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REVIEW

Cardiac autonomic testing and treating heart disease. "A clinical perspective"

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ABSTRACT

Background: Coronary heart disease (CHD) is a major health concern, affecting nearly half the middle-age population and responsible for nearly one-third of all deaths. Clinicians have several major responsibilities beyond diagnosing CHD, such as risk stratification of patients for major adverse cardiac events (MACE) and treating risks, as well as the patient. This second of a two-part review series discusses treating risk factors, including autonomic dysfunction, and expected outcomes.
Methods: Therapies for treating cardiac mortality risks including cardiovascular autonomic neuropathy (CAN), are discussed.
Results: While risk factors effectively target high-risk patients, a large number of individuals who will develop complications from heart disease are not identified by current scoring systems. Many patients with heart conditions, who appear to be well-managed by traditional therapies, experience MACE. Parasympathetic and Sympathetic (P&S) function testing provides more information and has the potential to further aid doctors in individualizing and titrating therapy to minimize risk. Advanced autonomic dysfunction (AAD) and its more severe form cardiovascular autonomic neuropathy have been strongly associated with an elevated risk of cardiac mortality and are diagnosable through autonomic testing. This additional information includes patient-specific physiologic measures, such as sympathovagal balance (SB). Studies have shown that establishing and maintaining proper SB minimizes morbidity and mortality risk.
Conclusions: P&S testing promotes primary prevention, treating subclinical disease states, as well as secondary prevention, thereby improving patient outcomes through (1) maintaining wellness, (2) preventing symptoms and disorder and (3) treating subclinical manifestations (autonomic dysfunction), as well as (4) disease and symptoms (autonomic neuropathy).

Keywords: Cardiac autonomic neuropathy, Cardiovascular risk factors, Heart disease, Mortality

Introduction

In the first article in this series, we briefly reviewed traditional, nontraditional, modifiable and nonmodifiable risk factors. We also reviewed (1) the failings of heart beat interval (HBI) alone (1-3) and noninvasive autonomic measures based solely on measures of HBI signals (e.g., heart rate variability (HRV) alone and beat-to-beat blood pressure (BP) (4-7)) and (2) the benefits of specific parasympathetic and sympathetic (P&S) monitoring or testing (8-16).

Based on the need to improve on the risk factors available, cardiovascular autonomic neuropathy (CAN) risk and its association with current risk factors was discussed, including (1) the association of CAN with cardiac mortality risk, (2) stratifying CAN risk, (3) CAN and diabetes risk, (4) CAN and nontraditional risk factors and (5) sudden cardiac death (SCD). In this article, we will discuss the treatment of CAN, specifically how treating autonomic balance (aka, sympathovagal balance (SB) (17)) modifies cardiovascular risk, and expected outcomes.

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Background

Treating heart disease carries several important responsibilities beyond diagnosing coronary artery disease (CAD), including risk-stratifying for an adverse cardiac event and treating the individual risk factors pharmacologically. For the

latter, exact dose, class and type of agent to use is often not clearly defined. For example, beta-blockers may be indicated in the postinfarction patient or in a patient with heart failure, but the optimal dose to titrate, or which type to use, is not known with certainty. The same applies to angiotensin antagonists, other antihypertensives and diuretics, as well as direct and indirect anticholinergics (e.g., antidepressants and anxiolytics). Antiplatelet therapy efficacy is very difficult to predict without genetic testing or *in vitro* laboratory testing. P&S testing, including the patient-specific physiologic measure of SB, provides more information. Studies have shown that establishing and maintaining proper SB minimizes morbidity and mortality risk (8, 18-23). As these studies have shown, more information through P&S testing promotes primary prevention, treating subclinical disease states, and secondary prevention, thereby improving patient outcomes through (1) maintaining wellness, (2) preventing symptoms and disorder and (3) treating subclinical manifestations (autonomic dysfunction), as well as (4) disease and symptoms (autonomic neuropathy) (8, 18, 20, 21).

