MEDICAL SCIENCE MONITOR

Effect of Breviscapine on Recovery of Viable Myocardium and Left Ventricular Remodeling in Chronic Total Occlusion Patients After Revascularization: Rationale and Design for a Randomized Controlled Trial

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: How to speed the recovery of viable myocardium in chronic total occlusion (CTO) patients after revascularization is still an unsolved problem. Breviscapine is widely used in cardiovascular diseases. However, there has been no study focused on the effect of breviscapine on viable myocardium recovery and left ventricular remodeling after CTO revascularization.

Material/Methods: We propose to recruit 78 consecutive coronary artery disease (CAD) patients with CTO during a period of 12 months. They will be randomly assigned to receive either breviscapine (40 mg) or placebo in the following 12 months. Blood tests, electrocardiogram, and Major Adverse Cardiac Events (MACE) will be collected at baseline and the follow-up visits at 1, 3, 6, 9, and 12 months. Low-dose dobutamine MRI will be applied for the assessment of viable myocardium, microcirculation perfusion, and left ventricular remodeling, and the concentrations of angiogenic cytokine, vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF) will be investigated at baseline and at 1- and 12-month follow-up. The recovery of viable myocardium after revascularization in CTO patients was the primary endpoint. Improvement of microcirculation perfusion, left ventricular remodeling, peripheral concentrations of VEGF and bFGF as well as MACE will be the secondary endpoints.

Results: Breviscapine treatment obviously improve the recovery of viable myocardium, myocardial microcirculation perfusion, and left ventricular remodeling after revascularization in CTO patients, and reduce the occurrence of MACE. We also will determine if breviscapine increases the peripheral blood angiogenic cytokine concentrations of VEGF and bFGF.

Conclusions: This study will aim to demonstrate the effect of breviscapine on the recovery of viable myocardium and left ventricular remodeling in CTO patients after revascularization.

MeSH Keywords: Angina, Stable • Cell Survival • Magnetic Resonance Imaging

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Background

With socioeconomic development in China, the incidence of coronary artery disease (CAD) has steadily increased. Chronic totally occluded (CTO) patients account for about 15–30% of all CAD patients [1]. Left ventricular dysfunction induced by CTO has become one of the most common causes of cardiac mortality and mobility.

Recent studies have shown that stunned or hibernating myocardium can survive in the area where the blood supply is provided by collateral circulation in the CTO lesions [2,3]. This part of viable myocardium can return to robust condition after myocardial revascularization, which provides the possibility for improvement of cardiac function. However, the recovery of viable myocardial function and improvement of left ventricular function is a continuous process that takes several weeks or months, suggesting that simple reconstruction of the effective blood flow and pressure is not sufficient. Previous studies reported that myocardial angiogenesis [4], establishment of collateral circulation, recovery of endothelial function [5], and improvement of microcirculation are also involved. Therefore, how to speed the recovery of viable myocardium and improve left ventricular function is a key point in the CTO therapy.

Breviscapine is a flavonoid extracted from the whole plant *Euphorbiaceae eucalyptus*, which has anti-microbial, anti-inflammatory, antioxidant [6], free radical-eliminating, and antineoplastic effects. It was also reported that breviscapine can inhibit protein kinase C (PKC) activity [7–9] and promote the recovery of endothelial function and microcirculation, thus ameliorating myocardial ischemia-reperfusion injury [10–12] and delaying the reversal of left ventricular hypertrophy and myocardial fibrosis induced by pressure overload [8]. However, there has been no study focused on the effect of breviscapine on viable myocardium and left ventricular remodeling after CTO revascularization.

In the proposed study, we will investigate whether Breviscapine therapy can improve the recovery of viable myocardium and left ventricular remodeling after CTO revascularization. We will use low-dose dobutamine MRI imaging to assess the effect of breviscapine on the recovery of viable myocardium, myocardial microcirculation, and left ventricular remodeling after CTO revascularization. We also will examine whether Breviscapine treatment can increase the peripheral blood concentrations of VEGF and bFGF angiogenic cytokine. Th proposed study is intended to provide evidence for further clinical application of breviscapine in the recovery of cardiac function of CTO patients after revascularization.

