Independent Association Between Plasma Leptin Levels and Heart Rate in Heart Transplant Recipients

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Background—Leptin, the protein product of the ob gene, has been linked to a faster heart rate in animal and human studies. The interaction between leptin and heart rate in the denervated heart is not known. Therefore, we studied the relationship between plasma leptin levels and heart rate in heart transplant recipients.

Methods and Results—We studied 32 male patients (mean age, 56.5±9.3 years; range, 41 to 74 years) after orthotopic heart transplantation. All subjects underwent a physical examination, anthropometric measurements, blood chemistry analysis, and office blood pressure measurements. A blood sample was collected from each subject while fasting. In univariate analysis, heart rate was related to leptin levels (r=0.47, P=0.007) but heart rate was not related to systolic or diastolic blood pressure, mean arterial pressure, body mass index, or catecholamines. Leptin levels were only strongly associated with heart rate and body mass index (r=0.73, P<0.0001). In multivariate analysis, heart rate was independently and positively associated with leptin levels (F=2.61, P=0.017). We also observed a strong, independent association between leptin levels and body mass index (F=5.8, P<0.00001).

Conclusions—We show an independent association between leptin levels and heart rate in heart transplant recipients. We speculate that this may be due, in part, to a direct effect of leptin on heart rate, conceivably mediated through cardiac leptin receptors. (Circulation. 2001;104:384-386.)
The novel finding of this study is the independent relationship between leptin levels and heart rate in the denervated heart in cardiac transplant patients. This interaction cannot be explained only on the basis of catecholamine levels. In the innervated heart, the mechanisms by which leptin may participate in the elevation of heart rate are unknown. Possible explanations include activation of the sympathetic nervous system or withdrawal of parasympathetic tone; evidence exists to support both these mechanisms. However, in heart transplant recipients, other factors may play a substantial role. Transplantation of the heart results in sympathetic and parasympathetic cardiac denervation. This may conceivably lead to enhanced direct effects of leptin on heart rate, possibly through cardiac leptin receptors. Alternatively, changes in the sensitivity of other cardiac receptors, particularly adrenergic receptors, may potentiate the relative effect of catecholamines on rate control.

The strength of the correlation between heart rate and plasma leptin levels in cardiac transplant recipients is more striking than that present in studies of humans with preserved cardiac neural innervation. Indeed, in autonomically intact humans, the leptin–heart rate association is strongest at night, when the relative effect of the sympathetic-mediated increase in heart rate is at a nadir. It is interesting, therefore, that heart rate seems independently linked to leptin in the setting of cardiac denervation.

Leptin binds to at least one receptor in the brain. The full leptin receptor (Ob-Rb) is a protein containing a single transmembrane domain. In mice, the gene for the leptin receptor seems to encode at least 6 alternatively spliced variants of the receptor. Interestingly, mRNA for the leptin receptor is expressed not only in the hypothalamus, but also in the choroid plexus, adipose tissue, heart, kidney, liver,

### Results

Demographic data are presented in the Table. In univariate analysis, heart rate was related to leptin levels (r=0.47, P=0.007) and drug effect (P=0.03), but heart rate was not related to systolic or diastolic blood pressure, mean arterial pressure, or body mass index. Importantly, heart rate was unrelated to catecholamine levels. Leptin levels correlated only with heart rate (P=0.007) and body mass index (r=0.73, P<0.0001).

In a multivariate analysis using heart rate as the dependent variable and adjusting for all covariates except the drug effect, heart rate was independently and positively associated with leptin levels (F=2.61, P=0.017; Figure). Including the drug effect within the multivariate analysis revealed an even stronger independent association between heart rate and leptin (F=3.13, P=0.006). In addition, heart rate was independently associated with drug effect in this analysis (F=2.12, P=0.05). We also observed a strong, independent association between leptin levels and body mass index (F=5.8, P<0.0001).

### Discussion

The novel finding of this study is the independent relationship between leptin levels and heart rate in the denervated heart in cardiac transplant patients. This interaction cannot be explained only on the basis of catecholamine levels. In the innervated heart, the mechanisms by which leptin may participate in the elevation of heart rate are unknown. Possible explanations include activation of the sympathetic nervous system or withdrawal of parasympathetic tone; evidence exists to support both these mechanisms. However, in heart transplant recipients, other factors may play a substantial role. Transplantation of the heart results in sympathetic and parasympathetic cardiac denervation. This may conceivably lead to enhanced direct effects of leptin on heart rate, possibly through cardiac leptin receptors. Alternatively, changes in the sensitivity of other cardiac receptors, particularly adrenergic receptors, may potentiate the relative effect of catecholamines on rate control.

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Leptin binds to at least one receptor in the brain. The full leptin receptor (Ob-Rb) is a protein containing a single transmembrane domain. In mice, the gene for the leptin receptor seems to encode at least 6 alternatively spliced variants of the receptor. Interestingly, mRNA for the leptin receptor is expressed not only in the hypothalamus, but also in the choroid plexus, adipose tissue, heart, kidney, liver,
spleen, pancreatic islets, and testes, although the presence of the full-length receptor splice variant has not been demonstrated in all of these tissues. The functional effects of cardiac leptin receptors are unknown. Our data suggest they may conceivably be involved in heart rate control.

The small number of subjects did not allow us to establish any difference in the leptin–heart rate relationship early compared with late after heart transplantation. Partial autonomic reinnervation may occur in long-standing heart transplant recipients, although this is not invariable. Over-all, the data suggest that functional reinnervation, if it occurs, is mediated by relatively small numbers of sympathetic or parasympathetic neurons. We tried to reduce the potential influence of reinnervation of the heart on heart rate by taking into account the time since transplantation in multiple regression analysis.

In conclusion, we show an independent association between leptin levels and heart rate in heart transplant recipients. We speculate that in the denervated transplanted heart, this association may be due, in part, to a direct effect of leptin on heart rate that may conceivably be mediated through cardiac leptin receptors. Alternatively, leptin levels may be a surrogate for one or more substances that influence the rate of contraction of the transplanted heart.

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