Treating risk factors in heart disease

As discussed in the companion article, establishing a risk factor may also guide therapy. Demonstrating that therapy actually lowers risk is still needed. For example, it was well established in the 1970s and 1980s that elevated serum cholesterol levels significantly contributed to heart attacks and heart-related deaths (24). This was termed the "lipid hypothesis" (25) since it was not established at that time that lowering cholesterol reduced heart attacks and heart deaths. Eventually, well-designed trials did demonstrate that lowering cholesterol with pharmacological agents reduced cardiac mortality and coronary heart disease (CHD) complications (26-34). Findings included that atherosclerosis progression may be halted or reversed (35), with formulae developed to potentially reduce and reverse coronary plaque (24). The influence of statin therapy on plasma-oxidized low-density lipoprotein (LDL) biomarkers and high-sensitivity C-reactive protein (CRP) was demonstrated (see Fig. 1) (36). Subsequently, Dr. Nissen demonstrated that LDL-lowering statins could slow or halt the progression of atherosclerosis (37). Recently, it has been demonstrated that very low levels of serum LDL, down to 50 mg/dL, reduce mortality risk (38).

Examples of risk factors that are still in need of treatment standardization include BP and blood glucose. Attaining normotensive systolic BP is important. It is known that treating hypertension reduces stroke, heart attack and heart failure. However, an absolute target level has not been clearly demonstrated (39). Optimal target blood sugar (hemoglobin A1c) in diabetics is also not known. Initial hypotheses that intensive control of blood sugar would lower cardiac heart disease events have not been proven. Results from recent studies involving various subsets of patients appear to contradict the initial hypotheses (9).

Furthermore, while specific therapies for heart disease have been recommended, optimal dosing recommendations have not been standardized (e.g., beta-blocker therapy). Evidence for beta-blocker use in CHD is derived from relatively old studies. It has subsequently been widely extrapolated to patients with CAD and even to patients at high risk for, but without established, CAD. It is not known if these extrapolations are justified. Moreover, the long-term efficacy of beta-blockers in patients treated with contemporary medical therapies is not known, even in patients with prior myocardial infarction (MI). At issue is that beta-blockers are not without adverse effects and their tolerability is not ideal. Therefore, the benefit of beta-blocker use is unclear. Recently published in *JAMA*, the REACH study assessed the association of beta-blocker use in stable patients with known risk for cardiovascular events. REACH concluded that the use of beta-blockers is not associated with a lower risk of composite cardiovascular events (40).

Risks associated with cardiovascular autonomic neuropathy

Treating cardiovascular autonomic neuropathy associated with cardiac mortality risk

Decreased HRV, specifically decreased resting parasympathetic activity, defines CAN (8, 19, 41, 42). Because of the higher mortality with CAN (43), investigators have suggested that individuals with abnormal autonomic testing should be candidates for closer surveillance and more aggressive pharmacological therapy. Suggested therapy targets values that achieve autonomic balance, even if the patient is asymptomatic or subclinical (8, 20). Using the quantitative measures of P&S activity (14, 15) and P&S balance as targets for treatment decisions, pharmacological agents (e.g., sympatholytics if too much sympathetic activity or anticholinergics if too much parasympathetic activity) may be appropriately titrated and utilized with more precise selection of class and dosing for the individual patient (21).

While many researchers in many subpopulations of heart disease patients have documented reduced autonomic activity with increased mortality (43-47), increased sympathetic activity and decreased parasympathetic activity often require different treatment modalities. Curtis and O'Keefe state:

"Any factor that leads to inappropriate activation of the sympathetic nervous system can be expected to have an adverse effect on … patient outcomes, while any factor that augments vagal tone tends to improve outcomes. Insulin resistance, sympathomimetics medications, and negative psychosocial factors all have the potential to affect autonomic function adversely and thus cardiovascular prognosis. Congestive heart failure and hypertension also provide important lessons about the adverse effects of sympathetic predominance, as well as illustrate the benefits of β-blockers and angiotensin-converting enzyme inhibitors, two classes of drugs that reduce adrenergic tone. Other interventions, such as exercise, improve cardiovascular outcomes partially by increasing vagal activity and attenuating sympathetic hyperactivity" (20).

HRV-alone or beat-to-beat BP may not clearly differentiate low parasympathetic from high sympathetic activity. Independent, simultaneous P&S information is required (8, 41). Tsuji found that his patients appeared to be free of any significant underlying CHD, suggesting that reduced autonomic activity may simply reflect a subclinical cardiac disease state (42).

