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TESI DI DOTTORATO

Cardiac Markers of Preclinical Disease in Adolescents with the Metabolic Syndrome: The Strong Heart Study.

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Introduction

The metabolic syndrome (MetS) is characterized by clusters of metabolic risk factors (1), which might increase cardiovascular (CV) risk beyond what is predicted by single components (2-5). The MetS is associated with increased risk of cardiac mortality also in the absence of diabetes and independently of arterial hypertension (6-8). It has been previously reported that MetS is related to abnormal left ventricular (LV) geometry and function in non diabetic adults with high prevalence of obesity, and that increased blood pressure is the component of MetS most strongly associated with markers of pre-clinical CV disease even in the absence of traditionally defined hypertension (9).

The rising prevalence of obesity and hypertension among children and adolescents is now a major health concern with both epidemiological and economic implications (9-11). We have already reported that LV hypertrophy can be found in 30 percent of obese adolescents at mean age<18 years, despite a low prevalence of hypertension (13). And it has also been observed that obese adolescents often have MetS, suggesting that the increased LV

mass might be a response not only to increased hemodynamic load but also to possible neurohormonal effects of clustered metabolic factors influencing LV growth (13). To date, little information is available on whether the presence of MetS is associated with significant cardiac abnormalities in adolescents, or whether the impact of MetS on cardiac phenotype is independent of the single components of the syndrome. Accordingly the present analysis has been designed to study the CV effects of MetS in adolescents from a population-based sample.

METHODS

Study population.

The Strong Heart Study (SHS) is a longitudinal study of CV risk factors and prevalent and incident CV disease in American Indian communities in Arizona, Oklahoma, and North/South Dakota. As previously described (14), 4,549 members of 13 tribes age 45 to 74 years were recruited from defined sampling frames (overall participation rate>61%) for baseline examination in July 1989 to January 1992. The 4th SHS examination (13), conducted in 2001 to 2003, enrolled members of large three-generation families that included a total of 460 adolescent participants (age<20 years, mean 17.3±1.5 years; 53.2% female). After excluding participants with ADA-defined diabetes (N=10) and/or significant valvular disease (N=4), 446 adolescents (14-20 years of age) were included in the present analysis.

Physical examination and laboratory testing.

The examination included medical history, computerized electrocardiogram, measurement of brachial blood pressure, fasting glucose

and insulin, glycated hemoglobin, lipid and lipoprotein levels, and a 2-h, 75-g glucose tolerance test (15). Blood pressure was measured as recommended by the Fifth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (15). Laboratory tests and anthropometric measures (weight, height, and waist circumferences) were taken as previously reported (16). Fat-free mass and adipose body mass were estimated by the use of an RJL impedance meter (model B14101, RJL Equipment Co., Clinton Township, Missouri) and equations based on total body water validated in the American Indian population (17).

Definition of obesity, hypertension, and metabolic syndrome.

As recommended, 95th percentiles of body mass index (BMI)-for-age charts developed by the National Center for Health Statistics (18), were used to define obesity. Guidelines correction was applied (19) so that the limit separating overweight and obesity did not exceed a BMI of 30 kg/m^2.

For adolescents up to 18 years of age, hypertension was assessed by using age-, gender-, and height specific partition values according to the

Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (20). For adolescents over 18 years of age, recommendations from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure were followed (21). MetS was preliminary identified using adult ATPIII (22) definition (with partition value of 100mg/dL for fasting glucose), and then applying the ATPIII modified definition developed by Jolliffe and Janssen for adolescents (23). Accordingly, diagnosis of MetS was made when at least three of the five components of the syndrome (increased waist circumference, high blood pressure, high triglycerides, high fasting glucose and low HDL-C) were present, applying age- and gender- specific partition values (see Appendix 1).

Echocardiography.

