Author's response to reviews

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Understanding of Chest Pain in Microvascular Disease Proved by Cardiac Magnetic Resonance Image (UMPIRE): Study Protocol for a Randomized Controlled Trial

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Abstract

**Background:** Microvascular angina (MVA) is characterized by anginal chest pain, an abnormal stress test, and normal coronary arteries on coronary angiography. Although the exact pathogenesis remains to define, endothelial dysfunction contributes to it. To date, there exists no specific therapy for this disease entity. Phosphodiesterase-5 inhibitor improves the endothelial function and subsequently microvascular circulation. The aim of this study is to identify whether udenafil offers benefits in treatment of MVA in female patients, who have perfusion defect in cardiac magnetic resonance image (CMR), but normal coronary arteries.

**Methods:** The ‘Understanding of Chest Pain in Microvascular Disease Proved by Cardiac Magnetic Resonance Image: (UMPIRE)’ trial is a multi-center, prospective, randomized, placebo controlled trial, designed to evaluate the effect of udenafil on myocardial ischemia and symptoms in female patients with MVA. The myocardial ischemia will be quantified by myocardial stress perfusion defect in CMR. A total of 80 patients with proven perfusion defect in adenosine-stress CMR will be randomly assigned to udenafil treatment group (daily 100 mg) or placebo group for 3 months. The primary endpoint is the improvement in perfusion defect size >25% in adenosine-stress CMR from baseline. The secondary endpoints include improvement in perfusion defect size <25%, chest pain frequency, ST-depression in stress test, Duke score in stress test, quality of life (QoL) assessment by SF-36 questionnaire, sexual dysfunction assessment by BISF-W self-questionnaire, and biomarkers for endothelial function.

**Discussion**

The UMPIRE trial is the first randomized controlled trial to evaluate the efficacy of udenafil in female MVA patients. If udenafil demonstrates cardioprotective effects, it may provide a novel therapeutic option to reduce myocardial ischemia and improve cardiac function in female MVA patients.

**Trial registration:** ClinicalTrials.gov: NCT 01769482 (Nov 20, 2012)
Keywords: microvascular angina; PDE-5 inhibitors, cardiac MRI
Background

Microvascular angina (MVA), also known as cardiac syndrome X, is characterized by anginal chest pain, an abnormal stress test indicative of myocardial ischemia and normal coronary arteries on angiography. The condition is not as benign as originally reported. While patients with stable MVA have excellent prognosis [1], “unstable” MVA-patients presenting with acute coronary syndrome have an increased risk of death or myocardial infarction [2]. Women are more affected than men. The current therapeutic options for MVA are limited.

An impairment of endothelium-dependent vasodilation due to reduced nitric oxide (NO) release is mainly accounted for the proposed mechanisms of MVA [3]. NO availability plays a critical role in the regulation of microvascular, endothelial functions and the arterial structure [4-6]. Many of the biological actions of NO are mediated by 3’5’-guanosine monophosphate (cGMP), which is rapidly degraded by cGMP phosphodiesterase (PDE). Recently, Phosphodiesterase-5-inhibitor (PDEi) has been reported to improve the endothelial function in animal and clinical studies [7-10]. PDE inhibitors improve cardiac performance in patients with heart failure [11] and reduce infarct size and attenuate cardiac dysfunction after ischemia/reperfusion injury or permanent coronary artery occlusion [12]. While short-term cardiovascular effects of PDE inhibitors have been studied, the effects of chronic PDEi-administration are not well known, especially in women with MVA.

In the ‘Understanding of Chest Pain in Microvascular Disease Proved by Cardiac Magnetic Resonance Image: (UMPIRE)’ study, we tested the hypothesis whether udenafil offers benefits in treatment of female MVA-patients, who have documented perfusion defect in CMR.

Methods/ Design

1. Overview
This trial will be a multicenter, prospective, randomized, double-blind, placebo controlled trial to
demonstrate the superiority of therapeutic benefit of low-dose udenafil over placebo in treatment of
female MVA-patients. The working hypothesis is ‘udenafil improves vascular function and,
consequently, alleviates ischemia in women with MVA, who have confirmed perfusion defect in CMR,
and normal coronary arteries on coronary CT angiography (CCTA) or coronary angiography.

