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Theoretical Model of Back Filtration for Acute Tubular Obstruction in Oliguric/Anuric Acute Kidney Injury

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Abstract

Introduction. It is a very common clinical observation that cardiogenic and septic shocks as well as acute tubular damages result in anuria and acute kidney injury. This condition is associated with high mortality. The model was developed to protect the kidneys from acute damages and recover to its partial functional potential.
Methods. The governing equations by the renal modelers across the world for renal function, which include glomerular and tubular functions, were studied. A theoretical model for a single kidney was developed based on the governing equations.
Results. The single nefron glomerular filtration rate (SNGFR) can be modified by transient occlusion. The backpressure transiently reduces filtration, however, the permeability (k) and surface area (S) of the filtration and nephron recruitment (n) increases. By altering the chloride levels (Σ) in the macula densa the tubuloglomerular feedback (g) and the afferent arteriolar diameter can be modified or dilated. By increasing the back diffusion, the hydrostatic pressure and the diameters of the ascending as well the descending tubular sizes can be increased. By altering the pH of the back diffusion fluid, the obstructed tubules can be opened. By addition of proteolytic enzymes the inflammasomes and inflammatory proteins could be modified or degraded and the tubular recovery may be achieved. By increasing the back diffusion pressure to hydro-nephrotic range the glomerular filtration pores could be cleansed and opened. Hence, the final model is transient pulsatile occlusion of the pelvicalyceal ureter and back diffusion by fluids of low chloride and pH near 5.5, and pressure of about 30 mm Hg with proteolytic enzymes in the fluids. The proposed time for occlusion of the ureter could be about 5 to 6 min.
Conclusions. There is potential for a novel back-diffusion method for the recovery of anuric or oliguric kidneys. Further experiments need to be performed in animal models to prove the concept.

Key words: back diffusion, acute renal failure, mathematical models

Introduction

Acute renal shut down due to shock syndromes is often seen in clinical practice [1]. The etiology leading to this condition resulting in anuria is varied. It could be pre-renal causes, renal glomerular or tubular obstructive pathologies. Septic shock syndromes [2] and cardiogenic shock disorders [3], though the pathogenesis is different, frequently lead to oliguria/anuria, which could result in fatal outcomes. Snakebite with hemolytic disorders leads to tubular obstruction and anuria or oliguria. Drug/contrast-induced renal failure leads to renal tubular obstruction. A recovery of this oliguria renal failure is difficult with supportive therapy with optimal fluids, diuretics, and dialysis if required. Inotropes are frequently required to correct associated hypotension. High mortality is observed in these scenarios irrespective of the etiology leading to oliguric renal failure. Hence, in this study a novel treatment is proposed by following the existing governing equations in renal function.

The model of back filtration in acute kidney injury

Acute renal failure due to various etiologies results in tubular obstruction and restriction in the glomerular filtration process. The various etiologies often lead to activation of inflammatory cascade through inflammasomes, and a variety of proteins are synthesized in the tubules, and also the ultrafiltrated inflammatory proteins tend to occlude the glomerulus and the tubules [4-6]. Heat shock proteins also play an essential role in acute kidney diseases [7]. A search was made for mathematical modeling of renal physiology and transport, and the governing equations were studied [8-13].
A model is proposed for this condition, which could eventually reduce the renal failure or relieve the oliguria. The normal pelvic pressure is about 7 to 13 cm of water, and in hydronephrosis, it reaches about 20 to 30 cm of water or more. Hence, raising the pressure to about 23 mm Hg or 30 cm of water would result in hydronephrosis and functionally it induces back diffusion in the nephrons [14-16].

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The concept is a transient occlusion for about 5 to 6 min. of the ureter of the unilateral kidney, which could result in back diffusion, which is similar to the hydro-nephrotic range of changes. Also, a device design has been proposed which could have mechanisms of perfusion in the distal end of the catheter. Figure 1 shows the proposed device method and the possible variations that can be done with this simple balloon catheter system. The proximal end of the catheter is located near renal pelvis with perforations in the distal end of the catheter. The proximal end of the catheter can be connected to a pressure controlled by the system. The pressures and the pulses of applied pressures can be altered.

