Protamine-induced hypotension and bradycardia in a cardiac transplant patient

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Purpose: The potential for functional reinnervation of the transplanted heart in man is controversial. We report the sudden onset of bradycardia in a cardiac transplant patient following a period of hypotension subsequent to the administration of protamine. Possible mechanisms underlying this response, including reinnervation of the transplanted heart, are assessed.

Clinical features: Eight weeks after cardiac transplantation, a patient returned to hospital for a left femoral- tibial artery bypass vein graft. The patient was anaesthetized using general anaesthesia. Upon completion of the procedure, protamine was administered to reverse the heparin-induced anticoagulation. Although administration of a 5.0 mg "test-dose" appeared to be without cardiovascular effect, after an additional 20.0 mg, blood pressure decreased from 98/52 to 62/40 mmHg. After blood pressure reached its nadir, heart rate decreased precipitously from 57 to 29 beats·min^{-1}.

Conclusions: This report demonstrates that heart rate can change considerably in patients who have undergone cardiac transplantation. It is argued that the change in heart rate observed in the present report cannot be explained by reinnervation of the transplanted heart, as the patient had undergone transplantation only eight weeks previously. Rather, we suggest that the change was mediated by mechanisms intrinsic to the transplanted heart and extrinsic to the CNS.

Objectif : La réinnervation éventuelle du coeur humain transplanté demeure un sujet controversé. Nous rapportons une tachycardie subite chez un transplanté après un épisode d'hypotension subséquente à l'administration de protamine. Les mécanismes possibles de ce phénomène, incluant la réinnervation du coeur transplanté, sont discutés.

Éléments cliniques : Huit semaines après une transplantation cardiaque, un patient était réhospitalisé pour un pontage fémoro-tibial gauche. L'intervention s'est déroulée sous anesthésie générale. À la fin de l'intervention, la protamine était administrée pour neutraliser l'héparinisation. Bien que la dose-test de 5,0 mg n'ait pas provoqué d'effets cardiovasculaires, après l'ajout de 20 mg la pression artérielle a fait une chute précipitée passant de 98/52 à 62/40 mmHg. Au niveau le plus bas de la pression artérielle, la fréquence cardiaque a subitement chuté de 57 à 29 b·min^{-1}

Conclusions : Ce compte rendu montre que la fréquence cardiaque peut changer considérablement chez le cardiaque transplanté. Comme la transplantation cardiaque ne datait que de huit semaines, il est peu probable que le changement de la fréquence cardiaque observé ici s'explique par la réinnervation du greffon. Nous suggérons plutôt que ce changement était sous médiation de mécanismes intrinsèques au greffon et extrinsèques au SNC.

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HARVESTING of the donor heart for cardiac transplantation results in complete extrinsic denervation of the organ and there is substantial evidence that denies reinnervation of the transplanted heart.[1] For example, sympathetic and parasympathetic reinnervation has been refuted on the basis of a lack of appropriate reflex changes in heart rate or heart rate variability.[2–6] Afferent reinnervation has been denied on the basis of the inability of most cardiac transplant recipients to perceive pain secondary to myocardial ischaemia in spite of the presence of graft coronary atherosclerosis.[7] On the other hand, recent studies suggest that limited cardiac reinnervation may occur in some patients. For example, the possibility of afferent reinnervation is supported by reports of angina accompanied by objective evidence of cardiac ischaemia (ECG changes, angiographic and echocardiographic evidence of coronary artery disease) in a few cardiac transplant patients.[8,9] Evidence for sympathetic reinnervation is supported by the observation of a low-frequency heart rate variability in some cardiac transplants, some of whom also demonstrated tachycardia in response to amyl nitrate-induced hypotension,[10] and from experiments demonstrating catecholamine uptake, storage or release from presumed cardiac sympathetic postganglionic neurones in the transplanted heart.[11,12] In addition, there are observations in transplant patients of appropriate, albeit diminished, reflex changes in heart rate in response to exercise and changes in posture which develop over time during the post transplant period.[13] Evidence for parasympathetic reinnervation includes the observation of an atropine-sensitive high-frequency variability in heart rate in one transplanted patient.[14] In addition, there are a few reports describing vasovagal syncopal-like episodes in cardiac transplant patients.[15–17] While the evidence for limited cardiac reinnervation is intriguing, a careful review of this subject concluded that functional reinnervation of the transplanted heart rarely, if ever, occurs.[1] Accordingly, it is anticipated that rapid alterations in heart rate normally produced by altered cardiac autonomic tone are absent in this unique type of patient and therefore, during the course of anaesthesia administered to this type of patient, a relatively stable heart rate is expected. In this case report, we describe the sudden onset of bradycardia in a cardiac transplant patient following an episode of hypotension subsequent to the administration of protamine.

