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To the Editor:

We appreciate the comments of Dr. Martin-Denavit and co-workers on our report and the information they presented, which throws additional light on the use of serum procalcitonin (PCT) for the diagnosis of neonatal infection. They regard markedly increased serum PCT as a marker of materno-fetal infection, although fetal involvement is difficult to confirm. In the absence of microbiological evidence, the diagnosis of infection relies on clinical signs, which can be found in a variety of conditions. Alternatively, the high serum PCT concentrations measured in eight neonates could represent maternal PCT, increased by an infection not involving the fetus, after passage through the placenta. Given the low molecular mass (≈12 kDa) of PCT *(1)*, transplacental passage of this substance must be considered, although we are not aware of any study dealing with this issue. Parallel measurements of maternal and neonatal serum PCT concentrations at delivery could give insight into the possible sources of increased PCT in the first hours of life.

Regarding the serum PCT concentrations in newborn infants without infection, the data presented by Dr. Martin-Denavit and co-workers combine with those presented by another group *(2)* and our group to give a clearer picture of a physiological peak in serum PCT occurring between 12 and 36 h after birth. Physiological peak PCT concentrations generally are <20 μg/L; therefore, values exceeding that limit can be regarded as a sign of infection even in this time period.

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Influence of Age and Sex and Day-to-Day and Within-Day Biological Variation on Plasma Concentrations of Fatty Acid-binding Protein and Myoglobin in Healthy Subjects

To the Editor:

Fatty acid-binding protein (FABP), like myoglobin (Mb), increases significantly within ~3 h after onset of symptoms of acute myocardial infarction (AMI) and returns to health-related values within 12 to 24 h *(1)*. For the early assessment or exclusion of AMI, FABP performs better than Mb *(2, 3)*. Although FABP, like Mb, is also found in skeletal muscle, the distinct ratio of the contents of Mb over FABP in heart (ratio, 4–5) and skeletal muscle (ratio, 20–70) allows the discrimination between myocardial and skeletal muscle injury *(4)*.

For the assessment of clinical reference values, it is important to know the possible influence of biological variations such as age, sex, and day-to-day and within-day fluctuations *(5)*; however, for FABP such data are lacking. The aim of the present study was to establish these parameters for FABP first in a large group of volunteers of different ages. Mb was also measured to delineate possible effects of age and sex on the ratio of the plasma concentrations of Mb over FABP. We also studied day-to-day and within-day biologic variation (within-person) for both FABP and Mb concentrations in another group of volunteers.

For the first substudy, plasma samples were taken from 312 donors (110 women and 202 men; ages, 21–70 years) visiting the blood bank of Liège, Belgium. EDTA was added to samples to prevent clotting. For the study of within-person biologic variation, blood samples were obtained from young and apparently healthy volunteers (six men and six women; ages, 19–27 years) recruited from the student population of Maastricht University. Samples were obtained at the following time points: on day 1, at 0930, 1100, 1400, 1700, 2000, and 2300; on day 2, at 0300, 0700, 0930; and on days 8, 15, 22, 29, and 57 at 0930. Citrate was added to prevent clotting, and samples were immediately aliquoted and frozen at −80 °C until use. The study was approved by the medical ethics committee of the Academic Hospital Maastricht, and all subjects gave informed consent. FABP was measured with a sensitive noncompetitive sandwich-type ELISA *(6)*, using recombinant human (heart-type) FABP as the calibrator *(7)*. Mb was measured with a turbidimetric im-

