Effects of sildenafil on myocardial infarct size, microvascular function, and acute ischemic left ventricular dilation

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Abstract

Objective: Adverse cardiac events in patients treated with the phosphodiesterase-5 inhibitor sildenafil for erectile dysfunction raised concerns about its safety in ischemic heart disease. Methods: In anesthetized open-chest rabbits, receiving 1.45 mg/kg sildenafil intravenously or saline 30 min prior to ischemia (n=12, each), infarct size (IS, triphenyltetrazolium), the area of no-reflow (ANR, thioflavin S) (% of the risk area, RA, blue dye), and regional myocardial blood flow (RMBF, radioactive microspheres) were measured after 30 min of coronary occlusion and 180 min of reperfusion. Left ventricular hemodynamics and dimensions (echocardiography) were determined in a separate series of animals (n=5, each). Results: Sildenafil significantly lowered arterial blood pressure before occlusion (217 to 219 mmHg over 30 min), but during ischemia and reperfusion hemodynamics were comparable to controls. IS in treated animals (51±4%) did not significantly differ from control animals (47±4%). No major arrhythmias or lengthening of QT/QTc occurred. While sildenafil slightly increased RMBF and significantly reduced specific vascular resistance in the RA during reperfusion (51±7 versus 73±10 mmHg g min/ml, P<0.05), the ANR (46±3%) was similar to control animals (44±4%). Sildenafil reduced left ventricular dP/dt (P<0.05) and dP/dt max (P<0.01) in non-ischemic conditions, and slightly during ischemia, along with a pronounced decrease in ischemic left ventricular end-diastolic pressure (9±2 versus 15±2 mmHg after saline, P<0.05), but did not attenuate acute ischemic left ventricular dilation. Conclusions: Sildenafil reduced cardiac pre- and afterload, and parameters of left ventricular contractility. Myocardial necrosis and microvascular dysfunction were neither exacerbated nor attenuated.

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Keywords: Coronary circulation; Hemodynamics; Infarction; Reperfusion; Regional blood flow

1. Introduction

Sildenafil, the first oral agent approved for treatment of erectile dysfunction, is a selective inhibitor of the isoform 5 of the enzyme phosphodiesterase, which is responsible for the breakdown of 3’,5’-cyclic guanosine monophosphate (cGMP) in smooth muscle cells of the corpora cavernosa, and systemic and pulmonary vasculature [1]. Soon after the approval of sildenafil, several reports of cardiac events among men treated with sildenafil raised some concern about its safety in patients with coronary artery disease [2–4]. However, these spontaneous reports of adverse events did not find their correlate in randomized trials and retrospective analyses [5,6]. Since patients with erectile dysfunction share most of the risk factors with patients suffering from ischemic heart disease [7], and on the other hand sexual activity might bear a slightly increased risk for a cardiac event [8], detrimental side effects of sildenafil in myocardial ischemia would be of utmost importance. Furthermore, recent investigations reported benefits of sildenafil in pulmonary arterial hypertension [9], and in congestive heart failure [10]; again two conditions that are frequently associated with coronary artery disease.

Among others, three basic concepts could theoretically explain accelerated myocardial necrosis during ischemia or a decreased threshold for arrhythmias: firstly, Phillips et al. described that treatment with sildenafil in healthy vol-
unteers was accompanied by sympathetic activation [11]; secondly, experimental studies reported a prolongation of the cardiac action potential under sildenafil [12]; and thirdly, elevated concentrations of cGMP could theoretically result in increased levels of myocardial 3',5'-cyclic adenosine monophosphate (cAMP), the breakdown of which is dependent on hydrolysis by the phosphodiesterase isofrom 3, which can be inhibited by cGMP [13–15].

On the other hand, sildenafil, as a venous and arterial vasodilator, might reduce cardiac pre- and afterload, which could attenuate acute ischemic left ventricular dilation. In addition, sildenafil was shown to increase coronary flow reserve in patients [16]. As initial concerns about a potential coronary steal effect under sildenafil, shifting blood flow from the ischemic territory towards non-ischemic myocardial tissue, were not supported by experimental investigations [17,18], vasodilating properties of sildenafil might also be beneficial.

Therefore, we investigated whether sildenafil might exacerbate or attenuate myocardial necrosis and microvascular dysfunction in experimental ischemia and reperfusion.