Echocardiograms were performed by expert sonographers, according to standardized methods and reviewed off-line by two independent readers (MC, RBD) using computerized review station with digitizing tablet and monitor

screen overlay for calibration and performance of needed measurements (25). Left ventricular internal dimension, septal and posterior wall thickness were measured at end-diastole and end-systole by American Society of Echocardiography recommendations on three cycles (26,27). As previously described (28), left atrial (LA) anteroposterior diameter was measured in long-axis view in end-systole, and aortic root diameter was measured at level of the sinus of Valsalva in end-diastole. Since normal LA size in children increases with growth (29), LA diameter was normalized for body height to account for differences in body maturation. Partition values for the definition of LA dilatation were 2.23 cm/m in boys and 2.11 cm/m in girls, representing age-, gender- and ethnic-specific 95^{th} percentiles derived in a subgroup of 92 normal adolescent participants. A necropsy-validated formula was used to calculate LV mass (30), which was normalized for body height in meters to the allometric power of 2.7, which linearizes the relations between LV mass and height (i.e. body growth) and identifies the impact of excess body weight (31). Partition values for the definition of LV hypertrophy were 40.75 $g/m^{2.7}$ for boys and 38.49 $g/m^{2.7}$ for girls, representing previously reported age-,

gender- and ethnic-specific cut-off points (13). To evaluate the concentricity of LV geometry, myocardial thickness (wall + septum) was divided by LV minor axis (diameter) to generate a relative wall thickness (RWT). Because normal RWT increases with age (32), its raw value was adjusted for age (RWTa) by previously reported equations (32). LV systolic performance was assessed by LV ejection fraction, and by LV shortening measured at the mid-wall level (midwall shortening) (33). Stroke volume was determined by an invasively-validated Doppler method (34) and used to calculate cardiac output.

Left ventricular diastolic properties were assessed by Doppler interrogation of transmitral peak early (E) and late (A) velocities and by measurement of the deceleration time of peak E velocity. Isovolumic relaxation time was measured between mitral valve closure and aortic valve opening.

Statistical analysis.

Statistical analyses were performed using SPSS 12.0.0 (SPSS Inc., Chicago, Illinois) software. Data are presented as mean±SD for continuous variables and as proportions for categorical variables. Descriptive statistics were based on normal or χ^2 distributions. Population was dichotomized according to the presence of MetS. Comparison of demographics and laboratory tests was performed by independent t-test. Comparison of cardiac geometry and function was performed by analysis of covariance (ANCOVA) correcting for differences in age, gender, heart rate and body height (considered as an estimate of body maturation at a given age and gender). In addition, binary logistic multiple regression modeling was performed, controlling for confounders (age and gender), with the specific aim of determining whether clustered MetS confers additional and independent risk of presenting markers of preclinical cardiovascular disease (i.e. LV hypertrophy and LA dilatation) as compared to single risk factors. Covariates were entered in the model using a hierarchical enter procedure in the following order: 1) age and gender; 2) presence of obesity; 3) systolic blood pressure 4) single metabolic components of MetS (including fasting glucose,

HDL-C and Triglycerides); 5) presence of MetS. Alternative models were also performed replacing obesity with waist circumference, and fasting glucose with either plasma insulin or HOMA-index.

Results

Distribution of Risk Factors.

Adult ATPIII criteria for the definition of MetS, identified 71 participants with the syndrome (15.9% of population, 53.5% girls). According to the adolescent criteria, MetS was instead present in 111 participants (24.9% of population, 55.9% girls; Kappa Score between criteria=0.66) with similar prevalence in women (26.3%) and men (23.3%; p=ns). The most prevalent component of the MetS in the studied population was increased waist circumference (54.3%), followed by low HDL cholesterol (46.4%), high blood pressure (30.3%), increased serum triglycerides (27.8%), and increased fasting glucose (2.5%). Of the 446 participants, 102 (22.9%) had no component of the MetS, 116 (26%) had only one risk factor, 117 (26.2%)

had two clustered risk factors, 77 (17.3%) had three, 32 (7.2%) had four, and only 2 participants (0.4%) showed clustered presence of all five.

Clinical and laboratory characteristics of the population by MetS class.

Participants with Mets had similar age, gender distribution and heart rate, compared to non-MetS (Table 1). Comparison of antropometrics, body composition and laboratory tests identified the expected unfavorable phenotype in the MetS participants as opposed to non-MetS, characterized by higher fat and fat-free body mass, higher BMI and higher blood pressure values. Prevalences of obesity and hypertension were also significantly higher in MetS participants (both $p<0.001$). Similar prevalence of smoking habit and alcohol drinking were observed between the two groups (p=ns).

