

Increase Renal Tubular Pressure to Treat Congestive Renal Failure

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Research

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Abstract

Background: Congestive renal failure commonly result from cardiorenal syndrome related renal venous hypertension(RVH) which is more linked to the renal venous pressure than mean arterial pressure and systematic vascular resistance. But its mechanism and treatment strategy is still being explored.

Methods: We did an investigator-initiated,open-label study to explore a novel treatment strategy and mechanism of renal venous hypertension related acute kidney injury(AKI).A patient with acute kidney injury(AKI) due to cardiorenal syndrome related renal venous hypertension was enrolled.The estimated pressure of renal vein (ePrv) was measured by ultrasound. Prior to the trial,residual urinary was detected by bedside ultrasound so as to rule out lower urinary tract obstruction.A three-lumen catheter was inserted into bladder for elevating tubular pressure and monitor intrabladder pressure.In the first phase,pressure of intrabladder was maintained equal to ePrv+8mmHg for 3 hours.In the second phase, intrabladder pressure was adjusted and maintained equal to ePrv for 21 hours. The urine volume is equal to the fluid expelled from bladder minus infused 0.9% Sodium chloride.

Result: 130 milliliter urine output was secreted in the first phase and 370 milliliter in the second phase.A total of 500 milliliter urine output was secreted during the trial period (24 hours). 5 days after treatment, the patient's creatinine level dropped significantly.

Conclusions: We first proposed a new therapeutic exploration, acute kidney injury secondary to cardiorenal syndrome related renal venous hypertension can be treated by increasing tubular pressure.Tubular compressed or even collapsed under renal venous hypertension may be an important mechanism of acute kidney injury due to RVH.

Background

Renal venous hypertension(RVH) occurs commonly in patients with cardiorenal syndrome. Elevated venous pressure is associated with impaired renal function and mortality [1]. Accumulated studies had showed that RVH resulted in kidney injury independent of cardiac output (CO), arterial systolic blood pressure (SAP), arterial diastolic blood pressure (DAP), mean arterial pressure(MAP), pulmonary capillary wedge pressure (PCWP) and systematic vascular resistance(SVR) [2]. However,the mechanism of this unique phenomenon is unclear.

In the 1930s, the correlation between acute renal vein obstruction and kidney dysfunction, reduced renal blood flow and sodium retention was reported [3]. By the 1960s,it was recognized that renal venous hypertension occurred in chronic heart failure [4]. Since then,the mechanism of AKI due to renal venous hypertension has been explored by a variety of studies.Early studies found that intrarenal distribution of blood flow occurred in renal venous hypertension [5-9]. But other researchers did not confirm the same phenomenon [10-11]. Experimental studies in vitro and in vivo show that elevated renal interstitial pressure and proximal tubular pressure in renal venous hypertension were reported by a lot of studies [12-16]. Some studies have described the overall renal hemodynamicin of renal venous hypertension.They

found that initial increase in renal venous pressure from about 0–15 mmHg did not result in any change in either peritubular capillary pressure or intratubular pressure. But a further increase resulted in a linear increase in pressure in both the tubules and peritubular capillaries, as well as interstitial pressure [12]. As renal venous pressure gradually increases, it in turn affects RBF, GFR and then urine output. Lately, a significant increase in the width of Bowman's had been found in animal RVH models [12-16]. Owing to the outfall of tubular is open to low pressure area of outside kidney, the expansion of Bowman's width hint the possibility of tubules compressed or even collapsed in renal venous hypertension. We have explored a new treatment method in the clinic to treat acute kidney injury secondary to renal venous hypertension associated with cardiorenal syndrome by increasing renal tubular pressure.

Methods

Study design and the patient:

We did an investigator-initiated, open-label study to explore a novel treatment strategy and mechanism of renal venous hypertension related acute kidney injury (AKI). A 78-year-old man presented to the department of cardiology of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine because of cardiac and renal failure.

The patient underwent mitral valvuloplasty 36 years ago for rheumatic heart disease. A mitral mechanical valve replacement was performed 17 years ago. From fifteen years early, he was repeatedly hospitalized in many hospitals for dyspnea and leg edema and was diagnosed with heart failure. Two weeks early, the patient was admitted to another hospital due to warfarin-induced gastrointestinal bleeding. There was no history of diabetes or chronic kidney disease except for congestive renal failure.

The patient was admitted to our hospital because of worsening dyspnea and edema for a week. On examination, the temperature was 36.3°C, orthopnea, the blood pressure 133/80 mmHg, the heart rate 123 beats per minute, the pulse 101 beats per minute, and the respiratory rate 25 breaths per minute. The patient's head and neck examination showed a distend neck vein jugular. He had good breath sounds bilaterally with rales at half of both lungs but without wheezing. Heart examination showed a metal-like valve sound. S2 accentuation can be heard in the pulmonary valve auscultation area. The abdominal examination furthermore revealed hepatomegaly and ascites sign. There was moderate pitting edema in two legs. An ECG showed atrial fibrillation, right bundle branch block and a heart rate of 129 bpm. A chest radiograph showed enlarged heart images and increased extravascular lung water. Two days after admission, a cardiac ultrasonographic examination was performed (Table 1). Thoracic ultrasound: bilateral pleural effusion (left 7.7 cm, right 10.5 cm).

