

Metabolic syndrome in fifth grade children with acanthosis nigricans: results from the CARDIAC project

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Background: A number of cardiovascular disease (CVD) risk factors have been linked to obesity and associated negative health outcomes in children. However, no consistent definition of metabolic syndrome exists for children. In addition, research is needed to systematically examine the prevalence of metabolic syndrome in high-risk children, including those with insulin resistance. This study explores several definitions of metabolic syndrome and determines the prevalence of metabolic syndrome in a large sample of children with acanthosis nigricans (AN).

Methods: The study used results from a large-scale screening of fifth-grade students in West Virginia to explore the prevalence of metabolic syndrome among 676 male and female participants who had mild to severe AN.

Results: In this high-risk sample of students who had AN, 49% met the criteria, i.e., three risk factors including insulin resistance, high body-mass index, and elevated blood pressure or dyslipidemia, when tested for metabolic syndrome. Children with AN who were classified as obese or morbidly obese were at significantly increased odds of having metabolic syndrome.

Conclusions: Results are discussed in terms of systematically defining metabolic syndrome for high-risk children, as well as public health and clinical interventions targeting children who are overweight or obese. The presence of AN and morbid obesity might be easily observed markers for metabolic syndrome.

World J Pediatr 2009;5(1):23-30

Key words: acanthosis nigricans; children; metabolic syndrome; obesity; risk factors

Introduction

Consistent with a rise among adults,^[1] obesity in childhood is reaching epidemic proportions.^[2,3] Obesity in children and adolescents is associated with various cardiovascular disease (CVD) risk factors, including hypertension, dyslipidemia, and elevated insulin levels,^[4-6] as well as an increased risk of CVD morbidity and mortality in adulthood.^[7] The clustering of CVD risk factors has been labeled metabolic syndrome and is associated with atherosclerosis and type 2 diabetes.^[8-11] Elevated body-mass index (BMI) and certain CVD risk factors, including hyperinsulinemia, have also been linked to acanthosis nigricans (AN) in both adults^[12] and children.^[13,14]

Guidelines from the 2001 National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) estimate that 22% of US adults have metabolic syndrome.^[15] The World Health Organization (WHO) uses a set of slightly different, disease-based criteria for metabolic syndrome,^[16] but adult prevalence using this definition is similar to that found with the NCEP guidelines.^[17] There is no set definition of metabolic syndrome for children, and adult definitions may not be applicable. A recent literature review^[15] found 27 publications about metabolic syndrome in children and adolescents. In these 27 publications, 40 unique definitions of metabolic syndrome were used, generally following adaptations of the WHO, NCEP, and the European Group for the study of Insulin Resistance (EGIR) adult guidelines. In general, these studies defined the metabolic syndrome as a number of components, generally including some measures of glucose/insulin resistance or diabetes along with 2 or more additional criteria including some measures of body fat (generally BMI or waist circumference), high-

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doi:10.1007/s12519-009-0004-7

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density lipoprotein cholesterol (HDL-C), triglycerides (TRIG), and blood pressure (BP). Based on the metabolic syndrome literature in children, Cruz and Goran^[16] recommended 1) individual components should be similar to those of adults for the sake of comparison and tracking, 2) current recommendations and cut-off values need to be developed or re-evaluated particularly for waist circumference, dyslipidemia and hyperglycemia, and 3) the use of single cut-off values as opposed to multiple cut-off values based on age/gender may be easier to apply but less sensitive in identifying children at risk. Based on their review, they also recommend that because metabolic syndrome is relatively uncommon except in overweight youth, only overweight children should be screened for metabolic syndrome. Nonetheless, there remains some questions as to exactly what risk factors should be included and how many of those risk factors constitute the clustering necessary for a definition of metabolic syndrome in children.

Regardless of how metabolic syndrome is defined, there is ample evidence to demonstrate that not only metabolic syndrome components (including BMI, insulin resistance, TRIG/HDL-C, and BP) cluster across the developmental life-span,^[18] but also the clustering of CVD risk factors has severe, negative effects on children's health and later health outcomes.^[19,20] Of prominent notice is that metabolic syndrome in children is irrevocably linked to obesity^[21-23] and is generally associated with low levels of physical activity,^[24] although more research is needed on how activity and diet specifically affect metabolic syndrome outcomes.^[25] More research is also needed on metabolic syndrome prevalence in high-risk populations (such as medically-underserved communities) and other diabetic risk factors, such as AN.

