Peer reviewed article

Acute effect of nitroglycerin on cyclosporine-induced hypertension after cardiac transplantation

Isabella Sudano[*u], Mazda Farshad*[*u], Andreas J Flammer[a], Lukas Spieker[a], Daniel Periat[a], Frank Enseleit[a], Mathias Wolfrum[a], Frank Ruschitzka[a,b], Thomas F Lüscher[a,b], Georg Noll[a,b], Roberto Corti[a]*

[a] Cardiovascular and Transplantation Center, Cardiology, University Hospital Zurich, Switzerland
[b] Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland

Summary

Background: Cyclosporine represents a milestone in immunosuppression following organ transplantation. Its use, however, comes at the cost of significant side effects, such as arterial hypertension which is rarely controllable by currently available anti-hypertensive drugs. The aim was to investigate the effect of acute administration of nitroglycerin in heart-transplanted patients with cyclosporine-induced hypertension.

Methods: The sample included 18 cyclosporine-induced hypertensive patients (HTX group) scheduled for elective cardiac catheterization following heart transplantation, as well as 6-matched essential hypertensive patients (HT group). The blood pressure (BP) in the aorta and pulmonary artery, before and after administration of nitroglycerin, was measured simultaneously.

Results: After injection of 50 µg and 100 µg nitroglycerin, BP significantly decreased both in HTX (systolic [s] BP $p = 0.0001$; diastolic [d] BP $p = 0.0001$) and in controls (sBP $p = 0.006$; dBP $p = 0.05$). This reduction was more pronounced in HTX (sBP $p = 0.022$; dBP $p = 0.018$ for group-comparison). Following analysis of the data in relation to its individual baseline, a significantly higher reduction of the BP induced by 100 µg nitroglycerin was observed in the HTX group compared to the HT group ($p = 0.02$ for sBP and $p = 0.03$ for dBP). 8 ± 3 minutes after the last nitrate infusion, BP remained significantly reduced compared to baseline in HTX ($p < 0.001$), whereas it came back to baseline in controls. The reduction in sBP was correlated to cyclosporine A levels ($p = 0.04$ after 50 µg nitroglycerin; $p = 0.05$ after 100 µg nitroglycerin).

Conclusion: After application of nitroglycerin, sBP is reduced immediately in HTX with uncontrolled cyclosporine-induced hypertension. Further studies are needed to evaluate the long-term effect of nitrates in these patients.

Key words: heart transplantation; cyclosporine; hypertension; nitroglycerin

Introduction

Cyclosporine A (CsA) is still the most commonly prescribed immunosuppressive drug following heart transplantation, however its use is limited by side effects, particularly arterial hypertension, deterioration of renal function, thromboembolic complications and graft atherosclerosis [1–6].

CsA induces vasoconstriction in the systemic circulation thereby increasing arterial blood pressure (BP). Moreover, vasoconstriction in the kidney vessels results in a decreased renal blood flow and represents the pathophysiological basis for the nephrotoxicity observed during CsA treatment. As a consequence, many patients develop hypertension or exhibit deterioration of existing hypertension during immunosuppressive treatment. Unfortunately, the cyclosporine-induced hypertension is rarely controllable by currently available anti-hypertensive drugs [7].

The precise mechanisms underlying cyclosporine-induced hypertension still remain to be elucidated [5], but cyclosporine-induced vasoconstriction is believed to be due to an imbalance of vasodilation (induced by prostacyclin, nitric oxide, Ca^{2+} influx) and vasoconstriction (due to thromboxane, endothelin, angiotensin II, sympathetic nervous system) [5, 8, 9].

CsA induces endothelial dysfunction in animal models [7, 10]. Aortic rings dissected from rats treated for several days with CsA show reduced endothelium-dependent relaxation [11]. CsA inhibited the endothelial nitric oxide synthase activ-

* both authors contributed equally to this paper.

No author declared any conflict of interest. This study was supported by the Swiss National Research Foundation (NF 3200B0-105759), and by the MERCATOR Stiftung.

ity and reduced urinary nitrate/nitrite excretion *in vivo* in rats, suggesting depressed nitric oxide production [12–14]. In healthy volunteers, acute administration of CsA enhances both basal and receptor-stimulated nitric oxide activity [15], while in heart transplanted (HTX) patients treatment with CsA caused a reduction of basal and stimulated release of nitric oxide [16], and a reduced flow mediated dilation [17] was found. Moreover, in patients treated with CsA, endogenous vasodilators such as prostacyclin and nitric oxide are suppressed, whereas vasoconstrictors, including endothelin, are increased [8].

In experimental models of heart transplantation, cyclosporine also increases oxidative stress [12] and influences production of important pro-inflammatory mediators such as substances showing a potential pro-fibrotic effect [18].

