ORIGINAL ARTICLE

The oral glucose tolerance test induces myocardial ischemia in healthy older adults

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Abstract

Purpose: Postprandial myocardial ischemia has been observed in frail older adults with postprandial hypotension and in patients with severe coronary artery disease, especially after high doses of carbohydrates. The impact of oral glucose on myocardial oxygen supply and demand in healthy older adults without postprandial hypotension or postprandial angina remains unexamined. We hypothesized that oral glucose would result in decreased myocardial oxygen supply relative to demand in a healthy older subject pool free of postprandial hypotension, reversible coronary risk factors and postprandial angina.

Methods: 19 older adults (mean age 71.9 ± 1.1 yr) were screened for reversible coronary risk factors. Subjects were given a standardized oral glucose load (75 g) or a sham isovolumetric unsweetened drink during two separate sessions. Indirect measures of oxygen supply (Diastolic Pressure Time Index, DPTI) and demand (Rate Pressure Product, RPP; Systolic Pressure Time Index, SPTI) were obtained from aortic arterial blood pressure waveforms. The Subendocardial Viability Ratio (SEVR, DPTI/SPTI) and DPTI/RPP were also calculated.

Results: Oral glucose resulted in decreases in both SEVR ($P=0.016$) and DPTI/RPP ($P=0.028$) in the glucose session, indicating a decrease in the relative myocardial oxygen supply to demand. This was due solely to a decrease in myocardial oxygen supply while measures of myocardial oxygen demand did not change significantly.

Conclusions: Oral glucose decreases myocardial oxygen supply in older adults free of severe coronary artery disease and without postprandial hypotension. This represents a previously unrecognized complication of oral glucose tolerance tests in healthy older adults.

Keywords: postprandial hypotension, postprandial angina, myocardial ischemia, oral glucose tolerance test

It has been long recognized that blood pressure falls after a meal^{1, 2} and after an oral glucose load² in the older adult population. In fact, all subjects demonstrate a chronotropic inodilatory response (consisting of a simultaneous increase in heart rate and vasodilatation) to oral glucose³ but frail older subjects fail to maintain blood pressure⁴ for uncertain pathophysiological reasons.⁵ Postprandial responses in older adults result in considerable morbidity and mortality^{4, 6} through injurious falls, symptoms due to presyncope⁷, cerebral ischemia⁸ and myocardial infarction.⁶

The mechanism underlying postprandial myocardial infarction in healthy older adults remains poorly explained.⁶ Postprandial decreases in blood pressure could result in serious decreases in end-organ perfusion, resulting in myocardial ischemia in the frail elderly that suffer from this condition.⁴ Postprandial angina is also well-described in patients with severe

symptomatic multi-vessel coronary disease.^{9, 10} The effects of a meal or a large oral dose of glucose on myocardial perfusion in healthy older adults without known coronary disease or postprandial hypotension remains unstudied. Given that it is the carbohydrate component that induces the greatest degree of postprandial myocardial ischemia¹⁰, this suggests that there could be a possible risk in older adults of large doses of oral sugar, such as during an oral glucose tolerance test.

In the current placebo-controlled study we examined the effect of an oral glucose load in healthy normal adults on markers of myocardial oxygen supply and demand, as determined from the aortic blood pressure waveform. We hypothesized that oral glucose would result in decreased myocardial oxygen supply relative to demand in a healthy older subject pool free of postprandial hypotension, reversible coronary risk factors and postprandial angina.

Methods

This study was approved by the Human Subjects Committee of the University of British Columbia, and all subjects gave written informed consent.

Subjects (Table 1)

Nineteen older adults (12 males, 7 female, mean age 71.9 ± 1.1 yr) were recruited ranging in age from 65 to 81 (71.9 ± 1.1). All subjects had to be > 65 yr and were excluded if they had any history of angina, myocardial infarction, stroke, hypertension, chronic pulmonary disease, diabetes, or smoking in the last 5 years. Hypertension was defined as an average blood pressure (based on three measurements) with a systolic blood pressure greater than 140 mm Hg or a diastolic blood pressure greater than 90 mm Hg. Subjects were also excluded if they took beta-blockers, calcium channel blockers, or any other agent with the potential to influence autonomic function. Entry requirements included a normal blood pressure, a normal physical exam, normal resting electrocardiogram, and a normal hematocrit, and creatinine. A fasting lipid profile was performed and all subjects had a total cholesterol < 5.2 mmol/L and a low-density lipoprotein (LDL) cho-

