Impaired Hypoxic Ventilatory Drive Induced by Diabetic Autonomic Neuropathy, A Cause of Misdiagnosed Severe Cardiac Events. Brief Report of Two Cases.

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Case Report

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Abstract

Background: Sudden cardiac death are twice more frequent in diabetic patients with cardiac autonomic neuropathy. Sudden cardiac death etiologies remain unclear and no recommendation are made to identify factor associated with cardiorespiratory arrest in diabetic patients. We hypothesized, from two clinical cases, that impaired hypoxic ventilatory drive, induced by diabetic autonomic neuropathy, is a cause of misdiagnosed severe cardiac events.

Case presentation: We describe the cases of two patients with isolated low blood saturation on pulse oximeter during the systematic nurse check-up (77% and 85% respectively) contrasting with the absence of any complaint as well as any dyspnea, polypnea or other respiratory insufficiency signs observed during the clinical examination. Arterial blood gas measurements subsequently confirmed that blood saturation was low and that both patients were indeed hypoxemic. Patient 1 suffered of vascular overload complicated by cardiac arrest caused by hypoxemia in light of the quick recovery observed after ventilation. Pulmonary edema was diagnosed in patient 2. The common denominator of these 2 cases described in this brief report is the absence of respiratory failure clinical signs contrasting with the presence of confirmed hypoxemia. Also, in both cases, such absence of precursory signs seems to be induced by an impaired ventilatory drive to hypoxemia. This appears to be related to the autonomic diabetic neuropathy encountered in those 2 patients.

Conclusions: Therefore, we describe, in this brief report, cardiac autonomic neuropathy as a cause of impaired hypoxic ventilatory drive involved in severe acute cardiorespiratory events in two type 1 diabetic patients. We assume that altered response to hypoxemia due to cardiac autonomic neuropathy and non-functional central neurological breathing command could play a key role in sudden deaths among diabetic patients. A point to emphasize is that hypoxemia can be easily missed since no clinical signs of respiratory failure are reported in these two clinical cases. Systematic screening of cardiac autonomic neuropathy in diabetic patients and proactive detection of impaired hypoxic ventilatory drive for early management (e.g. treatment of hypoxemia) should be systematically undertaken in diabetic patients to prevent its dramatic consequences such as cardiorespiratory arrest and death.

Background

Among diabetic complications, neuropathy has been thought to be nonlethal and is often poorly evaluated. Different surveys reveal that about only 65% of diabetic patients yearly have a 10-g monofilament testing for neuropathy screening and certainly many fewer have a cardiac autonomic neuropathy screening. The reported prevalence of CAN varies greatly according to the criteria used to define it, as well as to the characteristics of the population investigated. CAN prevalence ranges from as low as 2.5% in the primary prevention cohort in the Diabetes Control and Complications Trial (DCCT) to as high as 90% in patients with long-standing type 1 diabetes who were potential candidates for pancreas transplantation. Several studies suggest that the mortality rate of diabetic patients is higher in those with established diabetic neuropathy, particularly cardiac autonomic neuropathy (CAN), than
Of note, whereas sudden cardiac deaths (SCD) mainly account for such increased mortality rate in diabetic patients suffering from CAN, SCD mechanisms are probably multiple and not yet clearly understood.

Clinical Manifestations of CAN are numerous. Some are minor, such as resting tachycardia, exercise intolerance, orthostatic tachycardia and bradycardia syndromes. Some others may lead to complications, including intraoperative and perioperative cardiovascular instability, orthostatic hypotension, silent myocardial ischemia, or autonomic cardiopathy associated with left ventricular diastolic dysfunction.

Ewing et al. proposed 5 tests in 1985 to evidence CAN in diabetic patients.

We assumed that altered response to hypoxemia due to CAN and non-functional central neurological breathing command could play a key role in these sudden deaths, and such assumption has set the stage for this brief report of sudden serious cardiorespiratory events without clinical signs associated that have occurred in 2 diabetic patients with severe CAN hospitalized in our department.

**Case Presentation**

Ewing’s tests were used to diagnose CAN in our 2 patients. Heart rate responses to deep breathing and to standing up were measured using an electrocardiogram. Blood pressure response to standing up was measured automatically by Dinamap®. We couldn't perform the Valsalva test because of proliferative retinopathy presence in the 2 patients.

