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Low systolic blood pressure values, renal resistive index measurement and glomerular filtration rate in a non-dialysis dependent chronic kidney disease population

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Summary
Objective: A longitudinal prospective case control study was organized to explore the relationships between glomerular filtration rate (GFR), renal resistive index (RRI) and blood pressure values in a non-dialysis dependent adult population affected by chronic kidney disease and exposed to low systolic blood pressure (SBP) values.
Material and methods: The study sample (54 patients: 31 males and 23 females with an average age of 61.7 ± 19.2 years) was randomly selected from a population of adult non-dialysis dependent patients that scored a SBP < 100 mmHg at the medical examination. The patients were equally divided in two groups defined by the presence and absence of chronic kidney disease, (i.e. a GFR less or greater than 60 ml/min/1.73 m^2, respectively). Patients were submitted to a full therapeutic and dietetic intervention to correct the hypotension until reaching a steady SBP > 100 mmHg.
Results: In the group with chronic renal disease, the comparison between the data recorded with SBP < 100 mmHg (t0) and those detected with SBP ≥ 100 mmHg (t1) showed a statistically significant decrease of serum creatinine as well as an increase of GFR (mean serum creatinine t0 – serum creatinine t1: 0.194 ± 0.35, p < 0.01; mean GFR t0 – GFR t1: -4.615 ± 8.8, p < 0.013). There was also a statistically significant reduction of the RRI (mean right kidney RRI t0 – mean right kidney RRI t1: + 0.082 ± 0.03, p < 0; mean left kidney RRI t0 – mean left kidney RRI t1: 0.076 ± 0.03, p < 0).
Conclusion: We concluded that, in CKD, when aorta is stiffed, a decrease of SBP can limit the renal perfusion that, in this condition, is mostly dependent by stroke volume, causing an increase of RRI and a decrease of GFR that we suppose as reversible with the restoration of SBP.

KEY WORDS: *Longitudinal prospective case control study; Chronic kidney disease; Renal Doppler ultrasonography; Renal resistive index; Low systolic blood pressure.*

INTRODUCTION

Recently it has emerged that in a non-dialysis dependent population suffering from *chronic kidney disease* (CKD) and subjected to conventional therapeutic and dietary treatment there is a statistically significant correlation between reduction of *renal resistive index* (RRI) (which if high, i.e. ≥ 0.7, represent an unfavorable prognostic index of renal disease progression) and reduction of *systolic blood pressure* (SBP) (1).
While it is known what should be the normal range for resistance indices (0.47-0.70) (2), the same cannot be said about the ideal thresholds for arterial pressure.
In this regard, although there is consensus in setting a target for blood pressure lower than 140/90 mmHg for most individuals, according to some Authors the achievement of blood pressure values lower than 130/80 mmHg could guarantee an improvement of the clinical outcome compared to the 140/90 mmHg threshold in adults with chronic kidney disease (3, 4). However, there is no consensus on what may be a minimum threshold for the same blood pressure and this despite it being well known how damage can occur if intensive blood pressure treatment is implemented in patients with chronic renal failure (3). In particular, in a cohort of over 650.000 American veterans suffering from chronic kidney disease, patients who had an "ideal" blood pressure (< 130/80 mmHg) showed an increase in mortality due to the inclusion in this group of individuals with low systolic and/or diastolic arterial values. This association was confirmed both in diabetics and in non diabetics, or in those who had microalbuminuria or not (5).
We organized a longitudinal prospective case control study with the intent to explore the relationships between renal function, renal resistive index (RRI) (used as a monitoring tool) and blood pressure values in a non-dialysis dependent adult population affected by chronic kidney disease and exposed to reduced systolic blood pressure values (SBP < 100 mmHg).

MATERIALS AND METHODS

A longitudinal prospective case control type study was planned.
The study sample (54 patients: 31 males and 23 females with an average age of 61.7 ± 19.2 years) was randomly selected from a population of adult non-dialysis dependent patients attending the outpatient nephrology clinic of *San Donato Hospital in Arezzo* that scored a systolic blood pressure < 100 mmHg at medical examination.
The study population was initially affected by hyperten-

sion and/or diabetes mellitus and/or chronic glomerulonephritis with or without chronic kidney disease or albuminuria. Patients with obstructive uropathy, acute glomerulonephritis, tubulointerstitial renal diseases, renal artery stenosis and malignant disease were excluded. Pregnant women and children were also excluded.

