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Original Paper

Arterial Stiffness is an Independent Risk Factor for Anemia After Percutaneous Native Kidney Biopsy

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Key Words
Brachial-ankle pulse wave velocity • Bleeding • Hemoglobin • Renal biopsy

Abstract
Background/Aims: Bleeding is the most common complication after renal biopsy. Although numerous predictors of bleeding have been reported, it remains unclear whether arterial stiffness affects bleeding complications. ***Method:*** We performed an observational study of the renal biopsies performed in our division over an approximately 6-year period (May 2010 to May 2016). The clinical and laboratory factors were analyzed to reveal the risk factors associated with bleeding, with a focus on anemia (defined as a ≥10% decrease in hemoglobin [Hb] after biopsy). The brachial-ankle pulse wave velocity (baPWV) was measured to evaluate arterial stiffness. ***Results:*** This study included 462 patients (male, n=244; female, n=218). Anemia (defined above) was observed in 54 patients (11.7%). The risk of anemia was higher in women, older patients, and patients with lower serum albumin, lower eGFR and lower diastolic blood pressure after biopsy. We then performed a further analysis of 187 patients whose baPWV data were available. Multivariate analysis revealed that a higher baPWV was an independent risk factor for anemia. ROC analysis for predicting anemia found that a baPWV value of 1839 cm/s had the best performance (AUC 0.689). ***Conclusion:*** An increased baPWV may be a more valuable predictor of bleeding than any of the other reported risk factors.

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Introduction

Kidney biopsies are essential for the diagnosis and management of many diseases. Since the 1950s, renal biopsy techniques have improved and the incidence of complications has been minimized [1]. Bleeding is the most frequent complication of percutaneous renal biopsy. Previous studies have revealed a number of predictors of bleeding complications. Multivariate analyses in prospective studies of kidney biopsies, have revealed that female gender, older age, hypertension, anemia, an elevated partial thromboplastin time (PTT), an elevated bleeding time (BT) and elevated serum creatinine levels are independent risk factors for bleeding complications [1-4]. Anatomic characteristics, such as small kidneys with thin cortices, cysts in the lower renal pole, or horseshoe kidney, may contraindicate a biopsy in some patients. Patients with kidney atrophy, which usually occurs due to glomerular sclerosis, should not undergo biopsy due to the high possibility of bleeding and less diagnostic value. Although the atherosclerosis is widely believed as an important factor for bleeding complications, few studies have investigated the correlation between the intensity of atherosclerosis and the risk of bleeding after biopsy.

Atherosclerosis has two components of thickening (atherosis) and stiffening (sclerosis) of the arterial wall [5]. The intima-media thickness (IMT) of the arteries has been used as a noninvasive index of atherosis, whereas the pulse wave velocity (PWV) is an established marker of arterial stiffness. Aortic PWV is known to be associated with left ventricular hypertrophy and an increased pulse pressure; it was previously shown to be an independent risk factor for stroke and cardiovascular mortality [6-8]. An increase in large artery stiffness results in an increased cardiac workload, the transmission of arterial pressure oscillation to the microcirculation and organ damage, including brain and kidney damage. In a cross-sectional population study, an increased brachial–ankle PWV (baPWV) affected the microcirculation of the brain and kidneys in a manner that led to silent cerebral microbleeds [9] and renal albuminuria [10], respectively. An increased PWV should influence the possibility of bleeding complication after renal biopsy.

The objective of this study was to investigate the association between arterial stiffness, estimated by the baPWV and the incidence of bleeding, with a focus on the change in the hemoglobin (Hb) values after biopsy.

Subjects and Methods

Patients

This retrospective study included 462 patients who underwent renal biopsy over an approximately 6-year period (May 2010 to May 2016) in the Renal Unit of Okayama University Hospital. All patients underwent percutaneous ultrasound-guided biopsies of the native kidney. All of the procedures in the present study were carried out in accordance with the institutional and national ethical guidelines for human studies, and the guidelines proposed in the Declaration of Helsinki. The study was approved by the Ethical Committee of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (KEN1608-501, 2016). The patients were informed about the research protocol by the Internet homepage of our institution and posters on the notice board for outpatients. This study was registered with the Clinical Trial Registry of the University Hospital Medical Information Network (registration No. UMIN000026270).

Ethical statement and Informed consent

All of the procedures in the present study were carried out in accordance with the institutional and national ethical guidelines for human studies, and the guidelines proposed in the Declaration of Helsinki. The study was approved by the Ethical Committee of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (KEN1608-501, 2016). The patients were informed about the research protocol by the Internet homepage of our institution and posters on the notice board for outpatients.

