Mechanisms of posttransplant hypertension

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Summary. Hypertension is a common problem in renal failure patients both before and after renal transplantation. The stable allograft can maintain salt, volume, and blood pressure homeostasis and is not intrinsically a hypertensive model. The causes of severe posttransplant hypertension are multiple. Renal vascular tone, body salt and volume status, and renin release are all connected and influenced by immunosuppressive medications, allograft function, and native kidney presence and function. The role of each of these in posttransplant hypertension is reviewed. In most cases, severe hypertension in the stable transplant patient without rejection or transplant renal artery stenosis is greatly improved following native bilateral nephrectomy. Transluminal angioplasty is the preferred initial treatment for transplant renal artery stenosis.

Introduction

The majority of patients with end-stage renal disease (ESRD) are hypertensive. In approximately 15%–20% of ESRD patients, malignant hypertension is the major factor leading to renal failure, whereas in other patients hypertension worsens secondary to chronic salt and volume overload as renal function declines. Sagalowsky and Peters [31] and Helderman [12] have published detailed reviews on hypertension following renal transplantation. Throughout this article, reference will be made to those two reviews, where the interested reader may find additional references for material presented below.

Indirect evidence for a negative influence of pretransplant hypertension on ultimate renal allograft survival is provided from series in the 1970s, when overall cadaver graft survival (GS) was approximately 50%. At that time, GS was 12% lower in black males than in whites, and there was a 6-fold higher incidence of malignant hypertension among black males compared with whites. In contrast, other causes of ESRD have not shown a race-related influence on GS. In more recent series, overall GS is reported to be significantly improved, primarily due to improved immunosuppression with cyclosporine, but also due to altered immunosuppressive strategies including closer histocompatibility matching for DR loci or the use of pretransplant blood transfusions. Now that the 1-year cadaver GS is 75%–80%, the detrimental impact of hypertension is more difficult to demonstrate but, in my experience, still present.

The reported incidence of hypertension among renal transplant recipients varies from 13% to 83%, with approximately one-third of patients hypertensive at any given point in time [12, 31]. In a retrospective review at our center, at ≥6 months postsurgery, 31% of stable adult transplant recipients who had serum creatinine levels of ≤2.0 mg/dl and received < 0.25 mg/kg prednisone were hypertensive. In essentially all series, the incidence of hypertension is higher in pediatric than in adult transplant recipients. The reported incidence of hypertension is higher for cadaver allograft recipients than for living related donor transplants; however, the improved blood pressure in the latter group may be due to the lower incidence of rejection. Interestingly, the severity of hypertension prior to transplantation and immediately postsurgery does not predict which patients will have chronic severe hypertension. Apart from causing damage to the allograft, the real threat of hypertension in terms of patient survival occurs in recipients with fixed myocardial function (limited left ventricular response to stress) as a result of primary or secondary hypertension.

Posttransplant hypertension may be exacerbated in the perioperative period by salt and volume overload, azotemia, high-dose glucocorticoids, and hypercalcemia [31]. Hypertension is worsened during treatment with bolus steroids for acute rejection. However, the pressor response may be the consequence of renal vasospasm, and renin release, and volume overload due to rejection itself rather than an effect of steroids. In several series, the investigators failed to find a statistical correlation of steroid dose with blood pressure at any point or a longitudinal association of blood pressure and the chronic steroid dose [12]. Proponents of an important influence of steroid dose on blood pressure point to improved control in patients on alternate-day steroids. Detractors argue that patients who can retain graft function on alternate-day steroids are an intrinsically more stable group and therefore have better blood pressure. Rigorous proof that steroid dose determines blood pressure regulation in a domi-
nant fashion is lacking despite extensive study. Other concomitant factors such as rejection are more likely to be the most important influences on hypertension in the transplant patient. Indeed, acute rejection, chronic rejection, and recurrence of the original renal disease may all cause hypertension.

Excessive stimulation of the renin-angiotensin-aldosterone axis may produce so-called renovascular hypertension in the transplant recipient. The graft may release excess renin due to chronic rejection, acute rejection, or transplant renal artery stenosis, in decreasing order [31]. The end-stage native kidneys may also be a source of excess renin production.