Nitrates are predominantly used for the treatment of cardiovascular diseases including coronary artery disease, and congestive heart failure [19–23]. Their pronounced effect on vascular smooth muscle and the release of nitric oxide are believed to be key mechanisms of their anti-ischemic properties [24–27]. Nitrates may have a role in modifying the imbalance induced by CsA through many different mechanisms, including increasing nitric oxide, reducing angiotensin II and endothelin, and modifying Ca^{2+} influx.

This study was designed to investigate the potential role of nitrates as a therapeutic strategy in CsA-induced hypertension in HTX patients.

For this aim, we investigated the acute haemodynamic effects of nitroglycerin (GTN) in HTX patients with cyclosporine-induced hypertension compared with a control group of essential hypertensive patients (HT).

Methods

Patients

Eighteen hypertensive HTX patients on cyclosporine therapy and 6 HT controls were included. All HTX patients had been treated with CsA since their heart transplantation (mean treatment duration 11 ± 4.8 years). The diagnosis of hypertension was made 2.5 ± 0.7 months after the heart transplantation and after starting therapy with cyclosporine. All patients received state of the art treatment at the moment of inclusion in the study and they did not discontinue drug intake prior to the invasive procedure.

Six essential HT patients, without prior transplantation and scheduled for a diagnostic cardiac catheterization, served as a control group. Patients with significant coronary lesions, as well as patients receiving immunosuppressive drugs of any kind or nitrate derivatives were excluded.

All patients signed an informed consent for an invasive diagnostic procedure and agreed to undergo nitrate injection for the study. The local ethics committee of the University Hospital Zurich approved the study protocol and all procedures were in accordance with institutional guidelines.

Coronary angiography and effect of acute infusion of nitrates

First, coronary angiography and left ventriculography were performed. After reaching a stable steady haemodynamic state, the effect of GTN was evaluated by simultaneous continuous measurement of intra-arterial systolic (sBP) and diastolic blood pressure (dBP) and heart rate (HR), by the haemodynamic monitoring system routinely used in our cardiac catheter laboratory (Schwarzer evo, Schwarzer GmbH, Medical Equipment for Diagnosis, Munich, Germany), in the aorta and pulmonary artery at baseline and within a minute following intracoronary injection of 50 μg and 100 μg of GTN as bolus, respectively. At the end of the angiographic examination, BP and HR were measured again.

Blood sample

A blood sample for the analysis of the CsA trough levels (in the HTX group only), total cholesterol, HDL and LDL cholesterol, triglycerides, glucose, creatinine, sodium, potassium and calcium was obtained at the day of the coronary angiography.

Statistical analysis

Results are presented as mean ± SD. Changes in BP and HR before and after nitrate infusion were analyzed with ANOVA for repeated measures, comparisons of clinical data were made by 2-tailed paired or unpaired t-test and, where appropriate, the relationship between CsA levels and changes in BP and HR was analyzed by simple regression (Stat View 4.5, Abacus Concepts, USA). Statistical significance was accepted at $p < 0.05$. Due to the clinical indication for the examination, the interventional cardiologist performing the examination was not blinded. However, data analysis was performed by an investigator blinded to the group (HTX/controls).

Results

Patients

The clinical characteristics of the study population are shown in table 1. Age, weight and cardiovascular risk factors were not different between groups. HTX patients showed a higher dBP ($p = 0.01$) and HR ($p = 0.04$), while no significant difference in sBP was found. None of the patients included in the control group had significant coronary stenosis and none required an interventional procedure.

Renal failure was more severe in HTX patients probably as a consequence of CsA treatment; he-

patic function was similar in the two groups. The medications used by the patients included in our study are shown in table 2.

Acute effects of nitrate injection on BP and heart rate

Within a minute following injection of 50 μg and 100 μg GTN, both the HTX-group and the control group showed a dose-dependent decrease in BP (sBP $p = 0.0001$ for HTX and $p = 0.006$ for controls; dBP $p = 0.0001$ for HTX and $p = 0.05$ for controls). In the aorta, both sBP and dBP decreased more in the HTX patients group than in the reference group (sBP $p = 0.04$, dBP $p = 0.03$, for group comparison) (fig. 1). When the data were analysed as percent change, compared to baseline, it was observed that the BP reduction induced by 100 μg nitroglycerin was significantly higher in the HTX group compared to the HT group (p 0.02 for sBP and $p = 0.03$ for dBP) while the effect of 50 μg nitroglycerin was not significantly different in the two groups.

