Clinical correlates of arterial stiffness assessed by the cardio-ankle vascular index in peritoneal dialysis patients

Jen-Pi Tsai, Yu-Hsien Lai, Chih-Hsien Wang, Bang-Gee Hsu, Te-Chao Fang

Abstract

Objective: The cardio-ankle vascular index (CAVI) is a novel and accurate method, independent of the effect of blood pressure, and is used as a predictor of arterial stiffness (AS). However, the application of CAVI to identify the prevalence and clinical correlates of AS in peritoneal dialysis (PD) patients remains under investigation. The objective of this study was to explore the clinical correlates of PD patients with AS diagnosed by the CAVI examination compared with PD patients without AS.

Materials and Methods: A total of 50 patients who had undergone PD for more than 3 months were enrolled in this cross-sectional study. AS was defined as a CAVI ≥ 9. The clinical correlations between CAVI and AS in PD patients were studied.

Results: These PD patients had a high prevalence (42%) of AS. Age, systolic blood pressure, history of cardiovascular disease, hematocrit, glucose level, and phosphorus level were positively correlated with AS in PD patients compared with those without AS. Furthermore, multivariate regression analysis showed that age [adjusted odds ratio (OR) = 1.116, p = 0.010]; systolic blood pressure [adjusted OR = 1.080, p = 0.013]; and history of cardiovascular disease [adjusted OR = 1.896, p = 0.006] were all independently correlated with AS in PD patients.

Conclusion: The prevalence of AS in PD patients was high. Older age, elevated systolic blood pressure, hematocrit, and history of cardiovascular disease were positively related to the AS process shown by CAVI assessment in PD patients. However, further studies are needed to elucidate these factors, especially the hematocrit, affecting AS in PD patients after long-term follow-up.

1. Introduction

Cardiovascular mortality is very predominant in renal failure patients, especially in those on chronic dialysis [1]. One cause of cardiovascular mortality in dialysis patients is arterial stiffness (AS) [2]. The causal risk of AS in dialysis patients can be briefly divided into two principal types of factors: (1) well-defined factors, such as aging, hypertension, hyperphosphatemia, hypercalcemia, and hyperparathyroidism; and (2) other aggravated factors, including malnutrition; lower fetuin-A levels; increased homocysteine, fibroblast growth factor-23, and endogenous nitric oxide synthesis inhibitor (asymmetric dimethylarginine) levels; hepatitis C infection; use of beta-blockers; and so on [3–5]. Therefore, the clinical correlates of AS in dialysis patients have been investigated.

The traditional assessment of AS in dialysis patients uses brachial-ankle pulse wave velocity (baPWV) [6,7]. Disappointedly, the actual evaluation of the baPWV is influenced by a changeable blood pressure during measurement [8]. Emerging data have verified that the cardio-ankle vascular index (CAVI), a novel and noninvasive method, is an accurate parameter of AS independent of the effect of blood pressure [9,10]. For example, the CAVI has been used as a clinical parameter of AS in patients with essential hypertension [11], diabetes mellitus [12], obesity and metabolic syndrome [13], and end-stage renal disease (ESRD) [9,14].

CAVI has been proved to be better than baPWV in assessing AS in dialysis patients [9,14], suggesting that this is a superior screening test to detect AS in dialysis patients. However, the clinical correlates of AS using CAVI assessment in peritoneal dialysis (PD) patients remain under investigation. The objective of this study was to...
explore the clinical correlates in PD patients with AS, diagnosed by a CAVI examination, compared with those in PD patients without AS.

2. Materials and methods

2.1. Patient characteristics

All experimental procedures were carried out in accordance with and after the approval from the Ethics Committee and Human Subjects Institutional Review Board of Tzu Chi Hospital, Hualien. All patients were carefully instructed with respect to the study details, and written informed consent was obtained from each participant.

A total of 50 uremic patients undergoing continuous ambulatory PD (CAPD) for more than 3 months were studied in this cross-sectional study in April 2009. Patients on CAPD exchanged 2 L of dialysate containing 1.5%, 2.5%, or 4.25% glucose four times per day. Patients with acute illness were excluded from the study. Patient characteristics and medical history were obtained from direct interview or medical records, including age; gender; height; body weight; smoking habits; primary causes of ESRD; duration of dialysis; history of cardiovascular disease (CVD), diabetes, hypertension, and peripheral arterial occlusive disease; and use of anti-hypertensive, hypoglycemic, and lipid-lowering agents and vitamin D. The body mass index (kg/m$^2$) was calculated according to the standard formula. Waist circumference was measured midway between the inferior margin of the last rib and the top of the hip bone on a transverse plane. The adequacy of dialysis, such as fractional urea clearance ($\text{Kt/V}$), weekly creatinine clearance, and normalized protein catabolic rate, was also evaluated.

