Metabolic Syndrome

Lead Article

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B. M. Egan, S. Julius

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Role of sympathetic overactivity in the pathophysiology of the metabolic syndrome

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The global obesity epidemic is driving metabolic (insulin-resistance) syndrome–related health problems, including an approximately 3- to 4-fold increased coronary heart disease risk. Autonomic dysfunction, ie, increased sympathetic drive and reduced vagal tone, may participate in the pathogenesis and complications of the metabolic syndrome—comprising higher blood pressure (BP), more active renin-angiotensin system, insulin resistance, faster heart rates, excess cardiovascular disease, including sudden death—and possibly aggravate the tendency to weight gain and obesity. Components of the metabolic syndrome that may enhance sympathetic drive include alterations of insulin, leptin, nonesterified fatty acids (NEFAs), cytokines, triiodothyronine, eicosanoids, sleep apnea, nitric oxide, endorphins, and neuropeptide Y (NPY). Of note, high plasma fatty acids are an independent risk factor for hypertension and sudden death. In short-term human studies, fatty acids can raise BP, heart rate, and α1-adrenoceptor vasoreactivity, while reducing baroreflex sensitivity, endothelium-dependent vasodilatation, and vascular compliance. Efforts to further identify the mechanisms and consequences of sympathetic dysfunction in the metabolic syndrome may provide insights for therapeutic advances to ameliorate the excess cardiovascular risk and adverse outcomes.

SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ATP III</td>
<td>Adult Treatment Panel–III</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>CHD</td>
<td>coronary heart disease</td>
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<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>MSNA</td>
<td>muscle sympathetic nerve activity</td>
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<tr>
<td>NEFA</td>
<td>nonesterified fatty acid</td>
</tr>
<tr>
<td>NHANES III</td>
<td>Third National Health And Nutrition Examination Survey</td>
</tr>
<tr>
<td>NPY</td>
<td>neuropeptide Y</td>
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<td>PPS</td>
<td>Paris Prospective Study</td>
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in a global population that is aging. The health and economic toll taken by the metabolic syndrome is very high and has the potential to produce a level of devastation exceeding that of major armed conflict. Evidence implicates a fundamental role for the autonomic nervous system in the pathogenesis and complications of the metabolic syndrome. This review summarizes that evidence and attempts to provide a foundation for informing and guiding rationale efforts to more effectively prevent and treat the growing global epidemic of metabolic syndrome–related health and economic problems.

THE METABOLIC SYNDROME

Definition

The metabolic syndrome as defined by The World Health Organization (WHO) and ATP III definitions of the metabolic syndrome, while similar, are not identical. The two definitions are summarized in Table I.1-3

Associated risk factors

In addition to the clinical criteria used to define the metabolic syndrome, the syndrome is associated with postprandial hyperinsulinemia and resistance to insulin’s glucose- and fatty acid–lowering actions, greater density, and numbers of low-density lipoprotein (LDL)-cholesterol particles,8 decreased levels of the cardioprotective high-density lipoprotein (HDL)-cholesterol, and skewing of the residual HDL particles toward smaller and less beneficial fractions. Obesity and the metabolic syndrome are also linked with high levels of inflammatory risk markers/factors, such as interleukins, tumor necrosis factor–α (TNFα), and C-reactive protein (CRP),9 and defects in fibrinolysis, such as elevated plasminogen activator inhibitor–1 (PAI-1)10 and a greater magnitude of oxidative stress.11,12 Other evidence indicates the metabolic syndrome is associated with microalbuminuria,13 abnormalities in autonomic cardiovascular regulation, and activation of one or more components of the renin-angiotensin-aldosterone axis. The autonomic nervous system appears to play an integral role in multiple facets of the metabolic syndrome, including its pathophysiology and complications.14

Prevalence

WHO Definition

The WHO criteria for the metabolic syndrome were applied to eight different European cohorts, and the prevalence of the syndrome determined for men and women 40 to 55 years of age and for those older than 55 years.2 The prevalence for each of these age and gender subgroups is summarized in Table II.

Table I. Clinical criteria defining the metabolic syndrome.1-3

Abbreviations: ATP III, Adult Treatment Panel–III; BMI, body mass index; HDL, high-density lipoprotein; WHR, waist-to-hip ratio.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence, %</td>
<td>23%</td>
<td>13%</td>
</tr>
<tr>
<td>Risk factors, mean±SD</td>
<td>1.7±1.2</td>
<td>2.1±1.2</td>
</tr>
</tbody>
</table>

Table II. Metabolic syndrome prevalence by WHO criteria in 8 European studies.2
NCEP definition

The ATP III criteria for diagnosis of the metabolic syndrome when applied to the Third National Health and Nutrition Examination Survey (NHANES III) in the US in 1988 to 1994 generated an age-adjusted estimated prevalence of 23.7% or ≈47 000 000 adults. Although body mass index (BMI, kg/m²) is not a criterion used by the ATP III to define the metabolic syndrome, it is, nevertheless, very strongly related to BMI in both men and women, as summarized in Table III.16

Future trends in prevalence

The metabolic syndrome is at epidemic proportions and likely to become endemic in the next several years given the rapid increase in the prevalence of obesity magnified by two powerful demographic trends.

The risks of obesity, including hypertension, diabetes, and an excess of cardiovascular and renal diseases, were well described 80 years ago.17 Subsequent studies showed that obesity, especially when linked with a truncal or abdominal fat distribution, is associated with hypertension, faster heart rates, hyperinsulinemia, and insulin resistance with related abnormalities of carbohydrate and lipid metabolism.8,14,18 Moreover, the syndrome is associated with premature cardiovascular morbidity and mortality, with an excess of sudden deaths.7,8 Despite the recent explosion of information about the health risks of excess body weight, the epidemic of overweight (BMI 25 to 30 kg/m²) and obesity (BMI >30) continues to expand at unprecedented rates.

The estimated age-adjusted prevalence of obesity, ie, BMI >30 kg/m², among US adults increased from 22.9% in 1988 to 1994 to 30.5% in 1999 to 2000.19 The prevalence of overweight (BMI >25 kg/m²) increased between these two NHANES surveys from 55.9% to 64.5%. More recent self-reported information from a random telephone survey of adult Americans suggests the prevalence of obesity increased further in 2001 from self-reports in 2000.20 Epidemiological data indicate that obesity in subjects free of cardiovascular risk and disease at baseline is associated with impressive increases in relative risk for these adverse outcomes during the ensuing decade, especially in men.21 Moreover, the obesity epidemic has metastasized to affect young adults and children not only in economically developed countries, but also several emerging economies worldwide.7 In fact, on a relative basis, the obesity epidemic is growing faster in these newer targets.22

In view of the strong relationships between obesity, the metabolic syndrome (Table II), and the development of cardiovascular risk factors and events, over the next decade among overweight and obese adults without risk or disease (Table IV), the magnitude of metabolic syndrome and related health problems is positioned to escalate dramatically in the years ahead. If we now look at future age trends, the median age of populations in most of the developed world is increasing rapidly as birth rates decline. The prevalence of the metabolic syndrome is highly age-dependent in the USA and Europe (Table II). In the USA, for example, among adults 20 to 29 years of age, ≈7% met the ATP III criteria for the metabolic syndrome. The prevalence of the metabolic syndrome rose to 40% or more among adults aged 60 years and older. In view of these facts, the absolute number of adults with the metabolic syndrome is likely to rise in the future as a consequence of aging populations throughout most developed countries.

Clinical significance: impact on CHD, CVD, and total mortality

The clinical significance of the metabolic syndrome is not defined by its prevalence, but by its impact on health and health care costs. The metabolic syndrome...
as defined by both WHO and ATP III in Table I is associated with significantly greater risk for mortality from coronary heart disease (CHD), overall cardiovascular disease (CVD), and all causes.5,6 When the WHO and ATP III criteria for the metabolic syndrome were applied to a population of 1209 Finnish men followed from their enrollment in 1984 to 1989 until 1998, an impressively positive relationship was found with mortality from CHD, CVD, and all causes (Table V).5

### Economic impact

The costs of obesity in the USA alone, estimated at between $46 to $68 billion in 1990, rose to ≈$99 billion in 1995 and have likely exceeded that level on an annualized basis.25 While obesity accelerates degenerative joint disease and increases cancers of the breast, uterus, prostate, and colon,26 much of the excess costs attributed to obesity are generated by the association with diabetes, hypertension, and heart disease, ie, metabolic syndrome–related health risks and events.27

Given the prevalence, future trends, clinical impact, and economic significance of the metabolic syndrome, this disorder constitutes a major health problem of potentially escalating proportions. Efforts to further identify the mechanisms and consequences of sympathetic dysfunction in the metabolic syndrome may provide insights for therapeutic advances to ameliorate the excess cardiovascular risk and adverse outcomes. We will now explore the literature, which addresses the interrelationships between the sympathetic nervous system, obesity, and the metabolic syndrome.

#### OVERWEIGHT, OBESITY, AND INSULIN DYNAMICS AND ACTION

Body weight (BMI) and insulin dynamics and action are closely linked.1 For example, among Italians, hyperinsulinemia and insulin resistance affect only ≈10% of individuals with BMIs <25 kg/m², but 60% or more of individuals with BMI ≥35 kg/m².28 In some ethnic groups, eg, Asians and African-Americans, significant risk for insulin resistance and various facets of the metabolic syndrome begins at BMI values well below 25 kg/m².29,30

In this review, an attempt is made to synthesize information from the community to the bench and bedside to further elucidate the pathogenesis underlying sympathetic activation (Table VI) and the cardiovascular and metabolic consequences of that activation (Table VII) among individuals with the insulin resistance syndrome. Evidence suggests both that abnormalities in neurogenic regulation are driven in part by various facets of the syndrome and that increased sympathetic drive can contribute to dimensions of the metabolic syndrome and associated end-organ complications. Consequently, a better understanding on the causes and consequences of sympathetic overactivity in the metabolic syndrome may enhance efforts to more effectively prevent and manage this condition and related complications.

#### SYMPATHETIC FUNCTION IN OBESITY

Obesity is not an entirely homogeneous disorder. In both animals and man, evidence for underactivity and overactivity of the sympathetic nervous system has

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**Table V. The metabolic syndrome and mortality from CHD, CVD, and all causes.**4,5 ATP, Adult Treatment Panel.

<table>
<thead>
<tr>
<th>Mortality</th>
<th>WHO definition</th>
<th>ATP definition*</th>
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<tbody>
<tr>
<td>CHD</td>
<td>2.9 (1.2-6.8)</td>
<td>4.2 (1.6-10.8)</td>
</tr>
<tr>
<td>CVD</td>
<td>2.6 (1.4-5.1)</td>
<td>2.5 (1.1-5.8)</td>
</tr>
<tr>
<td>All cause</td>
<td>1.9 (1.2-3.0)</td>
<td>2.0 (1.1-3.6)</td>
</tr>
</tbody>
</table>

*102 cm waist circumference for men.

**Table VI.** Factors that may contribute to sympathetic activation in obesity.*

*Based on the literature review, the factors that are more likely to activate the sympathetic nervous system in obesity are listed first, whereas those that are less likely (speculative) are listed last.

- Hyperleptinemia
- Hyperinsulinemia
- Visceral obesity
- Sleep apnea
- Elevated nonesterified fatty acids (NEFAs)
- Disturbances in nitric oxide
- Suppressed anger
- Altered eicosanoid metabolism
- Increased cytokines
- High levels of active T3
been documented. On balance, the literature strongly suggests sympathetic hyperfunction in a substantial subset of obese individuals. Several studies provide clues on the pathogenesis and consequences of sympathetic overactivity in obesity.

In at least a substantial subset of obese subjects, sympathetic drive is increased at key target organs in obesity, including the kidney, skeletal muscle, and peripheral vasculature. There is less evidence for increased sympathetic drive to the heart, especially in obese normotensive humans. Nevertheless, disturbances of autonomic control of heart rate variability, which include decreased vagal tone, either with or without increased sympathetic tone, are very well documented. Sym pathetic activation at the various target sites appears to play an important pathophysiological role in obesity-associated insulin resistance, hypertension, activation of the renin-angiotensin system, and sudden death.

We will now examine the evidence from various animal and human studies documenting that the sympathetic nervous system is activated with obesity and insulin resistance.

### Evidence of sympathetic activation with obesity and insulin resistance from animal studies

Evidence for both sympathetic hypofunction and hyperfunction has been documented in animal models of obesity. In fact, sympathetic underactivity appears to underlie the lower metabolic rates that contribute to obesity in some rodents. Conversely, in healthy animals, obesity induced by overfeeding is associated with sympathetic activation and hypertension. Sympathetic activation is an early abnormality induced by overfeeding and reversed with weight loss. Feeding-induced sympathetic changes appear to precede and perhaps drive alterations in renin-angiotensin system activity. In at least some of these models, hypertension is prevented or reversed by centrally acting α₂-adrenoceptor agonists or combined α₁- and β-adrenergic receptor antagonists.

Observations from animal research have also helped to elucidate the potential mechanisms by which obesity and insulin resistance activate the sympathetic nervous system and contribute to cardiovascular risk and disease. While these experiments have provided important insights, the results indicate that the relationship between obesity, insulin resistance, and sympathetic function is complex and modified by genetic and environmental factors.

In normotensive rats, high sucrose diets, even without weight gain, induce insulin resistance and hypertension that is blunted by central sympatholytics acting as agonists at α₂-adrenoceptors. Hypertension induced by high sucrose or high fat diets is abrogated by clonidine, whereas the hyperinsulinemia is variably affected.

### Evidence of sympathetic activation with obesity and insulin resistance from human studies

Plasma and urine catecholamines, systemic and regional norepinephrine turnover, and direct sympathetic nerve recording, or microneurography, have been used to measure sympathetic drive in humans. Each of these methods has yielded evidence for sympathetic hyperfunction among individuals with obesity and the metabolic syndrome.

