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## **Endothelial Dysfunction: An Early Cardiovascular Risk Marker in Asymptomatic Obese Individuals with Prediabetes**

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### **Authors' contributions**

*AKG conceived the study, initiated the manuscript and compiled the final version for submission. ER, DLJ, AJS and WTC collected the data and participated in editing of the manuscript. WDJ directed the statistical analyses and participated in editing of the manuscript. All authors have read and agreed for publication of this manuscript.*

**Research Article**

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### **ABSTRACT**

**Aims:** To elucidate if endothelial dysfunction is an early CV risk marker in obese men and women with prediabetes.

**Study Design:** Cross-sectional study.

**Place and Duration of Study:** Clinical Research Unit, Pennington Biomedical Research Center, Baton Rouge, LA. United States.

**Methodology:** Overweight and obese status denotes an increasing adipose tissue burden which spills over into ectopic locations, including the visceral compartment, muscle and liver. Associated co-morbidities enhance cardiovascular (CV) risk. Endothelium which is the largest receptor-effector end-organ in our bodies, while responding to numerous physical and chemical stimuli maintains vascular homeostasis. Endothelial dysfunction (ED) is the initial perturbation, which precedes fatty streak known to initiate atherosclerosis: insidious process which often culminates as sudden catastrophic CV adverse event. Asymptomatic men and women; [n=42] coming in after an overnight fast had demographic, anthropometric, clinical chemistry and resting endothelial function [EF: increased test finger peripheral arterial tone (PAT) relative to control; expressed as

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relative hyperemia index (RHI)] assessments.

**Results:** Adults with desirable weight [n=12] and overweight [n=8] state, had normal fasting plasma glucose [Mean(SD)]: FPG [91.1(4.5), 94.8(5.8) mg/dL], insulin [INS, 2.3(4.4), 3.1(4.8)  $\mu$ U/ml], insulin sensitivity by homeostasis model assessment [HOMA-IR, 0.62(1.2), 0.80(1.2)] and desirable resting clinic blood pressure [SBP/DBP, 118(12)/74(5), 118(13)/76(8) mmHg]. Obese adults [n=22] had prediabetes [FPG, 106.5(3.5) mg/dL], hyperinsulinemia [INS 18.0(5.2)  $\mu$ U/ml], insulin resistance [HOMA-IR 4.59(2.3)], prehypertension [PreHTN; SBP/DBP 127(13)/81(7) mmHg] and endothelial dysfunction [ED; reduced RHI 1.7(0.3) vs. 2.4(0.3); all  $p < 0.05$ ]. Age-adjusted RHI correlated with BMI [ $r = -0.53$ ;  $p < 0.001$ ]; however, BMI-adjusted RHI was not correlated with age [ $r = -0.01$ ;  $p = 0.89$ ].

**Conclusion:** Endothelial dysfunction reflective of cardiometabolic changes in obese adults can be an early risk marker for catastrophic CV events.

*Keywords: Fasting plasma glucose; healthy adults; reverse cholesterol transport pathway; insulin resistance; body weight; relative hyperemia index.*

## ABBREVIATIONS

*ADA: American Diabetes association; BMI: body mass index; CVD: cardiovascular disease; CV: cardiovascular; DBP: diastolic blood pressure; ED: endothelial dysfunction; EF: resting endothelial function; FPG: fasting plasma glucose; HOMA-IR: homeostasis model assessment; INS: insulin; JNC 7: Joint National Commission 7; LDL-C/HDL-C: low density lipoprotein cholesterol to high density lipoprotein; NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III; PAT: peripheral arterial tone; PreDM: prediabetes; PreHTN: prehypertension; PBRC: Pennington Biomedical Research Center; RHI: relative hyperemia index; SBP: systolic blood pressure; Total-C/HDL-C: total cholesterol to high density lipoprotein cholesterol; TG/HDL-C: triglycerides to high density lipoprotein cholesterol; WC: waist circumference.*

