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# The Impact of Donor Hypertension on Intragraft Changes in Chronic Rat Cardiac Allograft Rejection

Markus J. Wilhelm, Johann Pratschke, Dustin M. Paz, Igor A. Laskowski, Christof Schmid, Hans H. Scheld, Wayne W. Hancock, and Nicholas L. Tilney

Due to the declining number of suitable donors, organs from hypertensive donors are increasingly used. The purpose of this study was to investigate the effect of donor hypertension on graft performance in a model of chronic rat cardiac allograft rejection. Hypertension (HTN) was induced in F344 rats by narrowing the right renal artery. After 10 weeks, hearts from such animals were transplanted heterotopically into Lewis rats treated with cyclosporine. Hearts from sham-operated animals (SHAM), also engrafted after 10 weeks, served as controls. Hearts from SHAM were normal at explantation, whereas hearts from HTN donors exhibited some mild medial hypertrophy and medial vacuolization in elastic arteries. Thirty and 60 days after transplantation, hearts from HTN exhibited increased focal mononuclear cell infiltration, expression of IL-2R, production of cytokines (TGF- $\beta$ , PDGF), and interstitial fibrosis (each  $P < 0.01$ ) as compared with SHAM grafts. After 90 and 120 days, HTN donor hearts showed widespread fibrosis with only small areas of residual myocardium. By contrast, SHAM hearts exhibited some subendocardial and subepicardial fibrosis, and the myocardium appeared still well preserved. Hearts from HTN donors appear to induce increased alloresponsiveness in the recipient. As a result, fibrosis develops more rapidly in such hearts, ultimately leading to a loss of myocardial integrity.

## Introduction

The divergence between available donor organs and the number of patients on the waiting list for organ transplantation continues to increase. Therefore, there is a tendency to accept organs from marginal donors. These are characterized, among other factors, by age  $> 65$  years, increased ischemic time, and conditions such as diabetes mellitus and hypertension. With particular respect to heart transplantation, ischemic heart disease, reduced left ventricular function, and left ventricular hypertrophy are considered to render a donor heart marginal. Each of these conditions may decrease donor organ quality and significantly affect transplantation outcome. In heart transplantation, donor age and ischemia time have been shown to be associated with

a higher 1- and 5-year mortality.<sup>1</sup> The effect of donor hypertension on graft behavior after transplantation has not been clearly elucidated to date. The purpose of this study was to investigate the impact of this condition on the recipient immune response in a model of chronic rat cardiac allograft rejection.

## Materials and Methods

Hypertension (HTN) was induced in F344 rats by narrowing the right renal artery with a 0.05 mm silver clip. After 10 weeks, hearts from such animals were engrafted heterotopically into Lewis (LEW) rats. Control animals (SHAM) underwent the same surgical procedure except for the positioning of the renal clip. Hearts from SHAM were also transplant-

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ed into LEW rats 10 weeks after the procedure. The recipient rats were treated with cyclosporine 2.5 mg/kg daily for 30 days, and every other day thereafter. Grafts were analyzed by histology and immunohistology at the time of explantation and at 30, 60, 90, and 120 days posttransplantation.

### Results

Ten weeks after clip placement, at the time of donor organ removal, HTN donors exhibited a systolic blood pressure that was significantly higher than was measured in SHAM-operated donors 10 weeks following the sham operation ( $180 \pm 17$  vs  $131 \pm 10$  mmHg,  $P < 0.0001$ ). At explantation, hearts from SHAM showed normal histology, whereas hearts from HTN exhibited some mild medial hypertrophy and medial vacuolization in elastic arteries. Thirty and 60 days after transplantation, focal mononuclear cell (MNC) infiltrates were seen in all the grafts. Infiltrates consisted of  $> 75\%$  macrophages and  $< 25\%$  T cells in both groups. Quantitative image analysis, however, revealed increased MNC infiltration ( $P < 0.01$ ) and interstitial fibrosis ( $P < 0.01$ ) in hearts from HTN donors as compared with those from SHAM-operated donors. Additionally, in grafts from HTN donors, immune activation, as measured by the number of IL-2R<sup>+</sup> cells ( $P < 0.01$ ), and cytokine expression (TGF- $\beta$ , PDGF), was greater ( $P < 0.01$ ) than in hearts from SHAM-operated donors. Ninety and 120 days following engraftment, hearts from SHAM exhibited focal infiltrates and some subendocardial and subepicardial fibrosis. In general, however, the myocardium appeared still well preserved. By contrast, hearts from HTN donors showed dense multifocal infiltrates and widespread fibrosis, with only small areas of residual myocardium.