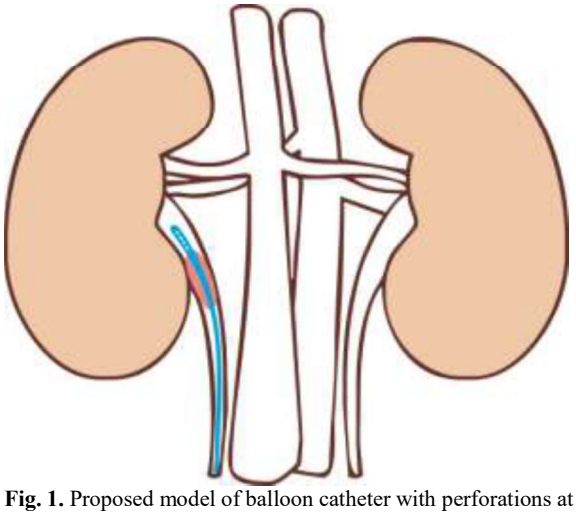

Fig. 1. Proposed model of balloon catheter with perforations at the tip for fluid infusion and pressure transmission

A balloon, located in the distal tip which could be inflated, and the pressure in the renal pelvis could be increased to the hydro-nephrotic range which is usually about 20 mm Hg. When the renal pelvic pressure increases to 23 mmHg (30 cm of water) hydro-nephrotic changes in the glomerulus and the tubules can be introduced, which is dilatation of the tubules and the globular apparatus. By pulsatile application of the pressures, the effects in the renal tubules and the glomerulus can be more exaggerated than the constant non-pulsatile application of pressures through the proposed catheter model. A pulsatile model has advantages over a continuous flow model [17]. This has been consistently observed in the left ventricular assist devices, which perform better with pulsatile characteristics. This is due to reduced wall shear stress ($\delta p/\delta y$) and the pressure in the center of the lumen ($\delta p/\delta x$) is higher compared to the continuous flow methods, in which the pressure dynamics is vice versa. However, the pulsatile design is not mandatory as the fluid is applied in lower pressure, unlike left ventricular assist devices, which function at higher pressures.

The single nefron glomerular filtration rate (SNGFR) would be modified by this transient occlusion. The back-pressure transiently reduces filtration due to higher glomerular pressures, however, the permeability (k) and surface area (S) of the filtration and nephron recruitment (n) increase. The chloride levels highly control the tubule-glomerular feedback, which has a major role in renal auto-regulation. By altering the chloride levels in the macula densa the tubuloglomerular feedback (γ) and the afferent arteriolar diameter can be modified or dilated. When the chloride levels are reduced in the back diffusion, fluid afferent arteriolar vasodilatation could be achieved.

When the back diffusion is increased further, it could result in tubular injuries. The time frame of 5 to 6 min. is suggested as prolonged pressures can result in damage to the ureters or the pelvicalyceal junction. It has to be emphasized that this model is proposed to be used in one kidney.

Acidification is a known technique to denature proteins. Acidification of the fluid used to perfuse the nephrons with back diffusion can result in denaturation of the obstructive proteins in the tubules [18,19]. Normal pH of the urine is in the range of 5 to 8 [20,21]. A pH of about 5.5 is physiologic, and it would result in acidification of obstructive proteins in a milieu of tubular obstruction induced by the inflammasomes and ultrafiltrated proteins.

Increasing the temperature of the back diffusion fluids to the upper limit of physiological milieu, for example, 39 to 40C, could further accelerate the lytic changes in these proteins [22-24]. This is a usual technique observed for denaturation of proteins. However, a very high increase in temperature could lead to release of heat shock proteins in the tubular podocytes. Hence, a safe temperature limit has to be determined by experimental studies.

Adding specific proteolytic enzymes in appropriate/diluted doses can disrupt the tubular obstruction, and it can even disrupt or dissolve the deposits beneath the glomerular membranes. Pepsin and trypsin are powerful proteolytic enzymes, which are well known for their proteolytic activity [25-28].

This proposed model could be used for a wide range of etiologies causing this condition. Hence, it is necessary to investigate this concept for further analysis. Conversion of this oliguria to non-oliguric renal failure has a significant therapeutic advantage in a critically ill patient, and if the modeling works in real-time patients, it will have a significant therapeutic benefit and lifesaving. This will have mortality benefits and reduction in the hemodialysis or development of chronic renal failure in the future. The catheter model is simple and practical, and it is easy to design this balloon-catheter device. At this moment, it is a theoretical proposal, which needs to be validated with animal models after creating an oliguria renal failure. Also, as a therapeutic measure it is proposed in only one kidney in the initial stages, and if successful results are obtained in the experiments, bilateral interventions could be tried to recruit more functional nephrons.

Conclusion

This novel method has a potential to induce transient back diffusion in the anuric kidney for recovery of renal function as a theoretical method. Further experiments need to be performed in animal models to evaluate the clinical benefits of the proposed technique.

Conflict of interest statement. None declared.

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