#### Plasma catecholamines

Several studies have identified elevated plasma catecholamines in obese human subjects, particularly those
with elevated blood pressure. Moreover, weight loss was associated with a relatively rapid reduction of plasma norepinephrine, which correlated with the decline of blood pressure that accompanies negative calorie balance. Studies have demonstrated that plasma norepinephrine is elevated in obese children with high blood pressure and predicts the decline of blood pressure that occurs with salt restriction. These data suggested that sympathetic overactivity contributes to sodium retention and blood pressure elevation in obese children, an impression that is consistent with evidence from studies of regional norepinephrine turnover in obese adults.

**Regional norepinephrine kinetic studies**

Esler and colleagues, using regional norepinephrine kinetics, identified increased sympathetic activity to the heart and kidneys in hypertensive patients. The sympathetic activation likely plays a key role in the pathogenesis of hypertension in these individuals. While the pathogenesis of sympathetic activation has not been fully elucidated, studies in hypertensive patients identified increased norepinephrine turnover in the brain, which may underlie the increased sympathetic drive to the heart and kidneys. These observations are consistent with research by Julius and colleagues indicating a central neurogenic basis for hyperkinetic borderline hypertension characterized by faster heart rates and higher cardiac outputs with a transition phase to the more typical high-resistance, normal cardiac output phase of sustained hypertension.

Using regional norepinephrine turnover, increased sympathetic drive to the kidney was identified in obese normotensive and obese hypertensive subjects. Since the kidney is of fundamental importance in blood pressure control, the implications of sympathetic overactivity in obese normotensive subjects is difficult to interpret. Obesity is associated with relative (to height) volume expansion, and renal sympathetic overactivity may participate in maintaining volume expansion at a given (normal) blood pressure level in the presence of the renal vasodilation that occurs in obesity. However, if the sympathetic activity results in greater sodium retention and volume expansion than can be balanced by the natriuretic effects of renal vasodilation, then a higher arterial pressure would be required to maintain sodium-volume homeostasis, resulting in hypertension.

Based on studies using norepinephrine turnover, sympathetic drive to the heart does not appear to be elevated in obese normotensives and appears to be only modestly elevated, on average, in obese hypertensives. The studies of norepinephrine kinetics suggest that regional differences in sympathetic function exist between obesity, hypertension, and their combination.

**Muscle sympathetic nerve activity (MSNA)**

MSNA is higher in obese normotensive and obese hypertensive subjects than in lean normotensive controls and may be explained by central differences in autonomic regulation. Grassi and colleagues showed that weight loss in obese normotensives reduced MSNA, lowered plasma norepinephrine, and improved deficits in baroreflex sensitivity and whole-body glucose disposal.

The changes in MSNA and glucose disposal may be linked. An elegant regional hemodynamic study by Jamerson and colleagues, demonstrated an inverse relationship between vascular \(\alpha\)-adrenergic tone and insulin-mediated glucose disposal. Thus, it is tempting to speculate that the increased MSNA in obese normotensives enhances \(\alpha\)-adrenergic vasoconstriction and contributes to impaired insulin-mediated glucose disposal. While vasoconstriction from any cause has been implicated in insulin resistance, the effects of \(\alpha\)-adrenergic vasoconstriction on glucose disposal appear more adverse than a similar vasoconstriction induced by angiotensin II. Conversely, the marked reduction in MSNA with weight loss in obese normotensives could have reduced their \(\alpha\)-adrenergic vasoconstriction and improved insulin-mediated glucose disposal.

While it is challenging to separate the effects of caloric restriction from those of weight loss on MSNA in obese subjects, it appears that significant weight loss and not just reduced calorie intake is necessary. For example, after 3 days of semistarvation diets in obese women, MSNA was not changed. However, measurements obtained by Andersson and colleagues when the women lost 7% of their initial weight showed a significant decline in MSNA.

MSNA is reportedly higher in men than in women. In studies to assess these gender differences, Jones and coworkers analyzed the relationship of body fat to MSNA in men and women. They found that MSNA was more strongly correlated to central than peripheral body fat. Several studies demonstrate that the central, or male, fat pattern is associated with greater degrees of hyperinsulinemia, insulin resistance, hypertension, diabetes, and CHD than the peripheral or gynoid fat pattern characteristically seen in women. The largest
sexual dimorphism in body fat distribution is present in younger adults and decreases as women gain weight with a centripetal fat distribution as they age. Furthermore, overweight is more strongly related to hypertension in men than in women <45 years old. These findings relating MSNA to body fat pattern, in view of the literature noted, raise the possibility that greater sympathetic activation among individuals with abdominal obesity contributes to their propensity to insulin resistance, hypertension, and diabetes.

Obesity and hypertension have separate and additional effects on MSNA. In studies by Grassi and colleagues, MSNA was significantly and similarly elevated by ≈40% to 50% in both lean hypertensive and obese normotensive subjects than in lean normotensive volunteers. In obese hypertensive subjects, MSNA was nearly double the level observed in lean normotensive volunteers, suggesting that the effects of obesity and hypertension on MSNA were approximately additive. These investigators showed that reflex alterations of MSNA evoked by blood pressure changes were impaired in obese normotensive patients compared with both lean normotensives and lean hypertensives. The defects in baroreflex-mediated changes of MSNA were greater in obese hypertensive than obese normotensive subjects. These findings indicate that obesity is associated with increased MSNA as well as impaired regulation of MSNA by arterial baroreceptors. The abnormalities of MSNA in obesity are amplified by concomitant hypertension.

**Spectral analysis**
Obese patients are more susceptible to ventricular arrhythmias and sudden death than lean individuals. Faster heart rates are a powerful predictor of sudden death, especially in men. Autonomic abnormalities play an important role in the faster heart rates observed in some hypertensive patients. Of note, both sympathetic and parasympathetic abnormalities of heart rate control are greater in women with upper body (abdominal), and especially visceral adiposity, than in women with lower body obesity. Moreover, weight loss resulting from caloric restriction improved cardiac parasympathetic tone at night and reduced the ratio of sympathetic/parasympathetic cardiac tone during the day without changes of resting heart rate. While this review is focused on the sympathetic nervous system, obesity is also associated with abnormalities of parasympathetic function that may have clinically important consequences. Many of the autonomic abnormalities associated with obesity appear to improve with weight loss.

**Potential mechanisms contributing to sympathetic activation in obesity**
The literature implicates several factors in the sympathetic activation that occurs with obesity. Since obesity is a heterogeneous condition, the relative contribution of these factors may vary based upon other modifying biological factors, both genetic and environmental. Evidence will now be examined for several factors that may increase sympathetic activity in obesity. This list is not intended to be exclusionary, and other factors may participate.

The possibility that a primary increase in sympathetic tone might in some individuals play a primary role in the development of the metabolic syndrome obesity is supported by the observations in the Osaka study. The authors followed normal volunteers for a period of 10 years. An elevated plasma norepinephrine at the baseline predicted future higher BP readings, gain of weight, and higher insulin values. Whereas the mechanism whereby the sympathetic vasoconstriction could cause higher insulin values has been demonstrated, the processes by which a primary increase in sympathetic tone could lead to increased weight are less well understood. We recently reviewed the literature that supports the concept that enhanced sympathetic tone downregulates β-adrenergic receptors, which in turn, could decrease a person’s ability to dissipate calories. β-Adrenergic receptors are known to mediate the increased thermogenic response to food and the basal metabolic rate. The possible primacy of sympathetic overactivity is further supported by the study of Neutel and colleagues in which normotensive children of hypertensive parents exhibited higher plasma norepinephrine values and mild dyslipidemia. Finally, as noted earlier, studies in dogs support the crucial importance of sympathetic overactivity in the genesis of insulin resistance. When they were fed a diet of boiled lard, dogs developed the metabolic syndrome of overweight, insulin resistance, and high blood pressure. The authors then treated the animals with clonidine to decrease the sympathetic tone emanating form the central nervous system, which prevented (reversed) the hypertension.

**Insulin**
An extensive literature in animals and man indicates that elevations of plasma insulin, even within the physiological range, activate the sympathetic nervous system. In fact, theories linking hyperinsulinemia and insulin resistance to hypertension are based on the premise that potential pressor actions of insulin are
maintained, eg, sympathetic activation and renal sodium retention, while potential depressor effects are reduced, eg, vasodilation—a debate which exceeds the scope of this review.

A series of experiments by investigators at the University of Iowa demonstrated that euglycemic hyperinsulinemia raises MSNA similarly in healthy younger and older subjects and individuals with borderline hypertension. Despite differences in insulin action and peripheral vasodilation, blood pressure does not increase during the short term in any of these groups. In other studies, MSNA correlated most strongly with BMI (r=0.67, P<0.001) and total body fat (r=0.64, P<0.001) and less strongly with plasma insulin (r=0.34, P=0.04). These data suggest that hyperinsulinemia may account for only a comparatively small portion of the sympathetic activation observed in obesity. Moreover, in contrast to reports by other investigators, this group observed that obese subjects were resistant to insulin’s effect to increase MSNA, but equally responsive to other stimuli that raise MSNA. Collectively, the evidence implicates leptin and other effects that are depressor. For example, insulin, has some actions that are potentially pressor since nitric oxide appears to attenuate α-adrenergic vasoconstriction and raises blood pressure. In normotensive rats, infusion of oleate into the portal vein induces sympathetic activation and blood pressure elevation. The oleate-induced pressor response is blocked by α1-adrenoceptor antagonists. In dogs, unlike rats, infusion of oleate did not induce sympathetic activation or a pressor response.

In minipigs, a rise in plasma NEFAs evoked by infusion of Intralipid, a source of triglycerides, and heparin, which activates lipoprotein lipase and accelerates the hydrolysis of fatty acids from triglycerides, induces vasoconstriction and raises blood pressure. An elevation of plasma fatty acids in humans also acutely impairs baroreflex sensitivity, while enhancing sympathetic and impairing parasympathetic control of heart rate variability. Since less heart rate variability is associated with higher mortality rates, these observations may provide a potential mechanism linking elevated fatty acids to sudden death in the PPS.

Cytokines

The link between cytokines and sympathetic activation in obesity is speculative. Adipocytes produce several different inflammatory cytokines in proportion to their volume. Obesity is associated with an increase in several of these proinflammatory signaling peptides. Patients with congestive heart failure and those with sleep apnea have increased cytokines and sympathetic activation, which implies an association, while not establishing a causal link.
**Triiodothyronin**

The ratio of active-to-reverse triiodothyronine (T3) is linked to caloric intake, especially carbohydrate. The ratio of active-to-reverse T3 rises rapidly with overfeeding and falls with fasting. Similarly, overfeeding is associated with increases, and caloric deprivation with decreases in measures of sympathetic activity, as discussed previously. While these associations raise the possibility of a causal connection, the evidence linking excess thyroid hormone (T4) to sympathetic activation is variable, with some data suggesting that sympathetic drive is inhibited by hyperthyroidism. Further studies may be useful to determine if the effects of T4 and T3 on autonomic function are similar.

**Eicosanoids**

Adipose tissue produces several peptide- and lipid-signaling molecules, which may be increased among obese individuals. Eicosanoid products modulate autonomic activity in a clinically significant manner. Thus, abnormalities of eicosanoid metabolism in obesity could potentially contribute to defects in sympathetic activation and related downstream effects.

**Nitric oxide**

Nitric oxide is a neurotransmitter and local autacoid that modulates sympathetic activation centrally and neurogenic vasoconstriction peripherally. Of interest, leptin increases nitric oxide and increases sympathetic drive. Inhibition of nitric oxide during exogenous infusion of leptin significantly enhances the increase in sympathetic drive, especially to the heart.

**Endorphins**

Central endorphins can modulate sympathetic nervous system activity, appetite, and glucocorticoid (hypothalamic-pituitary-adrenal axis) function. Endorphins also appear to mediate the sympatholytic effects of central α2 /imidazole receptor agonists. In short-term studies in human volunteers, opioid antagonists, eg, naloxone, are potent modulators of sympathetic activity. The effects of endorphins/opioids on sympathetic function are variable, depending upon the specific site of action and the subtype of receptor activated. The evidence suggests that abnormalities of endorphins could contribute to disturbances in energy intake relative to expenditure, the hypothalamic-pituitary-adrenal axis, and autonomic function described in obesity.

**Neuropeptide Y**

Neuropeptide Y (NPY) acting at the hypothalamus reduces appetite and sympathetic outflow, whereas NPY acting peripherally enhances sympathetic function. As with endorphins, several NPY receptor subtypes exist to mediate the various tissue-specific effects. While peripheral NPY levels appear normal in obesity, alteration in central levels and/or peripheral and central actions of NPY could also contribute to defects in autonomic drive and tone.

**Sleep apnea**

Sleep apnea, unlike the previously cited factors that may contribute to neurogenic activation in obesity, is a medical condition and not a peptide- or lipid-signaling molecule. Sleep apnea is an obesity-associated medical condition that is both common and often unrecognized. Sleep apnea may affect as many as 50% of hypertensive patients. Sleep apnea is associated with multiple changes, including severe insulin resistance, hyperleptinemia, hypercytokinemia, and sympathetic activation. Thus, several factors already discussed may contribute to adrenergic activation in patients with sleep apnea. In addition, hypoxemia, by activating peripheral chemoreceptors and/or central effectors, eg, C1 or catecholamine-containing neurons in the medulla, may play a major role in the sympathetic activation that occurs in sleep apnea. Imidazolines, like clonidine, suppress sympathetic activation by effects on C1 neurons. Thus, activation of these receptors by hypoxia could potentially contribute to neurogenic hypertension in obese patients with sleep apnea.