Barthel and coworkers (48), based on years of follow-up, demonstrated that autonomic dysfunction is a significant risk

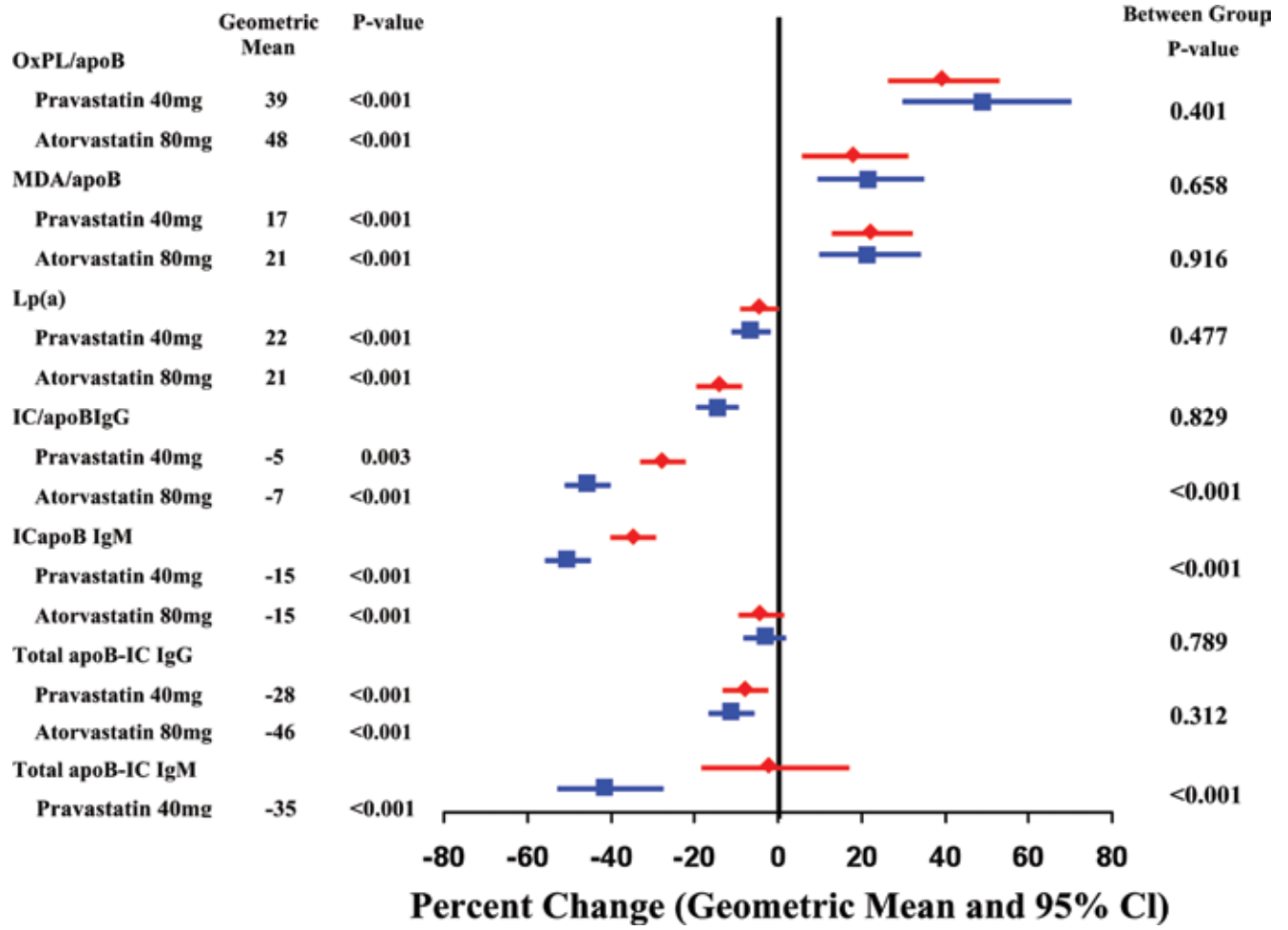

Fig. 1 - The influence of statin therapy on plasma-oxidized low-density lipoprotein (OxLDL) biomarkers and high-sensitivity C-reactive protein (CRP). apoB-IC = apolipoprotein B-100 immune complexes; CI = confidence interval; IC/apoB = immune complexes per apolipoprotein B-100; Ig = immunoglobin; Lp(a) = lipoprotein (a); MDA = malondialdehyde; MDA/apoB = malondialdehyde epitopes per apolipoprotein B-100; OxPL/apoB = oxidized phospholipid epitopes per apolipoprotein B-100. From The New England Journal of Medicine, Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. Vol. 345, No. 23, pp. 1667-1675. Copyright © 2001 Massachusetts Medical Society (83). Adapted with permission from Massachusetts Medical Society. See text for details.

