

The Predictive Value of Aortic Stiffness in Detection of Acute Pulmonary Edema in Patients with Acute Dyspnoea

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Abstract

Objective: Acute pulmonary edema (APE) is potentially fatal cause of acute respiratory distress, often a result of acute decompensate heart failure, a state with increased capillary pressure. The aim of this study was to find correlation between aortic stiffness and APE in patients with acute dyspnoea, measuring the carotid – femoral pulse wave velocity (PWV) by Doppler ultrasonography.

Methods: We conducted PWV estimation at 47 hospitalized patients with acute dyspnoea aged 57.8 ± 9.4 years. Seventeen of them had clinical signs of APE. The PWV was determined from time diversity propagation of the common carotid artery and femoral artery by Doppler ultrasound.

Results: The mean PWV of the patients with or without APE was: 10.4 ± 1.64 m/s vs. 8.54 ± 1.51 m/s, respectively ($p = 0.0005$). We found by receiver operating characteristic (ROC) a highest sensitivity of 76.47% and specificity of 80.0%, area under the ROC curve (AUC = 0.803, $p < 0.0001$) at PWV cut-off = 9.1 m/s in the prediction of APE by PWV; by the multiple backward regression analysis, we found $\beta_{st} = 0.1252$ ($p = 0.0010$) and $R^2 = 0.3413$. The positive and negative predictive values of PWV in prediction for APE are: 68.42% and 85.71%, respectively.

Conclusion: PWV as measure of arterial stiffness is predictor of left ventricle failure and APE in patients with acute dyspnoea, assessed by simple, indirect, reproducible, and noninvasive evaluation of regional arterial stiffness.

Keywords: Acute Pulmonary Edema; Aortic Stiffness; Pulse Wave Velocity; Doppler Ultrasonography; Systolic Dysfunction

Introduction

Cardiogenic pulmonary edema is a common and potentially fatal cause of acute respiratory distress. It is most often a result of acute decompensate heart failure (ADHF). ADHF is most commonly due to left ventricular systolic or diastolic dysfunction, with or without additional cardiac pathology, such as coronary artery disease or valve abnormalities [1]. The most common cause of acute pulmonary edema (APE) is increased capillary pressure. An increase in pulmonary venous pressure also increases pulmonary capillary pressure; this is most commonly caused by left ventricular failure. The reasons for this hemodynamic condition are coronary artery disease, cardiomyopathies, myocardial infarction, arrhythmias (atrial fibrillation, tachyarrhythmia absoluta), valve disease and excessive workload of the heart caused by hypertension [2].

Increases in left ventricular end-systolic and arterial elastance occur with aging, and may result in ventricular-vascular stiffening leading to heart failure with preserved ejection fraction [3]. Increased arterial stiffness [(measured as pulse wave velocity (PWV)) and augmentation index are independently associated with impaired systolic and diastolic dysfunction and with functional limitations [4,5]. Increased PWV independently predicts cardiovascular events in a healthy population. Arterial stiffening is a marker for increased cardiovascular risk, including myocardial infarction, heart failure, and total mortality, as well as stroke, dementia, and renal disease [6]. The PWV as a measure of arterial stiffness is strong independent predictor of cardiovascular mortality in general population patients [7] and chronic dialysis patients [8]. Increased stiffness of the aortic wall causes corresponding increase in aortic PWV. Arterial stiffness is often determined by measuring the velocity of pulse wave travel in a segment of vessel [9]. Increased aortic stiffness leads to premature return of reflected pressure wave from the peripheral arterioles, to return earlier to the heart and to boost (augment) pressure in late systole rather than in early diastole. This is the primary mechanism for increased pulse pressure, systolic hypertension, increased aortic diameter and left ventricular hypertrophy [10,11]. Arnold JMO, *et al.* (1999) estimated the interaction of the heart with the stiffness of systemic vasculature as a major determinant of net cardiovascular performance. They found that increased effective arterial stiffness favors the progression of myocardial systolic function impairment which leads to reduced left ventricular (LV) and-systolic elastance with progressive chronic congestive heart failure and LV failure with increased impedance to ventricular outflow [12,13].

Aim of the Study

The aim of this prospective observational study was to find correlation between aortic stiffness and APE in patients with acute dyspnoea measuring the aortic PWV by Doppler ultrasonography.