The protocol of the trial has been registered at http://www.clinicaltrials.gov (NCT 01769482)
and a brief flowchart of the whole study is summarized in Figure 1.

2. The endpoints

The primary endpoint is the improvement in perfusion defect size >25% in adenosine-stress CMR
from baseline to 3 months udenafil treatment. The secondary endpoints include the improvement in
perfusion defect size <25%, chest pain, quality of life and sexual functions after 3-months udenafil
therapy. Detailed endpoints are listed in Table 3.

3. Patient population

Patient at least 18 years of age, who have chest pain and positive adenosine-stress CMR, and normal
coronary artery on CCTA or coronary angiography will be included in this study. A positive
adenosine-stress CMR is defined as a perfusion defect >25% of transmurality. Two high-volume
centers in Korea participate and enroll the eligible patients. The following patients are excluded from
the study; patients with contraindication to MR contrast media or MR Imaging; any heart rhythm
other than sinus rhythm; congestive heart failure, chronic kidney disease, contraindication to PDEi,
uncontrolled diabetes mellitus. The detailed inclusion and exclusion criteria are summarized in Table
1.

If all of the inclusion criteria are met and none of the exclusion criteria apply, the patients will be
obtained written informed consent, as required by the institutional review board (Samsung Medical Center Institutional Review Board, Seoul National University Bundang Hospital Institutional Review Board) in accordance with the Declaration of Helsinki.

4. Randomization and interventions

After the patients are enrolled in the study, the patients will be randomized to udenafil treatment group or placebo group by a web-based computerized program which will be independently managed at T&W software. The flowchart of the study design is shown in Figure 1.

5. Udenafil treatment protocol

After random assignment, patients in the udenafil treatment group will receive 100 mg udenafil daily (Dong-A Pharmaceutical, Korea) for 3 months. Since headache and facial flushing are common side effect of udenafil, the dose of study medication will be reduced by 50% when severe headache develops. In patients with serious side effects study medication will be stopped.

6. Cardiac Magnetic Resonance Imaging (CMR)

6.1. CMR imaging

6.1.1 Cine imaging

All CMR studies will be performed using a 1.5 T MRI scanner (Siemens Avanto, Erlangen, Germany or Intera CV release 10; Philips Medical Systems, Best, Netherlands) with a phased array cardiac coil. Hemodynamic parameters, oxygen saturation and lead vector ECG rhythm will be continuously monitored throughout the exam. Following image localizers, ventricular long and short axis cine images will be acquired in end expiration with retrospectively ECG-gated steady-state free precession sequences (image matrix 128 × 128, read field of view (FOV) 340 mm, phase FOV 75–100% of the
FOV read, echo time 1.12 ms, flip angle 70°) with slice thickness 8 mm and intersection gaps of 12-15 mm. The adenosine stress CMR protocol is illustrated schematically in Figure 2.

6.1.2. Adenosine infusion protocol

Adenosine (Adenoscan®, Sanofi-Synthelabo) will be infused at 140 µg/kg/min [13], via a 20-gauge cannula sited in an antecubital vein, using a syringe pump (Graseby® 3500). Adenosine will be infused for a minimum of 6 min before acquiring stress images. Indications for terminating adenosine infusion are persistent or symptomatic 3rd degree atrioventricular block, severe hypotension (systolic blood pressure < 90 mmHg) or bronchospasm. Scans will be supervised by an MRI trained clinician with access to immediate resuscitation facilities.

6.1.3 Perfusion imaging

Patients will undergo pharmacological stress and rest perfusion. In 1.5 T scanners (Siemens Avanto, Erlangen, Germany or Intera CV release 10; Philips Medical Systems, Best, Netherlands), a breath-hold MR first-pass perfusion examination will be performed. Electrocardiographic gating and triggering will be performed using the vector cardiographic method. Fast survey images will be acquired to determine the true short axis of the left ventricle. After the acquisition of rest cine scans in the standard views, adenosine will be infused at a dose of 140 µg/kg/min for up to 6 minutes [13]. During the adenosine infusion, electrocardiographic activity will be continuously monitored, and blood pressure and heart rate measurements will be obtained every minute. Within the last minute of infusion, the adenosine stress MR perfusion scan will be performed to visualize the 3 short-axis slices of 8 mm section thickness using 40 dynamic acquisitions. During the inspiratory phase of the second breath, a bolus of gadodiamide (Omniscan; GE healthcare, U.S.A) will be injected, using a power injector (Spectris; Medrad, Indianola, PA), into an antecubital vein at a dose of 0.1 mmol per kilogram
of body weight and an injection rate of 4 ml/s and followed by a 20 mL-saline flush. Stress perfusion MR images will be obtained with a gradient-echo sequence by using saturation-recovery steady-state free precession (SR-SSFP). After 15-25 minutes, identical MR perfusion scan at rest will be continued to allow adequate clearance of the first bolus of the contrast agent.

