gene on cardiovascular mortality, Tanus-Santos et al. recalled that the former SNP alters the gene responsiveness to statins: statins would up-regulate eNOS expression (2) more potently in -786C homozygous (3) and therefore, these subjects would generate more NO while on statins than subjects with the other genotypes. Accordingly, atorvastatin increased NO availability and reduced inflammatory marker concentrations in CC, but not in TT healthy men (4). However, we found no significant interaction between statin treatment and the T-786C SNP affecting cardiovascular mortality (1). Moreover, only a minority of our patients were on statins (5); therefore, this mechanistic explanation is unlikely.

As with Tanus-Santos et al., we also found that the T-786C SNP did not affect nitrite/nitrate levels; however, functional data (6) indicate that the T-786C SNP affects NO bioactivity by altering the gene responsiveness to shear stress (7). Thus, the “Janus” nature of eNOS might reveal itself under conditions of oxidant stress, leading to decreased plaque stability and cardiovascular events (1).

Antoniades et al. raised another appealing hypothesis: an interaction of the 786T with the 894T allele constituting the 894T/786T haplotype might lower eNOS expression and increase susceptibility of eNOS to proteolytic cleavage, resulting into transiently increased oxidant stress and inflammatory status during acute conditions (8). However, the G894T SNP lies within a loop on the external surface of eNOS and does not make contact with either the active site of the enzyme, or the dyzermining interface, suggesting that, if functional, this SNP could act by a mechanism independent of eNOS catalysis. Moreover, the increased susceptibility to cleavage of the Asp298-encoded eNOS enzyme has been shown to be artifactual (reviewed by Casas et al.) (9). Therefore, whether the 894T allele bears functional consequences remains controversial. Nonetheless, the linkage disequilibrium of the T-786C and G894T SNP (1) can explain the association of the latter SNP with coronary heart disease (CHD), as we pointed out.

Antoniades et al. stated that an increased risk of CHD (odds ratio [OR] = 1.31) for the 894T allele carriers was reported; however, the excess risk deriving from meta-analysis of cross-sectional association studies, which are prone to stratification biases, should be viewed cautiously. In fact, a much larger meta-analysis led to a markedly reduced estimate of risk (OR = 1.17) (9). Consistent with prospective study results in high-risk patients (1,10), we found no evidence for a prognostic effect of the 894T allele. Thus, even if the 894T homozygosity would imply a blunted NO production and/or higher levels of oxidized low-density lipoprotein and proinflammatory cytokines during acute coronary events, overall prospective cohort studies show no prognostic effect in high-risk patients.

Finally, although underlying the fact that intriguing results such as ours are crucial for generating novel hypotheses, we agree that the elucidation of the complex interplay between the eNOS gene haplotypes and environmental factors deserves further research.

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Noncardiac Findings in Computed Tomography Coronary Angiography

The report by Onuma et al. (1) on noncardiac findings in multidetector computed tomography (MDCT) and the accompanying editorial comment by Rumberger (2) raise interesting issues. Onuma et al. (1) found that approximately 23% of 503 patients undergoing CT coronary angiography demonstrated significant noncardiac pathology requiring follow-up. This included 2 lung and 2 breast malignancies. Similarly, Baum et al. (3) have recently reported a high prevalence of extracardiac disease, including malignancies, among over a thousand patients undergoing MDCT.

Rumberger (2) suggests medico-legal and moral imperatives to seek noncardiac pathology. The patient’s entire chest and upper abdomen have been irradiated, after all, and the imaging data are there awaiting reconstruction. Although this approach seems very reasonable, I believe we need to keep an open mind, recognizing the absence of hard evidence that the pursuit of extracardiac pathology leads to overall improved patient outcomes. Much of the noncardiac pathology, such as liver and renal cysts, is relatively unimportant and probably unrelated to the symptom of chest pain. With regard to more serious pathology, several questions arise: When found, are the newly discovered malignancies curable or amenable to treatment that prolongs life or improves quality of

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REPLY

Dr. Fleet raises important questions, and there is legitimate concern that computed tomography (CT) scan “incidentalomas” can result in unnecessary or inappropriate testing at the expense of the insurance system and/or risk to the patient (1,2).

