Hormone Replacement Therapy and Cardiovascular Events

The matter regarding hormone replacement therapy and cardiovascular events has been the subject of multiple publications. While observational studies depicted a protection from coronary events in patients receiving hormone replacement therapy, recent randomized trials have failed to show that promising evidence. The Heart and Estrogen/Progestin Replacement Study (HERS), a randomized, blinded, placebo-controlled trial of 4.1 years in duration, and a subsequent, open-label, observational follow-up for 2.7 years (HERS II) enrolled 2,763 women with documented coronary artery disease to receive either conjugated equine estrogens (0.625 mg) and progestin medroxyprogesterone (2.5 mg) or placebo. The results of HERS demonstrated that hormone replacement therapy did not have a positive overall effect on cardiovascular outcomes, such as nonfatal infarction and mortality from coronary heart disease. A more detailed analysis of this trial demonstrated that during the first year of treatment, there was a significant increase in adverse coronary heart disease events (52% excess cardiovascular events); and during the follow-up period, including an additional 2.7 years, hormone replacement therapy did not confer any protective effects. Although the underlying mechanisms by which this may occur are speculative, a prothrombotic, proarrhythmic, or proischemic effect of hormonal replacement therapy could account for the early increased risk of coronary heart disease. These early detrimental effects, however, are steadily offset by the favorable changes in low- and high-density lipoprotein cholesterol of hormone replacement therapy, thus delaying the progression of underlying atherosclerosis. The large cohort of postmenopausal women included in HERS and the long-term follow-up have allowed the investigation of other issues that are relevant to women cardiovascular disease. Recently, a prospective substudy form the HERS cohort demonstrated that although randomization to hormone replacement did not increase the risk of heart failure, the presence of diabetes, myocardial infarction, atrial fibrillation, creatinine clearance of 40 mL/min, systolic BP of 120 mm Hg, current smoking, body mass index of 35, left bundle-branch block, and left ventricular hypertrophy were identified as strong risk factors for the development of heart failure in women. Of all the predictors, diabetes was the strongest risk factor (adjusted hazard ratio, 3.1; 95% confidence interval, 2.3 to 4.2). In the issue of CHEST (see page 1498), Nair et al report another very interesting observation from the HERS cohort. The authors examined the potential role of pulse pressure in the development of cardiovascular events in the HERS cohort. In addition, the authors explore another interesting and controversial issue: the effects of hormone replacement therapy on pulse pressure and vascular stiffness.

Pulse Pressure and Cardiovascular Events

As Mahomed wrote, “since the information which the pulse affords is of so great importance and so often consulted, surely it must be to our advantage to appreciate fully all it tells us, and to draw from every detail that is capable of imparting.” Although the study of the pulse dates back to Egypt, it was Frederick Akbar Horatio Mahomed, late in the nineteenth century, who recognized the importance of study in detail the radial pulse waveform. Utilizing a quantitative self-developed sphygmograph, Mahomed recognized the characteristics of the pulse waveform in hypertension:

The characteristic features of a pulse of high tension may be enumerated as follows: (1) a pressure above one ounce, and sometimes as high as ten ounces, is employed to develop the pulse tracing to its greatest extent; (2) the percussion wave is usually well marked and distinctly separated from the tidal; (3) the dicrotic wave is very small, and often scarcely perceptible; the vessels, however, are full during the diastolic period and collapse slowly; (4) the tidal wave is prolonged and too much sustained.

More recently, pulse waveform and indexes of vascular compliance and stiffness have been clinical and prognostic tools in patients with cardiovascular disease. For example, in patients with hypertension the combination of increased vascular stiffness and peripheral resistance produces a disproportionate increase in systolic pressure compared to mean diastolic pressure in the major central arteries, leading also to an increase in pulse pressure. The increase in systolic BP and pulse pressure has been shown to be a major risk factor for heart failure, myocardial infarction, and stroke, underscoring not only vascular stiffness as an important clinical measurement, but also as a prognostic factor for an increase in cardiovascular risk.

Several methods have been evaluated to measure arterial stiffness in humans. However, pulse pressure, as the difference between systolic BP and diastolic BP, is a simple albeit indirect and clinically relevant measure of vascular stiffness.
Pulse pressure rises markedly after the fifth decade of life due to arterial stiffening with age, as the elastic function of the aorta lessens. The rise in vascular stiffness leads to several aberrations, such as an increase in ventricular afterload and myocardial oxygen demand, impairment of ventricular relaxation, and subendocardial ischemia. Hence, the aging heart is most susceptible to left ventricular dysfunction and ischemia. Increased pulse pressure is a prognostic factor for multiple cardiovascular events in prospective cohorts. Thus, it is associated with risk of myocardial infarction and mortality for cardiovascular disease in normotensive and hypertensive populations. Higher pulse pressures in patients after myocardial infarction and left ventricular dysfunction confer a greater risk for the future development of reinfarction and cardiovascular mortality.