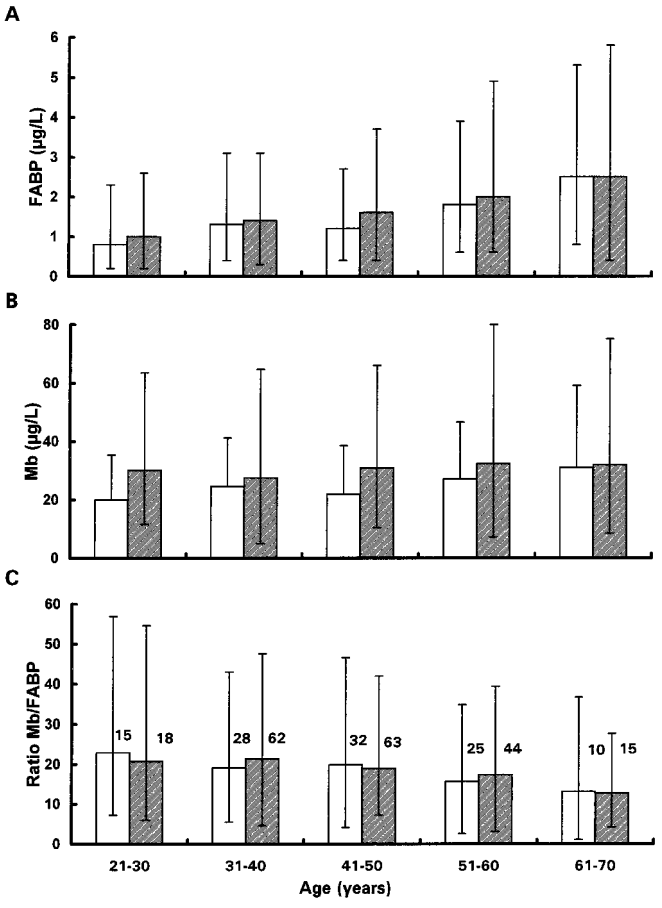

Fig. 1. Median plasma concentrations (25 and75 percentiles) of FABP (*A*), Mb (*B*), and the ratio of Mb over FABP (*C*) in apparently healthy men (■) and women (□) of different age groups. *Numbers* above bars refer to the number of subjects studied.

munoassay (Unimate 3 Myo; Roche Diagnostic Systems) on a Cobas Mira plus analyzer (Roche). The inter- and intraassay analytical imprecision (CV) was <10% for FABP *(6)* and <6% for Mb (Unimate 3 performance data; Roche). Both assays showed no interference from either citrate or EDTA (data not shown). BMDP Statistical software was used for statistical analysis. All data are presented as medians, with 25 and 75 percentiles in parentheses. Samples with values below the detection limit of 0.3 µg/L FABP or 7.5 µg/L Mb were assigned the detection limit.

The median plasma concentrations of FABP and Mb in the first substudy (n = 312) were 1.5 µg/L (25–75 percentiles, 1.1–2.1 µg/L) and 27 µg/L (25–75 percentiles, 20–36 µg/L), respectively. The median ratio of the plasma concentrations of Mb over FABP was 19 (25–75 percentiles, 13–24). Plasma concentrations of both cardiac markers showed a sex dependency. Plasma FABP ($P < 0.005$; Mann–Whitney test) and Mb ($P < 0.0001$) values were lower in women than in men (Fig. 1). The ratio of Mb over FABP showed no significant difference between sexes.

Both cardiac markers also showed an increase in the health-related plasma concentration during aging (Fig. 1). The effect of aging was more prominent in the plasma concentration of FABP ($P < 0.0001$; regression analysis) than Mb ($P < 0.01$). As a result, the ratio of Mb over FABP was also age-dependent ($P < 0.001$).

The day-to-day variation in plasma concentrations of FABP and Mb, expressed as mean CV (within-person) of seven time points (days 1, 2, 8, 15, 22, 29, and 57) of all 12 subjects and calculated as CV^2 within-person = CV^2 total − CV^2 analytical imprecision *(5)* was 14% for FABP and 18% for Mb. For analysis of within-day variation of FABP and Mb, three time blocks were used: daytime as the most active period (0930–1700), evening as a more relaxed period (1700–0100), and night as the resting period (0100–0930). For plasma FABP, a significant increase was seen ($P < 0.005$; BMDP Statistical Software, program 2V) from daytime (0.8 µg/L) to evening (0.9 µg/L) to night (1.1 µg/L). For Mb, a similar trend was found from daytime (20.9 µg/L) to evening (22.6 µg/L) to night (23.1 µg/L); however, this did not reach statistical significance. The overall values for men [FABP, 1.2 µg/L (0.6–1.6 µg/L); Mb, 25 µg/L (22–29 µg/L)] and women [FABP, 0.7 µg/L (0.4–1.2 µg/L); Mb, 20 µg/L (15–22 µg/L)] confirm the data of the first substudy (age group, 21–30 years).

