学位論文の要旨

氏名　菅森　峰

学　位　論　文　名	Increased Nitric Oxide in Proportion to the Severity of Heart Failure in Patients With Dilated Cardiomyopathy − Close Correlation of Tumor Necrosis Factor-α With Systemic and Local Production of Nitric Oxide −
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著　　者　　名	Takashi Sugamori, Yutaka Ishibashi, Toshio Shimada, Nobuyuki Takahashi, Takeshi Sakane, Shuzo Ohata, Yoshitsugu Kunizawa, Shin-ichi Inoue, Ko Nakamura, Yoko Ohta, Hiromi Shimizu, Harumi Katoh, Nobuyuki Oyake, Yo Murakami, Michio Hashimoto

論 文 内 容 の 要 旨

INTRODUCTION

Recent studies have demonstrated that pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), induce large amount of nitric oxide (NO) and that the amount is increased in patients with congestive heart failure (CHF). There are, however, few reports regarding the relationships among NO production, cytokines, and the severity of heart failure. In the present study, we used the basal plasma concentration of brain natriuretic peptide (BNP) to assess the severity of heart failure instead of the New York Heart Association (NYHA) classification, because the former index is more objective than the latter. Upon such patients assessment as above, we measured the plasma concentrations of nitrite and nitrate (NOx) to estimate the systemic NO production, and also examined the vasoconstrictive response to an NO synthase (NOS)-inhibitor N^G-monomethyl-L-arginine (L-NMMA) in the forearm to assess local production and release of NO, because there are methodological limitations in determining the actual production of NO in human studies.

MATERIALS AND METHODS

We examined 45 patients with CHF caused by idiopathic dilated cardiomyopathy (29 males/16 females; mean age: 60 years, range: 41–78 years) and the 26 age- and sex-matched healthy control subjects (16 males/10 females; mean age: 60 years, range: 36–78 years). Current smokers and the subjects who had been smoking within 2 years were excluded.

Forearm blood flow (FBF, ml/min per 100 ml of forearm tissue volume) was determined in the non-dominant arm in all participants, using venous occlusion strain-gauge plethysmography.

Before FBF measurement, plasma concentrations of atrial natriuretic peptide, BNP, NOx, and of TNF-α were determined in all participants from 20 ml of venous blood.

FBF measurements were performed before and during the *i.a.* administration of graded doses of acetylcholine (ACh) and nitroglycerin (NG), respectively. After completion of the measurements that were made during incremental infusion of the first drug, the study participants took a rest until his/her FBF returned to the baseline.

RESULTS AND DISCUSSION

Plasma concentrations of both NOx and TNF-α were significantly higher in the patient group than in the control group ($p<0.001$ for both indices) and correlated closely with BNP concentrations ($p<0.001$ for both). There was a positive relationship between NOx and TNF-α concentrations ($r=0.80$, $p<0.001$). Administration of L-NMMA significantly reduced the FBF in both groups, and the percent change in FBF from its baseline was significantly correlated with TNF-α concentrations ($r=0.63$, $p<0.001$). The FBF response to ACh was depressed in the patient group and inversely correlated with TNF-α concentrations. In contrast, the FBF response to NG was not correlated with TNF-α concentrations.

In normal vessels, ACh induces NO synthesis by activating endothelial constitutive NOS (*e*NOS). Conversely, in patients with CHF, the vasodilating response to ACh is blunted, whereas the NO donor administration exerts a vasodilating response which is quite similar to that observed in normal subjects, suggesting the integrity of the vascular smooth muscle cells. The impaired endothelium-dependent vasodilatation observed in the patient group of the present study is consistent with those of previous reports; in this respect, it seems probable that the increased NO originates from another isoform of NOS, inducible NOS (*i*NOS), which can produce large amounts of NO.

Recent studies have demonstrated the increased expression of *i*NOS mRNA in the skeletal myocytes, monocytes, cardiac myocytes, and myocardial vasculature (endothelial cells and smooth muscle cells) of patients with CHF. The present data suggest that TNF-α might suppress *e*NOS and activate *i*NOS in CHF patients, resulting in the enhanced production of NO. In the present study, however, plasma NOx concentration and the vasoconstrictive responses to NOS-inhibitor varied widely. Thus, in patients with severe heart failure (BNP >300 pg/ml), NOx concentration and the effects of L-NMMA on both FBF and forearm vascular conductance were considerably greater than those in the control subjects, but in patients with mild heart failure (BNP <100 pg/ml) NOx concentration and the L-NMMA effects tended to be less than in the control subjects. It is difficult to interpret what these findings mean, but it is likely that in mild heart failure patients, NO production *via i*NOS pathway may be absent, while endothelium-derived NO production is yet impaired, resulting in an overall decrease in NO production.

Previous experimental studies demonstrated that high doses of TNF-α directly reduced *e*NOS mRNA concentrations in vascular endothelial cells. Plasma TNF-α concentrations in our CHF patients were lower than those reported in septic shock patients or in normal subjects after endotoxin injection. Yet, the mild increase in TNF-α plasma concentration noted in the present patients may have been sufficient to downregulate the *e*NOS.

TNF-α increases the expression of *i*NOS in macrophages, vascular endothelial cells, and vascular smooth muscle cells. Coincidence of TNF-α and *i*NOS in the cardiac myocytes and endothelium of patients with dilated cardiomyopathy and human immunodeficiency virus-associated cardiomyopathy has been demonstrated in clinical studies, suggesting that local availability of TNF-α could be relevant to *i*NOS induction and the resultant high production of NO.

CONCLUSION

The CHF patients showed higher plasma concentrations of NOx and TNF-α than did the normal subjects; concentrations of these factors were highly correlated with plasma BNP concentrations, respectively. Furthermore, plasma TNF-α concentrations were inversely correlated with ACh-induced vasodilatation in the CHF patients, and correlated significantly with plasma NOx concentrations and the forearm vasoconstrictive responses to L-NMMA. These findings suggest that NO production and TNF-α concentrations may be increased in CHF patients according to their severity, and that the enhanced NO production could be induced by *i*NOS rathaer than by *e*NOS.