Metabolic characteristics of the study population are shown in table 2. As expected, participants with the MetS showed worse glicemic profile (higher fasting glucose, insulin, and HOMA index), worse lipid profile (higher total cholesterol, LDL cholesterol and triglycerides and lower HDL cholesterol), and

higher values of plasma fibrinogen, with similar plasma creatinine levels between groups.

Cardiac Geometric and Functional Characteristics by MetS class.

After adjustment for age, gender, height and heart rate, LV chamber size (diameter), aortic root and left atrial diameter were greater in Mets adolescents compared to non-MetS (Table 3). LV mass and RWTa were also significantly higher in MetS participants (all $p<0.0001$). Accordingly, prevalence of LA dilatation (63.1 vs 21.9 %) and LV hypertrophy (43.2 vs 11.7%) were markedly higher in the presence of MetS (both $p<0.001$). Stroke volume and cardiac output were increased in MetS participants, due to enlarged LV chamber size. Ejection fraction was similar in the two groups; in contrast mid-wall shortening was lower in MetS than in non-MetS adolescents. Finally, MetS adolescents exhibited significantly lower transmitral E/A ratio and slightly longer deceleration time of E velocity, but no significant difference in isovolumic relaxation time. Results were confirmed also when applying adult ATPIII criteria for the definition of MetS (data not shown).

Predictors of Left Artial Dilatation and Left Ventricular Hypertrophy

In univariate binary logistic regression, LA dilatation was predicted mainly by the presence of obesity (OR=26.26; CI=10.33-66.77; p<0.001) and higher systolic blood pressure (OR=1.04; CI=1.02-1.06; p<0.001), and then by higher triglycerides (OR=1.01; CI=1.00-1.02; p<0.01) and male gender (OR=1.65; CI=1.47-1.77; p<0.01), and negatively by higher HDL cholesterol (OR=0.96; CI=0.94-0.98: p<0.01), with no significant impact of fasting glucose or age (p=ns). As shown in Table 4a, in hierarchical multivariate regression, male gender (OR=3.32; CI=1.80-6.13), obesity (OR=4.17; CI=2.62-6.66; both p<0.001) and systolic blood pressure (OR=1.03; CI=1.01-1.06; p<0.01), still predicted LA dilatation, with no significant impact of age and single metabolic components of the MetS. In contrast, a significant effect was observed for clustered MetS, which conferred an additional 2.3 fold increased risk of LA dilatation (OR=2.33; CI=1.14-4.73; p=0.020), independently of demographics and single components of the syndrome.

Similar results were also observed for LV hypertrophy. In univariate binary logistic analysis, LV hypertrophy was predicted mainly by the presence of obesity (OR=12.10; CI=4.29-33.99; p<0.001) and higher systolic blood pressure (OR=1.03; CI=1.01-1.06; p<0.001), and then by higher triglycerides (OR=1.02; CI=1.01-1.04; p<0.05), and older age (OR=1.19; CI=1.01-1.41; p<0.05), and negatively by higher HDL cholesterol (OR=0.96; CI=0.94-0.99: p<0.01), with no significant impact of fasting glucose or gender (p=ns). As shown in Table 4b, in hierarchical multivariate regression, obesity (OR=2.38; CI=1.41-4.04) and systolic blood pressure (OR=1.04; CI=1.01-1.07) still predicted LV hypertrophy (both p<0.01), with no significant impact of age, gender and single metabolic components of MetS. In contrast, a significant effect was observed for clustered MetS, which conferred an additional 2.6 fold increased risk of LV hypertrophy (OR=2.57; CI=1.21-5.44; p=0.014), independently of demographics and single components of the syndrome. When adult ATPIII definition was applied, no additional independent risk was found for MetS for either LA dilatation or LV hypertrophy.

Alternative models replacing obesity with waist circumference, and fasting glucose with either HOMA-index or insulin did not significantly change the reported results.

Discussion

The present study provides the first evidence of a strong impact of MetS on cardiac phenotype in an unselected population of adolescents applying criteria for the definition of MetS specifically designed for this age range (23, 35-37). To our knowledge, only one recent report has attempted to identify possible independent impact of MetS on cardiovascular phenotype in adolescents and has failed to shown a significant association between MetS and intima-media thickness (38).