The total number of patients was selected to be equally divided in two groups defined by the presence (case) and absence (control) of chronic renal disease, defined by a *glomerular filtration rate* (GFR) less or greater than 60 ml/min/1.73 m^2, respectively.

The average GFR (calculated by the CKD EPI equation) (6), was 38.5 ± 12.7 ml/min/1.73 m^2 for case group and 82.3 ± 17 ml/min/1.73 m^2 for control group (Table 1). A prevalence of male gender was observed in both study and control groups. The anthropometric parameters (weight, height, age, sex and body mass index) did not differ statistically (at a significance level of 95%) in the two groups (Table 1). At the time of enrollment a written informed consent was obtained by all the patients.

After the enrollment the patients were submitted to a complete medical examination, comprehensive of the recording of weight and height. A measure of blood pressure was taken with a mercury sphygmomanometer applied around each patient's non-dominant arm after the patient had rested for 15 minutes in a sitting position and with his/her arm placed at the level of the heart. Two consecutives blood pressure recordings, taken at 5 minute interval, were averaged to provide clinic systolic and diastolic blood pressure values.

Blood and urine samples were obtained for measurement of serum creatinine, glycated hemoglobin and 24-hour urinary albumin excretion. Finally, renal Doppler ultrasonography examination was carried out by the same nephrologist experienced in ultrasound examination using the same ultrasound device that was a Logiq S7 (*GE Medical Systems Italy S.P.A. Milan, Italy*) sonographic system equipped with 3 to 5 Mhz transducers. Doppler signals were obtained from the interlobar arteries from the upper, middle and lower third of both kidneys and resistive index was calculated as the average of 6 measurements (3 from each of the 2 kidneys) taken for each patient. The Doppler angle was chosen as close to 0°as possible and special care was taken not to compress the kidney and not to have the patient performing Valsalva maneuver because both of them can increase the renal resistive index value. We recorded also the diameters in the longitudinal axis of each kidney and the cortical thickness of each kidney, measured in the portion closer to the upper pole and the lower pole of the same kidney.

Table 1.
Baseline characteristics of the population enrolled.

	GFR group (ml/min/1.73 m^2)	N°	Mean	Standard deviation	Mean standard error
Age t0 (years)	< 60	26	69.35	18.974	3.721
	> 60	25	54.36	16.671	3.334
Height (cm)	< 60	26	164.038	10.5356	2.0662
	> 60	24	167.5	8.3406	1.7025
Weight t0 (kg)	< 60	26	73.146	12.2153	2.3956
	> 60	24	76.817	15.1616	3.0948
Body mass index t0 (kg/m^2)	< 60	26	27.1753	3.6804	0.721794187
	> 60	24	27.25421	4.3580	0.88958826
creatinine t0 (mg/dl)	< 60	26	1.7892	0.6175	0.12112
	> 60	25	0.9456	0.1712	0.03424
GFR t0 (ml/min/1.73 m^2)	< 60	26	38.615	12.9648	2.5426
	> 60	25	82.96	17.3505	3.4701
proteinuria t0 (gr/24h)	< 60	25	0.2256	0.3884	0.0776993
	> 60	20	0.31645	0.5184	0.1159197
Hba1c t0 (%)	< 60	6	6.75	0.5089	0.2078
	> 60	4	5.975	0.5123	0.2562
SBP t0 (mmHg)	< 60	26	90.115	5.2484	1.0293
	> 60	25	91.6	4.7697	0.9539
DBP t0 (mmHg)	< 60	26	58.192	9.9881	1.9588
	> 60	25	66.72	6.9072	1.3814
right kidney RRI t0	< 60	25	0.746	0.06212	0.01242
	> 60	23	0.6265	0.05407	0.01127
left kidney RRI t0	< 60	24	0.7413	0.06306	0.01287
	> 60	20	0.63	0.07138	0.01596
right kidney diameter t0 (mm)	< 60	26	99.538	12.7349	2.4975
	> 60	23	109.478	13.5139	2.8178
left kidney diameter t0 (mm)	< 60	24	103.958	12.2065	2.4916
	> 60	22	116.045	12.0217	2.563
age t1 (years)	< 60	26	68.46	19.59	3.842
	> 60	25	53.04	16.352	3.27
Weight t1 (kg)	< 60	25	74.44	13.4028	2.6806
	> 60	23	78.448	15.3239	3.1952
Body mass index t1 (kg/m^2)	< 60	25	27.62463	4.0364	0.807297865
	> 60	23	27.65597	4.3396	0.904875025
creatinine t1 (mg/dl)	< 60	26	1.5946	0.43552	0.08541
	> 60	25	0.978	0.17769	0.03554
GFR t1 (ml/min/1.73 m^2)	< 60	26	43.231	13.5685	2.661
	> 60	25	81.4	21	4.2
proteinuria t1 (gr/24h)	< 60	22	0.323682	0.5561	0.118575
	> 60	18	0.342389	0.5020	0.1183385
Hba1c t1(%)	< 60	5	6.34	0.5727	0.2561
	> 60	2	6.05	0.2121	0.15
SBP t1 (mmHg)	< 60	26	114.654	10.2526	2.0107
	> 60	25	109.44	7.6381	1.5276
DBP t1 (mmHg)	< 60	26	74.154	13.5135	2.6502
	> 60	25	76.84	8.0658	1.6132
right kidney RRI t1	< 60	24	0.6638	0.06309	0.01288
	> 60	23	0.6348	0.07391	0.01541
left kidney RRI t1	< 60	24	0.665	0.06164	0.01258
	> 60	22	0.6355	0.07645	0.0163
right kidney diameter t1 (mm)	< 60	26	101	13.1088	2.5708
	> 60	24	110.417	14.7852	3.018
left kidney diameter t1 (mm)	< 60	24	104.458	12.7381	2.6002
	> 60	23	116.13	11.8372	2.4682

