the participants, 45% were female, 70% had hypertension, 9% has diabetes and 4 % had atrial fibrillation (Table 1). In the present study, the mean PPs were 56 ± 21 mm Hg and 69 ± 28 mm Hg from aortic artery and radial artery, respectively. The mean AIx@75 was (21 ± 9)% and (17 ± 10)% from aortic artery and radial artery, respectively.

Patients were followed for a mean 2.0 year (median=1.6, IQR 0.6, 3.0) during which 36 patients had an adverse events. Adverse events as defined (cardiovascular death/MI/cardiovascular hospitalization/stoke/TIA). During the followup, 5 of cardiac death (including congestive heart failure, sudden death cardiac arrest and shock), 4 of renal failure, 15 patients of stoke or TIA and 7 of onset AF/Af, 5 of hospitalization for the suspected myocardial pectoris.

Cox proportional hazard models for individual clinical and pulsatile parameter were presented in Table 2. In model that adjusted for the age, gender, DM, current smoking, radial AIx@75, aortic AIx@75 and discharge medication, aortic AIx@75 was associated with the increased risks for the clinical events with hazard ratios (HR) of 1.23, 95% CI, 1.01 to 1.70, P=0.037.

	Univariate model		Multivariate model	
	HR (95%)	P value	HR (95%)	P value
Age	0.96 (0.62-1.04)	0.86	0.98 (0.68-1.16)	0.76
Gender(F/M)	0.89 (0.70-1.60)	0.36	0.80 (0.65-1.54)	0.42
EF (%) per 10% increase	1.31 (0.80-2.10)	0.28		
HR (bp/m) per 10 increase	1.05 (0.98-1.24)	0.6		
DM	1.09 (1.02-5.30)	0.04		
Current smoking				
HNT	1.05 (0.99-1.20)	0.5		
Hyperlipidemia	0.58 (0.40-1.20)	0.41		
Family history	1.25 (0.80-1.96)	0.3		
AF/Af	1.55 (0.89-3.25)	0.28		
Aortic PP	1.01 (0.98-1.06)	0.79		
Aortic AIx@75	1.68 (1.05-2.35)	0.014	1.23(1.01-1.70)	0.037
Radial PP	1.02 (1.01-1.05)	0.01		
Radial AIx@75	1.46 (1.01-2.88)	0.035		
Discharge Medicine				
ASA	1.02 (0.98-1.04)	0.01		
Clopidogrel	2.87 (1.90-5.21)	0.02		
β-blocker	1.56 (0.85-2.16)	0.25		
Statin	1.40 (0.90-1.80)	0.65		

Table 2: Univariate (age and sex adjusted) and multivariable hazard ratio analysis.
EF: Ejection Fraction; AF/Af: Atrial Fibrillation/Atrial Flutter; ASA: Aspirin; DM: Diabetes Mellitus; HNT: Hypertension

When stratified by the optimal cut-off point (Figure 2), the adverse events rate was 14% in patients with Aix ≥ 0.15 vs. 4% of patients with AIx@75<0.15 (P=0.045) in the Kaplan-Meier survival curves (Figure 3). The AUC analysis showed in Figure 4, the discriminatory powers of AUC to distinguish the clinical events artery stiff parameters for the aortic AIx@75, radial AIx@75, and aortic PP and radial PP were 0.75, 0.54, 0.68 and 0.52, respectively. The aortic augmentation index @75 (AUC 0.75) demonstrated a significant better predictive power compared with radial AIx@75 (AUC 0.54, P=0.01) and radial PP (AUC 0.52, P=0.006) but not for aortic PP (AUC 0.68, P=0.16). The aortic PP (AUC 0.68) also demonstrated a significant better predictive power compared with radial AIx@75 (AUC 0.54, P=0.027) and radial PP (AUC 0.52, P=0.013).

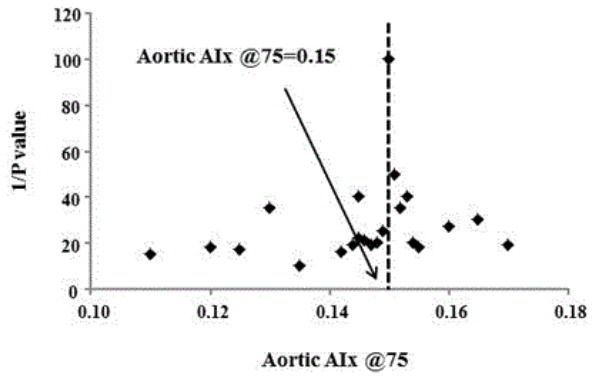


Figure 2: Plot of p-values vs. aortic AIx@75 cut-points in survival reliability analysis.

