Can the Central Sympathetic Blockade Profile be Advantageous in the Management of Patients with Metabolic Syndrome?

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Abstract:
Metabolic syndrome, the association of obesity, hypertension and hyperlipidaemia in conjunction with impaired glucose tolerance or frank diabetes, is a rising global pattern and has been subjected to a useful consensus re-definition in recent months¹. Its origins are fixed in changing dietary and activity patterns across the developed world but also increasingly affecting all developing economies. The obvious sequelae of this spiraling pattern are increases of atherosclerotic vascular disease and subsequent occlusive vascular events, morbidity and premature mortality for affected patients. Given its emerging importance we should consider carefully the role of the sympathetic nervous system in the overlapping management of the pathophysiology of obesity and hypertensive vascular disease; the recognition of the metabolic syndrome and its definition in practice; and whether new trial results pertinent to managing hypertension in the overweight patient with metabolic syndrome using the central imidazoline antagonist drug, moxonidine, might prompt reconsideration of this established strategy for lowering blood pressure.

Key Words: Metabolic syndrome; blood pressure; moxonidine; ALMAZ trial; obesity; antihypertensive; insulin resistance; metformin

Does the sympathetic nervous system have an independent role in Hypertension and/or Obesity?

Across a wide range of ages the diameter and stiffness of muscular arteries increases with obesity. In elastic arteries the relationship between arterial stiffness and obesity (as indicated by the traditional BMI) may be more complex and varies with gender and age². A potent mediator of these functional and structural changes is the autonomic nervous system and particularly activation of the sympathetic nervous system (SNS). While there are many techniques to define sympathetic nerve function in man, essential hypertension, obesity and congestive heart failure have been characterised in many studies by an increase in sympathetic nerve activity in muscle. Changes in the SNS in obesity are probably dependent upon blood pressure and there is some debate as to whether obesity is associated with SNS activation. However studies have linked obesity-related sympathetic overactivity to insulin resistance and baroreflex impairment that, in turn, affect both vascular tone and distensibility³. The pattern of obesity plays an increasingly recognised role. Central (centripetal; or visceral) obesity is characterised by sympathetic activation of a greater magnitude than that seen in peripheral obesity. This is not related to gender or to altered baroreflex mechanisms but to metabolic factors, i.e. to the greater insulin resistance associated with central obesity. A hypo-caloric diet with normal sodium content while able to exert a marked reduction in sympathetic activity via central sympatho-inhibition in normotensive subjects is less effective in hypertensive obese subjects.

Redefining Metabolic Syndrome:
Modern understanding of the impact and associations of obesity has developed over 15 years following the recognition of the important association of excess visceral fat mass and insulin resistance in the development of atherosclerotic disease⁵. Visceral based fat is crucial to this association as it feeds the production of dense atherogenic LDL-Cholesterol and reduces HDL-C production in conjunction with reduced degradation of apolipoprotein B and rising VLDL particle release. A range of adipokines associated with abdominal obesity including TNF alpha, interleuki 6, plasminogen activator inhibitor, leptin and adiponectin all directly and cumulatively exacerbate endothelial dysfunction and thereby accelerate atherosclerosis. This combined with the secondary hyperlipidaemia of metabolic syndrome is associated with a major 20-fold relative rise of coronary artery disease in this patient group. This focus on visceral and not generalised obesity is no better il-
Illustrated than in the re-analysis of mortality and morbidity data from the INTERHEART study(6) where quintiles of obesity categorised from BMI showed a relatively modest gradient of risk of future recurrent events whereas the gradient of events when categorised by waist circumference or waist-to-hip ratio (WHR) was marked. Targeting the management of this patient profile (perhaps the first easily recognisable phenotype in asymptomatic hypertension?) can take into account confirmation by waist circumference (taking into account ethnic origin), blood pressure, glycaemic and lipid chemistry. Can the latter modifiable characteristics be better treated by specific means to improve their risk of vascular events whether by blood pressure reduction; lipid lowering or glycaemic control?

What is suggested by the ALMAZ Study results?

Given the linkage of these factors and the availability of many excellent blood pressure controlling treatments, the profile of comparative response among blood pressure lowering agents in different patients becomes a significant factor. If we correctly identify visceral obesity as an increasingly recognisable phenotype in the hypertensive population are there any new indications of management advantages which may be gained in this group? In the metabolic syndrome patient improvements in insulin sensitivity (or reduced insulin resistance) can be a critical step in modifying treatment strategies. In the ALMAZ trial a surprising result was seen when a cohort (n=202) of obese, borderline hypertensive, insulin-resistant patients was treated to compare the effects of adjuvant low dose metformin (500mg BDS, a conventional insulin sensitising agent by its impact on glucose (7)) or moxonidine (200μg BDS, a conventional centrally acting imidazoline antagonist which lowers blood pressure(8)). While brachial blood pressure regressed to the mean in a largely comparable way with both treatments there was a significant impact using the blood pressure lowering therapy moxonidine on insulin sensitivity index (the insulin response to standard glucose load), predictably without any notable decrease in HbA₁c. This improvement in insulin sensitivity was mediated by reduced insulin response with preserved glucose disposition subsequent to centrally reduced neurally mediated sympathetic tone. It compared to the expected impact of metformin which caused a similar improvement in insulin sensitivity but by glucose disposition at unchanged levels of insulin response. This of course is quite the opposite to what is seen with peripheral beta blockade (blocking both innervated and non-innervated beta adrenoceptors) whereby insulin resistance is increased(9). Given the suggested role of circulating hyper-insulinaemia in the vascularopathy of metabolic syndrome this result suggests this is a valuable profile in these patients in response to moxonidine. Secondly given that the recognised mode of action of moxonidine on central sympathetic nervous system function and this response of attenuation of insulin response it is likely to be mediated through moxonidine’s central mechanism of action.

Such an integrated mechanism of action and response is a profile well suited therefore to more widespread application in this expanding patient group. Moreover it may well suggest a more logical combination therapy in metabolic syndrome patients who, like the majority of the hypertensive population, are unlikely to respond to monotherapy, and fill the gap in patients where beta blockade is increasingly seen as potentially a less valuable treatment option(10).

References:
