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Effect of Phosphodiesterase Type 5 Inhibition on Microvascular Coronary Dysfunction in Women: A Women's Ischemia Syndrome Evaluation (WISE) Ancillary Study

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SUMMARY

Background—Microvascular coronary dysfunction (MCD) is associated with symptoms, signs of ischemia, and adverse outcomes in women without macrovascular obstructive coronary artery disease (M-CAD). Although, MCD can be quantified using coronary flow reserve (CFR), treatment is poorly defined.

Hypothesis—Phosphodiesterase type 5 (PDE-5) inhibition acutely improves MCD in these women.

Methods—The subjects were 23 symptomatic women (age 54±11 years) participating in an ancillary study of the Women's Ischemia Syndrome Evaluation (WISE) with baseline CFR ≤3.0 (Doppler flow wire and intracoronary adenosine) and without M-CAD. CFR was re-measured 45 minutes after PDE-5 inhibition (100 mg oral sildenafil). The primary measure of interest was change in CFR adjusted for baseline variables.

Results—The relationship between $\log_2$ transformed CFR post–PDE-5 inhibition (adjusted) and baseline was different from the line of identity (slope: 0.55 vs. 1.0, P=0.008; intercept: 0.73 vs. 0.0, P=0.01), indicating that PDE-5 inhibition improves CFR and the lower the baseline CFR, the greater the response. Among women with baseline CFR ≤2.5 (N=11), CFR increased from 2.1±0.2 to 2.7±0.6 (P=0.006). For women with baseline CFR >2.5 (N=12), CFR did not change (3.1±0.3 to 3.0±0.6; P=0.70).

Conclusions—For women with symptoms and signs of ischemia and no M-CAD, PDE-5 inhibition is associated with acute improvement in CFR and the effect concentrates among those with CFR ≤2.5. If these acute effects are sustained, then PDE-5 inhibition would provide a rational strategy for management of MCD in symptomatic women without M-CAD. The longer-term effects warrant study in a randomized trial using a sustained acting PDE-5 inhibitor.

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All authors had access to the data and a role in writing the manuscript.

Keywords

Women; Microvascular coronary dysfunction; Coronary flow reserve; Phosphodiesterase type 5 inhibition

INTRODUCTION

Microvascular coronary dysfunction (MCD) may be associated with angina-like chest pain and/or test findings of ischemia among women without macrovascular obstructive coronary artery disease (M-CAD).[1] Although first described >40 years ago, and recently linked with adverse outcomes in the Women's Ischemia Syndrome Evaluation (WISE),[2] the specific etiology and course of MCD remains unclear. As a consequence, treatment is poorly defined. One hypothesis is that MCD involves a component of reduced bioavailability of nitric oxide (NO).[3,4] This reduced bioavailability affects the NO-soluble guanylate cyclase signaling pathway and limits conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), resulting in vascular smooth muscle activation. Since phosphodiesterase type 5 (PDE-5) degrades cGMP, its inhibition would impair cGMP degradation, promoting vascular smooth muscle relaxation. Therefore, PDE-5 inhibition may prove useful for treatment of MCD and may provide relief to affected women.

The WISE is a National Heart, Lung and Blood Institute-sponsored study designed, in part, to explore mechanisms for symptoms and myocardial ischemia in the absence of M-CAD in women.[5] This ancillary study used an open-label, nonrandomized prospective cohort design with repeated measures of coronary flow reserve (CFR) to investigate effects of acute PDE-5 inhibition on MCD in WISE subjects.

METHODS

The WISE design, methods, and principal results have been published.[5-7] For this ancillary study, responsibilities were divided among the University of Florida (UF; patient recruitment and CFR core lab); Rhode Island Hospital (angiographic core lab); Cedars-Sinai Heart Institute (steering committee chair); and the University of Pittsburgh (data coordinating center). The WISE enrolled women aged ≥18 years undergoing clinically indicated coronary angiography for further evaluation of chest pain and/or suspected myocardial ischemia. For this ancillary study, additional inclusion criteria consisted of a baseline CFR ≤3.0. Exclusion criteria included angiographic-documented M-CAD (≥50% stenosis), use of sildenafil or long acting nitrates within 24 hours of study, known hypersensitivity to sildenafil, pregnancy, serum creatinine ≥2.0, and systolic blood pressure <90 mmHg. Both the WISE and this ancillary study were approved by the UF Institutional Review Board, are in accordance with the Declaration of Helsinki, and each subject provided informed written consent.

