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## Early Progression of the Autonomic Dysfunction Observed in Pediatric Type 1 Diabetes Mellitus

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**Abstract**—To focus on early cardiac and vascular autonomic dysfunction that might complicate type 1 diabetes mellitus in children, we planned an observational, cross-sectional study in a population of 93 young patients, under insulin treatment, subdivided in 2 age subgroups (children:  $11.5 \pm 0.4$  years; adolescents:  $19.3 \pm 0.2$  years). Time and frequency domain analysis of RR interval and systolic arterial pressure variability provided quantitative indices of the sympatho-vagal balance regulating the heart period, of the gain of cardiac baroreflex, and of the sympathetic vasomotor control. Sixty-eight children of comparable age served as a reference group. At rest, systolic arterial pressure and the power of its low-frequency component were greater in patients than in controls, particularly in children ( $14.0 \pm 2.3$  versus  $3.1 \pm 0.3$  mm Hg<sup>2</sup>). Moreover, baroreflex gain was significantly reduced in both subgroups of patients. Standing induced similar changes in the autonomic profiles of controls and patients. A repeat study after 1 year showed a progression in low-frequency oscillations of arterial pressure and a shift toward low frequency in RR variability. Data in young patients with type 1 diabetes mellitus show a significant increase in arterial pressure, a reduced gain of the baroreflex regulation of the heart period, and an increase of the low-frequency component of systolic arterial pressure variability, suggestive of simultaneous impairment of vagal cardiac control and increases of sympathetic vasomotor regulation. A repeat study after 1 year shows a further increase of sympathetic cardiac and vascular modulation, suggesting early progression of the autonomic dysfunction. (*Hypertension*. 2009;54:987-994.)

**Key Words:** autonomic nervous system ■ baroreflex ■ children ■ diabetes mellitus ■ sympathetic nervous system ■ vasculature

Cardiovascular autonomic neuropathy is a severe, frequently underrecognized complication of diabetes mellitus, of which the presence approximately doubles the all-cause mortality risk.<sup>1</sup> Traditionally, clinical markers of diabetic cardiovascular autonomic neuropathy are based on a battery of tests<sup>2</sup> requiring the active collaboration of patients; however, new methods have been described to assess the integrity of autonomic function, such as spectral analysis of RR interval variability<sup>3,4</sup> or baroreflex sensitivity (BRS)<sup>5,6</sup>, that can be obtained automatically from computer analysis of noninvasive ECG and arterial pressure wave recordings, without needing the active participation of patients. These latter methods have been considered more sensitive<sup>7</sup> than traditional tests and, thus, could be particularly suited to assess initial changes in autonomic performance, particularly in young patients affected by type 1 diabetes mellitus (T1DM).

In adults, available data suggest that, with time, cardiovascular autonomic neuropathy<sup>8</sup> becomes characterized by reduced vagal control of the sinoatrial node, as expressed by reduced RR variance and baroreflex gain, together with impaired vascular regulation, as exemplified by reduced

orthostatic tolerance (as a consequence of standing induced hypotension).<sup>1</sup> Recently, an increase in the low-frequency (LF) power of systolic (S) AP variability has also been reported, in addition to BRS impairment in young adults affected by T1DM.<sup>9</sup>

Given the relatively abrupt beginning of the disease, we reasoned that children with T1DM might represent a unique window on initial, preclinical autonomic disturbances and harbor the potential to furnish suggestions on possible mechanisms. These are likely to be multifactorial and to an extent reversible<sup>9</sup> and assessable well before any anatomic (mal)adaptation has taken place.

Thus, we planned the following observational study in a population of children and adolescents affected by T1DM, all under insulin treatment, to assess initial changes in cardiac and vascular autonomic regulation and their early progression over time by repeating observations in patients after 1 year. Children with T1DM show early and progressive alterations in indices of cardiac vagal regulation that are reduced and indices of sympathetic cardiovascular markers that are increased.