The percutaneous renal biopsy procedure

Written informed consent was obtained from the patients prior to biopsy. The complete blood count (CBC), the international normalized ratio of prothrombin time (PT-INR), activated partial thromboplastin time (APTT), renal function and the size of the kidneys (especially the thickness of cortex) were checked routinely. Medications that were associated with an increased risk of bleeding, such as anticoagulants and antiplatelet agents were discontinued or switched to intravenous heparin within an appropriate amount of time before the procedure. The biopsy was performed by a nephrologist or a doctor-in-training with 3 years of experience under the supervision of a nephrologist. The patients with uncontrolled blood pressure (especially values of >160 mmHg) were continuously administered with intravenous Nicardipine Hydrochloride throughout the procedure. Disposable, semi-automated devices with 18- or 16-gauge needles (MONOPTY; BARD, Tempe, USA) were used under the real-time ultrasonographic guidance. The kidney was punctured to obtain about two or three samples, which were adequate for determining a diagnosis. Immediately after the biopsy, the puncture site was pressed firmly for approximately 15 min, and then a pressure dressing was applied; the patient was kept in a supine position on an ice pack. The patient's vital signs were checked regularly, and the hematoma size on ultrasonography was checked every three hours from just after the biopsy until the night. The next morning (approximately 20 hours after biopsy), the patient's vital signs, CBC and hematoma size on ultrasonography were checked again. If there were no problems, the pressure dressing was removed and the patient was allowed to get out of bed.

Data collection

The information collected from the medical records included the age, gender and the body mass index on hospital admission. Two blood pressure measurements were taken on admission and at the night after biopsy. All of the patients had a CBC and laboratory blood test, the PT-INR, APTT, the serum levels of total protein, albumin and creatinine, and urinary protein were evaluated. The cyanmethaemoglobin method was adopted for haemoglobin determination in our facility. The eGFR was calculated using the simplified version of the MDRD (Modification of Diet in Renal Disease) formula [11]. The patient's metabolic parameters (the HbA1c percentage and serum total-cholesterol level), usage of antihypertensive medication and diabetic mellitus status were also recorded. In the present study, we did not estimate the size of the punctured vessels in the biopsy specimens.

The assessment of bleeding complications

According to previous reports, the severity of complications was categorized as minor or major. Minor complications were defined as those that spontaneously resolved without the need for further intervention, such as gross hematuria and/or perinephric hematoma. Major complications were those that necessitated intervention, such as a transfusion of blood products or an invasive procedure (radiographic or surgical), and those resulting in acute renal obstruction or failure, septicemia, or death. We experienced only two major complications (blood transfusion was required in both cases). Most of the complications were minor. We set the changes in Hb values as the primary outcome, and the perirenal hematoma size, macroscopic hematuria and vasovagal reflex as the secondary outcomes. The decrease in Hb was expressed as a percentage, not an absolute difference, based on the study of Ishikawa et al. [12]. The anemia group was defined by a ≥10% decrease in the Hb level after biopsy. The size of a perirenal hematoma was defined as the product of the longest and the shortest diameters on two-dimensional ultrasonographic pictures.

The measurement of the baPWV

The measurement of the baPWV was conducted using an automatic device (form PWV/ABI BP-203RPE II; Colin, Komaki, Japan) after the patient had rested in a supine position for more than five minutes [13]. This device simultaneously records the PWV and the brachial and ankle blood pressures on both sides, in addition to an electrocardiogram and heart sounds. The baPWV was measured before the day of renal biopsy to evaluate the vascular complications for the diagnosis for renal disease.

Statistical Analyses

The results are expressed as the mean ± SD or the median and interquartile range (IQR) for continuous data, and as integers, frequencies, and percentages for categorical data. P values of <0.05 were considered

to indicate statistical significance. Differences between groups were analyzed using Student's *t*-test and the Mann-Whitney U-test for continuous data, and the chi-squared test and Fisher's exact test for categorical data. Multiple logistic regression was conducted to determine the baseline factors that were significant independent predictors of anemia after renal biopsy. This multivariate model was built using pre-specified variables including age, gender, serum albumin, eGFR, diastolic blood pressure after biopsy and the baPWV. Risk estimates were presented as the unadjusted odds ratio (OR, adjusted odds ratio (AOR) and the 95% confidence interval (CI). Receiver-operating characteristic (ROC) curves were constructed to determine the optimal sensitivity and specificity, and the area under the curve (AUC) was calculated. The statistical analyses were performed using the JMP software program (version 11, SAS Institute Inc., Cary, NC, USA).