TABLE 1. Subject characteristics

Mean $\pm$ SEM	Mean $\pm$ SE	Range
Age (yr)	71.7 ± 1.1	65 to 81
Weight (kg)	85.9 ± 3.4	55.7 to 107.0
Height (cm)	171 ± 3	151 to 194
Body Mass Index (kg/m ²)	29.2 ± 0.7	24 to 35
Fasting Blood Glucose (mEq)	5.6 ± 0.2	4.7 to 6.9
2-hour Blood Glucose (mEq)	8.6 ± 0.6	5.1 to 10.3
Glycosylated Hemoglobin (%)	5.7 ± 0.1	5.3 to 6.4
Lipid Profile (mmol / L)		
Total Cholesterol	4.90 ± 0.17	3.82 to 5.76
LDL Cholesterol	2.96 ± 0.17	1.63 to 4.09
HDL Cholesterol	1.35 ± 0.05	1.11 to 1.85

Demographic data for all subjects is as shown as mean $\pm$ standard error. LDL, Low-density lipoprotein; HDL, High-density lipoprotein

lesterol < 3.4 mmol/L. In order to exclude subjects with diabetes, subjects were excluded from the analysis if their fasting blood glucose was > 7.0 mEq or if their 2-hour glucose tolerance test resulted in a serum glucose > 11.0 mEq.¹¹ One subject met the criteria for impaired fasting glucose (fasting blood glucose between 6.1 and 6.9 mmol/L)¹¹ and one subject met the criteria for impaired glucose tolerance (2-hour glucose between 7.8 and 11.0 mmol/L)¹¹.

Study Protocol

Each subject underwent two sessions (placebo and oral glucose session) that occurred in random order on different days. Session order was determined a priori (before any subject recruitment) by a random number generator. The maximum amount of time between study sessions was 30 days. Subjects were examined in the fasting state. All study sessions were performed with the subject supine and occurred between 9 AM and noon for all subjects to avoid bias due to circadian rhythms.¹² Each subject was supine for 45 minutes before the start of data collection in order to reach

steady state. Subjects refrained from the consumption of alcohol or caffeine or undergoing vigorous exercise for the 24 hr prior to each session. After the initial baseline data collection each subject was either given 296 mL of a standardized oral glucose load (75 g glucose) or an isovolumetric non-glucose sweetened (aspartame) drink which the subject had to drink within 5 minutes. All measures were taken with the subject in the supine position.

Data Collection and Processing:

All data were collected in sections that were 20 minutes in duration, followed by a 5 minute rest session. After the baseline collection, data were obtained from 0 to 20, 25 to 45, 50 to 70, and 75 to 95 min. Heart rate (HR) was monitored continuously using a 3 lead-electrocardiogram. Blood pressure was monitored using a Finometer (Finapres Medical Systems BV, The Netherlands). The Finometer measures beat-to-beat blood pressure noninvasively using infrared plethysmography through a finger-cuff. Data for subsequent analysis were collected in durations of 20 min followed by 5 min rest (to avoid finger discomfort). Use of the Finometer and infrared plethysmography for monitoring blood pressure changes has been well established as a noninvasive measure of beat-to-beat blood pressure¹³, has been extensively validated against intra-arterial blood pressure monitoring in older adults.¹⁴ Both the electrocardiogram signal and the blood pressure signal were sampled at 1000 Hz (Powerlab, AD Instruments) and digitized for later analysis. Using commercially available software, beat-to-beat measures of blood pressure (Beatscope, Finapres Medical Systems BV, The Netherlands) and heart rate (Powerlab, AD Instruments) were calculated.

Derived Measurements

All post-collection analysis of the data was done in a blinded fashion. Prior to all derived measurements, each 20 min segment of raw blood pressure and electrocardiogram signal was manually examined in order to exclude artifacts. Indices of myocardial oxygen supply (diastolic pressure time index, DPTI) and de-

mand (systolic pressure time index, SPTI) were measured for each heart beat using commercially available software (Beatscope, Finapres Medical Systems BV, The Netherlands). This software uses waveform filtering and level correction methods to obtain brachial blood pressure from the finger cuff data^{14, 15} and aortic pressure waveform data is determined using an arc-tangent model of aortic mechanics.^{16, 17} Rate pressure product (RPP) was calculated as the product of heart rate and systolic aortic pressure¹⁸ and has been shown to change in a linear fashion with increasing oxygen demand.¹⁹

