CLINICAL RESEARCH STUDY

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# Incremental Value of a Single High-sensitivity Cardiac Troponin I Measurement to Rule Out Myocardial Ischemia

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## ABSTRACT

**BACKGROUND:** The aim of this study was to investigate the value of a novel high-sensitivity cardiac troponin I measurement to rule out exercise-induced myocardial ischemia in patients without known coronary artery disease.

**METHODS:** We included 714 patients without previously known coronary artery disease who were referred for rest/stress myocardial perfusion single photon emission tomography. All clinical information available to the treating cardiologist was used to quantify the clinical judgment regarding the presence of exercise-induced myocardial ischemia using a visual analogue scale twice: once before and once after bicycle exercise stress testing. High-sensitivity cardiac troponin I measurements were obtained before stress testing in a blinded manner. The presence of exercise-induced myocardial ischemia was adjudicated on the basis of myocardial perfusion single photon emission tomography combined with coronary angiography findings.

**RESULTS:** Exercise-induced myocardial ischemia was detected in 167 participants (23.4%). High-sensitivity cardiac troponin I levels were significantly higher in patients with exercise-induced myocardial ischemia (4.0 ng/L [95% confidence interval, 2.8-8.6] vs 2.6 ng/L [95% confidence interval, 1.8-4.1], $P < .001$) and remained an independent predictor of ischemia in multivariable analysis ($P < .001$). Combining clinical judgment before exercise testing with high-sensitivity cardiac troponin I levels increased diagnostic accuracy as quantified by the area under the receiver operating curve from 0.64 to 0.73 ($P < .001$), which also tended to be superior to clinical judgment after exercise testing (0.69, $P = .056$). A single resting high-sensitivity cardiac troponin I measurement provided similar diagnostic accuracy as integrated clinical judgment after exercise testing including work load, as well as symptoms and electrocardiogram changes (0.70 vs 0.69, $P =$ not significant).

**CONCLUSIONS:** High-sensitivity cardiac troponin I measurements seem to complement noninvasive clinical assessment in patients with suspected coronary artery disease.

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**KEYWORDS:** Exercise; High-sensitivity cardiac troponin I; Ischemia; Perfusion; Single photon emission tomography

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Coronary artery disease is the most common cause of death worldwide, and coronary artery disease incidence, mainly in emerging nations, is still strongly increasing.[1-6] Therefore, early detection of coronary artery disease and exercise-induced myocardial ischemia as its pathophysiologic hallmark is one of the most important tasks in modern medicine.

Cardiac stress testing, particularly with imaging such as rest/stress myocardial perfusion single photon emission tomography (MPI-SPECT), is the current standard of care in the noninvasive detection of exercise-induced myocardial ischemia.[7,8] However, these tests recently have become the focus of debates about increasing health care costs, inappropriate use, and patient safety in the context of radiation exposure.[9] A recent analysis of repeated cross-sectional data in the United States found a substantial increase in the number of cardiac stress tests with imaging performed, of which at least 34.6% were probably inappropriate, with associated annual costs and harms of $501 million and 491 future cases of cancer.[9] These findings are supported by another study also documenting that these tests are often applied in patients with low pretest probability resulting in positive test results in only 8% in a recent series of patients undergoing MPI-SPECT.[10] Therefore, there is an unmet clinical and economic need for an easily applicable, noninvasive, safe, and cost-effective method to particularly rule out exercise-induced myocardial ischemia.[11]

Cardiac biomarkers such as cardiac troponin I, a structural protein unique to the heart, may have value in this setting and are an integral part of the diagnosis of patients with suspected acute myocardial ischemia.[1,12,13] On the basis of promising observations made in recent pilot studies,[14-19] we hypothesized that cardiac troponin I, if measured with an assay with very high-sensitivity cardiac troponin I,[19-21] could provide incremental diagnostic value in addition to clinical judgment by a cardiologist.

## CLINICAL SIGNIFICANCE

- Serum cardiac troponin I levels were significantly higher in patients with exercise-induced myocardial ischemia and could serve as valuable tools in risk stratification of coronary artery disease.
- A single resting high-sensitivity cardiac troponin I measurement tended to provide better diagnostic accuracy than bicycle-ergometry stress testing in the detection of myocardial ischemia.
- Potential economic consequences of a cost-effective rule-out algorithm regarding the globally increasing incidence of coronary artery disease are large.

## MATERIALS AND METHODS

### Patient Population

We analyzed consecutive adult patients who were referred to the University Hospital Basel for coronary artery disease evaluation by MPI-SPECT and had given written informed consent. We took advantage of a unique setting in which MPI-SPECT is the cardiac stress test of choice for patients with a wide range of pretest probability for coronary artery disease.

Because preexisting coronary artery disease is a strong predictor of exercise-induced myocardial ischemia and the use of biomarkers would seem conceivable primarily in ruling out exercise-induced myocardial ischemia in patients with a low pretest probability, we exclusively analyzed patients without preexisting coronary artery disease. Predefined exclusion criteria were preexisting other cardiac disease known to be associated with cardiomyocyte damage and elevations in cardiac troponin I, such as atrial fibrillation and terminal renal failure requiring chronic hemodialysis (**Figure 1**).[22] The study was carried out according to the principles of the Declaration of Helsinki and was approved by the local ethics committee.

### Rest-Stress Myocardial Perfusion Single Photon Emission Tomography Protocol

All patients underwent a routine rest/bicycle stress dual isotope ($^{201}$Tl for rest, $^{99m}$Tc sestamibi for stress) MPI-SPECT protocol previously described in detail.[23,24] Patients who were unable or partially unable to perform treadmill exercise underwent pharmacologic stress testing or combined stress testing with

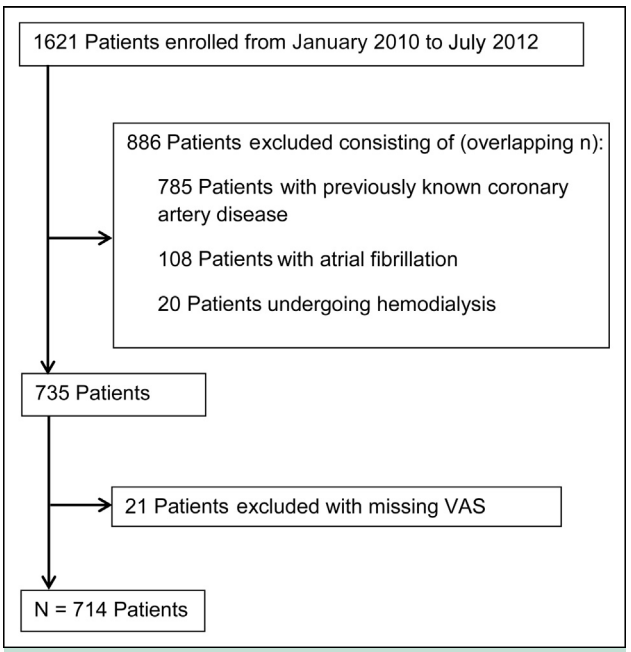


**Figure 1** Patient flow. VAS assessment is clinical judgment quantified on a VAS. VAS = Visual Analogue Scale.