2. Methods

The rationale was to investigate cardiovascular effects of sildenafil in experimental myocardial ischemia and reperfusion. The experiments were conducted in accordance with the national and institutional Guide for the Care and Use of Laboratory Animals. Good Samaritan Hospital’s Heart Institute is an AAALAC-accredited organisation.

2.1. Animal preparation

New Zealand White male rabbits (2.0–3.0 kg) were anesthetized by intramuscular ketamine (400 mg) and xylazine (200 mg). After tracheotomy, and initiation of ventilation (35 breaths/min, 15 ml tidal volume, adjusted after opening of the chest, Harvard Respirator, Model 665, 1.5 l/min oxygen) catheters were inserted into the right jugular vein for additional anesthesia (pentobarbital, as needed), sildenafil or saline, and into the right carotid artery. After left lateral thoracotomy (4th intercostal space) and pericardial incision, a major branch of the circumflex coronary artery was encircled by a suture (4-0 silk suture, Ethicon, Sommerville, NJ, USA). The two ends of the suture were threaded through a length of plastic tubing, forming a snare, which could be tightened. Body temperature was maintained by a heating pad under continuous monitoring of rectal temperature. An ECG was recorded throughout the protocol. After the surgical procedure, animals were allowed to stabilize for 15 min.

2.2. Protocol 1

A catheter was inserted into the left atrial appendage. After baseline hemodynamics, 1.45 mg/kg sildenafil (1 g/l sildenafil as pure powder in saline, pH 2.7) or 1 ml/kg 0.9% saline (pH 2.7) was administered intravenously in a randomized fashion over ~5 min (n = 12, each). Thirty minutes later, the snare around the coronary artery was tightened for 30 min. Then, reperfusion was allowed for 180 min. Regional myocardial blood flow (RMBF) was measured at 25 min of ischemia, and at 170 min of reperfusion.

2.2.1. Infarct size (IS), risk area (RA) and area of no-reflow (ANR)

At the end of the protocol, 1 ml/kg 4% thioflavin S (Sigma, St. Louis, MO, USA; dissolved in 0.9% saline, then centrifuged (1500 rev./min) for 5 min) was injected into the left atrium. Thioflavin S is a vital fluorescent stain for endothelium. To delineate the risk area (RA), the coronary artery was re-occluded, and 4 ml 50% Uniperse blue (Ciba Geigy, Hawthorne, NY, USA) was injected into the left atrium. The rabbit was euthanized by an intravenous overdose of xylazine (100 mg i.v.) and 12 mEq KCl (intraatrial). The left ventricle was sliced into 6–7 transverse sections, photographed under water, re-photographed under ultraviolet light (365 nm wavelength, Spectroline Model ENF 280 C, Spectronics, Westbury, NY, USA) using a Y48 barrier filter (Minolta), and again photographed after incubation in 1% triphenyltetrazolium chloride (37 °C, 15 min). Triphenyltetrazolium chloride stains viable myocardium red. The contour of each slice, the RA, not stained by the blue dye, the area of no-reflow (ANR), defined as the non-fluorescent area within the risk zone, and infarct size (IS), not stained by triphenyltetrazolium chloride, were traced manually from projected slides and planimetered. The RA was expressed as a percentage of the weight of the left ventricle, the ANR and IS as a percentage of the weight of the RA. As demonstrated in previous investigations, this experimental model does not result in myocardial necrosis or areas of no reflow without coronary occlusion [19].

2.2.2. Regional myocardial blood flow (RMBF), and specific vascular resistence

Approximately 500,000 microspheres per measurement, labeled with 141Ce or 103Ru, were injected into the left atrium and simultaneously an arterial reference blood sample (2.06 ml/min) was withdrawn. Radioactivity was counted in the tissue stained by the blue dye (non-ischemic tissue) and not stained by the dye (tissue at risk) in a multi-channel pulse-height analyzer (model ND62, Nuclear Data Schaumburg, IL, USA). RMBF was calculated after correction for background and crossover as the
ratio of counts in the tissue and the reference blood sample multiplied by 2.06 ml/min and divided by the weight of the tissue sample.

Before measuring RMBF, the central venous pressure was measured from the jugular catheter, and specific vascular resistance calculated as (mean arterial blood pressure−central venous pressure)/RMBF (units: mmHg×g×min/ml).

