For debates

Pharmacologic modulation of autonomic tone: implications for the diabetic patient

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Diabetic autonomic neuropathy (DAN) is divided into two categories: clinical DAN based on objective signs or subjective symptoms, and subclinical DAN which can be detected in asymptomatic patients by employing specific and sensitive diagnostic tests [1]. Although clinical features of autonomic neuropathy generally occur only in patients with diabetes mellitus of long duration, it has become evident that subclinical DAN, mainly in the form of cardiac autonomic neuropathy (CAN), evolves early in the course of diabetes [1–3], and in the absence of other microvascular complications [3–5]. The hallmark and earliest indicator of CAN is a reduced heart rate variability (HRV) [6]. CAN is diagnosed by using a battery of cardiac autonomic function tests that evaluate changes in HRV [1, 7]. Recently, power spectral analysis of heart rate variations has proved a useful tool in evaluating cardiovascular autonomic activity [5, 8]. Estimates of the prevalence of abnormal cardiovascular autonomic reflexes range from 8 % in recently diagnosed insulin-dependent diabetic patients [3] to 90 % in candidates for pancreas transplantation [9].

DAN carries an increased risk of mortality [10–13]. A proportion of diabetic patients with clinical DAN die suddenly and unexpectedly and many of these unheralded deaths are presumed to be due to cardiac arrhythmias [10, 11, 14]. The applicability of evidence incriminating DAN in the genesis of sudden cardiac death (SCD) to the wider population of patients with isolated CAN remains uncertain. However, several studies suggest that even subclinical autonomic dysfunction may be predictive of future mortality [12, 13, 15]. In addition, data from the Honolulu Heart Program indicate that diabetes may be independently associated with the risk of SCD, and that this predisposition is also related to increased risk for arrhythmic death [16].

In recent years compelling evidence has been provided for the existence of a close relation between the autonomic nervous system of the heart and the development of cardiac arrhythmias and SCD. The risk of fatal ventricular arrhythmia is likely to be greatest in patients who have both CAN and an arrhythmic substrate, as a result of myocardial damage and scarring (see below). Since cardiovascular disease is commonly present in diabetic patients, the proarrhythmic potential of coexistent isolated CAN is likely to be of clinical relevance. Furthermore, recent studies indicate that drugs exert a modulating effect on the autonomic nervous system, and hence have the potential to improve or worsen prognosis in selected patient populations.

Mechanisms for increased mortality in autonomic failure

A full understanding of the mechanisms by which CAN leads to an excess cardiovascular mortality is still lacking. The mechanisms by which DAN has been most frequently postulated to increase mortality include increased susceptibility to fatal ventricular arrhythmias, and increased propensity to cardiovascular events.

Increased susceptibility to ventricular arrhythmias

Extensive experimental and clinical evidence suggests that changes in autonomic neural activity are important in the genesis of cardiac arrhythmias [17]. In general, sympathetic activation or parasympathetic

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Abbreviations: CAN, Cardiac autonomic neuropathy; CAST, Cardiac Arrhythmia Suppression Trial; DAN, diabetic autonomic neuropathy; HRV, heart rate variability; MI, myocardial infarction; SCD, sudden cardiac death.

withdrawal facilitate formation of ventricular arrhythmias. In animal models of SCD reduced vagal activity has been associated with a greater risk for malignant ventricular arrhythmias whereas vagal stimulation reduces the incidence of ventricular fibrillation after myocardial infarction (MI) [17, 18]. Similarly, direct stimulation of cardiac sympathetic nerves has been shown to reduce the threshold for ventricular fibrillation [17].

Although fluctuations of heart rate are a complex phenomenon, determined by different autonomic influences, analysis of HRV provides a sensitive, non-invasive index of sympathetic and vagal modulation of the SA node, and can predict poor arrhythmic outcome. Clinical investigations have consistently shown that restricted HRV is a marker of autonomic imbalance that favours the development of cardiac arrhythmias and SCD mainly in conjunction with left ventricular dysfunction and in patients surviving MI [17]. In these patients, diminished HRV constitutes an independent risk factor for mortality [19–22]. Currently, prognostically important autonomic indices are being applied to evaluate patients at high risk for SCD [17, 19].

Another mechanism that may contribute to the risk of arrhythmia formation in diabetic patients affected by DAN is QTc interval prolongation. Based on the observation that the hereditary long QT interval syndromes are related to enhanced sympathetic tone, it has been suggested that autonomic imbalance in DAN results in QTc interval prolongation that predisposes diabetic patients to cardiac arrhythmias. A number of studies have shown a relationship between QTc interval and the presence and degree of autonomic dysfunction in diabetic patients [23, 24].