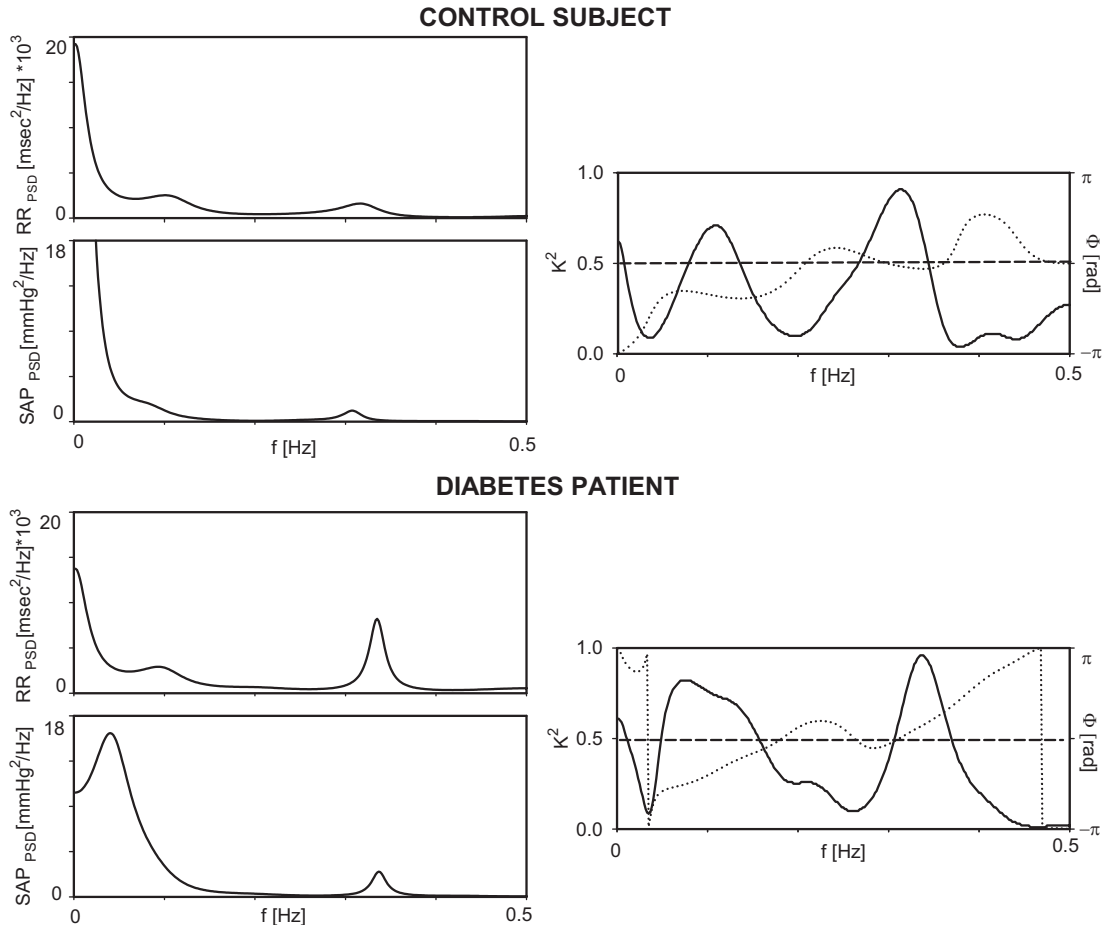
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**Figure 1.** Left, Example of the spectral profiles of a control subject (top) and a T1DM patient (bottom), for both RR interval variability (top tracings) and SAP variability (SAP; bottom tracings). Note the greater amplitude of the LF component of SAP variability ( $LF_{SAP}$ ). The center frequency of  $LF_{SAP}$  is also slightly lower in T1DM patients ( $0.081 \pm 0.002$  Hz) vs controls ( $0.090 \pm 0.002$  Hz;  $P < 0.05$ ; power=0.5). Right, Example of the bispectral analysis of the same signals: coherence functions between RR variability and SAP variability are represented with heavy lines and clearly indicate elevated values ( $>0.5$ ) in the correspondence of both the LF and HF components. The observed LF center frequency is lower ( $P < 0.01$ ; power=0.78) in the case of the diabetic group vs controls. The phase functions (dotted lines) are also presented for completeness and show a similar upsloping trend in both diabetics and controls.

## Methods

### Patient Selection

This study involved 93 consecutive young subjects affected by T1DM (mean overall age:  $15.6 \pm 0.4$  years; 54 boys; 39 girls; body mass index [BMI]:  $21.4 \pm 0.6$ ) who referred to our institutional diabetic pediatric clinic for management. Insulin treatment was optimized according to clinical evaluation. In all of the patients, the presence of concomitant diseases (other than diabetes mellitus), pharmacological treatment (other than insulin), or cigarette smoking, alcohol, or food abuse was excluded by standard medical examination, inclusive of a neurological examination, and usual clinical tests.

A group of 68 additional healthy children and adolescents (mean age:  $15.9 \pm 0.6$  years; 44 boys; 66 girls; BMI:  $20.1 \pm 0.6$ ) provided control values. Thirty-two T1DM patients (age:  $14.6 \pm 0.7$  years) were assessed a second time after  $366 \pm 18$  days to glean time-dependent dynamics of autonomic dysfunction.

The protocol of the study followed the principles of the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects (revised November 13, 2001, effective December 13, 2001) and was approved by the institutional ethics committee. All of the patients gave their informed consent to participate.