The measured median plasma FABP (1.5 µg/L) and Mb (27 µg/L) concentrations of healthy subjects are similar to previously published values of 1.6 µg/L for FABP and 33 µg/L for Mb *(1, 6)*, as are the differences in Mb plasma values between men and women *(8, 9)*. The observed increases of the FABP and Mb plasma concentrations with age, especially after 50 years, are most likely explained by the decrease in renal function in elderly people, which in the case of Mb may be partly counterbalanced by diminishing skeletal muscle mass, especially in men *(10)*. Both cardiac markers show differences between men and women, which might be explained by the fact that men have a relatively larger muscle mass than women.

The within-day variations found for FABP may be related to the reported increased glomerular filtration rate during the day *(11)*; however, this explanation is not confirmed by a significant within-day variation of Mb. A limitation of this substudy is that observations were made for subjects 19–27 years of age, whereas most acute coronary syndromes appear in older persons.

In conclusion, this study shows that when using FABP and (or) Mb as plasma markers for the diagnosis

of AMI, the time of day is of minor relevance; age and sex, however, are more important because these will influence the upper reference concentrations of both these markers. In addition, caution should be taken when using the Mb over FABP ratio to discriminate cardiac from skeletal muscle injury, especially for patients >50 years of age.

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Influence of Gender in Growth Hormone Status in Adults: Role of Urinary Growth Hormone

To the Editor:

A recent paper by Engstrom et al. *(1)* presented marked gender differences in plasma growth hormone (GH) values in young adults (21–26 years of age), evaluated in the consulting room and after overnight fasting. The authors observed higher values in the women than in the men. They proposed that something in the morning triggers a GH burst in almost all of the women but in very few of the men.

Veldhuis in the 24th International Symposium in Antwerp (*GH and Growth Factors in Endocrinology and Metabolism*, October 1997; information printed by Sterling Press, UK, for Pharmacia & Upjohn) affirmed that gender itself has a major impact on the secretion of GH in adults. Unfortunately, until now the basis of sexual dimorphism in GH secretory patterns/status in humans has not fully understood. However, several works suggest that estrogens play an important role in GH secretion in women compared with men. Lang et al. *(2)* observed a difference in response to growth hormone-releasing hormone (GHRH) in premenopausal, but not postmenopausal, women compared with men. Therefore, estrogens seem to increase the GHRH-stimulated GH secretion.

Main et al. *(3)* revealed a significant impact of gender on urinary GH values. They included children in the study and collected the first morning voiding for 3 days per subject.

The urinary GH values, collected from 70 healthy adults (22–61 years) drug free, in the ambulatory state-,and after overnight fasting are reported here. This population was divided twice (by gender and age) into four groups to investigate a possible influence of gender in GH status; these groups were as follows: group A, men less than 40 years of age (range, 22–39 years), n = 18; group B, women less than 40 years of age (range, 19–40 years), n = 25; group C, men more than 40 years of age (range, 43–61 years), n = 17; and group D, women more than 40 years of age (range, 41–59 years), n = 10 (five of the women were postmenopausal).

This study was approved by the Bioethics Committee of the Medical School of the University of Padova.

To evaluate GH status, other markers such as plasma GH and growth hormone-binding protein (GHBP) were analyzed. The latter is a circulating protein, generated from the extracellular domain of the GH receptor through a proteolytic cleavage.

Statistical analysis was performed using ANOVA-LSD.

The plasma GH concentration and urine GH excretion (reported as ng/L and as ng/g of creatinine) in 70 adults are summarized in Table 1. Values are expressed as mean ± SD. Urinary GH values (expressed both as ng/L and ng/g of creatinine) were higher in women than in men in the younger groups. In groups C and D, there was no difference between male and female urinary GH values (0.98 ± 1.50 vs 1.02 ± 1.52 ng/L and 1.55 ± 2.83 vs 1.90 ± 3.19 ng/g of creatinine, respectively). Further-