SECTION 5

Humoral and Cellular Mechanisms of Kidney Damage

CHAPTER 18

Renal Blood Flow and Perfusion Pressure

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OBJECTIVES

This chapter will:

1. Examine the relation between renal blood flow and renal perfusion pressure.
2. Investigate the determinants of renal perfusion pressure.

In healthy humans, renal blood flow (RBF) is around 1.2 L/min, which accounts for 20% of cardiac output. Contrary to many other organs, in which blood flow is regulated according to metabolic needs, renal metabolic work is a function of RBF. RBF is a major determinant of glomerular capillary filtration pressure and therefore of the glomerular filtration rate (GFR). The relationship between RBF and renal perfusion pressure is complex. According to Ohm's law, in kidneys as in all other organs, blood flow entering the organ is equal to

$$\Delta P/R$$

where ΔP = perfusion pressure = input pressure − output pressure and R = resistance to flow through that organ. Input and output pressures often are considered equal to mean arterial pressure (MAP) and organ venous pressure, respectively. However, important features must be taken into account to ensure a better understanding of renal hemodynamics. First, renal vascularization is autoregulated, meaning that RBF is constant over a broad range of values of renal perfusion pressure. In addition, as suggested by the previous equation, although MAP often is considered a surrogate of perfusion pressure, renal venous pressure should not be neglected, especially in certain clinical situations where it may be increased (heart failure, increased intraabdominal pressure, or septic shock).

Knowledge of the pathophysiologic characteristics of renal hemodynamics is essential to promote efficient resuscitation in critical patients. This chapter focuses on the relationship between RBF and renal perfusion pressure as well as on the determinants of renal perfusion pressure.

RELATIONSHIP BETWEEN RENAL BLOOD FLOW AND PERFUSION PRESSURE, OR RENAL AUTOREGULATION

Definition of Autoregulation

In kidneys, as in the brain[1] and the heart,[2] blood flow entering the organ is constant, regardless of perfusion pressure in a range of values called the *autoregulation zone* (Fig. 18.1).[3,4] In this zone, a decrease in renal perfusion pressure is associated with a decrease in intrarenal vascular resistances (mainly because of changes in afferent arteriolar tones); conversely, an increase in renal perfusion pressure is associated with an increase in intrarenal vascular resistances, leading to blood flow adaptation. Below the lower and above the upper autoregulation thresholds, organ blood flow is proportional to perfusion pressure.

Autoregulation Zone

Lower and upper autoregulation thresholds vary depending on the autoregulated organ[5] and on the patient's age and associated comorbidities (chronic hypertension in particular).

Physiologic Conditions

The autoregulation threshold is higher in the kidneys than it is in the heart or the brain.[5] In healthy dogs, when using models with an inflatable cuff placed around the renal artery to modify renal input pressure and various RBF measurements after stepwise reductions in renal input

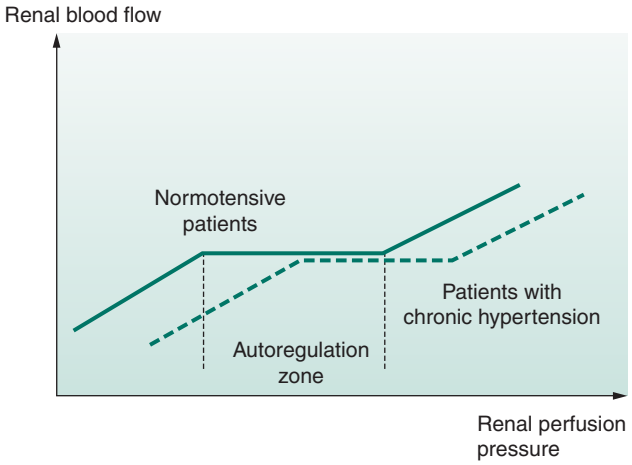

FIGURE 18.1 Renal autoregulation in patients with or without chronic hypertension. In the autoregulation zone, renal blood flow is constant, irrespective of the perfusion pressure. The lower and upper autoregulatory thresholds are higher in patients with chronic hypertension than in normotensive patients.

pressure, the lower renal autoregulation threshold ranges from 50 to 90 mm Hg.[6,7] However, precise renal autoregulation threshold values are not known in humans.

