

Blood pressure phenotypes in young patients with type 1 diabetes

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Aim. To study phenotypes of clinic and 24-hour ambulatory blood pressure (BP), to determine their associations with arterial stiffness parameters, and to assess global cardiovascular risk (CVR) in young patients with type 1 diabetes (T1D).

Material and methods. The presented cross-sectional single-center study included 81 T1D patients without a history of hypertension (HTN) and other cardiovascular diseases (CVD) (men — 39%; median age — 27 years; median duration of T1D — 6 years). All participants underwent a routine clinical and laboratory testing, measurement of clinic and 24-hour ambulatory BP (BPLab Vasotens), assessment of central BP and arterial stiffness parameters using applanation tonometry technique. BP phenotypes were analyzed with diagnostic criteria for HTN by ESC/ESH 2018 guidelines. CVR was assessed using the SCORE 10-year risk calculator (ESC 2019). The differences were considered significant at $p < 0,05$.

Results. The prevalence of true HTN was 6,2%, masked HTN — 38,3%. Isolated nocturnal HTN was revealed in 30,7% of patients with clinic BP $< 140/90$ mm Hg. The subgroup with masked HTN was dominated by patients with normal clinic BP (58,1%) and in most cases was characterized by isolated diastolic BP increase (64,5%). Masked HTN was associated with a higher carotid-femoral pulse wave velocity (PWV) (median — 7,2 versus 6,3 m/s, $p = 0,002$). The most common profiles of nocturnal BP decrease were non-dipper (63,9%) and night-picker (16,6%). High and very high CVR was recorded in 87,7% of patients.

Conclusion. Hypertension occurs in 44,5% of young patients with type 1 diabetes and is characterized by a high prevalence of masked isolated nocturnal HTN and non-dipping. Masked HTN is associated with a higher carotid-femoral PWV. High and very high 10-year CVR was recorded in 87,7% of patients.

Key words: type 1 diabetes, 24-hour ambulatory blood pressure monitoring, masked hypertension, arterial stiffness, cardiovascular risk.

Relationships and Activities: not.

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Type 1 diabetes (T1D) is one of the most common endocrine disorders developing in children and young adults, the prevalence of which has been increasing in recent years [1-3]. T1D is associated with an almost three-fold increase in mortality compared with the general population, which is primarily due to the premature atherosclerosis, and, as a result, cardiovascular events occur at least 10 years earlier [4-5]. The most important risk factor for the development and progression of macro- and microvascular complications in T1D is hypertension (HTN). According to various data, its prevalence ranges from 24 to 43% [6-7] and increases with the duration of diabetes [8].

The features of HTN in T1D patients have not been sufficiently studied, and blood pressure (BP) phenotyping is important. The concept of “phenotype” has firmly come into clinical practice with the development of personalized medicine. Phenotype is defined as a combination of signs characterizing differences in the severity of symptoms, clinical outcomes and mortality in patients with a certain disease [9]. Thus, phenotyping of T1D patients depending on changes in clinic and/or ambulatory BP can be of great importance in risk stratification and treatment strategy. Small studies have shown a relatively high frequency of masked and nocturnal HTN, as well as nondecrease in BP at night in T1D patients, which may explain cardiovascular risk (CVR) increase [10-12]. At the same time, despite guidelines, the frequency of 24-hour ambulatory blood pressure monitoring (ABPM) use in this population is relatively low in actual clinical practice.