DPTI and SPTI were defined as the areas under the diastolic and systolic portions of the aortic pressure waveform, respectively.^{20, 21} It is felt that DPTI is a marker of myocardial oxygen supply and SPTI reflects myocardial oxygen demand.^{20, 21} DPTI and SPTI were calculated for each beat of the blood pressure waveform and averaged for each 20 min of data collected. The subendocardial viability ratio (SEVR) was calculated as DPTI/SPTI and the ratio of DPTI/RPP was also calculated.^{20, 22} Both SEVR and DPTI/RPP have been established as indicators of the ratio of myocardial oxygen supply to oxygen demand in both animal^{18, 20} and human studies.^{15, 22-26} SEVR has been shown in population studies to decrease with various cardiac risk factors, and is felt to reflect the propensity for myocardial ischemia.²⁷⁻²⁹ SPTI and DPTI (and the ratios involving these values) have been used previously for the detection of changes in myocardial oxygen supply relative to oxygen demand in a variety of chronic diseases in middle-aged and older adults.^{15, 22-26} The use of peripheral blood pressure data to determine central values of SPTI and DPTI has been shown to be valid.³⁰ The markers used in the current study have been shown to have good intra-subject, inter-subject and long-term reproducibility.²³ In our laboratory both SPTI and DPTI had a one-month reproducibility of 86% and 91%, respectively (unpublished data).

Statistical Analysis

All data analysis was done in a blinded fashion using SPSS 11. Subject names and session labels (glucose

TABLE 2. Effects of oral glucose on hemodynamic and blood pressure waveform time indices

Measure	Baseline	0 min	25 min	50 min	75 min	P (time*session)
HR						
Placebo	59.4±1.8	58.9±1.6	59.8±1.8	59.4±1.8	59.5±1.7	0.007*
Glucose	59.2±1.6	62.2±1.7	63.3±1.7	62.2±1.8	62.8±1.8	
SBP						
Placebo	130.4±6.0	141.6±6.1	137.3±7.1	147.1±6.1	140.3±6.1	0.759
Glucose	137.3±3.6	145.5±6.0	147.4±6.6	149.5±4.6	147.2±4.5	
MAP						
Placebo	91.6±3.7	98.9±3.8	95.9±4.4	102.9±3.9	98.7±3.7	0.339
Glucose	94.6±2.4	92.7±5.7	98.9±3.5	99.7±2.1	98.9±2.8	
DBP						
Placebo	67.4±2.4	72.7±2.5	70.6±2.8	76.1±2.8	73.6±2.5	0.324
Glucose	69.9±2.0	71.1±2.1	71.9±2.1	73.1±1.5	72.9±2.3	
RPP						
Placebo	7660±371	8293±405	8163±473	8673±413	8347±468	0.491
Glucose	8121±306	8984±396	9328±531	9285±431	9225±441	
SPTI						
Placebo	38.4±1.8	42.0±1.8	40.8±2.1	43.7±1.8	40.9±1.6	0.435
Glucose	39.0±1.1	41.5±1.7	41.2±1.7	41.4±1.1	40.6±1.1	
DPTI						
Placebo	55.9±2.9	59.9±2.9	57.0±3.1	61.9±3.3	59.8±2.8	0.020*
Glucose	57.7±2.3	54.5±2.5	53.4±2.6	55.8±2.0	54.7±2.2	

Values shown are the effects of glucose versus placebo on heart rate (HR, beats per minute), systolic blood pressure (SBP, mm Hg), mean arterial pressure (MAP, mm Hg), diastolic blood pressure (DBP, mm Hg), rate pressure product (RPP, beats per minute X mm Hg), systolic pressure time index (SPTI, mm Hg x sec) and diastolic pressure time index (DPTI, mm Hg x sec). P values are for the effects of session X time as per 2-way analysis of variance (ANOVA).

versus placebo) were replaced by noninformative codes before performing a blinded analysis. All results are expressed as the mean ± standard error. A two factor mixed design analysis of variance (ANOVA) involving one independent measure (session) and one repeated measure (time) was used to determine the effect of glucose on HR, systolic blood pressure (SBP), mean blood pressure (MBP), diastolic blood pressure (DBP), SPTI, DPTI, RPP, SEVR, and DPTI/RPP.³¹ A value of $P \leq 0.05$ was considered significant.³¹

Results

Study Group Characteristics and Baseline Resting Measurements:

See Table 1.

