

NOCTURNAL HYPERTENSION AND SPECIAL - PERIOD HYPERTENSION IN TYPE 1 DIABETES MELLITUS

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Abstract

Background: One of the unique aspects of continuous ambulatory arterial-tension monitoring is the ability of recording the diurnal variations. The patients suffering from Type 1 Diabetes Mellitus (T1DM) may present higher nocturnal values of arterial tension and this rise can be determined by hyperinsulinism. The first hours in the morning (6 a.m. - 9 a.m.), the so-called special period, is correlated with a rise in the incidence of cardiovascular events and a rise in plasmatic catecholamine and of platelet aggregability. The main goal of this study is to analyze the particularities of the tensional profile with regard to nocturnal behavior and behavior in the special period, reported to glycemic variations. **Material and method:** The study analysed 351 patients known with T1DM, who have been suffering from this disease for more than 10 years, who were in the records of the Center of Diabetes, Nutrition and Metabolic Diseases of Iași and Suceava. The patients were assessed from a tensional and glycemic point of view, by continuous blood-tension (ABPM) and glycemia (CGMS) monitoring. **Results:** The occurrence of nocturnal hypertension in patients suffering T1DM is by 29.24 higher than in the case of hypertensive persons compared to the risk presented by the persons without blood hypertension. The continuous recording of blood hypertension during the asymptomatic hypoglycemia period showed increased values both for systolic blood tension and for diastolic one ($p < 0.05$). The hypertension risk is by 3.24 higher during the hypoglycemia period compared to the normoglycemic one. Tension variations during the special period were noticed in 87 patients who have been suffering from diabetes mellitus for 19.75 ± 4.57 years. These tension values are higher than the nocturnal ones, but lower than the diurnal ones. **Conclusions:** Hypoglycemia duration and magnitude induces increased tension values which adds another hemodynamic stress factor to the patient suffering from T1DM. In T1DM, in the first morning hours, in particular conditions, we can notice increased tension values, higher in patients with blood hypertension, which induces a stressed cardiovascular risk. Tension value increase during the special period overlaps the morning hyperglycemias. Therefore, there appears an apparently invisible impact on the cardiovascular condition of diabetes mellitus.

key words: type 1 diabetes mellitus, nocturnal hypertension, special period.

Background

The heart rate characterizes most of the fundamental physiological processes which are governed by the homeostatic mechanisms and an important role is assigned to hypothalamus suprachiasmatic nucleus which operates as a clock mechanism both by the direct neuronal impact and by the hormonal secretion control [1, 2]. Blood tension, such as heart rate, presents diurnal variations with higher values during the day compared to the night because of the combination of physical activity effects, postural changes and sleep-wakefulness transition [3]. Moreover, the behavioral and physiological effect of the alimentation *per se* has an impact on blood tension variation consisting of a rise in systolic blood tension [4].

One of the unique aspects of continuous ambulatory blood-tension monitoring is the ability of recording diurnal variations. A drop of about 10-20% during the night is normal, which coincides with the sleeping hours and is known as dipping. In about 25% of the hypertensive persons, we can notice a non-dipping aspect, the nocturnal tension drop being absent. Some authors used a classification which identifies persons with an excessive blood tension drop (extreme dippers whose nocturnal blood tension drops by more than 20 %) or even a rise (risers) [5]. Previous studies proved that patients with T1DM may present higher nocturnal blood tension values and this rise can be determined by hyperinsulinism [6]. The question is whether the strict control of T1DM determining hyperinsulinism and nocturnal subclinical hypoglycemia may cause or not a rise in nocturnal blood tension.

It is well known that myocardial infarction and stroke are more frequent during the first

morning hours (6-9 o'clock) – the said *special period*. Blood tension nocturnal drop is connected to sympathetic stimulation variation. This stimulation is higher when waking up, explaining therefore blood tension circadian behavior – of gradual rise towards the diurnal values. As a matter of fact, this period is correlated to the increase of cardiovascular events' incidence, with the increase of the plasmatic catecholamine and of the platelet aggregability. Extracellular volume increase together with the maintenance of a high nocturnal sympathetic tonus, leads to the maintenance of an abnormally increased cardiac flow during the night.