6.2. CMR analysis

6.2.1. Visual analysis

Visual analysis of myocardial perfusion will be performed off-line by consensus of 2 CMR specialists. Rest and stress perfusion images of the 3 short axis sections (base, mid and apex) will be viewed side by side. The first-pass study will be analyzed both in qualitative and semi-quantitative ways, with a 16-segment left ventricle model. On qualitative assessment, perfusion defects are defined as subendocardial or transmural visually dark myocardial areas, respecting coronary distribution, with a delay of at least 2 s compared with remote healthy myocardium, and persisting for at least 10 frames [13]. A score will be assigned for each left ventricular segment, according to the following scale: 0 = no perfusion defect; 1 = subendocardial perfusion defect with transmural extension < 25%; 2 = subendocardial perfusion defect with transmural extension between > 25% and 50%; 3 = subendocardial perfusion defect with transmural extension between > 50% and 75%; and 4 = subendocardial perfusion defect with transmural extension > 75%. For each patient a total score will be obtained as the sum of the individual scores of each segment. If a perfusion defect is also present at rest, the stress-related (ischemic) score will be calculated as the difference between the score after stress minus the score at rest. All cases will undergo evaluation for late gadolinium enhancement. A normal scan requires the absence of both reversible ischemia and late gadolinium enhancement. A representative example of a patient with inducible ischemia is shown in Figure 3.

6.2.2. Semi-quantitative analysis
Semi-quantitative analysis will be performed by signal intensity (SI)/time curves, with a commercially available software (QMass MR Enterprise Solution, Advanced Edition, Medis, Leiden, the Netherlands); endocardial and epicardial borders of the 3 slices were traced manually, and curves and bull’s eye plots will be obtained by 2 independent skilled operators, with divergences being resolved by consensus.

7. Echocardiography

Two-dimensional (2-D) transthoracic echocardiography (TTE) will be performed at patient’s screening and 12 weeks after enrolment. TTE will be performed with a commercially available echocardiographic instrument (Vivid 7, GE Medical Systems, Milwaukee, Wis or Sequoia 512, Acuson, Mountain View, California). A standard M-mode, 2-D echocardiogram and echocardiographic Doppler study were performed. All TTE recording will be interpreted by staff cardiologists.

8. Follow-up

All patients will visit our outpatient clinic at 1 week, 4 weeks, 8 weeks, 12 weeks, and 16 weeks after randomization. Each visit consists of clinical evaluation, blood analysis, and 12-lead electrocardiogram. After 3-month udenafil treatment, adenosine-stress CMR, echocardiography, and stress test will be performed (Table 2).

During follow-ups all adverse events including chest pain, headache, etc., will be documented. Serious adverse events will be immediately reported to the principal investigator. To ensure the quality of this trial, the clinical monitors will survey and document the trial process once a month in each participating hospital. Patient drop-outs and the reasons, and patients’ compliance will be recorded at 3 months after randomization.
9. Statistical Analysis

9.1. Sample Size calculation

We calculated sample size in this study using superiority categorical variable sample size formula. We assumed the improvement of perfusion defect size is > 25% in adenosine-stress CMR from baseline to 3-months after udenafil treatment. According to the researcher’s intuition, we assumed the improvement of perfusion defect is 2% in control group. If we applied two tails, 80% power, alpha-level of 0.05, and 10% drop-out rate the formula, we would need a total of 76 patients; 38 patients in the udenafil treatment arm and 38 patients in the control arm.

The prevalence of variant angina in Asian is reported to be between 1 to 5% [14]. For a total of 76 patients, 4 patients with variant angina will be possibly enrolled in this study. In order to achieve scientifically robust results, we will enroll a total of 80 patients (40 patients in the udenafil treatment arm; and 40 patients in the control arm).