The first patient was a 54-year-old woman, on insulin therapy since 2000, i.e. upon discovery of type 1 diabetes in context of polyuria-polydipsia syndrome. Since then, her diabetes was poorly controlled, with multiple hospitalizations for ketoacidosis and chronically elevated HbA1c level between 11 and 15% (97 and 140 mmol/mol respectively). Diabetes complications therefore developed, including laser-required diabetic retinopathy and end stage chronic kidney disease requiring dialysis. However, this patient had not experienced any history of impaired cardiac or respiratory condition. She was non-smoking and her last cardiovascular evaluation in 2015 reported no evidence of supra aortic trunks atheroma and a low coronary calcium score of 14.

The second patient was also a 55-year-old type 1 diabetic woman. Her diabetes was discovered in 1973 in relation to a ketoacid coma. Insulin therapy was immediately started. As her diabetes began early in childhood and was poorly controlled, she also developed a severe retinopathy that is treated, as well as an end-stage kidney failure that has required kidney transplantation. Many cardiovascular comorbidities are present, including ischemic cardiomyopathy with left ventricular dysfunction, multiple vascular lower limb stenting and bypass, hypertension and bilateral transtibial amputation. In contrast, there is no impaired respiratory condition detected so far. Her diabetes is actya

Both patients were admitted in the podiatry care unit of the Diabetology Department at the Pitié-Salpêtrière Hospital (Paris, France) due to an infected lower limb wound, respectively located on the left
heel and the right lower limb stump.

Like every new admitted patient, they were screened for CAN, confirmed in both cases to be severe, as per Ewing’s classification. Indeed, they both displayed an orthostatic hypotension associated to an inappropriate heart rate response to standing up and to deep breathing.

The common denominator of these 2 clinical cases was isolated low blood saturation on pulse oximeter during the systematic nurse check-up (77% and 85% respectively) contrasting with the absence of any complaint as well as any dyspnea, polypnea or signs of respiratory insufficiency signs observed during the clinical examination (Table 1). Of note, arterial blood gas measurements subsequently confirmed that blood saturation was low and that both patients were indeed hypoxemic.

Table 1
Patients CAN features and clinical respiratory outcomes during the episode.

|                           | Patient 1 | Patient 2 | Normal  |
|---------------------------|-----------|-----------|---------|
| CAN                       | HR to deep breathing | 1.05 | 1.01 | >1.11 |
|                           | HR to standing up | 1.0 | 1.09 | >1.12 |
|                           | BP drop to standing up | + | + | - |
| Acute hypoxemia           | SaO2 (%)  | 77 | 85 | >95% |
|                           | PaO2 (mmHg) | 59 | 60 | 83–108 |
|                           | PaCO2 (mmHg) | 55 | 37 | 32–45 |
|                           | Breath rate (/min) | 12 | 14 | 12–20 |
|                           | Dyspnea    | - | - | |
|                           | Labored breathing | - | - | |
|                           | Paradoxical breathing | - | - | |
|                           | Cyanosis    | + | - | |

CAN: cardiac autonomic neuropathy

HR: heart ratio

BP: blood pressure

PaO2: Partial pressure of oxygen in arterial blood

PaCO2: Partial pressure of carbon dioxide in arterial blood

SaO2: Oxygen saturation on pulse oximeter
Patient 1. Since few days before the acute event, no efficient ultrafiltration was performed because of patient drowsiness. The patient presents therefore vascular overload with lower limbs edema, pleural effusions and several hypoxemia episodes objectified by a daily pulse oximetry around 90–92% without oxygen therapy contrasting with the absence of dyspnea or signs of respiratory failure. Close monitoring of oxygen saturation was performed. Few minutes after the observation of 77% on the pulse oximeter and blood gas measurements (PaO₂ 59 mmHg - PaCO₂ 55 mmHg), the patient was found unconscious, without any cardiac pulse and breathing. She instantly had heart massage and endotracheal intubation for artificial ventilation. After 2 minutes of cardiopulmonary resuscitation, she recovered spontaneous cardiac rhythm without any cardiac electric shock or drugs. She was transferred to the intensive care unit. A thoracic CT scan eliminated a pulmonary embolism but reported abundant bilateral pleural effusion. Unchanged ECG, normal echocardiography and negative troponin were strong arguments against myocardial infarction. Fever and blood inflammation's markers were absent, as was evidence of obvious metabolic disorder like dyskalemia or hypoglycemia. Cardiac arrest was considered to be probably caused by hypoxemia in light of the quick recovery observed after ventilation, as well as blood gas analysis reporting hypoxemia and hypercapnia. As no drugs with central respiratory depressant effect had been given the previous days, the main retained risk factor of hypoxemia was vascular overload due to underestimated dialysis volume depletion. Continuation of dialysis sessions allowed for progressive volume depletion (decreased weight from 75.7 to 60.8 kg) and correction of hypoxemia with PaO₂ ≥ 90 mmHg on blood gas analysis control.