### Autonomic Evaluation

The day of the study, all of the subjects arrived at the laboratory  $\geq 2$  hours after a light breakfast, avoiding caffeinated beverages and

heavy physical exercise in the preceding 24 hours. Recordings were always performed between 10:00 AM and 12:00 PM to account for circadian variations.

After a preliminary 10-minute rest period in a supine position, allowing for stabilization, blood pressure waveforms, ECG, and respiratory activity were continuously recorded over a 10-minute baseline and over a subsequent 7-minute period of active standing. The ECG (CM5) and the respiratory signal were recorded in all of the subjects with a 2-way radiotelemetry system (Marazza), whereas AP waveform was continuously assessed noninvasively by a Finapres device (Finapres, Ohmeda), the accuracy of which, in tracking beat-by-beat blood pressure changes, has been documented previously.<sup>10</sup> Data were acquired with a personal computer using an acquisition rate of 250 samples per channel per second.

As described previously,<sup>11,12</sup> from the simultaneous autoregressive spectral analysis of the RR interval and SAP variability, a series of indices indirectly reflecting autonomic cardiovascular modulation were derived. The power of RR interval spectral oscillations was quantified considering, respectively, the component in the LF (0.03 to 0.14 Hz) and in the high-frequency (HF; 0.15 to 0.35 Hz) regions. The power of LF spectral components was normalized according to the formula  $P_{LF\nu} = [(P_{LF[ms]}^2) / (\text{VAR}_{RR[ms]}^2 - \text{VLF}_{[ms]}^2)] * 100$ , where  $P_{LF\nu}$  indicates LF powers in normalized units (nu), VAR indicates total variance, and VLF indicates very LF component ( $<0.03$  Hz). Similar normalization was performed for HF components. LF/HF of the RR interval variability power ratio was also computed. Within

**Table 1. Descriptive Statistics of Patients and Controls, Subdivided According to Age, Split Into Children and Adolescents**

Variable	Children		Adolescents	
	Controls	Diabetes 1	Controls	T1DM
n	32	46	36	47
Age, y	11.2±0.5	11.5±0.4	20.2±0.3†	19.3±0.2†
Sex, male/female, %	47/53	67/33	39/61	49/51
BMI, kg/m <sup>2</sup>	15.9±1.6	19.3±0.4*	21.6±0.3†	23.6±0.5*†
SAP, mm Hg	104.0±2.2	111.4±2.1*	111.7±1.6	122.2±1.8*†
DAP, mm Hg	61.8±1.4	60.7±1.0	63.8±1.9	67.5±1.0†
HR, bpm	72.5±1.6	71.9±1.7	66.7±1.9	63.5±1.8†
Diabetes duration, mo	NA	61±6	NA	127±9†
Creatinine, mg/dL	NA	0.56±0.02	NA	0.74±0.02
AER, mg/24 h	NA	22.3±6.5	NA	10.7±2.2
Hb1Ac, %	NA	8.2±0.2	NA	8.3±0.1

DAP indicates diastolic arterial pressure; HR, heart rate; AER, albumin excretion rate; NA, not applicable. Significance tested with 1-way ANOVA, followed by Tukey contrast, is indicated ( $\chi^2$  test used for sex).

\*Data were significantly different from the control group.

†Data were significantly different from the children group ( $P<0.05$ ).

the sympathovagal model, the balance between LF and HF components of RR variability (particularly using nu) reflects the changing dynamics of, respectively, sympathetic and vagal oscillatory modulation of the SA node. The power of SAP spectral oscillations was also quantified considering the component in the LF region (0.33 to 0.14 Hz) in absolute units,<sup>12</sup> as an index of sympathetic arterial blood pressure modulation.

The sensitivity of arterial baroreflex control of the RR interval was assessed by a frequency domain method ( $\alpha$  index: average of the square root of the ratio between the RR interval and SAP Spectral powers in the LF and HF regions),<sup>6</sup> and with a time domain method (baroreflex slope).<sup>5</sup> Baroreflex gain reflects tonic vagal cardiac regulation.

In all of the subjects included in the study, respiratory rate coincided with the HF component of RR variability. Bivariate spectral analysis was used to verify that the squared coherence value between RR and SAP variabilities at the LF and HF frequencies always exceeded 0.5 (Figure 1).

## Statistics

Data are presented in the text, figures, and tables as average±SEM. Controls and T1DM patients were both divided in 2 subgroups by median split of age and labeled as children and adolescents. This label was nominally maintained for simplicity even if the latter subgroup contained 8% of subjects >20 years of age, who had been enrolled and treated in the pediatric outpatient clinic since the inception of T1DM. Statistical evaluation included *t* test, Mann-Whitney, and one-way ANOVA, followed by Tukey contrasts, simple and multiple correlation,  $\chi^2$  test, and discriminant analysis, as appropriate. Computations were performed with a commercial statistical package considering observed  $\alpha$  levels of  $\geq 0.05$  and  $\beta$  levels of  $\geq 0.8$  (SPSS version 17.0, SPSS, Inc).

