Treatment of dilated cardiomyopathy caused by coronary microvascular dysfunction with anisodamine: a report of 5 cases

Xu Zhiwei, Wang Tong, Chen Liang, Lou Ying, Sun Xiaoyan, Jiang Jinqi

INTRODUCTION

Dilated cardiomyopathy (DCM) is a complex myocardial disease of multifactorial etiologies, including enlarged cardiac chambers and contractile dysfunction. The current mainstay of treatment is symptomatic management of heart failure and arrhythmia. Novel, effective therapeutic options are an unmet clinical need. Previous studies have shown that some patients with DCM have impaired coronary flow reserve (CFR) despite angiographically normal epicardial coronary arteries due to coronary microvascular dysfunction (CMD). In addition, reduced CFR has been reported to be a poor prognostic indicator and independent predictor of subsequent cardiac events in patients with left ventricular (LV) dysfunction. Anisodamine is a widely used Chinese herbal medicine extracted from the root of Scopolia tangutica maxima from Tibet, and has achieved a good effect in treatment of circulatory disorders such as disseminated intravascular coagulation (DIC) and septic shock. It has been reported that anisodamine can attenuate the no-reflow phenomenon, improve the left ventricular systolic function and CMD in patients with no-reflow phenomenon post AMI-PCI. The possible mechanisms of anisodamine in the treatment of CMD are as follows: (a) Anisodamine can effectively improve coronary microvascular and perfusion, reduce myocardial ischemic injury; (b) Anisodamine can enhance immune cells function, protect vascular endothelial cell function, and then reduce myocardial necrosis caused by ischemia and hypoxia; (c) Anisodamine can effectively inhibit Ca²⁺ influx, relieve coronary microvascular spasm and improve coronary microcirculation; (d)

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Abstract

The management of dilated cardiomyopathy (DCM) is well established. However, a subset of patients does not have recovery from or have recurrences of left ventricular (LV) dysfunction despite receiving optimal medical therapy. Coronary microvascular dysfunction (CMD) can result from structural and functional abnormalities at the intramural and small coronary vessel level affecting coronary blood flow autoregulation and consequently leading to impaired coronary flow reserve. Dilated myocardial phenotype may be responsible for CMD in DCM. Anisodamine can exert a significant effect on relieving microvascular spasm, and improving and dredging the coronary microcirculation. However, whether CMD can be potentially improved with anisodamine to make DCM better remains incompletely understood.
Anisodamine can effectively inhibit platelet aggregation and reduce the formation of microthrombus in coronary microvascular.10
Due to the possible mechanisms of anisodamine, we try to treat dilated cardiomyopathy caused by coronary microvascular dysfunction (DCM-CMD) with anisodamine. This study aimed to evaluate the clinical significance of anisodamine in DCM-CMD patients and to report the effects of a well-defined treatment protocol in 5 consecutive cases.

METHODS

Subjects
Five patients (2 male, 3 female, age 39, 40, 60, 67, 71 years) with DCM-CMD were enrolled from 2016 to 2018. The study was approved by the hospital’s ethical committee, and all patients gave informed consent to the use and reporting of their collected data. All 5 patients were hospitalized for chronic fatigue and dyspnea secondary to New York Heart Association (NYHA) class III-IV heart failure. Diagnosis of DCM-CMD was based on a LV ejection fraction (LVEF) ≤ 45%, LV end-diastolic diameter (LVEDD) ≥ 55 mm, and/or LV end-systolic diameter (LVESD) ≥ 45 mm by transthoracic echocardiography. Cardiac catheterization showed normal epicardial coronary arteries and radionuclide myocardial perfusion imaging (MPI) showed definite evidence of LV focal myocardial ischemia.

Anisodamine treatment
All 5 patients received standard anti-heart failure treatment (beta blockers, angiotensin converting enzyme inhibitors and spironolactone) for more than half a year and there was no significant improvement in clinical symptoms and echocardiography. Subsequently, anisodamine was administered intravenously at a dose of 0.05 mg·kg⁻¹·h⁻¹ in 10 h per day for 10 d while continuing standard anti-heart failure treatment.

Data collection and follow-up
Baseline data of clinical, echocardiography, radionuclide myocardial perfusion imaging and laboratory findings were collected before anisodamine treatment. Follow up data was collected 2 months later after anisodamine treatment. Clinical assessment included New York Heart Association (NYHA) heart functional class. NYHA I: patients that have no limitation of physical activity. NYHA II: (relative) patients with cardiac disease that results in slight limitation to physical activity with symptoms such as fatigue, palpations, dyspnea, or angina pain. NYHA III: (absolute) patients with cardiac disease who are comfortable at rest; however, less-than-ordinary activity causes fatigue, palpation, dyspnea, or angina pain. NYHA IV: (absolute) patients with cardiac disease that results in the inability to carry on any physical activity. Plasma levels of brain natriuretic peptide (BNP) were measured by use of a highly sensitive sandwich Elisa technique. Echocardiography and radionuclide MPI was routinely performed before and 2 months later after anisodamine treatment.

RESULTS
Follow-up data showed that all 5 patients had a significant improvement in clinical symptoms, a higher grade of NYHA heart functional class and a significant decrease in serum BNP compared to baseline. The baseline and follow up data are presented in Table 1. No complication was recorded. Transthoracic echocardiography showed that the LVEF values were significantly increased and the left ventricular end-diastolic volumes were significantly reduced. Left ventricular remodeling was observed. Radionuclide MPI demonstrated the same conclusion that the LVEF values were significantly increased and the myocardial ischemic area was improved definitely (Figure 1A, 1B).

DISCUSSION
In our study, we have evaluated the combined administration of anisodamine and standard anti-heart failure drugs in DCM-CMD patients. The results showed that the LVEF values were significantly increased and the left ventricular end-diastolic volumes were significantly reduced in all 5 patients. PET myocardial perfusion imaging demonstrated the myocardial ischemic area was improved. The coronary microcirculation was improved by anisodamine definitely. Also in our present study, administration dose of anisodamine was safe and well tolerated. The common adverse effects of anisodamine are reduced salivation, facial flushing, blurred vision, tachycardia, urinary retention. No complication was recorded in total 5 cases.
Our study has several limitations. First, the study was limited by the small sample size. And there was no drug free group for comparison. Additional large-scale research is required to confirm the impact of anisodamine in DCM-CMD patients. In conclusion, combined administration of anisodamine and standard anti-heart failure drugs in DCM-CMD patients is safe and has definite clinical benefits. Additional large-scale research is required to confirm the impact of anisodamine. But for DCM patients with unsatisfactory results in standard anti-heart failure treatment, anisodamine gives patients the hope of clinical benefits.

REFERENCES
Table 1 Baseline and follow up data of the 4 cases

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Notes: NYHA: New York Heart Association; BNP: brain natriuretic peptide; LVESD: left ventricular end-systolic diameter; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume.

Figure 1 Radionuclide myocardial perfusion imaging
A: before anisodamine treatment. Left ventricle myocardium is clear, the volume of the heart chamber is increased, and the left heart radioactivity is unevenly distributed. The left ventricular basal segment and the lateral wall near the basal segment have reduced myocardial perfusion. B: after anisodamine treatment. Left ventricular myocardium was clear, the volume of the heart chamber was slightly larger, and the left heart radioactivity was evenly distributed. No obvious ischemic areas were observed.