## 1. INTRODUCTION

An overweight and obese status both denote an increasing adipose tissue burden which spills over into ectopic locations, including the visceral compartment, the muscles and the liver (Blüher, 2009). Obesity associated co-morbidities which stem from a dysfunctional adipose tissue in ectopic locations and include dysglycemia, equivocally enhance cardiovascular risk (Goossens, 2008; DeFronzo et al., 2011). While the late effects of profound dysglycemia with diabetes mellitus are a well recognized cardiovascular risk equivalent (Juutilainen et al., 2005; Whiteley et al., 2005), the early subtle fasting and/or post-meal alteration in glucose with prediabetes, likewise, also accelerate cardiovascular adverse events (DeFronzo et al., 2011; Gupta et al., 2008). The major culprit for the sudden adverse cardiovascular events: atherosclerosis, is initiated at the endothelium by a host of factors like inflammation, oxidative stress due to reactive oxygen species, exacerbated pro-coagulants and/or dysglycemia (Ross, 1990, 1999). Endothelium is the largest body receptor-effector end-organ, which while responding to numerous physical (like blood pressure) and chemical stimuli (like inflammation, glycemia, oxidative state) maintains vascular homeostasis and reflects cardiovascular health (Vita et al., 2001; Petrie et al.,

1996). Endothelial dysfunction (ED) is the initial perturbation, which precedes the fatty streak known to initiate atherosclerosis, an insidious process which often culminates as sudden catastrophic cardiovascular adverse event (Deanfield et al., 2007; Corrado et al., 2008).

Healthy adults with no chronic medical conditions, on no prescription medications (n=24) and with low cardiovascular risk, in a randomized-order, cross-over clinical trial, with a 2 week washout period, exhibited improved endothelial function (measured with flow mediated dilatation) with a diet rich in antioxidants (Franzini et al., 2012). Healthy over weight and obese volunteers with normal glucose appear to attenuate flow mediated dilation after high glycemic index carbohydrate meals (Suessenbacher et al., 2011). In matched (age, work place, physical activity, tobacco use, blood pressure, serum lipids and family history of premature coronary artery disease) male shift and no shift workers, peripheral endothelial function (peripheral arterial tone (PAT) index obtained with the EndoPAT technique) was impaired in shift workers, suggesting elevated cardiovascular risk (Lavi et al., 2009).

Endothelial function thus appears to be an exquisitely sensitive marker for a variety of populations, under various conditions. Although endothelial function has been evaluated in numerous disease conditions and perturbed with a variety of agents, there has, to our knowledge, not been a comparison of resting endothelial function in free living healthy lean, overweight and obese subjects. Using a noninvasive assessment for resting endothelial function (by measuring the peripheral arterial tone, Bonetti et al., 2004), we tested the hypothesis that fasting glucose escalation in otherwise asymptomatic obese men and women is functionally reflected as endothelial dysfunction.

## **2. MATERIALS AND METHODS**

### **2.1 Study Design**

Healthy men and women (by self report free of any chronic disease), screening for clinical trials at the Outpatient Clinic, Pennington Biomedical Research Center (PBRC), were offered an opportunity to participate in this study. Each volunteer candidate was provided with the PBRC Institutional Review Board approved informed consent, followed standard consenting procedures and signed the informed consent form.

### **2.2 Study Subjects**

These adult (n=42) non-smoking men and women between 21-75 years in age with no personal history of or ongoing prescription or non-prescription medication treatment for any chronic medical condition/s, had come in after an overnight (10 hour) fast.

### **2.3 Demographic, Anthropometric and Laboratory Measures**

Standard demographic information and anthropometric measurements including height and weight for the calculation of body mass index (BMI), and waist circumference (WC) were recorded. A set of resting vital signs and an electrocardiogram were also obtained. This was followed by a comprehensive medical history and a complete physical examination by a physician. A fasting blood draw and resting endothelial function assessment were performed next. Fasting plasma glucose and insulin (for assessment of glycemic status and calculation of insulin resistance by HOMA-IR) (Matthews et al., 1985) and fasting complete lipid profile (for assessing serum lipid sub-fractions, and calculating cardiac risk ratios) were obtained.

The cardiac risk ratios included the ratio of total cholesterol to high density lipoprotein cholesterol (Total-C/HDL-C), low density lipoprotein cholesterol to high density lipoprotein cholesterol (LDL-C/HDL-C) and triglycerides to high density lipoprotein cholesterol (TG/HDL-C).