## Results

Table 1 shows average values for examined children and adolescents (respectively,  $\approx 11$  and 20 years of age) in both the T1DM and control groups. It is apparent that BMI and AP are more elevated in subjects with T1DM, in both age classes, with a differential in AP between patients and controls of >10 mm Hg in the adolescent group. In our study, only

**Table 2. Descriptive Statistics of Autonomic Variables in Patients and Controls, Subdivided According to Age, Split Into Children and Adolescents**

Variable	Children		Adolescents	
	Controls	T1DM	Controls	T1DM
RR, ms	839±18	853±18	922±24	971±26†
VAR <sub>RR</sub> , ms <sup>2</sup>	7122±1192	5866±680	4551±612	3856±482
LF <sub>RR</sub> , ms <sup>2</sup>	2418±488	1491±225	982±137†	1049±133
LF <sub>RR</sub> , nu	45.9±2.5	35.6±2.8	38.1±3.2	46.8±2.8†
HF <sub>RR</sub> , ms <sup>2</sup>	2662±482	2957±443	2056±434	1468±269†
HF <sub>RR</sub> , nu	47.5±2.7	57.0±2.7	56.7±3.2	48.6±2.8
LF/HF <sub>RR</sub>	1.2±0.2	1.1±0.3	1.1±0.2	1.7±0.3
SAP, mm Hg	103±3	113±3	108±2	128±4*†
VAR <sub>SAP</sub> , mm Hg	29±9	57±10	29±5	42±7
LF <sub>SAP</sub> , mm Hg	3.1±0.3	14.0±2.3*	3.6±0.8	8.9±1.3
HF <sub>SAP</sub> , mm Hg	2.0±0.2	3.9±0.5	1.6±0.2	2.9±0.5
Respiratory frequency, Hz	0.30±0.01	0.27±0.01	0.26±0.01	0.28±0.01
$\alpha$ index, ms/mm Hg	34±3	20±1*	27±2	18±1*
BRS, ms/mm Hg	32±4	18±2*	31±3	17±2*

RR indicates RR interval; VAR, variance; LF, LF component; HF, HF component; LF/HF, ratio between LF and HF components; SAP, SAP from Finapres. Significance was tested with 1-way ANOVA, followed by Tukey contrasts ( $\chi^2$  test used for sex).

\*Data were significantly different from control group.

†Data were significantly different from the children group ( $P<0.05$ ).

T1DM patients underwent blood drawing for ethical and organizational reasons, and, thus, creatinine and glycosylated hemoglobin values are provided only for patients in Table 1, with the latter ones being somewhat suboptimal in spite of intensive treatment. Signs of clinical diabetic autonomic neuropathy were absent, in particular, upon standing there were no signs of orthostatic intolerance, although a slightly significant drop in SAP was observed in subjects with T1DM.

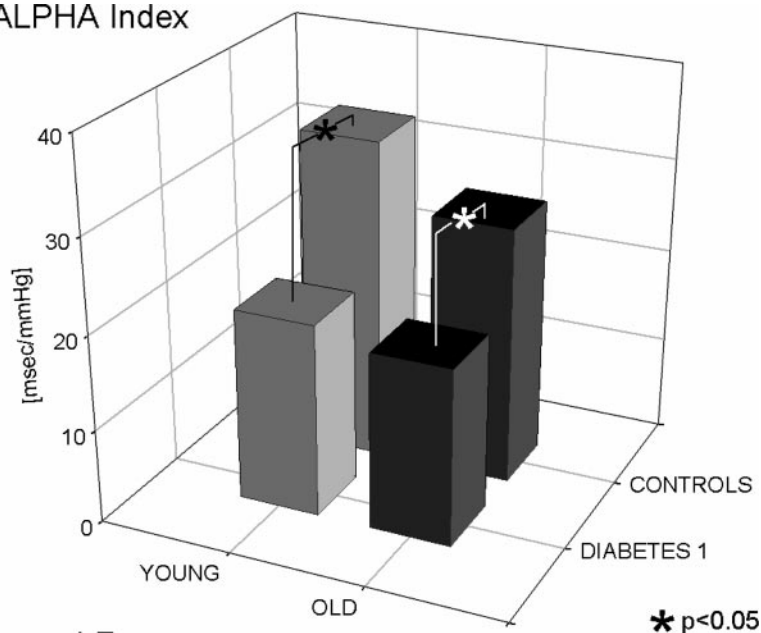
## Autonomic Analysis

As shown in Figure 1, spectral analysis of RR and SAP variability showed in both patients and controls the presence of LF and HF components, with a high coherence between corresponding oscillations. RR variance was similar in all of the subgroups (Table 2), whereas LF and HF oscillations in absolute values tended to be greater in controls, and LF in nu was more elevated in diabetic adolescents than in controls. In T1DM patients, notably, the power of LF<sub>SAP</sub> was greater than in controls, particularly in the children subgroup (see Figure 2, bottom). Conversely, baroreflex gain was significantly reduced (Figure 2, top) in both age subgroups.

