Subclinical Hypothyroidism as a New Therapeutic Target for Patients With Heart Failure With Preserved Ejection Fraction

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Subclinical hypothyroidism (SCH) is defined as an elevated level of thyroid-stimulating hormone (TSH) with a normal thyroxine (T4) level. The prevalence of SCH has been previously reported as between 7% and 10%,¹ and it is particularly common in older women. The cardiovascular system is a specific target of thyroid hormone. SCH is associated with hypercholesterolemia, left ventricular diastolic dysfunction, endothelial dysfunction, and increased serum C-re-

active protein (CRP) levels.² A recent meta-analysis revealed that SCH is associated with increased risk of coronary artery disease events and mortality.³ In addition, it is also associated with the development of heart failure (HF) in patients with and without underlying heart disease.^{4,5} The Health Aging and Body Composition population-based study showed that patients (aged 70–79 years) with TSH levels ≥ 7 mU/L, who were monitored for 4 years, had a higher risk of HF events than

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euthyroid patients.^{4,5} In the multivariate analysis, the hazard ratio was 2.58 (95% confidence interval [CI], 1.19–5.60) for patients with a TSH level between 7.0 and 9.9 mU/L and 3.26 (95% CI 1.37–7.77) for patients with a TSH level ≥ 10.0 mU/L or greater.^{3,4} Thus, SCH is a critical risk factor for cardiovascular diseases.

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In this issue of the Journal, Masaki et al firstly report a relationship between thyroid hormone levels and arterial wall stiffness as assessed by the cardio-ankle vascular index (CAVI) in patients with SCH.⁶ CAVI was significantly related to free triiodothyronine (FT3) concentrations, CRP, log N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP), and echocardiographic indices of left ventricular diastolic function.⁶ FT3 directly affects the vascular smooth muscle cells and enhances the production of endothelial nitric oxide, which promotes relaxation of the peripheral vasculature.^{1,4} Furthermore, SCH patients had significantly higher CRP levels than those with normal thyroid function, indicating that inflammation might also play an important role in the acceleration of atherosclerosis in patients with SCH.² These findings may well explain the relation between CAVI and thyroid hormone levels.

Masaki et al also show that SCH patients had impaired left ventricular diastolic function and elevated NT-pro BNP levels compared with euthyroid patients.⁶ The impaired left ventricular diastolic function is a critical pathophysiological mechanism of HF with preserved ejection fraction (HFpEF).⁷ SCH is common in older people, and HFpEF is also a common phenotype of the elderly HF population.⁸ Previous study has shown that 22% of patients with HFpEF had abnormal thyroid function, and increased BNP and severe diastolic dysfunction were independently associated with lower T3 levels.⁹ A low T3 level reduces sarcoplasmic calcium ATPase activity, with consequent impairment of left ventricular diastolic function.^{1,4,10} Thus, thyroid dysfunction is a likely potential cause of HFpEF.

Importantly, increased CAVI was associated with impaired left ventricular diastolic function in patients with SCH.⁶ Takeda et al¹¹ recently reported changes in vascular stiffness and the development of left ventricular hypertrophy after undergoing endovascular aortic repair (EVAR). They evaluated patients undergoing EVAR for abdominal and/or thoracic aneurysm with preserved ejection fraction, and showed that the brachial-ankle pulse wave velocity (baPWV), left ventricular mass index (LVMI), and left atrial volume index as markers of comprehensive diastolic dysfunction were significantly elevated after EVAR compared with baseline data. The changes in baPWV correlated with those in LVMI and were associated with decreased exercise tolerance, indicating that EVAR increased vascular stiffness and led to left ventricular hypertrophy and diastolic dysfunction. Kass proposed that vascular stiffening was accompanied by changes in left ventricular chamber stiffness, and that ventricular-arterial interaction might be an important pathophysiological mechanism of the develop-

ment of HFpEF.⁷ Therefore, in addition to the direct impairment of diastolic function, ventricular-arterial uncoupling may contribute to the development of HFpEF in patients with SCH (Figure).

Small studies have shown that T4 replacement therapy for 6 months improved systolic and diastolic function in patients with SCH.¹⁰ In addition, it also reduced systemic vascular resistance, which confirms a direct vasodilatory effect of thyroid hormone. The Cardiovascular Health Study showed that the risk of HF was significantly lower in T4-treated patients than in untreated patients.¹² Furthermore, patients with TSH >10 mU/L had an increased risk of HF during periods of T4 withdrawal than during its use.¹² These findings indicate that T4 therapy may reduce the risk of HF in patients with SCH.

Thyroid dysfunction is a reversible cause of HF, and T4 replacement therapy has beneficial hemodynamic effects in patients with SCH. Although the effect of such treatment on mortality remains unclear, thyroid function tests should be evaluated in any patients with newly diagnosed HF, especially HFpEF, and further investigations are necessary to evaluate the prognostic significance of T4 replacement therapy in HF patients with SCH.

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