## **2.4 Endothelial Function**

Assessment of resting endothelial function was done with the participant in fasting state, after having avoided stimulants (caffeine, tobacco, alcohol, exercise) for 12 hours, at the same fixed clock hour (range 8-10 AM), using the EndoPAT 2000 device manufactured by ITAMAR Medical®. This assessment technique has been previously validated (Bonetti et al., 2004), has been used in numerous (>250) peer reviewed publications (Carty et al., 2012; Kuvin et al., 2003) and has been in routine use in our clinical core. Briefly: subjects coming in from home, after an overnight fast and having avoided stimulants for 12-hours, were placed in a supine position for 20 minutes in a quiet room before the test. A patented single use finger sleeve was then placed on the index finger of each hand to continuously measure peripheral arterial tone. A blood pressure cuff applied to the upper arm of the non-dominant arm (test arm) was then used to occlude the brachial artery for 5 minutes. This was followed by a rapid release. The dominant arm without any manipulation served as the control. The built in, validated software integrated the data gathered from the finger sleeves of the control (undisturbed) and the test arms (during the baseline, occlusion and release phases), thus providing the relative hyperemia index (RHI) for the test arm. This flow mediated dilatation induced change in the test arm, relative to the control arm, served as the measure for endothelial function (RHI).

## **2.5 Study Subject Categorization**

Participants were categorized as being normal weight, overweight or obese (BMI <25, 25-29.9 and 30 kg/m<sup>2</sup>, respectively). Normoglycemia and prediabetes, for the purpose of cardiovascular disease (CVD) risk assessment, were defined as fasting plasma glucose less than 100 mg/dL and 100 mg/dL but <126 mg/dL, respectively (impaired fasting glucose: ADA diagnostic criteria) (ADA, 2007). The diagnosis of prehypertension [PreHTN] was based on resting (after a 5-minute rest) mean of clinic blood pressure (BP) measures (two successive assessments 1 minute apart) of systolic blood pressure (SBP) 120 but <140 and/or diastolic blood pressure (DBP) 80 but <90 mm Hg (JNC 7 criteria (Chobanian et al., 2003). The NCEP ATP III criteria for desirable anthropometric and serum chemistry concentrations were used to determine outside the desirable range measures from all subjects (NCEP ATP III, 2001).

## **2.6 Statistical Analyses**

All data analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary NC). Categorical data were summarized as counts and continuous data as means (95% confidence limits) and groups were compared using the chi-square and analysis of variance, respectively. The Bonferroni method was used to adjust p-values so that the global 0.05 level of significance is maintained for rejecting multiple null hypotheses. The logarithmic transformation was employed to analyze variables with skewed distributions and the means of the transformed data were transformed back to the original scale to obtain geometric means as final summary statistics.

### 3. RESULTS

#### 3.1 Demographic, Anthropometric and Laboratory Measures

Men and women with desirable, [n=12; Mean(SD): 23.4(1.4) kg/m<sup>2</sup>, 37(19.1) range (22-76) years] and overweight [n=8, 26.8(1.2) kg/m<sup>2</sup>, 27.4(3.9) range (23-35) years] status, on average had normal fasting plasma glucose [FPG, 91.1(64.5), 94.8(5.8) mg/dL], fasting insulin [INS, 2.3(4.4), 3.1(4.8) µU/ml], insulin sensitivity measured by homeostasis model assessment [HOMA-IR, 0.62(1.2), 0.80(1.2)] and blood pressure [SBP/DBP 118(12)/74(5), 118(13)/76(8) mm Hg] respectively. Obese adults [n=22, 35.3(4.8) kg/m<sup>2</sup>, 53.2(11.6) range (32-69) years], tended to have PreDM-FPG 106.5(3.5) mg/dL, hyperinsulinemia-INS 18.0(5.2) µU/ml, insulin resistance-HOMA-IR 4.59(2.3), PreHTN-SBP/DBP 127(13)/81(7) mm Hg, (all p<0.05) and endothelial dysfunction-reduced RHI [1.7(0.3) compared to normal weight 2.4(0.3), p<0.001]. Their respective waist circumferences were 81.1(5.5), 85.5(7.7) and 95.8(6.4) cm, respectively, (p<0.05 for both), indicating a greater than desirable WC in the obese. Since WC is a surrogate clinical measure for visceral adipose tissue (VAT), this also indicates higher VAT in the obese. The obese also had greater than desirable total cholesterol and triglycerides [206(39), 152(63) mg/dL]. Table 1 describes the means (arithmetic) and geometric means for demographic, anthropometric, laboratory and endothelial function for the participants after appropriate adjustments for age and gender or gender alone.