Table 1. The baseline characteristics of 462 patients and 187 patients whose baPWV data were available

	Patients (n=462)	Patients with baPWV (n=187)	P value
Sex (male, %)	244 (52.8%)	116 (62.0%)	0.035*
Age (years)	50.4 ± 18.2	53.6 ± 16.2	0.036*
BMI	22.8 ± 3.6	23.2 ± 3.4	0.159
TP (g/dl)	6.31 ± 1.03	6.42 ± 0.94	0.205
Alb (g/dl)	3.40 ± 0.92	3.53 ± 0.88	0.094
Cr (mg/dl)	1.28 ± 1.12	1.31 ± 1.04	0.733
eGFR (ml/min/1.73m^2)	62.2 ± 30.2	58.5 ± 28.7	0.152
Proteinuria (g/gCr)	1.03 (0.35-3.14)	0.91 (0.36-2.74)	0.576
Hb (g/dl)	12.6 ± 2.2	12.7 ± 2.1	0.458
Plt (*10^4/mm^3)	25.9 ± 12.3	25.7 ± 14.9	0.833
PT-INR	0.92 ± 0.08	0.93 ± 0.08	0.182
APTT (sec)	30.7 ± 6.3	30.6 ± 5.0	0.816
TCH (mg/dl)	222 ± 83.6	213 ± 73.9	0.225
HbA1c (%)	5.81 ± 0.75	5.94 ± 0.86	0.060
sBP on admission (mmHg)	132 ± 17.3	135 ± 17.6	0.049*
dBP on admission (mmHg)	79.8 ± 12.4	80.3 ± 12.4	0.668
Thickness of cortex (cm)	1.35 ± 0.33	1.31 ± 0.30	0.165
Diagnosis of diabetes	81 (17.7%)	45 (24.1%)	0.079
Medication for hypertension	232 (50.4%)	119 (63.6%)	0.0023*

BMI, body mass index; TP, total protein; Alb, albumin; Cr, creatinine; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; Plt, platelet; PT-INR, international normalized ratio of prothrombin time; APTT, activated partial thromboplastin time; TCH, total cholesterol; sBP, systolic blood pressure; dBP, diastolic blood pressure

Results

This study included 462 patients (male, n=244; female, n=218), with a mean age of 50.4 ± 18.2 years (range 15-90 years). The baseline characteristics are summarized in Table 1. The most common clinical diagnosis was chronic glomerulonephritis (n=268, 58.1%), followed by nephrotic syndrome (n=118, 25.5%). The distribution of the patients with each clinical diagnosis was similar to the large dataset (7,034 biopsies in 94 facilities) of the Japan Renal Biopsy Registry (J-RBR) from 2009 and 2010 [14]. The exact pathological diagnosis is indicated (Table 2).

The complications related to renal biopsy are as follows; two patients (0.43%) required a blood transfusion after biopsy. No patients required invasive procedures due to continuous bleeding. The mean decrease in the Hb level on the morning after biopsy was 0.33 ± 0.87 g/dl (2.5 ± 7.4%). A ≥1.0 g/dl decline in Hb was observed in 88 patients (19.1%), while a decline of ≥10% was observed in 54 patients (11.7%). Macroscopic hematuria occurred in 5 patients (1.0%), and perirenal hematoma was observed on ultrasonography in 386 patients (85.0%). The median hematoma size was 1.50 cm^2 (0.99-2.2). Transient hypotension developed in 35 patients (7.5%) due to the vasovagal response.

We divided patients into two groups: those with an Hb decrease of ≥10% (anemia group) and those with an Hb decrease <10% (control group). Table 3 shows the statistical differences in the clinical factors of the two groups. The patients in the anemia group tended to be women, of older age and to have a lower serum albumin level, a lower eGFR and a lower diastolic blood pressure after biopsy, in comparison to the patients in the control group. No differences were found between the two groups, regarding the blood pressure on admission, the serum level of total cholesterol, the HbA1c percentage, the proportion of patients with diabetic mellitus or the proportion of patients who were treated with antihypertensive medications. The median values of the hematoma size the next morning were indistinguishable between the two groups, but the mean value in the anemia group was significantly higher than that in the control group. There was a significant liner correlation between the hematoma size the next morning and the decrease in the Hb level after the biopsy (R=0.19, P<0.0001*).