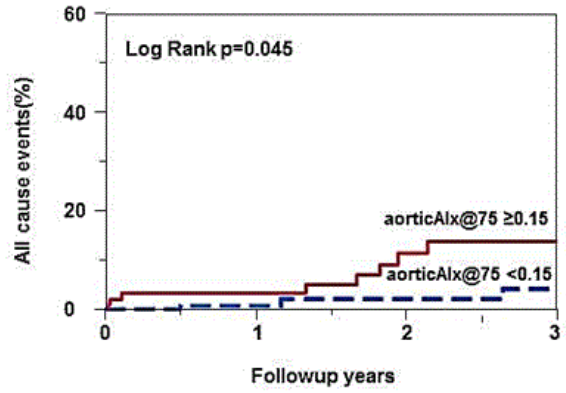
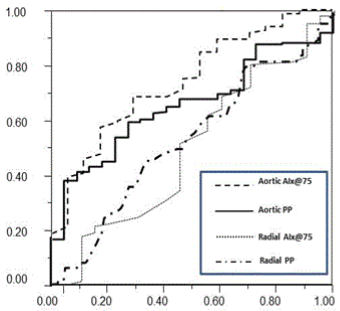


Figure 3: All cause events in patients according to the optimal AIx@75 cutoff point.



	Area under curve (95%confidence interval)
aortic AIx@75	0.75(0.66-0.84)
aortic PP	0.68(0.58-0.79)
radial AIx@75	0.54(0.48-0.68)
radial PP	0.52(0.47-0.70)

Figure 4: Receiver operating characteristic curves comparing the aortic AIx@75, radial artery AIx@75, aortic PP and radial artery PP in the enrolled patients.

Discussion

The main finding of present study was not only the central AIx@75 derived from the invasive catheter methods was independently associated with the adverse events during the followup, but also the clinical events were more frequent in patients with higher aortic AIx@75 (≥0.15) than those lower aortic AIx@75 (<0.15) . We also extended the finding that aortic AIx@75 and PP were more closely related to the clinical events than peripheral arterial stiffness parameter in the ROC analysis.

Over the 2 decades, the markers of noninvasive arterial stiffness have been established to be correlated with cardiovascular outcomes and as an emerging risk factor that provides prognostic information beyond standard stratification strategies involving hypertension, diabetes, obesity, dyslipidemia and smoking. The 2007 Guidelines for the Management of Arterial Hypertension of European Societies of Cardiology and of Hypertension included arterial stiffness as an intermediated end point in evaluating target organ damage [14]. However, due to the invasive nature, fewer studies emphasized on the events predictive value of invasive artery stiff parameters.

Previous studies [15-19] showed that central PP derived from the catheter predicted restenosis after percutaneous coronary intervention (PCI). Chirinos et al. [20] revealed that 10 mmHg increases in ascending aorta might be associated with an increase in all-cause mortality by 15%, but not independent relationship between brachial PP and CV risk during the coronary angiogram. In the ABPS (aortic blood pressure and survival), Jankowski et al. [21] first pointed out that independent predictive value of central PP (as measured invasively) in patients with CHD. To best of our knowledge, our study was the first to unveil the event predictive value of invasive artery stiff parameters. Theoretically, the arterial stiffness assessed by the invasive method could provide more information regarding to the risks of CV events compared to the noninvasive one.

Several reachers also have elucidated the relationship between arterial stiffness and organ damage. Hu et al. [22] observed that cardio-ankle vascular index (CAVI) ≥8.0 may be an optimal cutoff point for carotid arteriosclerosis prediction. Liu et al. [23] also revealed the relationship between the brachial-ankle pulse wave velocity (ba-PWA) and coronary heart disease and the cutoff point was at 15.64 m/s. We proved the predictive value of invasive aortic AIx@75 in patients without angiographically-established coronary heart disease. In the present study, we further noted that a 2 year cardiovascular event rate was 14% in patients with central AIx @75 ≥ 0.15 vs. 4% in those with central AIx@75<0.15 (Log Rank=0.045) in Kaplan-Meier curve analysis.

So far, data concerning the comparable predictive values between different arterial segments are still scanty. Chirino et al. [11] pointed out that aortic PP instead of brachial PP was an independent predictor of all-cause death. In the Strong Heart Study [24], central PP was more robust correlated with vascular hypertrophy, extent of atherosclerosis and cardiovascular events than branchial BP. Nevertheless, whether the aortic stiffness is more strongly related with cardiovascular events is still inconclusive, as Dart et al. [25] revealed that brachial PP had a greater prognostic impact than central PP. In our paper, we established that aortic AIx@75 demonstrated a significant better predictive power compared with radial AIx@75 and radial artery PP. The likely underlying explanation for the results might be the central indices represent the more accurate loading condition on the heart and coronary and cerebral vessel than the peripheral indices.

Limitations

There are some limitations in this article. Firstly, this is a retrospective study from a single center and our endpoints included not only the cardiac death but also onset of Af/AF, the ultimate results of using specific causes as end point are that “softness”. In addition, the exclusion of the unavoidable perfect overlapping of ascending arms of primary and reflected pressure waves will, in general, lead to the misestimation of the predictive value of arterial stiffness.

Conclusion

In conclusion, a higher central stiffness as derived by the invasive catheter was associated with higher adverse events in patients without known coronary heart disease during the followup. The invasive central stiffness could provide more predictable value than the peripheral arterial stiffness.

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