**Table 1. Demographic, anthropometric, laboratory and endothelial function measures: summary statistics by weight category**

Characteristic	Summary*	Desirable-weight (DW)	Over-weight (OW)	Obese (OB)	P-value		
					DW vs OW	DW vs OB	OW vs OB
Sample size	N	12	8	22			
RHI	Mean <sup>1</sup> CI	2.36 2.15-2.58	2.20 1.92-2.48	1.71 1.54-1.88	NS	0.0001	0.009
Gender (M/F)		10M/2F	5M/3F	10M/12F	NS	0.03	NS
Age (years)	Mean <sup>2</sup> CI	36.8 29.0-44.5	27.4 17.8-36.9	53.2 47.4-58.9	NS	0.004	0.0001
Glucose (mg/dL)	Mean <sup>1</sup> CI	91.1 86.6-95.6	94.8 89.0-100.5	106.2 102.7-109.7	NS	0.0001	0.004
Insulin (µU/ml)	Mean <sup>1</sup> CL	2.3 0.0-8.8	3.1 0.0-9.7	18.0 12.9-23.1	NS	0.003	0.004
Insulin (µU/ml)	Geo. Mean <sup>1</sup> CL	3.1 1.7-5.8	4.4 2.4-8.3	13.6 8.4-22.2	NS	0.003	0.02
HOMA-IR	Mean <sup>1</sup> CL	0.62 0.0-2.30	0.80 0.0-2.49	4.59 3.27-5.91	NS	0.003	0.005

**Table 1 continues.....**

HOMA-IR	Geo. Mean <sup>1</sup> CL	0.71 0.38-1.32	1.05 0.56-1.95	3.51 2.16-5.71	NS	0.001	0.01
Total-C (mg/dL)	Mean <sup>1</sup> CL	187.9 164.4-211	188.0 157.9-218	200.6 182.4-218.8	NS	NS	NS
HDL-C (mg/dL)	Mean <sup>1</sup> CL	60.4 51.4-69.3	61.4 49.9-73.0	50.3 43.3-57.2	NS	NS	NS
LDL-C (mg/dL)	Mean <sup>1</sup> CL	106.1 84.9-127.2	109.2 82.0-136.4	120.4 104.0-136.8	NS	NS	NS
TG (mg/dL)	Mean <sup>1</sup> CL	106.8 58.4-155.1	88.6 26.5-150.8	144.3 106.9-181.7	NS	NS	NS
TG (mg/dL)	Geo. Mean <sup>1</sup> CL	79.5 57.6-109.8	83.7 55.3-126.8	130.7 101.8-167.7	NS	0.02	NS
Total-C/HDL-C	Mean <sup>1</sup> CL	3.30 2.51-4.08	3.22 2.21-4.22	4.24 3.70-4.85	NS	0.05	NS
LDL-C/HDL-C	Mean <sup>1</sup> CL	1.85 1.26-2.44	1.91 1.16-2.67	2.59 2.13-3.04	NS	NS	NS
TG/HDL-C	Mean <sup>1</sup> CL	2.17 0.72-3.62	1.57 0.0-3.43	3.19 2.07-4.31	NS	NS	NS
TG/HDL-C	Geo. Mean <sup>1</sup> CL	1.12 0.89-2.05	1.40 0.82-2.39	2.68 1.94-3.71	NS	0.02	NS

\*CL + 95% confidence Interval, Geo Mean = Geometric Mean; <sup>1</sup>Adjusted for age and gender; <sup>2</sup>Adjusted for gender; M = male; F = female

### 3.2 Endothelial Function

The subjects with desirable and overweight body weight were significantly younger [36.7(19.1) and 27.4(3.9) years, respectively], than those who were obese [53.2(11.6) years]. We performed correlations between the measure for endothelial function (RHI) and confounding factors like BMI, age and gender. Age-adjusted RHI correlated with BMI [ $r=-0.53$ ,  $p<0.001$ ]; however, BMI-adjusted RHI was not associated with age [ $r=-0.01$ ,  $p=0.89$ ]. Fig. 1 depicts panels for the regression line for RHI as a function of age, (and BMI, glucose and HOMA-IR, respectively) superimposed on a scatter plot. No correlation was observed between endothelial function and age ( $r^2=0.07$ ), while endothelial function was highly correlated with body mass index, glucose and insulin sensitivity ( $r^2=0.3$ ).