AN is characterized by hyperpigmented skin and/or visible and palpable coarse "wrinkles". It most often occurs on the neck, in the axillae or groin. AN is typically graded using a point system from 1 (mild) to 4 (severe). AN is a reliable marker of hyperinsulinemia or insulin sensitivity in adults,^[12] and is related to the prevalence of type 2 diabetes in both adults and children^[26] even after controlling for BMI, age, and other diabetes risk factors. AN prevalence rates depend upon child age and race, likely related to different prevalence rates of hyperinsulinemia. For example, one study found that in children aged 7-17 who visited urban primary care practices, between 4% and 23% were diagnosed with the presence of AN,^[27] these rates being the lowest among Caucasian youths and the highest among African-American and Hispanic youths.

The relationship between AN and the various components of metabolic syndrome in children

has received mixed research results. The presence of AN is strongly associated with elevated BMI in children,^[13,27,28] with prevalence rates approximately at 66% among adolescents greater than 200% of ideal weight.^[14] It is generally believed that AN is caused by hyperinsulinemia which in turn is associated with obesity.^[29] If this connection is indeed correct, the presence of AN might be an easily observed marker for insulin resistance and metabolic syndrome in children as well. However, when the relationship among AN, hyperinsulinemia and elevated BMI is explored in children and adolescents, the results are mixed. Some studies have found AN to be an independent predictor of hyperinsulinemia,^[14,30-32] whereas others have argued that AN is not an independent predictor particularly when BMI is controlled for.^[28,33,34] Perhaps a reasonable explanation for this contentious relationship is that AN and high BMI in children are highly correlated.^[27] BMI might be the main predictor of hyperinsulinemia and AN only contributes to explaining a small portion of the variance of insulin sensitivity.^[32] This relationship is likely mediated by race and age,^[13,27] or other variables related to the degree of obesity. Regardless of this controversy, the fact remains that elevated BMI and the presence of AN are strongly associated.

Founded in 1998, the aim of the Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) project is to combat the unacceptably high prevalence of heart disease and related CVD risk factors in West Virginia.^[35,36] The CARDIAC project is unique in the study's large-scale screening design of a medically under-served, low-income, rural population. Specific to this study, the CARDIAC provided fifth-grade students with BMI, BP, and AN screening, as well as fasting lipid profiles to assess other anthropometric risk factors. If the student was found positive for AN, he or she was additionally tested for fasting insulin and glucose.

Due to the prevalence of obesity and subsequent health problems in this population, and the hypothesized link between metabolic syndrome and acanthosis nigricans, we believe that the prevalence of metabolic syndrome in this particular population would be higher than that typically found. Therefore, the objective of this study is to examine the prevalence of metabolic syndrome in fifth grade West Virginia public-school children with AN, along with the relationship of metabolic syndrome to obesity and morbidly obese BMI categories.

Methods

Based on expert recommendations,^[15,16] we followed adaptations of metabolic syndrome adult criteria for

children, and included the following criteria:

- 1) BMI \geq 85 percentile.
- 2) Insulin resistance: homeostasis model assessment (HOMA) index \geq 3.00.
- 3) Hypertension: systolic blood pressure (SBP) \geq 95 percentile or diastolic blood pressure (DBP) \geq 95 percentile.
- 4) Dyslipidemia: TRIG \geq 110 or HDL-C \leq 40.

Consistent with current literature on metabolic syndrome definitions in children and adolescents, we explored the definition of metabolic syndrome in three ways including 1) a stringent definition using all four of the above mentioned criteria, 2) three criteria which had to include BMI, insulin resistance, and one other criterion, or 3) a minimal definition of two criteria which included only BMI and insulin resistance. We explored these definitions in children who were positive for AN.

Participants

This study examined five years of CARDIAC screening (screening years 2003-2007), which included 40 361 public school children who had been screened for AN (mean age \pm standard deviation = 10.83 \pm 0.72 years, 46% girls). In this sample, 2224 (5.5%) were tested positive for AN. We limited our sample to those who tested positive for AN and had complete fasting lipid profiles (FLPs), and insulin and glucose tests. This restriction resulted in a total sample size of 676 (mean age 10.99 \pm 0.94 years, 59.2% girls). The majority of the sample were of Caucasian ethnicity ($n=544$, 80.5%) and African-Americans ($n=61$, 9%).