Since signs of CAN can be detected in young IDDM patients [2, 3], disturbed autonomic function is unlikely to be the sole determinant in the genesis of ventricular arrhythmias. Rather, CAN appears to be a contributing mechanism increasing the propensity for fatal ventricular arrhythmias in the presence of an arrhythmic substrate. The anatomic substrate for SCD is frequently a chronically abnormal myocardium harbouring various degrees of fibrosis (e.g. healed MI), and evidence of coronary artery disease [25]. Thus, diabetic patients with symptomatic DAN may be at higher risk for SCD compared with patients with isolated CAN [10, 12], simply because they represent a subgroup with advanced disease and multiple complications including myocardial damage and scarring secondary to coronary artery disease, diabetic cardiomyopathy, or hypertension.

Increased propensity to cardiovascular events

In the general population, the circadian pattern of cardiovascular events such as acute MI or SCD [26] parallels the temporal pattern of the autonomic nervous system. Moreover, in patients who sustained SCD as a result of a ventricular arrhythmia a marked circadian variation is observed, whereas the time of death from electromechanical dissociation or asystole is relatively evenly distributed throughout the day [27]. Sympathetic tone predominates during the daytime, when the onset of cardiac events is maximal. The circadian distribution of onset of symptoms of AMI is altered in the diabetic population with a shift from morning hours to the evening and night hours [28]. Recent studies indicate that diabetic patients with CAN have altered diurnal modulation of the autonomic tone with enhanced sympathetic tone during daytime and loss of the parasympathetic dominance during night-time [29, 30]. Hence, the longer exposure to the potentially deleterious effects of sympathetic predominance may trigger cardiovascular events [29, 30].

Pharmacologic interventions affecting autonomic balance

In susceptible patients, pharmacologic manipulation of cardiac autonomic function can induce a favourable or detrimental change in the electrophysiologic milieu of the heart [18, 19]. Consequently, the effect of various drugs on HRV may correlate with their beneficial or adverse effects on the propensity to SCD (Table 1).

Several pharmacologic interventions have been tested to determine their effectiveness in reducing the risk for SCD in high-risk patients. So far only treatment with β-adrenergic blockers has been proven effective [31]. Long-term therapy with β-adrenergic blockers without intrinsic sympathomimetic activity, increases HRV [32, 33], and is unequivocally associated with a substantial reduction of mortality in patients surviving MI [31, 34–37] (Table 1). The reduction in mortality has been primarily due to reduction in SCD, which has been most evident in so-called high-risk patients (elderly, patients with large infarcts, or congestive heart failure) [31, 34].

In contrast to their effect on lowering blood pressure or reducing ischaemia, the beneficial effect on mortality following MI does not extend to all types of β-blockers. Agents with intrinsic sympathomimetic activity (e.g. pindolol), which increase HRV [38], have shown no significant effect on mortality [34, 39]. Moreover, the long-term reduction in SCD has only been clearly shown with lipophilic agents that readily penetrate the blood-brain barrier [31], presumably because the reduction in SCD is, at least in part, mediated through the blockade of β_1-receptors in the central nervous system that decreases sympathetic outflow [31].

The effects of other drugs on the cardiac autonomic system also seem to correlate with their

Table 1. The effects of drugs on heart rate variation (HRV) in relation to their efficacy in preventing sudden cardiac death (SCD)

Drug	Effect on HRV	Effects on survival and SCD
Lipophilic β-blockers without ISA (e.g. metoprolol, timolol)	Increase [32, 33]	Metoprolol reduces post-MI SCD by 40% [37] Timolol reduces incidence of SCD post-MI by 44% [35] Propranolol decreases post-MI SCD by 28% [36]
β-blockers with ISA (e.g. pindolol)	Decrease [39]	No significant effect [34]. May increase mortality in diabetic patients [39]
Diltiazem	Decrease [19]	May decrease mortality in patients with preserved left ventricular function [60]
Dihydropyridine calcium-channel blockers (e.g. nifedipine)	No consistent effect [19, 33]	May increase mortality [61]
Amiodarone	No change [42]	No reduction in incidence of SCD [62]
ACE inhibitors	Increase [40]	Decreases mortality in patients with chronic congestive heart failure and following Acute MI
Class I c antiarrhythmic drugs (e.g. encainide, flecainide)	Decrease [42]	Increases mortality in patients after acute MI [43]

ISA, Intrinsic sympathomimetic activity

efficacy in preventing SCD (Table 1). For example, increased HRV may be an important factor in the improved prognosis conferred by angiotensin-converting enzyme inhibitors in patients with chronic congestive heart failure, beyond their beneficial haemodynamic effects [40, 41]. The mechanism for the observed effect of angiotensin-converting enzyme inhibition on the autonomic system is probably related to the reduction of elevated angiotensin-II in patients with congestive heart failure. Angiotensin II can both facilitate sympathetic drive [41], and suppress central parasympathetic activity [40].