**CONCLUSION**

Obesity is a growing worldwide epidemic. Metabolic syndrome–related health problems are closely related to this anthropometric change. With minimal efforts at hyperbole, the global epidemic is poised to escalate into a pandemic in the years ahead. The clinical epidemiological significance of the syndrome is highlighted by its association with a 2- to 4-fold increase in risk for coronary heart disease, total cardiovascular disease, and all-cause mortality. The rapidly growing burden of obesity together with a population that is becoming older and made up of an increasing proportion of high-risk ethnic minorities raises the importance of effective strategies for the primary prevention of the metabolic syndrome. Obesity is associated with multiple health risks that impact the structure and function of virtually every organ system. Obesity is a heterogeneous condition modulated by a variety of genetic, developmental, and environmental factors. The literature indicates that the sympathetic nervous system is activated in a substantial subset of obese individuals and appears to play an important role in the insulin
resistance, hypertension, tachycardia, target-organ complications, and sudden death that occur earlier and more frequently in obese patients. Sympathetic activation may also induce and/or exacerbate weight gain by downregulating β-adrenergic receptors.

Evidence strongly implicates leptin and hyperinsulinemia in the sympathetic activation that occurs in obese subjects. While more hypothetical, other factors, eg, fatty acids, endorphins, NPY, eicosanoids, and endorphins may play a role. In a more speculative mode, elevations of cytokines and increases in triiodothyronine may activate or create the appearance of sympathetic activation in obesity. Sleep apnea, which is a common and frequently unrecognized complication of obesity, may drive sympathetic activation by several mechanisms, including hypoxia acting at C1 neurons in the medulla and by exacerbating metabolic, neurohormonal, and inflammatory mediators associated with visceral obesity. Behavioral factors, eg, suppressed anger and hostility, could potentially contribute to autonomic changes in obese subjects.52,109

The principal goal of this review was to examine the causes and consequences of sympathetic activation in the metabolic syndrome. It is hoped that the effort will foster a better understanding of the factors that induce sympathetic activation and the consequences of that activation among individuals with insulin resistance. Scientific discovery and understanding are critical components driving novel therapeutic interventions to reduce at least some of the devastating health and economic consequences of the metabolic syndrome, and current evidence indicates several promising avenues of inquiry.

**THREE KEY QUESTIONS**

One of the major aspects of the metabolic syndrome clearly is its epidemic-like prevalence, closely linked to the spiraling worldwide growth of obesity: this alone justifies current efforts to better understand the components of the syndrome, its causes, its consequences, and of course to define optimal therapeutic strategies. Obviously, the scope of the problem encompasses a far greater number than the customary three key questions, and the Editors’ choice was a particularly tough one in this case. Ivana Zavaroni, Diego Ardigò, Silvio Valtueña, and Alessandra Dei Cas, seeking to lay sound foundations for an earlier identification of subjects at risk of coronary heart disease and a more aggressive lifestyle intervention ask: “Metabolic syndrome: what are the acknowledged markers, and how reliable are they?” We then singled out hypertension among many other possible topics worthy of review—we did say that we were faced with a difficult choice! Thus, Murray D. Esler, taking a close look at the recent neurogenic explanation for the development of hypertension in obesity, asks: “Metabolic syndrome and hypertension: what are the outstanding questions,” while Marcelo L. G. Correia, Kamal Rahmouni, and Allyn Mark focus their scrutiny on the role of leptin, asking, “By which mechanisms does leptin contribute to elevated blood pressure?” The Editors wish that this all-too brief foray into the realm of the metabolic syndrome will have whetted the reader’s appetite and encouraged further investigation of the topic.
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Metabolic syndrome: what are the acknowledged markers, and how reliable are they?

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Insulin resistance and its cluster of associated abnormalities, defined as the metabolic syndrome, are important coronary heart disease (CHD) risk factors. The report of the Adult Treatment Panel–III (ATP III) serves as a formal recognition of this, and the fact that approximately 25% of Western populations may be suffering from the untoward consequences of insulin resistance emphasizes the magnitude of the clinical problem. The aim of the definition of the metabolic syndrome based on ATP III criteria is to provide a tool able to identify insulin-resistant individuals, and it offers a pragmatic approach to the early identification of individuals at risk for CHD, with the potential benefit of a more aggressive lifestyle intervention and a more focused follow-up.

This article will provide a few comments rather than an answer to the question: “What are the acknowledged markers of the metabolic syndrome?” With the definition of metabolic syndrome, cardiologists have formally recognized the important role played by the defect in insulin action and associated abnormalities in increasing cardiovascular disease (CVD) risk.

DEFINITION OF THE METABOLIC SYNDROME AND INSULIN-RESISTANCE SYNDROME

The Adult Treatment Panel–III (ATP III) has stressed the importance in terms of coronary heart disease (CHD) risk factors of a “constellation of lipid and nonlipid risk factors of metabolic origin,” defining this cluster of abnormalities as “the metabolic syndrome,” and pointing out that “this syndrome is closely linked to insulin resistance.”

Table I (page 162) lists the 5 criteria selected by the ATP III to identify individuals with the metabolic syndrome (abdominal obesity, elevated blood pressure, impaired fasting glucose, and elevated triglycerides (TG), and low high-density lipoprotein cholesterol (HDL-C). All of these abnormalities are related to insulin resistance, and the presence of only 3 of these criteria is required to make a diagnosis of metabolic syndrome. A recent report, evaluating the database of the Third National Health And Nutrition Examination Survey (NHANES III) in terms of these criteria, estimated that 1 out of 4 adults living in the USA deserved the diagnosis of metabolic syndrome.

Insulin resistance syndrome and metabolic syndrome are not synonymous, but are closely related: resistance to insulin-mediated glucose disposal greatly increases the probability of developing one or more of the related abnormalities belonging to the metabolic

SELECTED ABBREVIATIONS AND ACRONYMS

| **ATP III** | Adult Treatment Panel–III |
| **CHD** | coronary heart disease |
| **CVD** | cardiovascular disease |
| **DECODE** | Diabetes Epidemiology, Collaborative analysis Of Diagnostic criteria in Europe |
| **FPG** | fasting plasma glucose |
| **HDL-C** | high-density lipoprotein cholesterol |
| **NCEP** | National Cholesterol Education Panel |
| **NHANES III** | Third National Health And Nutrition Survey |
| **TG** | triglyceride |
syndrome. Insulin resistance is characterized by decreased tissue sensitivity to the action of insulin, leading to a compensatory increase in insulin secretion. However, even when insulin-resistant individuals secrete enough insulin to maintain glucose homeostasis, they remain at increased risk of developing a cluster of abnormalities that have been collectively described as the insulin resistance syndrome. This denomination highlights the central role of insulin resistance and compensatory hyperinsulinemia in the development of the cluster of the associated abnormalities, and thus in the pathogenesis of the syndrome. The insulin resistance syndrome, with its related abnormalities, is an umbrella under which all of the abnormalities related to insulin resistance with compensatory hyperinsulinemia can be collected (Figure 1), and predicts the risk of developing type 2 diabetes, hypertension, CHD, and stroke.

Table II gives the abnormalities currently considered to be components of the insulin resistance syndrome, because of their relationship with insulin resistance and hyperinsulinemia:

**Glucose tolerance**

The majority of persons with the insulin resistance syndrome have a “normal” fasting plasma glucose (FPG) concentration (<110 mg/dL).
However, individuals with either "impaired fasting glucose" (FPG concentration >110 and <126 mg/dL) or "impaired glucose tolerance" (FPG concentration <126 mg/dL, and a plasma glucose concentration >140 mg/dL and <200 mg/dL 120 min after a 75-g oral glucose challenge) are most likely insulin-resistant.

**Dyslipidemia**

Elevated plasma triglycerides (TG) and low plasma HDL-C are common findings in insulin-resistant/hyperinsulinemic persons. This characteristic dyslipidemia is also associated with the presence of small, dense low-density lipoprotein (LDL) particles, and an increase in the postprandial accumulation of TG-rich remnant lipoproteins. These abnormalities are highly atherogenic and provide the most well-established mechanistic link between the insulin resistance syndrome and CVD.

**Hemodynamics**

The increased sympathetic nervous system activity and renal sodium retention documented in the insulin resistance syndrome are likely the link that might explain why approximately 50% of patients with essential hypertension are insulin-resistant/hyperinsulinemic. The insulin-resistant/hyperinsulinemic subset of patients with essential hypertension also shows the characteristic dyslipidemia of the insulin-resistance syndrome, and these individuals have a higher CVD risk.

**Uric acid metabolism**

Plasma uric acid concentrations are higher in insulin-resistant individuals, and this is associated with a decrease in uric acid renal clearance. However, plasma uric acid is not a very sensitive predictor of insulin resistance. Thus, though an elevated plasma uric acid concentration increases the probability that an individual is insulin-resistant, a normal concentration does not mean that an individual is insulin-sensitive.

**Inflammation**

There is evidence that other markers of inflammation are present in the insulin resistance syndrome, eg, C-reactive protein and higher white cell counts.

**Hemostasis**

Functionally, endothelium-dependent vasodilatation is reduced in insulin-resistant/hyperinsulinemic individuals. Mononuclear cells isolated from insulin-resistant/hyperinsulinemic individuals show greater adherence to cultured endo-
of the 5 components are arbitrary, resistance. The numerical values together as well as being more selected because they tend to clus-
ter together. The variables listed in developing CVD.

The appropriate diagnostic approach to the insulin resistance syndrome is the measurement of insulin sensitivity, but there is no single definitive test for insulin resistance available for use in clinical practice and standardized assays for plasma insulin, a surrogate measure of insulin resistance, are not available for routine use. The National Cholesterol Education Panel (NCEP) has made a major contribution by publishing the Adult Treatment Panel III (ATP III) diagnostic criteria for the metabolic syndrome. Its goal was to provide a tool able to identify insulin-resistant individuals at increased risk of developing CVD.

The variables listed in Table I were selected because they tend to cluster together as well as being more commonly associated with insulin resistance. The numerical values of the 5 components are arbitrary, not validated by hard data; however, abnormalities in all of them have been found to be associated with increased CHD risk. Use of the ATP III diagnostic criteria calls for the following comments.

### Obesity

Waist circumference as a measure of obesity was included among the criteria for the diagnosis of the metabolic syndrome. However, obesity should be viewed as a condition that has an adverse effect on insulin resistance and increases the likelihood that abnormalities associated with insulin resistance might also be present. Therefore, obesity and waist circumference (which is a measure of excess adiposity), are risk factors for the insulin resistance syndrome, but not a diagnostic criterion for the insulin resistance syndrome. Obesity, indeed, may be a cause of insulin resistance, and not a consequence. Not all overweight/obese individuals are insulin-resistant, and not all insulin-resistant individuals are overweight/obese.

However, this does not minimize the important role that the current epidemic of obesity plays in the increase in the prevalence of the metabolic syndrome. Therefore, since obesity is able to cause an insulin resistance syndrome similar to that of the primary nonobese syndrome, and given the fact that primary insulin resistance is rare while obesity is highly prevalent in the population, it is understandable why they are not kept separate and why obesity is considered a major criterion for the diagnosis of the metabolic syndrome.

### Plasma glucose

Fasting plasma glucose is the variable with the greatest positive predictive value, and a concentration between 110 and 126 mg/dL is highly predictive of insulin resistance/hyperinsulinemia. However, it is not a sensitive indicator, and the vast majority of insulin-resistant/hyperinsulenic individuals have a fasting glucose concentration <110 mg/dL.

The Diabetes Epidemiology, Collaborative analysis Of Diagnostic criteria in Europe (DECODE) Study Group showed that post glucose challenge plasma glucose concentrations were better than fasting value in predicting CVD, and that more than 25% of subjects with normal glucose tolerance were in the most insulin-resistant tertile.

Therefore, a significant number of individuals with normal glucose tolerance are insulin-resistant and at increased CVD risk.

### Blood pressure

Although hyperinsulinemia, a surrogate measure of insulin resistance, predicts the development of hypertension, no more than 50% of patients with essential hypertension are insulin-resistant. If patients with essential hypertension do not meet the criteria for hyperglycemia and dyslipidemia shown in Table I, it is possible that they are not insulin-resistant/hyperinsulinemic. Therefore, it may be more important to focus on whether or not an increase in blood pressure is associated with any of the manifestations of the insulin-resistance syndrome than simply consider the presence of hypertension.

### Dyslipidemia

The ATP III criteria are most likely able to identify insulin-resistant/hyperinsulenic individuals on the basis of plasma TG and HDL-C values. The TG/HDL-C concentration ratio is a powerful predictor of both
insulin resistance and CHD risk. The relationship between the TG/HDL-C concentration ratio and a specific measure of insulin-mediated glucose disposal has been found to have a correlation coefficient almost identical to that between insulin resistance and fasting plasma insulin concentration (a commonly used surrogate measure of insulin resistance). In addition, the TG/HDL-C concentration ratio provides an independent estimate of CHD risk. There is strong evidence that the dyslipidemic criteria proposed by the ATP III are characteristic of insulin-resistant/hyperinsulinemic subjects, highly predictive of CHD risk, and that treatment of dyslipidemia reduces the incidence of CVD.

ADVANTAGES OF THE ATP III DIAGNOSTIC APPROACH

The terms insulin resistance syndrome and metabolic syndrome are often used interchangeably to refer to the clinical consequences of insulin resistance and the compensatory mechanisms that develop to maintain homeostasis. However, the two terms are different and have different implications. The major point is that insulin resistance is not a disease, but a physiological change that increases the risk of developing one or more of the abnormalities listed in Table II. The more insulin-resistant an individual, the greater the degree of compensatory hyperinsulinemia, and the likelier the risk of developing one or more of the abnormalities listed in Table II. Conversely, the more abnormalities there are, the greater the chances that the individual is insulin-resistant. Not all insulin-resistant individuals develop these abnormalities, nor is their appearance confined to insulin-resistant individuals. On the other hand, the presence of any one of them indicates that the individual may be insulin-resistant, and increases the possibility that the other abnormalities may also be present.

The greatest benefit of the ATP III approach to the diagnosis of metabolic syndrome is the recognition that insulin resistance/hyperinsulinemia, and the consequences of these defects on insulin metabolism, must be taken into account in efforts aimed at decreasing CHD risk. The ATP III criteria do not have a pathophysiological value, but offer a pragmatic approach to improving the clinical outcome through implementation of lifestyle changes to decrease CVD risk. These criteria very probably reliably identify insulin-resistant/hyperinsulinemic individuals; however, they are based on arbitrary numerical scoring systems and are not validated by data.

CONCLUSION

Despite the limitations discussed above, the ATP III criteria should be considered as a useful tool, in the absence of better indicators, and their use is justified by the effort to enable early identification of individuals at risk of CHD, with the potential benefit of a more aggressive lifestyle intervention and a more focused follow-up.

The fact that approximately 25% of Western populations may be suffering from the consequences of insulin resistance emphasizes the magnitude of the clinical problem and the potential relevance of the metabolic syndrome.

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Recent studies in clinical and experimental obesity suggest that the hypertension enmeshed within the metabolic syndrome is neurogenic, ie, initiated and sustained by activation of the sympathetic nervous outflow to the kidneys. Whether the stimulus for this is hyperinsulinemia, leptin excess, or perhaps coexistent obstructive sleep apnea remains problematic. Weight reduction and an aerobic exercise program remain pivotal in normalizing obesity-related hypertension. If these fail, the ideal antihypertensive drug should target the underlying neural pathophysiology of the hypertension, but should not contribute to weight gain by inhibition of thermogenesis or worsen the existing insulin resistance. Centrally acting sympathetic nervous inhibitors of the imidazoline-receptor binding class appear to meet these prerequisites, though no definitive empirical evidence is yet available to establish them as the preferred drug class.

As the obesity prevalence soars in industrialized countries and progressively increases in the third world, with the appearance of altered patterns of nutrition and a reduction in work-related energy expenditure, obesity-related hypertension has become a truly global health issue. Although there is a validity to the central concept commonly proposed for the origins of obesity—a mismatch in the energy balance equation with an excess of dietary calorie intake over body energy expenditure (Figure 1)—this simple thermodynamic formulation leaves complex issues untouched.

Dietary calorie intake is modified by social, economic, and cultural issues. Further, the composition of the diet no doubt matters, as exemplified by recent evidence suggesting that calorie-restricted diets identical in energy content, but differing in carbohydrate and fat content, differ also in propensity for weight loss (greater on the low carbohydrate diet). Energy expenditure is influenced by demographic change (such as third-world transition from a labor-intensive agricultural economy to an industrial base), by patterns of transportation (exemplified by the benefits of cycling as an antihypertensive factor in the Dutch), by the degree of adoption of household labor-saving devices, by changed recreational habits, particularly in childhood (computer games instead of physical games), and by genetic influences on metabolic rate. The prevalence of childhood obesity is escalating, having whimsically, but not entirely unrealistically, been attributed to “potato chips and computer chips.”
Obesity and hypertension are intimately associated, and both very commonly coexist in individual patients with insulin resistance, hyperinsulinemia, and hyperlipidemia, this clustering of adverse health factors being designated as the metabolic syndrome. The pathophysiological mechanisms by which hypertension is linked so strongly with obesity (in particular with central obesity) and with hyperinsulinemia have remained uncertain. Understanding these processes might provide a more rational basis for drug treatment of obesity-related hypertension. Attempts at reduction in body weight, although pivotal in the treatment of obesity-related hypertension, more often than not fail, so that antihypertensive drug therapy is needed. But what are the preferred drugs?

**SYMPATHETIC NERVOUS SYSTEM ACTIVITY IN OBESITY**

On this issue there have been two enduring hypotheses. The first hypothesis, from Bray et al, is that sympathetic nervous system underactivity is present in human obesity, as it commonly is in animal models, and through consequential failed stimulation of thermogenesis provides a metabolic basis for the obesity. The second hypothesis, attributable to Landsberg, is that, in obesity, sympathetic nervous activation occurs with chronic overeating where it facilitates energy balance and weight stabilization, but at the cost of adverse consequences attributable to chronic stimulation of the sympathetic nervous system, in particular, elevation in blood pressure.

Methods involving measurements of rates of sympathetic nerve firing, clinical microneurography, and of organ-specific norepinephrine spillover to plasma provide the most secure basis for studying regional sympathetic nervous function in patients with obesity and obesity-related hypertension (Figure 2). Clinical microneurography can measure nerve firing rates in subcutaneous sympathetic nerves distributed to skin and skeletal muscle. Multifiber recordings of “bursts” of nerve activity synchronous with the heart beat and, more recently, single fiber traces, are generated. Sympathetic neurotransmitter release to plasma from an individual organ, regional norepinephrine “spillover,” can be studied using the principle of isotope dilution, with intravenous infusion of tritiated norepinephrine and sampling from the venous drainage of the organ in question.

In obese people with normal blood pressure, the whole-body norepinephrine spillover rate, a measure of overall sympathetic nervous activity, and the rate of secretion of epinephrine from the adrenal medulla are typically normal. In contrast, renal norepinephrine spillover on average is approximately twice normal, evidence of activation of the sympathetic outflow to the kidneys (Figure 2). The sympathetic nerves passing to the skeletal muscle vasculature are also stimulated, evident in the sympathetic microneurogram as increased multunit nerve firing. These findings of sympathetic nervous system activation in human obesity unequivocally support the Landsberg position. Perhaps surprisingly, the sympathetic outflow to the heart is subnormal, cardiac norepinephrine spillover being approximately 50% of that of healthy lean people (Figure 2). The low symp-
pathetic activity in the heart in established obesity, however, would have only a trifling impact on total energy balance, outweighed by increases in sympathetic activity in the kidneys and skeletal muscle vasculature, since the heart is responsible for approximately 2% to 3% only of whole-body energy expenditure.

**MECHANISMS OF SYMPATHETIC NERVOUS ACTIVATION IN OBESITY**

Since positive energy balance with overeating initiates thermogenesis by stimulation of the sympathetic nervous system, as suggested by Landsberg, the activation of sympathetic activation seen in obesity could perhaps represent an adaptive response to overeating, helping to stabilize body weight by stimulating thermogenesis, but at the price of sympathetic nervous activation in the kidneys and vasculature secondarily elevating blood pressure. How might this sympathetic nervous activation be mediated? Hyperinsulinemia and hyperleptinemia accompanying obesity are candidates, but as yet the evidence for both is inconclusive.

**Sympathetic activation or hyperinsulinemia: which comes first?**

In the clustering of hypertension with overweight, hyperlipidemia, insulin resistance, and hyperinsulinemia in the “metabolic syndrome,” whether the hyperinsulinemia is a cause or a consequence of the sympathetic nervous activation is still debated. With infusion of insulin in humans to acutely produce hyperinsulinemia, and clamping of blood glucose concentrations, activation of the sympathetic nervous outflow recorded in skeletal muscle is seen with microneurography. This effect of insulin is mediated through the central nervous system (CNS) either as a reflex response to vasodilatation or as a direct effect of insulin on forebrain areas regulating sympathetic outflow. While fasting serum insulin concentrations are higher in the obese, we have previously reported that serum insulin and renal norepinephrine spillover values are not quantitatively related overall, arguing against hyperinsulinemia per se causing the elevated renal sympathetic nervous activity. Further, euglycemic insulin infusion in humans (lean hypertensive patients were studied) does not appear to activate the renal sympathetic nerves.

It seems that the renal sympathetic nervous activation in obesity has origins in altered CNS regulation of sympathetic nervous outflow, but involving mechanisms other than hyperinsulinemia.

A viewpoint gaining favor is that the hyperinsulinemia of the metabolic syndrome is a secondary phenomenon, resulting from the underlying hemodynamic abnormalities present. Glucose utilization by skeletal muscle under the influence of insulin, which is the process largely determining measured insulin resistance, is dictated by muscle blood flow. Reduced skeletal muscle blood flow in hypertension resulting from neural vasoconstriction may possibly be the primary cause of the insulin resistance and the attendant hyperinsulinemia.

**Obstructive sleep apnea**

Hypertension is particularly common in obese people with episodic nocturnal airways obstruction. Apneic episodes at night are accompanied by intense sympathetic nervous activation, elegantly documented by Narkiewicz, Somers, and colleagues using microneurography. With time, and by an unknown mechanism, this episodic nocturnal sympathetic stimulation seems to have only a trifling impact on total energy balance, outweighed by increases in sympathetic activity in the kidneys and skeletal muscle vasculature, since the heart is responsible for approximately 2% to 3% only of whole-body energy expenditure.

**Metabolic syndrome and hypertension: what are the outstanding problems?**

Leptin in obesity: important in rodents, but not in human obesity?

It has been proposed that the sympathetic nervous activation of obesity might be driven by high plasma levels of leptin. Leptin, a 16-kDa protein derived principally from adipose tissue has been implicated in body weight homeostasis. In rodents, leptin has been demonstrated to promote negative energy balance and weight loss, an effect attributed to both suppression of appetite and sympathetically mediated thermogenesis. With intravenous infusion of leptin in rats, activation of the sympathetic outflows to the kidneys and hindlimb vasculature is seen, without any increase in heart rate, suggesting that the cardiac sympathetic nerves are not stimulated. These effects have a close parallel in the pattern of sympathetic nervous change seen in human obesity, suggesting that leptin stimulation of the sympathetic nervous system may be the underlying explanation.

Our own observations in human obesity, however, do not support this interpretation. We find plasma leptin concentrations in lean and obese normotensive men to be weakly related only to measures of whole-body and regional sympathetic activity. Unlike in some rodent models of obesity, the biological role of leptin in human obesity therefore is uncertain. Paradoxically, we find release of leptin from the brain in men with obesity, not seen in lean men, accompanied by increased turnover of serotonin. This is noteworthy in that it suggests a functional coupling in human obesity, perhaps as an adaptive response, albeit futile, of two brain systems known to cause satiety.
evolve into ongoing, continuous sympathetic nervous activation. The claim has been made that height-
ened sympathetic activity in the obese is seen only in those with ob-
structive sleep apnea, although this is disputed.

**IS OBESITY-RELATED HYPERTENSION NEUROGENIC?**

Activation of the sympathetic nervous system, involving the sympa-
thetic outflows to the kidneys, heart, and skeletal muscle vasculature, is a now very well documented patho-
physiological finding in lean young and middle-aged patients with es-
sential hypertension. Their hypertension is conceived as being “neuro-
genic,” initiated and sustained by the increased sympathetic nerv-
ous cardiovascular drive.

Obesity-related hypertension also seems to have an important neuro-
genic component, being characterized by activation of the sympathetic outflows to the kidneys and skeletal muscle vasculature. A large number of studies, reviewed by DiBona, have demonstrated the importance of the renal sympathetic nerves in the development of hypertension in various experimental models. The neurogenic hypothesis of human obesity-related hypertension, which emphasizes activation of the renal sympathetic outflow as a prime mover in the blood pressure elevation, is supported by evidence from obesity-induced hypertension in dogs, where sympathetic activation during overfeeding is accompanied by a marked retention of sodium despite increases in glomerular fil-
tration rate (GFR) and renal plasma flow.

There is, however, a problem. In pa-
tients with obesity-related hyper-
tension there is a comparable, but no greater, elevation of renal nore-
pinephrine spillover to that present in the normotensive obese. The higher renal sympathetic nervous activity in the obese thus may be important in the development of their hypertension, but it would seem to be a necessary rather than a sufficient cause. The search for pre-
disposing genetic or other factors among overweight people deter-
mining who might become hypertensive so far has proven futile.

**ARE THERE CONSEQUENCES OF SYMPATHETIC ACTIVATION THAT GO BEYOND BLOOD PRESSURE ELEVATION?**

Catecholamine toxicity to the myo-
cardium, in the form of focal necros-
es and myocyte deterioration, can be demonstrated when high doses of these agents are administered in experimental animals. Similarly, elevated catecholamine secretion in patients with pheochromocytoma sometimes leads to cardiomyopathy. Given this background, the ques-
tion has been put: while the sympathetic activation present in obesi-
ty-related hypertension no doubt contributes to the blood pressure elevation, are there adverse conse-
quences which go beyond this? In patients with heart failure, certainly, the case for adverse effects of high sympathetic tone in the failing heart, and protection from them with β-adrenergic blockade, is proven.

For obesity-related hypertension, as the sympathetic nervous activation spares the heart, the adverse effects of ongoing sympathetic activa-
tion no doubt are more circum-
scribed. It is only potentially noxious extracardiac effects of sympathetic activation that are of relevance, such as the undesirable metabolic con-
sequences of neural vasoconstric-
tion in skeletal muscle impairing glucose delivery to muscle, causing insulin resistance and hyperinsuli-
nemia, and perhaps in liver, retard-
ing postprandial clearing of lipids, contributing to hyperlipidemia.

**REVERSAL OF HYPERTENSION ON A LOW-CALORIE DIET: IS IT DUE SPECIFICALLY TO DIETARY ENERGY RESTRICTION OR TO WEIGHT LOSS?**

Blood pressure is often quickly lowered in our patients with obesity-
related hypertension when placed on a calorie-reduced diet, even be-
fore there is any material loss in weight. The explanation probably lies in the effects of dietary energy intake on the sympathetic nervous system. In the mid-1970s, Landsberg and Young made the totally un-
expected discovery in rats that calo-
rine restriction reduced sympathetic nervous system activity, while over-
feeding caused sympathetic activa-
tion. These findings were counterin-
tuitive (“doesn’t everyone feel their sympathetic nervous system being switched on if they miss a meal or two?”). The early phase of blood pressure reduction on a low-calor-
rie diet coincides with sympathetic nervous inhibition, with subse-
quent further blood pressure fall as body weight drops.