Assessment procedures

The study protocol was approved by the West Virginia University Institutional Review Board for the Protection of Human Subjects, and written permission for schools to participate was granted by each of the 55 county school superintendents before any assessments took place. All children enrolled in fifth grade classrooms throughout the state were eligible to participate in the CARDIAC project and, therefore, received a comprehensive consent packet that was distributed by project staff to be taken home for parental review. The consent packet included four pages outlining the purposes of the screening, screening procedures, reporting procedures, and included protocol elements such as the risks and benefits associated with participating in the screening project. An additional page was provided for parents who provided their consent as well as demographic information (e.g., family history, name, address, child gender). With the exception of the FLP results, which were incorporated later, the back of the form was used

by project staff to record the child's screening results.

Trained health professionals and health science students screened assenting children within the school setting. The CARDIAC project partnered with the West Virginia Rural Health Education Partnership, a statewide coalition of rural communities and higher education, with 13 site coordinators, 640 preceptors, and hundreds of health science students. This partnership provides the manpower for screenings, while at the same time provides health science students the opportunity to be an integral part of a community-based public health initiative. Students, local school nurses, and volunteer phlebotomists are trained by CARDIAC staff to conduct BP, AN, anthropometrical, and blood lipid testing. The comprehensive risk screening included calculation of BMI and age- and gender-corrected BMI percentile from height and body weight, resting DBP and SBP, and calculation of age-, gender- and height-corrected BP percentile, AN, and a FLP which included total cholesterol (TC), HDL-C, low-density lipoprotein cholesterol (LDL-C), and TRIG. Children's height (cm) and weight (kg) were measured using the SECA Road Rod stadiometer (78"/200 cm) and the SECA 840 Personal Digital Scale. In addition, fasting insulin and glucose tests were only available to those children who tested positive for AN due to the relative costs of glucose and insulin tests.

All participating children and their families received a comprehensive health report with their screening results between four and six weeks following the screening date. The health report provided information for each screening measure, the importance of including each measure in the screening procedure, how to interpret the screening results, and how to follow up with additional medical care or screening if needed. A toll free health hotline was also available to families who might have additional questions about the screening results of their children's medical needs.

Statistical analysis

Statistical analyses were conducted using SPSS, version 16.0, except for sensitivity and specificity calculations which were conducted by hand and checked for accuracy. In addition, age- and gender-adjusted (and height-adjusted for BP) percentiles were calculated for BMI and resting systolic and diastolic BP using HealthWatch-Pro.^[37] Variables were defined as at-risk using adaptations appropriate for children based on recommendations from the 2001 National Cholesterol Education Program Adult Treatment Panel:^[38] TC \geq 200, HDL-C \leq 40, LDL-C \geq 130, TRIG \geq 110, BP \geq 95th percentile. These cut-off values are

consistent with those of other studies using similar adaptations for children.^[39,40] The BMI categories used to describe the sample were classified according to the Center for Disease Control and Prevention (CDC) recommendations based on age- and gender-specific growth charts.^[41,42] Students were categorized into one of the following categories: underweight (<5th percentile), normal weight (BMI \geq 5th and <85th percentile), overweight (BMI \geq 85th and <95th percentile), obese (BMI \geq 95th percentile), and in some analyses morbidly obese (BMI \geq 99th percentile). Insulin resistance was calculated using the HOMA index and defined as a risk value \geq 3.00, which is generally considered as a reliable measure of insulin resistance in children.^[43]

Descriptive statistics were used to describe the number and percentage of children within BMI categories. Odds ratio estimates were used to determine significant differences between metabolic syndrome definitions (as compared to those who did not fit the definitions of metabolic syndrome) within obese and morbidly obese BMI classifications. The 95% confidence interval was used to determine statistical significance, a ratio that did not include a value of 1.00 was considered to be statistically significant. Sensitivity and specificity values greater than 0.70 were considered adequate. Odds ratio estimates were additionally used to determine significant differences between the obese and morbidly obese BMI classifications (as compared to those with BMI <95%) on the different definitions of metabolic syndrome.

