**Letter to Editor**

**Everolimus-Incorporated Therapy Reduces Myocardial Hypertrophy in Recipients of Heart Transplantation**

*To the Editor,*

Everolimus (EVL), one of the mammalian targets of rapamycin (mTOR) inhibitors, has recently been used as a next generation immunosuppressant in the recipients of heart transplantation (HTx). EVL is also used for its anti-proliferative effect, and we have consistently demonstrated that 1-year EVL therapy repressed the progression of cardiac hypertrophy in HTx recipients by using transthoracic echocardiography. However, the relationship between EVL therapy and myocardial cell hypertrophy remains unclear. This letter to the editor is a supplement to the previous paper about EVL and cardiac hypertrophy.

We enrolled 41 HTx recipients who had received EVL therapy at 150 days after HTx on the median and had been followed at our institution for > 1 year between 2008 and 2014 (EVL group). EVL was initiated in the case of renal dysfunction, the progression of cardiac allograft vasculopathy, digestive symptoms, or neutropenia due to mycophenolate mofetil, accompanied by the discontinuation of mycophenolate mofetil and dose reduction of the calcineurin inhibitor. At the initiation of EVL therapy, mycophenolate mofetil was discontinued and the target trough levels of calcineurin inhibitor were decreased to 70%. We also observed 17 HTx recipients who did not receive EVL therapy beginning at 150 days after HTx for 1 year (control group). All patients received endomyocardial biopsy at baseline and 1 year after the enrollment. At least 2 pieces of the myocardial sample were obtained from the interventricular septum, and transverse diameters crossing the cell nucleus were measured and averaged from 20 pieces of myocardial cell in each biopsy case. Doses of anti-HF medications such as β-blockers and angiotensin converting enzyme inhibitors remained unchanged in the two groups during the study period.

The mean transverse diameter of the myocardial cell in the EVL group was comparable to that of the control group at baseline (17.3 ± 2.2 versus 17.0 ± 2.1 μm, P = 0.516 by the unpaired t-test). There were no significant differences in baseline variables including general laboratory and echocardiographic data. The transverse diameter of the myocardial cells decreased significantly after 1-year EVL therapy (P = 0.001 by the paired t-test), whereas it remained unchanged during the 1-year study period in the control group (P = 0.115 by the paired t-test, Figure 1A). The decrease in size of the myocardial cells was significantly higher in the EVL group compared with the control group (P < 0.001 by the unpaired t-test, Figure 1B). Typical cases are shown in Figure 2.

In this study, we demonstrated that EVL therapy decreased the size of the myocardial cells. EVL may improve cardiac hypertrophy mainly through regression myocardial cell hypertrophy. Buss, et al consistently demonstrated in an animal model that EVL therapy reduced post-myocardial infarction remodeling with improved left ventricular function and smaller left ventricular cavity and cardiac myocyte size. The rationale of our result may lay in the inhibitory effect of EVL on the mTOR/α70 kinase signal transduction pathway, which plays a central role in myocardial cell hypertrophy. Whether regression of cardiac hypertrophy by EVL therapy improves HTx recipients’ quality of life and survival or not would be a future concern. As a limitation, we obtained at least 2 pieces of the myocardial sample and did not perform > 5 biopsies at a session, because repeated biopsies may facilitate myocardial fibrosis. Many biopsies may strengthen the accuracy of the data. Furthermore, we could not perform simple add-on therapy of EVL to specify the efficacy of EVL alone because of ethical concerns. In conclusion, EVL-incorporated therapy may improve cardiac hypertrophy mainly through a decrease in myocyte size in HTx recipients.

**References**


**Teruhiko Imamura, MD**
**Eisuke Amiya, MD**
**Daisuke Nitta, MD**

*Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo*

**Koichiro Kinugawa, MD**

*Second Department of Internal Medicine, University of Toyama, Toyama, Japan*

E-mail: kinugawa-ty@umin.ac.jp
Figure 1. Absolute value of transverse diameter of myocardium at baseline and 1 year after enrollment in the EVL group and control group (A) and those of changes during the study period (B). *P < 0.05 by the paired t-test. †P < 0.05 by the unpaired t-test.

Figure 2. Typical endomyocardial samples at baseline and 1 year after enrollment in the EVL group and control group. A scale bar represents 50 μm.