To manage disturbances in mineral and bone metabolism [calcium (Ca), phosphorus (P), and intact parathyroid hormone] in PD subjects, we treated patients according to the 2003 Kidney Disease Outcomes Quality Initiative clinical practice guidelines for bone metabolism and disease in chronic kidney disease [15]. Additionally, patients received recombinant erythropoietin (rHuEpo) to maintain their hematocrit levels between 33% and 36%, based on Kidney Disease Outcomes Quality Initiative clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease [16]. Patients regularly took iron and vitamin supplements.

2.2. Measurement of CAVI

CAVI was measured in each patient. A CAVI ≥9 was defined as the threshold value for AS, in agreement with that by Shirai et al [9] and with the instructions of the manufacturer of the equipment (VaSera VS-1000; Fukuda Denshi, Tokyo, Japan). According to the protocol, the patients rested in the supine position for at least 10 minutes before measurements were performed. Cuffs were applied to the four extremities, and electrocardiographic electrodes were attached to the upper extremities. A microphone was placed on the sternal angle for phonocardiography. The CAVI was automatically calculated using a waveform analyzer present in the equipment [9,17]. The complete measurement of the CAVI was usually achieved in less than 5 minutes.

2.2.1. Blood biochemistry and hematological assays

Blood was drawn from a peripheral vein after overnight fasting. Twelve milliliters of blood was taken from each patient before dialysis; 2 mL of whole blood was used for the measurement of the hematocrit using a Sysmex XE-2100, an automated analyzer (Sysmex, Kobe, Japan), and the remaining 10 mL was immediately centrifuged at 3000 g for 15 minutes, and the serum was stored at 4°C within 1 hour after collection for further examinations.

Serum levels of glucose, albumin, uric acid, total cholesterol, high-density-lipoprotein cholesterol, triglycerides, total Ca, P, and high-sensitivity C-reactive protein were measured with a Cobas Integra 800 analyzer (Roche Diagnostics, Indianapolis, IN, USA). Serum total homocysteine and intact parathyroid hormone levels were measured by an automated chemiluminescence immunoassay by means of an Advia Centaur Analyzer (Siemens, Muenchen, Germany) [18].

2.3. Statistical analysis

Data were expressed as either case numbers or means ± standard deviation. Student $t$ test was applied to compare the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of peritoneal dialysis patients with and without arterial stiffness</th>
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<tbody>
<tr>
<td></td>
<td>Without arterial stiffness (n = 29)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>45.3 ± 2.7</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
</tr>
<tr>
<td>Female</td>
<td>22</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>157.9 ± 1.7</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>59.1 ± 2.3</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>23.6 ± 0.8</td>
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<tr>
<td>Waist circumference (cm)</td>
<td>86.2 ± 1.9</td>
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<tr>
<td>SBP (mmHg)</td>
<td>120.8 ± 4.1</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>73.8 ± 2.4</td>
</tr>
<tr>
<td>Duration of dialysis (y)</td>
<td>3.0 ± 0.6</td>
</tr>
</tbody>
</table>

Data are presented as n or mean ± standard deviation. BMI – body mass index; CVD – cardiovascular disease; DBP – diastolic blood pressure; DM – diabetes mellitus; ESRD – end-stage renal disease; GN – glomerulonephritis; HTN – hypertension; PAOD – peripheral artery occlusive disease; SBP – systolic blood pressure.
means of continuous variables. Categorical variables were analyzed using Chi-square analysis or Fisher’s exact test. Statistical significance was defined as a p value < 0.05. All statistically significant variables (p < 0.05) were entered into a multivariate stepwise logistic regression model as independent variables, and AS was used as a dependent variable. All statistical analyses were performed with SPSS, version 13.0 (SPSS Inc., Chicago, IL, USA).

3. Results

The clinical characteristics of PD patients with and without AS are presented in Table 1. The prevalence rate of AS in these PD patients was 42% (21 of 50). PD patients with AS were older (p < 0.001) and had a higher systolic blood pressure (SBP) (p = 0.012) than those without AS. Additionally, a history of CVD was correlated with AS (p = 0.006). There were no significant differences in body weight; body mass index; waist circumference; height; diastolic blood pressure; duration of dialysis; smoking history; primary causes of ESRD; metabolic syndrome; clinical symptoms and signs of peripheral arterial occlusive disease; and the administration of antihypertensive, hypoglycemic, or lipid-lowering agents between groups.

Table 2 shows the clinical biochemistries of PD patients with and without AS. There were significantly higher hematocits (p = 0.033), glucose levels (p = 0.046), and P levels (p = 0.020) in PD patients with AS than in those without AS. Furthermore, there were no significant differences in albumin, uric acid, total cholesterol, triglycerides, high-density-lipoprotein cholesterol, intact parathyroid hormone, Ca, Ca × P product, total homocysteine, high-sensitivity C-reactive protein, Kt/V, weekly creatinine clearance, or normalized protein catabolic rate between groups.