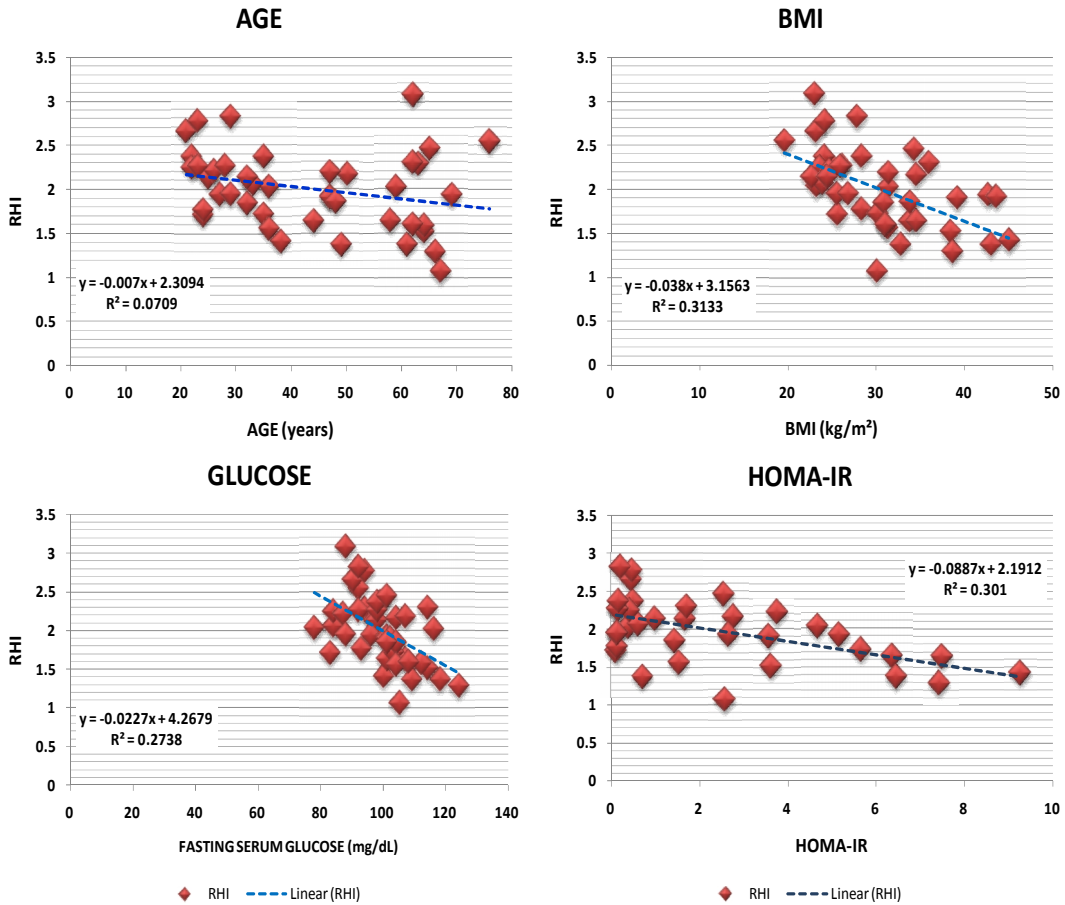


Fig. 1. Endothelial function with age, BMI, glucose and insulin resistance

#### 4. DISCUSSION

Asymptomatic obese adults with prediabetes (when compared to asymptomatic desirable weight and overweight adults with normal glucose), exhibit above the upper limits for desirable fasting plasma total cholesterol (>200mg/dL) and triglycerides (>150 mg/dL), but due to a relatively lower HDL-C display higher cardiac risk ratios (Total-C/HDL-C;  $p=0.05$  and TG/HDL-C;  $p=0.02$ ). A lower HDL-C and the elevated cardiac risk ratios are early clinical indicators for an impaired reverse cholesterol transport (RCT) pathway, a process by which cholesterol from the periphery is transported to the liver (Tall, 1998). The RCT pathway has been shown to be a sensitive indicator of the net flux (deposition vs. removal) of cholesterol homeostasis at the endothelium (Gupta et al., 1993; Tall et al., 2000). It is at the endothelium that the first fatty streaks, which over time deteriorate into atherosclerosis, have been shown to develop (Rosenfeld et al., 2000).