Blood tension significance in type 1 diabetes mellitus is complex: the association between blood tension and T1DM accelerates complications' occurrence, mainly atherosclerosis and its acute complications and it worsens the prognostic. As a matter of fact, after so many years of diabetes mellitus existence, it is difficult to assess which of the two diseases plays the most important role in prognostic and evolution. It was proved that the coexistence between T1DM and blood hypertension doubles the cardiovascular risk and the total mortality. On the other hand, the hypotension treatment improves in a significant way cardiovascular complications' evolution.

Despite the importance of the cardiovascular integrative mechanisms and of the glycemic homeostasis from functions and physiological responses coordination, the energetic consumption and the hormonal adjustment, mainly in the postprandial condition, the continuous correlation (*minute by minute*) between blood tension and glycemia has not yet been established.

In the context of these features of blood tension in T1DM, the main goal of this study is to analyze the particularities of the tensional profile with regard to the nocturnal behavior and to the one from the special period, reported to the glycemie oscillations.

Material and method

The study analysed 351 patients known with T1DM who have been suffering from this disease for more than 10 years, who were in the records of the Center of Diabetes, Nutrition and Metabolic Diseases of Iași and Suceava. The patients were assessed from a tensional point of view by the continuous surveillance of blood tension, by means of a portable oscilometer, a device type **Automatic Blood Tension Monitoring (ABPM) – Oscar 2**, which is graduated and periodically checked. [7] Several periods were defined:

- the day period from 6 a.m. to 10 p.m.;
- the nocturnal period which includes measurements from 10 p.m. to 6 a.m.;
- the special period for the interval from 6 a.m. to 9 p.m.

The continuous glycemie monitoring was performed by means of the device called

Continuous Glucose Monitoring System (CGMS) MiniMed Medtronic. In the selected sample, the glycemie assessment was performed at intervals of 15 minutes, simultaneously with the automate recording of the tension parameters. Therefore, 96 determinations were performed for a patient. Hypoglycemia characters were assessed according to ADA recommendations [8]:

- Documented symptomatic hypoglycemia – an episode with typical symptoms of hypoglycemia, accompanied by glycemie < 70mg/dl.
- Asymptomatic hypoglycemia – an episode which is not accompanied by typical symptoms of hypoglycemia, but glycemie value is lower than 70mg/dl.

Results

Of the 351 patients suffering from T1DM, 193 were male persons and 158 were female persons. Subjects' average age was 38.3 ± 11 years with variations between 18 and 50 years old. Diabetes mellitus age varied between 5 and 15 years with an average of 9.86 ± 3.92 years. (Table 1)

Table 1. Sample characteristics.

	No. = 351
Sex (men/women)	193/158
Age	38.3 ± 11 years old
Body mass index	24.08 ± 3.51 kg/m ²
Duration of type 1 diabetes mellitus	9.86 ± 3.92 years

Blood hypertension diagnosis seems to be an easy maneuver which is compulsory in any examination of a patient suffering from diabetes mellitus. The most correct assessment of blood tension diagnosis is the one performed in the ambulatory, registered on a 24 hours' duration, because it allows its assessment in patient's own environment and

during the development of his normal activities, including during the night.

The frequency of the cases presenting blood hypertension in the analyzed sample was of 33.9% (119 cases) (Figure 1).

The nocturnal blood hypertension, defined by the fact that tension values are higher during the night than during the day was

noticed in a number of 36 patients. (Table 2, Figure 2)

Nocturnal hypertension occurrence in patients with T1DM is by 29.24 higher in the

case of the hypertensive persons compared to the risk presented by those who do not present blood hypertension. (Table 3).