Case report

A 58-yr-old 72-kg white man underwent orthotopic heart transplantation for ischaemic cardiomyopathy. The patient's health was additionally compromised by insulin-dependent diabetes and peripheral vascular disease, with claudication of the left leg and gangrene of the first digit present before transplantation. The postoperative course was complicated by right-sided heart failure secondary to pulmonary hypertension, requiring the insertion of a right ventricular assist device approximately six hours after admission to the intensive care unit. The patient was discharged from hospital one month following transplantation in stable condition. Echocardiography demonstrated a left ventricle of normal size and contractility (ejection fraction 60–70%), and a right ventricle which, although mildly dilated, appeared to contract normally. There was no evidence of pulmonary hypertension, and pulmonary systolic pressures were estimated at 25–30 mmHg. Aortic and mitral valves appeared normal, but severe tricuspid regurgitation was observed. Two months after transplantation, the patient returned to hospital for a left femoral-tibial artery bypass vein graft. Laboratory investigations demonstrated an elevated blood glucose (14.0 $mMol \cdot L^{-1}$), BUN (20.7 $mMol \cdot L^{-1}$) and creatinine (168 $mMol \cdot L^{-1}$) and anaemia (haematocrit 0.31). A 12 lead ECG showed sinus rhythm at 80 $beats \cdot min^{-1}$ and a right bundle branch block. Endomyocardial biopsy indicated the possibility of early rejection, although there was no evidence of rejection subsequently. Coronary angiography demonstrated normal coronary arteries. The patient's medications were 175 mg cyclosporine bid, 125 mg azathioprine qd, 17.5 mg prednisone qd, 106 mg furosemide bid, 50 mg spironolactone qd, 80 mg sulfamethoxazole/trimethoprim DS qd, 300 mg ferrous sulphate tid, 1300 mg dolomite bid, and insulin (Humulin®) N 38 U/R 14 U a.m., R 10 U before dinner, N 12 U p.m. General anaesthesia included 225 mg thiopentone, 50 μg sufentanil followed by 14 $\mu g \cdot hr^{-1}$, 3.0 mg d-tubocurarine, 120 mg succinylcholine, 12 mg vecuronium, and pulmonary ventilation with isoflurane 0.3–0.6% and a nitrous oxide-oxygen mixture (F_IO_2 0.4). Other drugs administered intraoperatively included 1 g sodium cefazolin, 100 mg hydrocortisone, and a continuous infusion of dextrose 5% and insulin. Heparin 5000 units was administered prior to occlusion of the femoral artery, and an additional 2500 units were administered subsequently. Monitoring consisted of invasive blood pressure recording via a catheter inserted into the right radial artery, ECG (leads II and V), pulse oximetry, capnography, and a nerve stimulator.

Upon completion of the procedure, protamine was administered to reverse the heparin-induced anticoagulation. Although administration of a 5.0 mg "test-dose" appeared to be without cardiovascular effect, after administration of an additional 20.0 mg approximately three minutes later, blood pressure decreased from 98/52 mmHg to 62/40 mmHg (Figure). After

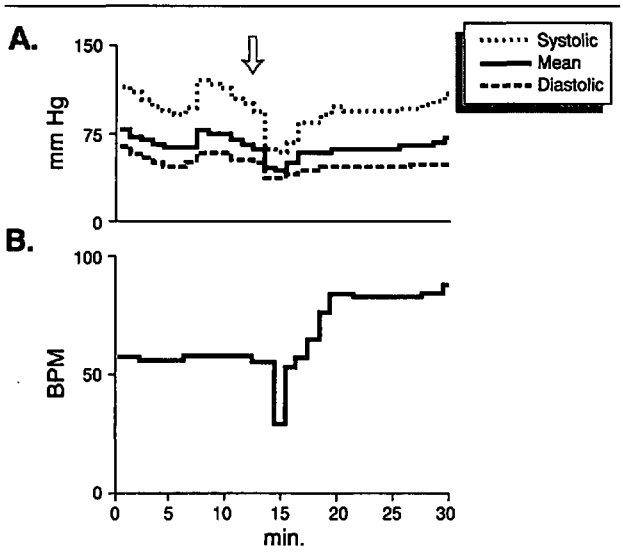

FIGURE Effects of protamine on systemic arterial blood pressure (panel A) and heart rate (panel B).

After systemic administration of protamine 25 mg (arrow), blood pressure decreased from 98/52 mmHg to 62/40 mmHg. After blood pressure reached its nadir, heart rate decreased precipitously from a rate of 57 beats·min^{-1} to a rate of 29 beats·min^{-1}. Hypotension and bradycardia were subsequently reversed by ephedrine and phenylephrine.

blood pressure reached its nadir, heart rate decreased precipitously from a sinus rate of 57 beats·min^{-1} to a junctional rate of 29 beats·min^{-1}. Following administration of 2 × 10 mg ephedrine and 0.1 mg phenylephrine, the hypotensive and bradycardic responses were reversed. Prior to induction, blood pressure was 135/65 mmHg and heart rate was 68 beats·min^{-1}.

Discussion

We report hypotension followed by a precipitous decrease in heart rate, after administration of protamine in a cardiac transplant recipient. Hypotension following protamine administration is a well-described phenomenon, and mechanisms to account for this include histamine release from mast cells, anaphylactoid and anaphylactic reactions.[18] It is the precipitous bradycardia following the hypotension which is so unusual.