Currently, cyclosporine is an integral part of the post-transplant regimen due to the favorable results it provides. However, this potent immunosuppressant also has profound effects on renal tubular function and hemodynamics that affect all of the previously listed mechanisms involved in blood pressure control. 

**Tubular function**

A discussion of mechanisms of hypertension following renal transplantation should be based on an initial understanding of intrinsic tubular function of the transplant model. Helderman [13] has provided a review of this aspect of allograft function, which is summarized below. First, one must recall that a transplanted kidney is denervated and remains so for at least several months. Renal denervation may affect the regulation of regional intrarenal blood flow and, in turn, tubular function. In the experimental dog model with a unilateral autotransplant and an intact contralateral kidney, there is a decrease in the glomerular filtration rate (GFR) and renal plasma flow in the transplant that lasts for several days. These findings are believed to be due to ischemia associated with the surgical technique. After the GFR and renal plasma flow return to normal, renal tubular function in terms of sodium, chloride, and potassium excretion and maximal concentrating and diluting ability is identical with that in the contralateral kidney. Thus, denervation at the time of transplantation does not alter renal tubular function in this model.

In the clinical setting of human renal transplantation, pre-, intra-, and postoperative factors influence salt and water handling by the allograft. Perioperative factors include the cause of donor death; donor management—especially with regard to the use of pressors — volume replacement, and avoidance of hyperosmolarity if diabetes insipidus is present; the organ procurement procedure, hypotension, warm and cold ischemia; and the type of preservation — cold flush vs pulsatile perfusion. Intraoperative factors include bleeding, hypotension, crystalloid and colloid volume replacement and the time required for vascular anastomoses. Postoperative factors include renal denervation; the initial uremic with solute and osmotic overload; immunosuppressive medications, especially corticosteroids and cyclosporine; and rejection. Assuming that tubular function is present, the kidney transplanted into a uremic host is polyuric for several hours due to solute and osmolar overload.

Regulation of the tubuloglomerular feedback set point for the influence of the presented solute load on the GFR in the transplant is especially interesting. A renal transplant into a recipient with a functioning native kidney retains the ability to alter the GFR according to solute load in the usual manner, i.e., an increased solute load leads to a decreased GFR. However, when the transplant kidney is the sole functioning renal unit, it resets the tubuloglomerular feedback so as to maintain the GFR despite a high solute load.

The early human identical-twin donor, living related renal transplants offered a unique opportunity to study the inherent renal tubular function of ideal transplants. Immunosuppression was not used, and the grafts functioned free of rejection. In this model, the transplanted kidney handled salt and water balance identically to the donor's remaining kidney [8].

In summary, the stable, nonrejecting renal allograft can exhibit many aspects of normal renal tubular function. Renal blood flow (measured by para-aminohippuric acid clearance) and the GFR (measured by inulin, creatinine, or iodathalamate clearance) are in the normal range. Handling of salt and volume are normal. Urinary acidification and alkalinization and divalent cation homeostasis are generally normal. Renin and angiotensin release and, usually, aldosterone release are normal (see below).

However, there are also relatively common syndromes of abnormal transplant renal tubular function that may impact on blood pressure homeostasis. During acute rejection, decreased solute excretion by the allograft causes sodium and volume retention, leading to a rise in blood pressure. All types of renal tubular acidosis (RTA, proximal, distal, combined) may occur with stable renal function or during rejection. Proximal RTA, which is the most common, occurs soon after surgery and usually disappears after several months. Hyperkalemia and hypoaldosteronism may occur immediately postsurgery due to impaired distal tubular transport. Normal or mild hypercalcemia and hypophosphatemia may occur secondary to persisting secondary hyperparathyroidism. Hypomagnesemia may occur due to increased urinary excretion of the cation.

**Renin-angiotensin-aldosterone involvement**

The potent renin-angiotensin system may be an important determinant of post-transplant hypertension if stimulation is excessive, regardless of the source of renin (i.e., allograft vs native kidneys) or the cause (i.e., renal artery stenosis, rejection, or altered feedback regulation). Many investigators [6, 11, 15, 17, 18, 21, 37] have shown that a denervated, stable renal allograft regulates renin secretion and, in turn, angiotensin production in response to changes in sodium and volume status and posture, in a normal manner. Aldosterone release is also normal in most cases. Blaufox and colleagues [7] studied stable,