**HOW DOES AN EXERCISE PROGRAM LOWER BLOOD PRESSURE IN THE METABOLIC SYNDROME?**

It took many years of research to establish that regularly performed physical exercise produces long-
term lowering of blood pressure, and to demonstrate that inhibition of the sympathetic nervous system is an important underlying mechanism of this, most clearly evident in the
The sympathetic nerves of the kidneys. The process by which regular exercise lowers sympathetic nervous activity remains uncertain, although stimulation of skeletal muscle mechanoreceptors in exercising muscle may possibly be involved. An exercise program has multifaceted benefit in hypertensive patients with the metabolic syndrome, improving insulin sensitivity and reducing blood pressure, in the long term this blood pressure reduction being a result of both weight loss and of sympathetic nervous system inhibition.

**WHAT ANTIHYPERTENSIVES ARE BEST IN THE METABOLIC SYNDROME?**

Might the findings on the neural pathophysiology of obesity-related hypertension have any implications for its rational treatment? Given that sympathetic activation in obese hypertensive patients seems to contribute both to the blood pressure elevation and perhaps to other adverse metabolic and cardiovascular effects, might it be appropriate to specifically recommend therapies inhibiting the sympathetic nervous system?

There are three principal points of clinical relevance to the choice of antihypertensive drugs for the hypertension of the metabolic syndrome.

**Does the action of the antihypertensive drug reverse the neural pathophysiology?**

Centrally acting sympathetic suppressants, imidazoline-receptor–binding agents such as rilmenidine and moxonidine, inhibit sympathetic outflow, including in the renal sympathetic nerves, and might be preferred on theoretical grounds.

**Would an antiadrenergic antihypertensive promote weight gain?**

A negative thermogenic effect of β-adrenergic blockers has been demonstrated experimentally, and weight gain has been observed clinically with β-blockers. Although perhaps expected, weight gain has not been documented with the suppression of sympathetic outflow produced by imidazoline-receptor–binding agents.

**Which antihypertensives would unfavorably modify insulin resistance?**

A diabetogenic effect has been unequivocally demonstrated for both diuretics and β-adrenergic blockers. The effect of imidazoline-receptor–binding agents, ACE inhibitors, angiotensin receptor blockers, and dihydropyridine calcium channel blockers on insulin resistance is neutral, or marginally positive, tending to increase insulin sensitivity.

A rational case could thus be made for perhaps preferring imidazoline-receptor–binding agents, but avoiding diuretics and β-adrenergic blockers in hypertensive patients with the metabolic syndrome. Large-scale trials would be needed to formally test this proposition.

“Tailoring” of antihypertensive therapy to pathophysiology, however, at present cannot be the primary therapeutic principle, in part because knowledge of both hypertension pathophysiology and the precise mechanisms of drug action remains imperfect. The same point can be made for pharmacogenomic profiling of hypertensive patients, which remains in its infancy. Overriding clinical considerations commonly apply in the choice of initial therapy, such as the presence of coexisting illnesses carrying particular pharmaceutical recommendations. Whether obesity-related hypertension has a specific sensitivity to antiadrenergic drugs, in fact, has not been adequately investigated. Despite these caveats, the two nonpharmacological measures most commonly applied in the treatment of obesity-related hypertension—dietary calorie restriction and an exercise program—are well known to suppress sympathetic nervous system activity.

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By which mechanisms does leptin contribute to elevated blood pressure?

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Leptin is an adipocyte-derived hormone that promotes weight loss by reducing appetite and by increasing energy expenditure through sympathetic stimulation to thermogenic tissue. Leptin also produces sympathoactivation to kidneys, hind limb, and adrenal glands, suggesting that the obesity-associated increase in sympathetic nerve activity could be due in part to these sympathetic effects of leptin. Leptin produces an array of autonomic and cardiovascular actions. Most human obesity appears to be associated with partial leptin resistance. However, recent studies indicate that leptin resistance may be selective, with preservation of adverse sympathetic effects despite the partial loss of favorable satiety and thermogenic (metabolic) actions of leptin. Understanding of the molecular mechanisms and spectrum of selective leptin resistance may have implications for understanding the role of leptin in the cardiovascular complications of obesity.

Although a strong association between obesity and hypertension is well established, the precise mechanisms linking obesity and hypertension remain unclear. Several mechanisms have been implicated, including hemodynamic changes, abnormalities of renal function, activation of the renin-angiotensin system, and sympathetic overactivity. The discovery of leptin and its effects on the sympathetic and cardiovascular systems represent a potential link between obesity and hypertension.

Leptin is a 167 amino-acid protein secreted by adipocytes that circulates in proportion to the adipose tissue mass to relay a satiety signal to the hypothalamus. Leptin from the plasma is transported to the central nervous system by a saturable, unidirectional system involving binding of leptin to the short form of the leptin receptor located at the endothelium of the vasculature and the epithelium of the choroid plexus. Although originally it was believed that leptin is secreted exclusively by the adipocytes, many additional sites of leptin production have recently been identified, including placenta, stomach, ovary, skeletal muscle, mammary gland, pituitary, and brain. Adipose tissue is, however, the main, if not the only source, of circulating leptin.

Leptin promotes weight loss by reducing appetite and food intake and by increasing energy expenditure (Figure 1, page 174). The profound obesity and the hyperphagia caused by the absence of leptin in rodents and humans make it clear that this hormone is fundamental for the control of body weight and food intake.

SYMPATHETIC EFFECTS OF LEPTIN

Using multifiber recording of regional sympathetic nerve activity (SNA) we, and others, evaluated the effects of leptin on the sympathetic outflow to different tissues and organs. Intravenous administration of leptin in anesthetized Sprague-Dawley rats caused a significant and dose-dependent increase in SNA to thermogenic brown adipose tissue. This was expected because thermogenic metabolism in brown adipose tissue was known to be sympathetic-
ly mediated. Unexpectedly, leptin also caused sympathoactivation to other beds not usually considered thermogenic, such as the kidney, hind limb, and adrenal. Satoh et al investigated the effect of leptin on circulating catecholamines and found that leptin administration caused a significant and dose-dependent increase in plasma concentration of norepinephrine and epinephrine.

Although Janus kinase–signal transducers and activators of transcription (JAK–STAT) signaling was initially thought to be the main pathway that mediates the leptin action in the hypothalamus, phosphoinositol-3 (PI3) kinase has been found to play a pivotal role in the feeding response to leptin. We have recently demonstrated that PI3 kinase also plays a major role in the transduction of leptin-induced changes in renal sympathetic outflow. We compared renal sympathoactivation to leptin before and after intracerebral administration of PI3 kinase inhibitors LY294002 and wortmannin. Both inhibitors markedly attenuated the increase in renal SNA induced by leptin, without affecting sympathoactivation to stimulation of the melanocortin system. The intracellular mechanism involved in leptin-induced sympathoactivation to other beds remains unknown, however.

After activation of leptin receptors in the central nervous system, the signal is transduced by a series of integrated neuronal pathways that regulate endocrine and autonomic function. Several hypothalamic neuropeptides, monoamines, and other transmitter substances have been identified as candidate mediators of leptin action in the hypothalamus. These include among others melanocortins, neuropeptide Y, and corticotrophin releasing hormone. Interestingly, leptin appears to induce regional sympathoactivation through different pathways. Both renal and lumbar sympathoactivation to leptin seems mediated by the melanocortin system because blockade of melanocortin receptors with SH9119 or agouti protein inhibits the renal and lumbar SNA response to leptin. Further evidence for a pivotal role of the melanocortin system in the renal SNA response to leptin derives from studying the melanocortin-4 receptor null mice. Indeed, we found a gene dose effect, with melanocortin-4 receptor heterozygotes having 50% of the normal renal SNA response to leptin, and homozygote knockouts having no renal SNA response to leptin.

The increase in brown adipose tissue SNA seems to depend on other neuropeptides than the melanocortin system because blockade of the melanocortin receptors does not affect leptin-induced sympathoactivation to brown adipose tissue. Our results show that a corticotrophin-releasing hormone receptor antagonist blocked leptin-induced sympathoactivation to brown adipose tissue, but not to the kidney. In summary, leptin appears to cause regional sympathoactivation via different neuropeptide pathways, with melanocortins mediating renal sympathoactivation and corticotrophin-releasing hormone mediating brown adipose tissue SNA to leptin.

**SYMPATHETIC EFFECTS OF LEPTIN IN OBESITY AND THE NOVEL CONCEPT OF SELECTIVE LEPTIN RESISTANCE**

Several lines of evidence suggest that enhanced SNA might play a major role in obesity-associated hypertension. Plasma and urinary catecholamines are increased in obese humans as well as in obese animal models. Using direct measurement with microneurography, many groups have shown increased SNA to skeletal muscle in...
Leptin and blood pressure

Correia and others

Obese subjects as compared with lean individuals. The study of regional SNA in obese humans using norepinephrine spillover has demonstrated that obesity is associated with increased SNA to the kidney, a key organ of blood pressure homeostasis. Long-term activation of the sympathetic nervous system could raise arterial pressure by causing peripheral vasoconstriction and by increasing renal tubular sodium reabsorption. Recent evidence indicates that leptin may represent a link between excess weight gain and high arterial pressure through its actions on the sympathetic nervous system.

Obesity is known to be associated with circulating hyperleptinemia, reflecting a high fat mass and partial resistance to leptin, because, despite the high circulating levels of leptin, such subjects remain obese. Under these circumstances, in order for leptin to have a role in obesity-related hypertension, one must postulate that leptin resistance can be selective, with preservation of sympathetic responsiveness despite resistance to the satiety and metabolic actions of leptin. Indeed, we have demonstrated that in some animal models, including agouti mice and mice with diet-induced obesity, leptin resistance is selective with sparing of the effects of leptin on renal SNA (Figure 2). For example, in agouti mice, the anorexic and weight-reducing effects of leptin were less in the obese mice compared with lean littermates, but the increase in renal SNA in response to leptin was similar in both lean and obese mice. Therefore, despite partial resistance to the satiety and metabolic actions of leptin in obesity, leptin may act on the sympathetic nervous system to increase blood pressure. This novel concept has been called selective leptin resistance (Figure 2). This concept is analogous to the concept of selective insulin resistance in syndrome X, or so-called metabolic syndrome, in which there is resistance to the effects of insulin on glucose-mediated uptake in skeletal muscle, but preservation of adverse sympathetic and lipid actions of insulin. We suggest that further understanding of the phenomenon of selective leptin resistance may have implications for understanding of the cardiovascular and renal complications of leptin did not alter water or salt excretion by the kidneys in rats. The absence of an overt change in sodium excretion would initially suggest that leptin did not alter sodium excretion, but leptin increased blood pressure, which would be expected to cause pressure-dependent natriuresis. The absence of pressure natriuresis despite an increase in blood pressure indicates that leptin shifted the pressure–natriuresis curve toward sodium conservation. This shift in the pressure–natriuresis curve may reflect leptin-dependent renal sympatoactivation. This conclusion is further supported by the observation that leptin promotes natriuresis in spontaneously hyper-
tensive rats whose kidneys had been denervated, but not in those with intact renal nerves. Renal damage of human obesity is characterized by increased glomerular filtration and progressive glomerulosclerosis. Leptin may contribute to the pathogenesis of the renal disease of obesity by promoting cellular proliferation and collagen synthesis. Interestingly, leptin administration causes glomerulosclerosis and proteinuria in nonobese rats. Even subtle pathologic changes promoted by leptin in the kidneys of obese subjects could potentially cause increases in blood pressure and, in the long run, overt renal dysfunction and hypertension.

**VASULAR EFFECTS OF LEPTIN**

Leptin might contribute to modulation of vascular tone through several distinct mechanisms including nitric oxide (NO), oxidative stress, and endothelin.

There have been mixed results regarding leptin actions on endothelial NO. Leptin increases endothelial secretion of NO in isolated vessels. Despite NO release, blood pressure reductions were only found in sympathetically denervated rats. Furthermore, chronic administration of leptin in combination with NO synthase inhibitors amplified the pressor and chronotropic action of leptin. These observations suggest that leptin-dependent sympathoactivation counteracts the NO-dependent vasodilator effect of leptin.

Contrasting with results showing a direct vasodilator effect, leptin did not alter mesenteric or hindquarter blood flow in conscious rats treated with NO synthase inhibitors either in presence or absence of α- and β-adrenergic antagonists. Furthermore, leptin treatment did not attenuate hind limb vasoconstriction caused by external stimulation of sympathetic nerves, suggesting that any direct vascular effect of leptin is insufficient to oppose sympathetically mediated vasoconstriction. Therefore, although high concentrations of leptin may promote NO generation and vasodilation, models of diet-induced obesity do not support this concept. Da Silva et al. have shown that chronic endothelin-A receptor (ET\textsubscript{A} receptor) blockade produces substantial, but comparable, reduction in blood pressure in hypertensive rats with diet-induced visceral obesity as compared with control rats fed regular rat chow for 12 months. These results do not support an enhanced role for endothelin in control of vascular tone in obese, hypertensive senescent rats.

Strong associations between hypertension, obesity and increased oxidative stress have been consistently demonstrated. The mechanisms linking obesity and augmented oxidative stress are unclear, but probably involve leptin. For instance, chronic administration of leptin markedly decreases lipoprotein-derived paraoxonase-1, an important endogenous antioxidant factor. Additionally, leptin promotes oxidative stress as reflected by substantial increases in plasma and urinary isoprostanes. Increased oxidative stress is associated with endothelial dysfunction and may explain, in part, the augmented risk of hypertension and atherosclerosis in obesity.
Leptin exhibits sympathetic, renal, and vascular actions related with blood pressure modulation and possibly obesity-related hypertension (Figure 3). However, obesity is a state of partial leptin resistance. Experimental evidence from obesity models in mice indicates that leptin resistance is selective, because leptin-dependent renal sympathoactivation is preserved despite resistance to the anorexigenic and weight-reducing effects of leptin. Therefore, despite leptin resistance, leptin may activate the sympathetic system to produce obesity-related hypertension.

