Hypertension in Patients with Cardiac Transplantation

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KEYWORDS

• Hypertension • Calcineurin inhibitors • Cardiac transplantation

KEY POINTS

- The physiology of the development of hypertension (HTN) after cardiac transplantation is explored.
- The importance of calcineurin inhibitors on the development of HTN after cardiac transplantation is discussed.
- The management of patients with HTN after cardiac transplantation is outlined.

INTRODUCTION

Despite the clinical success and improvement in survival of cardiac transplantation in the last 20 years, many patients develop chronic problems such as cardiac allograft vasculopathy and hypertension (HTN). The incidence of HTN after cardiac transplantation varies from 50% to 80% of recipients.[1] Development of HTN after cardiac transplantation is multifactorial. In the complex biosystem created by transplantation, patients are susceptible to multiple mechanisms for HTN. The unique physiology created by the cardiac allograft places these patients at risk for continued complications from cardiovascular disease and long-term mortality. Among these mechanisms are the use of immunosuppressive therapy (calcineurin inhibitors [CI] and glucocorticoids), surgical denervation, development of restrictive physiology, ventricular vascular uncoupling, and fluid sensitivity. This review describes the state of current literature pertaining to the pathophysiology and treatment of HTN in patients after cardiac transplantation.

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MECHANISMS OF HYPERTENSION AFTER CARDIAC TRANSPLANTATION

Predisposing Factors of the Recipient

Traditional risk factors of the recipient before cardiac transplantation, such as HTN, smoking, hypercholesterolemia, and pretransplant body weight do not have any correlation with the development of posttransplant HTN.[2] However, HTN as part of the pretransplant metabolic syndrome or its development within the first 3 months posttransplant, is associated with a greater risk of mortality and long-term renal dysfunction.[3]

Calcineurin Inhibitor–Mediated Effects

Although the use of CIs have greatly improved the success and survival of cardiac transplant recipients, these agents have several adverse effects, the most common being HTN and nephrotoxicity.[4,5] The development of posttransplant HTN and its possible underlying mechanisms has been studied most closely with relation to the use of cyclosporine.[6,7] It has been shown that patients receiving cyclosporine develop new-onset HTN requiring pharmacologic treatment in 82% of cases compared with 64% of those treated with tacrolimus.[8] Although in the new era of tacrolimus-based immunosuppression the incidence of HTN is less, it still represents a significant problem in the management of these patients. HTN has been shown to correlate with the use of cyclosporine for autoimmune diseases as well as for immunosuppression after other solid organ transplants.[9] We will discuss some of the mechanisms by which CIs, more specifically cyclosporine, can cause an increase in blood pressure in patients with cardiac transplantation.

Inhibition of peripheral vasodilation

CIs have a direct effect on free and intramuscular calcium ion concentrations through the involvement of the calcium-calmodulin–dependent phosphatase mechanism.[10] Increased calcium within the vascular smooth muscle leads to constriction and arterial HTN. Attenuation of this mechanism decreases the production of nitric oxide (NO), effectively leading to an inhibition of vasodilatation.[11]

Increased vasoconstrictor production

HTN, in cyclosporine-treated cardiac transplant recipients, is associated with reductions in cardiac output, increased vasoconstrictor sensitivity,[12] decreased prostaglandin levels, and increased thromboxane A2 synthesis.[13] Decreased prostaglandin synthesis leads to vasoconstriction of the afferent arterioles, which activates activation of the renin–angiotensin–aldosterone system (RAAS). This effect can be reversed within the renal vasculature through the use of thromboxane A2 antagonists, but such reversal does not demonstrate effects on systemic HTN.[14] Endothelin-1 is thought to contribute to stimulation of proinflammatory cytokines, tissue damage, and fibrosis seen in patients after transplantation.[15] Although the levels of endothelin-1 are independent of degree of HTN, it is thought that cyclosporine may have a role in increasing the endothelin receptors in the renal microvessels, which in turn produces vasoconstriction and renal-modulated HTN.[16,17]

Left ventricular remodeling and left ventricular hypertrophy

Calcineurin activates the genes that are associated with the development of left ventricular hypertrophy by dephosphorylating nuclear factor of activated T cells (specifically NFATc3); however, the use of CIs is not proven to prevent the development of left ventricular hypertrophy in animal models.[18] Similarly, after cardiac transplantation, patients with HTN, obesity, and CI-based immunosuppression demonstrate an increased in left ventricular mass and left ventricular hypertrophy, which may have