Material and Methods

Study program

The proposed research will be designed as a prospective, single-center, randomized, double-blind, placebo-controlled study. CAD patients with at least 1 CTO lesion confirmed either by coronary CTA or coronary angiography (CAG) in subjects who are randomly allocated to receive either breviscapine (40 mg) or placebo therapy for 12 months. All patients will receive basic standard drug therapy (including antiplatelet drugs, statins, ACEI/ARB [angiotensin-converting enzyme inhibitors/angiotensin receptor blocker], and β receptor blockers) for the treatment of coronary heart disease. All participants will provide written informed consent. Automated randomization (randomization and medication ordering system, Glaxo Smith Kline) will be used for a randomly permuted block of 4 subjects in a 2: 2 ratio for breviscapine: placebo distribution in the different treatment groups. The primary endpoint will be the change of viable myocardium percentage assessed by MRI after 12-month treatment with breviscapine or placebo when compared with the baseline. The secondary endpoints will be incidence of MACE, including death, myocardial infarction, stroke, recurrent angina, re-hospitalization rate, change of viable myocardium from baseline to 1 month, improvement of myocardial microcirculation perfusion, left ventricular remodeling, and change of peripheral concentrations of VEGF and bFGF angiogenic cytokine at baseline and at 1 and 12 months. Details of the proposed study, including the enrollment, exclusion criteria, and follow-up visit plan, are listed in Table 1.

This study will be funded by the Traditional Chinese Medical Science and Technology Plan Projects of Zhejiang Province. This trial protocol will be conducted in agreement with the ethics guidelines of the 1975 Declaration of Helsinki. Protocols and informed consent forms of the trial will be approved by the Institutional Ethics Committee of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, and informed consent forms will be approved by the Institutional Ethics Committee of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University. Written informed consent will be obtained from all patients. This trial will be registered in the Chinese Clinical Trial Registry (ChiCTR-IPC-16010161).

Study objectives

The proposed study will aim to verify the assumption that breviscapine (40 mg, 3 time a day [13,14], for 12 months) significantly promotes the recovery of viable myocardium and improves left ventricular remodeling after CTO revascularization, and to explore the potential mechanism. This study will be conducted over a 2-year period, including an estimated screening and enrollment period of 12 months and follow-up visit period

Table 1. Study plan.

Activity	Visit 0 Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Study month	0 day	1 m±7day	3 m±7day	6 m±7day	9 m±7day	12 m±7day
Informed consent	x					
Demography and medical history	x					
Inclusion/exclusion criteria	x					
Physical examination/Vital signs	x	x	x	x	x	x
12-lead ECG	x	x	x	x	x	x
Concomitant medication	x	x	x	x	x	x
Complete blood count	x	x	x	x	x	x
ALT/AST/ALB/TB/DB	x	x	x	x	x	x
Scr/BUN	x	x	x	x	x	x
TC/LDL-C/HDL-C/Lp(a)/TG	x	x	x	x	x	x
Cardiac MRI	x	x				x
Serum VEGF/bFGF concentration	x	x				x
Adverse events	x	x	x	x	x	x

ECG – electrocardiography; ALT – alanine aminotransferase; AST – aspartate aminotransferase; Scr – serum creatinine; BUN – blood urea nitrogen; TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – low-density lipoprotein cholesterol; TG – total triglycerides; Lp(a) – lipoprotein a; MRI – magnetic resonance imagingl VEGF – vascular endothelial growth factor, bFGF – basic fibroblast growth factor.

of 1 year. The main purpose will be to verify that Breviscapine can significantly promote the recovery of viable myocardium after CTO revascularization. The secondary objective will be to confirm that breviscapine can improve myocardial microcirculation perfusion and left ventricular remodeling, increase left ventricular function, and reduce MACE. The exploratory goal will be to establish the underlying mechanism among serum VEGF and bFGF, the viable myocardium, myocardial microcirculation perfusion, and left ventricular remodeling. Oral breviscapine therapy will be applied as an additional treatment on the basis of the standard drug therapy. Therefore, the fundamental efficacy and safety of the patients will be provided and ensured due to the standard drug therapy. In addition, Breviscapine's adverse effects such as bleeding, hepatic or renal function impairment, and other AEs will be carefully observed and documented.