Table 2. The pathological diagnosis of all patients

	n (%)
IgA nephropathy	146 (31.6 %)
ANCA associated glomerulonephritis	40 (8.65 %)
Lupus nephritis	37 (8.00 %)
Minimal change nephrotic syndrome	30 (6.49 %)
Benign nephrosclerosis	30 (6.49 %)
Membranous glomerulonephritis	26 (5.62 %)
Diabetic nephropathy	23 (4.97 %)
Focal segmental glomerulosclerosis	23 (4.97 %)
IgA vasculitis	16 (3.46 %)
Minor glomerular abnormalities	14 (3.03 %)
Acute interstitial nephritis	11 (2.38 %)
Obesity related glomerulopathy	11 (2.38 %)
Membranoproliferative glomerulonephritis	9 (1.94 %)
Chronic interstitial nephritis	7 (1.51 %)
Cryoglobulinemic glomerulonephritis	7 (1.51 %)
Renal amyloidosis	4 (0.86 %)
Acute tubular necrosis	3 (0.65 %)
Alport syndrome	3 (0.65 %)
Malignant nephrosclerosis	2 (0.43 %)
Others	20 (4.32 %)
Total	462 (100 %)

A multivariate analysis was performed to determine the baseline features that predicted anemia after biopsy. The risk of post-biopsy anemia increased independently with female gender (AOR 2.25; 95%CI 1.23-4.21; p=0.008). In addition, the risk of post-biopsy anemia decreased significantly with the serum albumin level (AOR 0.68; 95%CI 0.48-0.95; p=0.026, for every 1 mg/dl increase of serum albumin), and the diastolic blood pressure after biopsy (AOR 0.72; 95%CI 0.57-0.90; p=0.006, for every 10mmHg increase of blood pressure) (Table 4).

Subsequently, we performed a further analysis of the 187 patients whose baPWV data were available. We recognized a few significant differences of the clinical background between the group of all patients and patients with data on baPWV (Table 1). A higher baPWV value was found to be a risk factor for anemia (Table 3). A multivariate logistic regression analysis was performed to evaluate the impact of the baPWV on bleeding complications. There was a significant association between the baPWV and post-biopsy anemia (AOR 1.15; 95% CI 1.01-1.32; p=0.036) (Table 5). The baPWV was an independent risk factor for bleeding complications. The AUC for the ROC curve when baPWV was used to detect anemia after biopsy was 0.689. A baPWV value of 1839 cm/s, which showed the best performance, had a sensitivity of 63%, and a specificity of 77% for predicting anemia (Fig. 1). The ROCs of the other parameters showed that the eGFR, proteinuria, serum albumin and diastolic blood pressure after biopsy were not superior to the baPWV for predicting anemia.

Discussion

Bleeding is the most common clinically relevant complication after renal biopsy. It is difficult to clearly state the general bleeding rates because of how bleeding is defined and

diagnosed is different among studies. In a meta-analysis of 9,474 biopsies in 34 studies, the overall rate of erythrocyte transfusion was 0.9% (95%CI; 0.4%-1.5%), while that of macroscopic hematuria was 3.5% (95%CI; 2.2-5.1%) [15]. We observed that 0.43% of the patients required blood transfusion and 1.0% of the patients experienced macroscopic hematuria. The bleeding rates of hematoma on CT ranged from 57% to 91% (versus 70% on ultrasound) in studies from the 1970s and 1980s, which used older scanners, biopsy techniques, and needles [1]. We observed perirenal hematoma in 85% of the cases on ultrasonography, including tiny 1×1 square millimeter hematomas; the findings depended on the evaluations of several operators. Overall, the frequencies of major and minor complications were lower in our hospital. A decrease in the Hb level after biopsy is very common and there is little varia-