The main issue regarding cardiac CT is, of course, coincident imaging of the adjacent lungs. Although lung cancer is the number one cause of cancer-related deaths in all men and women in America, the finding of variable size “lung nodules” is much more common than true malignant disease. Dr. Fleet asks: “When found, are the newly discovered malignancies curable or amenable to treatment that prolongs life or improves quality of life?” We may never have a complete answer to this inquiry. However, the overall survival rates for lung cancer are dismal, and the most recent report from the ELCAP (Early Lung Cancer Action Program) study (3) may provide a partial response. Henschke and colleagues (3) did screening lung scans in adults over 40 years old with either a history of cigarette smoking, an occupational exposure risk, or significant exposure to second-hand smoke, and they found that stage I lung cancers discovered (and treated) resulted in a projected 80% 10-year survival rate. These subjects are, coincidentally, at greatest risk for atherosclerotic heart disease. Importantly, however, lung cancer was found in only 484 (1.5%) of 31,567 screened individuals.

Dr. Fleet asks, “What is the morbidity and mortality attendant to the biopsies and surgery for lesions that ultimately turn out to be benign?” This is a rhetorical question as we do not have this information; however, in most instances biopsies are unnecessary, and follow-up low-dose CT scanning may be the only suggested consequence. In medicine we tend to “pass the buck” when it comes to test results that are unanticipated, and the best way to reduce unnecessary follow-up testing or procedures is physician education. There are guidelines published by the ELCAP investigators (4), which prescribe follow-up on the basis of lung nodule dimensions. More recently the Fleischner Society (5) described the workup of small pulmonary nodules incorporating smoking history as part of the clinical algorithm.

I agree that we are at a crossroad to define the clinical impact of diagnostic CT angiography and “extravascular” pathology, regardless of whether it involves the heart/chest, neck, abdomen, or periphery. The issue clearly extends beyond traditional single-specialty medicine. Recently, a published commentary (6) addressed training in advanced cardiovascular imaging, stating that “specific interpretation of the extra-cardiac fields should be performed. . . . Regarding the cardiovascular medicine specialist performing a cardiac CT, the American College of Cardiology recognizes and endorses education and training of such individuals in the recognition of incidental scan findings in support of quality imaging care of patients with cardiovascular disease. . . . To this end, it is felt that Level 2 and Level 3 training should include review of all cardiac CT for noncardiac findings.”

REFERENCES


WE THANK DR. FLEET FOR HIS INTEREST IN OUR STUDY (1) AND APPRECIATE HIS COMMENTS. WE AGREE WITH DR. FLEET AS TO THE NECESSITY OF FURTHER EVIDENCE TO ESTABLISH THE CLINICAL SIGNIFICANCE OF NONCARDIAC ANALYSIS IN CARDIAC MULTIDETECTOR COMPUTED TOMOGRAPHY (MDCT). OUR STUDY LACKS LONG-TERM CLINICAL FOLLOW-UP TO DISCUSS CLINICAL OUTCOMES. IN ADDITION, WE DID NOT DISCUSS COST BECAUSE THE ACTUAL COST OF ADDITIONAL FOLLOW-UP, INCLUDING SURGERY, BIOPSY, AND IMAGING, VARIES AMONG COUNTRIES AND INSTITUTIONS. AS CLINICAL RESULTS AND COSTS COULD BE DIFFERENT DEPENDING ON HOW REFERRING PHYSICIANS...

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REPLY

We thank Dr. Fleet for his interest in our study (1) and appreciate his comments. We agree with Dr. Fleet as to the necessity of further evidence to establish the clinical significance of noncardiac analysis in cardiac multidetector computed tomography (MDCT). Our study lacks long-term clinical follow-up to discuss clinical outcomes. In addition, we did not discuss cost because the actual cost of additional follow-up, including surgery, biopsy, and imaging, varies among countries and institutions. As clinical results and costs could be different depending on how referring physicians...