Are leptin and selective leptin resistance relevant to obesity-related hypertension in humans? Conclusive responses to this issue await comprehensive clinical studies addressing the effects of leptin on the autonomic system and the characterization of leptin resistance syndromes in humans.

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Leptin decreases plasma paraoxonase 1 (PON1) activity and induces oxidative stress: the possible novel mechanism for proatherogenic effect of chronic hyperleptinemia.
Galen’s physiology, which dominated European medicine until the Renaissance, viewed the heart as a source of heat rather than as a pump. It was not until 1628, when William Harvey’s *De Motu Cordis* described the circulation, that heart failure could be understood in terms of abnormal hemodynamics. Autopsies carried out as early as the 16th century included descriptions of heart disease, but initially these were generally “two or three lines of symptomatology and four or five lines of gross autopsy findings.” Théophile Bonet’s *Sepulchreum*, published in 1679, noted sudden death in a man with calcific aortic stenosis, and dyspnea in a patient with a diseased heart, but provided no hemodynamic explanations for the clinical findings. Harvey himself wrote little about disease, but did observe that venous occlusion leads to edema and that impaired cardiac pumping can cause dyspnea by reducing blood flow through the lungs. It therefore remained for others to describe the hemodynamic causes of dropsy (fluid retention) and dyspnea, the major manifestations of heart failure. The first description of the hemodynamics in heart failure, like most discoveries, cannot be credited to a single individual. Assignment of priority in the 17th and 18th centuries is especially difficult because medical advances were widely discussed among authorities and there were few publications, many of which appeared after the author’s death. Within a century after publication of *De Motu Cordis*, four clinician-pathologists provided hemodynamic explanations for the signs, symptoms, and pathological findings of heart failure. Three, Rivière, Mayow, and Lancisi, related some clinical features of this syndrome to hemodynamic abnormalities. However, it was Vieussens who, by integrating a superbly written case history, a detailed and thoughtfully described autopsy, and a surprisingly modern discussion of pathophysiology, provided the first clear description of the mechanisms by which impaired hemodynamic function causes the syndrome we now recognize as heart failure.

**INITIAL DESCRIPTIONS OF HEMODYNAMIC ABNORMALITIES IN HEART FAILURE**

Lazare Rivière (1589–1655)

Rivière, who received his doctorate from Montpellier where in 1622 he became Professor of Medicine, was an early advocate of Harvey’s teachings and appears to have been the first to...
relate signs and symptoms of heart failure to impaired ventricular ejection. In his opera omnia, published posthumously in 1723, Rivière described a patient with what was probably aortic valve endocarditis. As translated by Major 6 “[the patient] had difficulty in breathing and his legs appeared swollen.” After several days of worsening dyspnea complicated by bloodstained sputum, the patient died, and at autopsy was found to have “round carbuncles. which resembled a cluster of hazelnuts and filled up the opening of the aorta.” Rivière stated that aortic obstruction could explain the failure of pulsations in the arteries [and cause the lung to be] filled with much blood from which the suffocation of the natural heat spread to each part… For the blood ascending continually by the vena cava not coming freely to the heart overflowed in the lung and filled it up.

Although Rivière recognized the hemodynamic consequences of left ventricular outflow obstruction, his case report ended by echoing Galen’s view that the heart is a furnace, suggesting that the carbuncles were caused by “excessive blood which the marked heat of the ventricle hardened and in this manner changed its substance.”

John Mayow (1643-1679)

Mayow, who at the age of 17 was appointed Fellow of All Soul’s at Oxford, published his remarkable Tractus Quinque Medico-Physici in 1674, shortly before his early death. This far-ranging text, translated by members of the Alembic Club in Edinburgh, 7 includes a discussion of how obstruction of blood flow into the aorta or pulmonary artery causes the ventricles to become “widely distended” and the arterial pulse to be “quite languid.” Mayow also described a patient who was “breathless and suffered from violent palpitation of the heart and faintness after any brisker movement.” After “a more violent attack, with frequent swoons and coldness of the extremities” the patient died and at autopsy the opening into the left ventricle was nearly closed by cartilage adhering to its interior, so that blood could scarcely enter the ventricle.” Referring to this patient, who almost certainly had mitral stenosis, Mayow noted that the blood could not, on account of the obstruction, pass into the left ventricle of the heart [so that] the pulmonary blood-vessels and also the right ventricle were necessarily distended with blood.

Mayow postulated that the “asthmatic paroxysm [was caused by] blood stagnating in the pulmonary vessels.” He also described overload-induced hypertrophy, noting that because the right ventricle in this patient was forced to contract violently so as to propel the mass of the blood as much as possible through the lungs into the left ventricle, this also accounts for the great thickness and strength of the right ventricle since muscles accustomed to more violent exercise increase more than others.

Giovanni Maria Lancisi (1654-1720)

Lancisi, who was educated in Rome and became physician to several popes, also recognized the hemodynamic consequences of obstruction to blood flow through the heart. In De Subitaneis Mortibus, published in 1707 and translated by Jarcho, 1 Lancisi described a young man with shortness of breath and a “buried strangling over the precordia” who died suddenly and was found at autopsy to have a very large heart that appeared to obstruct the descending aorta. Lancisi suggested that the oppression and… heaviness of the precordia from which the patient ultimately died [occurred because] the left ventricle… was prevented from propelling readily the larger amount of blood into the obstructed aorta. This delay of blood, to be sure, brought about the oppression of the precordia and ultimately the deadly suffocation and syncope.

Even though Lancisi’s explanation for the cardiomegaly is implausible, he accurately described the hemodynamic consequences of impaired left ventricular ejection.

Lancisi’s De Aneurysmatibus, published 25 years after his death in 1745 and translated by Wright, 8 expanded on his earlier text in stating that aortic valve narrowing causes blood to be “driven into the left cavity and retarded in the pulmonary vein as far as the vena cava,” and that this results in dyspnea and dilation of the chambers behind the obstruction. He related swelling of the feet and legs to impeded blood flow through the right heart and stated that “dilatation of the right cavities of the heart” could be diagnosed when the jugular veins “are in turn dilated, undulate, are agitated in a remarkable manner and collapse…” This text also described the hemodynamics of tricuspid insufficiency, noting that incompletely closed valves at the mouth of the vena cava [cause blood] to be driven back again through gaping chinks of the valves and forced back along the whole path of the superior vena cava, then from that path it flows straight on into the jugulars [to cause dilatation of the neck veins. This elegant description of the abnormal ‘v’ wave then notes that] when the systole of the heart ceases, the blood without delay flows back downward from the jugulars into the vena cava, hence the jugulars cease to swell and in their turn collapse.

INTEGRATION OF CLINICAL, PATHOPHYSIOLOGICAL, AND HEMODYNAMIC FINDINGS BY RAYMOND VIEUSSENS (ca 1633/1641-1715)

Although Rivière, Mayow, and Lancisi described the hemodynamic basis for several signs and symptoms of heart failure, Vieussens (Figure 2) provided the most complete early description of pathophysiology. Citing clini-
Vieussens presented a remarkably modern view of the relationship between key features of the history and physical examination, pathology, and abnormal hemodynamics.

We have few biographic details about Vieussens; even his date of birth is obscure, being placed by various sources between 1633 and 1641. We do know that in 1670 he received a doctorate in medicine in Montpellier where he was a physician at the St Éloi Hospital and that he performed more than 500 autopsies. However, there is disagreement among biographies as to whether he had been appointed to the Faculty of Anatomy at Montpellier. There is no dispute, however, regarding his many contributions to medical science.

**Anatomical and other contributions**

Although he published some early work on fermentation, Vieussens was most successful as an anatomist. He described several structures in the nervous system, including the anterior medullary velum between the cerebellar peduncles (valve of Vieussens), the mass of white matter within the cerebral hemispheres (centrum ovale or Vieussens’ centrum), a small space sometimes found beneath the corpus callosum within the septum pellucidum (fifth ventricle or Vieussens’ ventricle), the celiac ganglia (ganglia of Vieussens), and a loop of sympathetic fibers linking the middle and inferior cervical ganglia (ansa subclavia or Vieussens’ loop). In the heart, he described a pattern of collateral vessels connecting the left anterior descending and right coronary arteries (circle of Vieussens), a fold of endothelium at the junction of the great cardiac vein and coronary sinus ostium (Vieussens’ valve), and a depression along the margin of the fossa ovalis (limbus fossae ovalis or Vieussens’ annulus). According to Bing, Vieussens was the discoverer of the small communications, now generally called Thebesian vessels, that connect the coronary circulation to the ventricular cavities.

**Aortic insufficiency**

Vieussens’ *Traité Nouveau de la Structure et des Causes du Mouvement Naturel du Cœur* [New Treatise on the Structure and Causes of the Natural Movement of the Heart], published in 1715 (the year he died) and translated by Jarcho, describes a patient whose pulse was so strong that the artery of each arm struck my fingertips just as a strongly stretched and violently shaken cord would have done. The patient’s pulse, of which I have never seen and never hope to see the like, convinced me that he was suffering from a violent palpitation of the heart.

A few days later, the patient died and at autopsy the left ventricle was found to be “dilated to an extraordinary extent” and the aortic valves “greatly stretched and cut off at the end” so that during diastole “the aorta… sent back into the left ventricle a part of the blood that it had just received.”

**Mitral stenosis**

An even more noteworthy case report in Vieussens’ *Traité Nouveau* began by describing the normal mitral valve and how it prevents “blood carried by the blood vessels of the lung into the cavity of the [left] ventricle from going back into these vessels.” This anatomical description provided the basis for Vieussens’ discussion of the pathophysiology of mitral stenosis in a young man whose mitral valve had become “bony” because the “lymphatic juice which nourishes [this valve was] loaded with earthy saline particles.” Although Vieussens did not understand the etiology of what was clearly rheumatic mitral stenosis (Figure 3), his ability to relate clinical manifestations to autopsy findings, and then to deduce the pathophysiological basis for the patient’s dyspnea and pleural effusions, ranks among the most remarkable accomplishments in cardiology.

Vieussens began his case report by describing the patient:

> [He] was lying in bed with his head very high. It seemed to me that his breathing was very difficult. His heart was burdened by a violent palpitation. His pulse seemed very small, weak, and altogether irregular.
lips had the color of lead, his eyes showed great dejection, and his legs and thighs were swollen and were cold instead of warm.

A week later, the patient died and at autopsy the thoracic cavity was found to be filled with yellowish serum. The heart was huge, approaching the size of an ox heart, the right atria and ventricle were "excessively large," and the tricuspid valve annulus was dilated. Vieussens then identified the cause:

…the entrance of the left ventricle appeared to be extremely small and … looking for the cause of such a surprising fact I discovered that the [mitral valve leaflets] were truly bony [and] that the [mitral valve] had shrunk greatly… The entry of the left ventricle having become greatly contracted and its margin having lost all its natural suppleness, the blood could not pass freely and as abundantly as it should into the cavity of this ventricle. As soon as the circulation became impeded by this, it began to expand to an extraordinary extent the trunk of the pulmonary vein, because the blood remained there too long and accumulated there in too large an amount. The blood had no sooner begun to stay too long in the trunk of this vein than it delayed the flow of the blood in all the blood vessels of the lung, so that the branches of the pulmonary artery and vein, spread by all the tissue of this organ, were always too full of blood and hence so dilated that they compressed the vesicles [lung parenchyma] enough to prevent the air from entering freely and leaving just as freely. This is why the patient always breathed with great difficulty. Since the blood in the lung thickened considerably during its long sojourn in the blood vessels, part of its serum separated little by little and fell into the thoracic cavity.

Vieussens followed this discussion of the physiology of backward failure with an equally clear description of forward failure when he noted:

The smallness, the weakness, and the irregularity of his pulse were caused by the excessive smallness of the amount of blood that the left ventricle furnished to the aorta…

**CONCLUSION**

In discussing who first discovered the hemodynamic causes of heart failure, Jarcho gives “intellectual and historical” priority to Vieussens, although he notes that the decision “should be rendered by a sibyl, an augur, or some other virtuoso of ambiguity.” I gladly defer to Jarcho because I do not read Latin and so must depend on others for both translations and selections of works that warrant translation. Recognizing these limitations, which require that I evaluate these early clinical scientists mainly as a cardiologist and physiologist, I credit Vieussens with the first clear description of the pathophysiology of heart failure. My judgment is based on his skill in relating the signs and symptoms of heart failure to the cardiac pathology, his use of clinical and postmortem data to explain hemodynamic abnormalities, and his formulation of clear hypotheses regarding pathophysiology in the patients for whom he cared. Vieussens’ success in synthesizing these diverse lines of data within the hemodynamic paradigm made possible by Harvey’s discovery of the circulation ranks among the monumental achievements in cardiology.

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Autonomic nervous cardiovascular regulation in borderline hypertension

S. Julius, M. Esler

Am J Cardiol. 1975;36:685-696

In this article from 1975, the authors review the evidence for the hypothesis that most of the observed abnormalities in borderline hypertension can be explained by neurogenic mechanisms. This theory states that increased autonomic drive to the heart, vasculature, kidneys, and other organs results in hypertension. The authors believe that people with borderline hypertension make good subjects for research into the pathophysiology of hypertension. This is because unlike subjects with established hypertension they do not have secondary changes due to hypertension, which may bias research.

The authors begin by presenting the biochemical evidence for overactivity of the sympathetic nervous system in borderline hypertension. Norepinephrine levels have been demonstrated to be elevated in blood and urine in some patients with hypertension. Results are less conclusive in those with borderline hypertension. It has also been reported that patients with borderline hypertension have increased catecholamine responsiveness to stimuli, such as mental stress, that affect the sympathetic nervous system.