Pathophysiologic Conditions

Chronic hypertension is known to shift the autoregulation zone to the right (see Fig. 18.1).[8,9] Autoregulation mechanisms seem to be more efficient in maintaining RBF in high rather than low MAP ranges.[10] Furthermore, in some clinical situations (sepsis in particular), autoregulation may not be maintained, and if autoregulation is maintained, the autoregulation thresholds may change. Experimental and clinical data remain controversial with regard to sepsis. This question is complicated further by the role of vasoactive drugs on systemic and renal hemodynamics. In a model that used rats, early sepsis did not modify the relationship between RBF and MAP, suggesting that autoregulation may be conserved.[11] Data on renal autoregulation in septic patients are scarce. More generally, little is known about RBF changes in human sepsis. Rector et al. showed that RBF assessed by paraaminohippuric acid extraction ratio measurement after catheterization of the right renal vein increased in five out of six patients with severe sepsis.[12] In another study that involved using a percutaneously placed thermodilution catheter in the renal arteries of eight critically ill patients (seven septic), RBF increased from the time of initial evaluation to the time of follow-up evaluation 24 to 72 hours later. However, the time of initial evaluation during the course of sepsis was not determined.[13] In a study including septic patients with MAP between 70 and 100 mm Hg, RBF assessed by cine phase-contrast magnetic resonance imaging was lower in septic patients than in control healthy patients.[14] For all these studies, remember that renal hemodynamics may be different at different phases (initiation, maintenance, and recovery) of acute kidney injury (AKI).

As such, some authors assume that the objective of resuscitation should specifically target a MAP level higher than the lower autoregulation threshold to allow an adequate renal perfusion (cf. below). However, when drawing clinical conclusions from these physiologic data, physicians should be cautious, considering the autoregulation zone cannot be delineated in each specific patient, and the autoregulation phenomenon may even be altered in certain clinical situations.

Mechanism of Autoregulation

RBF autoregulation is mediated by at least two interacting control mechanisms: the intrinsic myogenic reflex of preglomerular vessels and the tubuloglomerular feedback (TGF).

The myogenic response occurs in all organs. In kidneys, it involves mainly the afferent arteriole (and secondarily the interlobular artery). Changes in arteriolar transmural pressure are sensed by vascular smooth muscle cells and transduced through the membrane potential of these cells. Membrane depolarization after an increase in arteriolar transmural pressure leads to the activation of L-type calcium channels and myogenic constriction.[3,15] This phenomenon is very quick: an increase in renal perfusion pressure induces the vasoconstriction of afferent arterioles within 300 ms.[10,16]

The TGF mechanism is slower than the myogenic response (approximately 1 s) and is specific to renal autoregulation. Changes in the volume and composition of the outflow of filtrate from the thick ascending limb are sensed by the macula densa. The exact nature of these changes is still a matter of debate, but it may include osmolality, sodium, or chloride concentration. An increase in one of these sensed signals indicates an increase in the GFR and leads to adenosine triphosphate (ATP) or adenosine liberation by macula densa cells, inducing an afferent arteriolar vasoconstriction (in turn inducing a decrease in capillary glomerular pressure and in RBF).[17,18]

Autoregulation mechanisms make it possible to maintain a constant RBF over a large renal perfusion pressure range. However, this phenomenon involves mainly the afferent arteriole and the interlobular artery and not postglomerular circulation. Peritubular capillaries, which vascularize tubules, are not involved directly in autoregulation mechanisms but are affected by preglomerular flow, depending on these mechanisms.

DETERMINANTS OF PERFUSION PRESSURE

Two major determinants affect perfusion pressure: MAP and venous pressure. In critical patients, interventions aiming at increasing MAP (i.e., catecholamines and fluid infusions) also may lead to an increase in venous renal pressure.[19]

Mean Arterial Pressure

MAP usually is considered a major objective for resuscitation. Given that autoregulation thresholds are lower in the kidneys than they are in the brain and heart, a MAP slightly higher than the renal lower autoregulation threshold may be the most adequate MAP target in patients with shock.