Materials and Methods

Patients

The patients were recruited from emergency ambulance of internal medicine with symptoms of difficulty in breathing, coughing, shortness of breath, paroxysmal nocturnal dyspnea, wheezing, palpitation and another different symptoms and signs of "fluid overload" auscultation manifested as end-inspiratory crackles. We estimated 47 hospitalized patients (38.29% or 18 female) with mean age 57.8 ± 9.4 years and their mean body mass index (BMI) = 27.79 ± 4.66 kg/m². Twenty six patients were smokers, 12 were diabetics and 23 were hypertensive. Severe hypertensive emergency (19 cases, 40.42%), fluid overload in chronic dialysis patients (5 cases, 10.63%), pericardial effusion with tamponade (2 cases, 4.25%), severe arrhythmias (5 cases, 10.63%), coronary anginosed syndrome (8 cases, 17.02%), dilatative cardiomyopathy (6 or 12.76%) and 2 cases (4.25%) of heart valve problems were the main reasons for this disease or overworked of left ventricle which is not able to pump enough of the blood that it receives from lungs. All participants signed an informed consent and the study was approved by the Ethics Committee of our institution.

We hospitalized 17 cases with dramatic clinical manifestation, life-threatening signs and oxygen reduction ($SpO_2 \leq 90\%$) at intensive care unit. We applied phlebotomy among all of them, after checking to be sure that the patients has normal hemoglobin and does not have a bleeding diathesis. Thirteen patients were improved markedly and did not required intubation. Pre-mean hematocrit was not change significantly in post phlebotomy ($p = 0.135$). All patients receiving phlebotomy survived. These 17 patients were treated in the intensive care unit because their life-threatening signs were designated as classic APE.

Assessment

We conducted PWV measurements in all 47 patients two days after the clinical stabilization of their health state. This was done to avoid any condition which may affect the PWV measurement (hypertension, arrhythmias, tachycardia, fluid overloading...) and not to harm of the patients health state. We used pulsed-Doppler ultrasound with linear array 10 MHz probe (General Electric Logiq 5 pro ultrasound, GE Medical System - USA, 4855W Electric Avenue, Milwaukee, WI 53215). We identified simultaneously both Doppler signals

[first from the left common carotid artery (CCA) and then from the left common femoral artery (CFA)] with electrocardiography (ECG). The Doppler waves were recorded transcutaneously at the base of the neck for left CCA and in the left groin for CFA. After that, we detect the delay or difference in arrival time of the flow wave at this two arterial locations (CCA and CFA). Anthropometric measure was made to find distance between this two sampling site, measured as straight line between the points on the body surface. PWV was determined as “foot to foot” velocity, and as the ratio of distance (D) to the transit time (TT). The “foot” of the wave is defined at the end of the diastole, where the rise of the CCA or CFA Doppler waveform begins. Dividing the distance “D” by time delay “TT” we got carotid-femoral PWV or [PWV (m/s) = D (m) TT (s)]. This method for carotid to femoral estimation of PWV has been previously described, reported and validated in many studies [14-16].

Six heart cycles measurements were taken and the average TT was calculated. The basic principle of PWV estimation is showed in figure 1. We needed only three parameters for foot-to-foot PWV calculating: T1 - time delay from R - wave of ECG to foot of the CCA wave, T2 - time delay from R - wave of ECG to foot of the CFA wave, and distance D measured from sternal notch(CCA) to the groin (CFA) [16]. Time diversity ΔT was calculated by the time differences T1 and T2 yielding the time delay: $TT = T2 - T1$ (Figure 1). The speed of pulse wave (V) is calculated by standard equation for the speed, $V = s/t$, hence, $PWV = D/TT$ (m/s).