Multivariate stepwise logistic regression analysis in PD patients with AS is summarized in Table 3. Age, SBP, history of CVD, hematocrit, glucose level, and P level were taken as independent variables, and AS, as assessed by CAVI, was taken as the dependent variable. Multivariate logistic regression analysis for risk factors in PD patients with AS showed that age [adjusted odds ratio (OR) = 1.116, p = 0.010]; SBP (adjusted OR = 1.080, p = 0.010); hematocrit

| Table 3 Multivariate stepwise logistic regression analysis of risk factors for arterial stiffness |
|---------------------------------------------------|------------------|-----------------|--|
| Variables                        | Adjusted OR | 95% CI | p   |
| Age                              | 1.116        | 1.011–1.233   | 0.010 |
| SBP                              | 1.080        | 1.018–1.145   | 0.010 |
| Hct level                        | 1.896        | 1.201–2.991   | 0.006 |
| History of CVD                   | 33.492       | 2.101–533.941 | 0.013 |
| Constant                         | 0.000        |             | 0.002 |

Dependent variable: arterial stiffness diagnosed by carotid-ankle vascular index. Independent variables: age, SBP, history of CVD, hematocrit, glucose, and phosphorus.

CI = confidence interval; CVD = cardiovascular disease; Hct = hematocrit; OR = odds ratio; SBP = systolic blood pressure.

(adjusted OR = 1.896, p = 0.006); and history of CVD (adjusted OR = 33.492, p = 0.013) were definitely related to AS in PD patients.

4. Discussion

Information about the application of CAVI to evaluate risk factors of AS in PD patients remains limited. In this study, it was well established that PD patients have a high incidence of AS (42%), and younger age, elevated SBP, higher serum hematocrit, and history of CVD were independent risk correlates of AS by CAVI examination in PD patients. Only age and elevated SBP were traditional independent risks correlated with AS in PD patients. The other traditional risk factors (e.g., diabetes mellitus and total cholesterol) did not show a significant contribution to AS in PD patients. The reasons are unclear. Possibly, the small case number might have made some traditional risk factors become insignificant or cause nontraditional risk factors to become more prominent in this study.

Studies have shown that aging can cause aortic stiffness in healthy individuals [19] and dialysis patients [14,20], similar to the results in this study. Aging causes remodeling of arteries. This process activates the upregulation of Type 2 matrix metalloproteinase in the aorta of rats and humans, causing intimal and medial thickening, vessel luminal dilation, fragmentation of the elastic membrane, and increased AS [21,22].

In our results, an elevated SBP was positively associated with AS in PD patients, consistent with reports in hemodialysis [20] and hypertensive patients [23]. A clinical study has suggested that achieving an optimal SBP in renal failure patients attenuates the process of AS [24]. Many uremic patients with AS have an elevated SBP, which induces a vicious cycle [25]. An elevated SBP leads to vessel hypertrophy, loss of elasticity, and arterial stiffening [26].

The hematocrit in our study was a significant contributing factor affecting AS in multiple regression models; the PD patients with AS had higher hematocrits and higher SBPs than PD patients without AS because patients in the AS group received more rHuEpo than those without AS. In contrast, patients in the AS group still had a greater anemia level compared with the general population owing to ESRD-related effects. This result is consistent with a study which showed that AS in patients with cyanotic congenital heart disease is affected by arterial pressure and anemia [27]. The exact mechanisms for this observation between AS and the hematocrit are unknown. Two explanations are possible. First, anemia itself activates the sympathetic nervous system to cause heart failure and AS [28]. Second, rHuEpo is used for the treatment of renal anemia in dialysis patients, and this treatment might induce greater systemic vascular resistance either by the rise of erythrocyte mass or the change in various endogenous vasopressors, including the direct action of rHuEpo itself [29]. These effects may be the cause of hypertension and the AS process. Therefore, in our study, the AS group had episodic anemia and received more rHuEpo; these factors may combine to evoke the development of vascular disorders and AS.
The influences of the hematocrit on the process of AS should be ascertained in long-term studies.

Our recent study showed that de novo AS, as determined by CAVI, in chronic dialysis patients was significantly associated with age and initial serum P after a 1-year follow-up [30]. Along with the focal process of atherosclerosis (mainly affecting the intima of the arteries), the diffuse pathological phenomenon of arteriosclerosis (affecting mainly the media of large- and middle-sized arteries) is prominent in chronic dialysis patients with CVD [5]. In this aspect, endothelial dysfunction, atheroma, oxidative stress, vascular calcification, and AS are closely related. Pathologically, chronic hypercalcemia impairs endothelium-dependent vasodilatation, accelerates deposition of Ca in the media and intima of the vascular wall and in individual myocardial fibers (dystrophic calcification), increases intima-media thickness of the artery walls, damages vascular compliance and capacitance, and induces development of AS [31]. Therefore, our study suggested that a history of CVD in PD patients is a major risk factor for AS.

In conclusion, our study demonstrates that these PD patients had a high prevalence of AS by CAVI assessment (42%, 21 of 50). Age, SBP, hematocrit, and history of CVD are closely associated with AS in PD patients. Age, SBP, and history of CVD are well-known predisposing factors. However, further studies of the hematocrit and CVD are needed to elucidate these factors affecting AS in long-term follow-up.

References