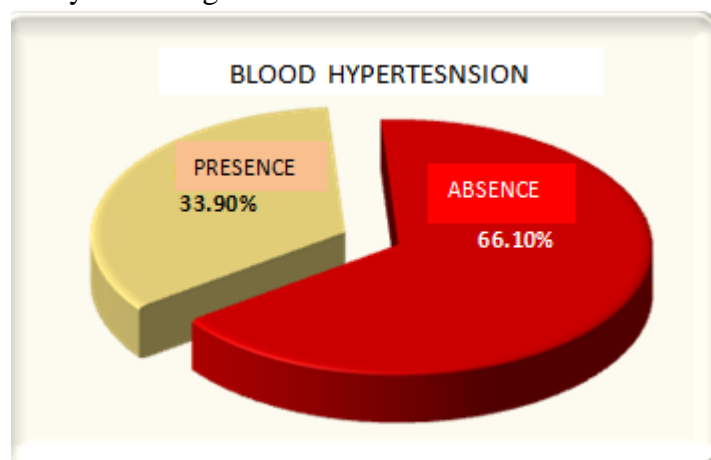


Figure 1. Cases distribution according to blood hypertension.

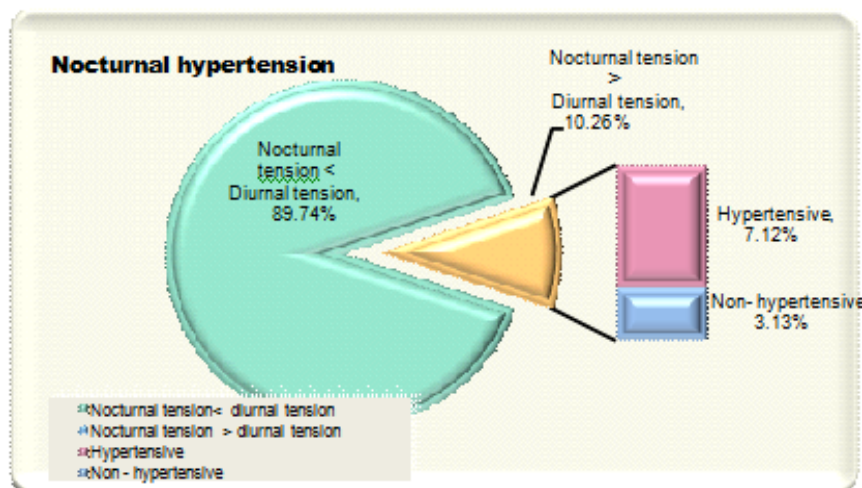


Figure 2. Nocturnal hypertension.

Table 2. Nocturnal hypertension.

Nocturnal hypertension	No. of cases	%
Nocturnal tension > diurnal tension	36	10.26%
Hypertensive persons	25	7.12%
Non-hypertensive persons	11	3.13%
Nocturnal tension < diurnal tension	335	89.74%
Total no. of cases	351	

Hypoglycemia itself can determine a rise in tension values. Therefore, an additional hemodynamic stress is added which increases the vital risk in these patients. We can hypothesize that nocturnal hyperinsulinemia

determines a relative condition of hypoglycemia that could have occurred in sleep which would have determined variations in the morning blood tension. In this study, a clear relationship between the nocturnal

decrease of glycemia and blood tension modification was proven by the analysis of blood tension vs. glycemia dynamics.

Table 3. Assessment of odds and risk parameters of blood hypertension vs. nocturnal hypertension.

