



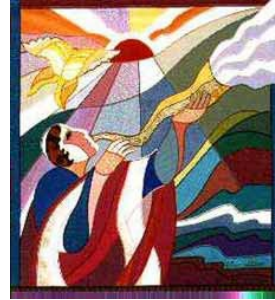
# *The Heart Institute Newsletter*

Volume 8, N<sup>o</sup>.1  
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## *Message from the Head of The Heart Institute*



To all our friends



Best wishes for a  
Happy and Healthy New Year

Dear friends and supporters,

The Jewish New Year is always an opportune time to reflect on our accomplishments of the passing year and to look towards the future.

The new Sarah Wetsman Davidson Tower continues to rise, diagonally across from our building, and we watch the progress with great anticipation. Last month I had the honor to be invited to a wonderful social event celebrating the Tower progress, at Stony Creek Ranch, the home of Karen Davidson, in Aspen Colorado. I was very touched by the warm expressions of commitment from those attending this gathering.

One of the topics pointed out to me by my fiends there – old and new – as “hot” is the issue of Women and Cardiology. In recent years it has become clear that many aspects of cardiology are gender-oriented, and cardiology professionals as well as women everywhere must focus on these differing needs in care. In this issue of our Newsletter Dr. Donna Zfat of our Echocardiography Unit gives an overview of female cardiology.

On the eve of the new Jewish year, I would like to express to you, all our friends and the extended Hadassah family, our deepest appreciation of your continuing interest and support, as well as best wishes for a happy, healthy and peaceful New Year.

As always, we welcome your comments, questions and contributions to our newsletter.

You are also warmly invited to visit us virtually on our website, at

[http://www.hadassah.org.il/English/Eng\\_SubNavBar/Departments/Medical+departments/Cardiology](http://www.hadassah.org.il/English/Eng_SubNavBar/Departments/Medical+departments/Cardiology) .

Shalom and Shana Tova,

*Professor Chaim Lotan*

Our Heartfelt Condolences  
to the family  
on the passing of  
our friend and supporter  
**Mr. Paul Milstein**

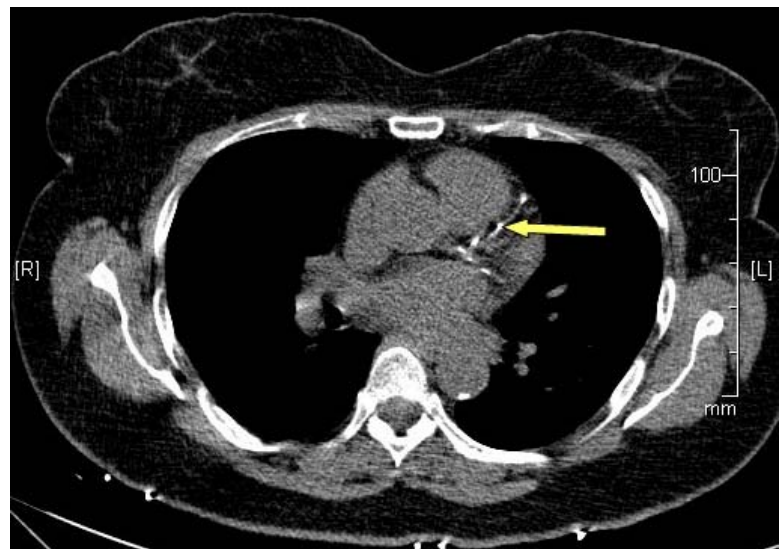
# Women and Heart Disease

Donna Zwas MD

The female heart is approximately 2/3 the size of the male heart, with smaller coronary arteries. Unfortunately, heart disease in women is by no means a “smaller” problem: more women than men suffer from heart disease. American women are 6 times more likely to die of heart disease than of breast cancer, and heart disease kills more women over age 65 than all cancers combined. Because women tend to develop heart disease 10 years later than their male counterparts, heart disease has traditionally been thought of as a “male” disease. But over 500,000 American women died of heart disease last year, and 435,000 suffered heart attacks. World-wide, 8.6 million women die of heart disease each year. It is important to note that heart disease is not just an important in older women. Ischemic heart disease is the number one killer of women of all ages, with annual mortality rates that affect more women under the ages of 35, 45, and 55 years than breast cancer.