9.2. Statistical Analysis

In comparison between udenafil treatment and control group, we would use student’s t-test for continuous variables and $\chi^2$-test for categorical variables. To evaluate improvement of perfusion defect size >25% between udenafil treatment and control group, we would analyze using Fisher’s exact test. The difference in the continuous outcome between experimental and control group will be assessed using generalized linear models. Frequency differences will be tested using $\chi^2$-test or Fisher’s exact test. We will be analyzing this data using an intention-to-treat analysis. All randomized patients will be included in the analysis. A $P$ value of less than 0.05 will be considered statistically significant.
10. Trial Organization

10.1. Executive Committee

The Executive Committee will be composed of the study chairperson and the principal investigators of the investigating centers. This committee will approve the final trial design and protocol issued to the Data and Safety Monitoring Board (DSMB) and the clinical sites. This committee will also be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications by members of the Steering Committee.

10.2. Data Safety Monitoring Board (DSMB)

An independent DSMB, composed of cardiologists, and a biostatistician abided by the applicable regulatory guidelines and did not participate in the trial. The DSMB committee will review the safety data from this study and will make recommendations, based on safety analyses of unanticipated device effects (UADEs), serious adverse events (SAEs), protocol deviation, and follow-up reports. In addition to the scheduled DSMB meetings, those will be determined prior to the initiation of the study; the board will convene a meeting at any time if safety problems become an issue. The DSMB are responsible for recommending the Executive Committee to modify or stop the study if there were any safety or compliance issue. However, the final decisions regarding study modifications will rest with the Executive Committee. Cumulative safety data will be reported to the DSMB and will review on an ongoing basis throughout enrollment and follow-up to ensure safety of the patients. Every effort will be made to allow the DSMB to conduct an unbiased review of the patients’ safety information. All DSMB reports will be made available to the appropriate agencies upon request but are otherwise remained strictly confidential. Prior to the DSMB’s first review of the data, the DSMB charter will be drafted. The plan defines the stopping rules for stopping the trial for safety. The first meeting of the DSMB will be requested for discussion of the protocol and an understanding of all the protocol elements. The DSMB will develop a consensus understanding of all trial endpoints and definitions.
used in the event adjudication process.

10.3. Clinical Event Adjudication Committee (CEAC)

The Clinical Events Adjudication Committee (CEAC) is comprised of cardiologists who are not participants in the study. The CEAC is responsible for the development of specific criteria used for categorization of clinical events and clinical endpoints in the study, which are based on protocol. At the onset of the trial, the CEAC establishes clear rules stating the minimum amount of data required, and the algorithm followed in order to classify a clinical event. All members of the CEAC are blinded to the primary results of the trial and meet regularly to review and adjudicate all clinical events in which the required minimum data was available. The Committee also reviews and rule on all deaths that occurred throughout the trial.

10.4. Data Coordination and Site Management

Data coordination and site management services were performed by the Clinical Trials Center at Seoul National University Bundang Hospital.

10.5. Ethical approval

The study was approved by the institutional review board of each center (Samsung Medical Center Institutional Review Board (2011-07-048-001), Seoul National University Bundang Hospital Institutional Review Board (B-1106-129-016)) and will be carried out in compliance with the Helsinki Declaration.

Discussion

Treatment option of MVA
There exist different therapeutic approaches. The primary goal of medical therapy is to ameliorate the chest pain. However, the conventional anti-anginal treatment is not often successful in MVA-patients [1]. Lanza et al reported that atenolol was associated with improvement in chest pain episodes, while amlodipine, and nitrate, were not [15,16]. Kaski et al reported that angiotensin-converting enzyme inhibition lessens exercise-induced ischemia in MVA patients [17]. Some authors define MVA as a part of visceral pain syndrome which is not related to myocardial ischemia, and reported that imipramine improved the symptoms in MVA patients, possibly through a visceral analgesic effect [18]. Taken together, there exists no standard treatment guideline for MVA.