The most important features of current clinical guidelines on HTN [13-15] are the orientation of management strategies to global CVR, which significantly changes the approach to treatment, especially in young patients, as well as lowering BP threshold for initiating antihypertensive therapy (AHT). According to ACC/AHA guidelines (2017), pharmacologic treatment is indicated for patients at high risk of atherosclerosis-related cardiovascular disease (CVD) with BP $\geq 130/80$ mm Hg [15]. According to ESC/ESH guidelines (2018), AHT should be considered in patients with high normal BP ($\geq 130/85$ mm Hg) and very high CVR due to CVD (especially coro-

nary artery disease) [13, 14]. Diabetes, in most cases, is associated with high or very high CVR, which makes early use of lipid-lowering and antihypertensive therapy important. Moreover, CVR in T1D patients may be underestimated, as well as HTN may be untimely diagnosed, which is associated by a high prevalence of masked HTN. This can lead to untimely prescribing of medication and the early development of complications. The prevalence of HTN and its phenotypes, the characteristics of CVR categories in the Russian population of T1D patients remain insufficiently studied. An additional important factor, probably affecting CVR in T1D patients, is an increase of arterial stiffness, which often precedes HTN manifestations and vascular events [16]. The association of arterial stiffness with masked HTN in this population requires further research.

The aim was to study phenotypes of clinic and 24-hour ambulatory BP, to determine their associations with arterial stiffness parameters, and to assess global CVR in young patients with T1D.

Material and methods

The current cross-sectional single-center study included patients aged 18 to 44 years with established T1D, who were monitored from January to December 2018. Exclusion criteria were any cardiovascular and clinically significant non-cardiovascular diseases. The main clinical and demographic characteristics, laboratory and instrumental data were recorded in the research database.

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. All patients signed informed consent.

BP was measured in the morning using the oscillometric device HEM-5001 (Omron Health Care, Japan) in accordance with the guidelines [13, 14]. When analyzing the data on clinical measurement, BP $\geq 140/90$ mm Hg considered threshold for HTN diagnosis. For characterization of clinic BP levels, a standard classification was used [13, 14].

ABPM was performed according to a standard technique from clinical guidelines [17]. To carry out the 24-hour ABPM, a portable BPLab device (OOO Petr Telegin, Russia) was used. The circadian BP

Table 1

24-hour BP classes

Class	Description	Range
Dipper	Normal nighttime BP decrease	10-20%
Non-dipper	Insufficient nighttime BP decrease	$\geq 0\%$ — $< 10\%$
Over-dipper	Excessive nighttime BP decrease	$< 0\%$
Night-picker	Steady nighttime BP increase	$> 20\%$

Abbreviations: BP — blood pressure, SBP — systolic blood pressure.

Table 2

Determination of BP phenotypes [15, 16]

BP phenotype	Clinic BP, mm Hg		ABPM data, mm Hg				
			24-hour BP		Daytime BP		Nighttime BP
Normotension	<140/<90	and	<130/<80	and	<135/<85	and	<120/<70
True HTN	≥140/≥90	and	≥130/≥80	and/or	≥135/≥85	and/or	≥120/≥70
White coat HTN	≥140≥90	and	<130/<80	and/or	<130/<85	and	<120/<70
Masked HTN	<140/<90	and	≥130/≥80	and/or	≥135/≥85	and/or	≥120/≥70

Note: standards are presented as follows: 2018 ESC/ESH or 2017 ACC/AHA.

Abbreviations: BP — blood pressure, HTN — hypertension, ABPM — ambulatory blood pressure monitoring.

rhythms in the aorta and brachial artery were analyzed using the standard dipping classification (Table 1) [17]. BP phenotypes were determined by comparing the clinic and ambulatory BP (2018 ESC/ESH criteria were used) (Table 2).

The parameters of central pulse wave and arterial stiffness were determined using a SphygmoCor device (AtCor, Australia), by means of applanation tonometry of radial artery and estimation of carotid-femoral pulse wave velocity (cfPWV). The test was performed according to the standard protocol [18]. An increase in cfPWV was considered at ≥10 m/s [13, 14].

Ten-year CVR was evaluated in accordance with the clinical guidelines [13, 19]: patients with established HTN-mediated organ damage (HMOD) or three or more risk factors or a diabetes duration >20 years were classified as very high risk; patients with diabetes >10 years without HMOD or with additional risk factor were classified as high risk; patients <35 years of age with diabetes <10 years without other risk factors were classified as moderate risk.