At the end of the angiographic study (mean duration after the last infusion of nitrates 8 ± 3 minutes), BP in controls returned to baseline, while in HTX patients BP remained significantly lower when compared to baseline (ΔsBP $p = 0.022$ HTX vs. controls; ΔdBP $p = 0.018$ HTX vs. controls) (fig. 1).

The central pressures measured during coronary angiography are listed in table 3.

After injection of GTN, systolic pulmonary artery pressure ($p = 0.001$ in the HTX group and $p = 0.01$ in controls) and diastolic pulmonary pressure ($p = 0.006$ in the HTX group and $p = 0.047$ in controls) decreased significantly in both groups. However, the reduction in systolic and diastolic pulmonary pressure was not significantly different in the HTX group compared to controls (n.s. for group comparison).

Table 1

Clinical characteristics of the study population. HTX: Heart-transplanted patients; sBP: systolic blood pressure, dBP: diastolic blood pressure, LDL: low density lipoprotein, HDL: high density lipoprotein, Na^+: plasma sodium, K^+: plasma potassium, Ca^{2+}: plasma calcium. Data are expressed as mean ± SD. Creatinine clearance was calculated according to the Cockcroft formula. *p <0.05 controls vs HTX patients.

	HTX N = 18	Controls N = 6	p
Baseline characteristics			
Gender:			
Male (%)	78	100	
Female (%)	22	0	
Age (years)	44 ± 5	42 ± 6	0.27
BMI (kg/m²)	27 ± 3	25 ± 14	0.80
sBP (mm Hg)	148 ± 19	134 ± 16	0.11
dBP (mm Hg)	82 ± 13	69 ± 12*	0.04
Heart rate (min^{-1})	82 ± 7	74 ± 11*	0.14
Cardiovascular Risk Factors			
Total cholesterol (mmol/l)	4.8 ± 0.9	4.3 ± 0.8	0.35
LDL (mmol/l)	1.2 ± 0.4	1.3 ± 0.4	0.86
HDL (mmol/l)	2.4 ± 0.9	2.5 ± 0.4	0.90
Triglyceride (mmol/l)	2.5 ± 1.7	1.5 ± 0.8	0.09
Smoker (%)	62	66.7	
Diabetes mellitus (%)	24	–	
Renal parameters			
Creatinine (μmol/l)	184 ± 120	106 ± 30	0.01
Calculated clearance (ml/min)	56.7 ± 26	81.7 ± 25.6	0.05
Na^+ (mmol/l)	139 ± 3	141 ± 1.2	0.05
K^+ (mmol/l)	4.3 ± 0.9	3.8 ± 0.3	0.09
Ca^{2+} (mmol/l)	2.2 ± 0.2	2.23	

Table 2

Medication taken by the patients recruited into the study. HTX: Heart-transplanted patients; ACE: angiotensin converting enzyme, AT: angiotensin, Ca^{2+}: calcium.

Medication (in %)	HTX n = 18	Control n = 6
Cyclosporine	100	0
ACE inhibitor/AT-receptor antagonist	77.6	66.7
Diuretic	22.2	33.3
Ca^{2+} antagonist	38.9	–
Beta blocker	50	50
Statin	83.3	66.7
Glucocorticoid	38.9	–
Macrolide	5.6	–
Azathioprin/Mycophenolate mofetil	100	–
Rapamicine	11.1	–