**Rationale for the use of udenafil in MVA patients**

The exact pathogenesis for MVA is unknown. However, it is of note that up to 50% of the resistance to blood flow in the epicardial coronary artery is determined by the small coronary blood vessels [19]. Therefore, “small vessels” exert significant effect on blood flow in the large vessels. Endothelial dysfunction, inflammation, and microcirculation abnormality are three mostly discussed mechanisms for the microvascular dysfunction [20]. Among them, endothelial dysfunction due to an impairment of endothelium-dependent vasodilation due to reduce NO release is the mainly proposed mechanism for MVA [3]. NO exerts many of the biological actions via cGMP, which is rapidly degraded by cGMP PDE. Thus, PDEi has potential to improve the endothelial function, which has been shown in animal and clinical studies [7-10].

**Rationale for the udenafil dosage in MVA patients**

Udenafil, Zydena®, was developed in 1997, and after clinical trials, the drug was approved by the Korea Food and Drug Administration (KFDA) in 2005. The commercially available and clinically used doses are 100 mg and 200 mg daily. Its half life time is 11-13 hours, and the estimated duration of action is approximately 24 hours. Thus, udenafil may be a good candidate drug for chronic use due to its favorable pharmacokinetic property among PDE-5 inhibitors (sildenafil: T1/2 = 2 hours,
duration of action = 4-8 hours; tadalafil: T1/2 = 17.5 hours, duration of action = 36 hours). In phase 3 clinical studies [21], the dose 100 mg and 200 mg showed similar efficacy (81% vs. 88.5%), however the side effect rate was lower with 100 mg daily dosing (flushing: 10% vs. 23%; headache: 0% vs. 23%; chest discomfort: 0% vs. 5.4%, etc.).

**Rationale for the safety of udenafil use in MVA patients**

Preclinical trial or phase 1 trial with PDE-5 inhibitors in coronary vasculature would minimize the risk for potential candidates being exposed to unnecessary risk. However, there exist a plenty of studies reporting the safe use of PDE-5 inhibitors in human, including those evaluating the effect of PDE-5 inhibitors on the coronary arteries in human. There exist at least 11 isoforms of PDE, and the differential distribution of PDE isoforms in various tissues is the basis for potential tissue-specific effect of PDE inhibitor. Various tissues have different PDE isoform activities. Corpus cavernosum contains high activities of PDE 2, 3, and 5; human pulmonary circulation has isoform 1,3,4, and 5; and coronary arteries have PDE 1,2,3,4,5 isoforms [22]. Consequently, human coronary arteries can be a target of PDE5-inhibitors.

In clinical trials, sildenafil contributes little to the increase in myocardial flow that occurs during exercise or reactive hyperemia [23], but coronary hemodynamics and circulation are not unfavorably altered after treatment with sildenafil and other PDE 5-inhibitors. These study results imply that PDE-5 inhibitors are safe, but less likely to be effective. Nevertheless, in patients with endothelial dysfunction, the PDE-5 inhibitors would lead to significant hemodynamic improvement. In dysfunctional endothelium, the release of nitric oxide by the endothelium is significantly compromised [24]. Halcox et al [25] demonstrated that coronary arterial segments with endothelial dysfunction dilated significantly after application of acetylcholine combined with sildenafil. This finding infers that the inhibition of cGMP breakdown by PDE-5 inhibitors may, at least in part, compensate for reduced nitric oxide–related cGMP production due to endothelial dysfunction.
Consequently, in patients with MVA with endothelial dysfunction the administration of PDE-5 inhibitors may significantly restore the NO-dependent vasodilation, leading to symptom improvement and improved perfusion in CMR.

As for the safety concern, animal’s studies did not show any coronary steal phenomenon caused by PDE-5 inhibitors [26, 27]. In human, oral sildenafil produced only small decreases (<10 percent) in systemic arterial and pulmonary arterial pressures, and it had no effect on pulmonary-capillary wedge pressure, right atrial pressure, heart rate, or cardiac output. Most importantly, sildenafil did not alter coronary flow at rest in stenosed arteries and arteries without angiographically high-grade stenosis, but it increased coronary flow reserve to a similar extent in stenosed and nonstenosed arteries (by 13%) rejecting the possible concern of coronary steal phenomenon [28]. Halcox et al [25] also showed a small beneficial effect on ST-segment depression during exercise testing in patients with known coronary artery disease. These studies demonstrate that coronary hemodynamics and circulation are not unfavorably altered after treatment with sildenafil and other PDE 5-inhibitors; indeed, coronary blood supply may experience a slight improvement. Taken together, there exist clinical data that PDE-5 inhibitors are not harmful in coronary artery patients, and although the effect of PDE5-inhibitor is limited in “normal” coronary circulation, in patients with endothelial dysfunction, the effect of PDE-5 inhibitors may be clinically significant.