Table 3. The clinical characteristics of the anemia and control groups

	Anemia group	Control group	P value
n	55	404	
Sex (male, %)	19 (35.1%)	223 (54.9%)	0.0063*
Age (years)	57.9 ± 17.3	49.2 ± 18.1	0.0009*
BMI	21.9 ± 3.49	22.9 ± 3.63	0.057
TP (g/dl)	6.14 ± 1.01	6.34 ± 1.03	0.18
Alb (g/dl)	3.04 ± 1.00	3.45 ± 0.89	0.0016*
Cr (mg/dl)	1.46 ± 0.15	1.26 ± 0.05	0.22
eGFR (ml/min/1.73m^2)	52.4 ± 28.3	63.3 ± 30.3	0.012*
Proteinuria (g/gCr)	1.50 (0.42-6.62)	1.01 (0.32-3.03)	0.052
Hb (g/dl)	12.3 ± 2.44	12.6 ± 2.19	0.40
Plt (*10^4/mm^3)	25.2 ± 9.28	25.9 ± 12.7	0.68
PT-INR	0.93 ± 0.11	0.92 ± 0.08	0.52
APTT (sec)	30.3 ± 4.53	30.7 ± 6.59	0.60
TCH (mg/dl)	238 ± 105	220 ± 80.3	0.14
HbA1c (%)	5.88 ± 0.80	5.80 ± 0.74	0.44
sBP on admission (mmHg)	135 ± 18.1	131 ± 17.2	0.15
dBP on admission (mmHg)	79.7 ± 10.6	79.8 ± 12.6	0.94
sBP after biopsy (mmHg)	121 ± 22.0	126 ± 20.3	0.11
dBP after biopsy (mmHg)	70.2 ± 13.8	75.9 ± 13.5	0.0037*
baPWV (cm/s)	1888 ± 474	1584 ± 415	0.0018*
Thickness of cortex (cm)	1.38 ± 0.34	1.35 ± 0.33	0.49
Hematoma size after biopsy (cm^2)	2.00 (1.2-3.61) 3.17 ± 3.38	2.00 (1.29-3.45) 2.74 ± 2.38	0.93 0.26
Hematoma size the next morning (cm^2)	1.50 (0.9-3.46) 2.91 ± 4.26	1.50 (0.99-2.02) 1.78 ± 1.58	0.30 0.0002*
Punctures (times)	2.40 ± 0.59	2.46 ± 0.73	0.57
16 gauge (n, %)	2 (3.70%)	10 (2.46%)	0.59
Diagnosis of Diabetes	12 (22.2%)	68 (17.0%)	0.34
Medication for Hypertension	27 (50.0%)	205 (50.7%)	0.91

BMI, body mass index; TP, total protein; Alb, albumin; Cr, creatinine; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; Plt, platelet; PT-INR, international normalized ratio of prothrombin time; APTT, activated partial thromboplastin time; TCH, total cholesterol; sBP, systolic blood pressure; dBP, diastolic blood pressure; baPWV, brachial–ankle pulse wave velocity

Table 4. The unadjusted and adjusted estimated risk of post-biopsy anemia in 462 biopsies

Risk factor	Unit of increase	Unadjusted odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)	P value
Female		2.11 (1.19-3.84)	0.010*	2.25 (1.23-4.21)	0.008*
Age (years)	10	1.31 (1.11-1.56)	0.0008*	1.18 (0.97-1.44)	0.102
Alb (g/dl)	1	0.63 (0.47-0.84)	0.002*	0.68 (0.48-0.95)	0.026*
eGFR (ml/min/1.73m^2)	10	0.88 (0.79-0.97)	0.011*	0.93 (0.82-1.05)	0.268
dBP after biopsy (mmHg)	10	0.71 (0.57-0.89)	0.002*	0.72 (0.57-0.90)	0.006*

CI, confidence interval; eGFR, estimated glomerular filtration rate; dBP, diastolic blood pressure

Table 5. The unadjusted and adjusted estimated risk of post-biopsy anemia in 187 biopsies in which the baPWV was evaluated

Risk factor	Unit of increase	Unadjusted odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)	P value
Female		2.11 (0.86-5.29)	0.101	2.04 (0.76-5.56)	0.151
Age (years)	10	1.53 (1.12-2.16)	0.005*	1.17 (0.74-1.89)	0.494
Alb (g/dl)	1	0.51 (0.32-0.82)	0.005*	0.68 (0.39-1.21)	0.184
eGFR (ml/min/1.73m^2)	10	0.99 (0.85-1.16)	0.982	1.16 (0.94-1.45)	0.162
dBP after biopsy (mmHg)	10	0.73 (0.51-1.01)	0.058	0.67 (0.45-0.96)	0.038*
baPWV (cm/s)	100	1.15 (1.04-1.27)	0.003*	1.15 (1.01-1.32)	0.036*

CI, confidence interval; eGFR, estimated glomerular filtration rate; dBP, diastolic blood pressure; baPWV, brachial–ankle pulse wave velocity

bility in the estimates of bleeding among physicians. We set a decrease in the Hb level as the primary outcome.