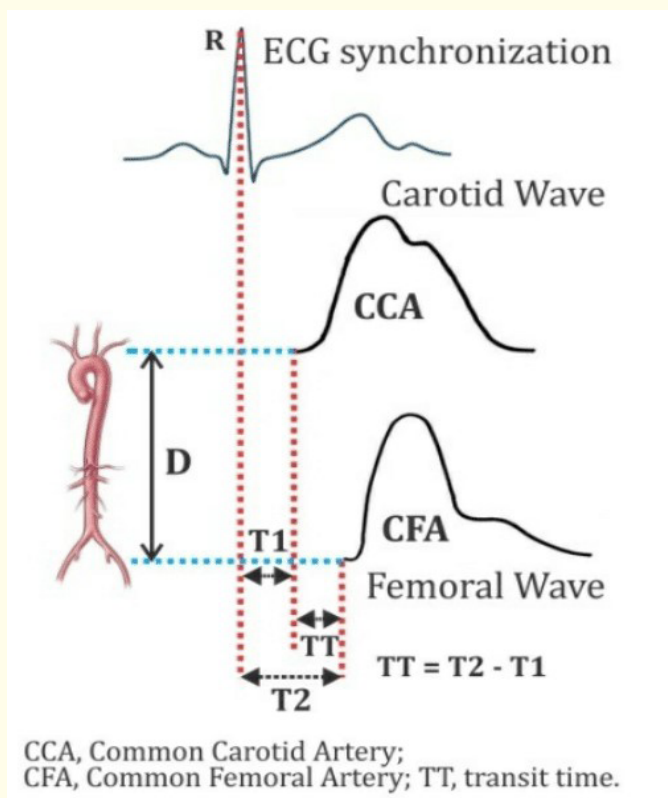


Figure 1: Pulse wave velocity determination by carotid-femoral time diversity.

Statistical analysis

The data were analyzed using MedCalc for Windows, version 15.8 (MedCalc Software, Ostend, Belgium). All results are expressed as means ± SD or percentage. Student’s t-test for unpaired data was used to compare the results from PWV (two-sided). Bivariate Pearson’s correlation analysis was used to find linear relationship between pairs of continuous variables and estimate the strength and direction of their relationships. Receiver operating characteristics (ROC) curve analysis were assessed to make distinction between patients with or without APE and to calculate the PWV cut-off point. Multiple backward regression analysis was used to predict outcome of a response variable, PWV in detection of APE. Predictive table with predictive value of PWV as risk for APE was made based of sensitivity, specificity and disease prevalence data.

Results

The mean PWV was 9.221 ± 1.790 m/s, 95% CI 8.696 to 9.747 m/s, median = 8.6 m/s, range 5.2 to 13.4 m/s, variance = 3.2061 and test or normal distribution = 0.5854.

Bivariate Pearson’s Correlation Analysis

The positive value of Pearson product-moment correlation coefficient (r) as the measure of the strength of linear dependence between two variables (pulmonary edema and one of the demographic characteristics of the patients or the aortic stiffness) indicated a significant positive correlation between APE and age (r = 0.471, p = 0.0008), APE and hypertension (r = 0.318, p = 0.029), APE and PWV (r = 0.508, p = 0.0003), but not significant correlation between APE with BMD, diabetes, sex and smoking status.

The Rank correlation coefficient between PWV and APE was $\rho = 0.505$ (p = 0.0003, 95% CI for $\rho = 0.254$ to 0.692).

Independent samples t-test

The mean PWV of the patients without APE was 8.54 ± 1.51 m/s vs. mean PWV = 10.4 ± 1.64 m/s in the patients with APE. There was a high statistical significance between the mean PWV in the group with or without pulmonary edema (p = 0.0005, assuming unequal variances, test statistic t = 3.961).

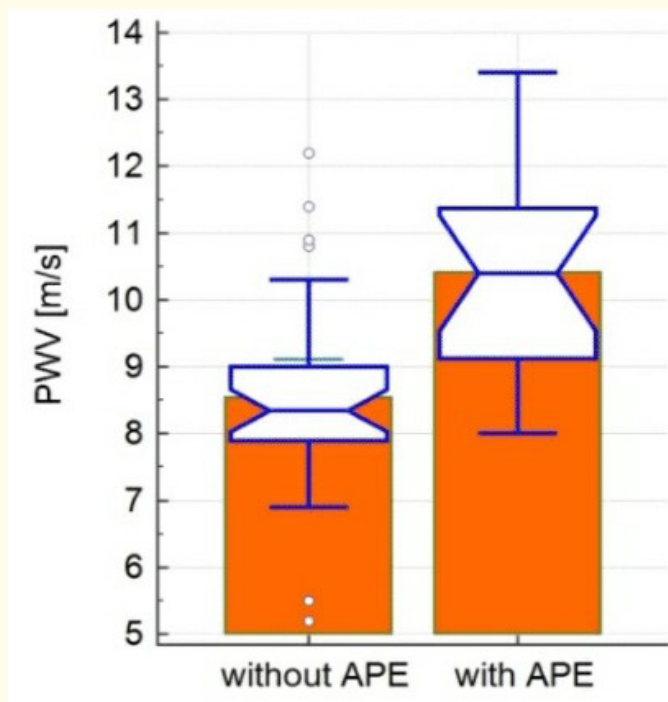


Figure 2: Box and whisker diagram of independent samples t-test between patients with or without acute pulmonary edema (APE).