Clinical Protocol

Subjects underwent clinical evaluation per protocol, which included medical history, physical examination, laboratory testing, and angiography with provocative studies of CFR according to the WISE protocol.[5] Evaluation of CFR utilized Doppler flow wire measurements (Cardiometrics; Mountain View, CA) and intracoronary adenosine at bolus doses of 18 mcg. Based on prior WISE studies and work of others a CFR < 3.0 was taken as evidence for possible microvascular dysfunction and ≤2.5 was considered definite evidence for microvascular dysfunction.[8] Subjects meeting this criterion without M-CAD, then received oral sildenafil (100 mg). After 45 minutes, angiography and provocative studies were repeated in the exactly the same manner used for the baseline study. The CFR

recordings were read at the WISE CFR core lab and the angiograms at the WISE coronary angiography core lab using qualitative and quantitative methods described previously[9] by investigators masked to all clinical data and treatment assignment.

The protocol required that the determination of patient eligibility be made by the investigator in the cardiac catheterization lab during the initial CFR study to avoid the risk and discontinuity of performing another catheterization after the independent CFR Core Lab reading was completed. The in-lab readings were made from the digital read out of the Cardiometrics flow console. The investigator was instructed to use the highest of 3 acceptable readings and if <3.0 the patient was considered eligible. The values reported here were those made at a later time at the CFR Core Lab The Core Lab independently inspected all coronary flow velocity recordings and rejected those that did not fill the diastolic period or had other quality issues, and then selected the highest among those remaining as the CFR for that patient. This accounts for the difference in the CFR readings for eligibility (made in the cardiac catheterization lab) and those reported in the manuscript made by the CFR Core Lab.

Statistical Analysis

All CFR data were $\log_2$ transformed as previously described.[2] The primary outcome measure was change in CFR from baseline to post-sildenafil adjusted for baseline clinical characteristics known to influence CFR. Data are presented as mean±standard deviation or number (percent). Analyses included Student's independent and paired t-tests. Linear regression was performed using $\log_2$ transformed CFR data. Covariates for predicting $\log_2$ transformed CFR post-sildenafil were age, $\log_2$ CFR pre-sildenafil, age*$\log_2$ CFR pre-sildenafil, HR*systolic blood pressure, menopause status, and histories of hypertension, diabetes mellitus, dyslipidemia, chronic obstructive pulmonary disease, and cigarette smoking.

RESULTS

Baseline Characteristics

The average age of qualifying women (N=23) was 54±11 years (Table 1), and this was similar to previous WISE and non-WISE reports.[2,5-11] The majority of women were postmenopausal, had a history of hypertension, were taking an angiotensin-converting enzyme (ACE) inhibitor, and had taken birth control pills in their past.

PDE-5 Inhibition and CFR

Primary outcome measure—The CFR post–PDE-5 inhibition and baseline CFR were significantly different as indicted from the line of identity (slope: 0.55 vs. 1.0, P=0.008; intercept: 0.73 vs. 0.0, P=0.01). For each woman, baseline and post–PDE-5 CFR data (adjusted for baseline covariates) are shown as $\log_2$ transformed values in Figure 1. The differences between the slope and intercept from the line of identity indicate that PDE-5 inhibition improved CFR (at least for baseline, non-transformed adjusted CFR <3.1), and that the lower the CFR, the greater the response. Consistent with this result, subgroup analysis showed that, among women (N=11) with baseline CFR ≤2.5, CFR increased from 2.1±0.2 to 2.7±0.6 (P = 0.006) (Figure 2). However, for women (N=12) with baseline CFR >2.5, CFR did not change (3.1±0.3 to 3.0±0.6; P=0.70). There were no apparent differences in pertinent clinical findings or other provocative testing among the two groups.

Baseline CFR therefore appeared to predict the response to PDE-5 inhibition: the lower the CFR, the greater the response. Multivariate analysis confirmed that $\log_2$ transformed

baseline CFR remained a significant predictor for CFR post-PDE-5 inhibition (Table 2). Additionally, HR*systolic blood pressure was a significant predictor.

Power Analysis

The trend among all 23 women was for unadjusted CFR to increase from baseline to post–PDE-5 inhibition (2.6±0.5 to 2.8±0.6; P=0.06). The increase in CFR (unadjusted) among all women post–PDE-5 inhibition was 0.20±0.54. Using a two-sided paired t-test for the comparison, there was therefore a power of 50% to detect this increase at a level of significance of 0.05. For the subgroup of 11 women with baseline CFR ≤2.5, the CFR increased by 0.60±0.50 post–PDE-5. The associated power was 95% to detect this increase at a level of significance of 0.05.