Impaired endothelial dysfunction is the first step in the process of atherosclerosis, even before the development of the fatty streak (Davignon, 2004; Ross 1999). These healthy obese men and women with prediabetes, prehypertension and impaired reverse cholesterol

transport pathway were assessed to have impaired resting endothelial function, which is consistent with latent early onset cardiovascular disease.

We have demonstrated a high prevalence of isolated prediabetes or prehypertension and co-existing prediabetes and prehypertension, among the otherwise healthy US adults (Gupta et al., 2011). We have also elucidated that asymptomatic obese adults with overly heightened systemic inflammation, tend to have prediabetes and prehypertension (Gupta et al., 2010a). These individuals by various conventional measures (larger waist circumference, exacerbated systemic inflammation, higher insulin resistance, elevated triglycerides, lower high-density lipoprotein cholesterol, above average cardiac risk ratios and a significant co-existence of two or three concomitant metabolic risk factors) appear to be on an accelerated pathway towards early adverse cardiovascular events (Gupta et al., 2010a, 2010b). With this study we provide a dynamic, non-invasive, functional correlate: significant resting endothelial dysfunction, as an early biomarker for pre-atherosclerosis in obese adults with prediabetes.

Excess ectopic adipose tissue is the hallmark of being overweight or obese. While the excess adipose tissue in the visceral compartment, increases overall cardiovascular morbidity and mortality, increased organ ectopic adipose burden especially in the muscle and liver appears to drive clinically recognizable adverse cardio metabolic changes (Hamdy et al., 2006). Increased inflammation (local and systemic) along with enhanced insulin resistance (liver, muscle) manifests as dysglycemia, dyslipidemia, excess reactive oxygen species, hyper-coagulability and loss of blood pressure control (Gastaldelli et al., 2010). Endothelium is the largest receptor-effector end-organ in our body, which while responding to all of the above mentioned physical and chemical stimuli, maintains vascular homeostasis. Endothelial dysfunction is the initial perturbation which precedes atherosclerosis, an insidious process which years later often culminates as a sudden catastrophic cardiovascular adverse event (Rubinshtein et al., 2010).

#### **4.1 Limitations**

Although this is a cross-sectional study, it employed an Institutional Review Board approved consent form with well characterized healthy volunteers coming in for clinical trials. All the assessments that were performed are routine and usual at this long established and well recognized research center. While the measures for inflammation, reactive oxygen species and hyper coagulability were not performed for the subjects in this study, these have been demonstrated in publications by us and others. The obese cohort was older (53.2 years; range 32-67 years) in comparison to the ideal bodyweight (36.7 years; range 21-76 years) and overweight (27.4 years; range 23-35 years) subjects. There, however, was a considerable overlap in ages between the three groups. Moreover, in healthy subjects ranging from 21-76 years, relative hyperemia index, the measure for endothelial function did not correlate with age, but did correlate with body mass index, fasting glucose and homeostasis model assessment for insulin resistance.

#### **5. CONCLUSION**

Endothelial dysfunction is a sensitive, early functional risk marker for the subtle changes in glucose concentration and blood pressure levels. This is the first step in atherosclerosis even before the appearance of a fatty streak. We demonstrate an early impairment in the reverse cholesterol transport pathway, indicating a net deposition versus removal of cholesterol at the endothelium. In asymptomatic obese men and women with predisease



conditions (prediabetes and prehypertension) when contrasted with ideal bodyweight or overweight adults with normoglycemia and normal blood pressure, resting endothelial dysfunction can be an early warning sign for future catastrophic cardiovascular adverse events.

## **COMPETING INTERESTS**

AKG, ER, DLJ, AJS, WTC and WDJ do not report any conflicts of interest. All authors have read this version and are agreeable for its publication. This work did not receive any funding.

## **CONSENT**

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

## **ETHICAL APPROVAL**

"All authors hereby declare that all human studies have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable."

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