Receiver operating characteristics curve

We used Receiver Operating Characteristics (ROC) curve as a graphical plot that illustrates the performance of binary classifier system (APE is presented, equal to 1; or it is not presented, equal to 0). We used this discrimination model, (estimation of cut-off point) to distinguish between patients with or without cardio-pulmonary event, exactly, patients with APE (registered as 1) and patients without it (registered as 0). In a ROC curve, the true positive rate (sensitivity) is plotted in function of the false positive rate (100 – Specificity) for different cut-off points of a parameter. We found 17 (36.17%) cases with APE, and 30 (63.82%) without. Area under the receiver operating characteristics curve (AUC) = 0.803, z-statistic 4.573, 95% Confidence Interval (CI) = 0.661 to 0.904, significance level (area = 0.5) < 0.0001.

The accuracy of the test depends on how well the test separates the group being tested into those with and without the disease (APE) in question. Accuracy is measured by the area under the ROC curve (Figure 3). Each point on the ROC curve represented a sensitivity/specificity pair corresponding to a particular threshold (PWV in the detection of APE). The PWV cut-off point where the parts of sensitivity/specificity points were the highest was 9.1 m/s, with sensitivity of 76.47% and specificity of 80.0%.

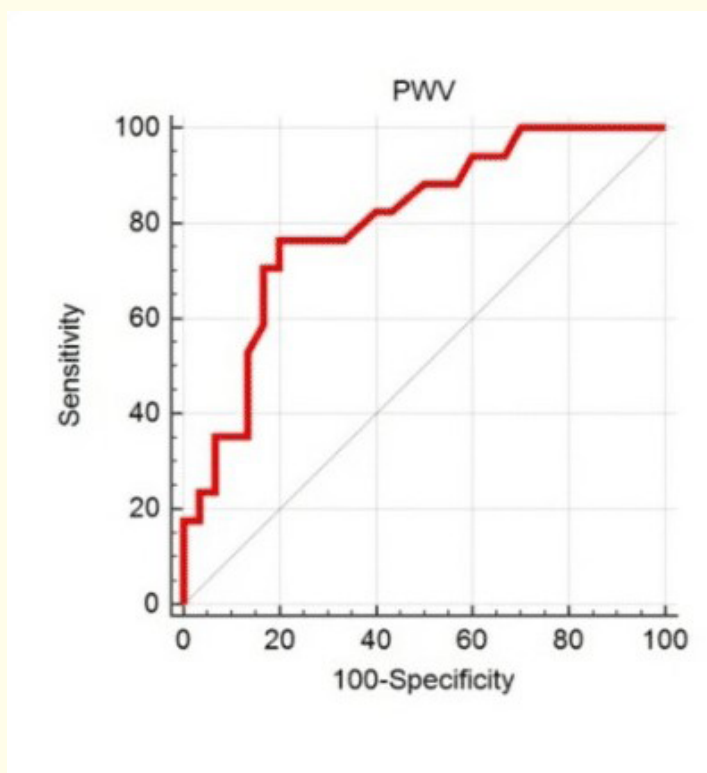


Figure 3: Receiver operating characteristics for PWV (Pulse Wave Velocity) as a prognostic diagnostic marker for APE and area under curve (AUC).

Multiple regression analysis

Assessments [standardized coefficient β (β_{st})], standard error of β_{st} , t, p-value and Variance Inflation Factor (VIF) of the dependent Y variable (APE) or determinants (PWV, Hypertension, BMI, diabetes, sex and smoking) for increasing of the risk for APE, after backward multiple regression analysis are shown in table 1.

Multiple regression (backward)					
Dependent Y		Oedema Pulmonum Acutum			
Enter variable if P < 0.1					
Remove variable if P > 0.5					
Coefficient of determination R ²		0.3413			
R ² -adjusted		0.2785			
Residual standard deviation		0.4125			
Sample size					47
Regression equation					
Independent variables	Coefficient β_{st}	Std. Error	t	P	VIF
PWV	0.1252	0.03533	3.543	0.0010	1.082
Hypertension	0.2118	0.1295	1.635	0.1096	1.095

Table 1: Multiple backward regression analysis of determinants of APE. Variables not included in the model: body mass index, diabetes, sex and smoking.

Because of his high collinearity (multicollinearity), between age and PWV, meaning that one variable can be linearly predicted from the other variables with a substantial degree of accuracy, variable age was not included in the model.

