RESPONSE TO COMMENT ON PAOLISSO ET AL.

Impact of Admission Hyperglycemia on Heart Failure Events and Mortality in Patients With Takotsubo Syndrome at Long-term Follow-up: Data From HIGH-GLUCOTAKO Investigators. Diabetes Care 2021;44:2158–2161

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In a letter in this issue of *Diabetes Care*, Madias suggests that norepinephrine, as mediator of admission hyperglycemia (AH), is an index of increased underlying sympathetic overactivity and/or diabetes comorbidity in patients with takotsubo syndrome (TTS) (1). Indeed, the 28 patients with AH versus the 48 patients without AH had a higher prevalence of diabetes (39.3% vs. 14.6%) (1,2). Notably, AH was a predictor of long-term prognosis in TTS patients (2). Moreover, the patients with AH showed lower left ventricular ejection fraction on admission and discharge and higher B-type natriuretic peptide and inflammatory markers, with the glucose values correlating with serum norepinephrine levels (2). Intriguingly, of the 30 patients who underwent a ^{123}I-MIBG cardiac scintigraphy, patients with AH showed lower late heart-to-mediastinum ratio values at a follow-up of 12 and 24 months than those without AH (2). Furthermore, the patients with AH had higher rates of heart failure (HF) and all-cause mortality after 24 months than those without AH, with tumor necrosis factor-α and serum norepinephrine being independent predictors of HF (2). Thereafter, the acute TTS event appears to link AH to HF via overinflammation and oversympathetic system activation (2).

First, after categorizing the patients with diabetes (DM) as those with versus without AH (DM-AH vs. DM-NAH), we noticed a significant overexpression of norepinephrine (2,489.45 ± 509.7 vs. 1,696.41 ± 435.4 pg/mL; $P = 0.004$) in the DM-AH group; this expression was significantly reduced in patients without diabetes (NDM) with AH (DM-AH vs. NDM-AH: 2,489.45 ± 509.7 vs. 2,000.17 ± 331.25 pg/mL; $P = 0.031$). Therefore, the oversympathetic activity of AH is more evidenced in TTS patients with diabetes than in TTS patients without diabetes. Second, according to Madias's query (1) and as previously discussed in our supplementary materials (2), due to the small number of TTS patients with diabetes, it is not possible to drive any definitive conclusion about the possible and independent effect of hyperglycemia regardless of diabetes status. Therefore, in this context, adequately powered multicenter prospective studies targeting a considerable number of patients with diabetes are warranted.

Finally, as previously suggested by Madias (3,4), euglycemic intravenous insulin therapy, carefully preventing both hypoglycemia and hypokalemia, could be beneficial in the management of TTS. Moreover, in future studies on TTS, we might confirm ameliorative effects on HF events and mortality, not unlike the results observed in patients admitted for acute myocardial infarction (5). Indeed, in patients with acute myocardial infarction, AH is an independent factor in patients with and without diabetes, conditioning a worse prognosis (5). However, insulin therapy could be considered among the first-line therapies in acute settings and to reduce glycemia and the linked oversympathetic activity and overinflammation (3–5). We might conclude by indicating TTS patients with AH as those with a different metabolic, inflammatory, and sympathetic phenotype, and as a population at high risk for worse prognosis.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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