there is evidence for S-RV in stable angina (3,5), and relative insufficiency probably is an invalid mechanism; cholesterol- and stress-reduction significantly improved angina in a month's time (6), long before CAD could be improved—a finding incompatible with classic relative insufficiency (3,5). Favorable to the concept, cholesterol reduction favors vasodilation and can improve vasodilation in one month (7) and, as stress can cause S-RV (3), stress-reduction reasonably is vasodilative. Also, while plaque rupture/thromboses are the accepted mechanisms of acute coronary syndromes, a recent analysis showed significant faults with this mechanism (5). For example, studies of infarction showing rising incidences of thromboses over time are incompatible with primary thromboses. If thromboses cause infarction, how can their incidence increase over time? And recognition of S-RV during ischemic episodes in unstable angina (8) is consistent with the S-RV cause of this angina.

The S-RV concept offers an explanation for the only occasional occurrence of vasospastic angina, and a viable explanation should help establish the reasonableness of the concept. As vasospastic angina is unassociated with CAD, this major vasoconstrictive force is absent, and angina occurs only when there are high levels of other risk factors as stress, gender and genetic factors, etc.—which occur only occasionally. In IHD associated with CAD, symptoms are attributed to the risk factor of CAD plus other risk factors such as stress; consistent with this, induced stress can cause myocardial ischemia in individuals with stable angina (9,10). Also, absence of IHD in many individuals with severe CAD is explained by the relative absence of other risk factors such as stress.

Although considerable evidence supports the standard position, there appears to be sufficient contravening evidence for the S-RV concept to prompt a comprehensive review of its positions.

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Thyroid Hormone and Arrhythmogenic Activity

We read with great interest the study by Chen et al. (1) in a recent issue of the *Journal*. The investigators report that thyroid hormone changes the electrophysiologic activity of the pulmonary vein cardiomyocytes, and they suggest that increased tri-iodothyronine-induced automaticity and enhanced triggered activity may increase the arrhythmogenic activity of cardiomyocytes in hyperthyroidism. They conclude that this mechanism contributes to arrhythmogenic activity of hyperthyroidism.

Hyperthyroidism is known to be an important risk factor in the etiology of atrial fibrillation (AF)(2). In a large retrospective study investigating an unselected, community-based population of older persons (3), we could demonstrate that the prevalence of AF was 2.3% in subjects with normal values for serum thyrotropin, 13.8% in patients with overt hyperthyroidism (both low serum thyrotropin values [≤0.03 mU/l] and elevated free tri-iodothyronine and free thyroxine concentrations), and 12.7% in patients with subclinical hyperthyroidism (low values of serum thyrotropin [<0.4 mU/l], and free tri-iodothyronine and free thyroxine concentrations within the normal range). The relative risk of AF in subjects with subclinical hyperthyroidism, compared with those with normal concentrations of serum thyrotropin, was 5.2 (95% confidence interval [CI] 2.1–8.7, $p < 0.01$). Thus, a low serum thyrotropin concentration was associated with a more than five-fold higher likelihood for the presence of AF, with no significant difference between subclinical and overt hyperthyroidism.

Individuals with low serum concentrations of thyrotropin regardless of concentrations of free tri-iodothyronine and free thyroxine should be considered as a population at risk for the development of AF (4). Thus, thyroid secretion needs not increase much, if at all, and serum concentrations of free tri-iodothyronine and free thyroxine can stay within normal values for AF to occur. Moreover, when AF occurs, there is only rarely either concurrent or subsequent overt hyperthyroidism, but it is more commonly associated with subclinical hyperthyroidism (5). We consider this topic important, because subclinical hyperthyroidism is, at all, more common than overt hyperthyroidism among people over age 60 (5) and does not progress to overt hyperthyroidism in most cases (6).

We agree with Chen et al. (1) that L-tri-iodothyronine-induced increased automaticity and enhanced triggered activity may be one mechanism that could increase the arrhythmogenic activity of cardiomyocytes in overt hyperthyroidism. But it is obvious from clinical data that mechanisms, other than those triggered by free tri-iodothyronine and free thyroxine, are important in AF associated with low serum thyrotropin.

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REPLY

Auer et al. (1) investigated the relationship between subclinical hyperthyroidism and atrial fibrillation (AF), and they concluded that subclinical hyperthyroidism has a risk of AF. They also speculated that the thyroid hormone may have little effect on the genesis of AF in subclinical hyperthyroidism. We appreciated the comment from Auer and colleagues. However, in the study from Auer et al. (1), 65% of patients with AF were associated with other heart diseases (coronary artery disease, dilated cardiomyopathy and valvular heart disease), and about half of these patients had atrial enlargement. Thus, AF in these patients may be due to the combined effects of thyroid hormone and underlying heart diseases.

Subclinical hyperthyroidism refers to a state with normal thyroid hormone concentrations and low serum thyrotropin concentration. Several causes of subnormal thyrotropin do not reflect the presence of subclinical hyperthyroidism. Serum thyrotropin concentrations are frequently low in patients with severe nonthyroid illness, especially those receiving glucocorticoid. In addition, low serum thyrotropin value may be associated with low or normal serum thyroid hormone in the early stage or shortly after treatment or spontaneous resolution of overt hyperthyroidism (2). In the study from Auer et al. (1), all the patients had underlying thyroid diseases of functional autonomy or autoimmune. It is difficult to diagnose these patients from limited blood samplings, and subclinical hyperthyroidism may be overestimated.

Subclinical hyperthyroidism has been considered to have increasing risk of AF. In the follow-up of 10 years, there was a threefold relative risk of AF in these patients (3). The negative feedback relationship between serum thyrotropin and thyroid hormone is log linear. Thus, the patients with slight excess of thyroid hormone would have low thyrotropin level, but would have serum thyroxine and tri-iodothyronine concentrations above the mean values for normal subjects but within the normal range. Patients with subclinical hyperthyroidism still have symptoms owing to the biologic effects of thyroid hormone. This means that patients with subclinical hyperthyroidism may still have excess thyroid hormone, and thyroid hormone can induce AF.

Although this experimental hyperthyroidism is not completely similar to usual hyperthyroidism, we investigated the direct effects of thyroid hormone on the electrophysiologic characteristics of pulmonary vein and atrial cardiomyocytes (4). We believe that thyroid hormone increases the arrhythmogenic activity of pulmonary vein cardiomyocytes, which may underlie the occurrence of AF in hyperthyroidism.

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Manifestation of Left Main Coronary Artery Stenosis Is Diffuse ST Depression in Inferior and Precordial Leads on ECG

In the November 1, 2001, issue of the *Journal of the American College of Cardiology*, Yamaji et al. (1) reported on a novel electrocardiographic (ECG) sign for prediction of acute ischemia caused by left main coronary artery obstruction. They found that ST elevation in lead aVR with less ST elevation in lead V_1 is a predictor of left main obstruction. Searching the English-language literature they found only 42 previous reported patients with acute left main stenosis. The ECG description in these studies included right bundle branch block, anterior ST elevation or precordial ST