Results

Consistent with our expectations that this would be a high-risk sample, 42 children (6.2%) of the CARDIAC children who were tested positive for AN, were classified as normal or underweight (BMI <85 percentile), 59 children (8.7%) were classified as overweight (BMI 85-94.99 percentile), 200 (29.6%) as obese (BMI 95-98.99 percentile), and 359 (53.1%) as morbidly obese (BMI \geq 99 percentile). Thus, 85% of the CARDIAC children with AN were either obese or morbidly obese. In addition, 60.8% of them had insulin resistance, 39.3% had hypertension, and 62.7% had dyslipidemia. Further descriptive information is given in Table 1.

The prevalence of metabolic syndrome with the entire sample, as by weight category is shown in Table 2. Our most stringent definition of metabolic syndrome (i.e., being positive for all four conditions of metabolic syndrome) was found in 19.5% of our high-risk sample, whereas our least stringent definition of metabolic syndrome (i.e., being positive for BMI \geq 85% and

insulin resistance) was found in 58.1% of the sample. The mid-level definition of metabolic syndrome (i.e., three conditions) was found in 49.0% of our sample. Fifty-seven percent of obese children and 67.9% of morbidly obese children met the criteria for three conditions of metabolic syndrome.

Next we explored the usefulness of the different definitions of metabolic syndrome. In accordance with recommendations of some investigators who advocate testing for metabolic syndrome in those who are at highest risk (e.g., those who are obese or morbidly obese), we examined metabolic syndrome as a measurement proxy for BMI (Table 3). Odds ratio estimates were significant for each weight category at all levels of defining metabolic syndrome compared to those who did not meet the criteria for metabolic syndrome; all odds ratios were significantly different from 1.00. However, all the confidence intervals between the three definitions overlapped; thus, no definition was found to be significantly different from the other definitions. Specificity and sensitivity indicators were then examined for further clarity. Based on these results, the three-condition definition of metabolic syndrome (BMI \geq 85%, insulin resistance, plus one other condition) had the best trade-off between sensitivity and specificity for those with morbid obesity; whereas the two-condition definition of metabolic syndrome (BMI \geq 85% and insulin resistance) had the best trade-off between sensitivity and specificity for those children with obesity. The most stringent definition had excellent specificity, i.e., distinguished all of those who did not have metabolic syndrome, but results from Table 3 demonstrate that having a stringent definition of metabolic syndrome alone was not sensitive enough to catch all of those with a BMI \geq 95% or BMI \geq 99%. The more sparse definition of metabolic syndrome, i.e., BMI \geq 85% and insulin resistance, had generally excellent sensitivity, i.e., distinguished all of those who have metabolic syndrome, but was not as specific as the three-condition definition. However, caution should be advised for the three-condition

Table 1. Number and percent of participants with acanthosis nigricans who also had each risk factor ($n=676$)

	Number	Valid percent
Insulin resistance (HOMA index \geq 3.00)	411	60.8
Hypertension (SBP or DBP \geq 95 percentile)	266	39.3
Dyslipidemia (TRIG \geq 110 or HDL-C \leq 40)	424	62.7
TRIG \geq 110	353	52.2
HDL-C \leq 40	249	36.8
BMI \geq 85 percentile	618	91.4
BMI \geq 95 percentile	559	82.7
BMI \geq 99 percentile	359	53.1

Table 2. Numbers and percentages of students with acanthosis nigricans who fulfilled different criteria for metabolic syndrome ($n=676$)

	All four conditions of metabolic syndrome (four conditions total)	BMI $\geq 85\%$ + HOMA ≥ 3.00 + one other condition (three conditions total)	BMI $\geq 85\%$ + HOMA ≥ 3.00 (two conditions total)
Number (percent) of students	132 (19.5%)	331 (49.0%)	393 (58.1%)
BMI $\geq 95\%$	131 (19.4%)	318 (47.0%)	373 (55.2%)
Percent within BMI $\geq 95\%$	23.4%	56.9%	66.7%
BMI $\geq 99\%$	68 (10.1%)	152 (22.5%)	176 (26.0%)
Percent within BMI $\geq 99\%$	30.4%	67.9%	78.6%