There has been numerous previous reports on the predictors of bleeding complications; a review about the risk factors for bleeding complications was published in 2016 [1]. As reported previously, aging, female gender and renal dysfunction were associated with bleeding complications. We hypothesized that because aging and renal dysfunction were strongly correlated with arterial stiffness, they were not independent risk factors. Women generally have higher risk of complications in the biopsy of various organs [16]. A possible explanation of the relationship between female gender and post-biopsy bleeding may be that the biopsy needle penetrates deeper into the renal parenchyma, potentially injuring more renal blood vessels, due to the smaller kidney size in women [15]. The lower amount of visceral fat in women could mean that pressing around the punctured site has less effect. A lower level of serum albumin and a diastolic blood pressure after biopsy were revealed as predictors of anemia in this study; neither has been reported previously.

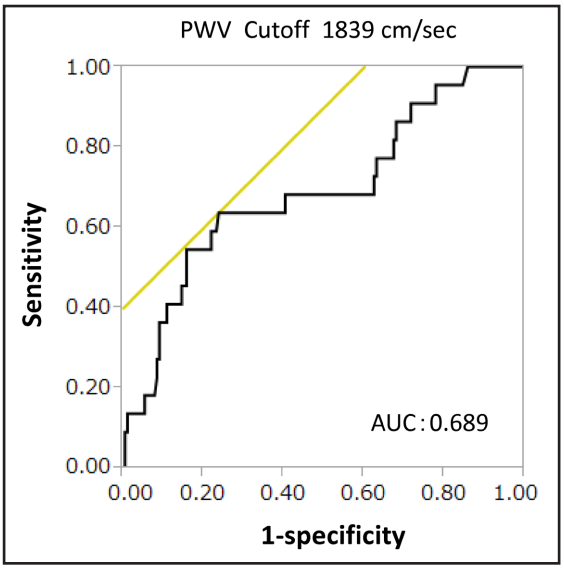

Fig. 1. The ROC curve of the baPWV for predicting anemia (≥10% decrease in Hb after biopsy). The AUC for the ROC curve where the baPWV was used to detect anemia was 0.689. A baPWV value of 1839 cm/s had a sensitivity of 63%, and a specificity of 77%.

The main result of our study was that increased baPWV was independently associated with the risk of bleeding complications. To best of our knowledge, there have been no reports on this association. The baPWV is a noninvasive measure of arterial stiffness; in particular, it reflects the stiffness of aorta and peripheral arteries, which are located between the brachial and ankle artery [17]. The increased risk of bleeding may be derived from a change in the microcirculation in the kidney. What are the mechanisms linking the reduced compliance in the large arteries and the hemodynamic changes in small vessels?

Some studies have shown a relationship between PWV elevation and microalbuminuria [10]. The mechanism underlying the relationship between arterial stiffness and microvascular damage remains unknown [18]. The aortic wall, which contains a high proportion of

elastin fibers, predominantly work as cushions. Whereas, the more-distal arteries have a higher proportion of collagen fibers, which makes them less distensible [19]. As the artery progressively stiffens, the pulse pressure generally increases. The pulsations are not completely absorbed and are enhanced as they extend to the microcirculation of organs such as the brain and kidney [20, 21]. The increased pulsatile stress damages small arteries and tears their endothelial and smooth muscle cells with the disruption of the vessel [10, 22, 23], which was shown in the small arteries of kidneys in a rat model of hypertension [24]. With regard to the brain, an increased PWV was significantly associated with carotid intraplaque hemorrhage, and silent microbleeds on cerebral MR [19, 25]. In the renal microcirculation, less distensible vessels and increases in the pulsation of the blood flow and pressure may be the main causes of the high rate of bleeding complications.

Arterial stiffness can represent a consequence of a number of disease states, including hypertension, diabetes, hypercholesterolemia, atherosclerosis, and chronic renal compromise [26]. The endothelial damages, seen in the brain and kidneys of patients with hypertensive disease, were largely reversible when disrupting forces were reduced [22]. Antihypertensive medications such as angiotensin converting-enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, and nitrates can reduce wave reflection and pulse pressure, and thereby have a beneficial effect on the microvascular function [22]. Statins and other cholesterol-reducing agents have been shown to have beneficial effects on arterial stiffening. In diabetes, advanced glycation end products may be a therapeutic target in efforts to prevent the progression of arterial stiffening [19]. Treatments that can reverse arterial stiffness may reduce the possibility of bleeding complications after renal biopsy.