The more we study heart disease in women, the more apparent it becomes that the female heart is not just a smaller version of the male heart. Women appear to have more diffuse atherosclerosis of the heart vessels, whereas men develop focal regions of narrowing. In one autopsy study of 83 patients, younger men and older women had more acute lesions than their gender counterparts in those age groups. In the men, active disease developed in the fourth decade of life, and plateaued in the sixth decade. In women, there was much less active disease in the fourth and fifth decades, but after menopause, the disease process accelerated, reaching a maximum in the eighth or ninth decades. Women had more extensive overall disease involvement of the coronary tree, although the overall plaque burden in men was greater.

Cardiac CT of a 60 year-old woman with hypertension and hypercholesterolemia, demonstrating diffuse coronary disease and coronary calcification (arrow). For any given degree of coronary calcification, women have a poorer long-term prognosis than men.



Arteries and smaller vessels display a greater degree of abnormal responsiveness in women compared with men. Perhaps because of the diffuse nature of the disease and this abnormal vessel reactivity, for any given extent of coronary artery disease, women are more symptomatic and have more unstable symptoms than men. Also, despite having less of what is called “obstructive” coronary artery disease, a nationwide US registry of 835,827 patients reported a consistently higher in-hospital mortality for stable and unstable chest pain for women compared with men.

When women do develop heart attacks, the mechanism is frequently different. Men tend to develop “plaque rupture”, where a tear in fat and cholesterol-laden plaque leads to sudden occlusion of the artery. Women tend to develop the more subtle but more dangerous

heart attacks called non-ST-elevation myocardial infarctions. Because women presenting with unstable symptoms are more frequently not found to have obstructive lesions, they don't have the opportunity to benefit from repair of those arteries by stents or bypass surgery. In women who do undergo revascularization, long-term outcomes are similar to those in men – even though the fact that they have less extensive and severe obstructive coronary disease and better overall heart function should portend a better outcome.

The differences described above may account for the differences in symptoms between men and women when they develop a heart attack. In retrospect, almost all women have symptoms prior to having a cardiac event, but frequently it is not the typical “chest pain radiating to the left arm”, so that they frequently go undiagnosed. In one study of 515 women who had an acute heart attack the most frequently reported symptoms were unusual fatigue, sleep disturbances, shortness of breath, indigestion and anxiety. Seventy-eight percent of women reported at least one symptom for more than one month before their heart attack, but only 30% reported chest discomfort! Even when they do describe chest discomfort, it is not what is considered “typical” angina; rather, women reported aching, tightness, pressure, sharpness, burning, fullness or tingling. These less classic symptoms create a challenge for the treating physician, who may not attribute what sounds like a gastrointestinal or musculoskeletal complaint to the heart. This may account for the fact that in women, in approximately 60% of cases the initial presentation of ischemic heart disease is heart attack or sudden cardiac death. There is also evidence that women themselves do not attribute their symptoms to heart disease, and may delay seeking medical attention for 3 or more hours, which affects the size and severity of a heart attack. Women's delay time is associated with depression and taking pain-killers. They also reported a need to put the needs of others before their own.

Differences between men and women are not limited to the coronary arteries. Women's hearts beat more quickly than men's hearts, and there are multiple differences in the myocardial cellular membrane in terms of the channel proteins that control the rhythms of the heart and the susceptibility to irregular heart rhythms. The syndrome known as congestive heart failure also differs between men and women. Heart failure is a condition marked by the inability of the heart muscle to pump enough blood to the body's tissue, and can occur even if the heart contractility is preserved. Heart failure tends to affect women at an older age, and they tend to have preserved heart function.

Often, the cause is hypertension or valve disease, rather than coronary artery disease. Women survive longer with heart failure than their male counterparts, but they tend to have a lower quality of life. This may result from greater physical limitations, more hospitalizations, and more cases of depression.