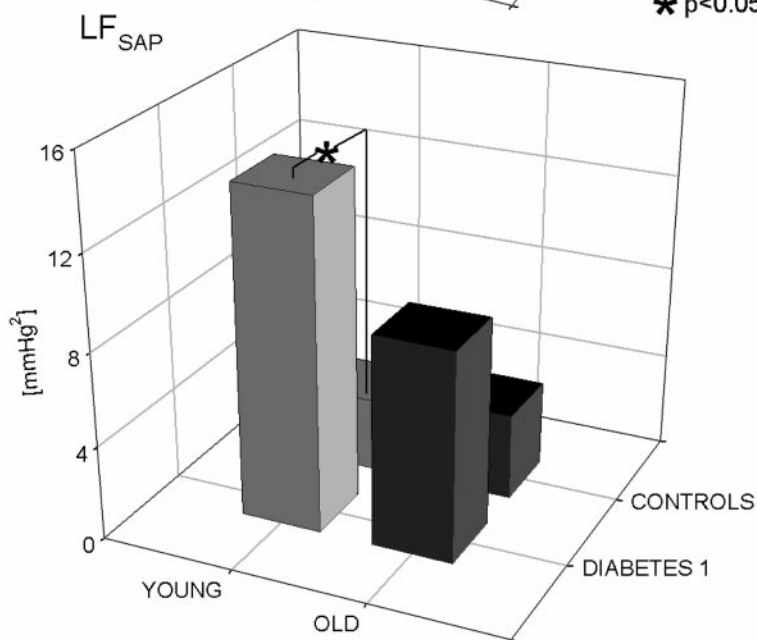
## Effects of Standing Up

Table 3 shows changes in hemodynamic and autonomic variables induced by active standing. As expected, the majority of indices of RR and SAP variability followed a pattern of sympathetic activation and vagal withdrawal. This was characterized essentially, like in adults, by a reduction of the RR interval, an increase in LF<sub>RR</sub> (nu; and concomitant reduction of HF), and a diminution of the  $\alpha$  index (as well as of BRS). These changes were similar in subjects with T1DM

## ALPHA Index



**Figure 2.** Top, Differences in a frequency domain index of baroreflex gain ( $\alpha$  index) in children (YOUNG) and adolescent (OLD) subgroups, according to the presence or absence (CONTROLS) of T1DM (DIABETES 1). Notice the significantly smaller baroreflex gain in both children and adolescents affected by diabetes. Bottom, Differences in a frequency domain index of sympathetic vasomotor regulation in children (YOUNG) and adolescent (OLD) subgroups, according to the presence or absence (CONTROLS) of T1DM (DIABETES 1). Notice the greater power of  $LF_{SAP}$  in diabetic children.



and in controls. The only notable difference was a small, yet significant, standing-induced reduction in SAP in patients, more apparent in adolescents, that was never accompanied by signs of orthostatic intolerance.

### Correlations

Table 4 shows a matrix of simple correlations between major autonomic variables and clinical indicators. It is apparent that baroreflex gain and LF oscillations of AP are independent from disease indicators, such as duration of disease, or creatinine or glycosylated hemoglobin values (similar results apply specifically to the children subgroup). RR-related variables (in particular,  $LF_{RR}$  in nu), also independent from glycosylated hemoglobin, correlate with creatinine (except for  $HF_{RR}$ ) and disease duration. Age appears instead correlated with SAP and RR and inversely with  $\alpha$  index. Plasma

creatinine is related to disease duration. In addition, BRS essentially replicates results obtained with the  $\alpha$  index (data not shown).

Stepwise regression analysis confirmed the importance of age and the lack of significant influence of metabolic parameters on major autonomic indices (significant models: age versus RR total power; disease duration and SAP versus both RR LF and HF in nu). Discriminant analysis, which is used primarily to predict membership in  $\geq 2$  mutually exclusive groups, was also performed here simply to assess the integrated capacity of hemodynamic and autonomic variables to discriminate between controls and T1DM patients. Notably, the use of all of the available information produced a percentage recognition ( $\approx 80\%$ ) that was only slightly superior to what could be obtained ( $\approx 70\%$ ) with only 3 significant variables: SAP,  $\alpha$  index, and  $LF_{SAP}$ .

