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Reply

Dr. Handelsman raises concerns with regard to the interpretation of findings in the recently published study by Caminiti et al. (1) and our accompanying editorial (2). His major point is related to testosterone's failure to improve cardiac function while having beneficial peripheral effects—a dichotomy he suggests may be explained by the mood-elevating effects of testosterone. He also raises concerns with regard to the suboptimal use of saline as placebo.

We have no problems with agreeing with Dr. Handelsman's view, and these aspects should be taken into account in the interpretation of the effects of testosterone in heart failure. In fact, the interaction between hormones such as testosterone, neurotransmitters, and inflammatory markers such as cytokines is an attractive target for therapy in several disorders such as chronic heart failure. Thus, if this mechanism contributes to the results of the study by Caminiti et al. (1), it should encourage rather than advise against further studies in this field. Moreover, although the authors did not find any effect on myocardial function, further long-term studies are needed before making any firm conclusions. There is clearly a need for new treatment modalities in heart failure, and testosterone supplementation might be an interesting approach, most probably operating through several mechanisms including those suggested by Dr. Handelsman.

***Pål Aukrust, MD, PhD**
Arne Yndestad, PhD

*Medical Department
Infectious Diseases
Rikshospitalet
Sognsvannsveien 20
Oslo N-0027
Norway
E-mail: pal.aukrust@rikshospitalet.no

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Dilated Cardiomyopathy Complicates Pregnancy Outcome: But How?

In a recent issue of the *Journal*, Grewal et al. (1) showed that the risk of adverse maternal events in pregnant women with dilated cardiomyopathy (DCM) is considerable, but the underlying mechanisms (in addition to increased hemodynamic load) remain uncertain. Medication was discontinued in many of the women before pregnancy or during the first trimester. Even without the physical burden of pregnancy, withdrawal of heart failure medication per se may lead to dramatic hemodynamic deterioration. It thus would be interesting to know whether the pregnant women whose medication was discontinued fared worse than those who continued to take their normal medication. It should be noted that several beta-blockers, notably labetalol, can be used safely during pregnancy. Thus, pregnancy outcome may not be quite as dismal as reported by Grewal et al. (1) when adequate therapy is provided.

Four of the 9 cases of heart failure occurred after delivery (1). Oxidative stress rises during normal pregnancy, culminating in the last trimester. Several signaling pathways have been shown to be necessary for protecting the maternal heart, including STAT3. In a mouse model, a deletion of *STAT3* caused proteolytic cleavage of prolactin into a potent antiangiogenic, proapoptotic, and proinflammatory factor associated with the development of peripartum cardiomyopathy (2). It is conceivable that peripartum oxidative stress caused additional damage to the left ventricle. In this respect, the fact that 5 women had doxorubicin-induced DCM may be relevant, because oxidative stress is deemed to play an important role in this type of DCM. It thus would be interesting to know whether Grewal et al. (1) found a difference in pregnancy outcome between the women with doxorubicin-induced DCM versus idiopathic DCM.

***Maarten P. van den Berg, MD, PhD**
Karin Y. van Spaendonck-Zwarts, MD
Dirk J. van Veldhuisen, MD, PhD

*Department of Cardiology
University Medical Center Groningen
University of Groningen
P.O. Box 30.001
9700 RB Groningen
the Netherlands
E-mail: m.p.van.den.berg@thorax.umcg.nl

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Reply

We thank Dr. van den Berg and colleagues for their interest in our paper (1), and agree that in addition to the increased hemodynamic