Could the cardiovascular response described in this study represent an episode of vasovagal syncope? This phenomenon is the perplexing autonomic response of the paradoxical withdrawal of sympathetic drive in response to hypotension, which results in vasodilatation and bradycardia.[19] It is believed that this vasodepressor reaction is activated by stimulation of mechanoreceptors in the underfilled left ventricle, with impulses conducted centrally via afferents contained within the vagus nerves.[19] Vasovagal-type responses have been previously reported in a few cardiac transplant patients. In one report, administration of nitroprusside to a patient transplanted 11 months previously resulted in a decrease in systemic arterial pressure beyond that originally produced by the vasodilating drug, decreased sympathetic nerve activity, a reduction in P wave rate recorded from the innervated recipient's atria, pallor, nausea and diaphoresis.[15] Importantly, there was no decrease in rate of the transplanted heart. In a second report, following a change in position from supine to upright in a patient transplanted 36 mo previously, there was a sudden decrease in heart rate by 16 beats·min^{-1}, and the onset of nausea, diaphoresis and syncope.[16] In a third report, application of lower body negative pressure to a patient transplanted four months previously produced a decrease in systemic arterial pressure in addition to that initially produced by this manoeuvre, followed by a sudden reduction in heart rate of the transplanted heart of 20 beats·min^{-1}, decreased forearm blood flow, pallor, nausea and dizziness.[17]

The patient described in the present report had undergone transplantation only eight weeks previously and, as reinnervation of the transplanted heart (when demonstrable) is not evident before one year after transplantation,[11-13] the response is unlikely to have been vasovagal. Notwithstanding the vasovagal reflex, with a normally innervated heart an increase in heart rate is anticipated in response to a decrease in blood pressure via decreased stimulation of baroreceptors. Assuming that cardiac reinnervation did not occur, it can be argued that the initial decrease in systemic arterial pressure evoked a reflex decrease in sympathetic outflow in response to activation of mechanoreceptors extrinsic to the transplanted heart (e.g., remnant atria, arterial baroreceptors).[15,17] Such withdrawal of sympathetic tone could produce a reduction in heart rate in a denervated heart via decreased catecholamine secretion from the adrenal glands, although it is anticipated that the heart rate would change gradually,[20] not precipitously, as was the case.

From the above, it seems reasonable to propose that the bradycardia described in the present report was mediated by mechanism(s) which did not involve reflex activation of the central nervous system. Possibly, the hypotension preceding the bradycardia resulted in cardiac ischaemia with decreased perfusion of the sino-atrial node of the donor heart. Such a mechanism has been suggested to account for the lethal bradyarrythmia observed in a transplant patient while wearing an ambulatory monitor.[21] In addition, it has been observed that bradyarrythmias arising during

the post-transplant period are highly correlated to disruption of the sinoatrial node blood supply in the transplanted heart.[22] Another possibility is activation of an intrinsic stretch-related mechanism in the transplanted heart. For example, increases in right atrial pressure in the denervated mammalian heart can evoke an increase in heart rate and, when the pressure is decreased, the pattern is reversed.[23] Such a mechanism may account for a small amplitude, high-frequency variability in heart rate observed in transplanted patients.[24] Finally, entrainment of the donor to recipient atria should be considered as a possible mechanism. Although the donor atria appear to be electrically isolated from the recipient heart tissue, there are observations in transplant patients of one contracting chamber bi-directionally entraining the other over a limited range of frequency.[25] It has been proposed that this is mediated mechanically, whereby one contracting chamber tugs on the other, producing stretch of conduction tissues which may be transduced into a change in the rate of depolarization.[25] However, such entrainment has been associated with much more modest changes in heart rate than that observed in the present report. In addition, it is not clear how entrainment could account for the transition from a sinus to a junctional rhythm.

Regardless of the aetiology underlying the cardiac response described in this report, it may be relevant that this patient demonstrated a sinus bradycardia of 57 beats·min^{-1} intraoperatively, before the administration of protamine, and a right bundle branch block pre-operatively, suggesting dysfunction of the sinus node and conducting pathway of the transplanted heart. Consideration should be given to the possibility that such dysfunction may have contributed to the cardiovascular response described in this report. In addition, the effects of anaesthesia or perioperative medications on the response are unknown.

The heart transplant recipient poses unique anaesthetic challenges resulting from the side-effects of the immunosuppressive agents, graft rejection and denervation of the donor heart. These patients are particularly sensitive to hypovolaemia, as cardiac output of the transplanted heart is so dependant on preload (Frank-Starling mechanism).[1,3] This report illustrates that hypotension in the transplant patient can be hazardous as it may produce bradycardia which can compromise cardiac output. Also, it emphasizes the ability of heart rate to change considerably in cardiac transplant recipients. It is suggested that the change in heart rate described in this report was most likely mediated by mechanisms intrinsic to the transplanted heart and extrinsic to the CNS. When changes in heart rate are observed in cardiac transplant recipients, this should not be misconstrued as unequivocal evidence for reinnervation of the transplanted heart.

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