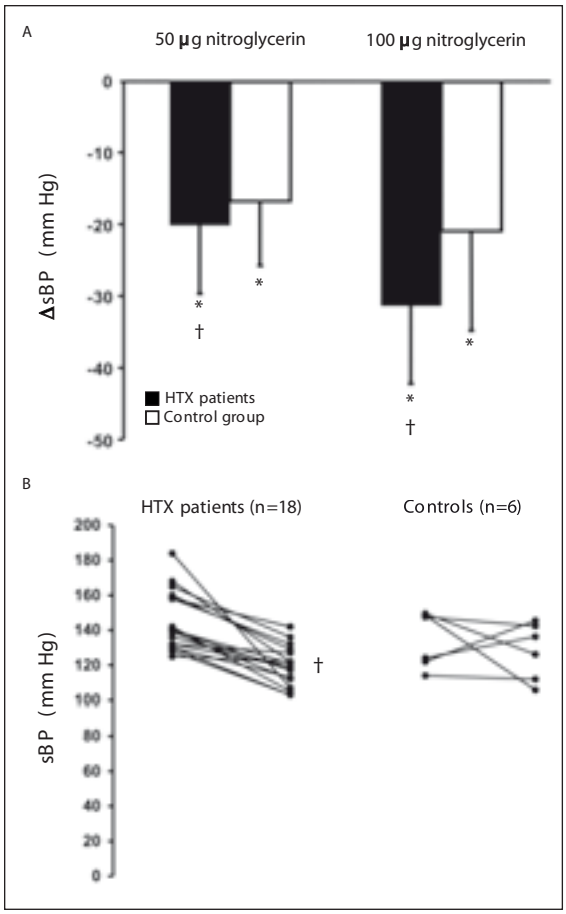

Figure 1

Delta systolic blood pressure (ΔsBP) in HTX patients and in the HT group within a minute after administration of 50 μg and 100 μg nitroglycerin (A) and during the recovery time (8 ± 3 minutes after the last infusion of nitroglycerin) (B). We found a treatment effect after nitroglycerin infusion (p <0.001). This effect was true for both groups (p <0.01 for both groups), Interestingly, the HTX group showed a significantly more pronounced effect on sBP (p = 0.038 for group comparison). * p <0.05 or less vs baseline; † p <0.05 or less HTX vs controls. Data are expressed as mean ± SD.

GTN injection increased HR in both HTX patients and the control group. In the HTX group, the increase in HR was maximal after 100 μg GTN, while in the control group the increase already reached its maximum after 50 μg GTN (fig. 2). No significant difference was found when the percent changes in HR in the HTX and in the control group were compared.

Table 3

Blood pressure at baseline and following nitroglycerin infusion. Blood pressure values measured in the aorta and the pulmonary artery during the haemodynamic study at baseline and following nitroglycerin infusion. Data are expressed as mean ± SD. HTX: Heart-transplanted patients; SBP: systolic blood pressure, DBP: diastolic blood pressure, MBP: mean blood pressure, SPP: systolic pulmonary pressure, DPP: diastolic pulmonary pressure, MPP: mean pulmonary pressure. Data are expressed as mean ± SD.

	HTX (n 18)	Control (n 6)
Baseline		
SBP aorta (mm Hg)	148 ± 19.4	134 ± 15.7
DBP aorta (mm Hg)	82 ± 13.0	69 ± 11.6
MBP aorta (mm Hg)	104 ± 13.9	90 ± 10.4
SPP (mm Hg)	26 ± 7.8	32 ± 10.0
DPP (mm Hg)	13 ± 4.2	14 ± 8.2
MPP (mm Hg)	17 ± 5.3	20 ± 8.2
After 50 μg nitroglycerine		
SBP aorta (mm Hg)	126 ± 14.2	117 ± 17.8
DBP aorta (mm Hg)	75 ± 12.9	64 ± 11.6
MBP aorta (mm Hg)	92 ± 12.6	82 ± 11.5
SPP (mm Hg)	23 ± 5.6	27 ± 10.1
DPP (mm Hg)	12 ± 4.5	14 ± 7.6
MPP (mm Hg)	15 ± 4.6	18 ± 8.1
After 100 μg <nitroglycerine		
SBP aorta (mm Hg)	113 ± 16.1	113 ± 26.0
DBP aorta (mm Hg)	70 ± 11.7	63 ± 11.9
MBP aorta (mm Hg)	84 ± 12.3	79 ± 14.6
SPP (mm Hg)	21 ± 5.9	24 ± 7.8
DPP (mm Hg)	10 ± 4.4	14 ± 6.9
MPP (mm Hg)	14 ± 4.6	17 ± 7.0

Cyclosporine blood concentration and effect of GTN

In the HTX group, a significant relationship was found between the absolute (50 μg nitrate: r: 0.57, $p = 0.01$; 100 μg nitrate: r: 0.48, $p = 0.04$) and percentage (50 μg nitrate: r: 0.54, $p = 0.02$; 100 μg nitrate: r: 0.46, $p = 0.05$) decrease in sBP with blood concentration of CsA. No correlation was obtained between the changes in dBP or HR.

Similarly, no correlation was observed between baseline sBP and dBP and CsA levels, while a significant correlation was found with HR (r: 0.55, $p = 0.02$).

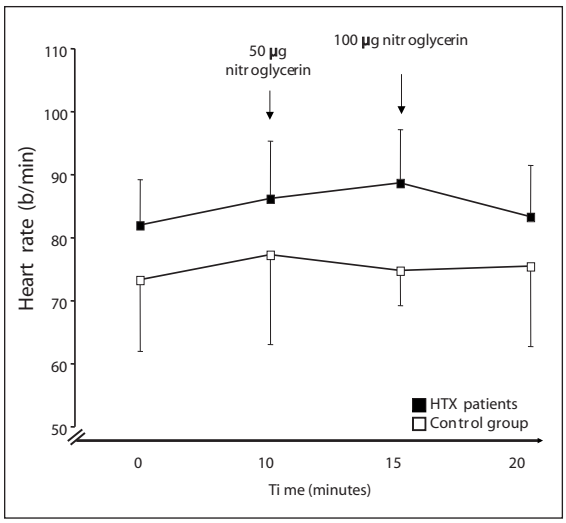

Figure 2

Changes in heart rate induced by nitroglycerin in heart-transplanted patients and in the control hypertensive group. Heart rate recorded in heart-transplanted (HTX) patients and in the hypertensive control group at baseline, after administration of 50 mg and 100 mg nitroglycerin and during the recovery time (8 ± 3 minutes after the last infusion of nitroglycerin). Data are expressed as mean ± SD.