Table 1
Results of Echocardiographic Studies

Variable	Result
Left atrium	55*58mm
Aorta (mm)	29.8mm
Left ventricular internal end-diastolic diameter	42mm
Left ventricular internal end-systolic diameter	20mm
Posterior wall thickness	12mm
The thickness of the interventricular septum	12mm
Left ventricular ejection fraction	82%
Right atrium (mm)	55*38mm
Right ventricle	47.9mm
Main pulmonary artery	21mm
Estimate pulmonary artery pressure	49mmHg
Mitral valve	metal valve(replaced)
Tricuspid valve	moderate regurgitation
Inferior vena cava	27mm

Laboratory-test results after admission showed the NTpro-BNP elevated to 5420ng/L and the Creatinine was 102umol/L. Medications after admission included metoprolol (12.5mg twice daily), Spironolactone (40 mg once daily), torsemide (20mg twice daily).

On the 5th day after admission, there were chills and fever. Urgent blood test showed that white blood cell(WBC) of venous blood increased to $11.9 \times 10^9/L$, Urgent urine test showed urine WBC increased to 1424/uL. Meropenem was given according to empiric selection(0.5g, every 12 hours, according to creatinine clearance rate). Blood bacterial culture reported a great deal of G-bacillus on the following day and then was identified as Klebsiella Pneumoniae (sensitive to meropenem) 5 days later. During the early days of anti-infective therapy, systolic blood pressure reduced (from 115mmHg to 89mmHg) and heart rate increased (from 87bpm to 137bpm). After fluid resuscitation and antibiotic treatment, blood pressure and heart rate return to normal gradually. But urine volume reduced dramatically and acute kidney injury occurred. Anuria sustained for 3 days and creatinine level increased to 202.5umol/L after infection controlled. Bedside ultrasound examination showed diffuse pathological change of kidney, bilateral renal atrophy (length of right:9.8 centimeter, length of left:10.3 centimeter) and enlarged IVC(2.9 centimeter). The level of NT-proBNP elevated to 16300ng/L. The patient complained of severe dyspnea,

leg edema, and abdominal distention. Furosemide(500mg/d) had been injected for three days and fluid input had been strict restricted but failed with anuria. The patient refused hemofiltration treatment.

Procedures:

After communicating with the patient and his family, we decided to try to increase the pressure of the renal tubules. The jugular venous pressure was 19 mmHg measured by ultrasound and was taken as the estimated renal venous pressure(ePrv=19 mmHg). The blood test was retested before the trial (Table 2). Before trial, urinary system ultrasound confirmed no urinary tract obstruction.

Table 2
Laboratory Data before and after the trial

Variable	baseline	7 days after the trial
Blood WBC	4.33×10 ⁹ /L	2.77×10 ⁹ /L
Neutrophils	66%	75.4%
HGB	78g/L	81 g/L
Urea nitrogen	11.92mmol/L	11.33 mmol/L
Creatinine	202.5umol/L	75.7 umol/L
NT pro-BNP	16300ng/L	6433 ng/L
albumin	30.9g/L	32.4g/L
Bilirubin(total)	15.0umol/L	12.4 umol/L
ALT	8u/l	20 u/l
AST	19u/l	44u/l
Potassium	3.6mmol/L	4.97 mmol/L
Sodium	136.8 mmol/L	140.2mmol/L

A three-chamber catheter was inserted in the bladder and 0.9% sodium chloride was injected into the bladder at a speed of 800 milliliter per hour through one cavity of the catheter whereas the other cavity of the catheter was connected to a pressure monitor. Taking the upper edge of the symphysis pubis as zero points, Pbla was measured and monitored(1mmHg=1.33cmH₂O). When the Pbla rised to the level of 27mmHg(ePrv+8mmHg), stopped infusion sodium chloride and maintained pressure level of 27mmHg (ePrv+8mmHg) for 3 hours by reopening the clip intermittently or re-injecting 0.9% sodium chloride intermittently according to the change of Pbla .After 3 hours,the Pbla was reduced to the level of 19mmHg (Pbla=Prv) and maintained the pressure level of 19mmHg for 21 hours. Record the urine output

during the trial and cumulate the total urine volume of 24 hours (the urine output is equal to the fluid expelled from bladder minus infused saline).