**Table 3. Stand Induced Changes in Autonomic Variables in Patients and Controls, Subdivided According to Age, Split Into Children and Adolescents**

Variable	Children		Adolescents	
	Controls	T1DM	Controls	T1DM
RR, ms	-163±13*	-205±14*	-195±18*	-245±18*
VAR <sub>RR</sub> , ms <sup>2</sup>	-4046±1131*	-3628±578*	-1583±637*	-807±501†
LF <sub>RR</sub> , ms <sup>2</sup>	-1136±490*	-174±213	690±226*†	679±226*
LF <sub>RR</sub> , nu	30.9±3.1*	43.0±3.0*	40.4±2.9*	38.8±3.5*
HF <sub>RR</sub> , ms <sup>2</sup>	-2186±456*	-2681±433*	-1743±412*	-1239±268*†
HF <sub>RR</sub> , nu	-30.3±3.1*	-40.9±2.8*	-39.1±2.6*	-37.8±3.4*
LF/HF <sub>RR</sub>	13.5±6.3*	12.8±2.9*	11.3±2.6*	17.7±2.8*
SAP, mm Hg	2.0±2.7	-7.5±3.0*	-2.4±4.5	-11.3±4.2*
VAR <sub>SAP</sub> , mm Hg <sup>2</sup>	6.6±9.7	20.5±11.0	29.7±8.1*	39.3±12.9*
LF <sub>SAP</sub> , mm Hg <sup>2</sup>	9.0±3.7*	22.9±7.0*	20.8±3.7*	29.1±7.0*
HF <sub>SAP</sub> , mm Hg <sup>2</sup>	1.0±0.5	3.0±1.0*	3.8±0.9*	3.3±0.8*
Respiratory frequency, Hz	-0.03±0.02	-0.10±0.05	-0.03±0.03	0.07±0.04
α index, ms/mm Hg	-18±3*	-13±1*	-17±2*	-11±1*
BRS, ms/mm Hg	-15.9±4.4*	-10.2±1.8*	-20.2±2.8*	-10.3±1.8*

RR indicates RR interval; VAR, variance; LF, LF component; HF, HF component; LF/HF, ratio between LF and HF components; SAP, SAP from Finapres; BRS, baroreflex slope. Significance was tested with 1-way ANOVA, followed by Tukey contrasts ( $\chi^2$  test used for sex). Note that data represent average±SEM changes (standing–resting) of values computed individually (subject by subject), both for absolute and relative indices (in nu or LF/HF).

\*Data show the significant difference between rest and standing.

†Data were significantly different from the children group ( $P<0.05$ ).

## Repeat Studies

In 32 patients with T1DM, a repeat study was performed  $\approx$ 1 year after the first study to assess early progression of autonomic dysfunction. Essential findings are shown in Figure 3: a small significant increase in heart rate should be contrasted with a clear shift of RR variability spectral components toward a sympathetic profile (increase of LFnu and decrease of HFnu), combined with a small nonsignificant reduction in baroreflex gain and a marked further rise in LF<sub>SAP</sub>.

## Discussion

The novel findings of this investigation are that T1DM is associated with marked alterations of indirect autonomic indices, such as a reduced baroreflex gain and an increase in slow frequency oscillations of SAP already in a pediatric population. Furthermore, longitudinal observations underscore the progressive nature of these autonomic alterations that also regard the balance<sup>11</sup> between LF and HF oscillations of RR variability.

Clinically, the present study addresses pediatric T1DM in a relative wide age range to better examine the influence of length of the disease. Disease duration appeared correlated with creatinine levels, yet within the normal range, potentially also reflecting its link with patient age and BMI ( $P<0.001$ ); disease duration was not, however, correlated with vascular autonomic alterations (or albumin excretion rate), but was linked to autonomic indices of cardiac LF and HF balance. The short duration of the disease in our pediatric population may also be reflected in the lack of signs of clinical complications, such as a very small RR variance or orthostatic hypotension. Indeed, in our patient group there

was a slightly smaller RR variance and a relatively clear, although limited, drop in SAP on standing.

Autonomic analysis at baseline disclosed a clear reduction in baroreflex gain in children and adolescents affected by T1DM, considering both time domain and frequency domain indices, extending recent observations in adults to this younger age.<sup>9</sup> This suggests that the impairment of the cardiac baroreflex might represent a sensitive, early quantitative indicator of diabetic autonomic impairment of the cardiac vagal regulation in children as well. Baroreflex gain is also selectively reduced in older patients affected by disturbances of glycemic metabolism, such as the metabolic syndrome,<sup>13</sup> or in patients with type 2 diabetes mellitus<sup>14</sup> and their offspring.<sup>15</sup> In this study, the repeat observations after 1 year suggest that the reduction in baroreflex gain is also accompanied by signs of progressive increase of sympathetic modulation to AP and of the autonomic balance to the sinoatrial node. A similar combination has been reported in prehypertensive adults<sup>16</sup> and children,<sup>17</sup> confirming that pediatric diabetes mellitus might represent an early window on altered cardiovascular autonomic control.