For primary data processing, descriptive statistics were used. Intergroup differences for quantitative variables were assessed using the Mann-Whitney and Kruskal-Wallis tests. For qualitative variables, contingency tables were created and the Pearson's chi-squared test was used. Differences were considered significant at $p < 0,05$. For data processing, software package Statistica 10.0 was used.

Results

We analyzed data on 81 patients with T1D (Table 3). At the inclusion in the study, there were no data suggestive of additional CVR, with the exception of hyperlipidemia, which indicates inadequate outpatient management of lipid metabolism disorders (all patients did not receive statins). It should be noted that cfPWV >10 m/s was detected only in 3 patients (3,7%).

The total prevalence of HTN was 44,5% ($n=36$). The distribution of patients by BP phenotypes is

shown in Figure 1. Among patients with normal clinic BP according to ESC/ESH criteria, optimal BP was recorded in 33,3%, normal — in 52%, and high normal in 14,7%. It should be noted that the prevalence of different BP phenotypes did not differ between subgroups with masked HTN and true normal BP. Although in relation to the latter, there was a tendency to a higher frequency of optimal BP (Figure 2).

An additional analysis revealed that patients with high normal BP, compared to patients with optimal BP, were older (31 (28; 35) years vs 27 (21; 28) years, $p=0,045$) and had higher levels of triglycerides (1,43 (1,16; 1,6) vs 1,08 (1,06; 1,39) mmol/L, $p=0,04$). There were no significant differences with the normal BP group. There were also no differences in ABPM data, dipping phenotypes, and arterial stiffness parameters.

To compare the clinical characteristics between all BP phenotypes, the Kruskal-Wallis test was used (Table 4). With the exception of obvious differences between clinic and ambulatory BP, higher nocturnal heart rate in patients with masked HTN were noted.

Given the clinical significance of masked HTN for CVR, an additional analysis was performed in this group, accounting for 41% of all patients with normal clinic BP. It was shown that 23 (74,2%) patients with masked HTN had isolated nocturnal HTN, 2 (6,5%) patients — isolated daytime HTN, and 6 (19,4%) patients — masked hypertension according to day- and nighttime measurements. Thus, isolated nocturnal HTN was observed in 30,7% of patients with normal clinic BP. Twenty (64,5%) patients with masked HTN had isolated diastolic HTN, 11 (35,5%) — systolic-diastolic HTN. Patients with masked HTN compared with the group of true normal BP were characterized by a longer duration of diabetes, older age, as well as higher albuminuria, cfPWV, and variability of SBP (Table 5). No other differences were found in arterial stiffness parameters and dipping phenotypes.

Table 3
Characteristics of T1D patients at inclusion in the study*

Parameter	Population (n=81)
Age, years, median	27 (23;34)
Male sex, n (%)	48 (39)
Duration of diabetes, years	6 (2,8;11)
BMI, kg/m ²	21,7 (20,2;24)
Smoking, n (%)	20 (24,7%)
Creatinine, $\mu\text{mol/L}$	82 (67;97)
GFR CKD EPI, ml/min/1,73 m ²	101 (87;122)
Total cholesterol, mmol/L	5,1 (4,1;5,7)
LDL, mmol/L	3,2 (2,9;4,1)
Triglycerides, mmol/L	1,2 (1,0;1,5)
HbA _{1c} , %	6,9 (5,6;7,9)
Albuminuria/Creatinine, mg/g	12 (6;24)
Mean SBP (clinic), mm Hg	120 (110;120)
Mean DBP (clinic), mm Hg	80 (70;80)
Daytime mean SBP, mm Hg	119 (111;126)
Daytime mean DBP, mm Hg	78 (69;81)
Nighttime mean SBP, mm Hg	112 (107;118)
Nighttime mean DBP, mm Hg	69 (62;78)
Central SBP, mm Hg	109 (100;118)
Central DBP, mm Hg	72 (67;76)
Central PP, mm Hg	40 (35;46)
Pulse wave velocity, m/s	6,3 (5,3;6,7)

Note: * — quantitative data are presented as median (interquartile range).