Odds PARAMETERS	Estimated value	95% Confidence interval	
		Minimum	Maximum
Odds report (OR)	33.23	4.54	68.5
Risk PARAMETERS			
Risk Report (RR)	29.24	3.91	21.8

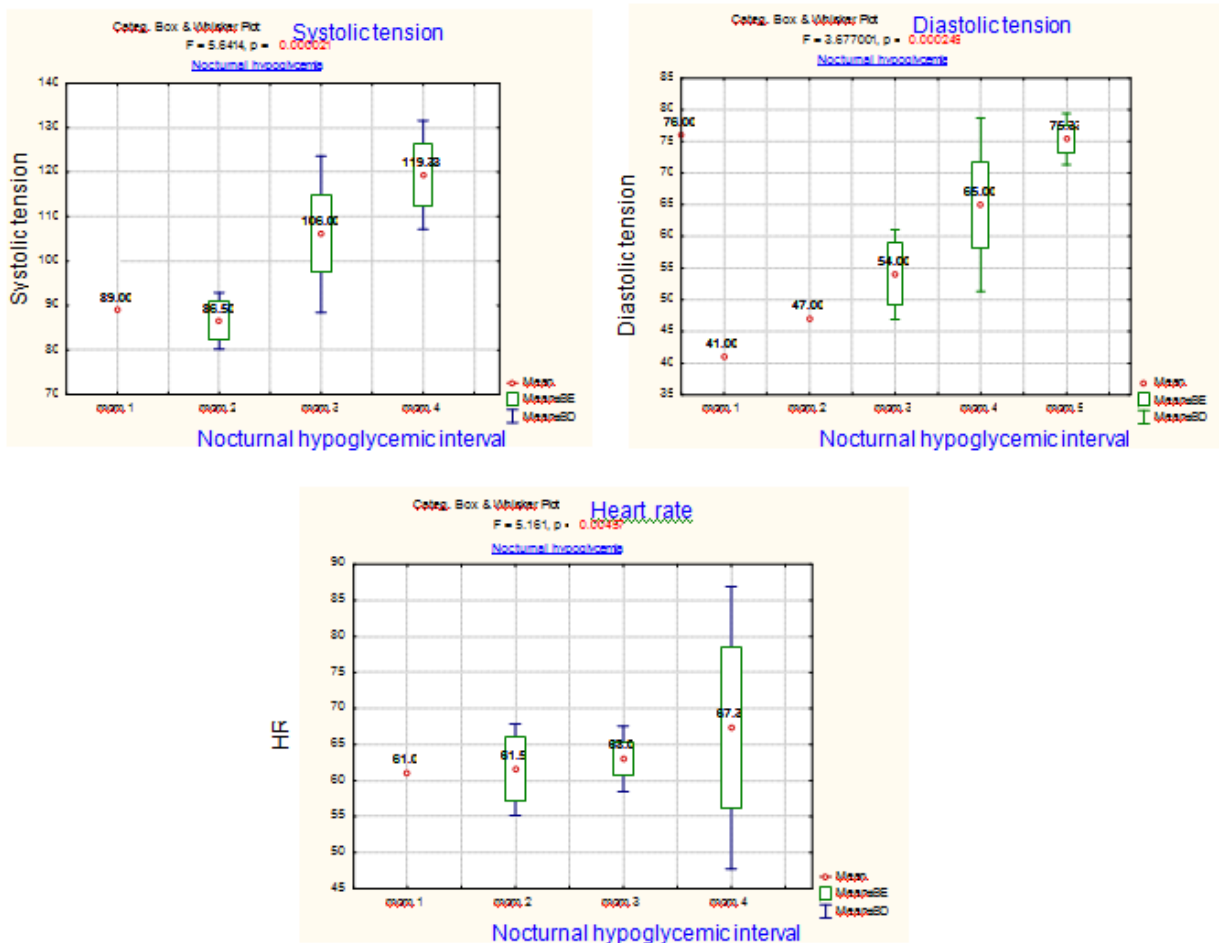


Figure 3. Average values of tension parameters and heart rate in the asymptomatic nocturnal hypoglycemia interval.

Periods of asymptomatic hypoglycemia were noticed in 44 patients who were distributed as follows: 29 cases of hypertensive persons and 15 cases of normotensive persons.