Considering that exogenous insulin increases efferent sympathetic activity<sup>18</sup> and provokes a shift of the balance between LF and HF components of RR variability toward LF,<sup>19</sup> we might hypothesize a mechanistic role for therapeutic insulin in the observed alterations in autonomic indices, in addition to the possible direct effects of endothelial dysfunction,<sup>20,21</sup> oxidative stress,<sup>22,23</sup> Rho/Rho-kinase pathway,<sup>24</sup> arginase mechanisms,<sup>20</sup> and adhesion molecules in initiating sympatho-sympathetic positive feedback reflexes<sup>25</sup> from the arterial sites and thereby reducing baroreflex gain. As a

**Table 4. Nonparametric Correlation Between Major Autonomic Variables and Disease Severity Indicators**

Variable	$\alpha$ Index	SAP	LF <sub>SAP</sub>	RR	LF <sub>RR</sub>	HF <sub>RR</sub>	HbA1c	Creatinine	Disease Duration	Age
$\alpha$ index	1.000									
SAP	-0.471*	1.000								
	0.000*									
LF <sub>SAP</sub>	-0.463*	0.276*	1.000							
	0.000*	0.000*								
RR	0.335*	0.115	0.119	1.000						
	0.000*	0.146	0.131							
LF <sub>RR</sub>	-0.275*	0.157*	0.139	-0.145	1.000					
	0.000*	0.047*	0.078	0.067						
HF <sub>RR</sub>	0.293*	-0.135	-0.142	0.220*	-0.967*	1.00				
	0.000*	0.089	0.073	0.005*	0.000*					
HbA1c	0.065	-0.092	-0.129	0.088	0.036	0.017	1.000			
	0.558	0.408	0.241	0.426	0.744	0.881				
Creatinine	-0.168	0.502*	0.076	0.502*	0.284*	-0.170	0.123	1.000		
	0.167	0.000*	0.533	0.000*	0.018*	0.162	0.317			
Disease duration	-0.047	0.351*	-0.103	0.345*	0.403*	-0.346*	0.214	0.510*	1.000	
	0.696	0.003*	0.393	0.003*	0.000*	0.003*	0.077	0.000*		
Age	-0.178*	0.313*	-0.107	0.288*	0.080	-0.040	0.166	0.710*	0.645*	1.000
	0.024*	0.000*	0.176	0.000*	0.313	0.613	0.132	0.000*	0.000*	

LF<sub>SAP</sub> indicates LF component of SAP variability; RR, RR interval; LF<sub>RR</sub>, LF component of RR variability in nu; HF<sub>RR</sub>, HF component of RR variability in nu; HbA1c, glycosylated hemoglobin. In every cell, top row indicates correlation coefficient and bottom row indicates significance. Correlations for HbA1c, creatinine, and disease duration are computed only for patients.

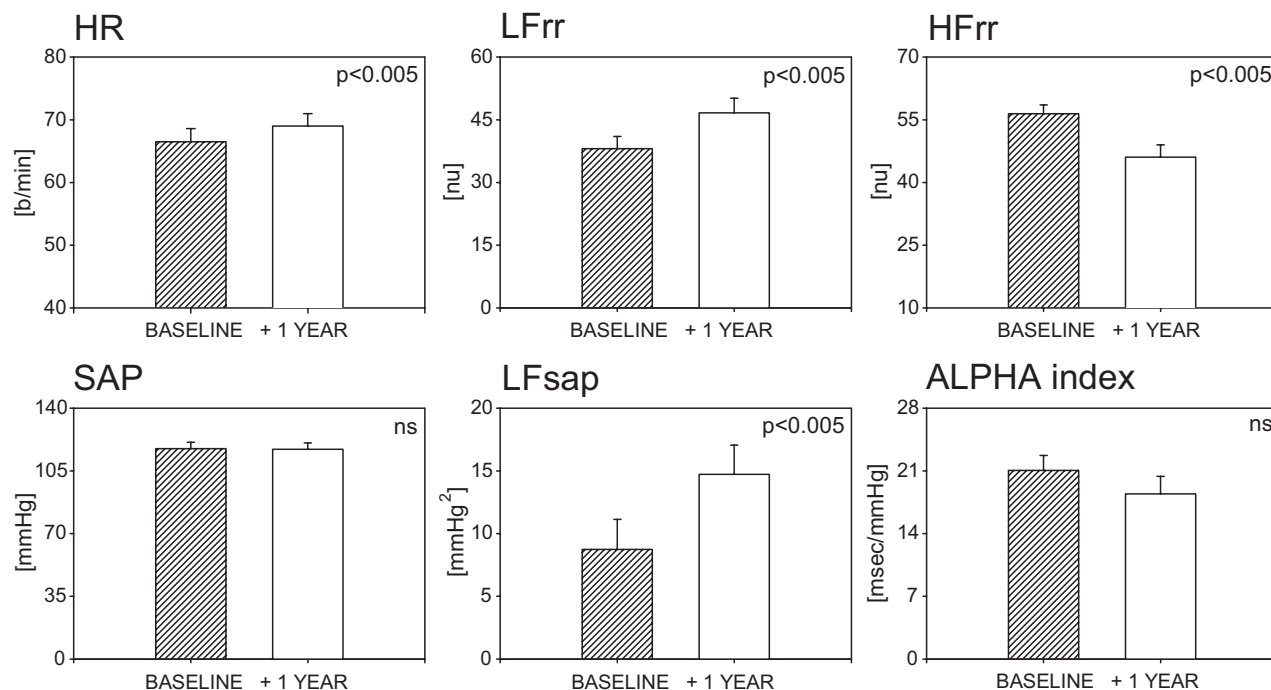
\*Data show significant correlations.

