majority of normal controls fulfilling the left ventricular hypertrabeculation (their term) criteria were black is not justified is somewhat non-sensensical, given that this is false tendons, and abnormally.

Their second point relating to the lack of neuromuscular disease in our patients is one that obsesssionally raise in written responses and review articles. We argue that there are many reports of an association between neuromuscular disease and a non-compaction phenotype. It is equally true that there are many reports of LVNC occurring in the absence of neuromuscular disease (most recently in association with cardiac sarcomeric protein gene mutations).2,3 As our study population consisted of a consecutive population of patients seen in a district general hospital adult heart failure clinic, it is not at all surprising that none of the patients had rare neuromuscular disorders. Their point that the high incidence of echoes fulfilling LVNC criteria in black patients and controls might be explained by a higher incidence of neuromuscular disease is barely credible.

Another recurring theme by Stollberger and Finsterer is that LVNC may appear and disappear during life. They quote their own case reports to justify this observation. In response, we believe that it is almost inconceivable that a congenital heart defect characterized by persistence of the embryonic non-compact layer can appear and disappear in such a magical fashion. On the other hand, it is possible that normal left ventricular trabeculae may become more prominent in certain disease states such as left ventricular hypertrophy and that, in such circumstances, echo criteria for LVNC may be fulfilled. In this situation, prominent trabeculation is an epiphenomenon rather than a marker of a unique pathology—exactly the point of our paper.

Finally, the authors suggest that in order to avoid overdagnosis of LVNC, trabeculations should be distinguished from aberrant bands, false tendons, and abnormally inserting papillary muscles. However, the fact that differentiation of these structures is almost entirely based on subjective criteria is a fundamental limitation shared by all current echocardiographic criteria for LVNC. In summary, we can agree that a 'uniform definition' of LVNC is required. This should, however, be based on rigorous quantitative analysis of normal individuals and not subjective scoring systems.

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Risk of type 2 diabetes mellitus in those with hypertension

Essential hypertension is common and is an important risk factor for coronary heart disease, stroke, atherosclerosis, and peripheral vascular disease. Free radicals, nitric oxide (NO), eicosanoids, pro- and anti-inflammatory cytokines, long-chain polyunsaturated fatty acids (LCPUFAs), folic acid, tetrahydrobiopterin (BH4), and vitamin C play a significant role in the pathobiology of hypertension. Vascular endothelium produces vasodilators: prostacyclin (PGI2), NO, and endothelium-derived hyperpolarizing factor, and other vasoactive factors such as endothelins and prostaglandin E1 (PGE1). Under physiological conditions a balance is maintained between endothelial vasoconstrictors and vasodilators such that normal blood pressure is maintained. When this balance is altered more in favour of vasoconstrictors and/or when the concentrations of vasodilators are reduced, hypertension develops. One mechanism by which endothelium-dependent vasodilation is impaired is due to an increase in the oxidative stress that inactivates NO and PGI2.

Polymorphonuclear leucocytes of patients with uncontrolled essential hypertension produce significantly large amounts of O2•−, hydrogen peroxide (H2O2), and lipid peroxides,2 indicating that an increase in oxidative stress occurs in hypertension. In addition, a decrease in the levels of superoxide dismutase (SOD), catalase, glutathione peroxidase, and vitamin E in the RBC membranes of uncontrolled hypertensives was noted. These biochemical abnormalities revert to normal after the control of hypertension.1,2 O2•− is a potent vasoconstrictor,3 implying that an increase in free radical generation could be responsible for the heightened peripheral vascular resistance in hypertension. Furthermore, SOD deficiency is seen in hypertension4 and SOD activity decreases with advancing age.5 Thus, decreased NO bioavailability and increased O2•− generation with increasing age due to enhanced NAD(P)H oxidase activity could be responsible for oxidative stress seen in hypertension.

An increase in pulse pressure was associated with elevated C-reactive protein (CRP) among healthy US adults.6 Elevated plasma IL-6 levels in women with hypertension and insulin resistance in men was noted.7 A graded positive relationship between blood pressure and levels of ICAM-1 (intercellular adhesion molecule-1) as well as IL-6 was noted in healthy men,8 suggesting that low-grade systemic inflammation occurs in hypertension.

Plasma levels of CRP, TNF-α, and IL-6 are elevated in subjects with type 2 diabetes.9 Subjects with elevated CRP levels were two times more likely to develop diabetes.10 Dietary glycemic load is significantly and positively associated with plasma CRP,11 suggesting that hyperglycaemia induces inflammation. Neutralization or inhibitors of CRP
abrogated the increase in infarct size and cardiac dysfunction, indicating that efforts designed to decrease inflammation produces cardioprotection, and might, possibly, decrease the risk of diabetes.

Acute raise in plasma glucose levels in normal and impaired glucose tolerance (IGT) subjects increased plasma IL-6, TNF-α, and IL-18 levels, and these increases were much larger and lasted longer in IGT subjects compared with control. TNF-α secretion was suppressed in younger subjects in response to glucose challenge, but not in the older subjects. Furthermore, hyperglycemia induced the production of acute phase reactants from the adipose tissue.

These data suggest that an increased incidence of type 2 diabetes in the elderly could be due to alterations in the homeostatic mechanisms that control TNF-α, IL-6, and CRP levels, and that low-grade systemic inflammation occurs in type 2 diabetes. Since low-grade systemic inflammation occurs both in hyperinsulinemia and type 2 diabetes mellitus, it is not surprising that Conen et al. observed blood pressure progression as a strong and independent predictor of occurrence of type 2 diabetes in hypertensives. It would have been more helpful had Conen et al. studied which of the inflammatory markers are more specific to predict the development of type 2 diabetes in hypertensives. In view of the overlap biochemical abnormalities in obesity, type 2 diabetes, hypertension, and insulin resistance such as cytokines, adipokines, reactive oxygen species, anti-oxidants, and NO, it is necessary to identify specific biochemical abnormalities that are true to each of these conditions, though common biochemical abnormalities suggest a more generalized pathophysiological process in them. It is likely that proteomics and gene expression profile studies could give more clues to such specific biochemical abnormalities in these conditions.

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Risk of type 2 diabetes mellitus in those with hypertension: reply

We appreciate the detailed description of potential mechanisms that may link blood pressure and type 2 diabetes mellitus. Similar pathophysiological pathways were mentioned in the discussion section of our article and have been the focus of our prior work. We agree that proteomics and gene expression studies could be helpful techniques in this regard. However, the main goal of our work was to assess the relationship between blood pressure and incident type 2 diabetes from a clinical perspective. Quantification of the magnitude of the association of increasing blood pressure levels with risk of developing type 2 diabetes is a helpful message for clinicians in day-to-day practice.

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