Abbreviations: HbA_{1c} — glycated hemoglobin, DBP — diastolic blood pressure, BMI — body mass index, LDL — low density lipoproteins, PP — pulse pressure, SBP — systolic blood pressure, GFR — glomerular filtration rate.

Regardless of the thresholds and phenotype of HTN, the most common profiles of nocturnal BP decrease were non-dipper (63,9%) and night-picker (16,6%) (Table 6). This, along with the high frequency of masked nocturnal HTN indicates a potentially higher risk of cardiovascular complications in this category of patients [20].

Assessment of 10-year CVR [19] revealed that 87,7% of patients were in the high and very high-risk categories (Figure 3). Significant differences in clinical, demographic and laboratory data, the level of peripheral and central BP, parameters of ABPM, arterial stiffness between the moderate and high/very high-risk groups have not been established. In the subgroup of masked HTN, there were 85,3% and 4% of patients at high and very high risk, respectively, and in the subgroup with no nighttime decrease in SBP — 82% and 6%, respectively. The distribution of patients with different levels of risk by BP and SBP

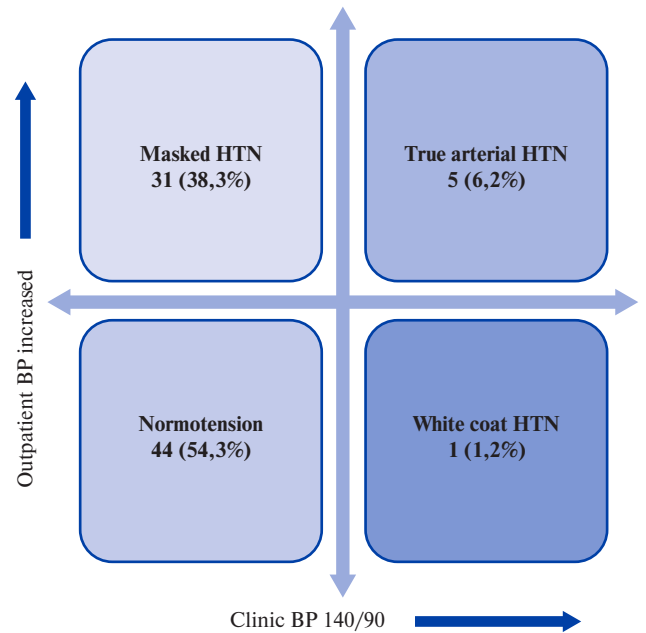


Figure 1. BP phenotypes in young patients with type 1 diabetes (n=81).

Abbreviations: HTN — hypertension, BP — blood pressure.

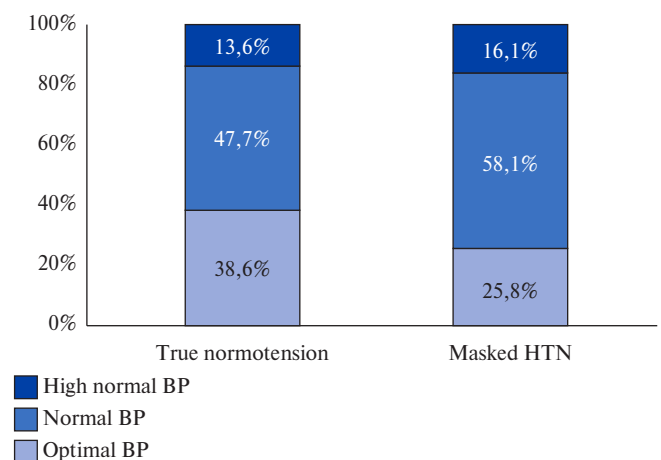


Figure 2. Characteristics of clinic BP phenotypes in patients with true normotension and masked HTN (n=75).