DISCUSSION

The original studies of PDE-5 inhibition investigated oral sildenafil as an anti-anginal treatment for patients thought to have M-CAD.[12] Improvement was reported in time to onset angina, time to limiting angina, and total exercise time.[13,14] Although not measured directly, these improvements were attributed to increased microvascular blood flow since studies in animals had showen increased coronary flow with and without a critical coronary stenosis.[15] However, early human studies quantitating the effect of sildenafil on coronary flow were limited and almost exclusively confined to men with M-CAD.[16,17] Nonetheless, these studies showed a small but significant increase in CFR following oral sildenafil. The only study that did not show an increase in CFR involved diabetic men with no symptoms of ischemia and negative stress testing, and they received only 50 mg of sildenafil.[18] To our knowledge, no study has focused on women or studied patients with the syndrome of chest pain and/or ischemic test findings and MCD in the absence of M-CAD.

A significant number of women suffer from symptoms and signs of ischemia in the absence of M-CAD.[1,8,9] Despite conventional therapy, most continue to have symptoms resulting in emergency room evaluations, hospitalizations, and repeat procedures.[19-21] Additionally, we and others have documented that MCD is a predictor of adverse events (e.g., death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure) during long-term follow-up, compared with women without MCD.[2,22,23] Thus women with MCD have a poor quality of life[24] and high associated health care costs.[25] New and evidence-based therapies are clearly needed.

The results of this exploratory study suggest that PDE-5 inhibition, using 100 mg oral sildenafil, is associated with an acute improvement in MCD in these women. Additionally, our results indicate that the degree of improvement is related to the severity of impaired baseline dysfunction: the worse the baseline dysfunction, the greater the improvement. Also, baseline heart rate-blood pressure double product seems to influence the degree of improvement achieved with PDE-5 inhibition.

The fact that PDE-5 inhibition is independent of the NO-soluble guanylate cyclase signaling pathway is attractive as a treatment for MCD because of the avoidance of non-specific interactions of NO with various biomolecules, variable responsiveness, and potential for development of tolerance following prolonged administration. Repeated administration of sildenafil has been largely well-tolerated in male cohorts with erectile dysfunction and in both sexes with pulmonary hypertension.[26] Our results provide a promising and rational strategy for women with MCD. There is a need to conduct an appropriately powered randomized clinical trial investigating the acute effects on CFR as well as the long-term efficacy and safety of a long acting PDE-5 inhibitor in these women.

This ancillary study has several important limitations. First and most importantly, the lack of a comparison group allows the possibility that the effects observed on CFR may be unrelated to sildenafil. For example, any change in hemodynamic state, including small changes induced by contrast media used during the cardiac catheterization,[27] may independently affect CFR.[28] Second, the relatively high concomitant use of ACE inhibitors which can beneficially impact coronary endothelial function[29] may have reduced our ability to assess the impact of the PDE-5 inhibitor. Other limitations are the relatively small sample size and limited power which was largely driven by enrolling some women with higher CFRs. In this regard, our findings provide a foundation for the design of appropriately power future studies.

CONCLUSIONS

For women with symptoms and signs of ischemia and no M-CAD, PDE-5 inhibition is associated with acute improvement in CFR and the effect concentrates among those with CFR ≤2.5. If these acute effects are sustained with longer acting PDE-5 inhibitors, such treatment would provide a rational strategy for management of MCD in symptomatic women without M-CAD. The longer-term effects need to be studied in a randomized trial using a sustained acting PDE-5 inhibitor.

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References

1. Cannon RO III. Microvascular angina and the continuing dilemma of chest pain with normal coronary angiograms. J Am Coll Cardiol. 2009; 54:877–885. [PubMed: 19712795]
2. Pepine CJ, Anderson RD, Sharaf BL, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia: Results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. J Am Coll Cardiol. 2010; 55:2825–2832. [PubMed: 20579539]
3. Chilian WM, Kuo L, DeFily DV, et al. Endothelial regulation of coronary microvascular tone under physiological and pathophysiological conditions. Eur Heart J. 1993; 14(Suppl I):55–59. [PubMed: 7904942]
4. Lapu-Bula R, Ofili E. From hypertension to heart failure: role of nitric oxide-mediated endothelial dysfunction and emerging insights from myocardial contrast echocardiography. Am J Cardiol. 2007; 99(6B):7D–14D.
5. Merz CN, Kelsey SF, Pepine CJ, et al. The Women's Ischemia Syndrome Evaluation (WISE) study: protocol design, methodology and feasibility report. J Am Coll Cardiol. 1999; 33:1453–1461. [PubMed: 10334408]
6. Shaw LJ, Bairey Merz CN, et al. WISE Investigators: Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. J Am Coll Cardiol. 2006; 47(3 Suppl):S4–S20. [PubMed: 16458170]