2.2.3. Hemodynamics

Hemodynamics were recorded from the carotid artery catheter using PowerLab equipment with Chart v4.1.2 software (ADInstruments, Castle Hill, Australia) at a sampling rate of 400/s, and averaged over three consecutive cycles.

2.3. Protocol 2a and b

2.3.1. Protocol 2a

The arterial catheter was advanced into the left ventricle under hemodynamic guidance. Heart rate, systolic left ventricular pressure, end-diastolic left ventricular pressure (LVEDP), maximal positive and negative first time-derivative of left ventricular pressure (dP/dt<sub>max</sub> and dP/dt<sub>min</sub>), were recorded (sampling rate 1 k/s) and averaged over three consecutive cycles at baseline, 15 and 30 min after coronary occlusion before the animal was euthanized. At 15 min of occlusion, animals received sildenafil (1.45 mg/kg) or saline (n=5, each) in a randomized fashion. QT-duration was measured from an electrocardiographic chest lead, positioned adjacent to the apex of the heart, and averaged over three beats. QTc was calculated according to Bazett’s formula as QT/[sqrt(60/heart rate)].

2.3.2. Protocol 2b

In a non-randomized set of four animals, left ventricular hemodynamics were measured at baseline and 15 min after administration of sildenafil without coronary occlusion.

2.4. Protocol 3

After surgery, the chest was closed by two sutures with the snare around the coronary artery not tightened. Two-dimensional echocardiographic images of the left ventricle on a short axis view at the midapillary level were recorded, using a 7.5 MHz transducer, connected to an echocardiographic imaging unit (Hewlett Packard, Sonos 1000 Ultrasound System). Diastolic and systolic left ventricular areas (LV-area) were planimetered and averaged over three consecutive cycles at baseline, 15 and 30 min after coronary artery occlusion before euthanizing the rabbit. Saline or 1.45 mg/kg sildenafil were then given in a randomized fashion after the 15-min recording (n=5, each).

2.5. Statistical analyses

Animals showing a RA of less than 20%, animals that did not survive, and in protocol 1, hearts with a regional myocardial blood flow of more than 0.2 ml/g/min within the RA during occlusion were excluded and replaced. Data are expressed as mean±S.E.M. The RA, ANR, IS, RMBF, and vascular resistance at the same time point were compared by a Student’s t-test in protocol 1. Hemodynamic data, body temperature, and echocardiographic measurements (protocol 3) were compared by two-way ANOVA for correlated measurements over time with Tukey’s test for post hoc comparisons. Linear regression analysis used Pearson’s minimal square method. ANR and RMBF versus IS were compared by ANCOVA with IS as a covariate, along with a test for homogeneity of the regressions. A P-value of <0.05 was considered statistically significant.

3. Results

3.1. Protocol 1. Infarct size (IS), area of no-reflow (ANR), and regional myocardial blood flow (RMBF)

3.1.1. Exclusions

One animal with a risk area of less than 20% of the left ventricle (sildenafil group), and two animals in the saline group (one animal with a regional myocardial blood flow of 0.76 ml/g/min in the risk area during occlusion, and one animal died during reperfusion from hypotension) were excluded from the analysis and replaced. Presented data are based on 12 animals in each group.

3.1.2. Hemodynamics (Fig. 1)

Application of 1.45 mg/kg sildenafil resulted in a moderate, but significant decrease of systolic and diastolic blood pressure (over 30 min, systolic and diastolic blood pressure: -17 to -19 mmHg versus baseline). During coronary occlusion, blood pressure further declined in both groups, but systolic blood pressure in the sildenafil group was only slightly lower compared with control (maximal: -3 mmHg). For the rest of the protocol, differences in blood pressure between the two groups were minimal; and heart rate, albeit slightly increasing after sildenafil, was not significantly different between the groups. Importantly, the heart rate–mean arterial blood pressure product during coronary occlusion was not significantly different (at 30 min of occlusion: 12,262±741 mmHg/min in saline animals versus 13,240±466 mmHg/min in the sildenafil group). No major arrhythmias occurred in either group, except for a few self-limiting ventricular arrhythmias (Table 1).
3.1.3. Risk area, infarct size, and area of no-reflow (Fig. 2)

The RA was similar in the two groups (Fig. 2). IS amounted to $47\pm4\%$ in the control group and $51\pm4\%$ in the sildenafil group (not significant). Concomitantly, the ANR was $44\pm4\%$ in the saline group and $46\pm3\%$ in the treated group (not significant). Infarct size and ANR demonstrated a close spatial concordance, and their size was significantly correlated with each other in both groups ($r=0.72–0.85$). Comparison of the relationship between IS and ANR by ANCOVA with IS as a covariate did not reveal a significant difference (adjusted means for ANR: control group 46%, sildenafil group 44%).

