recovery indices in athletic populations, there has been little systematic analysis of the recovery phase in a clinical context, with the few existing studies being mostly in patients with chronic heart failure [2–4]. This apart, it is not clear what advantage the inclusion of such indices might provide, particularly in prognostic evaluation and in the evaluation of therapeutic interventions. This lack of a critical mass of experimental data is the main reason why the recovery issue was not addressed in the 2007 Task Force document, which was intended to provide ''the evidence-based indications to the use of exercise testing in clinical practice''.

As S. Kostianev and co-workers state, analysis of the recovery phase could well provide additional information related to the metabolic (and also ventilatory and cardiovascular) demands imposed by exercise [5]. While some ''new'' physiological concepts relating to issues such as pulmonary gas exchange kinetics and the power–duration relationship were included in the online supplement, we nonetheless recognise that the recovery phase in patients with ventilatory and cardiac diseases would benefit from further investigation.

P. Palange* and S.A. Ward#

*Respiratory Physiopathology Service, Dept of Clinical Medicine, University of Rome ''La Sapienza'', Rome, Italy. #Institute of Membrane and Systems Biology, University of Leeds, Leeds, UK.

REFERENCES

1 Palange P, Ward SA, Carlsen K-H, et al. Recommendations on the use of exercise testing in clinical practice. Eur Respir J 2007; 29: 185–209.

2 Lacasse M, Maltais F, Poirier P, et al. Post-exercise heart rate recovery and mortality in chronic obstructive pulmonary disease. Respir Med 2005; 99: 877–886.

3 Bilsel T, Terzi S, Akbulut T, Sayar N, Hobikoglu G, Yesilcimen K. Abnormal heart rate recovery immediately after cardiopulmonary exercise testing in heart failure patients. Int Heart J 2006; 47: 431–440.

4 Stevenson NJ, Calverley PM. Effect of oxygen on recovery from maximal exercise in patients with chronic obstructive pulmonary disease. Thorax 2004; 59: 688–672.

5 Whipp BJ. Dynamics of pulmonary gas exchange. Circulation 1987; 76: 18–28.

Interferon-γ release assay tests to rule out active tuberculosis

To the Editors:

We read with interest the study by VAN LEEUWEN et al. [1] concerning the use of the T-SPOT™.TB (Oxford Immunotec, Oxford, UK) interferon-γ release assay (IGRA) to rule out the diagnosis of active Mycobacterium tuberculosis infection. We disagree, however, with the use of the IGRA tests for ruling out active M. tuberculosis infection, especially in immunocompromised subjects. Sensitivity of T-SPOT™.TB in immunocompromised subjects, although most certainly higher than that of tuberculin skin test (TST), is clearly <100%. The best sensitivities reported for HIV-infected subjects with active tuberculosis (TB) are 90% [2].

A Bayesian analysis of the cases presented illustrates the limitations of relying on IGRA tests to rule out TB [3, 4]. In case A, a young female refugee from Bosnia develops a lingular infiltrate and has acid-fast bacilli (AFB) on examination of bronchoalveolar lavage (BAL). Incidence of TB in Bosnia is 52×10^{-5} [5], almost eight times that of the Netherlands. Clinical presentation is compatible with rapid progression of TB after a recent infection; HIV status is not specified. Reported sensitivity for the T-SPOT™.TB ranges 83–100% and specificity is in the 96–100% range [6]. We would consider the probability of TB in this case as at least intermediate (0.25– 0.75) or high (>0.75). Post-test probability of TB, if T-SPOT™.TB is negative, would be 5–34% for a sensitivity of 83% and a specificity of 98%, and 2–13% for a sensitivity of 95%; if the pre-test probability is high, post-test probability increases markedly. In both cases, a negative IGRA test definitely cannot be used to rule out active TB.

Case B is that of an immunosuppressed 54-yr-old subject with an atypical radiological presentation for TB but with AFB on BAL smears. In this case, sensitivity of the T-SPOT™.TB assay is unknown but is, at best, 90% based on available data in HIV-infected subjects [2]. The same Bayesian approach, for an intermediate pre-test probability (i.e. 0.25–0.75), yields a post-test probability of disease, with a negative T-SPOT™.TB, of 3–23%. In an immunosuppressed individual, these values are too high to rule out active TB and therapeutic decisions must rely on the identification of the organism involved by PCR and cultures.

Cases C and D are also clinical presentations with at least an intermediate probability of M. tuberculosis infection. In case C, nonspecified mycobacteria grow on culture media, and, in case D, AFB were found on biological samples; thus the negative T-SPOT™.TB results in these settings at most suggest the possibility of an alternative diagnosis.

VAN LEEUWEN *et al.* [1] mention that speed to rule out TB is of great importance in terms of infection-control measures. However, with the exception of immunosuppressed individuals or young children in whom immediate clinical work-up is mandatory, IGRA tests and TST take 6–8 weeks to convert after infection: no large-scale contact-tracing procedure is warranted for the first 2 months following diagnosis and treatment of the index case.

Sensitivity, likelihood ratio in the event of a negative test and pre-test probability are of major importance to rule out active disease. Furthermore, sensitivity varies according to the IGRA test used and according to the population tested. FERRARA *et al.* [7] studied both IGRA tests in routine clinical practice and reported a 16–25% false-negative rate (a sensitivity of 75–84%) in 24 subjects with active TB, using both IGRA tests available. Sensitivity reported for T-SPOT^{TM}.*TB* is 83–100% and is 64–97% for QuantiFERON-TB GOLD (Cellestis, Carnegie, Victoria, Australia); this is on average slightly lower than that of T-SPOT^{TM}.*TB* [8–10].