In a previous report that analyzed data of the NHANES study, a highly representative study of the United States, Goodman et al. described a 4.2% prevalence of the MetS in the general adolescent US population, with a markedly higher prevalence, reaching 19.5%, in overweight/obese adolescents (35), when applying adolescent-ATPIII criteria. The evidence that MetS is associated with unfavorable cadiovascular phenotype and unfavorable clinical outcome also in the absence of overt hypertension and/or diabetes supports the hypothesis that MetS might represent a distinct medical condition, at least from an epidemiological point of view (39). The high

prevalence of MetS in adults and adolescents has increased medical attention on the syndrome (11-12, 35-37), also considering the increased burden of obesity and related metabolic complications found in epidemiological surveys in different countries (40).

In the present study, adolescents with MetS exhibit worrisome abnormalities of cardiac geometry and function, including aortic root and LA dilatation, a trend towards concentric LV geometry and a remarkable high prevalence of LV hypertrophy, present in over 40% of MetS adolescents. Furthermore, we found significant impairment in LV wall mechanics and diastolic function (as shown by reduced mitral E/A ratio and prolonged E wave deceleration time). Interestingly, the negative effect of MetS on cardiac phenotype was independent of the effect of the single risk factors defining the syndrome, consistent with the notion that also in adolescents, clustering of risk factors in MetS might be predictive of cardiovascular disease above and beyond the risk associated with its single components.

Other authors have reported independent correlations among body size, metabolic abnormalities and LV mass growth, in children and adolescents

(41-42), but MetS has not yet been considered as a pathologic entity in this setting. The Bogalusa Heart Study reported an association between insulin and LV mass growth in obese adolescent girls, also independently of blood pressure (43). In the present study multivariate modelling showed that the risk of LV hypertrophy and LA dilatation associated with MetS is additional to what caused by obesity and blood pressure, while single metabolic risk factors are associated to markers of cardiovascular disease only in univariate regression.

It has been recently reported that the prevalence of the MetS varies widely in overweight adolescents depending on the proposed definition (44) and that the instability in the diagnosis of the MetS in adolescents (caused by both gain and loss of the diagnosis) might imply a reduced clinical utility of the syndrome (45). In the present study we have tested, age- and gender-specific criteria for the definition MetS, proposed with the specific aim of minimizing the instability of MetS diagnosis in the adolescent age range (23,45). Remarkably, compared to adult definition of MetS, the proposed adolescent criteria were able to identify a strong, independent and additional

impact of the Mets on cardiac markers of preclinical disease. In addition, although follow-up data for the adolescents included in the present analysis are not yet available, the significant alteration of CV phenotype identified in the presence of MetS strongly suggests that the diagnosis of MetS even obtained from a single clinical exam should encourage prompt lifestyle risk-reducing interventions in otherwise healthy adolescents.

Study limitations

The present study has been performed on American Indians, a specific ethnic group on which adolescent-ATPIII criteria where not specifically tested in NHANES. However, in our sample of adolescents with high prevalence of obesity, MetS was present in 25% of the population, substantially similar to prevalence reported in the NHANES in the obese/overweight US adolescent population (35). As suggested by current guidelines for the definition of MetS, we have applied waist circumference partition values to identify the presence of abdominal obesity, although increasing evidence suggests that a direct measure of intra-abdominal fat should be preferred. However, it has been

recently shown in a population-based sample of boys and girls that waist circumference offers a feasible alternative to the MRI estimation of intra-abdominal adipose tissue (46). Eventually, determination of Tanner stage was not performed, and the relation between body maturation and cardiac geometry/function could not be investigated; of note, both LV mass and LA diameter were indexed by height, a method that has been previously shown to correct for body growth (30); in addition all participants were ≥14 years of age and, therefore, the possibility of significant prevalence of pre-pubertal participants was minimized.

Conclusions

In conclusion, in our cohort of adolescents, MetS was associated with a strikingly high prevalence of LV hypertrophy and LA dilatation, associated with increased aortic root diameter and impairment in both systolic and diastolic LV performance. The impact of MetS on cardiac markers of preclinical disease appears to be independent and additional to obesity, blood pressure and single metabolic abnormalities suggesting that, also in

adolescents, the risk associated with MetS might be beyond what is predicted by single risk factors. Our findings, paired with previous studies reporting a steep increase in the prevalence of obesity and associated metabolic abnormalities in children and young adults, suggest that presence of MetS in adolescents should prompt aggressive lifestyle modifications to reduce the increasing burden of future CV disease.

