

Autonomic neuropathy in anaesthesia

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Introduction

Autonomic neuropathy is a common problem encountered by anaesthetists, both in operating theatres and in the critical care setting. There are a wide variety of causes, many of them associated with significant co-morbidity. It is clear that it is a problem which involves every system on a number of levels, and many of the issues are of particular significance to the anaesthetist. This review will cover briefly the aetiology and diagnosis of autonomic dysfunction, before discussing the clinical manifestations and consequences of the disorder. The major focus will be on cardiovascular autonomic neuropathy (CAN) and its implications for the peri-operative phase. In addition, it will briefly look at the involvement of the enteric nervous system, as well as deal with some of the new concepts emerging in the literature.

The autonomic nervous system (ANS) is involved in the regulation of every organ system in the body. Its influence extends from manipulating blood pressure, heart rate and cardiac output to affecting thermoregulation, sleep patterns and bladder and bowel function. This is most apparent when one considers the stress response, which is a complex series of physiological mechanisms designed to optimise the body's ability to deal with some form of threat. The response of each organ system, while autonomous, is nevertheless interdependent, and the conductor of this integrated response is the ANS. Is it any wonder therefore that dysfunction of this system, even if mild, should have the potential to cause such a significant physiological impact?

Claude Bernard, considered by many to be the father of modern physiology, said that complex physiological mechanisms have a common purpose, and that is the maintenance of the stability of the interior in the face of stress.¹ His concepts of homeostasis should remind us that the hallmark of health is the ability to adapt, and at the heart of the response to a stressor, be it surgical, anaesthetic or otherwise, is the inherent "adaptability" of the organism. If the system which co-

ordinates all the other systems loses this plasticity, the organ systems under its control cannot hope to function effectively.

Aetiology and prevalence

The most common cause of autonomic neuropathy in developed countries is diabetes mellitus.² CAN is present in approximately 25% of the patients with type 1 diabetes mellitus and in 34% of those with type 2 diabetes mellitus. The prevalence of CAN progressively increases in direct proportion to age, duration of diabetes and worsening glycaemic control.³

Autonomic dysfunction is known to occur in patients with HIV⁴ and, in the South African context, it is likely to account for a significant number of patients presenting with autonomic dysfunction. Although it seems to be more frequent and severe in patients with AIDS, recent literature suggests that HIV positive patients in the early stages of infection may also show evidence of dysautonomia.⁴

There are very few studies which look at the prevalence of autonomic neuropathy in African patients, and only one that specifically examines the prevalence in sub-Saharan Africans. Compostella et al recently looked at CAN in HIV-positive patients in Mozambique.⁴ In a well-designed study, they estimated the prevalence to be approximately 30%, but looked at just 30 patients. Its prevalence in the literature ranges from 5% to 77%, depending on the population studied and on the definition of autonomic dysfunction used.⁴

Making the diagnosis

Ewing and Clark described a method for the evaluation of cardiovascular autonomic reflexes involving five simple tests which could be performed with routinely available equipment and in 20 minutes.⁵ While their method was described for diabetic autonomic neuropathy, they stated that the tests were "equally applicable in the diagnosis of autonomic damage caused by other disorders". Essentially the tests look

at the response of blood pressure and heart rate to a number of stimuli, and evaluate the integrity of both parasympathetic and sympathetic components of the autonomic system.

Tests evaluating cardiac parasympathetic function

- Heart rate response to Valsalva manoeuvre
- Heart rate variation during deep breathing
- Immediate heart rate response to standing

Tests evaluating cardiac sympathetic function

- Blood pressure response to standing
- Blood pressure response to sustained handgrip

Ewing and Clark recommended that all five tests be conducted in order to obtain as much information as possible about both parasympathetic and sympathetic pathways.⁵ They grouped their results into one of four categories:

1. Normal (no tests abnormal)
2. Early parasympathetic damage (at least one test abnormal)
3. Definite parasympathetic damage (at least 2 tests abnormal)
4. Combined parasympathetic and sympathetic damage (positive results in both categories)

The natural history of autonomic damage in diabetics appeared to be parasympathetic damage first, followed by sympathetic damage. This was the primary reason that Clark and Ewing gave for the grouping as described above.