7. Bairey Merz CN, Shaw LJ, et al. WISE Investigators: Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. J Am Coll Cardiol. 2006; 47(3 Suppl):S21–29. [PubMed: 16458167]
8. Reis SE, Holubkov R, Conrad Smith AJ, et al. WISE Investigators: Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: Results from the NHLBI WISE study. Am Heart J. 2001; 141:735–741. [PubMed: 11320360]
9. Sharaf BL, Pepine CJ, Kerensky RA, et al. WISE Study Group: Detailed angiographic analysis of women with suspected ischemic chest pain (pilot phase data from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation [WISE] Study Angiographic Core Laboratory). Am J Cardiol. 2001; 87:937–941. [PubMed: 11305981]
10. Kaski JC. Overview of gender aspects of cardiac syndrome X. Cardiovasc Res. 2002; 53:620–626. [PubMed: 11861032]
11. Hayward CS, Kelly RP, Collins P. The roles of gender, the menopause and hormone replacement on cardiovascular function. Cardiovasc Res. 2000; 46:28–49. [PubMed: 10727651]
12. Gillies HC, Roblin D, Jackson G. Coronary and systemic hemodynamic effects of sildenafil citrate: from basic science to clinical studies in patients with cardiovascular disease. Int J Cardiol. 2002; 86:131–141. [PubMed: 12419549]
13. Jackson G. Phosphodiesterase type-5 inhibitors in cardiovascular disease: Experimental models and potential clinical applications. Eur Heart J. 2002; 4:H19–23.
14. Fox KM, Thadani U, Ma PT, et al. CAESAR I (Clinical American and European Studies of Angina and Revascularization) investigators: Sildenafil citrate does not reduce exercise tolerance in men with erectile dysfunction and chronic stable angina. Eur Heart J. 2003; 24:2206–2212. [PubMed: 14659772]
15. Traverse JH, Chen YJ, Du R, et al. Cyclic nucleotide phosphodiesterase type 5 activity limits blood flow to hypoperfused myocardium during exercise. Circulation. 2000; 102:2997–3002. [PubMed: 11113052]
16. Halcox JPJ, Nour KRA, Zalos G, et al. The Effect of Sildenafil on Human Vascular Function, Platelet Activation, and Myocardial Ischemia. J Am Coll Cardiol. 2002; 40:1232–1240. [PubMed: 12383570]
17. Herrmann HC, Chang G, Klugherz BD, et al. Hemodynamic effects of sildenafil in men with severe coronary artery disease. N Engl J Med. 2000; 342:1622–1626. [PubMed: 10833207]
18. Dietz U, Tries HP, Merkle W, et al. Coronary artery flow reserve in diabetics with erectile dysfunction using sildenafil. Cardiovasc Diabetol. 2003; 2:8. [PubMed: 12952551]
19. Day LJ, Sowton E. Clinical features and follow-up of patients with angina and normal coronary arteries. Lancet. 1976; 2:334–337. [PubMed: 60568]
20. Ockene IS, Shay MJ, Alpert JS, et al. Unexplained chest pain in patients with normal coronary arteriograms: a follow-up study of functional status. N Engl J Med. 1980; 303:1249–1252. [PubMed: 7421961]
21. Isner JM, Salem DN, Banas JS Jr, et al. Long-term clinical course of patients with normal coronary arteriography: follow-up study of 121 patients with normal or nearly normal coronary arteriograms. Am Heart J. 1981; 102:645–653. [PubMed: 6792893]
22. Halcox JP, Schenke WH, Zalos G, et al. Prognostic value of coronary vascular endothelial dysfunction. Circulation. 2002; 106:653–658. [PubMed: 12163423]
23. Britten MB, Zeiher AM, Schächinger V. Microvascular dysfunction in angiographically normal or mildly diseased coronary arteries predicts adverse cardiovascular long-term outcome. Coron Artery Dis. 2004; 15:259–264. [PubMed: 15238822]
24. Johnson BD, Shaw LJ, Buchthal SD, et al. National Institutes of Health-National Heart, Lung, and Blood Institute. Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation. 2004; 109:2993–2999. [PubMed: 15197152]

25. Shaw LJ, Merz CN, Pepine CJ, et al. Women's Ischemia Syndrome Evaluation (WISE) Investigators: The economic burden of angina in women with suspected ischemic heart disease: results from the National Institutes of Health–National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation. Circulation. 2006; 114:894–904. [PubMed: 16923752]

