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Comparison of low and high dose intracoronary adenosine and acetylcholine in women undergoing coronary reactivity testing: results from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE)

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Keywords

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Women with signs and symptoms of myocardial ischemia who are referred for invasive coronary angiography often have no evidence of obstructive coronary artery disease (CAD) [1]. Forty-five to sixty percent of these patients have abnormal coronary vasomotion due to endothelial or non-endothelial dependent macro- or microvascular coronary dysfunction [1–3]. Abnormal coronary vasomotion is linked with adverse cardiovascular outcomes, suggesting that additional coronary reactivity testing (CRT), beyond standard angiography, is needed in clinical practice to appropriately risk stratify these patients [2–6]. CRT with

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intra-coronary adenosine and acetylcholine (ACh) is used to identify vascular dysfunction, yet ascending dosing of these agents is time-consuming. We aimed to determine if 1) coronary flow reserve (CFR) was different after low or high dose adenosine, and 2) change in coronary artery cross sectional area (CSA) and coronary blood flow (CBF) was different after low or high dose ACh.

Eighty -six women with no obstructive CAD, who were enrolled in the WISE Coronary Vascular Dysfunction Study (WISE-CVD, www.clinicaltrials.gov Identifier NCT00832702), underwent CRT using a Doppler guide wire (Volcano ®FloWire 300cm) in a proximal left coronary. CFR was recorded in response to low dose (18µg) and high dose (36µg) intra-coronary adenosine. Change in CSA and CBF were determined after intra-coronary low dose ACh (10^{-6} mol/L infusion for total of 0.364µg) and high dose ACh (10^{-4} mol/L infusion for total of 36.4µg). The protocol was approved by the local institutional review board, and written informed consent was obtained from each participant.

On average, the women included in this analysis were 54 (± 12.2) years old; 36.7% had hypertension; 13.9% had dyslipidemia; 45.6% had a history of tobacco use; 70.9% were Caucasian; and 10% had diabetes.

The average CFR after low dose adenosine was 2.6 ± 0.6 , and the average CFR after high dose adenosine was 2.5 ± 0.6 . The CFR obtained after low dose adenosine was not significantly different from the CFR obtained after high dose adenosine in the same subject (mean of paired difference 0.06 ± 0.3 , p-value = 0.11).

The changes in CBF and CSA after low and high dose ACh are shown in the Table. On average CBF increased $15\% \pm 32\%$ with low dose ACh, but increased $92\% \pm 102\%$ with high dose ACh. In the same subject the increase in CBF was 77% higher after high dose ACh compared with after low dose ACh (p-value < 0.0001). The CSA of the proximal left anterior descending artery (LAD) and the LAD 5 mm distal to the flow wire remained essentially the same after low dose ACh, but decreased slightly after high dose ACh. On average, in the same subject the change in CSA of the proximal LAD was 4% smaller after high dose ACh compared with after low dose ACh (p-value = 0.05).

Our data indicate that escalating dosing of adenosine to detect non-endothelial dependent microvascular coronary dysfunction may not be needed. These findings are consistent with previous work that suggests that intracoronary doses of adenosine as low as 16 µg achieve maximal hyperemia [7]. For the purpose of our testing, we have used relatively lower doses of adenosine (18 µg and 36 µg) that test its non-endothelial dependent effects on the coronary circulation. At higher doses of adenosine, it becomes an epicardial coronary vasodilator, and would test hyperemic CBF due to both endothelial and non-endothelial dependent effects [8].