predictor for poor outcome status after MI, history of previous MI, arrhythmia on Holter monitoring, poor glucose control and left ventricular ejection fraction (LVEF) less than 30%. This highlights the importance, even in low-risk patients, of performing P&S testing to risk-stratify for future cardiac events, including cardiac death. Prospective work in CHD and newly developing CAD by Liao and coworkers (49) expand the application of monitoring autonomic dysfunction beyond post-MI to a much larger patient base and the general population. Liao demonstrates that identifying autonomic dysfunction and CAN is important for secondary prevention, as well as primary prevention. Once identified, autonomic dysfunction should be treated to restore and maintain proper P&S balance.

Autonomic dysfunction also has been correlated with progression of CAD (50) and with silent ischemia. The latter leads to SCD and unexpected MI. Umetani et al found that autonomic activity declines normally with aging to below levels associated with increased risk of mortality (18). Wackers and coworkers (51) found that traditional cardiac risk factors, including inflammatory and prothrombotic markers, were not predictive, and emerging risk factors were not associated with abnormal stress tests or computed tomography imaging. By contrast, CAN was a strong predictor of ischemia. This offers more reason to test for P&S activity and treat autonomic dysfunction by restoring and maintaining balance to slow progression of autonomic dysfunction and neuropathy.

Minimizing cardiovascular autonomic neuropathy risk

CAN indicates very low parasympathetic activity, relative to sympathetic activity (42). CAN may be normal for geriatric and long-standing chronic disease patients. For example, based on Framingham risk factors, an 85-year-old has a greater mortality risk than a 45-year-old. More parasympathetic activity relative to sympathetic activity is known to be cardioprotective and reduces mortality risk (18). Chronic sympathetic

activation is known to increase cardiovascular risk (20). Depression is known to elevate mortality risk in heart disease (52), and depression is associated with abnormally high levels of parasympathetic activity relative to sympathetic activity.

The relationship between P&S activity at rest is known as SB (17). CAN risk (the risk associated with very low parasympathetic activity with respect to sympathetic activity) may be stratified based on SB. High SB indicates high relative resting sympathetic excess (SE). CAN with high SB is considered high risk (53-55). In these cases, titrating higher sympatholytic therapy or lower anticholinergic therapy may normalize SB. In CAN cases where SB is persistently high with low HR, low BP and abnormal left ventricular function, consider an electrophysiology study to further document risk and the potential need for a cardiac device. Very low SB (<0.4) indicates a relative, resting parasympathetic excess. Very low SB, as it is associated with (subclinical) depression, elevates CAN risk (52). In these cases, titrating higher anticholinergic therapy or lower sympatholytic therapy may normalize SB. Normal SB, indicating a balanced autonomic nervous system, is associated with normal CAN risk (20). This may still be too much sympathetic activity, especially in patients with high HR or BP. In these cases, treat as if SB were high, indicating high risk. Low-normal SB, indicating more parasympathetic activity, is associated with minimal CAN risk (18). This is the recommended level of balance for geriatric cardiology patients.

Diabetes risk and autonomic neuropathy

While we have been discussing CAN, a late-stage autonomic neuropathy, earlier stages of autonomic dysfunction have been identified, including diabetic autonomic neuropathy (DAN). DAN is defined, using P&S monitoring, as low parasympathetic or sympathetic activity at rest, but not yet critically low resting parasympathetic activity as occurs in CAN. DAN is a very serious and common complication in diabetes (8). Identifying and treating DAN may stay progression of autonomic decline to the more serious condition known as CAN. Symptoms of DAN include (1) resting tachycardia, (2) exercise intolerance and (3) orthostatic hypotension and may also include (4) a glycemic autonomic failure (abnormal compensatory reflexes to hypoglycemia episodes). Several of these symptoms are also typical in nondiabetic chronic disease patients (e.g., chronic obstructive pulmonary disease, Parkinson's disease, sleep apnea, and hypertensive cardiovascular disease). For these patients, we use the terminology AAD, and it likewise has low resting P or S activity, but not yet critically low resting P levels. Therefore, DAN and AAD have the same P&S measurements; the only difference is whether or not diabetes is present. These symptoms are often not associated with DAN, and DAN is misperceived as asymptomatic. DAN may impose a burden on an individual whose cardiac reserve may be compromised by underlying atherosclerosis or left ventricular abnormalities. Due to the potential for autonomic neuropathy, the American Diabetes Association (ADA) (56) recommends cardiac investigation before beginning physical activity that is more intense than usual. The ADA states that "hypoglycemia associated with autonomic failure can severely compromise stringent diabetes control and quality of life." It is known that both hypoglycemia and CAN are associated with increased mortality risk. Therefore, prior to treating diabetics with physical exercise and more stringent glucose control, consider P&S testing for DAN or CAN.