Discussion

In this study, it has been demonstrated that, in HTX patients treated with cyclosporine, an acute infusion of GTN on top of a standard antihypertensive therapy may induce a further reduction in BP. This reduction was significantly more pronounced and long lasting than that induced in HT patients enrolled as controls. Moreover, the reduction in sBP showed a significant correlation with cyclosporine concentration.

HTX patients receiving CsA often develop arterial hypertension that is unlikely to be treated, even with an optimal association therapy [9]. In animal models, nitrate showed the potential for reducing cyclosporine-induced hypertension [28, 29]. Due to the difficulty in controlling cyclosporine-induced hypertension, even when treated with more antihypertensive drugs, the HTX patients were characterized by higher dBP. Moreover, HR was also significantly higher in the HTX group. These data are in line with a previous report in patients soon, and later, after heart transplantation [30] and may be explained by the administration of CsA and the cardiac denervation following HTX, respectively.

An acute infusion of cyclosporine induces an increase in peripheral vascular resistance [31] and an increase in total peripheral vascular resistance was described in paediatric renal transplant patients treated with cyclosporine [32]. This increase in peripheral vascular resistance may explain the higher dBP found in the HTX group.

Donor-heart cardioectomy with subsequent orthotopic transplantation creates both afferent and efferent cardiac denervation. Cardiac efferent innervation mediates sympathetic and vagal nervous system effects on the heart. The absence of vagally mediated influences causes donor HR at rest to be higher [33]. Even if a partial sympathetic reinnervation is observed, HTX patients are usually characterized by high HR [34]. The

cyclosporine-induced increase in sympathetic nervous activity [35] may explain the correlation found between resting HR and CsA concentrations.

In patients with stable graft function after renal transplantation, Weingart and colleagues [36] showed that nitroglycerin spray may reduce mean arterial BP as well as the increase in renal vascular resistance induced by the treatment with CsA.

In this study, we observed a dose-dependent decrease in aortic BP following GTN injection in HTX patients treated with cyclosporine, as well as in hypertensive controls. This effect was significantly more pronounced and lasted longer in HTX patients compared to controls. Moreover, we observed a significant reduction of pulmonary pressures in HTX patients and controls. Therefore, we can speculate that the reduction we showed in the pulmonary circulation could be explained by the direct vasodilation induced by GTN, while in HTX patients the aortic BP reduction induced by GTN could be explained not only by direct vasodilation but also by acting on specific mechanisms of the cyclosporine-induced hypertension.

Cyclosporine was shown to decrease endothelial-dependent vasodilators and to increase endothelin level in animal models and in humans [3, 7, 8, 10–14, 37–44]. Whereas nitrates partly substitute deficient endogenous nitric oxide [45], they could shift the imbalance to vasodilation. Moreover, while endogenous nitric oxide may inhibit endothelin-1 production [46], the release of exogenous nitric oxide by nitrates could also lead to an inhibition of this potent vasoconstrictor and therefore have a role in reducing the vasoconstriction associated with cyclosporine-induced hypertension. Another mechanism leading to vasodilation after acute administration of nitrate could be an influence on Ca^{2+} mobilization. Nitrates may influence the Angiotensin-II induced Ca^{2+} mobilization in vascular smooth muscle cells by an increased amount of Ca^{2+} in Angiotensin-II sensitive intracellular Ca^{2+} stores [47], as well as by the effect of exogenous nitric oxide that may decrease free Ca^{2+}, inhibit Ca^{2+} influx and therefore support the relaxation of vascular smooth muscle [48].

Therefore, nitrates may counteract angiotensin II and endothelin-1 at the level of vascular smooth muscle by reducing Ca^{2+} inflow and facilitating the vasodilator effects of nitric oxide, and these effects may be responsible for the observed stronger and more prolonged aortic BP reduction which we observed in the HTX patient group.

Last but not least, animal studies have shown that cyclosporine induced a disequilibrium in the NO/cyclic guanosine-3′,5′-monophosphate (cGMP) system, which may contribute to the vascular hyperreactivity [12]. In rats, nitrate therapy may provide a valid choice to prevent this cyclosporine-induced NO-cGMP decrease, without a negative influence on the oxidative equilibrium [28, 29].