The UMPIRE study is a randomized clinical trial to investigate the cardioprotective properties of udenafil in female MVA-patients, by means of measuring adenosine-stress perfusion defect size in cardiac MRI. If udenafil improves myocardial perfusion, udenafil may provide a valuable therapeutic option to reduce myocardial ischemia and improve cardiac function in female MVA-patients.

**Study limitation**

Cardiac syndrome X, or microvascular angina (MVA), is generally characterized by patent coronary tree, chest discomfort (typical or atypical angina) with positive evidence of perfusion defect.
Prinzmetal angina patients also complain of chest pain with “normal” coronary tree during ‘attack-free’ period. Thus, if pharmacologic provocation test with e.g. ergonovine or acetylcholine is not performed, there will be a risk for enrolling variant angina patients and this may jeopardize the whole study. Variant angina patients have distinctive clinical features that may be used to distinguish them from MVA patients. First, the chest pain character differs: while most MVA patients complain of ‘exertional chest pain’, variant angina patients complain of ‘resting chest pain’ which often occurs during early morning and is aggravated by alcohol consume. Second, variant angina patients do not have vasospasm during attack-free period. Thus, when performing CMR during attack-free period, they will have a negative adenosine-stress CMR, and will not be enrolled. Third, even if the variant angina patients have coronary vasospasm without chest pain, the perfusion defect in CMR will likely to follow a coronary territory, since there exists a clear “vessel preference” in variant angina patients, mostly involving the right coronary artery. Although we may identify variant angina patients among “possible” MVA patients by using clinical characteristics and CMR-results, we cannot completely exclude the possibility enrolling variant angina patients. Because the prevalence of variant angina in Asian is reported to be between 1 to 5% [14], we will increase the sample size from 70 patients to 76 patients, in order to achieve scientifically robust results. Despite these measures, the possibility of enrolling patients with variant angina remains a major limitation.

**Trial status**

The trial is currently in the recruitment phase

**Abbreviations**

CCTA, coronary CT angiography; CEAC, Clinical Events Adjudication Committee; eGMP, 3’5’-guanosine monophosphate; CMR, cardiac magnetic resonance image; DSMB, Data and Safety Monitoring Board; ECG, electrocardiography; MR, magnetic resonance image; MVA, microvascular angina; NO, nitric oxide; PDE, phosphodiesterase; PDEi, Phosphodiesterase-5-inhibitor; 2-D, two-
dimensional; TTE, transthoracic echocardiography; SAEs, serious adverse events; SS-SSFP, saturation-recovery steady-state free precession; UADEs, unanticipated device effects; QoL, quality of life

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SJ: conception and design of the trial, data acquisition, critical establishment/management of the whole database, manuscript writing and final approval of the manuscript. JJ: conception and design and of the trial, data acquisition, critical establishment/management of the whole database, manuscript writing and final approval of the manuscript. SY: design of the study, performed the statistical analysis, critical revision and final approval of the manuscript. SA: design of the study, performed the statistical analysis, critical revision and final approval of the manuscript. SM: design the MRI protocols, data acquisition, critical revision and final approval of the manuscript. EJ: data acquisition, design the MRI protocol, critical revision and final approval of the manuscript. SI: design the MRI protocols, critically revised the manuscript for important intellectual content and final approval of the manuscript. YH: design the MRI protocols, critically revised the manuscript for important intellectual content and final approval of the manuscript. DJ: conception, design of the trials, critically revised the manuscript for important intellectual content and final approval of the manuscript. All authors read manuscript and have given final approval of the version of the manuscript to be published.

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Figure legends

**Figure 1.** Study flow.

**Figure 2.** Adenosine stress CMR protocol. Following image localizers, ventricular long cine images will be acquired. Adenosine (140 mcg/kg/min) will be infused for 6 min before stress perfusion imaging at the time of gadolinium injection. Early gadolinium imaging will be followed by short axis cine and then rest perfusion imaging. Late gadolinium enhancement images to evaluate scar/viability will conclude the scan. Study duration will be typically 35–40 min.

