（様式３号）

学 位 論 文 の 要 旨

氏名 CHANG YAOWEI

〔題名〕

Dantrolene, a RyR2 stabilizer, restores impaired diastolic function in the pressure-overloaded hypertrophied heart

(RyR2安定化薬であるダントロレンは圧負荷誘發性肥大心の拡張機能障害を回復させる)

〔要旨〕

Rationale: Cardiac hypertrophy is a well-known major risk factor for poor prognosis in patients with cardiovascular diseases. Our previous research reported that RyR2-stabilization can inhibits hypertrophic and improve survival by enhancing the binding affinity of CaM to RyR2 with the genetic therapy.

Objective: To investigate whether dantrolene improves the impaired diastolic function in the early pressure-overloaded hypertrophied heart.

Methods: Pressure-overloaded hypertrophy was developed by TAC in mice. Wild type (WT) mice were divided into 4groups; sham-operated mice (Sham), sham-operated mice treated with dantrolene (Sham-DAN, 20mg/kg/day, i.p.), TAC mice (TAC) and TAC mice treated with dantrolene (TAC-DAN). Then, they were followed up for 2 weeks.

Results: Histological examination showed that, in spite of no difference in fibrosis area of LV among 4 groups, LV hypertrophy was obviously induced in TAC, but not TAC-DAN 2 weeks after TAC. There was no difference in fractional shortening among 4 groups. Catheter-tip manometer showed that time constant (tau) of LV pressure decay was significantly prolonged in TAC, but not in TAC-DAN. In cell shortening and Ca^{2+} transient, diastolic function was significantly impaired in TAC, but not in TAC-DAN. An increase in diastolic Ca^{2+} spark frequency and a decrease in the binding affinity of CaM to RyR2 were observed in TAC, but they were improved in TAC-DAN.

Conclusion: Dantrolene prevented progression of hypertrophy as well as improved the impairment of relaxation by inhibiting diastolic Ca^{2+} leakage through RyR2 and dissociation of CaM from RyR2.

作成要領

１．要旨は、８００字以内で、１枚でまとめること。

２．題名は、和訳を括弧書きで記載すること。

（様式９号）

学位論文審査の結果の要旨

令和　5年3月13日

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学位論文題目名（題目名が英文の場合、行を変えて和訳を括弧書きで記載する。）

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（論文審査の要旨）

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本論文は RyR2 安定化薬であるダントロレンは圧負荷誘発性肥大心の拡張機能障害を回復させる について詳細に検討したものであり、学位論文として価値あるものと認めた

備考　審査の要旨は８００字以内とすること。