We found a significant correlation between sBP but not dBP changes and CsA concentration. The effect of cyclosporine on BP is dose-dependent. The lack of correlation between changes in dBP and CsA concentration might be explained by the fact that nitrates were added on a "state of the art" able to normalize dBP but not sBP (table 1).

Baseline HR [49] and HR response to physiological stimuli [50] are very important prognostic factors in HTX patients.

In this study, we observed a progressive increase in HR related to the increasing dose of GTN. In the control group, the increase of HR was maximal after the first dose of GTN (50 μg) while after the infusion of 100 μg the HR decreased. Due to parasympathetic and sympathetic denervation of the heart, cardiac transplant recipients have an elevated resting HR, and an attenuated HR response and a delayed normalization of HR after stimulation [51]. Functional sympathetic reinnervation has been demonstrated in humans [52–54], while most studies do not provide consistent evidence for parasympathetic reinnervation [55]. Therefore, it can be speculated that in the HT patients the response to the higher dose of GTN is the sum of the sympathetic and vagal stimulation, while in the HTX patients the parasympathetic component is not present or slower.

Limitations

The number of the control subjects included in the study is small but sufficient to assure a statistical power superior to 80%. Moreover, the BP was measured in lying position, a condition that may have led to an underestimation of the effect of nitrate. Finally, we did not assess the individual maximal response to nitroglycerin but just the change in BP observed within the first minute after intracoronary infusion of each dose of nitroglycerin.

Conclusions

The organic nitrates, like GTN, have similar mechanisms of action and exert their therapeutic effects through their active metabolite, nitric oxide. Some of the main functional alterations induced by cyclosporine and leading to hypertension, might be compensated by nitric oxide donors. Our results following acute administration of GTN indicate that the cyclosporine-induced hypertension can, potentially, be treated. The chronic use of GTN is, however, limited by the well-known tachyphylaxis. The chronic affect of NO donors, others than nitrates (such as sildena-

fil, valdenafil, and molsidomine), should be carefully evaluated in controlled clinical studies in patients with cyclosporine-induced hypertension.

The authors wish to express their gratitude to Mrs. Rosy Hug, Mrs. Priska Kaiser, Mrs. Astrid Hirt and Mrs Ines Bühler for their precious help.

Correspondence:
Isabella Sudano, MD, PhD
Cardiovascular Center Cardiology
University Hospital Zurich
Rämistrasse 100
CH-8091 Zurich
Switzerland
E-Mail: isabella.sudano@usz.ch