**Figure 3.** A representative example of a patient with inducible ischemia in perfusion MRI.
Table 1. Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tbody>
<tr>
<td>1. MVA patients with typical symptom and positive adenosine-stress CMR and with normal coronary artery in CCTA or coronary angiography.</td>
</tr>
<tr>
<td>2. Definition of positive adenosine-stress CMR: perfusion defect &gt; 25% of transmurality (by 2 radiologist based on visual assessment and qualitative assessment in core-lab)</td>
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<tr>
<td>3. Gender: female</td>
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<td>4. Age: 18-80</td>
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<table>
<thead>
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<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>1. The patient with contraindication to CMR contrast media or CMR Imaging</td>
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<tr>
<td>2. LVEF &lt; 50%</td>
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<tr>
<td>3. Any heart rhythm abnormality other than sinus rhythm</td>
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<td>4. Valvular heart disease with more than moderate degree</td>
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<td>5. Renal failure</td>
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<td>6. Congestive Heart Failure</td>
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<td>7. Myocardial infraction</td>
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<td>8. Myocarditis</td>
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<td>9. Congenital heart disease</td>
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<td>10. Pericarditis</td>
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<tr>
<td>11. Variant angina (positive provocation test with Ergonovine or acetylcholine)</td>
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<tr>
<td>12. GERD (conformed by esophagastroduodenoscopy)</td>
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<td>13. Pregnant women with suspected, pregnant women or women with lactation</td>
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<tr>
<td>14. QT prolongation syndrome or take drugs that prolong the QT interval</td>
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<tr>
<td>- Antiarrhythmics class IA; quinidine, procainamide</td>
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<tr>
<td>- Antiarrhythmics class III; amiodarone, sotalol</td>
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<tr>
<td>15. Preanalytical within 30 days of screening in a clinical trial that may affect the influence of</td>
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udenaflag

- Other PDE5 inhibitors (ex. Sildenafil, tadalafil)
- Nitrates/ NO donor (ex. Nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, amyl nitrate/nitrite, sodium nitroprusside, nicorandil)

16. Preanalytical within 7 days of screening in a clinical trial that may affect the metabolism of udenafil

- Antibacterials (ex. Erythromycin)
- Antifungals (ex. Itraconazole, ketoconazole)
- Antivirals (ex. Ritonavir, saquinavir, amprenavir, indinavir, nelfinavir)
- Cimetidine
- Grapefruit juice

17. Allergy or sensitivity with PDE 5 inhibitors

MVA; microvascular angina, CMR; cardiac magnetic resonance image, CCTA; coronary CT angiography, LVEF; left ventricular ejection fraction, GERD; gastroesophageal reflux disorder, PDE 5; Phosphodiesterase-5, NO; nitric oxide.
Table 2. Trial process chart

<table>
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<tr>
<th>visit</th>
<th>Visit 1</th>
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ECG; electrocardiogram, CMR; cardiac magnetic resonance image, CAG; coronary angiography, CCTA; coronary CT angiography.

1) The participant’s usual medication regimen was continued unchanged throughout study duration.

2) Check weight only after Visit 2

3) CBC: WBC, Hemoglobin, Hematocrit, Platelet; Chemistry: Total protein, Albumin, Globulin, Total bilirubin, AST, ALT, ALP, BUN, Creatinine, Uric acid; Electrolyte: Na, K, Cl; NT-proBNP; hs-CRP (NT-proBNP, hs-CRP: check visit 1 and visit 5)

4) child-bearing aged women

5) Stop all medications 3 days before CMR

6) Concomitant medications: beta-blockers, Calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, statin, and trimetazidine
Table 3. End-points

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>the improvement in perfusion defect size &gt; 25% in adenosine-stress CMR from baseline to 3-months after udenafil treatment</th>
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<tbody>
<tr>
<td>Secondary endpoints</td>
<td>the improvement in perfusion defect size &lt;25% in adenosine-stress CMR</td>
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<td>Decrement of frequency of chest pain</td>
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<td>Improvement of ST-depression in stress test</td>
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<td>Improvement of duke score in stress test</td>
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<td>Improvement of QoL assessment by SF-36 questionnaire</td>
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<td>Improvement of sexual dysfunction assessment by BISF-W self-questionnaire</td>
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<tr>
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<td>Improvement of biomarkers foe endothelial function</td>
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CMR; cardiac magnetic resonance image, QoL; quality of life.