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Table 1. Clinical Characteristics of Study Participants with and without Metabolic Syndrome.

	No MetS (N=335)	***Mets (N=111)***	***P***
Age (years)	*17.3±1.4*	*17.6±1.5*	*0.072*
Women (%)	*51.9*	*55.9*	*0.511*
Fat free mass (Kg)	*50.3±10.6*	*60.1±14.6*	*<0.0001*
Adipose mass (Kg)	*23.8±14.2*	*45.8±18.8*	*<0.0001*
Body mass index (Kg/m^2)	*25.9±6.4*	*37.0±8.1*	*<0.0001*
Systolic BP (mmHg)	*111.2±10.4*	*120.5±11.4*	*<0.0001*
Diastolic BP (mmHg)	*67.8±9.1*	*75.2±10.0*	*<0.0001*
Heart rate (bpm')	*64.7±10.5*	*65.6±11.9*	*0.312*
Obesity (%)	*37.1*	*92.8*	*<0.0001*
Hypertension (%)	*3.6*	*16.2*	*<0.0001*
Cigarette Smoking (%)	*22.1*	*20.3*	*0.312*
Alcohol drinking (%)	*55.2*	*46.8*	*0.133*

Table 2. Metabolic Characteristics of Study Participants with and without Metabolic Syndrome.

	No MetS (N=335)	***Mets (N=111)***	***P***
Fasting glucose (mg/dl)	*89.2±8.4*	*94.2±8.0*	*<0.0001*
Plasma insulin (IU/ml)	*13.2±10.7*	*28.7±37.2*	*<0.0001*
Log HOMA-index	*0.36±0.30*	*0.70±0.27*	*<0.0001*
Triglycerides (mg/dL)	*93.6±43.1*	*178.0±72.3*	*<0.0001*
Total cholesterol (mg/dL)	*149.7±26.7*	*168.6±27.7*	*<0.0001*
LDL cholesterol (mg/dL)	*79.9±23.1*	*95.1±25.0*	*<0.0001*
HDL cholesterol (mg/dL)	*51.3±12.1*	*40.1±10.1*	*<0.0001*
Fibrinogen (mg/dL)	*341.6±76.4*	*393.3±73.0*	*<0.0001*
Creatinine (mg/dL)	*0.79±0.15*	*0.77±0.13*	*0.179*

Table 3. Cardiac Characteristics of Study Participants with and without Metabolic Syndrome.

	No MetS (N=335)	***Mets (N=111)***	***P***
Left ventricular diameter (cm)	*5.21±0.39*	*5.38±0.44*	*0.001*
Aortic root (cm)	*3.03±0.25*	*3.14±0.31*	*0.001*
Left atrial diameter (cm)	3.31±0.41	3.79±0.35	<0.0001
Left atrial dilatation (%)	21.9	63.1	<0.0001
LV mass (g)	132.3±31.2	157.7±39.1	<0.0001
LV mass index ($g/m^{2.7}$)	*32.0±6.1*	*38.0±7.2*	*<0.0001*
LV hypertrophy (%)	*10.8*	*41.8*	*<0.0001*
Age adj. relative wall thickness	*0.27±0.04*	*0.29±0.04*	*<0.0001*
Stroke volume (mL)	*78.1±14.2*	*84.9±14.6*	*<0.0001*
Cardiac output (L/min)	*5.02±0.99*	*5.47±1.01*	*<0.0001*
Ejection fraction (%)	*59.9±4.4*	*59.7±4.8*	*0.612*
Mid-wall shortening (%)	*18.9±1.5*	*18.3±1.7*	*0.001*
Mitral E/A ratio	*1.86±0.45*	*1.71±0.40*	*0.001*
E deceleration time (msec)	*206.5±36.2*	*215.9±36.7*	*0.022*
IVRT (msec)	*71.9±8.5*	*79.9±9.1*	*0.318*

ANCOVA with Sidak's adjusted means for age, gender, heart rate and height.

Table 4a. Hierarchical multivariate regression for Left Atrial Dilatation.