Symptomatic Responses to Oral Glucose and Placebo:

None of the subjects experienced any symptoms of angina, chest pain, chest discomfort, shortness of breath, presyncope or syncope in either of the glucose or placebo sessions.

Haemodynamic Effects of Oral Glucose (Figure 1 and Table 2):

Subjects exhibited a tachycardic response in the oral glucose session that was different from the placebo session by two-way ANOVA ($F=4.436$, $P=0.002$). No difference was seen with respect to the SBP ($F=0.469$, $P=0.759$), MAP ($F=1.145$, $P=0.339$) or DBP ($F=1.177$, $P=0.324$) responses between the two sessions. The RPP, an indirect indicator of oxygen demand, did not show a significantly different response

FIGURE 1. *Tachycardic Response to Oral Glucose:* Oral glucose resulted in a mild tachycardic response when compared with the placebo session ($F=4.436$, $P=0.002$). Error bars represent standard error (confidence interval of 95%).

FIGURE 2. *Response of the Subendocardial Viability Ratio to Oral Glucose:* Older adults demonstrated a decrease in the relative myocardial oxygen supply to myocardial oxygen demand as measured by the subendocardial viability ratio (SEVR) when the two sessions were compared by two-way ANOVA ($F=3.185$, $P=0.016$). Error bars represent standard error (confidence interval of 95%).

between the glucose and placebo session ($F=0.859$, $P=0.491$).

Arterial Waveform Indices of Myocardial Oxygen Demand and Supply (Table 2):

There was no difference in the indirect measure of cardiac oxygen demand (SPTI) over time ($F=0.954$, $P=0.435$) after oral glucose as compared with the placebo session. The DPTI response demonstrated a progressive reduction in oxygen supply after oral glucose compared with the placebo session ($F=3.032$, $P=0.020$) as shown in Table 2. Similarly, both the SEVR ($F=3.185$, $P=0.016$) and the ratio of DPTI/RPP ($F=2.812$, $P=0.028$) decreased with oral glucose as compared with the placebo session. Both SEVR and DPTI/RPP became lower than placebo in the glucose session in the first 20 min post-glucose ingestion. This decrease in SEVR and DPTI/RPP persisted during the last data collected between 75 and 95 min (see Figures 1 and 2).

Impaired Fasting Glucose and Impaired Glucose Tolerance:

All statistical analyses were repeated excluding the two subjects that met the criteria for impaired fasting glucose or impaired glucose tolerance, and the results were unchanged.

Discussion

We found that the administration of oral glucose resulted in decreases in both the subendocardial viability ratio and the DPTI/RPP ratio. Oral glucose did not result in any increases in myocardial oxygen demand as measured by SPTI or RPP, but did result in a decrease in myocardial oxygen supply as measured by DPTI. This is the first time that it has been shown that oral glucose decreases myocardial oxygen supply in normal healthy older adults without postprandial hypotension or postprandial angina.

Our results are comparable with the postprandial response in middle-aged subjects with severe coronary

FIGURE 3. *Effect of Oral Glucose on DPTI/RPP:* Older adults demonstrated a decrease ($F=2.812$, $P=0.028$) in the relative myocardial oxygen supply to myocardial oxygen demand as measured by the ratio of the Diastolic Pressure Time Index (DPTI) and the Rate Pressure Product (RPP). Error bars represent standard error (confidence interval of 95%).

artery disease. Investigations of patients with documented postprandial angina demonstrated a reduction in myocardial oxygen supply (there was redistribution of blood flow from stenosed to healthy vessels) while myocardial oxygen demand as measured by the RPP remained unchanged.³² Similarly, a study of middle-aged patients with symptomatic left main or 3-vessel coronary artery disease demonstrated an earlier onset of both angina symptoms and ST-wave changes with exertion after a high-carbohydrate meal³³, indicating a decrease in myocardial oxygen supply relative to demand. While it has been well established that both balanced meals³² and high carbohydrate meals³³ result in a mild tachycardia, neither has been associated with increases in measures of oxygen demand (RPP), similar to the results of the present study. Therefore, we have shown that a high carbohydrate load can affect myocardial oxygen supply in healthy normal older subjects, not solely in patients with severe symptomatic coronary artery disease.³³