The coefficient of determination R² (0.3413) showed that 34.13% of the total variability was explained with the linear relation between APE and PWV accompanied by other determinants, or that 34.13% from incidence of pulmonary edema was dependent on aortic stiffness (PWV) as the predictor and other determinants (hypertension, diabetes, smoking etc). This means that any increase in PWV results in an increase of cardiovascular risk for APE.

The sensitivity of 76.47% express the probability that a test results will be positive (PWV > 9.1 m/s) when the disease (APE) is present (true positive rate). The specificity of 80% express the probability that a test results will be negative (PWV < 9.1 m/s) when the disease (APE) is not present (true negative rate).

The positive predictive value of 68.42% means that the disease (APE) is present when the test is positive, exactly when patient have increased PWV above cut-off point (9.1 m/s), they present symptoms of APE. When the patients do not present symptoms of the APE and PWV is below cut-off point, the predictive value of PWV to predict the disease is 85.71% (negative predictive value, results column in table 2).

Predictive values	
Sensitivity (%)	76.47
Specificity (%)	80
Disease prevalence (%)	36.17
Disease prevalence (N)	17
Total number of cases	47
Results	
Positive predictive values (%)	68.42
95% Confidence Interval	43.45 to 87.42
Negative predictive values (%)	85.71
95% Confidence Interval	67.33 to 95.97

Table 2: Predictive value of PWV as risk for APE.

Discussion

The association and correlation between PWV and acute dyspnoea are not sufficiently investigated. An electronic search under the term “pulse wave velocity and pulmonary edema” yielded zero reference. In this Google search only references for brachial-ankle pulse velocity and heart failure [17] and some studies about pulmonary edema associated with hypertension were offered, but nothing more about aortic stiffness and its impact on APE [13]. The small number of obtained references in the field of aortic stiffness and APE encouraged me to investigate about that and write this study.

In this prospective observational study we estimated 47 patients with acute dyspnoea caused by pulmonary stasis with aim to find correlation between aortic stiffness and APE. Each participant was subjected to noninvasive diagnostic Doppler ultrasonography in CCA and CFA anatomic regions (sternal notch and the groin, respectively). According to the results of the mean PWV (9.2 ± 1.8 m/s), it is obvious that we estimated relatively elderly population (57.8 ± 9.4 years) with increased risk for cardiovascular event. The measured mean PWV value in studied population is very close to the PWV cut-off point value (9.4 m/s) which corresponds to the point with highly increased risk for cardiovascular morbidity and mortality [7]. Certainly, the patients with verified APE that have statistically significant increase of the PWV (10.4 ± 1.64 m/s) have additionally increased cardiovascular risk because they exceed the critical threshold for PWV. This seemingly small difference in PWV between patients with or without APE (only 1.9 m/s) is still significant despite the fact that PWV increase the hazard ratio risk (HRR) for 1.3 times with each unit increase (1 m/s) in PWV. The results of our last study [7] is close to summary comparative results from meta-analysis of the predictive value of PWV for cardiovascular events presented by Vlachopoulos, *et al.* 2010 [18]: HR = 1.6 [19], HR = 1.44 [20], and HR = 1.20 [21].

We found by Bivariate correlation analysis significant positive correlation between APE and age. There are many studies which studied the age-related structural changes of the respiratory system and their consequences in clinical practice. The ageing heart increases cardiac output by increasing stroke volume rather than increasing heart rate [22]. The heart compensates increased vascular stiffness and consequently increasing of the PWV by increasing of a stroke volume. There are several studies that found positive correlation of speed stroke volume [23]. They found positive correlation between acute respiratory failure and age, too. Our results suggest significant positive correlation between hypertension and APE. Many of our patients had clinical and radiographic evidence of pulmonary edema the subsequently resolved with diuresis and control of hypertension. One third of our patients with APE were cleared when their blood pressure was lowered, hypertension may have contributed to the diastolic dysfunction [13], certainly expressed through the known mechanism of blood pressure impact on PWV. Stiffness is greater in hypertensive individuals when compared with age-matched control [24]. The pulse

pressure (PP) relates more closely to cardiovascular events than systolic blood pressure or diastolic blood pressure alone. A rise in PP is the major cause of the age-related increase in prevalence of hypertension and has generally been attributed to arterial stiffening [25].