Heart valve disease also differs between men and women. More than 60 percent of heart valve replacement procedures are performed in women. In rheumatic valvular disease, women's valves tend to become narrowed and restricted, whereas men develop leaky valves. In mitral valve prolapse, the most common form of valve disease, one or both of the mitral leaflets bulge backward into the left atrium, in some cases preventing the valve from closing properly. Although men and women are affected by mitral valve prolapse in equal numbers, men with prolapse are far more likely to require surgical treatment. As people age, valves may become calcified and narrowed. When this occurs to the aortic valve, there are also differences between men and women, as the hearts of women with aortic stenosis are more hypertrophied (thickened) and have better contractile function than those of men with this disorder. There are also differences in the valve itself that are mediated by the estrogen receptor. (See the Research Center portion of this edition for our laboratory's contribution to this topic).

The mechanisms of sex differences in this process are not well understood. Much of the attention has been focused on estrogen and progesterone, the female hormones, and on testosterone, although significant differences between men and women persist far into menopause. Here at Hadassah, we are exploring the impact of differences in the estrogen receptor on coronary disease in women. In fact, the biological basis of gender difference is far more complex than simply the presence or absence of hormones. Women have 2 x chromosomes, and more than 1000 genes reside on the x chromosome, including several involved in the inflammatory process. Women suffer to a greater degree from inflammatory syndromes such as auto-immune diseases, and the inflammatory and auto-immune diseases are associated with an increased risk of atherosclerotic heart disease. On the other hand, women have some innate anti-inflammatory mechanisms. Inflammatory cells from female coronary disease patients have a higher content of PPAR- $\gamma$  proteins, which are proteins that may have protective anti-atherosclerosis effects by decreasing the inflammatory activity. Higher levels of PPAR- $\gamma$  are associated with lower levels of pro-inflammatory proteins (cytokines). There are also differences between men and women mediated by bone marrow "progenitor cells," which are cells that are recruited by injured tissue to migrate to locations where there is inflammation and assist in the local repair process. Women have higher numbers of these cells, and they may incorporate into tissues differently. With aging and chronic disease, the number and efficacy of these cells decrease.

Other factors may also play a role. There are recent reports regarding an enzyme called glutathione peroxidase, which is a potent anti-oxidant. Premenopausal women have much higher levels of this enzyme than men of the same age, and the risk of cardiac events is inversely correlated with levels of this enzyme. As women enter the eighth decade, blood levels of this enzyme drop to the male levels. Trials of orally administered anti-oxidants, however, have not been shown to be of benefit.

Not only do women differ in the disease process, they also differ in their responses to therapy. Many therapeutic drugs affect men and women differently, and women tend to suffer more side effects from medications. Biological factors that may affect drugs in the body include differences in body weight, body fat, and gender differences in stomach emptying, acid levels and digestive enzymes. Furthermore, there are differences in the levels of certain enzymes in the liver which are involved in metabolism, and differences in kidney function. Women also suffer more complications from procedures, both from placement of coronary stents and from bypass surgery. Over the last 2 decades, techniques have improved, and the rates of complications are approaching those in men.

In conclusion, cardiovascular disease is the number one killer of women and of men. Important gender differences exist in cardiovascular disease that affect disease onset, diagnosis, and treatment. Atherosclerosis is qualitatively and quantitatively different in women and men; other forms of heart disease differ across gender as well. Unfortunately, we do not yet have an understanding of the mechanisms that account for these gender differences. Further research, including research in our basic science laboratories at Hadassah, is underway to examine sex-specific processes, and to develop novel therapies including new devices, tissue engineering, pharmacotherapies and stem cells, so as to improve outcomes in both women and men.

While research is ongoing to try to understand processes and to search for better diagnosis and therapy options, risk factor reduction is of paramount importance to improve outcomes in women as well as in men.

## *?? Questions and Answers: ?? Cardiac Syndrome X*

Q: What is Cardiac Syndrome X (CSX)?

A: Cardiac Syndrome X is a condition in which the patient experiences the pain of angina – a squeezing, suffocating or burning feeling in the chest – without having coronary artery disease (blockage of one or more coronary arteries). A blocked coronary artery will show up on a coronary angiogram or on a cardiac CT, but patients suffering from CSX will have a normal angiogram or cardiac CT.

Q: What causes CSX?

