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# Inconsistency amongst the diagnostic criteria based on Ewing's tests for diagnosing cardiac autonomic neuropathy in diabetes mellitus: an under-rated issue

Cardiac autonomic neuropathy (CAN) is a common yet overlooked complication of diabetes mellitus (DM) [1]. CAN poorly correlates with specific symptoms or clinical signs implying that it frequently remains unrecognized until late in the disease trajectory [2]. Moreover, the reported prevalence of CAN varies greatly from as low as 17% to as high as 73% [3, 4]. This huge variation in the prevalence of CAN is in part due to different diagnostic criteria used to identify CAN in various trials. Cardiovascular autonomic reflex tests (CARTs) [consists of 5 heart rate (HR) and blood pressure (BP) tests] proposed by Ewing et al. [5] are considered as the gold standard tests for diagnosing CAN in DM. There are various criteria which utilizes Ewing's test for diagnosing and staging CAN. Most widely used among these criteria is the Ewing's criterion which classifies CAN into no-CAN (all tests normal or 1 test borderline), early (1 HR test abnormal or 2 borderline), definite (two HR test abnormal) and severe (2 HR test abnormal + 1 or both BP tests abnormal) CAN category [5]. This criterion is based on the theoretical conception that sympathetic dysfunction precedes parasympathetic dysfunction in diabetic CAN and hence classifies patients with borderline HR test (which examines parasympathetic dysfunction) as early or

definite CAN and those with borderline or abnormal BP test (which examines sympathetic dysfunction) along with abnormal HR tests under severe category. In DM, similar to peripheral neuropathy, the autonomic neural dysfunction progresses in a length dependent fashion and the vagus nerve (longest autonomic nerve which mediates 75% of all parasympathetic activity) fibers are affected first followed by sympathetic denervation in the later stages [6]. The above discussion makes it clear that Ewing's criterion was certainly influenced by the sequential trend of autonomic dysfunction in diabetic CAN. On the contrary, some investigations have found a simultaneous occurrence of sympathetic and parasympathetic dysfunction without any chronological order for the development of CAN and on rare occasions abnormalities in BP tests may precede the abnormalities in HR tests in DM patients which makes the sequential staging of CAN by Ewing's criterion questionable [7-9]. There are various other classification criteria (based on Ewing's test) which are being used by researchers. Bellavere's criteria include only HR tests [deep breathing test (DBT), Valsalva maneuver (VM), and 30:15 ratio] into consideration and thus does not examine CAN holistically leaving the assessment of cardiac sympathetic function untouched [10]. Furthermore, CAN subcommittee of the Toronto Consensus Panel on diabetic neuropathy suggested combined examination of both CARTs and frequency domain indices of heart rate variability (low frequency power, high frequency power and LF/HF ratio) as a robust measure of CAN diagnosis. It staged CAN into early (1 positive test), definitive (2 or 3 positive test) and severe (orthostatic hypertension + one of the previous criterion) stages without contemplating the trend of

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Clinical Diabetology 2020, 9, 4, 269-270

DOI: 10.5603/DK.2020.0016

Received: 06.04.2020

Accepted: 04.05.2020

cardiac autonomic dysfunction in DM [11]. Mendivill et al. [12] examined the presence of CAN solely by HR tests (DBT, VM, 30:15 ratio) which led to higher reported prevalence (68%) of the disease in that study. Kempler et al. [13] considered only two tests (30:15 ratio and postural drop in BP) rather than the whole battery of CART for diagnosing CAN in DM patients and reported a much lower prevalence of the disease (36%). Similarly, many such studies exist which have not considered the entire Ewing's test battery and have either assessed sympathetic or vagal dysfunction and have left undiagnosed cases (6, 15, 16). For that reason, there is huge discrepancy in the combination of CARTs and the criteria used for the diagnosis and staging of CAN which has definitely contributed to incongruity in the reported prevalence of this condition across the population. This inconsistency is an important gap in the literature which needs to be addressed because using a particular group of CARTs might lead to either many under-diagnosed or incorrectly categorized cases. A more holistic and universal criterion should be designed by future studies for early and definitive diagnosis of CAN which considers early to advance dysfunction of autonomic nervous system rather than parasympathetic to sympathetic since there is still no clear consensus on the trend of autonomic dysfunction in DM. If the future researches could develop a more accurate criteria and implement a more consistent use of the same across the studies working towards diabetic CAN, an accurate diagnosis and staging of CAN would be possible which may help clinicians in implementing timely and appropriate management strategies. Also, an universal diagnostic and staging criterion will be sought out the variability in the reported prevalence of the disease and will make the comparison across different studies easier for research professionals working in the area of cardiovascular diabetology.

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