		P	OR	95.0% C.I.	
				Lower	Upper
Step 1	**Age (years)**	.058	.842	.706	1.006
	Gender (M)	**.001**	**3.322**	**1.800**	**6.130**
Step 2	**Presence of Obesity**	**.001**	**4.174**	**2.617**	**6.657**
Step 3	**Systolic Blood Pressure (mmHg)**	**.015**	**1.032**	**1.006**	**1.059**
Step 4	**HDL-C (mg/dL)**	.171	.985	.965	1.006
	Fasting Glucose (mg/dL)	.644	.992	.960	1.025
	Tryglycerides (mg/dL)	.557	.999	.994	1.003
Step 5	**MetS**	**.020**	**2.326**	**1.143**	**4.734**

OR= odds ratio, C.I = confidence interval.

Table 4b. Hierarchical multivariate regression for Left Ventricular Hypertrophy.

		P	OR	95.0% C.I.	
				Lower	Upper
Step 1	**Age (years)**	.368	1.093	.900	1.328
	Gender (M)	.518	1.241	.645	2.386
Step 2	**Presence of Obesity**	**.001**	**2.385**	**1.408**	**4.041**
Step 3	**Systolic Blood Pressure (mmHg)**	**.006**	**1.041**	**1.012**	**1.071**
Step 4	**HDL-C (mg/dL)**	.407	.990	.966	1.014
	Fasting Glucose (mg/dL)	.262	.980	.945	1.016
	Tryglycerides (mg/dL)	.946	1.000	.995	1.004
Step 5	**MetS**	**.014**	**2.565**	**1.210**	**5.438**

OR= odds ratio, C.I = confidence interval.

Appendix 1

a. Partition Values for the Definition of Metabolic Syndrome using modified ATPIII criteria.

Gender	*Waist (cm)*	*SBP (mmHg) or*	*DBP (mmHg)*	*HDL-C (mmol/L)*	*Triglycerides (mmol/L)*	*Glucose (mmol/L)*
Boys	*102*	*130*	*85*	*1.0*	*1.7*	*5.6*
Girls	*88*	*130*	*85*	*1.3*	*1.7*	*5.6*

b. Partition Values for the Definition of Metabolic Syndrome in Adolescent Boys and Girls (according to Jolliffe and Janssen).

BOYS						
AGE (years)	*Waist (cm)*	*SBP (mmHg) or*	*DBP (mmHg)*	*HDL-C (mmol/L)*	*Triglycerides (mmol/L)*	*Glucose (mmol/L)*
12	*94.2*	*121*	*76*	*1.13*	*1.44*	*5.6*
13	*96.2*	*123*	*78*	*1.10*	*1.48*	*5.6*
14	*98.0*	*125*	*79*	*1.07*	*1.52*	*5.6*
15	*99.5*	*126*	*81*	*1.04*	*1.56*	*5.6*
16	*100.6*	*128*	*82*	*1.03*	*1.59*	*5.6*
17	*101.4*	*128*	*83*	*1.03*	*1.62*	*5.6*
18	*101.8*	*129*	*84*	*1.03*	*1.65*	*5.6*
19	*102.0*	*130*	*85*	*1.03*	*1.68*	*5.6*
20	*102.0*	*130*	*85*	*1.03*	*1.70*	*5.6*

GIRLS						
AGE (years)	*Waist (cm)*	*SBP (mmHg) or*	*DBP (mmHg)*	*HDL-C (mmol/L)*	*Triglycerides (mmol/L)*	*Glucose (mmol/L)*
12	*79.5*	*121*	*80*	*1.25*	*1.60*	*5.6*
13	*81.3*	*123*	*82*	*1.25*	*1.53*	*5.6*
14	*82.9*	*125*	*83*	*1.26*	*1.46*	*5.6*
15	*84.2*	*126*	*84*	*1.26*	*1.44*	*5.6*
16	*85.2*	*128*	*84*	*1.27*	*1.46*	*5.6*
17	*86.2*	*128*	*85*	*1.27*	*1.53*	*5.6*
18	*87.0*	*129*	*85*	*1.28*	*1.61*	*5.6*
19	*87.7*	*130*	*85*	*1.29*	*1.68*	*5.6*
20	*88.0*	*130*	*85*	*1.30*	*1.70*	*5.6*