The continuous recording of blood tension during the hypoglycemia period showed

increased values both for the systolic blood tension and for the diastolic blood tension, values which were considered significantly statistic ($p < 0,05$) (Figure 3).

Hypertension risk is by 3.24 higher during the hypoglycemia period compared to the normal glycemia period. (Table 4).

Table 4. Assessing odds and risk parameters of blood hypertension vs. hypoglycemia.

	Estimated value	95% Confidence interval	
		Minimum	Maximum
Odds PARAMETERS			
Odds Report (OR)	3.53	0.05	29.27
Risk PARAMETERS			
Risk Report (RR)	3.24	0.21	7.42

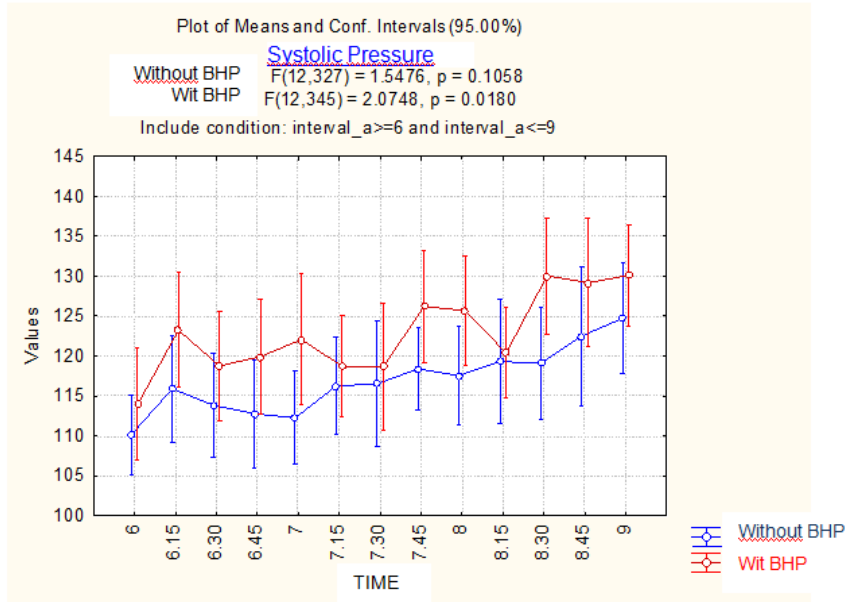


Figure 4. Average values of systolic tension in the special period vs. BHP.

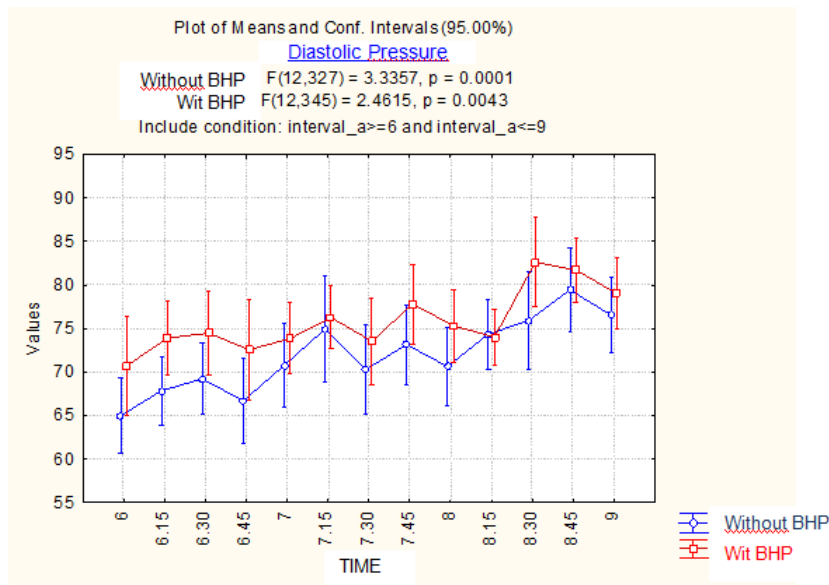


Figure 5. Average values of diastolic tension in the special period vs. BHP.