References

1 Kaye D, Thompson J, Jennings G, Esler M. Cyclosporine therapy after cardiac transplantation causes hypertension and renal vasoconstriction without sympathetic activation. Circulation. 1993; 88(3):1101–9.
2 Sturrock ND, Lang CC, MacFarlane LJ, Dockrell ME, Ryan M, Webb DJ, et al. Serial changes in blood pressure, renal function, endothelin and lipoprotein (a) during the first 9 days of cyclosporin therapy in males. J Hypertens. 1995;13(6):667–73.
3 Textor SC, Canzanello VJ, Taler SJ, Wilson DJ, Schwartz LL, Augustine JE, et al. Cyclosporine-induced hypertension after transplantation. Mayo Clin Proc. 1994;69(12):1182–93.
4 Ventura HO, Malik FS, Mehra MR, Stapleton DD, Smart FW. Mechanisms of hypertension in cardiac transplantation and the role of cyclosporine. Curr Opin Cardiol. 1997;12(4):375–81.
5 Zeier M, Mandelbaum A, Ritz E. Hypertension in the transplanted patient. Nephron. 1998;80(3):257–68.
6 Flechner SM, Kobashigawa J, Klintmalm G. Calcineurin inhibitor-sparing regimens in solid organ transplantation: focus on improving renal function and nephrotoxicity. Clin Transplant. 2008;22(1):1–15.
7 Taler SJ, Textor SC, Canzanello VJ, Schwartz L. Cyclosporin-induced hypertension: incidence, pathogenesis and management. Drug Saf. 1999;20(5):437–49.
8 Silverborn M, Ambring A, Nilsson F, Friberg P, Jeppsson A. Vascular resistance and endothelial function in cyclosporine-treated lung transplant recipients. Transpl Int. 2006;19(12):974–81.
9 Ventura HO, Mehra MR, Stapleton DD, Smart FW. Cyclosporine-induced hypertension in cardiac transplantation. Med Clin North Am. 1997;81(6):1347–57.
10 Calo L, Semplicini A, Davis PA, Bonvicini P, Cantaro S, Rigotti P, et al. Cyclosporin-induced endothelial dysfunction and hypertension: are nitric oxide system abnormality and oxidative stress involved? Transpl Int. 2000;13(Suppl 1):S413–8.
11 Bossaller C, Forstermann U, Hertel R, Olbricht C, Reschke V, Fleck E. Ciclosporin A inhibits endothelium-dependent vasodilatation and vascular prostacyclin production. Eur J Pharmacol. 1989;165(1):165–9.
12 Oriji GK, Keiser HR. Role of nitric oxide in cyclosporine A-induced hypertension. Hypertension. 1998;32(5):849–55.
13 Oriji GK, Keiser HR. Nitric oxide in cyclosporine A-induced hypertension: role of protein kinase C. Am J Hypertens. 1999;12(11 Pt 1):1091–7.
14 Vaziri ND, Ni Z, Zhang YP, Ruzics EP, Maleki P, Ding Y. Depressed renal and vascular nitric oxide synthase expression in cyclosporine-induced hypertension. Kidney Int. 1998;54(2):482–91.
15 Stroes ES, Luscher TF, de Groot FG, Koomans HA, Rabelink TJ. Cyclosporin A increases nitric oxide activity in vivo. Hypertension. 1997;29(2):570–5.
16 Bracht C, Yan XW, LaRocca HP, Sutsch G, Kiowski W. Cyclosporine A and control of vascular tone in the human forearm: influence of post-transplant hypertension. J Hypertens. 1999;17(3):357–63.
17 Lim SJ, Simeone AM, Kim CK, Tari AM. Cyclosporin A enhances the apoptotic effects of N-(4-hydroxyphenyl)retinamide in breast cancer cells. Int J Cancer. 2002;101(3):243–7.
18 Berthier CC, Pally C, Weckbecker G, Raulf F, Rehrauer H, Wagner U, et al. Experimental heart transplantation: effect of cyclosporine on expression and activity of metzincins. Swiss Med Wkly. 2009;139(15-16):233–40.
19 Berlin R. Historical aspects of nitrate therapy. Drugs. 1987;33(Suppl 4):1–4.
20 Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol. 2001;38(7):2101–13.
21 Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction--summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol. 2002;40(7):1366–74.
22 Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina – summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). Circulation. 2003;107(1):149–58.
23 Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). J Am Coll Cardiol. 2004;44(3):E1–E211.
24 Abrams J. Beneficial actions of nitrates in cardiovascular disease. Am J Cardiol. 1996;77(13):31C–7C.
25 Harrison DG, Bates JN. The nitrovasodilators. New ideas about old drugs. Circulation. 1993;87(5):1461–7.
26 Thadani U. Oral nitrates: more than symptomatic therapy in coronary artery disease? Cardiovasc Drugs Ther. 1997;11(Suppl 1):213–8.
27 Chong S, Fung HL. Biochemical and pharmacological interactions between nitroglycerin and thiols. Effects of thiol structure on nitric oxide generation and tolerance reversal. Biochem Pharmacol. 1991;42(7):1433–9.
28 Reis F, Rocha-Pereira P, Teixeira de Lemos E, Parada B, Baptista S, Figueiredo A, et al. Oxidative stress in cyclosporine-induced hypertension: evidence of beneficial effects or tolerance development with nitrate therapy. Transplant Proc. 2007; 39(8):2494–500.
29 Reis F, Teixeira de Lemos E, Almeida L, Parada B, Garrido AP, Rocha-Pereira P, et al. Dual effect of nitrate therapy for cyclosporine-induced hypertension on vascular and platelet morphofunctional markers; an animal model. Transplant Proc. 2007;39(8):2501–6.
30 Bracht C, Hoerauf K, Vassalli G, Hess OM, Ueberfuhr P, Hoefling B. Circadian variations of blood pressure and heart rate early and late after heart transplantation. Transplantation. 1996; 62(8):1187–90.
31 Navarro JF, Mora C, Marcen R, Teruel JL, Gamez C, Jimenez JJ, et al. Acute cardiovascular effects of intravenous cyclosporine. Int Urol Nephrol. 1996;28(4):575–81.
32 Matteucci MC, Giordano U, Calzolari A, Rizzoni G. Total peripheral vascular resistance in pediatric renal transplant patients. Kidney Int. 2002;62(5):1870–4.
33 Gaer J. Physiological consequences of complete cardiac denervation. Br J Hosp Med. 1992;48(5):220–5.