Inclusion and exclusion criteria

Seventy-eight CAD patients with at least 1 CTO lesion confirmed by CTA or CAG are expected to be included in Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University. The enrollment period is anticipated to be finished before 2018.

All eligible patients will be registered. More details of inclusion and exclusion criteria are listed in Table 2.

Exclusion criteria during the follow-up periods

1) Patients' demand to withdrew from the study and withdrawal the inform consent.
2) Study protocol deviation.
3) Lost to follow-up due to patients.
4) Patients bearing high risk (e.g., hepatic dysfunction as transaminase levels ≥3×ULN or renal dysfunction as eGFR ≤30 ml/min/1.73 m^2).
5) Pregnant women or new-onset malignant tumor during the study periods.

All of above conditions will be documented in the case report form (CRF). Patients who cannot complete the follow-up will be scheduled an additional visit if possible.

Study procedures

Figure 1 shows the study protocol. Enrolled patients will be randomly assigned to receive either Breviscapine (40 mg) or

Table 2. Inclusion and exclusion criteria.

Inclusion criteria
• Provision of informed consent prior to any study specific procedures
• Male and Female adults aged 18–70 years
• Coronary CTA or coronary artery angiography confirmed complete occlusion of at least one of the left coronary artery or right coronary artery or its main branches

Exclusion criteria
• Underwent myocardial infarction within 1 weeks
• Target lesion underwent PCI or CABG within 6 months
• Expected to undergo other surgery except CABG within 6 months
• Underwent cerebral infarction within 6 months
• Have other blood vessels need elective PCI treatment besides the CTO vessels
• Intolerent to dual antiplatelet or statin therapy or contraindication to breviscapine
• Current treatment with breviscapine
• Severe liver dysfunction defined as ALT or AST ≥3×ULN (upper limit of normal range) or bilirubin ≥1.5×ULN
• Heart failure classified as New York Heart Association IV, or EF ≤30%
• Severe renal dysfunction defined as serum creatinine ≥3 mg/dl or eGFR ≤30 ml/min/1.73 m^2
• Severe pulmonary disease defined as suspected lung infection, bilateral infiltrates on chest radiography or any other conditions that lead to a ratio of the partial pressure of arterial oxygen (PaO$_2$) to the fraction of inspired oxygen (FiO$_2$) of 300 or less
• Dilated cardiomyopathy, hypertrophic cardiomyopathy, or severe heart valvular disease and other severe systemic disease
• Already or expect to take a large dose of corticosteroids
• History of malignant tumor
• Life expectancy ≤12 months
• Women with a positive pregnancy test, or women of child-bearing potential who did not take appropriate contraceptive measures
• Already participating in other clinical drug or instrument trials or plan to attend another clinical trial in the next 12 months

CTA – computed tomography angiography; PCI – percutaneous coronary intervention; eGFR – estimated glomerular filtration rate; CABG – coronary artery bypass graft.

placebo, 3 times a day for 12 months. Besides the Breviscapine or placebo, all other interventions strictly comply with the standard. Demography and medical history as well as a simple physical examination, including measurement of weight and vital signs (supine systolic and diastolic blood pressure, heart rate) will be collected at baseline visit and every follow-up visit; blood tests and a 12-lead electrocardiogram inspection analysis will also be done at baseline and each follow-up visit. Blood tests will include complete blood count (CBC), serum creatinine (Scr), blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin (ALB), total bilirubin (TB), direct bilirubin (DB), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), lipoprotein a (LPa), triglyceride (TG). Cardiac low-dose dobutamine MRI will be done at baseline, 1 month, and 12 months follow-up to assess viable myocardium, microcirculation perfusion and left ventricular remodeling. Additionally, peripheral blood VEGF and bFGF cytokine concentrations will also tested at baseline, 1 month, and 12 months follow-up. All MACE and AEs will be recorded at each follow-up visit. We will evaluate all the AE and SAE and adjust the treatment plan in time if it is necessary. In case of a serious adverse event or severe reactions which patients cannot tolerate during the course of the trial, researchers can withdraw the medication according to the protocol of the study.