The present study is associated with several limitations. First, because it was performed in a single center, it is unknown whether the results can be generalized to other medical facilities. Furthermore, the retrospective nature of the study means that some complications may be underestimated and that some confounders may not have been considered. We need to investigate the relationship between the baPWV and bleeding complications in a multicenter prospective study. Second, we only estimated the arterial stiffness by baPWV, and did not investigate other vascular parameters, such as endothelial dysfunction, the intima-media thickness and arterial calcification. It remains unknown whether the baPWV is superior to other parameters of vascular dysfunction in predicting the possibility of bleeding complications. The baPWV is measured easily and non-invasively in comparison to the other parameters. Third, although anemia (defined as a ≥10% decrease in the Hb value) was set as the primary outcome in this study, the value of this outcome in predicting serious bleeding complications is not clear. In this study, there were few cases of severe bleeding complications; thus, the relationship between anemia and severe complications was difficult to estimate. According to previous reports [27, 28], a post-biopsy decrease in the Hb level of up to 1 g/dl might be observed in almost half of cases, due to hemodilution as a result of saline infusion, and pain causing elevated vasopressin levels, thereby leading to water retention. A ≥10% decrease in the haematocrit or Hb was chosen to indicate true bleeding in the several reports [12, 29]. We concluded that the outcome was valuable for predicting bleeding and it was superior as an objective measurement.

Conclusion

An increased baPWV was found to be independently associated with anemia after biopsy. It may therefore be a more valuable predictor of bleeding complications than any of the other previously reported risk factors. Future prospective studies should explore the development of a novel risk score including PWV to predict and prevent anemia after a renal biopsy.

Disclosure Statement

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References

1 Hogan JJ, Mocanu M, Berns JS: The Native Kidney Biopsy: Update and Evidence for Best Practice. Clin J Am Soc Nephrol 2016;11:354-362.
2 Korbet SM, Volpini KC, Whittier WL: Percutaneous renal biopsy of native kidneys: a single-center experience of 1,055 biopsies. Am J Nephrol 2014;39:153-162.
3 Eiro M, Katoh T, Watanabe T: Risk factors for bleeding complications in percutaneous renal biopsy. Clin Exp Nephrol 2005;9:40-45.
4 Manno C, Strippoli GF, Arnesano L, Bonifati C, Campobasso N, Gesualdo L, Schena FP: Predictors of bleeding complications in percutaneous ultrasound-guided renal biopsy. Kidney Int 2004;66:1570-1577.
5 Kimoto E, Shoji T, Shinohara K, Inaba M, Okuno Y, Miki T, Koyama H, Emoto M, Nishizawa Y: Preferential stiffening of central over peripheral arteries in type 2 diabetes. Diabetes 2003;52:448-452.
6 Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, Havlik R, Lakatta EG, Spurgeon H, Kritchevsky S, Pahor M, Bauer D, Newman A, Health ABCS: Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. Circulation 2005;111:3384-3390.
7 Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, Asmar R, Reneman RS, Hoeks AP, Breteler MM, Witteman JC: Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation 2006;113:657-663.
8 Hyun YY, Kim H, Sung SA, Kim SW, Chae DW, Kim YS, Choi KH, Ahn C, Lee KB: Association between Urine Creatinine Excretion and Arterial Stiffness in Chronic Kidney Disease: Data from the KNOW-CKD Study. Kidney Blood Press Res 2016;41:527-534.
9 Ochi N, Tabara Y, Igase M, Nagai T, Kido T, Miki T, Kohara K: Silent cerebral microbleeds associated with arterial stiffness in an apparently healthy subject. Hypertens Res 2009;32:255-260.
10 Ishikawa T, Hashimoto J, Morito RH, Hanazawa T, Aikawa T, Hara A, Shintani Y, Metoki H, Inoue R, Asayama K, Kikuya M, Ohkubo T, Totsune K, Hoshi H, Satoh H, Imai Y: Association of microalbuminuria with brachial-ankle pulse wave velocity: the Ohasama study. Am J Hypertens 2008;21:413-418.
11 Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A, Collaborators developing the Japanese equation for estimated GFR: Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982-992.
12 Ishikawa E, Nomura S, Hamaguchi T, Obe T, Inoue-Kiyohara M, Oosugi K, Katayama K, Ito M: Ultrasonography as a predictor of overt bleeding after renal biopsy. Clin Exp Nephrol 2009;13:325-331.
13 Kitagawa M, Sugiyama H, Morinaga H, Inoue T, Takiue K, Ogawa A, Yamanari T, Kikumoto Y, Uchida HA, Kitamura S, Maeshima Y, Nakamura K, Ito H, Makino H: A decreased level of serum soluble Klotho is an independent biomarker associated with arterial stiffness in patients with chronic kidney disease. PloS one 2013;8:e56695.