Next they turn their attention to the cardiovascular system. Patients with established hypertension have increased peripheral resistance with a normal cardiac output. In contrast, some patients with borderline hypertension have been found to have an increased cardiac output (termed hyperkinetic borderline hypertension). The authors' studies suggest that the autonomic nervous system may have a role in this increase in cardiac output.

Subjects with hyperkinetic borderline hypertension were injected with propranolol and atropine to block the effect of the autonomic nervous system: as a result, the increase in cardiac output was abolished. Both heart rate and stroke volume returned to normal, suggesting that both components of cardiac output were under neurogenic control. Peripheral resistance is normal in hyperkinetic borderline hypertension, but this can be seen as inappropriate because the expected response to increased cardiac output is a decrease in peripheral resistance. In addition, in patients with borderline hypertension, there is a diminished response to stimuli such as exercise and plasma volume expansion, which normally decrease peripheral resistance. Subjects with borderline hypertension and normal cardiac output have increased peripheral vascular resistance at rest. The authors demonstrated that in up to 30% of patients this may be determined neurogenically as the increase was abolished by the injection of an α-blocker.

The role of renin is discussed. It is noted that plasma renin activity has been shown to be elevated in some patients with borderline hypertension and that some patients show an excessive increase in renin with postural change. This may be related to increased sympathetic tone as renal sympathetic nerves have a role in renin release. Possible mechanisms to account for the autonomic changes are discussed. These include defective reuptake of norepinephrine or increased responsiveness of target organs to a normal level of stimulation. There is also some evidence of vascular hyperreactivity in borderline hypertension and this may play a part in end organ hyperresponsiveness. The authors consider the integrative areas of the medulla oblongata in the brain to control the abnormal autoregulation. They believe the parasympathetic system to be involved, too, as evidenced by the effect of atropine in reducing cardiac output in borderline hypertension. They suggest that arterial baroreceptors could be reset to allow higher resting sympathetic tone, although this hypothesis has not been tested.

Thus, this paper provided a comprehensive review of the role of the sympathetic nervous system in borderline hypertension.

1975

Soviet dissident Andrei Sakharov wins the Nobel Peace Prize;
Archbishop Oliver Plunkett becomes the first Irish-born saint in 7 centuries; and
Soviet spaceprobe Venera 9 lands on Venus
Insulin resistance is commonly recognized to occur in obesity and, when associated with other abnormalities, may be termed the insulin resistance syndrome. This study estimated the prevalence of insulin resistance in obesity using the database of the European Group for the Study of Insulin Resistance (EGIR). The database includes data from over 1000 healthy white men and women between 18 and 85 years old. Insulin resistance was measured in all patients using the euglycemic insulin clamp technique (the gold standard). This measures insulin sensitivity by infusing a constant amount of insulin and measuring how much intravenous glucose is required to maintain euglycemia. Insulin sensitivity is measured as glucose disposal rate (M). In addition, insulin secretion rates were calculated.

Data were contributed from 20 research centers in 9 different European countries. Each center contributed between 21 and 122 clamp studies in healthy patients with normal glucose tolerance, blood pressure less than 160/95 mm Hg, and no other cardiac, renal liver, or endocrine disease. This was the largest study to assess insulin resistance in healthy subjects.

A body mass index (BMI, kg/m²) greater than 25 was found in 47% of subjects in the study. The obese were older than the lean and had higher waist and hip circumferences, waist-to-hip ratio, fasting plasma glucose, fasting and steady state insulin concentration, and posthepatic plasma insulin clearance rates. The obese were more insulin-resistant, using all indices of insulin sensitivity. The average difference in insulin sensitivity was 24% to 34% when based on body weight, but fell to 15% to 25% according to indices based on fat-free mass. Differing definitions of obesity and insulin resistance resulted in ratios of insulin resistance in obese vs lean subjects in the range of 2.3 to 3.3. If insulin resistance was defined as the bottom 10% of M values in the lean group, then the frequency of insulin resistance was 19% in subjects with a BMI <30, 34% in subjects with a BMI <35, and 60% in subjects with a BMI >35. Insulin sensitivity (based on fat-free mass) decreased linearly with increasing BMI.

Using the upper 10% of fasting plasma insulin concentrations in the lean group, the frequency of hyperinsulinemia increased with BMI from 32% in those with a BMI <30, to 57% in those with a BMI <35, and to 77% in those with a BMI >35. Insulin hypersecretion also increased with BMI, from 28% in those with a BMI <30, to 49% in those with a BMI <35, and to 80% in those with a BMI >35.

In summary, the study highlighted the large variability in insulin sensitivity even in lean subjects. Obesity led to a highly significant decrease in insulin sensitivity. The prevalence of insulin resistance in the obese subjects was surprisingly low (although the study excluded subjects with hypertension, diabetes, or impaired glucose tolerance, and therefore may have selected an insulin-sensitive obese population). In addition, insulin hypersecretion was found to be more frequent than insulin resistance in the obese. Insulin resistance is difficult to measure, and the euglycemic clamp is still the best method available. This study was a masterpiece of organization, and allowed the clamp technique to be used in a large trial.

Scotland votes for a separate Parliament for the first time since 1707, while retaining ties with the British monarchy and the National government;

Mother Teresa, founder of the Order of Missionaries of Charity and Nobel Peace prizewinner, dies, aged 87, in the odor of sanctity;

and Patrick Rafter of Australia wins the US Open tennis championship, defeating Greg Rudsecki in the final
State-of-the-art lecture. Obesity-induced hypertension: new concepts from the emerging biology of obesity


Haynes. 1999;33(1 pt 2):537-541

Mark et al, in this article, challenge the view that obesity-induced hypertension is secondary to insulin resistance and hyperinsulinemia. The authors propose that advances in the understanding of the genetic and neurobiological mechanisms of obesity will provide insight into obesity and hypertension. They present the evidence for the sympathetic and cardiovascular actions of leptin and melanocortin receptor agonists.

Leptin. Leptin increases sympathetic nervous system (SNS) activity to brown adipose tissue and to the kidneys, adrenals, and hind limbs in rats. These actions are thought to be independent of the action of insulin because they occur in the absence of changes in insulin and glucose. Leptin may also have depressor activity, although the predominant effect seems to be pressor. In chronic administration, leptin causes increased arterial pressure in rats. This effect is seen despite an increase in insulin sensitivity, suggesting that insulin resistance is not the mediator. Decreased renal blood flow and increased renal vascular resistance and heart rate were seen, consistent with increased sympathetic activity. Conversely, naturessis was not seen. Transgenic mice that overexpress leptin have hypertension. Obese ob mice with genetic leptin deficiency have significantly lower blood pressure on a low salt diet than lean controls. Similar findings are reported with leptin-resistant rats. Therefore, obesity is not universally related to hypertension, and these genetic models show that leptin deficiency or resistance can result in decreased arterial pressure despite the presence of obesity.

Melanocortin-4 receptors. The agouti yellow obesity syndrome in mice is linked to a mutation in the agouti gene leading to an overexpression of the agouti protein. This protein binds to melanocortin-1 receptors and prevents alpha-melanocyte stimulating hormone (α-MSH) from stimulating melanin synthesis (hence the yellow hair). It also blocks α-MSH effects on hypothalamic melanocortin-4 receptors, which are involved in feeding regulation, thus resulting in obesity. The authors have found that stimulation of melanocortin-4 receptors by a receptor antagonist increases sympathetic nerve activity to brown adipose tissue and the kidney in rats, without any change in blood pressure. Agouti obese mice were found to have significantly higher arterial pressure than lean controls despite having less severe obesity than ob mice. Therefore, blood pressure effects of obesity may be critically dependent on the mechanism inducing the obesity.

Genetic factors. The authors also present evidence that genetic factors may modify the blood pressure response to obesity. The hypertensive response to obesity is less in Pima Indians, Hispanic-Americans, and African-Americans, compared with whites. Blood pressure is normal in 40% of obese people, suggesting modifying genes may have a substantial influence of phenotypic expression of obesity. Finally, findings in ob mice, Zucker obese rats, and Koletsky obese rats, suggest that the different genetic background of the rats influences the effect of leptin resistance on blood pressure.

In summary, the article suggests a role for leptin in obesity-induced hypertension and provides some possible underlying mechanisms (sympathetic, vascular, and renal). It also demonstrates the importance of the cause of obesity and how genetic factors may influence the blood pressure response to obesity.
Sympathetic overactivity as assessed by norepinephrine spillover and microneurographic recording of muscle sympathetic nervous activity (MSNA) has been shown to be present in normotensive overweight subjects. Similar increases have been shown in lean subjects with hypertension. The aim of this study was to determine whether these effects were additive.

A total of 57 subjects with age-range from 22 to 50 years were studied. They were divided into 4 groups, controls, obese, hypertensive, and obese hypertensive. They were classified as normotensive if blood pressure was less than 140/90 mm Hg, obese if BMI was greater than 27 kg/m$^2$ and lean if BMI was less than 25 kg/m$^2$. In each subject measurements of blood pressure, plasma norepinephrine, and MSNA were made. In addition, baroreceptor modulation of MSNA and heart rate was assessed following the intravenous administration of two vasoactive compounds, phenylephrine and nitroprusside. Phenylephrine should induce an increase in blood pressure and an accompanying drop in heart rate and MSNA. Conversely, nitroprusside causes a decrease in blood pressure and hence the opposite effect, an increase in MSNA and heart rate. MSNA was found to be greater in obese normotensive and lean hypertensive groups. A further increase was noted in the obese hypertensive group. Plasma norepinephrine showed a similar trend, but the between-group differences were not statistically significant. In multiple regression analysis, MSNA was related to BMI and blood pressure. Reflex heart rate responses to phenylephrine and nitroprusside were less in the obese normotensive and the lean hypertensive groups compared with normals. A further reduction was seen in the obese hypertensives. In lean hypertensives, reflex sympathetic responses were preserved, but they were reduced in obese subjects and more reduced in the obese hypertensives.

These results, therefore, confirmed that MSNA was greater in obese and hypertensive individuals. In addition, it showed an additive effect on MSNA in the presence of both conditions. The authors speculate that the observed reduction in baroreceptor reflex modulation may play a role in sympathetic overactivity in the obese and hypertensive. They keep their options open by suggesting other possible mechanisms such as cardiac hypertrophy, reduced insulin sensitivity, ischemic involvement of the chemoreceptors, and reduced renin, leptin, and endothelin secretion. They suggest there may be a link between sympathetic activation in the obese hypertensive and sudden death. They also suggest that their results would favor the use of drugs that act upon the central and peripheral sympathetic nervous system in patients with obesity and hypertension.

In summary, this paper provides experimental evidence for sympathetic overactivity in humans with obesity and hypertension. Additionally, it demonstrates that having both obesity and hypertension is associated with a further increase in sympathetic activity.
A comparison of the 10-year risk of developing chronic diseases such as high cholesterol level, hypertension, gallstones, type 2 diabetes, heart disease, stroke, and colon cancer in overweight and normal weight adults was carried out in 77,690 women from the Nurses’ Health Study (mean age 52.9 years) and 46,060 men from the Health Professionals Follow-up study (mean age 54.5 years). They were predominately white (>93%) and 14.8% of women and 8.2% of men had a body mass index (BMI, kg/m²) greater than 30 when measured in 1986.

It was the first study to use the US dietary guidelines and World Health Organization definition of overweight, which is a BMI equal to or greater than 25. The previously used US definition had been a BMI of greater than 27.3 for women and 27.8 for men. This change in cutoff led to an increased prevalence of overweight and also to confusion about whether what was previously taken to be a healthy weight was actually associated with increased morbidity.

The study found that the risk of developing diabetes, gallstones, hypertension, heart disease, and stroke increased with severity of overweight. In addition, the risk of developing more than one illness increased with weight. Those with a BMI of more than 35 were about 20 times more likely to develop diabetes than those with a BMI in the normal range.

Adults with a BMI between 25 and 29.9 were found to be at significantly greater risk of developing many common diseases. They were 3 times more likely to develop diabetes over 10 years and were also more likely to develop gallstones, hypertension, high cholesterol, and heart disease than those with a BMI of less than 25. Men with a BMI between 25 and 29.9 also had an increased risk of stroke.

There was also an increased risk of developing common diseases at the heavier end of the normal range. The risk of developing an outcome was significantly higher in those with a BMI between 22 and 24.9 compared with those with a BMI between 18.5 and 21.9. If the reference group for comparison was restricted to those with a BMI between 18.5 and 21.9, then the risks associated with higher BMIs (equal to or greater than 25) also increased. For example, there was a 17-fold increase in the risk of diabetes in a woman with a BMI of 35 compared with women with a BMI between 18.5 to 24.9, but this increased to a 30-fold risk if the reference group was those with a BMI between 18.5 and 21.9.

In summary, this study clearly demonstrated the risks of increasing BMI. It also demonstrated the risk of having a BMI between 25 and 30 and that even a BMI at the heavier end of the normal range was associated with additional risk of common diseases. Being overweight is bad news!

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2001

David Trimble, the First Minister of the Northern Ireland Assembly, steps down in protest against delays in IRA weapons decommissioning; Belgian surgeon Jacques Rogge is elected the eighth president of the International Olympic Committee; and Australian Ian Thorpe breaks his own world record and anchors Australia’s 400-m relay team to win gold at the FINA World Swimming Championships.
Summaries of Ten Seminal Papers - Brackenridge and Russell-Jones

Dialogues in Cardiovascular Medicine - Vol 9 - No. 3 - 2004

Sympathetic nervous system and insulin resistance: from obesity to diabetes

M. Esler, M. Rumantir, G. Wiesner, D. Kaye, J. Hastings, G. Lambert


Highlighting the role of obesity in the development of hypertension, insulin resistance, and diabetes in reference to the sympathetic nervous system (SNS), this article reviews studies that have quantified SNS function by measuring rates of sympathetic nerve firing (clinical microneurography) and measuring organ-specific norepinephrine (NE) spillover into plasma.