Determination of peripheral blood VEGF and bFGF cytokine concentrations

At baseline, 1 month, and 12 months follow-up visit, peripheral blood VEGF and bFGF cytokine concentrations will be assessed by ELISA assay following the manufacturer's instructions (R & D System, Minneapolis, MN, USA).

Cardiac magnetic resonance imaging (MRI)

Aruges software will be used to select the appropriate time to clearly record the endocardium. Left ventricular remodeling parameters such as the thickness and thickening rate of each segment of left ventricular, left ventricular mass, left ventricular mass index, ejection fraction, end-diastolic volume, end-diastolic volume index, end-systolic volume, end-systolic volume index, cardiac output, cardiac index and myocardial wall function index will be measured and calculated [15,16].

Myocardial delayed scan will be analyzed according to 17-segment method [17]. The results of semi-quantitative analysis will be used to determine the viable myocardium and myocardial microcirculation. The proportion of left ventricular wall thickness in delayed enhancement will be divided into 4 grades: no delayed enhancement was defined as 1 point, 1% to 25% for 2 points, 25% to 75% for 3 points, and >75% for 4 points.
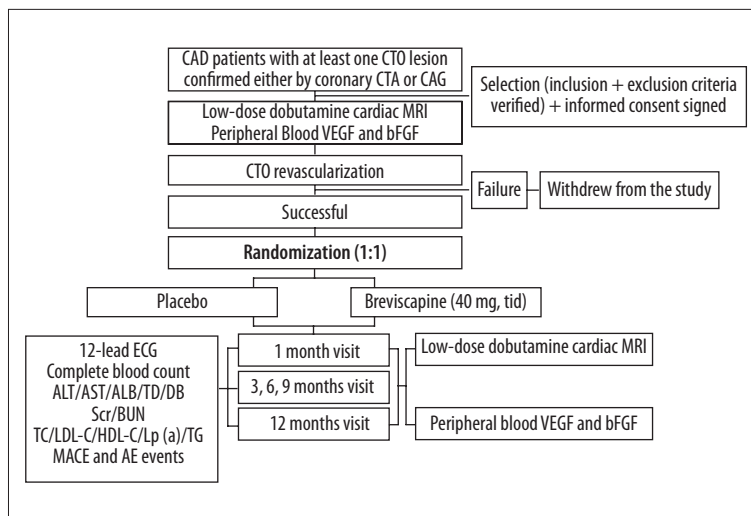
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Figure 1. Flowchart outlining the trial protocol.

Sample determination and statistical analyses

The minimum necessary sample size in the trial will be established by the requirement to detect the smallest expected clinically meaningful treatment difference between Breviscapine treatment and placebo. According to the clinical literature and our previous basic research, we set the hypothesis that the improvement of viable myocardium treated by Breviscapine (40 mg, 3 times a day) is 20% when compared with the control group. In the case of 80% power, the sample size is calculated as 35 cases in each group. According to the 10% loss rate, the total sample size is 78 cases, 39 cases in each group. All analysis will be performed on an intention-to-treat basis.

Categorical variables will be expressed in numerical values with their respective percentages and compared using the chi-squared test at baseline. Continuous variables will be expressed as mean ±SD and compared using the t test. Significance of primary and secondary endpoints will be evaluated with the paired-samples t test. A p value <0.05 indicates statistical significance. All data will be analyzed with SPSS software package, version 22.0 (SPSS Inc., Chicago, IL, USA).