14 Sugiyama H, Yokoyama H, Sato H, Saito T, Kohda Y, Nishi S, Tsuruya K, Kiyomoto H, Iida H, Sasaki T, Higuchi M, Hattori M, Oka K, Kagami S, Kawamura T, Takeda T, Hataya H, Fukasawa Y, Fukatsu A, Morozumi K, Yoshikawa N, Shimizu A, Kitamura H, Yuzawa Y, Matsuo S, Kiyohara Y, Joh K, Nagata M, Taguchi T, Makino H, Committee for Standardization of Renal Pathological D, Committee for Kidney Disease R, Japanese Society of N: Japan Renal Biopsy Registry and Japan Kidney Disease Registry: Committee Report for 2009 and 2010. Clin Exp Nephrol 2013;17:155-173.

15 Corapi KM, Chen JL, Balk EM, Gordon CE: Bleeding complications of native kidney biopsy: a systematic review and meta-analysis. Am J Kidney Dis 2012;60:62-73.

16 Yeow KM, See LC, Lui KW, Lin MC, Tsao TC, Ng KF, Liu HP: Risk factors for pneumothorax and bleeding after CT-guided percutaneous coaxial cutting needle biopsy of lung lesions. J Vasc Interv Radiol 2001;12:1305-1312.

17 Lin KC, Tsai MY, Chi CL, Yu LK, Huang LH, Chen CA: Serum ferritin is associated with arterial stiffness in hemodialysis patients: results of a 3-year follow-up study. Int Urol Nephrol 2015;47:1847-1853.

18 Rogowicz-Frontczak A, Araszkiewicz A, Pilacinski S, Zozulinska-Ziolkiewicz D, Wykretowicz A, Wierusz-Wysocka B: Carotid intima-media thickness and arterial stiffness in type 1 diabetic patients with and without microangiopathy. Arch Med Sci 2012;8:484-490.

19 Acampa M, Guideri F, Di Donato I, Tassi R, Marotta G, Lo Giudice G, D'Andrea P, Martini G: Arterial stiffness in patients with deep and lobar intracerebral hemorrhage. J Stroke 2014;16:184-188.

20 O'Rourke MF, Hashimoto J: Mechanical factors in arterial aging: a clinical perspective. J Am Coll Cardiol 2007;50:1-13.

21 Selwaness M, van den Bouwhuijsen QJ, Verwoert GC, Dehghan A, Mattace-Raso FU, Vernooij M, Franco OH, Hofman A, van der Lugt A, Wentzel JJ, Witteman JC: Blood pressure parameters and carotid intraplaque hemorrhage as measured by magnetic resonance imaging: The Rotterdam Study. Hypertension 2013;61:76-81.

22 O'Rourke MF, Safar ME: Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertension 2005;46:200-204.

23 Paapstel K, Zilmer M, Eha J, Tootsi K, Piir A, Kals J: Early Biomarkers of Renal Damage in Relation to Arterial Stiffness and Inflammation in Male Coronary Artery Disease Patients. Kidney Blood Press Res 2016;41:488-497.

24 Byrom FB, Dodson LF: The causation of acute arterial necrosis in hypertensive disease. J Pathol Bacteriol 1948;60:357-368.

25 Selwaness M, van den Bouwhuijsen Q, Mattace-Raso FU, Verwoert GC, Hofman A, Franco OH, Witteman JC, van der Lugt A, Vernooij MW, Wentzel JJ: Arterial stiffness is associated with carotid intraplaque hemorrhage in the general population: the Rotterdam study. Arterioscler Thromb Vasc Biol 2014;34:927-932.

26 Zieman SJ, Melenovsky V, Kass DA: Mechanisms, pathophysiology, and therapy of arterial stiffness. Arterioscler Thromb Vasc Biol 2005;25:932-943.

27 Bolton WK: Nonhemorrhagic decrements in hematocrit values after percutaneous renal biopsy. JAMA 1977;238:1266-1268.

28 Khajehdehi P, Junaid SM, Salinas-Madrigal L, Schmitz PG, Bastani B: Percutaneous renal biopsy in the 1990s: safety, value, and implications for early hospital discharge. Am J Kidney Dis 1999;34:92-97.

29 Shidham GB, Siddiqi N, Beres JA, Logan B, Nagaraja HN, Shidham SG, Piering WF: Clinical risk factors associated with bleeding after native kidney biopsy. Nephrology (Carlton) 2005;10:305-310.