Note: $p > 0,05$ using Pearson's chi-squared test for all phenotypes. **Abbreviations:** HTN — hypertension, BP — blood pressure.

dipping phenotypes is presented in Figure 4 (A and B).

Discussion

Phenotyping by the levels of clinic and ambulatory BP allows to identify patients with a higher CVR and, accordingly, a less favorable prognosis. This approach is of particular importance for young patients with T1D who may have underestimated risk.

An important result of this study is the confirmation of high frequency of masked HTN in young

Table 4

**Intergroup differences for different HTN phenotypes
(2018 ESC/ESH diagnostic criteria)***

Parameter	True HTN (n=5)	Masked HTN (n=31)	Normotension (n=44)	P
Age, years	28,0 (26;38)	31,5 (21;38)	27 (23;28)	H3
Male sex, n (%)	4 (80)	15 (50)	29 (63)	H3
Clinic SBP, mm Hg	160 (150;160)	120 (110;120)	120 (110;120)	0,01
Clinic DBP, mm Hg	95 (90;100)	76,5 (70;80)	79 (70;80)	0,01
Nighttime heart rate night, bpm	69 (62;75)	82 (75;88)	78 (71;82)	0,01
Daytime mean SBP, mm Hg	128 (126;134)	124 (119;128)	114 (110;120)	0,0001
Daytime mean DBP, mm Hg	83 (83;84)	79,5 (77;86)	72,5 (67;79)	0,0001
Nighttime mean SBP, mm Hg	117 (115;128)	118 (113;121)	108 (100;113)	0,0001
Nighttime mean DBP, mm Hg	78 (76;78)	79 (74;83)	65,5 (62;69)	0,0001

Note: * — quantitative data are presented as median (interquartile range).

Abbreviations: HTN — hypertension, DBP — diastolic blood pressure, SBP — systolic blood pressure.

Table 5

**Characteristics of T1D patients with normal clinic BP depending
on the presence of masked HTN***

Parameter	True normotension (n=45)	Masked HTN (n=30)	p
Age, years	26,4±5,5	31±8,6	0,02
Duration of diabetes, years	4 (0,65;8)	6 (3;12,9)	0,009
Urine ACR, mg/g	8 (3;17)	18,5 (11;29)	<0,001
Clinic SBP, mm Hg	120 (108;120)	120 (110;120)	0,78
Clinic DBP, mm Hg	77 (69;80)	78 (70;80)	0,96
Daytime mean SBP, mm Hg	114 (110;121)	124 (118;128)	<0,001
Daytime mean DBP, mm Hg	72 (67;79)	79 (76;86)	<0,001
Nighttime mean SBP, mm Hg	108 (100;114)	118 (110;121)	<0,001
Nighttime mean DBP, mm Hg	64 (62;69)	79 (74;83)	<0,001
Daytime SBP variability, mm Hg	19 (13;22)	14 (10;18)	0,03
Nighttime SBP variability, mm Hg	13 (9;19,5)	20 (11;28)	0,02
24-hour cfPWV, m/s	6,3 (5,8;6,8)	7,2 (6,2;8,2)	0,002

Note: * — quantitative data are presented as median (interquartile range).

Abbreviations: ACR — albumin/creatinine ratio, DBP — diastolic blood pressure, SBP — systolic blood pressure, cfPWV — carotid-femoral pulse wave velocity.

patients with T1D. It is important that 93,6% of patients had nocturnal HTN (74,2% — isolated nocturnal HTN). Thus, the diagnosis of masked HTN in most cases was based on the nocturnal BP, which emphasizes the importance of 24-hour ABPM in this population. To date, a relatively small number of studies on the BP phenotypes in patients with T1D have been published [10–12]. In the study by Rodrigues TC et al. (188 patients with T1D), masked HTN was detected in 7,4% (13,6% in the group with normal clinic BP), and isolated nocturnal HTN — in 23,3% [10]. In another study, among 85 T1D patients, the prevalence of masked HTN was 24%

