these patients results in reduced heart rates and improved cardiovascular efficiency during usual daily activities.

This is only the second report providing a systematic evaluation of the effects of programmed training on aerobic capacity after the Fontan operation. Namisawa et al.\textsuperscript{20} reported on a 2- to 3-month exercise training program (walking or jogging) held 2 or 3 times a week for 20 to 30 minutes in 19 teens and young adults after the Fontan operation. The exercise training in these patients resulted in an increase in maximal oxygen consumption (7%) and exercise time (4%). They also observed that heart rate tended to decrease during small workloads after training and oxygen pulse tended to increase. Our findings are similar but of greater magnitude, probably because the training period was longer. Further, we found definite improvement in cardiovascular efficiency at small workloads. In addition to the longer training program, these differences may be due to the personalized prescription of the exercise program, including a specific target heart rate range.

**Acknowledgment:** We gratefully acknowledge Francesca Forner, Francesca Gasbarro, and Professor Giorgio Andreaggi for their excellent assistance during the exercise training session and Cecilia Giron, MD, for the statistical analysis.


**Values of High-Sensitivity C-Reactive Protein in Each Month of the Year in Apparently Healthy Individuals**

Ori Rogowski, MD, Sharon Toker, MSc, Itzhak Shapira, MD, Samuel Melamed, PhD, Arie Shirom, PhD, David Zeltser, MD, MPH, and Shlomo Berliner, MD, PhD

The serum levels of high-sensitivity C-reactive protein were determined during a 12-month period. No seasonal variation was found in a group of 1,677 apparently healthy patients in whom the presence of clinically evident infection or inflammation was excluded by an appropriate questionnaire. ©2005 by Excerpta Medica Inc.

[Am J Cardiol 2005;95:152–155]
We used information obtained from the Tel Aviv Sourasky Medical Center Inflammation Survey, a relatively large cohort of apparently healthy patients who are evaluated during their annual checkups. The main advantage of this cohort is that we excluded any patient who had an infective or inflammatory condition during a 6-month period before his or her recruitment. This approach enabled us to examine the eventual changes in the concentration of this protein, not necessarily at the prevalence of intercurrent infections in the population.

Patients attending the Tel Aviv Sourasky Medical Center for routine health examination from December 1, 2002, to November 31, 2003 were included. A total of 2,053 subjects agreed (1,195 men, 858 women), yielding a compliance rate of 88%. Systematic examination of the reasons for participation yielded no effect of sociodemographic or biomedical variables. An additional 376 subjects were later excluded from the analysis because of known inflammatory diseases (arthritis, inflammatory bowel disease, etc.), pregnancy, steroidal or nonsteroidal treatment (except aspirin at a dose of ≤325 mg/dl), acute infection, or invasive procedures (surgery, catheterization, etc.) during the previous 6 months, or missing data for 1 of the study parameters. The study was approved by the local ethics committee.

We determined hs-CRP using the Behring BN II (Dade Behring Holding GmbH, Marburg, Germany) nephelometer and a method described by Rifai et al.

Statistical analysis was performed separately for men and women. The hs-CRP levels had a non-normal distribution, so we used a logarithmic transformation, and all the results expressed as hs-CRP are back-transformed as geometric means, SDs, SEMs, and medians. All data were summarized and are displayed as mean ± SD or mean ± SE of the mean for hs-CRP. Participants were divided first into groups on the basis of the months of the year. A 1-way analysis of variance was performed to compare log(hs-CRP) among the months of the year for the 2 genders. The Ryan-Einot-Gabriel-Welsch multiple range test was used for pairwise comparison among months. Participants were later grouped on the basis of the 4 seasons of the year to evaluate whether there was a difference among the seasons. Again, 1-way analysis of variance and the Ryan-Einot-Gabriel-Welsch multiple range test were used. In addition, we used the locally weighted scatterplot smoothing procedure with a smoothing parameter of 0.5 for the data divided by month, and finally, we used a rhythm analysis in which we found the best match between the hs-CRP data points and the sinus curve using the least-squares method to find the maximum and minimum dates. The level of significance used for all analyses was a 2-tailed p value <0.05. The SPSS statistical package (SPSS, Inc., Chicago, Illinois) and the SAS system (SAS Institute Inc., Cary, North Carolina) for Windows were used to perform all statistical evaluations.

We included a cohort of 1,677 patients (mean age

<table>
<thead>
<tr>
<th>Month</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>1.91 ± 3.02</td>
<td>1.43 ± 2.34</td>
</tr>
<tr>
<td>February</td>
<td>2.08 ± 3.40</td>
<td>1.49 ± 2.75</td>
</tr>
<tr>
<td>March</td>
<td>1.74 ± 3.30</td>
<td>1.31 ± 3.00</td>
</tr>
<tr>
<td>April</td>
<td>1.37 ± 3.90</td>
<td>1.72 ± 2.51</td>
</tr>
<tr>
<td>May</td>
<td>1.82 ± 3.34</td>
<td>1.31 ± 2.70</td>
</tr>
<tr>
<td>June</td>
<td>1.42 ± 3.14</td>
<td>1.53 ± 2.85</td>
</tr>
<tr>
<td>July</td>
<td>1.49 ± 3.02</td>
<td>1.25 ± 2.76</td>
</tr>
<tr>
<td>August</td>
<td>1.46 ± 3.48</td>
<td>1.55 ± 2.84</td>
</tr>
<tr>
<td>September</td>
<td>1.96 ± 3.49</td>
<td>1.34 ± 2.71</td>
</tr>
<tr>
<td>October</td>
<td>1.66 ± 2.90</td>
<td>1.48 ± 2.55</td>
</tr>
<tr>
<td>November</td>
<td>1.84 ± 3.03</td>
<td>1.46 ± 2.75</td>
</tr>
<tr>
<td>December</td>
<td>1.73 ± 3.11</td>
<td>1.53 ± 2.85</td>
</tr>
</tbody>
</table>