Despite the relatively small number of patients (only 36%) which presented with classic APE, by ROC curve analysis we obtained statistically significant data that determine PWV cut-off value. The calculated cut-off point value (9.1 m/s) is very close to the PWV cut-off point value (9.4 m/s) which corresponds to point with highly increased risk for cardiovascular event in other studies [7]. Some studies suggest a PWV cut-off value up to 10 m/s as threshold value, for relatively health population without additional risk factors for cardiovascular risk [26]. However, the mean PWV of our surveyed patients with APE exceed both suggested cut-off PWV values, which confirms the importance of the increased PWV to occur cardiovascular event like APE, whether it will be caused by arrhythmia, hypertension, ischemia etc. The high significance of $P (< 0.0001)$ gives us the opportunity to predict the disease (APE) by PWV value of every single case determined by relatively high sensitivity and specificity. We are sure that if we included the patients with less pronounced symptoms of pulmonary stasis in the analysis, the positive predictive values would be greater than 68.42%. We determined that PWV has pronounced impact of APE genesis than other traditional risk factors (variables: hypertension, BMI, smoking status etc), because even 34.13% from APE incidence was dependent on PWV as the predictor. That means one-third of APE as cardiovascular event is dependent on PWV as a predictor only, versus two-thirds which belong to other determinants, above-mentioned variables.

There are several main mechanisms which may explain the correlation between increased aortic stiffness and APE genesis. Reduced ejection fraction of the left ventricle is caused by increased arterial stiffness and premature return of reflected waves in late systole, which increase central PP and the load of ventricle with increase of myocardial oxygen demand [27]. Aortic PWV may represent a surrogate end point, which may in fact indicate which patients with high aortic stiffness translate into real risk for left heart failure.

The subjects with stiffer arterial system have increased wave propagation time which caused reflected pressure wave from distal vessels to arrive earlier at the left ventricle of the heart which additionally overloads the left ventricle. These changes in arterial function and backward wave reflection characteristic cause an increase in left ventricle afterload, myocardial oxygen demand and wasted left ventricular energy which worsened the pulmonary stasis [28]. During medical treatment of the patient we were focused on these two main goals: preload reduction (reduction of pulmonary venous return), afterload reduction (reduction of systemic vascular resistance). The patients with lower arterial stiffness provide better response to afterload reduction therapy, and faster improvement of oxygenation and diuresis. The hypotensive patients were not treated with medication which reduced their preload and afterload. We treated them by inotropic support to maintain adequate blood pressure. The fluid overloaded patients with lower PWV had a better response to afterload reduction therapy with better diuresis.

The impact of increased arterial stiffness is confirmed by experiments with animals. Yano M., *et al.* (1997) examined the influence of independent increase of aortic stiffness on global left ventricular function in intact hearts on anesthetized dogs. They increased the stiffness of thoracic aorta using a stiff tube and isolate increase in aortic stiffness which was associated with reduction in left ventricle stroke volume [29].

Many studies have examined aortic stiffness and left ventricular diastolic dysfunction and they found association between those variables [30]. Although we did not estimate the direct association between PWV and diastolic function, however we found a significant correlation between PWV and APE as a manifestation of impaired left ventricular function. Not only impaired systolic function, but also diastolic dysfunction is an important contributor to pulmonary edema in patients with normal systolic function. Many patients hospitalized with APE in association with hypertension have transient LV systolic dysfunction which is not present with decrease of LV ejection fraction before, or after the patients has been treated [13].

In all participants included in this study according to the different nature of the disease (hypertensive, chronic dialysis patients, coronary artery disease, arrhythmias, cardiomyopathy etc) has been shown that aortic stiffness increases, in our and in other studies.

Aortic stiffness may influence left ventricular structure and function, independent of arterial blood pressure [31]. It has been shown that aortic stiffness increases in patients with hypertension [19], coronary artery disease [32], chronic dialysis patients [8] and patients with irregular heart rhythm [33].

The salient finding of our study was that PWV was predictor of APE genesis with high-levels performance values, assessed by simple, indirect, reproducible, and noninvasive evaluation of regional arterial stiffness. In conclude, the current study's finding suggest that PWV as measure of arterial stiffness is predictor of left ventricle failure and APE in patients with acute dyspnoea. A standard PWV cut-off point in the patients with cardio-respiratory difficulties should be further investigated and estimated by large clinical studies. Despite the small number of participants let this study be a starting point for research on this topic, pulmonary edema and arterial stiffness. By incorporating carotid-femoral Doppler PWV measurements into standard regular diagnostic assessments for cardiovascular estimation, the patients which are at increased cardiovascular risk can be pinpointed earlier, with a recommendation for preventive appropriate APE treatment and stiffness reduction by therapy starting.

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