The role of pulse pressure as a risk factor for the development of heart failure was studied in the community based East Boston Senior Health Project. The population studied consisted of 1,621 elderly men and women (66%) without heart failure who had complete BP measurements and were followed up prospectively for 3.8 years. At baseline evaluation, hypertension was present in 54.6%, diabetes in 19.3%, coronary heart disease in 10.3%, atrial fibrillation in 2.8%, and valvular heart disease in 1.8% of the patients. Mean systolic BP was \(137 \pm 19\) mm Hg \((\pm SD)\), mean diastolic BP was \(75 \pm 10\) mm Hg, and pulse pressure was \(62 \pm 17\) mm Hg. The authors demonstrate in this cohort that for each 10-mm Hg elevation of pulse pressure, there was a 14% increase in risk of heart failure (95% confidence interval, 1.05 to 1.24; \(p = 0.003\)). Patients in the highest tertile of pulse pressure \( (> 67\) mm Hg) had a 55% increased risk of heart failure compared with those in the lowest tertile. These data support the concept that a rise in pulse pressure is a very significant risk factor for the development of heart failure.

Pulse Pressure as a Cardiovascular Risk Factor in Women

The data regarding pulse pressure as cardiovascular risk factor in women are inconsistent and somewhat difficult to interpret for several reasons, including sample size, underrepresentation of women in cardiovascular clinical trials, and other confounding factors. The results of the article reported herein add evidence to the existing literature on pulse pressure as a risk factor in women, since it analyzes the relationship between pulse pressure and cardiovascular events in HERS. The authors demonstrated that women in the highest quartile of baseline pulse pressure \( (> 70\) mm Hg) have a significantly higher of myocardial infarction or coronary heart disease death compared in women in the lowest quartile. The highest quartile of pulse pressure was associated with increased rates of hospitalization for heart failure and stroke or transient ischemic attacks. After adjusting for other confounding variables, the association between pulse pressure and myocardial infarction and coronary heart disease death was attenuated. The robust association of increased pulse pressure with heart failure support the data previously reported in the East Boston Senior Health Project, which included 66% women. Since the study did not investigate the underlying mechanisms by which this relationship may occur, the authors speculate that in the analysis of HERS, the convincing relationship between the rise in pulse pressure and heart failure can be related to the fact that the increase in vascular stiffness in heart failure is not only a marker of generalized atherosclerosis, but also a reflection of left ventricular hypertrophy, increased myocardial work, and impairment of diastolic filling.

Although clinically relevant and confirmatory, these data should be interpreted with caution. First, the population included in HERS consisted of women with underlying coronary artery disease, and therefore it should not be generalized to all women; second, the inherent limitations of pulse pressure measurement are an indicator of vascular stiffness; third, BP was not a primary outcome of HERS; and finally, there may be observational biases in the analysis of these data.

Hormonal Replacement Therapy and Vascular Stiffness

The effects of hormone replacement therapy on vascular stiffness measured by different methodologies have been investigated in several small observational and randomized studies. Similar to the controversies between observational and randomized trials evaluating cardiovascular events in women receiving hormone replacement therapy, the studies on the effects of hormonal replacement therapy on vascular stiffness have also achieved disparate results. The analysis of a non-randomized study utilizing estrogen alone and estrogen plus progestogen in 56 normotensive postmenopausal women demonstrated a decrease in pulse wave velocity; this an improvement in vascular stiffness in the hormonal replacement therapy group. Conversely, in a 2-year, double-blind, placebo-controlled, cross-over study in 34 healthy postmenopausal women randomized to transdermal estrogen alone (50 \(\mu g\)) or placebo, there was no improvement in BP, lipid profiles, or...
vascular stiffness, compared with placebo, suggesting that there might not be a beneficial effect of transdermal hormone replacement therapy on the vasculature in postmenopausal women. Another 2-year randomized trial\textsuperscript{25} of 99 perimenopausal women utilizing oral 17\(\beta\)-estradiol and desogestrel (17\(\beta\)E[2]-D), conjugated equine estrogens and norgestrel, and placebo failed to demonstrate an improvement in arterial compliance after 6 months and 24 months of follow-up. Whether differences in study populations, the presence of diabetes, hypertension, race or type dose, and duration of hormone replacement therapy are the culprit for the disparate effects on vascular stiffness observed in the above-discussed trials is a matter of debate but it seems unlikely.

In HERS, hormone replacement therapy caused a small but significant increase in BP due to an increase in systolic BP. In addition, this difference in pulse pressure between the hormone replacement therapy and the placebo groups was not affected by other comorbidities, such as heart failure and diabetes. To the best of our knowledge, even with the limitations of this analysis, these results are the first to demonstrate in a large number of women with coronary artery disease that hormone replacement therapy does not improve vascular stiffness and perhaps may be deleterious. Future trials are needed to confirm these results.