[11]. It should be noted that in both studies, the clinic BP threshold was 130/80 mm Hg, and the daytime BP threshold was 135/85 and 130/80 mm Hg, respectively. Therefore, these results cannot be compared with the data obtained by us. The closest to current work is the study by Lithovius R et al., which included 140 T1D patients, some of whom had a history of HTN and use of AHT. The prevalence of masked hypertension was 23%, true HTN — 33%, true normotension — 38% and white-coat HTN — 6% [12]. In our work, the prevalence of masked HTN according to European criteria was 38,3%, true HTN — 6,2%. Such a pronounced dif-

ference can probably be explained by lower mean age of the participants in our study (27 vs 47,3 years). In addition, we included patients without a history of HTN and AHT.

According to 2017 ACC/AHA guidelines [15], the clinic and ambulatory BP thresholds for HTN are different from those accepted in Russia. When analyzing BP phenotypes using ACC/AHA criteria, there is an increase in the HTN prevalence to 88,9%, mainly due to true hypertension (44,4%). It is interesting that the frequency of masked HTN using the American and European criteria was practically the same (35,8% vs 38,3%, $p=0,7$), although only 15 patients showed a concordance for this phenotype. It should be noted that when using the threshold proposed in the 2018 ESC/ESH guidelines, compared with 2017 ACC/AHA, there was a greater specificity with respect to HTN diagnosis due to a significant loss of sensitivity (sensitivity — 13,9% and 55,4; specificity — 97,8% and 50%, respectively). The accuracy of the criteria was comparable (60,5% and 54,3%, respectively).

Characteristics of arterial stiffness and pulse wave in T1D patients have been studied in a number of works: in some, higher augmentation index

values among T1D patients were recorded [21, 22], in others conflicting data were obtained [23]. In the present study, a deviation from the reference values for PWV was observed in 3,7% of cases, which indicates the need to evaluate cfPWV according to individual standards depending on sex and age [24]. It was shown that, despite the normal mean level of cfPWV, patients with masked HTN

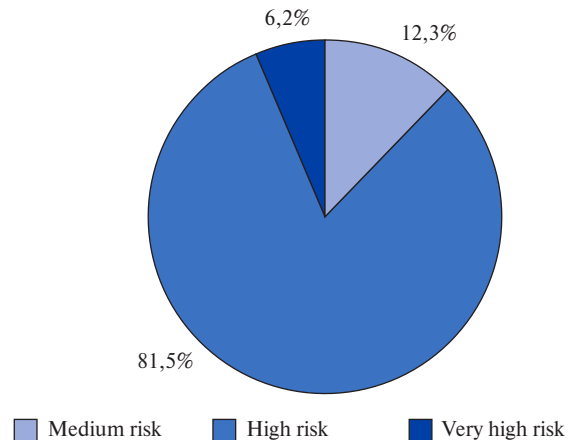


Figure 3. The distribution of T1D patients depending on 10-year CVR.

Table 6

Dipping classes in patients with various BP phenotypes (2018 ESC/ESH criteria)*

BP phenotype	Night-picker	Non-dipper	Dipper	Over-dipper
True HTN	0 (0)	4 (80)	1 (20)	0 (0)
WC-HTN	0 (0)	1 (100)	0 (0)	0 (0)
Masked HTN	6 (19,4)	19 (61,3)	2 (6,5)	4 (12,9)
True normotension	8 (18,2)	28 (63,6)	6 (13,6)	2 (4,5)
All phenotypes	6 (16,6)	23 (63,9)	3 (8,3)	4 (11,1)

Note: * — data are presented as n (%).

Abbreviations: HTN — hypertension, BP — blood pressure, WC-HTN — white coat hypertension.