We recorded any data about the therapeutic and dietary treatment of the patients with special regard to the use of drugs that may interfere with the RRI determinations such as *angiotensin II receptor blockers* (ARBs) or *angiotensin converting enzyme* (ACE) inhibitors and beta blockers and the use or not of an hyposodic, hypoproteic, hypoglicemic as well as hypocaloric diet.

Then the patients were submitted to a full therapeutic and dietetic intervention to correct the hypotension by a reduction of dosage or removal of hypotensive drugs.

After a variable interval period, depending from the time necessary to recovery a steady systolic blood pressure > 100 mmHg for on average one year, patients were submitted again to a new medical examination comprehensive of the recording of weight and clinic blood pressure values with the same modalities above mentioned. Values of serum creatinine, glycated hemoglobin and 24-hour urinary albumin excretion were collected again and a new renal Doppler ultrasonography was carried out by the above mentioned nephrologist experienced in ultrasound investigation by using the same ultrasound device. All data relating to the therapeutic and dietary treatment used by the patients were recorded again.

Statistical analysis

Descriptive statistics included mean and standard deviation for quantitative data, and frequency count and percentage for qualitative data. For quantitative variables, groups were compared with the Student t test for unpaired data or the Mann-Whitney rank test, respectively depending on the normal or non-normal distribution of population data. The normality was assessed by applying the Kolmogorov-Smirnov test to sample data. Comparisons between t0 and t1 were made using the Student t test for paired data or the Wilcoxon rank test for normal or non-normal data respectively. For dichotomous qualitative variables, frequency counts between groups were compared using the Fisher exact test applied to 2 x 2 contingency data. A statistical significance level of 95% was chosen for all statistical analyses ($p < 0.05$) that were performed using SPSS software, version 10.