...
47.1 ± 11.2 years; 1,067 men, 610 women). The mean daily hs-CRP concentration for women is reported in Figure 1, and that for men is reported in Figure 2. The mean ± SD and the median of hs-CRP in each month in men and women are listed in Table 1, and the graphic representation of these results (mean ± SE of the mean) is shown in Figure 3. The results of the 1-way analysis of variance to reveal potential differences between hs-CRP concentrations divided by month were negative, confirming the lack of differences among the different months of the year. The locally weighted scatterplot smoothing procedure was used with a smoothing parameter of 0.5 and did not demonstrate a significant seasonal variation among the months for men and women (data not represented). We also grouped the results of hs-CRP on the basis of the 4 seasons, and the results are displayed in Figure 4. Again, there was no significant difference among the seasons using 1-way analysis of variance and the Ryan-Einot-Gabriel-Welsch multiple range test in men and women. Finally, we found the best fit between the hs-CRP data and the sinus curve and demonstrated that there was a significant difference between men and women. In women, the maximum point of the fitted sinus curve was at the end of December (winter) and the minimum point at the end of June (summer), whereas in men, the maximum was in mid-April and the minimum in mid-October. Because there was no significant difference among the months of the year, the maximum and minimum points of the fitted sinus curves could be a matter of chance.

hs-CRP is an established cardiovascular risk factor and a useful marker for future events. Moreover, recent studies have suggested that it might be not only a biomarker but can also affect the process of atherothrombosis. Thus, the question of whether hs-CRP concentration is enhanced during periods of prevalent infections in the population is relevant for epidemiologic studies in which high-risk patients are singled out by this biomarker.

The question of seasonal variation in hs-CRP concentrations has been addressed in the past by several investigators. Fröhlich et al found no strong, consistent evidence for intra- and interpatient seasonal variation of CRP, except for men in the third Monitoring Cardiovascular Disease study, for whom a seasonal difference was found, with the largest CRP values observed in May. However, the investigators found a statistically significant lack of fit of the data, which could indicate that their model was not appropriate, and suggested that their data be interpreted with caution. In addition, participants in the Monitoring Cardiovascular Disease studies were observed for a period that covered 8 to 10 months, with a lack of data in August and September. In contrast, Woodhouse et al reported greater CRP concentrations in winter, with a peak in March, and Crawford et al found a significant seasonal variation of CRP, with a peak in late February. Thus, it is not completely clear from the data that are currently available whether a lack of seasonal variation is a consistent finding.

Although it has been determined that 2 or even 3 tests are needed before firm conclusions are drawn as to whether a certain patient has enhanced cardiovascular risk, most patients obtain a single test during their annual checkups. In addition, it has been suggested that cut-off points of up to 1, from 2 to 3, and >3 mg/L be used to categorized patients into groups of low, intermediate, and relatively high risk. Thus, changes of hs-CRP that relate to seasonal variation due to subclinical infections during the winter might...
have an impact on this classification. Our study is therefore significant, in that it shows a lack of seasonal variation in hs-CRP concentrations. This is, of course, when recent infection or inflammation has been excluded by an appropriate questionnaire.


**Comparison of Differing C-Reactive Protein Assay Methods and Their Impact on Cardiovascular Risk Assessment**

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A medium-sensitivity assay for C-reactive protein (CRP) was compared with a high-sensitivity, enhanced immunoturbidimetric assay in 803 angiographically studied patients. Different absolute CRP values were found by the assays, but there was a high correlation by quartile rank and similar predictive values for death and myocardial infarction. This suggests that the conclusions of previous studies performed using the medium-sensitivity assay are still valid but that cross-study comparisons should use percentile rank. ©2005 by Excerpta Medica Inc.

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Coronary artery disease (CAD) remains the leading cause of serious morbidity and mortality in adults. Standard risk factors explain much of population-level risk, but they provide incomplete and suboptimal assessment of risk in patients. During the past decade, the inflammatory basis of atherogenesis has been recognized.1–2 C-reactive protein (CRP) has emerged as the prototypic inflammatory predictor of primary and secondary risk in men and women and is the only inflammatory marker currently recommended for clinical application.1–4 Despite a wealth of data,3,5–7 controversy still surrounds CRP as a risk marker.8 Part of the controversy relates to questions about the comparability of CRP assays used in these studies. In our own and others’ experience with CAD risk prediction, medium- and high-sensitivity CRP (hs-CRP) assays have become variously available and used over several years.5–17 More recently, higher sensitivity assays have become more widely available and recommended as preferred for risk assessment.3–5 Despite this, few studies have actually addressed the comparability or differences in these assays and their predictive value, especially in diseased populations. In-