A: The name “Cardiac Syndrome X” comes from “x” symbolizing unknown – for many years, the name simply referred to angina of unknown origin. In fact, many female patients were told by their doctor that the complaint was related to low levels of estrogen (postmenopausal), enhanced pain perception, or even simply anxiety or hypochondria. However, research has shown that CSX is most likely caused by microvascular angina – constriction of capillaries (the smallest blood vessels) in the heart. This constriction reduces the blood flow in the heart, causing pain. These capillaries are so tiny, they cannot be detected on angiography.

There are quite a few mechanisms that can lead to microvascular dysfunction, so the syndrome may well be multifactorial.

Q: Is CSX a women’s disease?

A: CSX is much more common in women than in men, and especially in women near or after menopause, but it is not exclusive to women.

One theory is that women are more prone to CSX than men due to the changing level of the hormone estrogen in their bloodstream – first during regular menstrual cycles, and later during and after menopause. Estrogen affects the blood vessels – how they narrow and widen, and how they respond to injury – and the normal, relatively frequent fluctuations in estrogen level in women might make their blood vessels more susceptible to damage to the lining of the arteries and the smooth muscles in the arterial walls.

Q: How is CSX diagnosed?

A: Basically, the diagnosis is one of exclusion – once tests have been performed to exclude coronary artery disease, valvular disease, musculoskeletal problems, vascular dysfunction, throat problems, coronary artery spasm, hypertension, and perhaps psychological disorder, a diagnosis of CSX will likely be made.

Q: What is the treatment for CSX?

A: There are several types of anti-anginal medications, targeting reduction of oxidative stress in the blood vessels - including nitrates, beta-blockers, calcium-channel blockers, potassium-channel activators, statins and ACE-inhibitors. Individual patients will often respond to one medication and not another, so treatment must be on a trial-and-error basis. In addition, conjunctive therapies such as endurance exercise training and cognitive behavioral therapy have been shown to help in some cases.

Q: Can CSX be prevented or cured?

A: Until there is a better understanding of the syndrome, the answer is no.

However, it is always a good idea to maintain a healthy lifestyle – no smoking, being physically active and maintaining a good body weight, eating properly - and make sure that cholesterol, blood pressure and glucose levels are normal.

## *News of The Heart Institute*



We are pleased to welcome back to our Heart Institute Dr. Ronen Durst, one of the young cardiologists who trained at Hadassah, after 4 years of clinical and research fellowship at the Massachusetts General Hospital where he trained in advanced cardiac imaging, practicing new cardiac imaging modalities such as cardiac CT and cardiac MRI (which will be implemented in Hadassah in the very near future). Dr. Durst also carried out research on genetics of cardiovascular diseases at Harvard's Center For Human Genetic Research, and will continue his research in Hadassah.

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### *From our Cardiovascular Research Center Breast cancer therapy and cardiovascular damage*

Breast cancer is a disease affecting a large number of women worldwide. About a quarter of the women affected have a special marker on their cancer cells called ERB2, and therefore get treated with a medication called Trastuzumab (Herceptin®) that blocks these molecules and thus kills the cancer cells. This treatment is very effective and helps achieve cure or remission in many patients. Unfortunately, about 25%-30% of the patients treated with Herceptin will develop damage to the heart muscle.

Our Cardiovascular Research Center became interested from its inception in the reasons for cardiac muscle damage induced by this life-saving treatment. In a study, funded by the Hadassah Women's Health Research Fund and the Israel Cancer Association, we have managed to demonstrate in mice, using also modern techniques called "gene arrays", that Herceptin indeed blocks a critical pathway in heart cell survival, and thus prevents cell response to stresses. The cell dies in a mechanism called apoptosis or "programmed cell death" when it is exposed to such stresses.

This study has been published in the prestigious journal Breast Cancer Research, and is one of the most accessed articles in this journal. This research serves now as a basis for an ongoing project, in cooperation with a group in the Hebrew University, that investigates this mechanism on the gene activation level.

*To All Our Friends and Supporters*



*The entire Heart Institute staff  
Wishes you a very Happy and Healthy  
New Year*

**שנה טובה  
טובה**