26. Bella AJ, Deyoung LX, Al-Numi M, et al. Daily administration of phosphodiesterase type 5 inhibitors for urological and nonurological indications. Eur Urol. 2007; 52:990–1005. [PubMed: 17646047]

27. Schmid I, Didier D, Pfammatter T, et al. Effects of non-ionic iodinated contrast media on patient heart rate and pressures during intra-cardiac or intra-arterial injection. Int J Cardiol. 2007; 118:389–396. [PubMed: 17376548]

28. de Bruyne B, Bartunek J, Sys SU, et al. Simultaneous coronary pressure and flow velocity measurements in humans. Feasibility, reproducibility, and hemodynamic dependence of coronary flow velocity reserve, hyperemic flow versus pressure slope index, and fractional flow reserve. Circulation. 1996; 94:1842–1849. [PubMed: 8873658]

29. Mancini GB, Henry GC, Macaya C, et al. Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease. The TREND (Trial on Reversing ENdothelial Dysfunction) Study. Circulation. 1996; 94:258–265. [PubMed: 8759064]

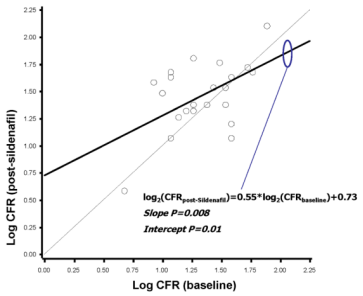

Figure 1.

Summary plot of $\log_2$ transformed CFR at baseline and after PDE-5 inhibition for each woman. The primary response variable, adjusted CFR post PDE-5 inhibition as a function of baseline CFR, is shown as the solid line. The line of identity, assuming no change in CFR, is shown as the dashed line. *CFR*, coronary flow reserve; *PDE-5*, phosphodiesterase type 5.

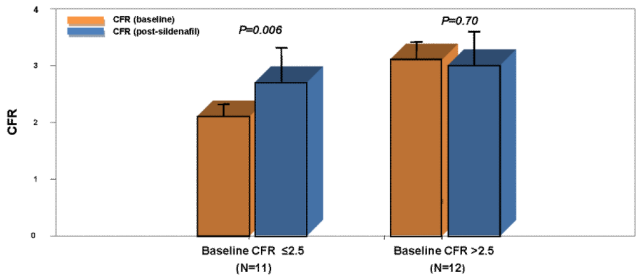

Figure 2.
Adjusted CFR as a function of baseline CFR (≤2.5 vs. >2.5), at baseline and post PDE-5 inhibition. *CFR*, coronary flow reserve; *PDE-5*, phosphodiesterase type 5.

Table 1

Baseline Clinical Characteristics (N=23).

Characteristic	Mean ± SD or No. (%)
Age (years)	54 ± 11
Ethnicity - White	21 (91)
BMI (kg/m^2)	32.7 ± 9.6
Waist Circumference (inches)	40.2 ± 8.3
Heart Rate (beats/minute)	75 ± 11
Systolic Blood Pressure (mm Hg)	133.7 ± 25.5
Diastolic Blood Pressure (mm Hg)	72.4 ± 10.5
Pulse Pressure (mm Hg)	58.6 ± 19.8
Duke Activity Status Inventory	22.5 ± 16.5
Medical History	
Hypertension	13 (57)
Diabetes	6 (26)
Peripheral Vascular Disease	0
Chronic Obstructive Pulmonary Disease	2 (9)
Cigarette Smoking (ever)	9 (39)
Chronic Renal Dysfunction	0
Dyslipidemia	8 (35)
Family History of Coronary Artery Disease	15 (65)
Post-Menopausal	17 (74)
Medications	
Hormone Replacement Therapy (ever)	11 (48)
Birth Control Pills (ever)	21 (91)
Angiotensin Converting Enzyme Inhibitors (active)	14 (61)
Statin (active)	7 (30)

BMI = body mass index

Table 2

Results of Multivariate Linear Regression Model for CFR.

	Beta (SE)	P Value
Intercept	1.03 (0.22)	0.0002
Baseline $\log_2$ transformed CFR	0.61 (0.17)	0.0025
Age*Baseline $\log_2$ transformed CFR	0.23 (0.13)	0.0945
HR*SBP at Baseline	2.98 (1.27)	0.0303

Dependent Variable: Log_2 transformed CFR post Sildenafil

Independent Variable: Baseline $\log_2$ transformed CFR

Covariates: Age*Baseline $\log_2$ transformed CFR, HR*SBP at baseline

R-Square of Model: 0.50

Results: Baseline CFR is significant after adjusting for other baseline potential risk factors.