The Centers for Disease Control and Prevention 2005 guidelines state that, for reasons of suboptimal sensitivity, a negative QuantiFERON-TB GOLD test cannot be used to exclude the diagnosis of active TB [11]. Although the sensitivity of the T-SPOT^{TM}.*TB* is probably better on average than that of the QuantiFERON-TB GOLD, there are too many clinical situations, such as all forms of immunosuppression, severe comorbidity, HIV infection, older subjects, in which its sensitivity is probably decreased and thus Centers for Disease Control and Prevention guidelines appear reasonable for both IGRA tests. T-SPOT^{TM}.*TB* may at the very best reasonably rule out *Mycobacterium tuberculosis* infection in immunocompetent individuals, without any risk factor for exposure to TB, and with a low clinical pre-test probability of *Mycobacterium tuberculosis* infection (<0.25).

J-P. Janssens
Geneva University Hospital, Geneva, Switzerland.

REFERENCES
1 van Leeuwen RM, Bossink AW, Thijsen SF. Exclusion of active *Mycobacterium tuberculosis* complex infection with the T-SPOT^{TM}.*TB* assay. *Eur Respir J* 2007; 29: 605–607.
2 Chapman AL, Munkanta M, Wilkinson KA, *et al.* Rapid detection of active and latent tuberculosis infection in HIV-positive individuals by enumeration of *Mycobacterium tuberculosis*-specific T cells. *AIDS* 2002; 16: 2285–2293.
3 Mayer D. Bayes' theorem and predictive values. *In*: Essential Evidence-based Medicine. Cambridge, Cambridge University Press, 2004; pp. 222–236.
4 Nendaz MR, Perrier A. [Bayes theorem and likelihood ratios.]. *Rev Mal Respir* 2004; 21: 394–397.
5 Dye C, Floyd K, Gunneberg C, *et al.* World Health Organization. Global Tuberculosis Control: Surveillance, Planning, Financing. Geneva, World Health Organization, 2007; p. 277.
6 Pai M, Kalantri S, Dheda K. New tools and emerging technologies for the diagnosis of tuberculosis: part I. Latent tuberculosis. *Expert Rev Mol Diagn* 2006; 6: 413–422.
7 Ferrara G, Losi M, D'Amico R, *et al.* Use of routine clinical pratice of two commercial blood tests for diagnosis of infection with *Mycobacterium tuberculosis*: a prospective study. *Lancet* 2006; 367: 1328–1334.
8 Dewan PK, Grinsdale J, Kawamura LM. Low sensitivity of a whole-blood interferon-gamma release assay for detection of active tuberculosis. *Clin Infect Dis* 2007; 44: 69–73.
9 Lee JY, Choi HJ, Park IN, *et al.* Comparison of two commercial interferon-gamma assays for diagnosing *Mycobacterium tuberculosis* infection. *Eur Respir J* 2006; 28: 24–30.
10 Pai M, Menzies D. Interferon-gamma release assays: what is their role in the diagnosis of active tuberculosis? *Clin Infect Dis* 2007; 44: 74–77.
11 Mazurek GH, Jereb J, Lobue P, Iademarco MF, Metchock B, Vernon A. Guidelines for using the QuantiFERON-TB Gold test for detecting *Mycobacterium tuberculosis* infection, United States. *MMWR Recomm Rep* 2005; 54: 49–55.

From the authors:

We would like to thank J-P. Janssens for his interest and comments on our recent paper [1]. We fully agree that the decision to use the T-SPOT^{TM}.*TB* (Oxford, Immunotec, Oxford, UK) to exclude active tuberculosis (TB) infection should not be taken lightly. We appreciate the opportunity to make some comments in reply to his letter.

First, he calculates the risk of suffering from active TB to be intermediate (0.25–0.75) in the patients described. His criteria for this risk estimation are not mentioned and could be arbitrary.

Secondly, because acid-fast bacteria were initially identified in all patients, one could easily say that the risk of active TB is high (>0.75). However, research in the Netherlands in 2005 demonstrated that ~600 (38%) out of 1,600 cultured isolates were Mycobacteria other than TB [2]. This would decrease the *a priori* likelihood for *M. tuberculosis* (MTB) infection considerably.

Thirdly, in our case study we described four patients with a relatively high probability for active MTB infection (condition A) and the use of a test to confirm or exclude active MTB infection (condition B). As we noted in the paper, the sensitivity of the T-SPOT^{TM}.*TB* test in our hospital, with our patient population, was 100%. To date, we have identified 33 patients with active TB. One patient had an indeterminate test result and the remaining 32 patients were all T-SPOT^{TM}.*TB* positive. Thus, condition B has a probability of 1 and Bayes theorem should not be used if one of the conditional probabilities is 1 [3].

J-P. Janssens correctly mentioned that the sensitivity of T-SPOT^{TM}.*TB* for detecting active TB is not 100% in different studies. Therefore, we were cautious in our paper not to use this approach in severely immunocompromised patients and, furthermore, not to incorrectly interpret indeterminate results as negative. Case B was immunocompromised based on the use