Discussion

Recent studies have found viable myocardium in the CTO lesion where the blood supply is provided by the collateral circulation [2,3]. In 258 patients with chronic ischemic LV dysfunction, recovery of global LV function [defined as improvement ≥5% in LV ejection fraction (EF)] after revascularization was observed in 39% of patients [18]. Studies have shown that patients with viable myocardium have a better prognosis after revascularization; however, patients with non-viable myocardium have worse outcomes with higher perioperative morbidity and mortality subsequent to revascularization [19]. In

patients with viable myocardium, an improvement of LVEF was observed (37–45% on average), while patients without viability did not improve in LVEF [20]. More importantly, the presence of viable myocardium has been proved to be related with long-term outcome. In 17 available retrospective prognostic studies, outcome was better in patients with viable myocardium who were revascularized compared with those without viable myocardium [21]. Thus, CTO patients with viable myocardium could benefit from revisualization, the extent of viable tissue predicted the magnitude of improvement of LVEF after revascularization. However, the recovery of myocardial function and the improvement of left ventricular function is a long and sustained process. In addition to effective revascularization, it may also involve blood reconstruction of myocardial neovascularization [4], collateral circulation, endothelial function recovery [5], microcirculation improvement, and other factors.

Currently, the imaging methods to identify viable myocardium include positron emission computed tomography (PET), single-photon emission tomography (SPECT), dobutamine stress echocardiography (DSE), myocardial contrast echocardiography (MCE), and magnetic resonance imaging (MRI). MRI has some advantages, such as high spatial resolution, no radiation, no violation, higher repeatability of three- dimensional images measurement. It allows for high-resolution assessment of the area at risk, myocardial necrosis, and microvascular damage (microvascular obstruction). Moreover, assessment of the occurrence and extent of reperfusion injury as well as the regional LV function (functional imaging) can be performed with MRI in a manner similar to echocardiography. Cine-MRI can directly measure the volume of heart cavity, as well as the thickness and the motion of ventricular wall, which provides objective and reproducible indicators for left ventricular remodeling [22–26]. Recent studies have proved that MRI can accurately assess the perfusion of myocardial microcirculation [27,28] and

endothelial dysfunction [29]. Additionally, contrast-enhanced MRI can characterize myocardial ischemic injury, and has the ability to distinguish viable from nonviable zones [30]. Thus, the use of MRI imaging has unparalleled advantages over other methods in assessing viable myocardium, microcirculation perfusion, and ventricular remodeling in CTO patients.

Late gadolinium enhancement by MRI combined with low-dose dobutamine is the best technique for determining viable myocardium. The major advantages of dobutamine MRI over dobutamine stress echocardiography are the image quality and the possibility of quantifying the extent and severity of the wall motion abnormalities [31,32]. Similar to low-dose dobutamine echocardiography, lower dosages of dobutamine (10 µg/kg/min) MRI are mainly used to detect contractile reserve (and hence viability) in dysfunctional myocardium. The approach of low-dose dobutamine (10 µg/kg/min) MRI has been applied successfully in patients with chronic coronary artery disease [33,34]. Baer et al. [35] compared dobutamine MRI with FDG PET and dobutamine echocardiography and demonstrated excellent agreement among these 3 approaches. Subsequently, these authors showed that dobutamine MRI could adequately predict improvement of regional LV function after revascularization; moreover, the diagnostic accuracy of dobutamine MRI was superior to that of resting MRI (using EDWT ≥5.5 mm as a "viability marker"). Therefore, in the current study, we will choose low-dose dobutamine MRI to assess viable myocardium and cardiac function because it has the advantages of non-invasiveness, no radiation, no violation, higher repeatability, and image quality.