Table 3. Odds ratios for obese and morbidly obese BMI classifications and different criteria for metabolic syndrome (as compared to those who did not meet the metabolic syndrome criteria)

	All four conditions of metabolic syndrome (four conditions total)	BMI $\geq 85\%$ + HOMA ≥ 3.00 + one other condition (three conditions total)	BMI $\geq 85\%$ + HOMA ≥ 3.00 (two conditions total)
Obese (BMI $\geq 95\%$)			
Odds ratio (95% CI)	30.61 (4.23, 221.56)*	8.93 (4.87, 16.37)*	8.12 (4.83, 13.66)*
Sensitivity	0.23 (0.20, 0.27)	0.57 (0.53, 0.61)	0.67 (0.63, 0.71)
Specificity	0.99 (0.94, 0.99)*	0.87 (0.79, 0.93)*	0.80 (0.71, 0.87)*
Morbidly obese (BMI $\geq 99\%$)			
Odds ratio (95% CI)	4.42 (2.79, 7.03)*	3.83 (2.77, 5.30)*	3.92 (2.82, 5.44)*
Sensitivity	0.30 (0.25, 0.35)	0.65 (0.60, 0.70)	0.74 (0.69, 0.78)*
Specificity	0.91 (0.87, 0.94)*	0.67 (0.62, 0.73)	0.58 (0.52, 0.63)

Sensitivity denotes the true positive rate and specificity denotes the true negative rate. *: Odds ratios that did not cross one were considered statistically significant. Sensitivity and specificity greater than 0.70 were considered statistically significant.

Table 4. Odds ratios for the criteria for metabolic syndrome and obese and morbidly obese BMI classifications (as compared to those with BMI <95 percentile)

Metabolic syndrome	Obese (BMI 95%-98.99%)	Morbidly obese (BMI $\geq 99\%$)
All four conditions		
Odds ratio (95% CI)	14.29 (1.91, 107.03)*	41.90 (5.77, 304.29)*
Sensitivity	0.96 (0.78, 0.99)*	0.99 (0.94, 0.99)*
Specificity	0.36 (0.31, 0.42)	0.28 (0.24, 0.33)
Three conditions		
Odds ratio (95% CI)	5.00 (2.62, 9.55)*	12.52 (6.73, 23.30)*
Sensitivity	0.87 (0.78, 0.92)*	0.95 (0.91, 0.97)*
Specificity	0.43 (0.36, 0.50)	0.41 (0.35, 0.48)
Two conditions		
Odds ratio (95% CI)	4.66 (2.65, 8.18)*	11.59 (6.73, 19.95)*
Sensitivity	0.84 (0.76, 0.90)*	0.93 (0.89, 0.96)*
Specificity	0.47 (0.39, 0.54)	0.47 (0.39, 0.54)

Sensitivity denotes the true positive rate and specificity denotes the true negative rate. $n=301$ for obese and $<95\%$ BMI categories. $n=460$ for morbidly obese and $<95\%$ BMI categories. *: Odds ratios that did not cross one were considered statistically significant. Sensitivity and specificity greater than 0.70 were considered statistically significant.

definition as the sensitivity and specificity are slightly lower than generally advised (0.70), which might result in elevated error rates.

Finally, we examined the usefulness of selecting only those AN positive children who were morbidly obese or obese (as compared to those with BMI $<95\%$) as a measurement proxy for the different definitions of metabolic syndrome (Table 4). Results from Table 4

show that having AN and being classified as obese or morbidly obese significantly increases children's odds of having metabolic syndrome with high sensitivity; however, specificity remains low.

Discussion

Currently, a set definition of metabolic syndrome in children does not exist. Due to the increasing problem of obesity in children, and links between obesity and number of risk factors for CVD, metabolic syndrome needs to be systematically examined. Our results support research claiming that applying a definition of metabolic syndrome based on all of the criteria consistent with adult guidelines is likely too stringent. In our high-risk population (children positive for AN), only 19.5% were classified as having metabolic syndrome when stringently defined.

Our data suggest that a less stringent definition of metabolic syndrome is likely to give a more accurate picture: 49.0% of those classified with AN had three conditions including BMI, insulin resistance, and one other criterion. Fifty-eight percent of those with AN had two conditions including BMI and insulin resistance. Whereas the two-condition definition might be too lenient, these numbers emphasize the real possibility that many high-risk children in WV likely have metabolic syndrome.

