

EDITORIAL COMMENT

Hypertension in Heart Transplant Recipients: More Than Just Cyclosporine*

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Cardiac transplantation offers definitive therapy for selected patients with end-stage heart failure and thus provides significant improvements in survival in these recipients. Heart transplantation comes with a cost, however, resulting from the actual transplantation procedure, the subsequent allo-immune response to the transplant and the immunosuppressive medications required to keep the allo-immune response under control. Patients are subject to different types of morbidities after transplant compared to pre-transplant. The medical consequences of the allo-immune response or rejection and the side effects of immunosuppressive medications—in particular, the mainstay immunosuppressive agent cyclosporine—have been well described (1). The consequences of denervation have been studied, in particular, with regard to the blunted exercise response and subsequent limitations to maximal exercise that have been observed posttransplantation (2–4). The role of denervated heart in other posttransplant sequelae, such as hypertension, has not been well defined.

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Earlier explanations for the mechanisms of the hypertension observed in heart transplant recipients have primarily focused on the crucial immunosuppressive agent, cyclosporine. Cyclosporine has been implicated in activation of the sympathetic nervous system in heart transplant recipients, resulting in hypertension (5). Additionally, cyclosporine has been well documented as a cause of chronic nephropathy, and this too can result in hypertension (6). However, patients who do not receive cyclosporine often develop hypertension (7). This raises the possibility that alternative mechanisms may account for the development of hypertension in cardiac transplant recipients regardless of their immunosuppressive regimen. Braith and colleagues (8–10) have previously shown that infusing saline into heart transplant recipients resulted in elevations in systolic and dia-

stolic blood pressures, in response to volume expansion from the saline infusion. In particular, extracellular fluid expansions on the order of 14%, which can occur routinely in the clinical setting of cardiac transplant recipients, can result in hypertension. It has also been shown that heart transplant recipients have an abnormal and decreased response to saline infusion, with a decreased natriuretic response (8). The etiology of this was not exactly clear. Prior evidence suggested the possibility of abnormal responsiveness of the renin-angiotensin-aldosterone system (RAAS) to fluid retention in heart transplant recipients resulting in hypertension (8). The disease occurs rapidly after transplantation, usually within a matter of weeks to months, and its pathogenesis remains complex (7,11). Often, hypertension in heart transplant recipients does not respond to single agents and requires multiple antihypertensive drugs (7,11).

In the present study by Braith and colleagues (12), stable heart transplant recipients receiving cyclosporine had their antihypertensives stopped, after which their blood pressure, RAAS profile, including plasma angiotensin II, and aldosterone, and vasopressin, atrial natriuretic peptide (ANP), urine flow rate, and urinary salt excretion were assayed during saline infusion. These parameters were measured again more than 16 weeks after the baseline studies and after pretreatment with the angiotensin-converting enzyme (ACE) inhibitor captopril followed by another saline infusion. Stable liver transplant recipients taking cyclosporine went through the same two-part protocol as controls. Saline infusions in heart transplant, but not liver transplant, patients resulted in elevations in systolic and diastolic pressures, and in angiotensin II and aldosterone levels that were abolished with pretreatment with captopril. Urine flow rate and urinary sodium secretion were significantly lowered in heart transplant recipients during salt infusion compared to baseline, but this too was reversed with ACE inhibition. The investigators (12) conclude that salt expansion failed to suppress RAAS in cardiac transplant recipients owing to denervation of cardiac volume receptors.

It has previously been demonstrated that heart transplant patients appeared to have RAAS that does not suppress with volume loading. Furthermore, volume expansion has been associated with hypertension in heart transplant patients, and blood pressure appears to be responsive to salt in these patients (10). Furthermore, plasma renin activity and ANP are chronically elevated in heart transplant recipients, indicating abnormal responsiveness of the cardiac mechanoreceptors that regulate elaboration of these hormones (13). The present study ties all these findings into a unified pathophysiologic framework with clinical implications. The volume expansion from salt loading in heart transplant recipients fails to suppress RAAS, and the net result is hypertension and decreased urinary salt excretion and urine flow rate. Liver transplant recipients did not show these findings despite also receiving cyclosporine with similar trough level. This would indicate that the volume-dependent form of hypertension seen

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Temple University School of Medicine, Philadelphia, Pennsylvania. Supported by a grant from the American Heart Association National Center.

in heart transplant recipients is a result of failure of cardiac volume receptors to respond to changes in loading conditions as a result of cardiac denervation after heart transplantation. Administration of ACE inhibitors to ablate the RAAS reversed these observations.

This work has important implications for the management of hypertension in heart transplant recipients. It would appear that ACE inhibition would be the treatment of choice for hypertension in cardiac transplant patients. This class of drugs would be ideal in blunting the effects of the neurohormonal systems that fail to respond to volume expansion. Further, Braith's study raises another intriguing issue, which is that aggressive restriction of salt intake may be a successful strategy for managing hypertension in heart transplant recipients. This strategy would be akin to that used in patients with congestive heart failure (though for different purpose) but would represent a departure from the standard management of heart transplant recipients at many centers. This would require patient education to enable physiologically guided therapy for hypertension in heart transplant patients. It is thus possible that nonpharmacologic therapy with salt restriction could result in improvement in hypertension in these individuals.

Several interesting questions remain regarding the potential mechanism of salt-expansion-induced hypertension in heart transplant recipients and the role of RAAS. One would expect that this form of hypertension would be as likely to occur in patients receiving tacrolimus as in those receiving cyclosporine, yet patients receiving the latter are more likely to be hypertensive (14). Thus, it would appear that cyclosporine has an additive and perhaps independent effect on blood pressure. Further, cardiac reinnervation has been demonstrated in heart transplant recipients several years out from transplant by assessing tyramine-induced release of norepinephrine (15). It would be interesting to see whether these patients develop a RAAS that is responsive to volume loads.

Finally, many transplant centers have been performing bi-caval heart transplants, thus essentially transplanting almost the entire donor heart. The present study involved patients with bi-atrial transplants. Though the issue of denervation would still be present, differences in response to volume loads may be identified in bi-caval transplant recipients.

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