Our ACh dosing was selected based on the pioneering work by Ludmer et al. that demonstrated that patients with atherosclerosis and suspected endothelial dysfunction have paradoxical vasoconstriction in response to intra-coronary infusions of ACh at doses of 10^{-6} mol/L or less [9]. Other studies have demonstrated a very high incidence of abnormal coronary spasm in response to intracoronary ACh in patients with suspected endothelial

dysfunction when using even higher doses of intracoronary ACh (100–200 µg) [1,10]. The results of our analysis also suggest that higher dose ACh (36.4µg [10^{-4} mol/L]) has greater diagnostic utility than lower dose ACh (0.364µg [10^{-6} mol/L]), as higher dose ACh resulted in a significantly greater increase in CBF compared with low dose ACh, and on average only high dose ACh demonstrated an inappropriate decrease in CSA in this group of women with suspected endothelial dysfunction.

Among women with evidence of ischemia but no obstructive CAD, low and high dose adenosine produced similar augmentation in coronary flow velocity, but low and high dose ACh produced different results. For clinically indicated CRT, low dose adenosine but high dose ACh appear to be indicated.

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References

1. Ong P, Athanasiadis A, Borgulya G, Mahrholdt H, Kaski JC, Sechtem U. High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries The ACOVA Study (Abnormal COronary VAsomotion in patients with stable angina and unobstructed coronary arteries). *J Am Coll Cardiol.* 2012; 59:655–62. [PubMed: 22322081]
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; 55:2825–32. [PubMed: 20579539]
3. von Mering GO, Arant CB, Wessel TR, et al. Abnormal coronary vasomotion as a prognostic indicator of cardiovascular events in women: results from the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation.* 2004; 109:722–5. [PubMed: 14970106]
4. Halcox JP, Schenke WH, Zalos G, et al. Prognostic value of coronary vascular endothelial dysfunction. *Circulation.* 2002; 106:653–8. [PubMed: 12163423]
5. Schächinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation.* 2000; 101:1899–906. [PubMed: 10779454]
6. Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR, Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation.* 2000; 101:948–54. [PubMed: 10704159]
7. Wilson RF, Wyche K, Christensen BV, Zimmer S, Laxson DD. Effects of adenosine on human coronary arterial circulation. *Circulation.* 1990; 82:1595–606. [PubMed: 2225364]

8. Cox DA, Vita JA, Treasure CB, et al. Atherosclerosis impairs flow-mediated dilation of coronary arteries in humans. *Circulation*. 1989; 80:458–65. [PubMed: 2527643]
9. Ludmer PL, Selwyn AP, Shook TL, et al. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. *N Engl J Med*. 1986; 315:1046–51. [PubMed: 3093861]
10. Ong P, Athanasiadis A, Hill S, Vogelsberg H, Voehringer M, Sechtem U. Coronary artery spasm as a frequent cause of acute coronary syndrome: The CASPAR (Coronary Artery Spasm in Patients With Acute Coronary Syndrome) Study. *J Am Coll Cardiol*. 2008; 52:523–7. [PubMed: 18687244]

Table

Comparison of cross-sectional area and coronary blood flow change with use of low vs. high dose acetylcholine.

Dose of Acetylcholine	N	Mean ($\pm$ SD) of Responses to Acetylcholine	Mean ($\pm$ SD) of Paired Difference Between Doses	P value
Change in CBF				
Low dose ACh	50	14.9% ($\pm$ 32%)	77.3% ($\pm$ 107%)	<0.0001
High dose ACh		92.1% ($\pm$ 102%)		
Change in CSA 5mm distal to flow wire				
Low dose ACh	50	6.6% ($\pm$ 22%)	-7.2% ($\pm$ 34%)	0.14
High dose ACh		-0.57% ($\pm$ 28%)		
Change in CSA of Proximal LAD				
Low dose ACh	67	0.65% ($\pm$ 19%)	-3.8% ($\pm$ 15%)	0.05
High dose ACh		-3.1% ($\pm$ 21%)		
Change in CSA of Distal LAD				
Low dose ACh	85	-8.1% ($\pm$ 22%)	-1.3% (23%)	0.60
High dose ACh		-9.4% ($\pm$ 23%)		

ACh = acetylcholine, CBF= coronary blood flow, CSA= cross sectional area, LAD = left anterior descending artery.