Results

130 milliliter urine output was secreted from the kidney in the first 3 hours and 370 milliliter in the following 21 hours. Urine volume increased from lower than 50 milliliter per day to 500 milliliter per day in the first 24 hours. There were not infection, bleeding and worsening renal function occurred. 5 days after treatment, the patient's creatinine level dropped significantly (Table 2).

Discussion

We adopted a new strategy to increase renal tubular pressure to treat RVH-related AKI. The result showed a significant clinical effect. Urine volume increased from lower than 50 milliliter per day to 500 milliliter per day in the first 24 hours. This physics and mechanics strategy avoided loop diuretic side effects such as diuretic resistance, activating the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS), which could induce prerenal response and reduce renal blood flow (RBF) [17–18]. This strategy also avoided hemofiltration method's side effects such as injury, infection and expensive cost. However, the effect of 500 milliliter urine output per day did not meet clinical requirement of 800–1000 milliliter or more per day for severe volume overload patient with cardiorenal syndrome. Possible reasons are as follows: i) residual effect of antibiotic: meropenem was stopped at the former day of the trial, but residual side effect on the kidneys may still exist; ii) renal venous hypertension as a major factor of affecting renal perfusion still exists: a volume of 500 milliliter fluid reduction did a little influence on severe volume overload and renal A-V pressure difference; iii) hypoproteinemia, The concentration of albumin was 30.9g/L during the trial. Hypoproteinemia may result in renal interstitial edema which in turn results in a reduction of renal perfusion or other effects. No urinary tract infection, urinary tract injury, bleeding or deterioration of renal function occurred during the whole intervention. This strategy is a successful attempt to treat overload in patients with cardiopulmonary syndrome.

Mechanisms Of Kidney Injury Due To Renal Venous Hypertension

In this case study, injecting saline into bladder to increase renal tubular pressure improved anuria of kidney injury. The result is of great significance for exploring the mechanism of kidney injury due to renal venous hypertension. Owing to congestive renal failure depending more on RVH or CVP than on cardiac output, mean arterial pressure and systematic vascular resistance [2]. There may exist other mechanism or mechanisms of RVH related kidney injury. The possible mechanism, independent of the arterial-venous pressure difference mechanism, have been explored by a variety of studies. Intrarenal distribution of renal blood flow was found by some researchers [5–9] but others did not [10–11]. So early studies showed that mild to moderate elevated

RVH(lower than 15mmHg) did not influence peritubular capillary pressure or intratubular pressure [12, 19]. A further increase resulted in a linear increase in pressure in both the tubules and peritubular capillaries,as well as interstitial pressure.In summmary, as renal venous pressure gradually increases, it in turn affects RBF, GFR and then urine output.Latterly, elevated renal interstitial pressure and proximal tubular pressure in renal venous hypertension were reported by all of the related studies[12-16]. Interestingly,they were consistent with each other. Expansion of width of Bowman's were found by the latest RVH studies[15-16]. Simultaneously,reduced urineoutput were found as well. Given the outfall of tubules is open to low pressure area of outside kidney,this contradiction is a mystery and it may allure us to explore the mechanism.

Based on these previous findings, we proposed a hypothesis that renal tubule compressed or even collapsed under renal venous hypertension condition may be an important pathophysiological mechanism(figure1). In detail, renal venous hypertension result in tubular capillaries expansion and renal interstitial edema and expansion, and in turn result in compressing tubule which increase the pressure of Bowman's. Increased Bowman's pressure further leads to a decrease in GFR and compressed or even collapsed tubules impede urine output. At present, it has not been confirmed that renal tubular obstruction or occlusion occur under the condition of renal venous hypertension. The enrolled patient's tubular pressure was elevated by fluid pressure reverse transmission along the urinary tract and achieved diuretic effect. The finding of this study has filled the gap of evidence indirectly. Prior to the trial, 1.96 milliliter residual urinary was detected by bedside ultrasound so as to rule out lower urinary tract obstruction. Upper urinary tract obstruction was excluded after ultrasound examination showed no hydronephrosis in both renal pelvis. These ultrasound image results supported the hypothesis indirectly by excluding other cause of acute kidney injury.

Conclusions

Anuria associated with acute kidney injury caused by renal venous hypertension can be treated by increasing renal tubular pressure.

Declarations

Ethics approval and consent to participate[Signed, see attachment.Consent for publication[Signed, see attachment.

Acknowledgments:Declared none.

Availability of data and materials: Information about a real patient is available at pangxxbj@163.com.Dr.Xingxue Pang respond to the information, sharing their reasoning with the reader.

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Authors' contributions: Xian Wang and Xingxue Pang proposed clinical trial design and implemented the trial. Xiaowan Han participated in the trial experiment. Xingxue Pang and Xiaowan Han composed the manuscript and figure.

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Figures

Image not available with this version

Figure 1

hypothesis mechanism of Kidney injury due to renal venous hypertension