Mechanisms of posttransplant hypertension

Arthur I. Sagalowsky
Division of Urology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75235-9031, USA

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 \( \geq 6 \) months postsurgery, 31% of stable adult transplant recipients who had serum creatinine levels of \( \leq 2.0 \) 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 con-
comitant factors such as rejection are more likely to be
the most important influences on hypertension in the
transplant patient. Indeed, acute rejection, chronic rejec-
tion, and recurrence of the original renal disease may all
cause hypertension.

Excessive stimulation of the renin-angiotensin-
aldosterone axis may produce so-called renovascular hy-
pertension in the transplant recipient. The graft may re-
lease excess renin due to chronic rejection, acute rejec-
tion, or transplant renal artery stenosis, in decreasing or-
der [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 superior results it provides.
However, this potent immunosuppressant also has pro-
found effects on renal tubular function and hemodyna-
mics that affect all of the previously listed mechanisms in-
volved in blood pressure control.

Tubular function

A discussion of mechanisms of hypertension following
renal transplantation should be based on an initial under-
standing of intrinsic tubular function of the transplant
model. Helderman [13] has provided a review of this as-
pect of allograft function, which is summarized below.
First, one must recall that a transplanted kidney is den-
ervated and remains so for at least several months. Renal
denervation may affect the regulation of regional in-
trarenal 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. Preoperative factors in-
clude the cause of donor death; donor management—es-
specially with regard to the use of pressors — volume re-
placement, and avoidance of hyperosmolarity if diabetes
insipidus is present; the organ procurement procedure, hy-
potension, warm and cold ischemia; and the type of pres-
ervation — cold slush vs pulsatile perfusion. In-
traoperative 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 kid-
ney retains the ability to alter the GFR according to sol-
ute 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
de spite 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 func-
tioned 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 func-
tion. Renal blood flow (measured by para-aminohippuric
acid clearance) and the GFR (measured by inulin, creatin-
ine, or iodathalamate clearance) are in the normal
range. Handling of salt and volume are normal. Urinary
acidification and alkalinization and divalent cation ho-
meostasis are generally normal. Renin and angiotensin re-
lease and, usually, aldosterone release are normal (see be-
low).

However, there are also relatively common syndromes
of abnormal transplant renal tubular function that may
impact on blood pressure homeostasis. During acute re-
jection, 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, prox-
imal, distal, combined) may occur with stable renal func-
tion or during rejection. Proximal RTA, which is the most
common, occurs soon after surgery and usually disap-
ppears after several months. Hyperkalemia and hypoaldo-
steronism may occur immediately postsurgery due to im-
paired distal tubular transport. Normal or mild hyper-
calcemia and hypophosphatemia may occur secondary to
persisting secondary hyperparathyroidism. Hypomagnesemia
may occur due to increased urinary ex-
creton of the cation.

Renin-angiotensin-aldosterone involvement

The potent renin-angiotensin sytem may be an important
determinant of post-transplant hypertension if stimula-
tion 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,