### Discussion

It has been shown that hypertension may cause left ventricular hypertrophy and arterial changes throughout the vasculature including heart and kidney.<sup>2,3</sup> Retrospective clinical analyses have recently revealed that hypertension of the donor might lead to inferior graft survival rates following heart and kidney transplantation.<sup>4,5</sup> The experimental data from the present study indicate that hearts from HTN donors may experience severe structur-

al changes over time following transplantation, which might contribute, at least in part, to the impaired posttransplant performance of such hearts. At the time of explantation, the morphology of hearts from HTN appeared almost unchanged, although some minor alterations of elastic coronary arteries were visible. Following transplantation, however, they experienced a more pronounced host inflammatory response than was seen in grafts from SHAM-operated donors. Donor hypertension might have caused an increased immunogenicity of the graft, which was augmented by an additive injury, such as the transplant procedure. The enhanced host alloresponsiveness toward hearts from HTN donors was associated with an increased production of inflammatory mediators, such as TGF- $\beta$  and PDGF. These cytokines might have mediated the pronounced fibrotic remodeling within the myocardium, since they have been shown to be involved in the induction of fibrotic processes.<sup>6,7</sup> In contrast, hearts from SHAM-operated donors developed only minor fibrotic areas, similar to those that have been demonstrated in models of chronic cardiac allograft rejection.<sup>8,9</sup> In summary, hearts from hypertensive donors might experience an insult induced by this condition, which, following transplantation, provokes an increased host inflammatory response, ultimately leading to a loss of intact myocardium and replacement by fibrotic tissue.

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### REFERENCES

1. Hosenpud JD, Bennett LE, Keck BM, Fiorello B, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: sixteenth official report—1999. *J Heart Lung Transplant* 1999;18:611-26.
2. Vaudo G, Schillaci G, Evangelista F, Pasqualini L, Verdecchia P, Mannarino E. Arterial wall thickening at different sites and its association with left ventricular hypertrophy in newly diagnosed essential hypertension. *Am J Hypertens* 2000;13:324-31.
3. Newton NM, Fine LG. Inference of the existence of high blood pressure as a cause of renal disease in the mid-19th century: observations on vascular structures in the kidney. *Am J Nephrol* 1999;19:323-32.
4. Marelli D, Laks H, Fazio D, Moore S, Moriguchi J, Kobashigawa J. The use of donor hearts with left ventricular hypertrophy. *J Heart Lung Transplant* 2000;19:496-503.

5. Ojo AO, Leichtman AB, PUNCH JD, Hanson JA, Dickinson DM, Wolfe RA, et al. Impact of pre-existing donor hypertension and diabetes mellitus on cadaveric renal transplant outcomes. *Am J Kidney Dis* 2000;36:153-9.
6. Brooks WW, Conrad CH. Myocardial fibrosis in transforming growth factor beta(1)heterozygous mice. *J Mol Cell Cardiol* 2000;32:187-95.
7. Hagood JS, Miller PJ, Lasky JA, Tousson A, Guo B, Fuller GM, et al. Differential expression of platelet-derived growth factor-alpha receptor by Thy-1(-) and Thy-1(+) lung fibroblasts. *Am J Physiol* 1999;277:L218-24.
8. Shen J, Chong AS, Xiao F, Liu W, Huang W, Blinder L, et al. Histological characterization and pharmacological control of chronic rejection in xenogeneic and allogeneic heart transplantation. *Transplantation* 1998;66:692-8.
9. Orosz CG, Huang EH, Bergese SD, Sedmak DD, Birmingham DJ, Ohye RG, et al. Prevention of acute murine cardiac allograft rejection: anti-CD4 or anti-vascular cell adhesion molecule one monoclonal antibodies block acute rejection but permit persistent graft-reactive alloimmunity and chronic tissue remodelling. *J Heart Lung Transplant* 1997;16:889-904.