3.1.4. Regional myocardial blood flow (RMBF), and specific vascular resistance (Figs. 3 and 4)

RMBF and vascular resistance in the RA during coronary occlusion were not significantly different between the two groups (Fig. 3). In the treated group, RMBF values were slightly higher without reaching statistical significance. At 170 min of reperfusion, vascular resistance within the RA was significantly lower in the sildenafil group ($P<0.05$). RMBF within the RA, expressed as a percentage of non-ischemic flow, was inversely correlated with IS (Fig. 4). Comparison of the relationship between both parameters by ANCOVA with IS as a covariate did not demonstrate a significant difference.
both groups during the protocol. After the decline of $dP/dt_{\text{max}}$ and $dP/dt_{\text{min}}$ with coronary occlusion, the slight additional decrease by 30 min of occlusion was not significantly different after saline or sildenafil treatment.

3.2.1.3. Left ventricular end-diastolic pressure (LVEDP, Fig. 5) LVEDP significantly increased with coronary occlusion (Fig. 5). Sildenafil application led to a reduction of LVEDP back to the range of baseline values.

3.2.1.4. QT-duration and QTc QT amounted to 235±3 ms at baseline, 223±6 ms at 15 min of occlusion and 215±8 ms after sildenafil (QTc: 398±10 ms, 384±12 ms, 378±16 ms, respectively, not significant). Similar to protocol 1, no major arrhythmias were recorded when sildenafil was administered during occlusion.

3.2.2. Protocol 2b

3.2.2.1. Effects of sildenafil on LV-hemodynamics without coronary occlusion Fifteen minutes after administration of sildenafil without coronary occlusion, systolic LV-pressure was decreased from 75±5 to 55±9 mmHg ($P<0.01$), $dP/dt_{\text{max}}$ from 1711±158 to 1210±142 mmHg/s ($P<0.05$), and $dP/dt_{\text{min}}$ from $-2375\pm363$ to $-1575\pm389$ mmHg/s ($P<0.01$). LVEDP was also reduced from $5.3\pm0.3$ to $3.8\pm0.6$ mmHg ($P<0.05$).

3.2.3. Protocol 3. Acute ischemic left ventricular dilation

3.2.3.1. Exclusions One animal in the control group was excluded because of failed occlusion, another control animal died during occlusion from ventricular fibrillation. They were replaced, and presented data are derived from five animals in each group.

3.2.3.2. Left ventricular dimensions In both groups, coronary occlusion led to a significant increase in diastolic and systolic left ventricular areas, as measured by two-dimensional echocardiography (Fig. 6). The values measured after 15 min of occlusion remained relatively stable, and no significant changes were observed after the application of sildenafil. Statistical comparison revealed a time-related effect due to the increase of dimension during coronary occlusion without interaction.

4. Discussion

This study investigated effects of sildenafil on intraventricular hemodynamics, acute ischemic left ventricular dilation, microvascular function and infarct size in a rabbit model of myocardial ischemia. The dose of 1.45 mg/kg, used in this study, represents the upper range of what can be expected in the treatment of erectile dysfunction.
According to Walker et al., pharmacology of sildenafil in both men and rabbits is similar, including an identical volume of distribution (1–2 l/kg) and only slightly longer half life in men [20]. While in young healthy volunteers, oral bioavailability was limited by a hepatic first pass effect and amounted to ~40% [21], these values were doubled in the elderly [22] and further increased in patients with hepatic dysfunction [22]. Therefore, we chose an intravenous dose of 1.45 mg/kg, parallel to 100 mg per 70 kg body weight, as a single oral dose in patients to achieve concentrations similar to the upper range in patients treated for erectile dysfunction.