RESULTS

Considering the two groups with GFR < 60 and GFR ≥ 60 ml/min/1.73 m^2 separately, within the group with GFR < 60 ml/min/1.73 m^2, the comparison between the data recorded with systolic blood pressure (SBP) < 100 mmHg (t0) and those detected with SBP ≥ 100 mmHg (t1) showed that, passing from time 0 to time 1, there was a statistically significant increase of *body weight* (BW) (mean BWt0 - BWt1: -1.428 ± 3.2; $p < 0.04$), although the clinical significance of this observation was not very relevant as it was about 2%. A statistically and clinically significant decrease of serum creatinine as well as a statistically and clinically significant increase of the glomerular filtrate rate was observed (mean creatinine t0 - creatinine t1: 0.194 ± 0.35; $p < 0.01$; equal to a reduction of approximately 11%; mean GFR t0 - GFR t1: -4.615 ± 8.8, $p < 0.013$, equal to an increase of over 12%). A statistically and clinically significant decrease of

the renal resistive index (RRI) was also observed (mean right kidney RRI t0 – mean right kidney RRI t1: + 0.082 ± 0.03, $p < 0$, equal to a 10.8% reduction. Mean left kidney RRI t0 – mean left kidney RRI t1: 0.076 ± 0.03, $p < 0$, equal to a reduction of 10.2%).

Comparison for paired data also identified a statistically significant reduction of the glycated hemoglobin data, to which, however, given the small number of diabetics on the total (6 out of 27 equal to about 22% of the total), it was not possible to attribute a clinical relevance.

Within the control group (GFR ≥ 60 ml/min /1.73 m^2) there was no statistically significant variation between times t0 and t1 except, of course, the increase in the arterial pressure values (systolic and diastolic), a finding that was also found in the cases (GFR < 60 ml/min /1.73 m^2) confirming the respect of the working hypothesis.

Finally considering the two groups together, the comparison for all the variables between time zero and time 1 confirmed a statistically significant increase of body weight as well as a statistically significant decrease in serum creatinine levels and a statistically significant reduction of the intrarenal arterial resistance indices of the right kidney and of the left kidney. In the comparison for paired data a statistically significant reduction of glycated hemoglobin was found for the entire population such as , both for the two groups separately.

The comparison of data from the two groups for all the variables, confirmed the quality of the above exposed observations by detecting a significant difference between groups for creatinine at both time intervals, GFR at both time intervals, right kidney RRI and left kidney RRI at time 0 as well as right kidney diameter and left kidney diameter at both time intervals.

DISCUSSION

A unique feature of the kidney is that it is continually and passively perfused at high volume flow throughout systole and diastole. Its vascular resistance is very low so that in comparison to other vascular beds resistance is closer to input and characteristic impedance (7). It is therefore susceptible to upstream influences that may increase fluctuations of pressure and flow, whereas small vessels in other organs are protected by relatively intense vasoconstriction upstream (7).

In patients with *chronic kidney disease* (CKD) and *end-stage renal disease* (ESRD) all epidemiological studies have clearly shown that an accelerated arterial and cardiac aging by atherosclerosis is characteristic of these populations. Atherosclerosis is a generalized arterial disease of the arterial intima characterized by the presence of plaque and occlusive arterial lesions. The functional consequence of these structural alterations is hardening/sclerosis of vessel walls (arteriosclerosis) and loss of compliance, that is increased stiffness.

When the arterial premature aging involves the aorta it stands out for an aortic stiffening and for the disappearance of stiffness/impedance gradients between the central and peripheral arteries. These changes have a double impact: on the heart, upstream, with high systolic and pulse pressures and decreasing diastolic pressure, increased cardiac afterload and arterial circumferential

stress. All these factors promote *left ventricular hypertrophy* (LVH) which may evolve toward heart failure. Downstream, on renal and brain microcirculation, with decrease in glomerular filtration and cognitive functions (8). Proof of all this is the fact that strong associations between aortic stiffness and indicators of renal dysfunction (glomerular filtration rate and microalbuminuria) have been described such as with cognitive impairment and dementia besides (as previously mentioned), left ventricular hypertrophy and left ventricular dysfunction (8). Physiologically, the higher compliance of the aorta coupled with a progressively lower compliance in peripheral vessels creates a "*stiffness gradient*" that works as a "*hydraulic filter*" and acts to buffer pressure pulsations and their transmission to microcirculation and capillary network (principally in the main parenchymal organs such as the kidney and the brain). The more distensible the arterial wall (that is, the lower the stiffness) the smoother the provision of proper flow to peripheral tissues. When the aorta is rigid and cannot be stretched, the entire stroke volume flows through the arterial system and peripheral tissues only during systole with two consequences: intermittent flow and short capillary transit time with reduced metabolic exchanges (9).