In their discussion of CAN under "Neuropathy screening and treatment" ((pS37), 56), the ADA states that "special testing is rarely needed and may not affect management or outcomes." This, of course refers to the symptomatic nature of CAN, implying that once symptoms present, management is already in place and outcomes are known without special testing. However, they recommend testing "at least annually" for diabetic polyneuropathy (DPN), for the autonomic aspect of DPN is largely asymptomatic until autonomic neuropathy is evident, and even then it is (silently) progressive and continues to affect morbidity and mortality. The majority of the recommendations for autonomic dysfunction are for early testing to specify and customize autonomic therapy to delay autonomic neuropathy onset and reduce morbidity and mortality risk. "Medications for the relief of specific symptoms related to autonomic neuropathy are recommended, including tri-cyclic drug recommendations and other therapy dosing ((table 16, pS38), 57)), as they improve the quality of life of the patient …. The early recognition and appropriate management of neuropathy in the patient with diabetes is important for a number of reasons[.] … [A]utonomic neuropathy may involve every system in the body, and CAN causes substantial morbidity and mortality" ((pS37), 57). The therapy recommendations are known to affect SB. Normalizing autonomic dysfunction (balance, including SB) is known to reduce morbidity and mortality risk (8, 18-21, 58-63).

Nontraditional risk factors and autonomic neuropathy

CRP is a useful biomarker of increased long-term risk of SCD (64). CRP is associated with decreased autonomic function, even after controlling for traditional risk factors that decrease CAD (65). It is postulated that autonomic dysregulation may represent one pathway leading to CAD, even with treatment of risk factors to prevent the development of CAD. Inflammation is a significant contributor toward atherosclerosis and is a nontraditional risk factor with incremental value (65). The association of diminished autonomic function with elevated CRP levels is potentially significant. Restoration of autonomic balance is possible and has been shown with therapeutic lifestyle changes, increased physical activity, beta-blockers, aldose reductase inhibitors, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and potent antioxidants such as alpha-lipoic acid. There are also exciting new prospects for pathogenesis-oriented intervention (63).

Microalbuminuria has been associated with an increased risk of cardiovascular mortality independently of other known coronary artery risk factors (66,67). The Hoorn study (68) supports the fact that it may be useful to treat both microalbuminuria and CAD in populations at a high risk for cardiovascular mortality.

Treating autonomic balance modifies autonomic neuropathy risk

Identifying CAN early (specifically parasympathetic or sympathetic dysfunction) and treating it aggressively (based, at

least in part, on the autonomic findings) may reduce the emergence of CHD and the ancillary complications. More prospective studies are needed in this area, as the majority of the data are hypothesis generating. However, treatment to establish and maintain proper P&S balance has been known to minimize mortality risk (18). It therefore makes empiric sense to attempt to normalize autonomic dysfunction. Treatment to modulate one autonomic branch or the other (e.g., with sympatholytics, such as beta-blockers or antihypertensives (20), or anticholinergics, such as low-dose antidepressants or anxiolytics (52)) has been shown to reduce mortality as well as morbidity risk in some studies. This evidence suggests that treating in an attempt to normalize P&S balance may reduce CAN risk (21).

In many cases, P&S assessment may provide more information where required. For example, LVEF between 35% and 40% is considered moderately depressed and a borderline indication for implantable cardioverter defibrillator (ICD) placement. CHD patients who present moderately depressed LVEF with high BP or HR (including arrhythmia) may be treated pharmacologically with more sympatholytics (20), as confirmed by documenting SE. However, for CHD patients who present moderately depressed LVEF with SE and low BP or HR, more sympatholytics may not be appropriate. Typically, these patients demonstrate parasympathetic insufficiency, indicating a potential inability to prevent a sympathetically mediated ventricular tachyrhythm from becoming fibrillation or worse. Parasympathetic insufficient patients with low HR and BP may require a lower threshold for the clinician to implant a defibrillator device or undertake more sophisticated electrophysiology studies in an individual patient.

