論文の内容の要旨

論文題目　Effects of Cardiac Myosin Isoform Variation on Myofilament Function and Crossbridge Kinetics in Transgenic Rabbits

和訳　心筋ミオシンアイソフォーム変化の
筋フィラメント機能・架橋に与える影響
―遺伝子過剰発現ウサギを用いた検討―

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Background: The left ventricles of both rabbits and humans express predominantly β-myosin heavy chain (MHC). Transgenic (TG) rabbits expressing 40%α-MHC are protected against tachycardia-induced cardiomyopathy, but the normal amount of α-MHC expressed in humans is only 5% to 7% and its functional importance is questionable. This study was undertaken to identify a myofilament-based mechanism underlying tachycardia-induced cardiomyopathy protection and to extrapolate the impact of MHC isoform variation on myofilament function in human hearts.

Methods and Results: Papillary muscle strips from TG rabbits expressing 40% (TG40) and 15%α-MHC (TG15) and from nontransgenic (NTG) controls expressing ≈100%β-MHC (NTG40 and NTG15) were demembranated and calcium activated. Myofilament tension and calcium sensitivity were similar in TGs and respective NTGs. Force-clamp measurements revealed ≈50% higher power production in TG40 versus NTG40 (P<0.001) and ≈20% higher power in TG15 versus NTG15 (P<0.05). A characteristic of acto-myosin crossbridge kinetics, the "dip" frequency, was significantly higher in TG40 versus NTG40 (0.70±0.04 versus 0.39±0.09 Hz, P<0.01) but not in TG15 versus NTG15. The calculated crossbridge time-on was also significantly shorter in TG40 (102.3±14.2 ms) versus NTG40 (175.7±19.7 ms) but not in TG15 versus NTG15.

Conclusions: The incorporation of 40% α-MHC leads to greater myofilament power production and more rapid crossbridge cycling, which facilitate ejection and relengthening during short cycle intervals, and thus protect against tachycardia-induced cardiomyopathy. Our results suggest, however, that, even when compared with the virtual absence of α-MHC in the failing heart, the 5% to 7% α-MHC content of the normal human heart has little if any functional significance.