corollary, the lack of relationship between glycosylated hemoglobin and other parameters suggests that this index might be a less sensitive indicator of diabetic complications affecting cardiovascular regulatory mechanisms, in particular, changes in heart rate variability and blood pressure variability. A clinical advantage of this approach might be that indirect autonomic monitoring could furnish a surrogate outcome to assess not only early cardiovascular damage but also the beneficial effects of therapy, such as provided by respiratory and exercise training,<sup>26</sup> on autonomic dysregulation or therapies targeting more directly endothelial function,<sup>27</sup> such as with angiotensin-converting enzyme inhibitors. An additional clinical observation regards the significant increase in SAP observed in these young T1DM patients, particularly apparent in the adolescent subgroup. Considering that in adults even small increases in AP carry an adverse prognosis<sup>28</sup> and that diabetes mellitus has a supra-additive effect with regard to cardiovascular risk, this finding might suggest a more stringent focus on blood pressure control, even at an earlier age. The critical role of cardiovascular dysregulation in early T1DM can also be gleaned by the observation that controls can clearly be discriminated from patients by the simple information carried by autonomic variables; indeed, only 3 of these indicators (ie, baroreflex gain, AP, and LF<sub>SAP</sub>) are capable of providing a discriminative power of  $\approx 70\%$ . Future studies should address whether initial alterations in metabolism or in vascular function (such as an increase of intima-media thickness or an impaired endothelium-dependent relaxation<sup>29</sup>) might play a mechanistic role in the observed alterations in autonomic indices.

Limitations must also be stressed. This is an observational study that considers a wide age range, thus providing data for both children and adolescents. The longitudinal observation, although limited in time, clearly showed a worsening in autonomic indices within just 1 year. However, longer observation time might lead to more apparent worsening of autonomic indices as shown, for example, by Ko et al<sup>30</sup> in type 2 diabetes mellitus patients. Autonomic dysregulation was not assessed directly, although we used a battery of several indirect indicators of both cardiac and vascular autonomic regulation. We used both monivariate and bivariate indices and used a modern software tool<sup>31</sup> based on autoregressive algorithms that requires a minimum of operator interaction. Metabolic control was not optimal, in spite of the use in several of these children of an insulin pump.

### Perspectives

We have also shown that children and adolescents affected by T1DM show marked autonomic alterations, characterized by a significant increase in AP, a reduced gain of the baroreflex regulation of the SA node, a progressive increase of LF<sub>SAP</sub>, a shift of the balance between LF and HF RR oscillations toward LF, suggestive of a simultaneous impairment of vagal cardiac control and increases of sympathetic cardiovascular regulation, possibly linked to insulin treatment. Given the well-known beneficial effects of exercise training<sup>32</sup> on these disturbances in adults affected by important cardiovascular disease, such as hypertension, coronary artery disease, and congestive heart failure, it may be hypothesized that, also in children with T1DM, exercise, eventually combined with other functional treatments, such as deep breathing<sup>33,34</sup> or



**Figure 3.** Summary of the differences in key indices from HR and SAP variability in the repeat study, performed 366 days after the first recording, to focus initial trends in autonomic dysfunction in patients with T1DM. HR indicates heart rate; LFrr, LF component of RR variability, in nu; HFrr, HF component of RR variability, in nu; LFsap, LF component of SAP variability; ALPHA index, frequency domain measure of baroreflex gain; ns, not significant. Significance (p) is indicated in all of the panels.

relaxation,<sup>35</sup> might represent a useful adjunct to standard therapy. This hypothesis, although attractive, requires direct testing with longer studies on larger populations of patients.

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### Disclosures

None.

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