Conversely, class I c antiarrhythmic drugs (e.g. encainide hydrochloride) significantly decrease HRV [42]. In the Cardiac Arrhythmia Suppression Trial (CAST), these agents have been shown to increase the incidence of sudden arrhythmic death compared to placebo in post-MI patients [43]. In addition, arrhythmic death in the CAST active treatment group occurred mainly during the circadian peaks of sympathetic nervous system activity [44]. Thus, the increased mortality rate associated with these agents may be mediated through their unfavourable effects on the autonomic nervous system.

In summary, collective data appear to indicate that in certain groups of susceptible patients drugs that decrease HRV are associated with decreased incidence of fatal arrhythmias and sudden death, whereas drugs that increase HRV may increase mortality. Moreover, this association holds true even within the same group of drugs (i.e. β-adrenergic blockers). Thus, the influence of a given drug on the occurrence of arrhythmic events seems to be related to the effect of the drug on the autonomic tone, rather than its general mechanism of action. Based on these data pharmacologic enhancement of parasympathetic activity has been suggested as a useful alternative approach to prevent arrhythmias and may become a routine therapeutic manipulation for high-risk patients [18, 45].

Modulation of autonomic tone in diabetic patients

When initiating drug therapy for a diabetic patient the physician will usually consider the anticipated effects on glucose homeostasis or lipoprotein profile. However, since pre-existing abnormality in autonomic balance occurs frequently in diabetic patients, pharmacologic interventions that modify autonomic discharge may also be clinically relevant.

Clinical evidence appears to confirm that the above principles apply for diabetic patients surviving MI. Because these patients have pre-existing CAN, as well as high post-infarction morbidity and mortality [46], benefits from β-adrenergic blockers without intrinsic sympathomimetic activity following MI seem particularly likely while β-adrenergic blockers with intrinsic sympathomimetic activity may be deleterious. In trials using timolol, propranolol, and metoprolol, the reduction in both recurrent MI and mortality was higher in diabetic than in non-diabetic subjects [31, 47–49]. The data appear sufficient to justify β-blocker therapy in diabetic patients surviving MI despite potential side effects [31]. By contrast, in post-MI diabetic patients pindolol therapy was associated with an almost twofold increase in mortality compared to the placebo group [39].

Several other drugs may pose a threat to diabetic patients with CAN through their potential to adversely modify the autonomic balance. Perhaps the best example of such drugs are tricyclic antidepressants. These drugs are frequently used for treatment of painful diabetic sensory neuropathy [50]. Amitriptyline [51], imipramine [52], and desipramine [53], decrease HRV at usual therapeutic doses. This effect

is most likely mediated thorough their anticholinergic effects. By contrast, selective serotonin reuptake inhibitors that are less potent than anticholinergics (e.g. paroxetine, fluvoxamine) do not decrease HRV [51]. Unfortunately, these drugs seem to offer less analgesic effects [50, 54]. Tricyclic antidepressants can also increase the risk for arrhythmias by prolonging QTc interval. Other drugs used in diabetic patients which decrease HRV include α_1-receptor blocking agents (e.g. prazosin) [55] and α_2-receptor blocking agents (clonidine) [56].

Episodes of cardiorespiratory arrest in diabetic patients with clinical evidence of DAN have been precipitated by the induction of general anaesthesia [14, 57]. Interestingly, induction of general anaesthesia is associated with a substantial reduction in HRV [58]. Sedatives, analgesics, and anaesthetics have a negative influence on HRV, presumably through central mechanisms [19]. Considering that Holter monitoring studies have shown a decrease in HRV shortly before the onset of ventricular arrhythmias [59], it is conceivable that acute perturbations in the autonomic tone may contribute to the occurrence of perioperative arrhythmias.

Conclusion

Present data indicate that the prevailing sympathetic and vagal activation is a critical factor in determining the vulnerability to serious ventricular arrhythmias and SCD in patients with underlying heart disease. Although the interpretation of these findings is not straightforward, the inference drawn is that reduction in vagal activity during drug therapy can predispose to the development of ventricular arrhythmias especially in the presence of structural heart disease. Thus, the effect of drugs on HRV should become an important clinical consideration in diabetic patients. In addition, novel pharmacological approaches to the prevention of SCD, aiming at the most favourable sympathetic-parasympathetic balance, may be particularly beneficial in diabetic patients.

In patients with known heart disease (e.g. history of MI or congestive heart failure) or symptomatic DAN (most of whom have coexistent coronary artery disease) drugs that decrease HRV should probably be avoided. Patients without evidence of heart disease or overt autonomic neuropathy pose a more difficult problem. Although in general these patients may be at a lower risk, the issue is complicated by the high frequency of silent MI and ischaemia [46] among diabetic patients, and the fact that early detection of CAD in diabetic patients is usually not part of the routine care. A marked diminution of HRV based on spectral or conventional analysis of HRV [5] or a significant prolongation of QTc interval should identify patients at particularly high risk. Clearly, studies

are needed to evaluate the impact of drug therapy on SCD rates among diabetic patients.

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