Studies have shown that obese normotensive people have a normal whole-body NE spillover rate, but increased NE spillover in the kidneys, suggesting increased SNS activation of the kidney. There is also evidence of increased SNS activation in skeletal muscle from microneurography, which shows increased nerve firing in the vasculature of skeletal muscle. Interestingly, obese people with normal blood pressure have been shown to have subnormal cardiac NE spillover. Obese people with hypertension also show increased SNS activation in the kidney and skeletal muscle. However, cardiac NE spillover is almost double that of the obese normotensives and 25% higher than that of healthy volunteers, and this may partly explain the development of hypertension.

The question as to how SNS activity is stimulated in obesity is discussed. Landsberg’s hypothesis suggests that SNS overactivity is a mechanism to help stabilize body weight in overeating by stimulating thermogenesis. However, this increase in SNS activity also affects the kidneys, heart, and blood vessels, increasing the blood pressure. Increased insulin secretion is seen as the mediator. An alternative explanation is that SNS activation is driven by leptin. Intravenous infusion of leptin into rats causes activation of SNS activity of the renal and hind limb vasculature without affecting heart rate (a similar pattern of SNS activation to that seen in obese humans). However, the authors have found that, in humans, leptin levels are not related to measurement of SNS activity.

How this increase in SNS activity leads to hypertension is discussed. The renal sympathetic nerves have been demonstrated to be important in the development of hypertension in animal models. The underlying mechanism is thought to be through stimulation of renin release and reabsorption of sodium in the renal tubule. However, renal SNS overactivity is present in both normotensive and hypertensive obese humans. No predisposing or genetic factors have been identified yet that explain this.

Obesity and hypertension are often associated with hyperlipidemia and insulin resistance. The authors suggest that insulin resistance may be secondary to SNS overactivity. Vasodilation decreases muscle blood flow and hence decreases glucose uptake by muscle, resulting in insulin resistance. A similar mechanism is proposed to explain the lipid abnormalities seen in obesity, with vasodilation leading to decreased chylomicron clearance.

Whether SNS activation in hypertension has implications for the treatment of hypertension is discussed. Exercise and diet are known to reduce SNS activity and are suggested as first-line therapy in the obese. Some drugs cause reduction in SNS firing, e.g., the imidazoline-binding agent rilmenidine. Other drugs, such as diuretics and some calcium channel blockers, cause reflex SNS activation. Drugs that favor vascular resistance tend to improve insulin sensitivity and, theoretically, this may make these drugs particularly useful in the management of obesity-related hypertension and insulin resistance.

2001

George Harrison, lead guitarist with the Beatles, dies of cancer, aged 58; an American jetliner bound for Santo Domingo plunges into the Queens neighborhood in New York just after takeoff; and the head of Hamas, Mahmoud Abu Hunud, is killed in an Israeli helicopter attack in Jerusalem.
Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey

E. S. Ford, W. H. Giles, W. H. Dietz

JAMA. 2002;287:356-359

Similar to the paper by Park et al (2003) from the Archives of Internal Medicine (see review), this brief report seeks to establish the prevalence of the metabolic syndrome as defined by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III). It uses the same diagnostic criteria for the metabolic syndrome in a population of subjects recruited into the Third National Health and Nutrition Examination Survey between 1988 and 1994. However, it includes a slightly smaller sample, 8814 participants instead of 12 861.

The results are comparable. Among male subjects, Mexican-Americans and whites had a higher prevalence of abdominal obesity and dyslipidemia, and African-American males had a higher prevalence of hypertension. Mexican-American males had the highest rates of hyperglycemia. Among women Mexican-Americans and African-Americans had the highest prevalence of abdominal obesity. African-American women had the highest prevalence of hypertension. Mexican-American women had the highest prevalence of hyperglycemia and dyslipidemia. The prevalence of the metabolic syndrome was 21.8% unadjusted and 23.7% age-adjusted. The prevalence increased with age and was similar in men and women.

The authors comment on the high prevalence of the metabolic syndrome in American adults. They also comment that these figures probably underestimate current prevalence, as they are based on statistics from 1988 to 1994. They feel there is an urgent need to direct efforts towards controlling the epidemic of obesity and inactivity, and that the results may have implications for health care costs in the future.

“Wall Street Journal” reporter Daniel Pearle is kidnapped in Pakistan while investigating Muslim fundamentalist groups, and murdered; the master of horror Stephen King announces that he will retire when his present contract expires; and on 1st January 2003, the Europeans start using their new currency, the Euro (€)
Frequency of the WHO metabolic syndrome in European cohorts, and an alternative definition of an insulin resistance syndrome


Diabetes Metab. 2002;28:364-376

The World Health Organization (WHO) Expert Committee on the Diagnosis and Classification of Diabetes Mellitus defined the metabolic syndrome in 1999. The European Group for the Study of Insulin Resistance (EGIR) proposed an alternative definition called the insulin resistance syndrome. The two definitions aim to describe the same condition and recognize its importance in the development of diabetes and cardiovascular disease. However, the criteria for diagnosis differ. The WHO definition applies to people with or without diabetes and requires either an objective measure of insulin resistance using the hyperinsulinemic euglycemic clamp or evidence of impaired glucose regulation and 2 or more of raised blood pressure, central obesity, microalbuminuria, and raised triglycerides with low HDL cholesterol. By contrast, the EGIR definition applies only to the nondiabetic population and uses a surrogate marker of insulin resistance, hyperinsulinemia, as the core feature. In addition, patients must have 2 or more of hyperglycemia, hypertension, dyslipidemia (high triglyceride, low HDL), and central obesity. EGIR includes treatment for hypertension and dyslipidemia in the definition. The purpose of this paper was to compare the frequency of the syndrome in different European populations using the WHO and EGIR definitions.

Data were contributed from 8 different studies between 1981 and 1997 in 7 different European countries. In total, 8200 men and 9363 women were studied. Because none of the studies give any data on insulin resistance measured using the clamp technique as specified by the WHO criteria, the authors have used fasting insulin as a surrogate measure. Overall, the prevalence of abnormalities as defined by either the WHO or the EGIR method varied markedly between different studies depending on the population studied. Abnormalities were more frequent in males than females and increased with age. The overall prevalence of the syndrome as defined by the WHO increased with age from 14% and 4% in men and women under 40, respectively, to 23% and 13% in men and women between 40 and 55, respectively, and to 41% and 26% in men and women over 55, respectively. By comparison with EGIR, the frequency of impaired glucose regulation was higher in the WHO definition, which used the oral glucose tolerance test (OGTT) rather than fasting glucose. Using the WHO definition, more than 50% of people over 55 had raised blood pressure. The frequency of hypertension was higher in the EGIR definition, which included people on antihypertensive medication. Central obesity was more common in men using the WHO definition. In contrast, obesity was more common in women with the EGIR definition. Overall, the WHO syndrome was more frequent than the EGIR syndrome, but the difference was less marked in women compared with men. This was mainly due to the differing definition of obesity.

The authors suggest that the definition of obesity needs to be refined.

To summarize, this article concludes that the frequency of the metabolic syndrome varies depending on how the metabolic syndrome is defined. It also varies depending upon the population studied and how measurements such as insulin level and waist measurement are made. Ongoing studies will hopefully demonstrate the usefulness of diagnosing the metabolic syndrome and which diagnostic criteria have the greatest prognostic implications.
Lakka and colleagues, in this article, assessed the association of the metabolic syndrome as defined by the National Cholesterol Education Program (NCEP) and the World Health Organization (WHO) with cardiovascular and overall mortality during an 11-year follow-up in a population of middle-aged Finnish men with no diabetes or cardiovascular disease at baseline. The NCEP definition differs from the WHO definition, as it does not include hyperinsulinemia, uses waist circumference as the measure of obesity rather than waist-hip ratio and body mass index (BMI) used in the WHO definition, and has slightly less generous cut-offs for blood pressure and high-density lipoprotein (HDL) cholesterol.

Data were analyzed for 1209 men. The WHO definition of the metabolic syndrome was modified to not include microalbuminuria and to have a lower definition of hypertension than the original proposal.

Deaths were ascertained by computer linkage to the Finnish National Death Registry using the Finnish social security number with no patients lost to follow-up. The median follow-up was 11.6 years. There were 109 deaths during follow-up: 46 were due to cardiovascular disease (CVD), of which 27 were due to coronary heart disease (CHD). The prevalence of the metabolic syndrome at baseline was quite low, 9% to 14%, depending on the definition used.

Factors associated with CVD, CHD, and all-cause mortality were blood pressure, BMI, waist circumference, smoking, and alcohol intake. Blood glucose and insulin levels were associated with CVD and all-cause mortality, but dyslipidemia was not.

The Kaplan-Meier estimate of overall survival at 13.7 years of men with vs without the metabolic syndrome was 79% vs 90% using the NCEP criteria with a waist cutoff of 102 cm, 83% vs 90% for the NCEP criteria using a waist cutoff of 94 cm, 84% vs 90% for the WHO definition based on the waist-hip ratio, and 83% vs 90% for the WHO definition with a waist cutoff of 94 cm.

The metabolic syndrome was associated with a 2.4 to 3.4 times higher mortality from CHD and this was increased by taking into account other conventional risk factors. In subjects with the metabolic syndrome, age-adjusted mortality from CVD was 2.5 to 2.8 times higher, although using the NCEP criteria this association did not reach statistical significance. Men with the WHO criteria had a 1.9 to 2.1 higher overall mortality, but using the NCEP criteria this association only tended toward statistical significance. The association between metabolic syndrome and cardiovascular mortality remained when patients with fasting hyperglycemia were excluded.

In summary, this study demonstrated in a prospective population-based cohort study that the metabolic syndrome was associated with increased total and cardiovascular mortality. This was independent of other risk factors such as smoking, low-density lipoprotein (LDL) cholesterol levels, and fasting hyperglycemia. The impact on overall mortality from the metabolic syndrome was mainly mediated through increased CHD deaths with a contribution from CVD deaths. The NCEP definition was better at predicting mortality rate if the waist cutoff of 102 cm was used, but the WHO definition more consistently predicted cardiovascular and overall mortality.

Opposition leader Mwai Kibaki is elected president of Kenya; opponents of Venezuelan president Hugo Chavez launch a nationwide strike against his government, demanding a referendum on his presidency; and Israeli prime minister Ariel Sharon accepts a US-sponsored peace plan that includes the formation of a Palestinian state on the condition that Yasir Arafat is removed from power.


Arch Intern Med. 2003;163:427-436

Using the Third Report of the National Cholesterol Education Program Adult Treatment Panel (ATP III) guidelines for diagnosis of the metabolic syndrome, this paper aimed to examine the prevalence of the metabolic syndrome by ethnicity, age, body mass index (BMI), socioeconomic status, and lifestyle factors. The criteria used are 3 or more of abdominal obesity (using waist circumference), high triglyceride, low high-density lipoprotein (HDL) cholesterol, high blood pressure, and high fasting plasma glucose. These were chosen since they are easily measurable in clinical practice. An initial study had indicated that the prevalence of the metabolic syndrome was 21.8% unadjusted and 23.7% age-adjusted.

Data were collected from the Third National Health and Nutrition Examination Survey, which was conducted in two 3-year phases from 1988 to 1991 and from 1991 to 1994 in 89 centers across the USA. A total of 12 861 individuals from a variety of ethnic backgrounds had the required anthropometric measurements and were included in this study. All participants were 20 years or older.

The overall percentage of the metabolic syndrome in US adults was 22.8% for men and 22.6% for women. It was 13.9%, 20.8% and 24.3% for black, Mexican-American, and white men, respectively. It was 20.9%, 22.9%, and 27.2% for black, white, and Mexican-American women, respectively. For men and women, the prevalence of the metabolic syndrome increased sharply after the third decade and peaked in men between 50 and 70 years old and in women between 60 and 80 years old. A steep increase in the prevalence of the metabolic syndrome was noted in overweight people (BMI 25-30 kg/m²). The prevalence was 4.6%, 22.4%, and 59.6% in normal weight, overweight, and obese men and the corresponding prevalence rates for women were 6.2%, 28.1%, and 50%, respectively.

Some patterns emerged when looking at components of the metabolic syndrome. Black men had higher blood pressure and white women had lower waist measurements in the younger age groups. Multiple regression analysis showed that current smokers were significantly more likely to have the metabolic syndrome. Other factors associated with the metabolic syndrome were low household income, no alcohol consumption, high carbohydrate intake, and physical inactivity.

Thus, this large study confirmed that the metabolic syndrome was widespread among American adults. The prevalence rates varied among different ethnic groups, age-groups, and with factors such as cigarette smoking, activity levels, and carbohydrate intake. Interestingly, black men had the lowest prevalence, although they have the highest coronary heart disease mortality of any group. The authors question the validity of the metabolic syndrome diagnostic criteria when applied across different age, sex, and ethnic groups.

The Yugoslavian Parliament votes to rename the country Serbia and Montenegro, a move aimed at reflecting Montenegro’s drive for independence; the space shuttle “Columbia” breaks up as it reenters the Earth’s atmosphere, killing all seven crewmembers; and architect Daniel Liebeskind’s design is selected for the rebuilding of the site of the Twin Towers in New York, featuring a recessed memorial to the 9/11 victims and a 1776-foot tower.
Bibliography of One Hundred Key Papers

selected by Brent M. Egan, MD; Stevo Julius, MD, ScD
Medical University of South Carolina, SC (B. M. E.)
University of Michigan - Ann Arbor, Mich (S. J.) - USA


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