Second, women who were considered "nonresponders" were reportedly different from women included in the analysis. The investigators indicated that they were younger and thus more likely to harbor HPV deoxyribonucleic acid but probably less likely to present CVD than the "responders."

Third, of the 44 women with cervical cancer listed in the their Table 1 (1), 22 were HPV negative. This is not consistent with the fact that HPV is the etiologic agent for cervical cancer.

Fourth, in their Table 3, Kuo and Fujise (1) presented the odds ratios (ORs) for CVD comparing women with cancer-associated HPV types or other HPV types with those who are negative for HPV. In the first model, the OR was 2.87 for women with cancer-associated HPV types. The OR was 2.13 for women with other HPV types, namely, low-risk HPV types that are not able to induce p53 and pRB degradation. If the physiopathology hypothesis is correct, we would expect a nonsignificant OR. As for models 2, 3, and 4, we would also expect lower ORs for CVD in women with other HPV types.

Finally, the overall physiopathology hypothesis is very unlikely. Indeed, HPV fails to produce classic viremia. Rather the virus replicates locally until it is cleared by an efficient immune response. In case of viral persistence, the virus remains localized to the site of infection, and associated lesions can occur after an increased expression of E6 and E7. The virus does not disseminate throughout the body. It is therefore very unlikely that E6 and E7 have a systemic effect leading to atherosclerosis.

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Reply

We thank Dr. Prétet and colleagues for their insightful comments on our report (1). Brief, point-by-point responses provided here illuminate the need for further research on the link between human papillomavirus (HPV) infection and atherosclerosis.

First, on the basis of recent survey from the National Health and Nutrition Examination Survey 2003 to 2006, the weighted prevalence of genital HPV infection among 2,787 women was estimated to be 44.5% (2), which is close to the unweighted prevalence we reported (46.6%) (1). Using the research use–only Linear Array genotyping assay (Roche Diagnostics GmbH, Mannheim, Germany) has resulted in a higher HPV prevalence than previously reported (3).

Second, we do not know if the "nonresponders" (n = 543) were more likely to harbor HPV deoxyribonucleic acid, because they did not submit swab specimens or submitted inadequate swab specimens. The crude prevalence of cardiovascular disease (CVD) among responders and nonresponders was 2.6% and 2.2%, respectively (p = 0.612).

Third, ascertainment of cervical cancer was by self-report and may have suffered from recall bias and a certain degree of disagreement as to "true measures" of cervical cancer compared to "self-report." We reanalyzed the data for the HPV-CVD association without using self-reported cervical cancer as a covariate, and the results were the same.

Fourth, the association between other HPV types and CVD was significant in model 1 (odds ratio: 2.13; 95% confidence interval: 1.12 to 4.06) but not in models 2 to 5. Low socioeconomic status, associated with both HPV infection and CVD, is an important confounder for which we were not able to control (4).

Finally, although the mechanism by which HPV infection could promote atherosclerosis remains unknown, several possibilities exist. First, chronic local inflammation caused by HPV infection and resultant circulatory inflammatory mediators can facilitate atherosclerosis as seen in *Porphyromonas gingivalis* infection (5). Second, macrophages and monocytes (MΦ) recruited to HPV-infected tissue (6,7) can take up the virus (8), leading to the degradation of MΦ-p53 by E6 and E7. HPV-infected MΦ can then enter atherosclerotic plaques and facilitate atherosclerosis. The lack of functional p53 in MΦ facilitates atherosclerosis in mouse models of atherosclerosis (9,10). These hypotheses, although plausible, need to be experimentally tested.

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Echocardiographic Evaluation of Pulmonary Artery Pressure in Patients With Heart Failure

We read with great interest the report by Bursi et al. (1) on the prognostic value of pulmonary pressure in heart failure (HF). The investigators used Doppler-determined pulmonary artery systolic pressure (PASP), which requires an estimation of right atrial pressure by the diameter and respiratory variation of the inferior vena cava. This approach was initially followed to provide values comparable with those of right-heart catheterization. However, the almost arbitrary estimation of right atrial pressure and the use of reference values for PASP derived by right-heart catheterization worsen the reproducibility and reliability of Doppler measurements. We first identified this problem 15 years ago while studying pulmonary hypertension in beta-thalassemia, and we proposed the use of tricuspid regurgitant velocity and peak systolic tricuspid pressure gradient alone (2). To determine a reference range for tricuspid pressure gradient, we studied a group of healthy subjects and found an upper normal limit of 30 mm Hg, which corresponds to a tricuspid regurgitant velocity of 2.7 m/s (3). At present, tricuspid regurgitant velocity, with a threshold of 2.7 m/s, is the proposed method for the echocardiographic screening of pulmonary hypertension (3).

A tricky aspect in the echocardiographic evaluation of PASP in HF is the loading conditions at the time of examination (4). Patients with acute HF and lung congestion would have considerably high PASP reflecting the acutely increased left ventricular filling pressures, not the true, steady-state passive and active component of pulmonary hypertension. This parameter should be taken under consideration while evaluating patients with acute HF, and the examination should be repeated after clinical stabilization. Furthermore, it should be stressed that ejection fraction is a rough estimate of systolic left ventricular function, and this may account for the lack of association between PASP and systolic dysfunction severity observed by Bursi et al. (1).

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Reply

We thank Drs. Farmakis and Aessopos for the opportunity to clarify important aspects of the prognostic use of pulmonary artery systolic pressure (PASP) measured by Doppler in patients with heart failure (1). Although Doppler is the preferred tool to measure pulmonary pressures in practice (2), we agree that the estimation of right atrial pressure has limitations (3).

The upper limit of normal of 2.7 m/s corresponding to a peak gradient of 30 mm Hg was tested in a small group of younger (mean age 38.9 ± 12.7 years), healthy, nonsmoking subjects (4). Thus, it is applicable to similar, relatively young populations such as patients with beta-thalassemia or pulmonary arterial hypertension and when right atrial pressure is thought to be normal (5). Hence, this cutoff is of less relevance in older populations with greater comorbidity, as PASP increases with age, and patients with heart failure are elderly. Because there is no universally accepted cutoff value to define pulmonary hypertension, we analyzed the entire distribution of pulmonary pressures and analyzed PASP with tertiles or continuously, rather than applying an arbitrary cutoff. We showed that the higher the PASP, the worse the prognosis, and the estimation of right atrial pressure has no bearing on this continuum of risk.

We defined heart failure by epidemiological criteria, and our goal was not to distinguish the acute increase in filling pressures from the chronic passive or active component of pulmonary hypertension. We demonstrated that Doppler estimation of PASP was feasible in most patients (91%) in the community and that when elevated, it strongly and independently predicted outcome regardless of the mechanism of pulmonary hypertension.