Atorvastatin and other statins have been shown to be most effective in treating dyslipidemias, especially in patients with risk factors for coronary atherosclerosis or those with underlying coronary atherosclerosis. Atorvastatin has both anti-inflammatory and lipid-lowering effects, reducing CRP and LDL cholesterol (69). This study involving 20 patients with stable CAD and 20 patients without CAD demonstrated that atorvastatin improved autonomic function. Landmark survival studies with statins have shown significant benefit with their institution, plausible mechanisms for reduction of clinical events and that primary and secondary CAD prevention may include not only lowering LDL cholesterol and inflammatory CRP (70), but also possibly normalizing autonomic dysfunction, as demonstrated by Gentlesk et al (58). Again, increased parasympathetic activity is known to be cardioprotective (18). Therefore, for individuals with abnormal autonomic function, aggressive lipid-lowering treatment with statins may be indicated based on these findings.

Sudden cardiac death

Lastly, one cannot discuss diagnosis and treatment of cardiovascular diseases without addressing SCD (71). Approximately 67% of symptoms of SCD are related to CHD (72-74). Approximately 450,000 individuals per year have SCD in the United States (75), and this is probably an underestimate of the frequency. The risk is three times greater in men than in women, based on the Framingham Study data (76). People at high risk for SCD may be treated with ICDs or have other precipitating factors corrected so as to prevent further episodes.

Important risk factors for SCD are underlying CAD, heart failure, left ventricular dysfunction and prior MI. The risk factors for CAD are the same risk factors for SCD. Heart failure is also a significant risk factor for SCD. Significant genetic factors for SCD (77) showed that parental SCD is an independent risk factor for sudden death in a middle-aged man. The existence of familial risk factors for SCD may help us better explain subjects at a high risk and enable us to prevent SCD early on (78-80). Patients with left ventricular dysfunction are at high risk for SCD. This risk is used as an index for aggressive treatment for devices such as defibrillators. A community-wide study showed that only one-third of the evaluated SCD patients having severe left ventricular dysfunction met the criteria for prophylactic cardioverter defibrillator implantations (81). Prophylactically implanted cardiac device trials may represent a minority of SCD population (82). Therefore, screening patients for SCD based on left ventricular dysfunction is not a very sensitive technique and will miss approximately two thirds of SCD patients.

In a review article, Myerburg (75) states that SCD is an unresolved problem despite more insight into the mechanisms and therapeutic advances. Prediction and prevention of SCD should not be restricted to assessing an individual for the presence of CAD, coronary ischemia, left ventricular dysfunction or heart failure. This is a much more complicated issue underlying various diseases and risk factors. It is anticipated that independent, simultaneous P&S testing for cardiac autonomic dysfunction will provide additional information to understand these issues, to guide therapy and treatment and affect improved outcomes. P&S testing allows for the risk assessment of patients for major adverse cardiac events, even when they are asymptomatic and have no clinical CAD. Subclinical CAD is associated with CAN. Therefore, testing for CAN and SB may be extremely productive in identifying and treating patients at high risk for cardiac events (21, 62, 63).

Conclusion

CAN is associated with increased cardiac morbidity and mortality. Identifying and addressing CAN early, especially in a subclinical cardiac patient, will further differentiate which asymptomatic patients require more aggressive therapy. The results from P&S testing documenting CAN may be used as a baseline. One should view these test results as a guide toward more individualized treatment. A more specific selection of medications and dosing based on these results is possible. P&S test results represent objective data which are useful in guiding pharmacological and lifestyle changes. In addition to normalization and improvement of CAN (21), independent and simultaneous P&S testing, providing objective P&S activity levels, may guide the physician toward the type and dosing of pharmacological agents necessary to achieve an objective clinical target or outcome. The pharmacopeia includes adrenergic (beta-blockers, antihypertensives, bronchodilators and vasopressors) and cholinergic (antidepressants, anxiolytics and antipsychotics) agents. This would eliminate arbitrarily dosing medications without a clear target outside of HR and BP. Also, the threshold for the implanting of prophylactic devices such as cardiac defibrillators may be better defined by

assessing and following P&S dysfunction. While further studies are indicated, the clinical and epidemiological data are too compelling not to test for, diagnose and aggressively treat CAN with abnormal SB to guard the patient's well-being, not only in diabetics (62, 63), but in all patients with risk factors for heart disease.

Disclosures

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