The impact of the MAP target on renal function has been studied primarily in patients with septic shock. In such cases, the Surviving Sepsis Campaign Guidelines recommend a MAP target higher than 65 mm Hg.[20] However, a higher target may be appropriate to prevent the occurrence of AKI.

Some observational studies have attempted to delineate an optimal MAP target in septic patients.[21,22] Varpula et al.

showed that the best predictive MAP threshold value for 30-day mortality was 65 mm Hg and that the time spent under this value was correlated with 30-day mortality. However, these results were limited by the strong correlation between MAP level and disease severity. In the study by Dünser et al. that included 274 patients with sepsis or septic shock, results were adjusted according to disease severity.[22] The hourly time integral of MAP drops below 55 mm Hg during the first 24 hours was associated with a significant increase in 28-day mortality. However, there was no difference in 28-day mortality between MAP drops below 60, 65, 70, and 75 mm Hg. Moreover, the area under the ROC curve to predict the need for renal replacement therapy was highest for the hourly time integral of MAP drops below 75 mm Hg, which suggests that a MAP level higher than 65 mm Hg may be necessary to prevent AKI. Conversely, in a posthoc analysis of a large randomized trial,[23] the MAP level was not associated with mortality or the occurrence of disease-related events when using logistic regression models.[24] Age and chronic arterial hypertension did not affect the association between MAP and mortality or AKI. In an observational prospective study involving 217 patients, a low MAP averaged over 6 hours or 12 hours to 24 hours was shown to be associated with a high incidence of AKI at 72 hours only in patients with septic shock and AKI at 6 hours.[25] A MAP threshold between 72 and 82 mm Hg was found to predict AKI at 72 hours. In 423 patients with severe sepsis from a large prospective observational FINNAKI study,[26] time-adjusted MAP was lower in patients presenting progression of AKI within the first 5 days of admission into the intensive care unit (ICU) than in patients without AKI progression.[27] The threshold of 73 mm Hg was shown to be the MAP value to predict progression of AKI. However, as in the study by Badin et al.,[25] results were not adjusted depending on the severity of the disease.

Several prospective interventional studies were aimed at delineating an optimal MAP target in septic patients to preserve kidney function.[28–30] Designs of these studies were globally similar. MAP levels were increased from 60 or 65 mm Hg to 85 or 90 mm Hg over a short period of time by increasing the catecholamine infusion rate. Urine output[28,29] and renal function[28] were not altered during these studies. However, in a study assessing the renal resistive index measured by echography in 11 septic patients, an increase in MAP from 65 to 75 mm Hg for 2 hours resulted in an increase in urinary output and a decrease in the renal resistive index.[30] A further increase from 75 to 85 mm Hg did not lead to any changes in these parameters. The renal resistive index does not represent renal resistance but is influenced by many other determinants.[30,31] Patients included in these small interventional studies usually were already hemodynamically stabilized. Assessment timing is probably a key point in understanding the relation between MAP and renal function given that pathophysiologic mechanisms of renal failure may vary during the progression of sepsis, from mainly pressure-dependent mechanisms to mainly injury-dependent mechanisms.

The SEPSISPAM study, a randomized open-labeled trial, including 776 patients within 6 hours after the initiation of vasopressors, showed that a MAP level higher than 65 mm Hg may be necessary to prevent the occurrence of AKI in patients with a history of chronic hypertension.[32] Patients were randomized into two MAP target groups (65–70 vs. 80–85 mm Hg) with stratification according to previous chronic hypertension. The MAP target was maintained from day 1 to day 5 (or until the patient was weaned from vasopressor support). Twenty-eight and 90-day mortality rates and overall rates of organ dysfunction did not differ in the two groups. However, the incidence of AKI (defined by the doubling of serum creatinine levels) and the rate of renal replacement therapy were lower in the high MAP target group in the prospectively defined group of patients with previous hypertension.