With the modernization of Chinese traditional medicine and technology, an increasing number of Chinese herbal medicines are used clinically. Breviscapine is a total flavonoid extracted from *Erigeron breviscapus* (Vant) Hand-Mazz. Studies have shown that Breviscapine can dilate capillaries, reduce vascular resistance, inhibit platelet aggregation, scavenge free radicals, and improve microcirculation [36–39]. A meta-analysis suggests that Breviscapine plus standard therapy achieved a superior therapeutic effect compared to standard Western medicine therapy for improving angina pectoris symptoms [40]. Meanwhile, severe adverse effects have rarely been reported for Breviscapine (including headache, palpitation, and fatigue).

Basic research has revealed that Breviscapine can inhibit protein kinase C (PKC) activity [7–9] and increase the mitochondrial function of myocardium, consequently ameliorating the myocardial ischemia-reperfusion injury [10–12]. Our previous study also suggested that Breviscapine significantly inhibited high glucose-induced PKC signaling pathway activation, thereby attenuating cardiac hypertrophy, regulating calmodulin, and then enhancing myocardial contractility [7,41]. In addition, we also found that Breviscapine could inhibit ERK (extracellular signal-regulated

kinase) signaling pathways, resulting in downregulation of high glucose-induced smooth muscle cell proliferation and migration [42]. Therefore, a series of basic research results have shown that Breviscapine can improve endothelial function, microcirculation perfusion, and cardiac function. However, no has study focused on the effect of Breviscapine on viable myocardium and left ventricular remodeling after CTO revascularization.

Vascular endothelial growth factor (VEGF) is a signal protein produced by cells that stimulates vasculogenesis and angiogenesis [43,44], which has the function of creating new blood vessels (collateral circulation) to bypass blocked vessels. Basic fibroblast growth factor (bFGF) is a member of the fibroblast growth factor family [45], which presents in basement membranes and in the subendothelial extracellular matrix of blood vessels [46,47]. bFGF is also a major mediator of vascular angiogenesis, having the function of mediating the formation of new blood vessels and playing a central role in the development of coronary collaterals [48]. Clinical studies have shown that patients with myocardial ischemia and infarction have elevated levels of VEGF mRNA in myocardial tissues, potentially as an important cardiac response to hypoxia [49,50]. Through their proven angiogenic effect, the administration of VEGF and bFGF have been explored as an indicator of increased collateralization in patients with end-stage coronary heart disease.

Limitations

First, though the proposed study is designed as a prospective, randomized, double-blind, placebo-controlled study, it will be a single-center study, which may cause the baseline drift of the selected patients. At the same time, the study sample size will be relatively small.

Second, there is a relatively high rate of in-stent restenosis (ISR) in CTO lesions when compared with non-CTO lesions [51]. According to several studies, CTO lesions have a 1.4- to 5-fold higher rate of ISR than standard coronary lesions [52], which may present as unstable angina (16–66%) or myocardial infarction (1–20%) [51]. Therefore, the incidence of ISR occurs in the 1-year follow-up may lead to myocardial ischemia, which will affect the results of the study, causing biased results, as the myocardial ischemia induced by stent restenosis will influence the treatment efficacy of Breviscapine.

Third, CTO patients are more common in the presence of other non-significantly-narrowed coronary arteries. In the Canadian CTO Registry [53], multi-vessel CAD (>50% diameter stenosis) was present in three-fourths of patients with CTO. Those non-CTO lesions are more likely to progress gradually compared with lesions not combined with CTO. Thus, the original existence of non-CTO lesions that may advance at the time of 1-year follow-up will also lead to results bias.

Fourth, some patients with CTO lesions may not be able to tolerate dobutamine stress MRI before revascularization or during subsequent follow-up visits for various reasons; for example, those with severe cardiac insufficiency cannot tolerate the load test or contraindication to dobutamine, which results in selection bias.

CTO patients after revascularization. We expect that the study results will confirm whether Breviscapine treatment can significantly promote the recovery of viable myocardium and improve left ventricular remodeling, as well as microcirculation after CTO revascularization.

Conclusions

The proposed study will be the first to investigate the influence of Breviscapine on the recovery of viable myocardial in

Conflict of interest

None.

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