Tension modifications in the *special period* were noticed in a number of 87 patients who have been suffering from diabetes mellitus for 19.75 ± 4.57 years. Even in the

absence of target organs damage, these tension values are higher than the nocturnal ones, but lower than the diurnal ones. (Figure 4, 5)

Discussions

Nocturnal hypertension is a type of hypotension diagnosed exclusively by continuous monitoring. Normally at nighttime, during sleep, the blood tension values decrease by about 10% from their diurnal value (dipper profile). The decrease under this value characterizes the non-dipper profile. Nocturnal hypertension means an exacerbation of the phenomenon, in which blood tension values at nighttime are higher than the diurnal values (*reverse dipper* or *riser* profile).

Clinical situations that determine the occurrence of this phenomenon in T1DM are as follows:

- Diabetic nephropathy that determines secondary blood hypertension;
- Autonomous neuropathy;
- Effect on target organs.

The production mechanism is represented by a rise in hydrostatic tension at a glomerular level which leads to a form of sodium-induced hypertension. The disorder may lead to the affection of the target organs, especially in stroke [9]. If the nocturnal tension rise manifested as nocturnal blood hypertension determines microalbuminuria, this observation is useful as a potential marker of nephropathy and may supply an argument for the treatment of susceptible persons before microalbuminuria onset.

A recent study assessed on a group of young patients with T1DM the factors that are associated with the rise of nocturnal blood hypertension (*risers*) [10]. These factors are:

- Nocturnal heart rate (rise by 4 mmHg of the average blood hypertension for every increase by 10 beats/minute of the heart rate);

- Subjects height (rise by 4 mmHg of the average blood tension for every 10 cm difference in height);
- Degree of metabolic control (difference of 2 mmHg for 1% change in HbA1c).

The short-term improvement in metabolic control, although it produces a slight decrease in clinical blood tension, it does not influence significantly the continuous monitoring of blood hypertension, a moderate rise in nocturnal values (stressing the non-dipper phenomenon) mostly in patients with frequent hypoglycemia [11].

The conclusions of DCCT determined the benefits for the insulin intensive care in order to normalize glycemic values [12]. To delay microvascular and neurological complications, this therapy was recommended for all patients with T1DM. Unfortunately, the frequency and the seriousness of hypoglycemic episodes is high in this therapy. Insulin therapy in the intensified scheme, in order to maintain glycemia close to normal may determine the damage of the counter-regulation mechanisms of T1DM patients, a short period of moderate hypoglycemia reduces the hormonal response and symptoms the next day after the experimentally-induced hypoglycemia. In intensive care, counter-regulation and hypoglycemic symptoms occur at lower glycemic levels than in the conventional therapy.

In our study, all asymptomatic hypoglycemic episodes were accompanied by tension changes. As the plasmatic glucoses rapidly decreases, a series of adapting feedbacks are produced, such as the release of catecholamines and the rise of heart beats with the rise in systolic and diastolic blood tension which leads to a significant cardiovascular stress. The T1DM and the blood hypertension

get associated which is demonstrated by several clinical trials and hyperinsulinemia may be considered a case of hypertension.

Our study is one of the few specialized studies that followed the cardiovascular feedback (in terms of tension values and heart rate) with hypoglycemia in type 1 diabetes mellitus. We noticed that T1DM patients show a significant rise of systolic and diastolic tension values during hypoglycemia that, together with the higher heart rate, determines a significant rise in heart flow. Cardiovascular changes in hypoglycemia were similar in magnitude but delayed in hypertension patients.