The mechanisms behind the relative drop in myocardial oxygen supply in healthy older adults remain

speculative. Frail older adults with postprandial hypotension likely suffer from postprandial ischemia and infarction through a decrease in end-organ perfusion.⁴ This mechanism is unlikely to be playing any role in our population, given that our healthy well-screened older adults were able to successfully maintain postprandial blood pressure, congruent with other studies of this healthy population.³⁴

Postprandial angina in severe coronary artery disease has several postulated mechanisms, but their applicability to our older healthy adults population remains unclear. Hyperglycemia has been shown to directly impair the availability of nitric oxide³⁵ in human subjects, and induce endothelium dysfunction³⁶⁻³⁸ in rat arterioles, possibly through the generation of superoxide-anion radicals.³⁷ The release of insulin induces both a pressor response (increased autonomic sympathetic activity and increased plasma epinephrine levels) and a depressor response (increased forearm vasodilation).³⁹ However, when severe coronary artery disease was simulated in dogs using graded coronary occlusion, it was found that hyperglycemia impaired autoregulation of the coronary vascular bed through an insulin-independent mechanism.⁴⁰ When postprandial changes in regional blood flow were examined by positron emission tomography, patients with severe coronary artery disease demonstrate coronary “steal” from stenosed vessels to healthy vessels, resulting in a regional deficit in myocardial oxygen supply.³² Although the age of our subjects constitutes a coronary risk factor, the lack of most reversible coronary risk factors (absence of hypertension, normal cholesterol, no previous cardiac or cerebrovascular events, no angina symptoms, absence of diabetes) and the fact that our subjects did not suffer from postprandial angina makes this mechanism an unlikely explanation for the changes in SEVR and DPTI/RPP observed. The exact mechanism underlying the decrease in myocardial oxygen supply in normal healthy older adults will require further investigation.

What are the clinical implications of the change in SEVR and DPTI/RPP with oral glucose? The magnitude of the drop in SEVR was approximately 15%. This change in the relative myocardial oxygen supply to demand is similar in magnitude to the difference in

SEVR between diabetic subjects and age-matched normals^{28, 29} and is slightly less than half of the difference in SEVR in a comparison between smokers and non-smokers.²⁷ Given the large impact that both smoking and diabetes have on the coronary vasculature^{41, 42} this suggests quite a large decrease in myocardial oxygen supply relative to demand, especially in a subject population relatively free of coronary risk factors and free of all exertional or postprandial angina symptoms. Obviously, the short-term decrease in SEVR with oral glucose does not have the same clinical implications as the long-term decrease with smoking and diabetes. Although there is no data in the literature to suggest that the observed change in myocardial oxygen supply with oral glucose tolerance tests results in adverse cardiovascular outcomes in healthy older adults, the presence of such a heretofore-unrecognized phenomenon suggests that vigorous physical activity soon after such an investigation should be discouraged.

Limitations

Although both SEVR and DPTI/RPP have been well established as indicators of the ratio of myocardial oxygen supply to oxygen demand in animal^{18, 20} and human studies^{15, 22-26}, there are several important limitations to their use.²⁰ Abnormal levels of hemoglobin (anemia or polycythemia)⁴³ have been shown to alter DPTI and SPTI, but given that we excluded all subjects with abnormal hemoglobin this is unlikely to be a factor. Cardiac hypertrophy has also been shown to change both SEVR and DPTI/RPP values⁴⁴, but most of these subjects would have been excluded by virtue of a normal electrocardiogram. It has been shown that DPTI only shows close correlation with more invasive measures of myocardial oxygen supply during either resting or mild inotropic stimulation.¹⁸ The results of both the present and other studies³⁹ have shown that the response to oral glucose is characterized by mild inotropy--exactly the conditions under which DPTI best reflects acute changes in myocardial oxygen supply.¹⁸ Therefore, we feel that the change in SEVR and DPTI/RPP observed in our study reflect real changes in relative myocardial oxygen

supply to demand despite the above limitations. The indirect measures of myocardial oxygen supply and demand used in our study do not allow us to make observations about regional changes in myocardial blood flow and the exact mechanisms underlying the observed response requires further investigation.

Conclusion

Oral glucose results in a decrease in the relative myocardial oxygen supply to demand in a group of older adults free of both postprandial angina and hypotension. There was no increase in myocardial oxygen demand with oral glucose indicating that the observed change in SEVR and DPTI/RPP was due to a change in myocardial oxygen supply. This represents a previously unobserved effect of oral glucose in healthy older adults and the mechanisms underlying this phenomenon require further study.

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