In this study 1.45 mg/kg sildenafil resulted in significant reduction of systolic and diastolic blood pressure, confirming the pharmacologic efficacy in this model. The moderate blood pressure lowering effect, the reduction of \( dP/dt_{\text{max}} \) and \( dP/dt_{\text{min}} \), and the attenuation of LVEDP by sildenafil did not transfer into detectable attenuation of acute ischemic left ventricular dilation, as assessed by two-dimensional echocardiography.

Concomitantly, infarct size was not reduced nor was myocardial necrosis exacerbated by sildenafil treatment. Albeit slightly improving RMBF and reducing specific vascular resistance in the RA during reperfusion, sildenafil did not reduce anatomic no-reflow, which remained closely associated with myocardial necrosis. No major arrhythmias occurred with sildenafil during occlusion, and the QTc-duration was not lengthened.

### 4.1. Sildenafil and myocardial necrosis in ischemia–reperfusion

Our results contrast with a recent study by Ockaili et al., performed in a very similar rabbit model [23], that described pronounced infarct size-reducing effects of sildenafil (0.7 mg/kg), mediated by activation of mitochondrial \( K_{\text{ATP}} \)-channels, mimicking a preconditioning-like effect. While infarct size in their control group was slightly lower than in the control group of the present study, the...
Fig. 5. Top panel, maximal and minimal values of the first time-derivative of left ventricular pressure (dP/dt\textsubscript{max}, dP/dt\textsubscript{min}) under baseline conditions, 15 min after coronary occlusion, and after application of intravenous sildenafil (n=5) or saline (n=5) during occlusion (protocol 2). Two-way ANOVA revealed a time-related effect (P<0.05 for dP/dt\textsubscript{max}, P<0.01 for dP/dt\textsubscript{min}) due to the decrease after coronary occlusion without interaction or group effects.

Lower panel, left ventricular end-diastolic pressure (LVEDP) under baseline conditions, 15 min after coronary occlusion and after administration of saline or sildenafil during ischemia (protocol 2). LVEDP after sildenafil was significantly lower than after saline administration. Comparison by two-way ANOVA showed a significant time-related effect (P<0.01) due to the rise in LVEDP during ischemia (*P<0.05 versus control).

Fig. 6. Left ventricular cross sectional area (LV-area) on the mid-papillary level, as assessed by two-dimensional echocardiography at baseline, 15 min after coronary occlusion, and 15 min after application of saline or sildenafil (protocol 3). Two-way ANOVA revealed a significant time-related effect due to acute ischemic left ventricular dilation without significant changes after sildenafil treatment or interaction effects.
rest of the study protocol, including anesthesia with ketamine/xylazine, appears to be comparable.

We tested whether infarct size in our study correlates with the degree of the initial pressure drop after sildenafil, which might be an indirect measure of the amount of cGMP accumulation after sildenafil, or theoretically could be interpreted as a potential preconditioning-like stimulus by transiently reducing coronary perfusion. The amount of pressure drop correlated positively, but not significantly with infarct size in our study ($r=0.47$). We tried to avoid major transient hypotension (range of systolic pressure drop after sildenafil: $-5$ to $-31$ mmHg) by slow administration of sildenafil over $\sim 5$ min. One might speculate that more pronounced transient periods of hypotension might be able to activate signal pathways involved in ischemic preconditioning.

After Ockaili's work had been published, we performed additional experiments parallel to protocol 1, in which pretreatment with $0.7$ mg/kg sildenafil was compared with saline treatment ($n=5$, each) in order to investigate whether the higher dose used in our study was responsible for the different results. In these experiments again, sildenafil did not reduce IS (107% of IS in control animals) and ANR (105% of ANR in control animals) (not significant). As effects of sildenafil on arterial blood pressure in Ockaili's investigations and the present study were similar, the contradictory results largely remain unexplained, but emphasize that additional factors, due to subtle differences in the experimental model, might be able to modify the cardiovascular response to sildenafil and should be considered carefully in clinical circumstances.

4.2. Sildenafil: beneficial or detrimental in myocardial ischemia?

The clinical importance of a variety of cardiovascular effects after treatment with sildenafil is still a matter of debate. A direct translation of this experimental model of ischemia/reperfusion to various clinical conditions might not be possible; however, the results could help to estimate the relevance of some proposed actions of sildenafil.

