Biomedicine

Kathy A. Fackelmann reports from New Orleans at the American Heart Association's scientific sessions

Early glimmerings of heart disease

An experimental method of detecting abnormalities in blood vessel function may someday help physicians identify and treat people with very early coronary artery disease.

Scientists don't know precisely how coronary artery disease begins, but most believe it involves damage to the endothelium, the inner lining of blood vessels, which plays a key role in the vessels' ability to contract and relax. Some suggest the disease starts when sections of the vessels lose their ability to regulate dilation and constriction. These sections tend to constrict, accumulating cholesterol and other fatty deposits that can narrow them further. Called atherosclerosis, the condition can lead to a heart attack.

Joseph A. Vita at the Harvard Medical School in Boston and his colleagues studied 34 people who had no detectable evidence of clogged arteries as measured by angiography, an X-ray examination of the blood vessels that allows doctors to visualize plaque buildup. Despite the normal test results, all of these patients had experienced chest pain or other symptoms that had led their doctors to suspect the beginnings of coronary artery disease.

The Boston researchers gave each patient an injection of acetylcholine, a substance produced by nerve cells that causes healthy coronary arteries to dilate. Of the 34 patients, 18 responded to this test with a narrowing, rather than opening, of blood vessels. Looking back at the subjects' medical histories, the researchers found that patients whose arteries constricted in response to the injection tended to have more heart disease risk factors, such as high blood cholesterol or a family history of the disease, than did those who responded normally.

Vita says the abnormal test response may represent the glimmerings of atherosclerosis that go undetected in routine tests such as angiography. Alternatively, problems with vessel dilation may precede plaque buildup, he says. The Boston team plans to follow the 34 to see which individuals go on to develop full-blown coronary artery disease.

Vita and his colleagues are also investigating the acetylcholine test as a way to help identify heart transplant patients who will get advanced atherosclerosis. Some heart transplant patients develop a rapid accumulation of debris on their vessel walls, and thus face a high risk of heart attack. Preliminary results from this study suggest that acetylcholine can help predict which transplant patients will go on to develop atherosclerosis.

Although the test is too costly and invasive for use in screening the general population, Vita's research may lead to a practical method of identifying the first signs of heart disease in especially high-risk patients, comments Suzanne Oparil of the University of Alabama at Birmingham. The findings could even lead to treatment aimed at preventing coronary artery disease, she adds.

Treatment-oriented research is already underway. Vita's group is currently using the acetylcholine test to see whether a fish oil regimen would improve the constricted vessels' ability to dilate. In a preliminary study, the scientists put eight patients with narrowed coronary arteries on a six-month regimen of fish oil. Prior to treatment, all eight had vessels that constricted after acetylcholine injection. After treatment, six showed vessel dilation in response to the injection. These results suggest fish oil can improve the vessels' ability to relax, Vita says.

Scientists can't say exactly how fish oil would improve arterial tone, but Vita suggests it may stimulate endothelial cells to release endothelium-derived relaxant factor, a substance that normally causes blood vessels to dilate. Animal research suggests diseased coronary arteries don't produce enough of this substance, he says.

Chemistry

Making bigger, better crystals . . .

On Earth, trying to get proteins or other large molecules to settle into a crystal is like trying to fill a football stadium by letting everyone rush in at once to choose their own seats: You end up with a scattering of empty places, says crystallographer Charles E. Bugg of the University of Alabama at Birmingham. But in the near-zero gravity of space, the molecules line up single-file, seating themselves side by side on the surface of a growing crystal.

Microgravity conditions enabled three protein crystals on the September 1988 space shuttle flight to grow bigger and more uniformly than similar ones grown on Earth, yielding new information about their molecular structure, Bugg and his colleagues report in the Nov. 3 SCIENCE.

Scientists try to discern the structure of molecules by forming them into crystals, bouncing X-rays off them and analyzing the pattern and strength of the reflected rays. But Earth's gravity creates a subtle turbulence in protein solutions as they precipitate, marring the crystal structure. Bugg's team arranged to crystallize 11 proteins in space using double-barreled syringes that slowly extruded and mixed a protein solution and a precipitating agent into a chamber lined with absorbent material. After the shuttle touched down, the scientists used X-ray diffraction to compare the space-grown crystals with Earth-grown controls.

Six proteins formed crystals too small to analyze; difficulties on Earth prevented the analysis of two others. Bugg says the researchers have harvested plenty of new data from the remaining three: porcine pancreatic elastase (a pig enzyme similar to one that damages lung tissue in leukemia patients); isocitrate lyase (an enzyme in nematodes); and gamma interferon (a protein that stimulates the immune system). On future flights, researchers will try to crystallize reverse transcriptase, an enzyme in the AIDS virus.

. . . and self-assembling chemical parts

Sicily once was known as Trinacria, a name legendarily ascribed to the island's three-pointed shape. Trinacria's emblem – a human head with three legs fanning out symmetrically like a pinwheel – reflected this configuration. Now, British and Italian researchers say they have assembled a large, three-pronged molecule that resembles Trinacria's emblem, using a powerful new strategy of chemical synthesis. They call the molecule trinacrene.

In the September international edition of the West German journal ANGEWANDTE CHEMIE, the researchers describe the procedure, known as structure-directed synthesis, as a sort of "precision molecular LEGO," in which selected molecular pieces snap together according to the chemical constraints, or "pegs," inherent in those pieces. Chemists J. Fraser Stoddart and Peter R. Ashton of the University of Sheffield and coworkers at the University of Whiteknights in Reading and the University of Messina, Italy, report making trinacrene in two steps using two readily available starting chemicals. One chemical, called a bisdiene, contains several sets of double bonds, each of which could free up a bond for linking with an appropriate chemical suitor. With three lobes that can each react with available bonds, the other cloverleaf-shaped reactant makes a perfect suitor.

In the first step of the reaction, separate bisdiene molecules connect to each lobe of the cloverleaf molecule to form an open, three-pronged intermediate. This leaves each bent prong tipped with a pair of double bonds, creating a structure strategically arranged to accept another cloverleaf component. In the second and final step, the researchers add more of the cloverleaf-shaped reactant to the intermediate to cap the awaiting prongs.