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IM - COMMENTARY

Non-dipper blood pressure pattern and glycemic alterations: does post-prandial glucose rise predict lack of nocturnal pressure drop?

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Type 2 diabetes (T2DM) and non-dipping pattern of blood pressure (that is, when nocturnal systolic blood pressure falls by < 10% from the daytime systolic blood pressure values) during 24-h ambulatory blood pressure (ABPM) monitoring are two factors both increasing the risk for cardiovascular disease. Little is known about the relationship between the circadian profile of blood pressure dipping pattern and insulin glucose metabolism in patients without any known overt metabolic diseases.

The daily pressure oscillations are related to increased risk of organ damage. A defective function of sympathetic nervous system-mediated regulation of blood pressure can be responsible for pathological nocturnal dipping patterns. There are several observations supporting a link between pathological dipping status and increased risk of silent and clinical cerebrovascular disorders, coronary artery diseases, and heart failure [1].

Similarly, patients with 1-h post-load plasma glucose > 155 mg/dl, during an oral glucose tolerance test, display an increased risk to develop T2DM, clinical/subclinical organ damage, and CV disease than patients with 1-h plasma glucose levels < 155 mg/dl [2].

ABPM non-dipping status is an independent predictor of glucose intolerance. It has been previously shown that a reduction in the actions of insulin may be one of the important physiological defects underlying the abnormal circadian rhythm of blood pressure in patients with T2DM and other related diseases [3]. Insulin resistance was associated with abnormal control of blood pressure and sympathetic activation even in the healthy offspring of T2DM patients [4].

Vice versa, stimulation of the sympathetic activity has been reported to be able to antagonize insulin-mediated glucose uptake in skeletal muscle [5].

In the manuscript by Sciacqua et al. [1], published in Internal and Emergency Medicine, 1-h post-load glycemia higher than 155 mg/dl discriminates those with pathological BP drop (non-dipping and reverse dipping phenotypes) with a strong message for clinical practice, the recommendation to screen for dipping status in normal glucose tolerance (NGT) > 155 and vice versa to perform OGTT with 1-h post-load glycemia in patients with non-dipping blood pressure pattern.

In 810 patients, the proportion of non-dippers among subjects with NGT > 155 mg/dl (36.4%) was higher than in those with NGT < 155 mg/dl (29.6%) and impaired glucose tolerance (IGT) (34.8%), but lower than in T2DM group (52.6%). On stepwise multiple regression analysis, 1-h glucose was the major independent predictor of nocturnal BP reduction, accounting for 6.7% of its variation.

In a previous manuscript by the same group [6], the authors demonstrated that patients with NGT 1-h high are characterized by reduced beta-cell function, and that these patients have an impairment of incretin's ability to potentiate insulin secretion. Thus, 1-h OGTT glucose > 155 mg/dL can discriminate subjects with lower insulin sensitivity and impaired beta-cell function. There is evidence that the brain controls metabolism and that the autonomic nervous system (ANS) can directly regulate blood glucose levels. The parasympathetic branch stimulates pancreatic beta-cells to potentiate insulin secretion and enables enhanced tissue glucose uptake. In contrast, the sympathetic nervous system reduces insulin secretion, leading to an increase in blood glucose.

Glucagon-like peptide 1 receptor agonists (GLP-1Rs) have been found in the neuronal cell body and dendrites in the central nervous system, and liraglutide and the other synthetic GLP-1RAs are able to readily cross the blood–brain barrier. GLP-1 RAs induce a small but significant change in

