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Acute Effect of Ivabradine in Mitochondrial Cardiomyopathy

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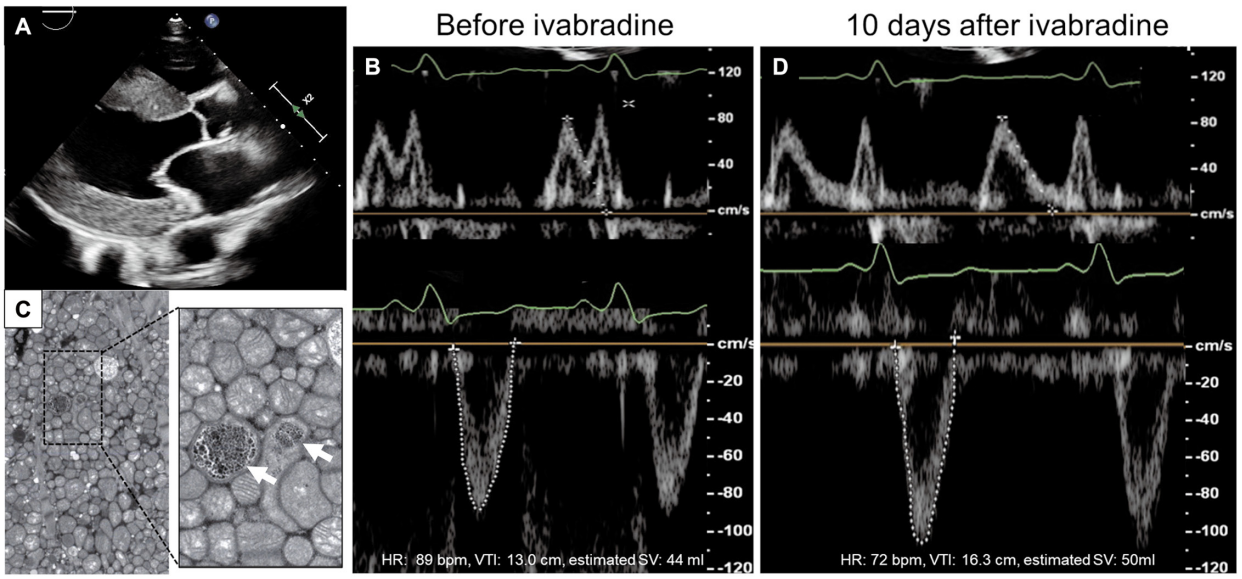

Figure. (**A**) Echocardiographic parasternal long-axis view, (**B**) transmitral and left ventricular (LV) outflow tract flow velocity patterns before ivabradine, (**C**) electron microscopic images showing mitochondrial abnormalities, and (**D**) transmitral and LV outflow tract flow velocity patterns after ivabradine.

A 44-year-old man with a history of hearing impairment, diabetes mellitus, and kidney transplantation was admitted for breathlessness on exertion. He had been diagnosed with mitochondrial cardiomyopathy (mitochondrial A3243G mutation) at the age of 41, and treatment of heart failure (HF) with taurine, perindopril, carvedilol (5 mg/day) and pimobendane had been initiated 1 year prior to this admission. The dose of carvedilol had not been increased, because of hypotension, and 1 month prior to hospitalization, oral furosemide (20 mg/day) failed to relieve the breathlessness and instead increased the level of B-type natriuretic peptide.

On admission, the patient's blood pressure was 105/58 mmHg, and heart rate (HR) was 100 beats/min. Chest X-ray showed cardiomegaly and slight pleural effusion. Echocardiography (**Figure A**) showed diffuse left ventricular (LV) hypertrophy and hypokinesis, LV ejection fraction of 34%, and stroke volume of 44 mL estimated from the LV outflow tract velocity-time integral (**Figure B**). Fusion of the transmitral E and A waves, and slowing of the early transmitral annular velocity were observed. Right heart catheterization revealed a cardiac index of 2.71 L/min/m^2, pulmonary artery wedge pressure of 7 mmHg, and right atrial pressure of 3 mmHg. Electron microscopy of a myocardial biopsy showed increased numbers of mitochondria and mitochondrial glycogen inclusion (**Figure C**).

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The standard intial dose of ivabradine (5 mg/day) was initiated, and after the dose was increased to 10 mg/day, his symptoms were relieved, and blood pressure was maintained. At 10 days after ivabradine treatment, the E and A waves were completely separated, leading to an increased stroke volume of 50 mL (**Figure D**). The 6-minute walk distance increased from 431 m to 504 m (17%) with larger HR increase during the walking test but slower peak HR after ivabradine.

Force- and relaxation-frequency relations are impaired in HF patients,[1] and tachycardia impairs mitochondrial energy metabolism. The observed acute effects of ivabradine are likely due to an increase in cardiac output during exercise, which was attributed to the larger increase in HR from rest and improvements in LV diastolic function and mitochondrial energy metabolism.

Reference

1. Kass DA. Force-frequency relation in patients with left ventricular hypertrophy and failure. *Basic Res Cardiol* 1998; **93:** 108–116.