It is really important to evaluate ischemic heart disease accurately and non-invasively because the currently available methods used to evaluate ischemia (not including coronary stenosis) are not sufficient in terms of sensitivity and specificity. In addition, invasive methods such as coronary angiography and cardiac computed tomography do not always give us enough information to determine the subsequent treatment. In other words, coronary stenosis is not always related to the functional flow reserve, and functional evaluation, including coronary vasodilating capacity, with high sensitivity and specificity avoids other methods. Exercise tests, such as treadmills and ergometers, are broadly used despite restricted accuracy; however, ST evaluation is fundamentally limited in the case of poor and restricted exercise tolerance, abnormal rest ECG (including old myocardial infarction (OMI)), left ventricular hypertrophy (LVH) and left bundle branch block (LBBB).

It is well known that coronary flow reduction directly affects the $O_2$ supply to the working muscle because it is mostly dependent on coronary flow compared with an A-VO$_2$ difference in the heart, which is markedly different from peripheral muscle. It means that when the extractable $O_2$ flow falls below demand, either metabolic change will soon follow or lipid predominance in producing adenosine triphosphate (ATP) shifts to glucose dependence in the ischemic cardiac muscle, following ATP depletion above the point of aerobic oxidation. Thus, functional derangement and recovery related to ischemia depend on myocardial oxidative metabolism. Functional failure is followed by increased end-diastolic pressure, ST change and finally the symptoms of ischemia, in this order (Figure). It is important to point out that functional derangement precedes ST depression or symptoms. Diagnostic accuracy theoretically decreases in this order; that is to say, the earlier the stage of finding the ischemic process or $O_2$ kinetics, the more accurate is the diagnostic power of ischemia.

Metabolic change induced by the $O_2$ kinetics in cardiac muscle leads to functional failure or regional wall motion disturbance, which that the stroke volume is affected by ischemia before the ischemic change on ECG, followed by decreased cardiac output, which are the products of heart rate and stroke volume. Thus, in the stage above the anaerobic threshold (AT), a higher work rate independent of a change in ventilation leads to a decrease in cardiac output, meaning decreased $O_2$ supply to the working muscle, which is the product of cardiac output and the A-VO$_2$ difference. Thus, above the AT point, $O_2$ supply and demand will be mismatched, followed by delayed VO$_2$ kinetics and $O_2$ debt in the tissue. After cessation of exercise, the $O_2$ debt will be repaid in the tissue afterwards. The tissue $O_2$ demand rapidly returns to the fundamental level after the disappearance of the ischemic insult, and gradually the debt will be decreased with the remaining cardiac output depending on the oxidative capacity of the peripheral muscle and blood flow. This scenario is classical but fundamental $O_2$ gas kinetics. If this process of $O_2$ kinetics is clinically applied, it will lead to a

![Reduced Coronary Flow](image)

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**Reduced Coronary Flow**

$O_2$ Kinetic Change

Metabolic Change

Diastolic Dysfunction

Systolic Dysfunction

Increased EDP

ECG Change

Angina Symptom

**Figure.** Process of ischemia (modified from ref. 3).
The authors tried to apply this process for evaluating ischemia with a cardiopulmonary exercise test (CPET). The CPET was fit to evaluate O₂ kinetics, including O₂ debt after ischemic insult. The decreased cardiac output and VO₂/work rate above the point of ischemia were already reported in a previous paper. The authors purified the patients' profiles, such as the ischemia-proven group, and the O₂ debt was clearly visualized in this process, to obtain an effective and sensitive tool for evaluating ischemia. The data of several cases followed up enhances the authors conclusion.

This non-invasive diagnostic method gives us an old but new concept. First, ischemia can be visualized, including the size of the ischemic area, coronary severity and the effect of ischemia on the patient, meaning the real effect of total ischemia on the body or real information for treating the patient. Follow-up evaluation using this method will indicate the improvement in ischemia, as well as improved function and adaptation after invasive treatment. Non-essential invasive treatment and operations, such as percutaneous coronary intervention and coronary artery bypass grafting, can then be apportioned.

Second, this method will provide a functional and qualitative evaluation of the coronary artery using a purely non-invasive method with the best predictive ability. Patients with OMI, LVH with strain type or LBBB are also candidates for this method because of the limited understanding of ECG diagnosis. We look forward to seeing the results.

Third, heart failure treatment, including exercise prescription, is important in advanced ischemic heart disease. In addition to the working capacity, the severity of the ischemia contributing to heart failure, or O₂ debt, will be precisely evaluated with this method; that is, central and peripheral information will be easily reported with O₂ kinetics. This exclusive method of evaluating ischemia and the severity of cardiac function will indicate the prognosis, and will be the ideal non-invasive method of treating heart failure.

References