Analysis of onset mechanism for tyrosine kinase inhibitor imatinib induced-left ventricular diastolic dysfunction

Koki Chiba[1], Mihoko Hagiwara-Nagasawa[2], Ryuichi Kambayashi[2], Ai Goto[1], Tsukasa Hara[3], Ryosuke Amagai[3], Yoshio Nunoi[2], Hiroko Izumi-Nakaseko[1,2], Ayako Okado-Matsumoto[3], Akio Matsumoto[4], Atsushi Sugiyama[1,2,4]

[1]Dept. Pharmacol., Grad. Sch. Med., Toho Univ., [2]Dept. Pharmacol., Faculty Med., Toho Univ., [3]Lab. Biochem., Dept. Biol., Faculty Sci., Toho Univ., [4]Dept. Aging Pharm., Faculty Med., Toho Univ.

Introduction: Imatinib is a tyrosine kinase inhibitor used for treating various types of cancers. The other tyrosine kinase inhibitors sunitinib and dasatinib have been reported to induce diastolic dysfunction; however, such information is lacking for imatinib.

Methods: Exp. 1: Imatinib mesylate in doses of 1 and 10 mg/kg, i.v., were administered to the halothane-anesthetized dogs (n=4). Cardiovascular variables along with biomarkers reflecting myocardial injury were measured. Exp. 2: Mitochondria isolated from the rat heart (n=2) were incubated with tyrosine kinase inhibitors, of which effects on mitochondrial respiratory complexes were assessed.

Results: Exp. 1: The low dose decreased the total peripheral vascular resistance with prolonging the isovolumic relaxation time, prolonged the QTc and J-T_{peak}c, and increased AST and LDH. Moreover, the high dose suppressed the ventricular relaxation, increased the left ventricular end-diastolic volume, prolonged HV interval and increased CPK. Exp. 2: The activity of complex II were decreased by the inhibitors.

Conclusions: Imatinib may induce myocardial injury, resulting in the left ventricular diastolic dysfunction, in which mitochondrial dysfunction might play an important role.