Patient 2. During the systematic nurse check-up, low saturation at 85% on the pulse oximeter was objectified. There was no dyspnea nor respiratory discomfort. The patient was immediately put on 9L oxygen and recovered 95% pulse oximetry. She was then transferred to the cardiac intensive care unit, following evidence of pulmonary edema detected by pulmonary examination and chest CT scan. In view of increased troponin, modified ECG and cardiac hypokinesia during echocardiography, a diagnosis of pulmonary edema secondary to acute coronary syndrome was retained. The patient recovered normal oxygen blood saturation after diuretics medication and then received specific cardiovascular therapy.

Discussion And Conclusion

The common denominator of the above 2 cases is the absence of dyspnea or precursory signs of the sudden cardiorespiratory event contrasting with the presence of confirmed hypoxemia by pulse oximeter plus blood markers, and real cause of hypoxemia.

Also, in both cases, such absence of precursory signs seemed to be related to the severity of the diabetic neurological autonomic disorder which could be objectified by CAN screening. That is why these particularities are suspected to cause sudden cardiac deaths. Those observations seem to be aligned with previously published reports of unexplained sudden deaths in patients with CAN. A recent meta-analysis of 14 studies involving a total of 5647 SCD cases and 346,356 participants evidenced a two-fold higher risk of SCD in subjects with diabetes. Presence of CAN was found to be a significant contributor
to such observations. Indeed, in an analysis of 2900 diabetic subjects, Vinik et al. showed that the subset of those with CAN (defined by an abnormal Ewing's test) had a significant 2.14 relative risk of death, even escalating up to 3.65 if CAN was defined by the presence of more than 2 abnormal quantitative autonomic function tests \(^2\), thereby showing a clear relationship between CAN severity and mortality. Several 90's studies previously brought to light dysfunction of the central neurological breathing command in patients with CAN leading to hypoxemia. For example, central obstructive sleep apnea \(^7\) and desaturation episodes under 85% \(^8\) were shown to be more prevalent in diabetic patients with CAN than in those without. Furthermore, impaired hypoxic ventilatory drive in diabetic patients with CAN was also underlined by numerous studies\(^9\)\(^10\). In fact, compared to control participants, basal baroreflex sensitivity is blunted in type 1 diabetic patients with CAN. These latter are not able to spontaneously increase their ventilation to fight against hypoxia, and short-term oxygen administration could restore temporarily the baroreflex sensitivity\(^11\).

All those results constitute a solid body of evidence suggesting that patients with CAN lose their ability to increase minute ventilation to hypoxia. Physiopathologically, chemosensors of ventilatory drive are no more stimulated by hypoxemia. Since chemosensors such as carotid bodies, sensitive to arterial oxygen pressure, are innervated by parasympathetic system, patients displaying a severe CAN probably present an impaired hypoxic ventilatory drive response by impairment of their autonomic nervous system. Delayed hypoxemia management due to absence of warning clinical signs could favor occurrence of sudden cardiorespiratory event and lead to dramatic consequences such as death.

A point to emphasize is that hypoxemia can be easily missed since no clinical signs of respiratory failure are reported in these two clinical cases. Systematic screening of CAN and proactive detection of impaired hypoxic ventilatory drive for early management (e.g. treatment of hypoxemia) should be systematically undertaken in diabetic patients to prevent its dramatic consequences such as cardiorespiratory arrest and death. This would also allow for careful handling of respiratory depressant medications in this population at higher risk of SCD, particularly in case of associated cardiac and pulmonary chronic diseases, general anesthesia, severe sleep apnea syndrome or any medical situation exacerbating hypoxemia.

**Abbreviations**

BP
blood pressure
CAN
Cardiac autonomic neuropathy
DCCT
Diabetes Control and Complications Trial
HR
heart ratio
PaO2
Partial Pressure of Oxygen in arterial blood
PaCO2
Partial pressure of Carbon dioxide in arterial blood
SaO2
Oxygen saturation on pulse oximeter
SCD
sudden cardiac deaths

Declarations

Ethics approval and consent to participate: this brief report meets local ethical criteria; patients gave their consent for clinical and biological data collection.

Consent for publication: The patients gave informed consent for clinical data use and for publication.

Availability of data and materials: Data are available on request from the corresponding author.

Competing interests: No conflict of interest in the area of this study.

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Authors' contributions: L.S., S.L., F.P. contributed to the acquisition of the data. ; L.S., F.P. and O.B. interpreted the data and drafted the report. S.L. and A.H. contributed to the review of the report. All authors read and approved the final version for submission. O.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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