Fewer data are available on the relationship between MAP, RBF, and renal function in other clinical situations.

In a situation close to septic shock, in 12 postcardiac surgery patients with vasodilatory shock and AKI, an increase in MAP from 60 to 75 mm Hg was shown to improve renal oxygen delivery, the renal oxygen delivery/consumption relationship, and the glomerular filtration rate.[33] However, an increase from 75 to 90 mm Hg did not lead to any changes in these parameters.

In patients with hemorrhagic shock, a high MAP target may lead to a major fluid overload resulting in coagulopathy because of dilution of coagulation factors and hypothermia. Moreover, it may favor the bleeding process. These elements led some authors to develop the concept of hypotensive resuscitation. To the best of our knowledge, however, the impact of this strategy on the kidneys has not been assessed.

Renal Venous Pressure

The impact of increased renal venous pressure on RBF (and GFR) has long been known in physiologic studies[34] and has been described especially in patients with heart failure.[35] In right-sided heart failure, the increase in right atrial pressure causes an increase in the backup venous pressure in all abdominal organs (including the kidneys) and a decrease in the gradient between the mean circulatory filling pressure and the right atrial pressure. In addition, this situation often is associated with a decrease in the cardiac output and with a neurohormonal vasoconstrictor response. All these mechanisms lead to AKI in right-sided cardiac heart failure, as in cardiac tamponade, a right-sided myocardial infarction or a severe pulmonary embolism. The mechanisms also explain the AKI frequently observed in patients with global heart failure.

The role of renal congestion has been described more recently in critically ill patients outside the situation of heart failure. In an observational study involving 12,778 patients admitted into an ICU, venous congestion (defined as presence of either peripheral edema or increased central venous pressure) was associated with an increased risk of AKI.[36] A study has shown that, in patients with sepsis, an increase in central venous pressure (and probably of renal venous pressure) was associated with AKI.[37] This harmful effect may be linked with the numerous descriptions of the deleterious effect of positive fluid balance in critical patients.[38] The negative outcome probably is due at least in part to an increase in renal interstitial pressure.

Pathophysiologic mechanisms seem to be close to those observed in cases of intraabdominal hypertension.[39] In critically ill adults, intraabdominal pressure usually ranges from 4 to 7 mm Hg. Intraabdominal hypertension is defined as sustained or repeated pathologic elevation of intraabdominal pressure ≥12 mm Hg. The abdominal compartment syndrome, corresponding to a severe form of intraabdominal hypertension, is defined as sustained elevation of intraabdominal pressure ≥20 mm Hg associated with new organ dysfunction.[40] However, kidney function may be altered with much lower intraabdominal pressure levels.[41,42] Experimental models have shown that an increase in renal parenchymal and renal vein pressures may lead to a decrease in renal perfusion pressure and may render the occurrence of AKI more likely.[43,44] However, an

isolated increase in renal parenchymal pressure does not seem sufficient to cause AKI.[45] In addition, intraabdominal hypertension also may lead to a decrease in cardiac output, which is associated with a decrease in RBF. Furthermore, an increase in inflammatory mediators may be observed in case of intraabdominal hypertension and may induce AKI.[46]

CONCLUSION

RBF is autoregulated, meaning that it is constant over a broad range of perfusion pressure. In patients with shock, an MAP target higher than the lower autoregulation threshold may be sufficient for an adequate RBF. However, autoregulation thresholds are not known in humans and may be altered in patients with chronic hypertension. Moreover, autoregulation may be altered in patients with shock (particularly in the case of sepsis). Furthermore, changes in renal venous pressure may lead to significant changes in renal perfusion pressure and play a major role in the occurrence of AKI in certain clinical situations.

Key Points

1. Renal blood flow is constant over a broad range of perfusion pressure.
2. Autoregulation thresholds are not known in humans and may be altered in patients with chronic hypertension or in the case of sepsis.
3. Changes in renal venous pressure may lead to significant changes in renal perfusion pressure and play a major role in the occurrence of AKI in certain clinical situations.

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A complete reference list can be found online at ExpertConsult.com.

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