

# The Acute and Short-Term Effects of Polyphenols on Coronary Flow Reserve: Serial Assessments by Transthoracic Doppler Echocardiography A Phase I Prospective Clinical Trial

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## A. Background

The French Paradox, which suggests that routine consumption of wine contributes to the lower coronary artery disease (CAD)-related mortality observed in France, has been an intriguing topic for decades (1, 2). It is thought that alcohol exerts its cardiovascular benefits by increasing HDL, preventing platelet aggregation, and increasing fibrinolysis. Red wine, its polyphenolic components in particular, was discovered to provide additional protection by inhibiting LDL oxidation (3). In healthy man, red wine, when compared to white wine and vodka, was found to preferentially increase coronary flow reserve (CFR), a marker inversely proportional to the severity of CAD. (4). The cardioprotective effect of red wine, its ability to augment CFR, was attributed to the antioxidant polyphenols found in red wine. The effects of the polyphenols in patients with coronary artery disease, however, have never been studied. This study is designed to address that specific question using noninvasive transthoracic Doppler echocardiography (TTDE) to measure CFR in the left anterior descending (LAD) coronary artery (5).

## B. Hypothesis

Polyphenols, isolated from red wine, increase CFR in patients with and without coronary artery disease.

## C. Methods

### a. Study Groups

All patients, male or postmenopausal female not on hormone replacement therapy, between the ages of 40 and 70, who had undergone cardiac catheterization at CPMC between April 2000 and April 2001 are screened as possible subjects for this study.

### b. Patients without CAD

Ten age-matched subjects, without angiographic evidence of obstructive CAD are recruited for the study. Asymptomatic patients, without prior cardiac catheterization, may also enter the study. Exclusion criteria are as follow:

- 1) CAD risk factors
- 2) Coronary stenosis greater than 50% in any vessels
- 2) History or EKG evidence of old myocardial infarction (MI)
- 3) Daily red wine drinker
- 4) Vitamin preparations consumer
- 5) Active smoking within one year
- 6) History of allergy or hypersensitivity to blood, blood products or albumin

### c. Patients with CAD

Ten age-matched subjects with angiographic evidence of CAD are recruited for the study. Exclusion criteria include:

- 1) Anterior wall MI
- 2) LAD stenosis greater than 50%
- 3) Recent MI within six months
- 4) Ejection fraction less than 40%
- 5) Uncontrolled hypertension, diabetes and hypercholesterolemia
- 6) Daily red wine drinker
- 7) Vitamin preparations consumer
- 8) Active smoking within one year
- 9) History of allergy or hypersensitivity to blood, blood products or albumin
- 10) Obesity
- 11) Bronchial asthma

#### **D. Study Protocol**

This is a Phase I clinical trial to test the effect of polyphenols on CFR in healthy and CAD patients. CFR is calculated as the ratio of the peak hyperemic (induced by adenosine infusion) average peak velocity (APV) to basal APV. APV is measured directly from the spectral Doppler recordings. The average from three cardiac cycles will be used for each APV. Typically, a CFR less than 2 suggests functionally significant stenosis.

The study spans a 14-day period. During this time, the subject is to abstain from caffeine and to take 1 gram of polyphenols (dissolved in 100 ml of water) after breakfast. The initial dose will be given in the Echo lab on Day 1. Then, the CFR, both before and after consumption of the polyphenols, is recorded. On Day 15, the subject will return to the lab for the third and final CFR recording. Each subject should be fasting, except for regular medications, prior to arriving to the lab.

Venipuncture: A 10 ml sample of venous blood will be drawn from the forearm for analysis of lipids and glucose levels. One sample will be collected at each of the three measurements of CFR.

Transthoracic Doppler Echocardiography (TTDE): An 18-gauge intravenous catheter (IV) is inserted for the infusion of adenosine. The subject is placed in the left decubitus position to facilitate the search for the LAD. After the LAD coronary flow is located under color Doppler mapping guidance, the spectral Doppler tracing of the flow velocity is recorded on 1/2-inch VHS videotape for offline determination of the baseline APV. In case of inability to locate the LAD, 0.2-0.5 ml of Optison, an albumin-coated fluorocarbon, can be infused via the IV as contrast to enhance LAD flow signals (6). Next, a hyperemic state is induced by constant infusion of adenosine via the IV (0.14mg/kg/min for 2min). The hyperemic APV obtained is later divided by the initial baseline APV to give the baseline CFR. For the next portion of the study, the subject drinks the 1 gram of polyphenols (derived from 1/2 bottle of red wine) pre-dissolved in 100 ml of water. Thirty minutes after consumption, the post-polyphenol CFR is recorded. The entire TTDE study spans 40-50 minutes. The subject's heart rate, and EKG is monitored continuously. The blood pressure is also recorded at baseline, every minute during adenosine infusion, and at recovery.

#### **E. Statistical Analysis**

Using a paired t test, the acute effect of polyphenols is assessed by comparing the difference between the pre and post-polyphenol CFR data acquired on Day 1. The short-term effect of polyphenols is calculated similarly by comparing the CFR on Day 15 with the baseline CFR on Day 1. A group size of 10 has a 80% power to detect significant difference at  $p=0.05$ . The difference in lipid profiles before and after polyphenols will also be assessed using a paired t test.

#### **F. Risk and Benefits**

Polyphenols are naturally found in many food substances including tea and wine. There has been no documented side effect in previous trials. At the dose used, no significant side effect is anticipated.

TTDE is a completely noninvasive test. The use of adenosine and Optison can lead to some side effects that may be considered as risks associated with this project. The use of adenosine for the evaluation of CFR has been tested in several trials without complications (5, 7-9). The common side effects of adenosine include flushing (18%), dyspnea (12%), chest pressure (7%), nausea (3%), headache (2%), light-headedness, dizziness, arm tingling and numbness (M), sweating, palpitation, chest pain and hypotension (less than 1 %). These side effects can be quickly reversed with termination of the IV infusion due to adenosine's short half-life. The most frequently sited side effect of Optison are transient altered taste (2.5%), headache (2%), flushing (2%) and dyspnea (1%)(6).

### **G. Study Limitations**

The inability to obtain adequate echocardiographic windows and LAD flows is the major limitation of the study.

### **H. Confidentiality**

All research data will remain confidential and to be kept within the researchers' possession.

### **I. Location**

All studies will be performed in the Echocardiography Laboratory in PH 9-963.

### **J. Compensation**

The subject will be compensated with \$250.00 at the completion of the study. If a patient is disqualified due to technical difficulty in obtaining adequate Echo windows, he will receive \$50.00 for his time and participation.

### **K. Future Studies**

A prospective, randomized, double-blinded, placebo controlled clinical trial can next be conducted to assess the effects of polyphenols in CAD patients. Data will be analyzed using unpaired t test. Assuming the same standard deviation and effect, a sample size of 14 in each group is needed to give the study an 80% power to detect significant differences at  $p=0.05$ .

### **L. References**

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