It was an additional goal of this study to explore the

relationship between different definitions of metabolic syndrome and obesity in our high-risk sample. Consistent with other research, obesity classification was related to metabolic syndrome. This finding is consistent with other research,^[22] suggesting that the prevalence of metabolic syndrome is increased with severity of obesity (reaching 50% of severely obese children in non high-risk sample). Our data show that metabolic syndrome is best used as a proxy for BMI when metabolic syndrome is defined as the three (for morbidly obese children) or two (for obese children) condition criteria, giving the best trade-off between sensitivity and specificity.

Finally, we examined the usefulness of selecting only those AN positive children who were morbidly obese or obese (as compared to those with BMI <95%) as a measurement proxy for the different definitions of metabolic syndrome. Results showed that morbidly obese children were 42 times as likely as those with a BMI <95% to have all four conditions of metabolic syndrome, and nearly 12 times as likely to have at least two conditions of metabolic syndrome.

While we suggest that these data indicate that the three risk factor condition gives the most relevant results for metabolic syndrome, there are some limitations that need to be taken into account. Our data are based on cross-sectional screening, making predictive inferences difficult. Future research should strive to determine the longitudinal risk relationship between different definitions of metabolic syndrome and outcomes such as cardiovascular disease and type 2 diabetes mellitus. Data of insulin resistance were only collected on participants with AN; thus, comparisons could not be drawn between this group and children without AN. This study does not include multiple measurements of CVD risk factors to ascertain the best measurements used; for example, waist circumference (consistent with adult definitions) would inform different results. In addition, these data specifically targeted high-risk students with AN, which makes results difficult to compare to other studies. These screening data encompass a population specific to WV and may not be applicable to other states. Finally, there may have been some systematic measurement error that we could not statistically control for difficulties in accurately assessing the presence of AN despite extensive training. It has also been suggested that, due to the high percentage of students who are overweight or obese in our screening data and due to an active consent process, there might be some selection bias. However, examinations of demographics among our larger sample (all CARDIAC children not just those with AN) revealed only two

statistically significant differences; i.e., parents of participating children are more likely to have health insurance and participating children are more likely to have regular health care providers.^[44] This suggests that our active consent process might be under representing rather than over representing the health problems of WV children.

Our data suggest that pre-teens with AN, and in particular those students with BMI greater than or equal to the 99th percentile, should specifically be referred to early intervention programs, particularly public health and clinical interventions, that can target and improve the abnormalities associated with metabolic syndrome in children. These results suggest the need for further research to determine the effectiveness of using the presence of AN as an easily observed marker for this definition of metabolic syndrome. We also suggest that, although this study has limitations, many of the limitations are strengths when considering WV's unique characteristics and problems with childhood (and adult) obesity. Other locales with different demographic or health care characteristics, both in the US and other countries, may result in more or less pronounced prevalence of metabolic syndrome. However, we hope that these findings highlight the high prevalence of metabolic syndrome in our rural, medically-underserved population, and efforts be made to prevent and treat metabolic syndrome in these children.

Acknowledgements

We thank all of those associated with the CARDIAC project for their assistance in collecting and preparing the data for this manuscript. We also acknowledge the West Virginia Rural Health Education Partnership Coordinators who conduct many of the CARDIAC screenings. Finally, we would like to thank the children and families who participated in the screening project.

Funding: The CARDIAC project is mutually funded by the WV Bureau of Public Health, the Claude Worthington Benedum Foundation, and the Robert Wood Johnson Foundation.

Ethical approval: The study protocol was approved by the West Virginia University Institutional Review Board for the Protection of Human Subjects, and written permission for schools to participate was granted by the school superintendents.

Competing interest: None.

Contributors: Ice CL provided statistical analyses and prepared the manuscript. Murphy E assisted in manuscript preparation and CARDIAC interventions. Minor VE assisted in writing medical descriptions and is the co-founder and associate director of the CARDIAC project in addition to being the project coordinator of CARDIAC surveillance. Neal WA edited the manuscript and is the founder and director of the CARDIAC project.

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Received June 30, 2008

Accepted after revision November 10, 2008