Questionnaires

Is it possible to ascertain whether a patient has autonomic dysfunction from a history? Various questionnaires have been designed for this purpose, including the Autonomic Symptom Profile (known as COMPASS, the composite autonomic symptom scale) from the Mayo Clinic in Rochester.⁶ It consists of 169 questions, although 57 of these relate to demographics. It was designed predominantly as a research tool, and is unlikely to be administered on the premed visit! It also relies on symptoms to make the diagnosis, and will thus miss more subtle levels of dysfunction that autonomic testing may elicit.

Heart rate variability

There are numerous problems inherent in the above methods of testing, but perhaps the biggest challenge is finding a method that can be used in a practical manner on a pre-operative visit. None of the techniques described above is likely to be routinely performed. So is there no easier way to access the autonomic nervous system? The answer may lie in measurements of heart rate variability (HRV). Physiologic systems constantly change over time and in response to different stimuli. In young, healthy subjects they exhibit marked physiologic signal variability and complexity, whereas

ageing or diseased systems show a loss of variability, decreased complexity, and increased regularity.⁷

The loss of variability in the heart rate is one of the earliest signs of autonomic dysfunction, and the technology behind this method has been used for decades by obstetric staff with their analysis of the cardiocogram (CTG). While the CTG provides a visual assessment of heart rate variability, newer methods involve a variety of forms of analysis, including time-domain, frequency domain and non-linear mathematics. In essence, all that is required is an ECG trace and the ability to measure the time between R-R intervals. The trace can be obtained on a patient at rest, or during various manoeuvres such as deep breathing or standing. The raw data are processed by software which is freely available on the internet. These results are available within 5 minutes and could be requested as easily as an ECG.

Clinical consequences

Cardiovascular autonomic neuropathy

CAN is one of the most clinically significant complications of diabetes mellitus, but one of the least frequently diagnosed.⁶ The following clinical manifestations may be associated with CAN: resting tachycardia, severe orthostatic hypotension, syncope, exercise intolerance, peri-operative instability, asymptomatic myocardial ischaemia and infarction, left ventricular diastolic and systolic dysfunction, and increased risk of renal diseases, chronic renal failure, stroke, and sudden cardiac death.⁶

Filipovic⁸ showed that heart rate variability abnormalities (using frequency domain analysis) before induction of anaesthesia was a strong and independent predictor of both all-cause mortality and major cardiac events within two years in patients with documented or suspected coronary artery disease undergoing major noncardiac surgery. This result confirmed their previous findings about the prognostic value of heart rate variability for 1-year mortality in a similar population, and is consistent with findings in the general population and in non-surgical patients with acute coronary artery disease and congestive heart failure.⁸

Several studies of cardiac patients suggest that decreased HRV as well as baroreceptor dysfunction are more powerful predictors for cardiovascular mortality than established clinical predictors, such as left ventricular ejection fraction and ventricular premature complexes.⁹

HRV is also being used in a number of other settings. It appears that HRV may reflect the functional state of the central nervous system in the setting of severe brain damage, and has been correlated with severity,

survival and neurological outcome.⁷ HRV has also been suggested as a complementary tool in the diagnosis of brainstem death.

It has been hypothesised that septic shock results in an uncoupling of organ system interconnectivity, and that the uncoupling phenomenon could be quantified as a loss in HRV.¹⁰ Studies in paediatric critical care, as well as in healthy volunteers administered endotoxin, have supported this hypothesis.¹¹ It has also been observed that the loss of fine variability may herald the onset of multiple organ dysfunction syndrome, and that its return may signal the return to health. This is somewhat ironically referred to as *de-complexification*.¹² Uncoupling of autonomic regulation has also been witnessed in healthy athletes, and investigators speculate that it may rather be a failure of *re-coupling* that is being observed in the critically ill patient. Regardless of mechanism, this information is being used to diagnose and prognosticate as well as to inspire new forms of therapy. The new therapies, many of them theoretical, have exciting names like chaos control and chaos anti-control,¹ the principle being that external stimuli can be used to alter physiological dynamics and hopefully improve patient outcome.