Therefore we believe that, in such a condition, a reduce of the systolic arterial blood pressure, such as a SBP < 100 mmHg, can further and definitely limit the renal perfusion that is already damaged by lacking of a proper aortic buffer.

About the Doppler *renal Resistive index* (RRI) described by *Pourcelot* (10) ((peak sistolic velocity-end diastolic velocity)/peak sistolic velocity) we observe that RRI is a traditional index used as a measure of vascular resistance. A value of 0.60 is considered as a normal value for renal RRI, whereas 0.70 is usually considered the upper threshold of normal RRI in adults. Several factors have been described to influence Doppler renal arterial waveform and therefore the RRI as renal vascular compliance, central hemodynamics (especially arterial stiffness, blood pressure and heart rate), and other factors including age, underlying acute or chronic renal disease and drugs too (11). In this regard it is known that RRI decreases with use of *renin angiotensin system* (RAS) inhibitors, due to hemodynamic changes induced by these antihypertensive agents (12) while RRI, significantly and independently, increased with use of beta-blockers (13).

In the setting of an acute kidney injury the first clinical application of RRI was the detection of renal obstruction because renal vasoconstriction is believed to be a key factor in the pathophysiology of acute kidney obstruction. Platt et al had proposed that an RRI ≥ 0.7 was in favor of an acute renal obstruction and may precede pyelocalicectasis (14). Afterwards in 91 patients with *acute kidney injury* (AKI), *Platt et al.* demonstrated that mean RRI was significantly higher in patients with persistent AKI than in patients with transient AKI (15). Lastly in a small number of patients with septic shock, *Deruddre et al.* have shown a significant decrease in renal RRI when increasing *mean arterial pressure* (MAP) with norepinephrine from 65 to 75 mmHg. This study suggests that Doppler renal ultrasound may help to determine in each patient the optimal MAP for renal tissue perfusion and

may be a relevant end point to titrate the hemodynamic treatment in septic shock (16). Accordingly, we believe that RRI may be used as a noninvasive and repeatable tool to assess changes in renal perfusion and it may be useful to determine the optimal therapeutic/preventive modalities for kidney perfusion at the bedside (11).

CONCLUSIONS

On the basis of all the above mentioned, we therefore believe that, when in CKD the aorta is stiffed and cannot be stretched, a decrease of the systolic arterial blood pressure, even temporary, can limit the renal perfusion that, in this condition, it is mostly (or entirely) a function of the stroke volume, causing an increase of the RRI and a reduction of the glomerular filtration rate as proven by this paper.

This scientific work shows that reduced systolic arterial pressure values (i.e. SBP < 100 mmHg) have an effect of worsening of renal function only when there is already a pre-existent significant impairment of the GFR (such as a GFR < 60 ml/min/1.73 m ^ 2) and not when a similar kidney damage is not present. However we believe that, since this decrease in renal function is a function of reduced systolic arterial pressure values, the restoration of the systolic pressure may recover the decrease of renal function that therefore can be considered reversible.

These observations appear congruent with what has already been reported by *Judd et al.* and *Kovesdy et al.* (3, 5) who, inspired by the association of low arterial pressure values with an increase in mortality, warns that "*lowering SBP to the strict limits recommended by current guidelines (i.e. SBP < 130 mmHg or even lower) in patients with CKD (at the expense of lowering DBP below approximately 70 mmHg) may be deleterious*".

Above all, the data of this study are fully supported by the results of the SPRINT trial (17) which showed as an intensive blood pressure control (i.e. SBP < 120 mmHg) produces a significant cardiovascular benefit in high-risk patients with hypertension at the price of an higher risk of hypotension, syncope, and accelerated reductions in GFR.

In fact in the SPRINT trial, acute kidney injury or acute renal failure occurred more frequently in the intensively treated group than in the standard-treated group and the Authors of this trial believe that the differences in adverse renal outcomes may be related to a reversible intrarenal hemodynamic effect of the greater reduction in blood pressure.

Furthermore the Authors of the SPRINT trial, as the Authors of the present paper, believe that with the currently available data, there is no evidence of substantial permanent kidney injury associated with a treatment with the goal of lower systolic blood-pressure although the possibility of a long-term adverse renal outcome cannot be excluded (17).

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