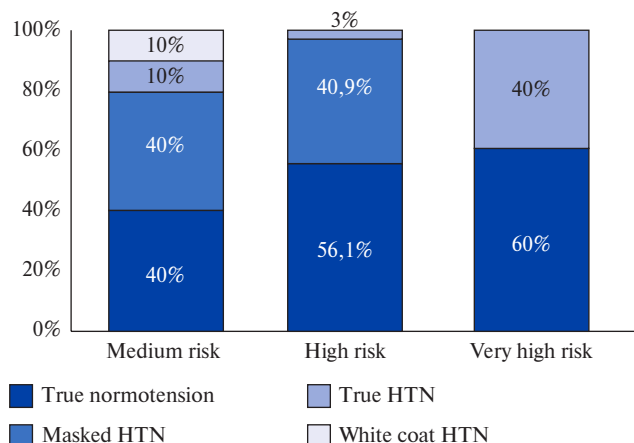


Figure 4 (A). The distribution of T1D patients by BP phenotypes depending on the risk category.

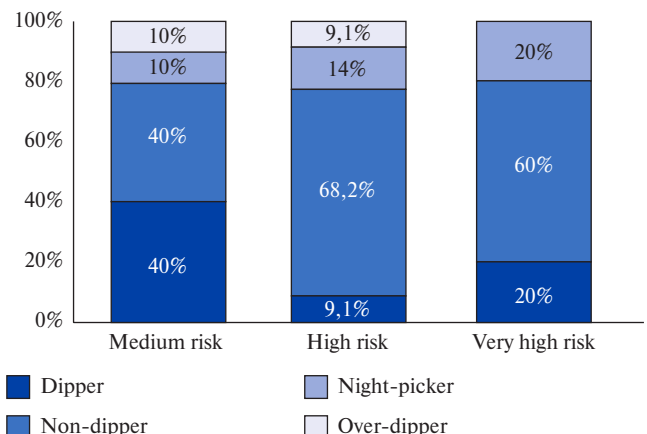


Figure 4 (B). The distribution of T1D patients by dipping classes depending on the risk category.

had its significant increase compared to true normotension. In the study by Lithovius R et al., a similar data was obtained [12]. The tendency to arterial stiffness increase in patients with masked HTN may reflect early arterial changes and, probably, contributes to an increase in CVR.

It is known that circadian BP disorders are associated with an increased risk of cardiovascular events [25]. Diabetes is associated with an increase in the frequency of non-dipping. In this study, the frequency of overall non-dipping BP was 74,5%, indicating a potentially higher risk of unfavorable cardiovascular outcomes.

Estimation of CVR level when choosing the optimal management strategy is a key recommendation of most world cardiology societies [13-15]. Correct assessment of CVR is especially important in young patients without a history of significant CVD, since in this group complex approach to risk evaluation [26] can significantly change the treatment strategy and contribute to earlier drug therapy. Obviously, patients with diabetes cannot be considered a low-risk group, but risk of some T1D patients, due to young age and absence of comorbidities, may be significantly underestimated. In our study, it was shown that almost 90% of patients belonged to high and very high-risk groups, even

without HTN history, established cardiovascular and renal diseases. This is due to both the long duration of diabetes (>10 years in 36% of patients) and the high prevalence of dyslipidemia and other risk factors. All patients did not received lipid-lowering therapy or AHT.

Thus, young T1D patients without a history of CVD and AHT often have masked (including isolated nocturnal) HTN and high CVR, which requires a review of treatment and diagnostic strategies and, possibly, use of therapy even with high normal BP. Further studies are required for assessing the impact of such an approach on CVR and outcomes.

Conclusion

Young T1D patients without a history of chronic diseases had HTN (true and masked) in 44,5% of cases. A high frequency of potentially unfavorable BP phenotypes was established — masked HTN, isolated nocturnal HTN, and non-dipping. Masked hypertension is associated with a higher cfPWV compared with the true normotension group. Most patients with T1D have a high and very high 10-year CVR, which requires a revision of diagnostic and treatment strategies.

Relationships and Activities: not.

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