Letters to the Editor


TNF-α system in CHF

Van Riemsdijk-van Overbeeke et al(1) reported on the TNF-α system in patients with chronic heart failure and after heart transplantation. The main conclusion is, that ‘patients with end-stage heart or renal failure and after transplantation suffer from generalized immunosuppression’(1). The authors do not provide data on end-stage renal failure and we think the evidence for the presence of end-stage heart failure in their 11 hospital-admitted chronic heart failure patients is limited (no data on peak VO2, cardiac dimensions, cachexia, and diuretic treatment was required in only six of 11 patients).

The discussion is mainly based on the fact that TNF-α was not detectable, either in patients or controls. There are at least ten studies(2-11) that have reported measurable, reproducible, and mostly increased TNF-α plasma concentrations in study patients with chronic heart failure. In these studies, TNF-α was measurable in virtually all cases, particularly when Medgenix test kits (total TNF-α) or R&D Systems Quantikine high sensitivity kits (trimeric, i.e. bioactive TNF-α) were used. Studies that have reported detectable TNF-α only in subgroups of chronic heart failure patients, and that did not find TNF-α in control subjects, mostly date from the early 1990(9). Soluble TNF receptor 1 and 2 were reported to be increased; this is further evidence that inflammatory cytokine activation is indeed present in chronic heart failure patients(8,9).

To some degree, soluble TNF receptors may reduce TNF-bioactivity, but soluble TNF receptors also increase the TNF-α half-life time by providing an intravascular storage pool. It has been stated that the chronic heart failure patients required hospital admission because of progression of heart failure. Therefore they may have had oedema (not reported). In oedematous chronic heart failure patients we and others recently found elevated TNF-α plasma concentrations(8,7).

What if the test kit used simply had poor sensitivity compared to those in other studies? This would make it impossible to draw any conclusion from the non-detectable TNF-α concentrations in this study.

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References


A reply

We appreciate the comments of Drs. Doehner and Anker regarding our paper about the TNF-α system in heart failure and after heart transplantation (Eur Heart J 1999; 20: 833-40).

Their main concern is that we drew our conclusions from non-detectable TNF-α levels. In order to overcome this problem elegantly, we measured mRNA expression levels, which provide indirect information about TNF-α production, and soluble TNF-receptors (sTNF-R), which are produced after TNF-α binding to their specific membrane receptor. Levels of sTNF-R can serve as a reflection of this binding process and thus the activity of the pro-inflammatory cytokine TNF-α.

In the study in question we measured oedematous as well as non-oedematous patients with chronic heart failure (NYHC III or IV, mean left ventricular ejection fraction 18%). There were no statistically significant differences between patients with or without oedema in TNF-α mRNA expression levels or sTNF-R levels. In none of the patients (with heart failure or after heart transplantation) or controls was free TNF-α detectable.

After reading the paper by Niebauer et al(1), we performed another TNF-α study in patients with severe heart failure and oedema. In this study we used the Quantikine high sensitivity ELISA kit for TNF-α (R&D Systems), with a detection limit of 0.5 pg·ml⁻¹. This ELISA kit was also used by Niebauer et al(1). As positive controls we measured TNF-α plasma levels in renal transplant recipients, who received rabbit-anti-thymocyte-globulin (r-ATG) as rejection treatment. Healthy volunteers served as controls. TNF-α levels were 349 pg·ml⁻¹ after r-ATG treatment, 1.2 pg·ml⁻¹ for healthy controls and 4.0 pg·ml⁻¹ in patients with heart failure, which did not significantly decrease after treatment. These data, especially the results of the patients suffering from heart failure, are in line with our previous study. We are not able to reproduce the data on TNF-α levels found in healthy controls and in heart failure, as described by Niebauer et al(1). Their levels of sTNF-R are comparable to our data. Moreover, it is known that for various reasons, different TNF-α measurements are hard to compare(2).

The sensitivity of the ELISA kit used in the previous study was low (detection limit 4 pg·ml⁻¹), but the TNF-α results, measured by the high sensitivity R&D ELISA kit, do not force us to change our conclusions. The approximately 1000-fold excess of sTNF-R may interfere with the function of low free, bioactive TNF-α concentrations. Therefore, we...
think that measuring TNF-α mRNA by RT-PCR is a more reliable method of analysing cytokine systems of chronic heart failure patients. Data on the TNF-α system in end-stage renal failure are reported in our article, which will be published soon[3].

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References


Myocardial perfusion imaging and pilot certification

The article by Underwood[1] is focused on a largely neglected field, although by the 1980s the role of myocardial perfusion imaging was regarded as important in high risk professional groups, such as pilots, at risk of coronary artery disease.

We would like to draw attention to pertinent previous literature (UHL, GS, N.N. Kay, J.R. Hickmann, M.A. Montgomery, G.M. Mc. Granaham: Detection of coronary artery disease in asymptomatic aircrew members with 201-Thallium scintigraphy. Aviation, Space and Emission Med 1980; 51: 1250–1256) which is missing from the reference list of this article, despite other articles not directly related to the topic being cited.

We are not aware of any major nuclear cardiology study on this field and fear there are no reports at all on PET studies in pilots. In our city, which has one of the world’s largest airports, there is no regular nuclear cardiology investigation programme for pilots, not even for those who have suffered a previous myocardial infarction, apart from those with asymptomatic myocardial ischaemia or atypical chest pain.

In more than 20 years the number of pilots examined in our nuclear medicine clinic is poor. What is the situation on nuclear medicine in London?

It would be worthwhile initiating comparative or multicentre trials on this field to alert doctors in airport clinics and to open their eyes about an important field of internal medicine and cardiology: nuclear cardiology.

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Reference