Perioperative instability

Peri-operative cardiovascular morbidity and mortality are increased two- to three-fold in patients with diabetes. Compared with non-diabetic subjects, diabetic patients undergoing general anaesthesia may experience a greater degree of decline in heart rate and blood pressure during induction of anaesthesia, and less of an increase after tracheal intubation and extubation. Vasopressor support is needed more often in diabetic individuals with CAN than in those without CAN.¹³ Recent studies have shown that altered HRV parameters can identify patients at risk of developing severe hypotension during spinal anaesthesia for Caesarean delivery or for prostate gland procedures in ASA I or II patients.^{14,15} In addition, there is an association between CAN and more severe intra-operative hypothermia¹⁶ that results in decreased drug metabolism and impaired wound healing. In a recent review, Laito et al concluded that low HRV was a major risk factor for adverse cardiovascular events in surgical patients, and that HRV measurements could be used to stratify postoperative cardiovascular risk.⁹

Gastroparesis: rapid sequence induction?

One of the principal concerns for anaesthetists, when considering patients with autonomic neuropathy for surgery, is the degree of gastroparesis and whether or not endotracheal intubation is required. Discussions often centre on the need for a rapid sequence induction to prevent aspiration. It should be remembered that proving cardiovascular autonomic dysfunction does not necessarily mean that enteric involvement is inevitable. In diabetic patients, gastrointestinal symptoms are relatively common, but are more likely

due to other factors than to autonomic dysfunction.¹⁷ Gastroparesis in diabetics is usually clinically silent, and the presence of symptoms should prompt investigation for other causes. Gastric emptying in HIV positive patients is often delayed, but this may not necessarily correlate with autonomic dysfunction, and is multifactorial in nature.¹⁸

Even if we assume that there is some degree of gastroparesis present, should this lead to a rapid sequence induction in fasted patients? To assist in answering this question, it is instructive to look back at Mendelson's original paper on the subject of aspiration.¹⁹ He examined 44 016 cases of women who underwent general anaesthesia for Caesarean section. They were anaesthetised with nitrous oxide and ether administered by a face mask. There were only 66 cases of aspiration (0.15%), two of which subsequently died (0.005%). This is a population group with a classically high risk of aspiration, having increased residual gastric volumes and delayed gastric emptying, as well as a number of physiological and anatomical changes which predispose to reflux and regurgitation.

So what should we do in fasted patients with documented autonomic neuropathy? We know that the risk of aspiration is reasonably low even in a high risk group. It is also apparent that many researchers are choosing cardiovascular stability over rapid sequence intubation in their studies. In particular in diabetic patients, autonomic neuropathy is commonly accompanied by vascular involvement such as coronary artery disease. There is little evidence to provide clarity on the subject. It does seem reasonable, however, that in the absence of other risk factors for aspiration, a rapid sequence intubation is not necessarily essential, particularly if other co-morbidity suggests that haemodynamic stability is important.

Conclusion

Autonomic neuropathy is thus a disorder that involves every organ system and has a wide number of clinical consequences. While reasonably simple, testing is time consuming, requires specialised equipment and may be difficult to obtain. Newer methods of analysis show promise in eliminating these issues. Autonomic dysfunction has been shown to be predictive of significant cardiovascular risk, both in the intraoperative and postoperative phases and accurate evaluation of the autonomic nervous system appears to be a goal worth pursuing. Recent techniques of analysis are allowing a greater insight into ageing and many disease processes, and it is possible that, in the future, measures of autonomic function may become routine. Anaesthetists need to be aware of the issues surrounding autonomic neuropathy in order to anticipate and possibly prevent peri-operative complications.

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