As potentially harmful under ischemic conditions, one might mention three basic concepts. Phillips et al. described a pronounced sympathetic activation in healthy volunteers after $100$ mg oral sildenafil [11]. In the present study, performed in anesthetized animals, heart rate slightly increased after sildenafil administration, which might be most likely explained as a response to the lowered blood pressure. Heart rate--pressure product after sildenafil was not increased (17,340±885 mmHg/min at baseline vs. 14,739±569 mmHg/min 15 min after sildenafil).

Gellen et al. demonstrated an inhibitory effect of sildenafil on the rapid component of the delayed rectifier potassium channel [12], which in theory could lead to lengthening of action potential duration and in turn increase myocardial contractility during ischemia via enhanced calcium transients. But, also action potential-shortening effects of sildenafil have been described [24], and the concentrations, needed for the effects reported by Gellen et al. were probably above the therapeutical level [25]. In the present investigation, we did not observe major arrhythmias with sildenafil treatment; furthermore, sildenafil did not lengthen QT or QTc duration during ischemia. These findings are in accordance with a recent report in patients with chronic heart failure, that did not find alterations of the QT duration or major arrhythmias [26].

A third concern is related to a potential 'cross-talk' between cGMP and cAMP [13]. Moderately increased levels of cGMP were shown to inhibit phosphodiesterase 3, the enzyme responsible for hydrolysis of cAMP, and thereby may enhance myocardial contractility as a consequence of higher cAMP levels. However, the presence of phosphodiesterase 5 in cardiomyocytes, a prerequisite for this theoretical cross talk, is controversial: in isolated dog trabeculae carneae, stimulated by isoproterenol, sildenafil did not exhibit effects on myocardial contractility in contrast to the selective phosphodiesterase 3 inhibitor milrinone [1], which argued against a significant PDE 5 activity in cardiac myocytes. However, Senzaki et al. reported evidence for PDE 5A expression in canine cardiomyocytes [15], and Stief et al. demonstrated increasing cAMP (and cGMP) concentrations in response to sildenafil in tissue obtained from human auricles [27].

In contrast to cAMP, higher levels of cGMP might exhibit negative inotropic effects by antagonizing effects of cAMP [28]. The dose, used in the present study, reduced parameters of contractile performance. Thus, increased contractility due to cross-talk between cGMP and cAMP did not seem to be relevant.

On the other hand, sildenafil, as a venous and arterial vasodilator, might also exhibit beneficial effects in myocardial ischemia by reducing pre- and afterload [29] or by improving coronary perfusion. In the present investigations, effects of sildenafil on arterial blood pressure were mild, but LVEDP was markedly reduced during ischemia. These hemodynamic changes, while potentially beneficial, were apparently too small to transfer into significant effects of left ventricular dilation during ischemia.

RMBF, however, demonstrated a tendency of improvement with sildenafil treatment; and specific vascular resistance in the risk area at the end of the protocol was significantly reduced. However, the size of perfusion defects, the anatomic basis of the no-reflow phenomenon in reperfused infarcts, was not reduced and remained closely related to infarct size. As demonstrated by Hermann et al. in patients with coronary artery disease [16], sildenafil increased coronary flow in stenosed coronary arteries and coronary arteries without a significant stenosis to a similar extent; and a coronary steal phenomenon under the influence of sildenafil was not supported in animal
studies [17,18]. Given the close relationship between IS and RMBF in the RA, ANCOVA analysis demonstrated that blood flow in the previously ischemic tissue during reperfusion was not significantly compromised in comparison with non-ischemic flow (Fig. 4).

5. Summary

In this in-vivo model of coronary occlusion and reperfusion, sildenafil did not exacerbate or attenuate myocardial necrosis. While markedly reducing LVEDP during occlusion, reduction of cardiac afterload was mild with sildenafil, and apparently did not transfer into attenuation of acute ischemic left ventricular dilation. No evidence for increased myocardial contractility during ischemia, proarrhythmic effects or lengthening of QT duration with sildenafil was observed. Regional myocardial blood flow in the reperfused myocardium was slightly increased, along with reduced vascular resistance in the risk area, but the amount of anatomic no-reflow was not altered by sildenafil. Overall, sildenafil seemed to be neutral, but safe, in myocardial ischemia–reperfusion in this model.

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