**FUTURE IMPLICATIONS**

This valuable observation in postmenopausal women obtained from the HERS cohort lends support to the value of an increase in pulse pressure, a measure of vascular stiffness, as a significant predictor of cardiovascular events. Women randomized to hormone replacement therapy had an increase in vascular stiffness compared to women in the placebo group. It will be important in the future not only to confirm these results but also to investigate in large clinical trials the potential utilization of pulse pressure as a therapeutic target in men and women with cardiovascular diseases. Furthermore, it will be also essential to explore the underlying mechanisms, including the particular contribution of hormone replacement therapy, by which vascular stiffness occurs in women. Studies\textsuperscript{1,26} have suggested that components of the renin-angiotensin system, matrix metalloproteinases, intracellular signaling, and extracellular matrix may be implicated in increasing vascular stiffness. Interventions intended at these targets may reduce vascular stiffness and may improve outcomes for men and women with cardiovascular diseases.

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Severe Pulmonary Hypertension in COPD

Is It a Distinct Disease?

Pulmonary hypertension (PH) is frequently observed in patients with advanced COPD as a consequence of chronic alveolar hypoxia. In patients with respiratory disease, PH is generally defined by a resting mean pulmonary artery pressure (PAP) measured in the recumbent position of > 20 mm Hg. This definition is slightly different from that of idiopathic pulmonary hypertension (resting PAP, > 25 mm Hg), but the latter has been adopted for all forms of PH following the World Health Organization meetings held in Evian, France, in 1998 and in Venice, Italy, in 2003.

It is recognized that one of the main characteristics of PH in COPD patients is its mild-to-moderate degree, with a resting PAP in a stable state of the disease usually ranging between 20 and 35 mm Hg, which is very different from the levels observed in patients with thromboembolic or idiopathic PH in whom PAP is most often > 40 mm Hg and may exceed 80 mm Hg in some patients. In an earlier study from our group, PH (PAP > 20 mm Hg) was present in 62 of 175 patients with moderate-to-severe COPD (mean [± SD] FEV₁, 1,230 ± 470 mL), and the mean PAP of these 62 patients was 27 ± 6 mm Hg, which indicates a mild level of PH. In 120 patients who were evaluated for participation in the National Emphysema Treatment Trial, Schaar et al observed that only 6 patients (5%) had a PAP > 35 mm Hg. Our group has reported that 27 of 998 stable COPD patients who were investigated from 1990 to 2002 had severe PH, which was defined by a PAP of > 40 mm Hg, and only 11 patients (1.1%) had COPD as a unique cause of their PH. Thus, a resting PAP of > 35 to 40 mm Hg is unusual in COPD patients except when they are investigated during an acute exacerbation or when there is an associated cardiopulmonary disease, such as left heart disease, collagen vascular disease, or obesity-hypventilation syndrome.

In this issue of CHEST (see page 1531), Thabut and colleagues confirm the uncommonness of severe PH in patients with advanced COPD. They investigated 215 COPD patients by right heart catheterization, candidates for lung volume reduction surgery or lung transplantation, and who were observed that the occurrence of moderately severe PH (35 to 45 mm Hg) and severe PH (> 45 mm Hg) was rather infrequent, occurring in 9.8% and 3.7% of the patients, respectively. Of higher interest, they have individualized by statistical analysis (“cluster” analysis) a particular subgroup of 16 “atypical” patients (7.4%) who were characterized by a moderately severe bronchial obstruction (mean FEV₁, 48.5 ± 11.8%) contrasting with severe PH (mean PAP, 39.8 ± 10.2 mm Hg) and profound hypoxemia (mean PaO₂, 46.2 ± 15.7 mm Hg), but without hypercapnia (mean PaCO₂, 39.7 ± 10.9 mm Hg). The atypical patients were less severely obstructed than the remainder, more hypoxic, and less hypercapnic, and, indeed, their PAP was markedly higher (see Table 3 of the article by Thabut et al). None of these patients had a right-to-left shunt identified on a lung perfusion scan.

Thabut et al propose that this small subgroup represents a subset of COPD patients in whom pulmonary vascular disease is predominant. They emphasize the fact that Schaar et al failed to identify such a subgroup, which could be explained by the exclusion criteria of the National Emphysema Treatment Trial study with regard to arterial blood gas levels (patients with PaO₂ < 45 mm Hg could not be included). On the other hand, the 11 patients in our own study with COPD as a unique cause of severe PH were very similar to the “atypical” subgroup of Thabut et al, with the following mean values: FEV₁, 50% predicted; PaO₂, 46 mm Hg; PaCO₂, 32 mm Hg; PAP, 48 mm Hg; and alveolar-arterial pressure dif-