34 Mattila S, Heikkila L, Sipponen J, Verkkala K, Kyosola K, Mattila T, et al. Heart transplantation in Finland 1985-1995. Ann Chir Gynaecol. 1997;86(2):113–20.
35 Scherrer U, Vissing SF, Morgan BJ, Rollins JA, Tindall RS, Ring S, et al. Cyclosporine-induced sympathetic activation and hypertension after heart transplantation. N Engl J Med. 1990;323(11):693–9.
36 Weingart C, Leingartner T, Bergler T, Kruger B, Boger C, Mack M, et al. Increase in renal vascular resistance after intake of cyclosporin A and tacrolimus and reversal by nitroglycerin spray: a study in patients with stable renal allograft function. Int J Clin Pharmacol Ther. 2006;44(9):422–7.
37 Bunchman TE, Brookshire CA. Cyclosporine-induced synthesis of endothelin by cultured human endothelial cells. J Clin Invest. 1991;88(1):310–4.
38 Perico N, Dadan J, Remuzzi G. Endothelin mediates the renal vasoconstriction induced by cyclosporine in the rat. J Am Soc Nephrol. 1990;1(1):76–83.
39 Perico N, Ruggenenti P, Gaspari F, Mosconi L, Benigni A, Amuchastegui CS, et al. Daily renal hypoperfusion induced by cyclosporine in patients with renal transplantation. Transplantation. 1992;54(1):56–60.
40 Rezzani R, Rodella L, Bianchi R. Induction of endothelin in rat kidney after cyclosporine A treatment. Acta Histochem. 2001;103(4):423–31.
41 Kon V, Sugiura M, Inagami T, Harvie BR, Ichikawa I, Hoover RL. Role of endothelin in cyclosporine-induced glomerular dysfunction. Kidney Int. 1990;37(6):1487–91.
42 Schiffrin EL. State-of-the-Art lecture. Role of endothelin-1 in hypertension. Hypertension. 1999;34(4 Pt 2):876–81.
43 Cauduro RL, Costa C, Lhulier F, Garcia RG, Cabral RD, Goncalves LF, et al. Endothelin-1 plasma levels and hypertension in cyclosporine-treated renal transplant patients. Clin Transplant. 2005;19(4):470–4.
44 Letizia, C, De Biase L, Caliumi C, Verrelli, C, Semeraro, R, Subioli, S, et al. Endothelin-1 circulating levels increase in patients with orthotopic heart transplantation and in chronic therapy with cyclosporine. Minerva Cardioangiol. 2001;49(1):15–22.
45 Ruschitzka FT, Noll G, Luscher TF. The endothelium in coronary artery disease. Cardiology. 1997;88(Suppl 3):3–19.
46 Lüscher TF, Vanhoutte PM. The endothelium: modulator of the cardiovascular function. 1990, Boca Raton, FL: CRC Press.
47 Pfeilschifter J. Cyclosporin A augments vasoconstrictor-induced rise in intracellular free calcium in rat renal mesangial cells. Biochem Pharmacol. 1988;37(21):4205–10.
48 Cohen RA, Weisbrod RM, Gericke M, Yaghoubi M, Bierl C, Bolotina VM. Mechanism of nitric oxide-induced vasodilatation: refilling of intracellular stores by sarcoplasmic reticulum Ca2+ ATPase and inhibition of store-operated Ca2+ influx. Circ Res. 1999;84(2):210–9.
49 Anand RG, Reddy MT, Yau CL, Myers L, Amin RR, Stahls PF, et al. Usefulness of heart rate as an independent predictor for survival after heart transplantation. Am J Cardiol. 2009;103(9):1290–4.
50 Kaser A, Martinelli M, Feller M, Carrel T, Mohacsi P, Hullin R. Heart rate response determines long term exercise capacity after heart transplantation. Swiss Med Wkly. 2009;139(21-22):308–12.
51 Rudas L, Pflugfelder PW, Menkis AH, Novick RJ, McKenzie FN, Kostuk WJ. Evolution of heart rate responsiveness after orthotopic cardiac transplantation. Am J Cardiol. 1991;68(2):232–6.
52 Burke MN, McGinn AL, Homans DC, Christensen BV, Kubo SH, Wilson RF. Evidence for functional sympathetic reinnervation of left ventricle and coronary arteries after orthotopic cardiac transplantation in humans. Circulation. 1995;91(1):72–8.
53 Kaye DM, Esler M, Kingwell B, McPherson G, Esmore D, Jennings G. Functional and neurochemical evidence for partial cardiac sympathetic reinnervation after cardiac transplantation in humans. Circulation. 1993;88(3):1110–8.
54 van De Borne P, Neubauer J, Rahnama M, Jansens JL, Montano N, Porta A, et al. Differential characteristics of neural circulatory control: early versus late after cardiac transplantation. Circulation. 2001;104(15):1809–13.
55 Arrowood JA, Minisi AJ, Goudreau E, Davis AB, King AL. Absence of parasympathetic control of heart rate after human orthotopic cardiac transplantation. Circulation. 1997;96(10):3492–8.