Previous research saw a low catecholamine feedback, mostly with recurrent hypoglycemia [13, 14, 15]. As expected, the counter-regulation feedback in this study is changed, manifested by wider tensional changes, but occurring later on since the hypoglycemia onset. In most type 1 diabetes mellitus patients, the feedback of glucagon in hypoglycemia lowers till disappearance a few months after the diabetes onset. On the other hand, more than 45% of the long-time type 1 diabetes mellitus patients show an alteration in glucagon secretion and in adrenaline secretion which is triggered at lower levels of glycemia than it is normal, the level dropping even more after a recent hypoglycemia [16]. Thus, the cardiovascular feedback is affected, the tensional values rising significantly but later than the hypoglycemia period.

Finally, with or without nocturnal hyperinsulinemia in the case of intensively treated patients, a relative condition of hypoglycemia may appear and may determine catecholamine increase with the secondary increase of the nocturnal blood tension. This aspect imposes the revision of hypoglycemia

treatment in order to avoid nocturnal tension variations which have a definitive and irreversible impact on the specific chronic complications.

In our study, tension values' increase during the *special period* overlaps the morning hyperglycemias. There are three mechanisms of morning glycemic values' increase:

1. Dawn phenomenon which refers to the increase of glycemia and insulin necessary in the morning (between 5 a.m. and 8 a.m.). It is the consequence of peripheral sensitivity decrease at insulin action because of STH hyper secretion,
2. Somogyi phenomenon is the consequence of a nocturnal hypoglycemia, (un) noticed by the patient. The hyperglycemic reaction is determined by the hyper secretion of counter adjustment hormones and of the secondary hepatic glycogenolysis,
3. Underinsulinization by using an insulin type whose action duration and dose do not fully cover the nocturnal period.

An important aspect is the pathological significance of these particularities and their clinical relevance. There are some potential methods by which the tension rise may change the prognostic:

- if the diurnal tension is used as reference level, these patients are exposed to an increased blood tension which can determine the damage of the target organs,
- an excessive morning increase has a pathogenic significance, therefore, considering this criterion, the non-dippers should be among those presenting low risk [17],
- an excessive decrease of the nocturnal blood tension is associated with the ischemic troubles of different organs.

Several studies proved that there are no significantly statistic correlations between

hyperinsulinemia and blood tension increase. Peters et al. proved that this increase of the morning blood tension is not determined by hyperinsulinemia, but by the increase of serial catecholamine level. [18]. Moreover, a reason against insulin role comes from the studies on patients with insulinoma. Just like the patients with insulinoma and compared to the persons with type 2 diabetes, the patients with T1DM have a hyperinsulinemia which is not given by the insulin resistance [19]. Pecis et al. proved a tendency to increased tension values in the morning in patients with T1DM, who are normotensive, normoalbuminuric with the prevalence of the sympathetic activity [20].

In the case of these patients, the continuous blood-tension monitoring represents a real advantage, being an important reason for implementing the treatment, the solution being represented by the use of some antihypertensive solutions with longer action duration which have the capacity of covering this period too.

Conclusions

The study proves a positive correlation between decreased glycemic values and tension values. The statistic analysis showed the fact that there are significant statistic variations during the asymptomatic

hypoglycemia period both for the systolic blood tension and for the diastolic blood tension and heart rate. Hypoglycemia's duration and magnitude induce increased tension values, aspect which adds another hemodynamic stress factor to the patient with type 1 diabetes mellitus.

In T1DM, during the first morning hours, in particular conditions, we can notice increased tension values, higher in patients with blood hypertension which induces a stressed cardiovascular risk. Tension value rise during the *special period* overlaps the morning hyperglycemias.

Continuous blood-tension monitoring in patients with type 1 diabetes mellitus show particular aspects of the tension behavior – variations which are not seen in investigations. The connection between blood hypertension and T1DM results, mainly in the medical practice from the current conception proposed by the European Society of Cardiology which adds the notion of **total** cardiovascular risk [21]. The association between diabetes mellitus and blood tension shows the previous existence of a major coronary incident. This way, we can describe the apparently invisible impact of diabetes mellitus on the cardiovascular condition [22].

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