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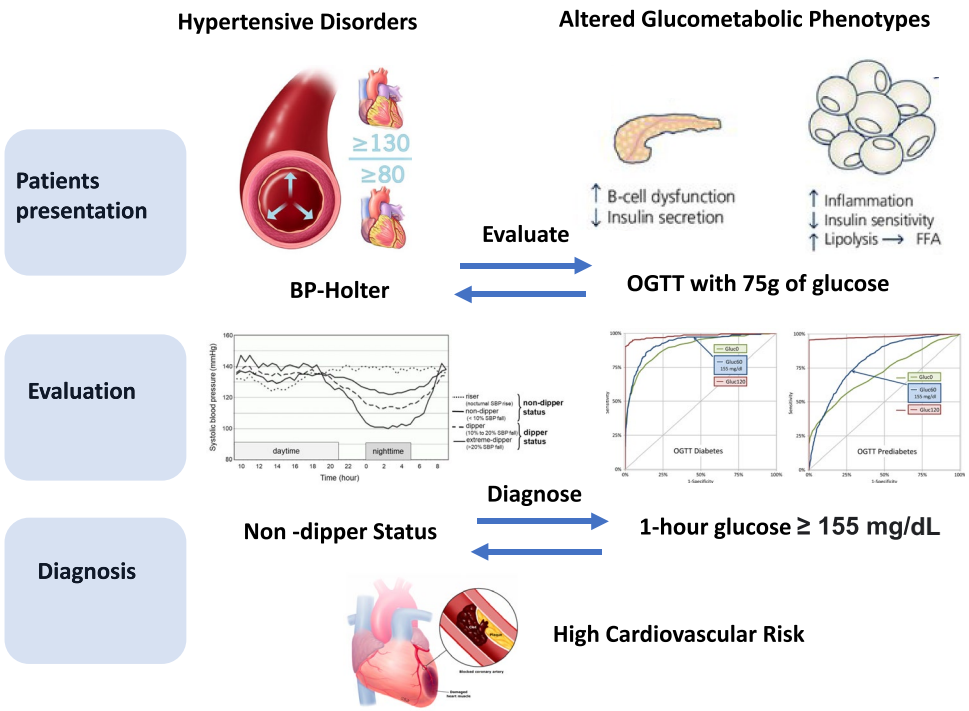

Fig. 1 Management of patients with newly diagnosed hypertension and with altered glucometabolic profile. Patients with non-dipper status may be evaluated also with an OGTT, and patients with 1-h glucose ≥ 155 mg/dL may be evaluated with an BP-Holter, to better stratify cardio-metabolic risk

SBP that occurs early (2–3 weeks after the start of treatment) and appears to be independent of baseline characteristics known to influence BP and the degree of glucose lowering and weight loss. On the other hand, GLP-1 RAs stimulate insulin secretion, inhibit glucagon secretion at pancreatic α cells and improve the incretin effect.

Restoration of the incretin effect, which is impaired in these subjects with 1-h OGTT glucose > 155 mg/dl, with GLP-1RA therapy, may act bi-univocally on both blood glucose and blood pressure pattern, although data on the sympathetic system are scarce. Early chronic metformin treatment normalized the ANS activity of obese rats with metabolic dysfunction. However, whether metformin, able to cross the blood–brain barrier and localize in several brain areas, directly affects the ANS or if acts indirectly through the improvement of metabolic dysfunction is not clear. Thus, while a potential rationale for an early use of both GLP-1RA and metformin exists in those with 1-h OGTT glucose > 155 mg/dl, the benefit of these potential strategies on metabolic, hemodynamic and clinical hard endpoints should be tested in ad hoc studies.

Pregnancy complicated by hypertensive disorders recapitulates the complex pathophysiological intertwining between the described metabolic perturbation and blood pressure patterns and may be an interesting mechanistic model. Indeed, pregnant women with gestational diabetes have increased risk of pregnancy-associated hypertension compared with nondiabetic women; vice versa pregnant patients with hypertension are at increased risk for developing gestational diabetes mellitus; this strong association could be due, at least in part, to insulin resistance [7]. Insulin resistance may probably induce hypertension with mechanisms at the cellular, circulatory, and neurological levels. Intrauterine growth restriction has been linked to a higher risk of vascular disease in adult life.

Sciacqua et al. [1] interestingly observed that male gender was protective for pathological nocturnal BP drop, reducing the odds by 29.4%; thus, female gender may be a risk factor per se for the link between early glucose abnormalities and lack of nocturnal blood pressure drop, and pregnancy may be a paradigm for this ominous association. We can speculate that 1-h post-loading OGTT in pregnant women may identify those at risk of preeclampsia. Ad hoc studies should further improve our comprehension of the underlying pathophysiology.

In conclusion, the findings by Sciacqua et al. [1] should prompt the practicing physician to test with an OGTT patients with non-dipping blood pressure pattern after 24-h ABPM, and vice versa to perform a 24-h ABPM in patients with an abnormal OGTT in terms of 1-h blood glucose above 155 mg/dL, to better stratify the cardiometabolic risk profile (Fig. 1). The feasibility and clinical read-out of this approach should be challenged with longitudinal, adequately sized studies.

Data availability not applicable.

Declarations

Conflict of Interest We uploaded in submission the Conflict of Interest for each author.

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