ABSTRACT

Objective: To evaluate a mathematical model to study the dynamics of renal failure in patients with acute kidney injury. Methods: A mathematical model was applied to simulate the "dynamic path of renal lesion" in patients with acute kidney injury. Results: The dynamics of glomerular filtration rate was simulated with the real data of a patient attended at the Intensive Care Unit. Conclusions: The applicability of a mathematical model allowed studying the modifications of renal failure along the occurrence of acute kidney injury.

Keywords: Kidney/injuries; Mathematical models; Creatinine

INTRODUCTION

Acute renal failure (ARF) is defined as an abrupt decrease in the renal function, representing a severe clinical problem usually associated with high mortality rates\(^1\). Although there are several syndromes associated with acute kidney injury, this study will only refer to the clinical-pathological entity called acute tubular necrosis.

The clinical course is didactically divided into three phases. The initial phase, corresponding to organ exposure to nephrotoxic agent or period of ischemia; the maintenance phase with onset of the kidney injury, characterized in several cases as decreased urinary output, with an approximate duration of one to three weeks; and the recovery phase, associated with the process of tubular regeneration and partial or total repair of the initial injury\(^4\). The duration of each phase is determined by the presence of preexisting kidney injury and nature (and duration) of the insult.

The progress of clinical treatment in ARF has been frustrating. Several therapeutic agents (e.g., growth factors, antiapoptotic agents, etc.) in ARF did not reproduce in the clinical setting the good results obtained in experimental models\(^3\). This scenario can be partially justified by difficulty in identifying the above-mentioned phases in practice.

Because ARF is an extremely dynamic disease, it can be postulated that mathematical models describing this dynamics may guide us towards a better understanding of this condition.

OBJECTIVE

To evaluate the use of a mathematic model involving creatinine production and filtration to study the dynamic changes of renal function in patients with acute kidney injury.

METHODS

Mathematical model of acute kidney injury dynamics

The model proposed by Hübler e Buchman\(^7\) takes into account the variation rates of quantities involved in homeostasis of serum creatinine level, relating these rates in a system of differential equations in a way that it is possible to simulate several system status.
dynamic system status is specified at any moment by the value of creatinine concentration and the rate at which it varies over time (phase space).

The concept of phase space was initially described by the French mathematician Henri Poincaré, in the 19th century, in the analysis of all possible stages of a certain physical phenomenon\(^9\). Each possible status is represented by a dot in the phase and, as time goes by, the union of these dots describes the system path over time.

Therefore, the differential equation involved predicts the speed with which this concentration varies over time. The theoretical basis for the model is that the quantity of creatinine in plasma becomes invariant if muscular production is balanced by renal clearance (secretion and filtration). These variables are related in the differential equation below:

\[
d\frac{[Cr]}{dt} = \frac{1}{V} (R - S) - \frac{1}{V} (GFR + \frac{dV}{dt})Cr
\]

where,

- $Cr$: serum creatinine
- $V$: body water volume
- $R$: rate of creatinine production
- $S$: rate of tubular creatinine secretion
- $GFR$: glomerular filtration rate
- $d\frac{[Cr]}{dt}$: plasma creatinine variation rate.

This model was implemented by using the MATLAB software so that it could be simulated the “dynamic path of kidney injury”, by using serum creatinine measurements.

**RESULTS**

Subsequently, there is a simulation using real data of a patient who developed acute kidney injury with total recovery of renal function.

**Clinical case**

A 73-year-old female hypertensive patient was admitted at the emergency room with intense headache, not characterized upon the admission examination, measured temperature of 38°C and body chills. No abnormalities in the physical examination at admission were showed. General exams were requested, along with brain magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) exam. Brain computed tomography (CT) and MRI without abnormalities. CSF showed 330 cells (82% lymphocytes); proteins, 87; glucose, 49; chloride, 684; lactic acid, 17.5. The result of bacteria was negative. Presumptive diagnosis of lymphohemocytic meningoencephalitis (viral meningitis? herpetic meningoencephalitis?). Acyclovir administration was initiated. Patient evolved with an increase in creatinine levels from 0.7 to 2.6 mg/dl (presumptive diagnosis of drug-related kidney injury?), nonoliguric. Urinalysis with no abnormalities; the ultrasound of kidneys and urinary tract did not show signs of chronic nephropathy. Patient was evaluated by Nephrology and the hypothesis of nephrotoxic acute kidney injury caused by acyclovir was hypothesized. Serum creatinine achieved 5.5 mg/dl with total recovery of renal function. There was no need for dialysis treatment.

In Figure 1, a progressive increase in serum creatinine from 0.7 to 5.5 mg/dl in approximately four days can be seen, followed by a return to values close to the baseline values within ten days of clinical course.
In Figure 3, creatinine variation rate is plotted with serum creatinine level. This type of graphic better illustrates the system course over time. One can verify that at S timepoint (t2), corresponding to a creatinine level of 5.5, there is no variation in the rate of creatinine, suggesting a critical point in the system. However, the rate of creatinine increase can be noted in S timepoint (t1), in which the curve becomes more pronounced, suggesting a system phase transition. At this point, glomerular filtration would theoretically stop decreasing and renal recovery would begin.

Figure 3. Course of acute kidney injury demonstrated in a phase space graphic

DISCUSSION

Creatinine is the renal function marker most used in clinical practice. It is a product of muscle metabolism and is basically eliminated by two mechanisms: tubular secretion and glomerular filtration. Jaffe reaction technique used in the measurement of plasma creatinine has low specificity with overestimation of its plasma concentration. This difference is normally disregarded, counterbalancing the urinary creatinine load coming from tubular secretion in such a way that creatinine clearance becomes, in practical terms, an approximate marker of glomerular filtration.

It is known that creatinine does not have a temporal relation with the course of acute kidney injury, with a “delay” between the increase of creatinine and the start of ARF, i.e., when there is a decrease of glomerular filtration as a result of ischemia, toxicity, or a combination of both, normal creatinine levels are present for a while. However, despite these inconveniences, it is the choice marker for acute kidney injury; therefore, associating the functional, morphological and molecular abnormalities with serial creatinine measurements may help understand the ARF phenomena in time with the phases of creatinine variation curve. An International Consensus (Acute Dialysis Quality Initiative – ADQI) proposed an index for the diagnosis of ARF (RIFLE classification), in which the injury severity is measured by the grade of creatinine increase.

Recently, however, a mathematic model involving creatinine production and filtration was proposed to better study these dynamic changes that identified the previously mentioned phases, using serial measurements of creatinine in patients with acute kidney injury. After implementing the models, the dynamics of glomerular filtration rate with real data of a patient seen at the Intensive Care Unit with acute kidney injury was simulated. Despite the model simplification, it suggests that the renal function course, measured by the glomerular filtration rate, is not paralleled with the tool available to us clinicians, that is, serum creatinine. The better understanding of the dynamics of acute kidney injury may help the doctors at moments, when knowledge about the course would enable defining management regarding diagnosis (best timing for renal biopsy) and treatment (best timing to initiate dialysis).

CONCLUSION

Application of a mathematic model allowed studying the changes of renal function in the setting of acute kidney injury, thus providing better understanding of the renal function dynamics.

REFERENCES


