READERS' COMMENTS

Coronary Plaque Composition: Multifactorial Contribution

We read with interest the report by Qian et al[1] describing the effects of age and gender on virtual histologic assessment of coronary plaque composition. Although the question being addressed is of potential interest, a number of important confounders are not detailed, making interpretation of the analysis difficult. This includes no reporting of the prevalence of unstable and stable coronary presentations in each group; differences in medications, including statins, between groups; and differences in cardiovascular risk factors between groups. Some or all of these factors are known to affect plaque composition and, if disproportionately present in the analyzed groups, could skew the analysis, leading to either important differences being missed or incorrect interpretations of observed differences.

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Multi-Plane Three-Dimensional and Four-Dimensional Echocardiography Against Multi-Slice Computed Tomography and Magnetic Resonance Angiography

I read with great interest the report "Usefulness of Live Three-Dimensional Transesophageal Echocardiography in a Congenital Heart Disease Center" by Baker et al[1] in a recent issue of *The American Journal of Cardiology*. The investigators studied 27 cases, consisting of 16 interventional catheterizations, 4 intraoperative studies, and 7 diagnostic evaluations using 3-dimensional transesophageal echocardiography at a tertiary congenital heart disease center. All patients except 1 were successfully examined with adult-sized probes without general anesthesia, although the congenital defects examined were not complex as in interatrial defects.

The diagnosis of congenital heart defects needs special attention and experience in cardiology and radiology. For the diagnosis of congenital heart disease, various imaging tools have been used, including invasive (cardiac catheterization), semi-invasive (computed tomography [CT], multislice CT), and noninvasive (echocardiography, magnetic resonance imaging [MRI]) imaging. All have advantages and disadvantages. Its invasive nature, use of ionizing radiation, and use of contrast agents are major disadvantages of catheterization. Ionizing radiation and contrast agents are also negative features of CT and multislice CT. Long process times, claustrophobia, and the exclusion of patients with cardiac pacemakers or implantable cardioverter-defibrillators are disadvantages of MRI. Intra- and interobserver variability, inexperienced sonographers, and relatively poor temporal and spatial resolution compared with radiologic tools are disadvantages of echocardiography. Recently, new technologies, such as multislice CT and MRI with high spatial and temporal resolution, have been increasingly used for congenital heart diseases.[2,3] However, echocardiography should be the initial diagnostic tool, because it is inexpensive and reproducible and demonstrates cardiac function in real time. The localization, relation to adjacent structures, and function of congenital heart defects can be demonstrated on echocardiography. Especially with multiplane and 3-dimensional devices (3-dimensional and 4-dimensional echocardiography), anatomic relations and localization can be better defined.[4] The application of this technology to the transesophageal field has expanded the usefulness of echocardiography for diagnostic and interventional purposes.[1]

In conclusion, 3-dimensional and 4-dimensional echocardiography, either transthoracic or transesophageal, should be the initial tool for diagnosis and intervention in congenital heart diseases. In case of insufficient diagnosis, other radiologic methods, such as multislice CT and MRI, can be used.

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Seasonal Variation in Lipids: Should We Consider It More?

We read with interest the report by Tung et al,[1] describing seasonal variation in the lipid status of a cohort of patients enrolled in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE-IT–TIMI-22) study. The investigators found no differences in lipid levels at baseline, but with treatment, low-density lipoprotein (LDL) cholesterol levels were significantly higher in winter than in summer (+6.25% and +9.7% in the pravastatin and atorvastatin groups, respectively, $p < 0.001$ for each), whereas high-density lipoprotein cholesterol was higher in summer than in winter (+4.87%, $p < 0.001$). Moreover, the achievement of optimal LDL cholesterol levels was significantly higher in summer than in winter (+4.87% and +7.69% in the pravastatin and atorvastatin groups, respectively). A slight seasonal variation in blood lipid levels, characterized by a peak in winter and a trough in summer (with amplitude values of 1.8% and 2.5% of the average cholesterol levels, respectively) was also reported by Ockene et al,[2] in a cohort of 517 younger and healthy volunteers. However, a particularly interesting finding from this study was that subjects with cholesterol levels ≥240 mg/dl showed a higher relative increase in winter, especially women (47% vs 7% in men), and about 22% more subjects showed total cholesterol values ≥240 mg/dl in winter rather than in summer. Thus, the hyperlipemic effect in winter seems to be more pronounced in women only at a younger age (average 48 years), and this could be taken into account in considering that better achievement of LDL cholesterol levels in summer was obtained by Tung et al[1] in a mostly male (78%) and relatively older (58 years) population. Moreover, Tung et al[1] did not indicate in their report whether the female subgroup exhibited the same temporal pattern as men. The seasonal variation of cholesterol, more pronounced in subjects with active coronary disease treated with statins, might open further questions. Evidence has accumulated demonstrating that the onset of acute myocardial infarction is not randomly distributed over time but follows a seasonal pattern characterized by a winter peak. Data from the Second National Registry of Myocardial Infarction reported about 53% more cases in the winter than in the summer, and winter was also characterized by a peak in the rate of fatal cases (9%).[3] A previous single-center study from our group reported a 16% excess of acute myocardial infarctions in winter compared with summer ($p = 0.007$),[4] and a further larger study conducted on the database of the Emilia-Romagna region of Italy[5] (>64,000 infarctions from 1998 to 2006) confirmed the seasonal winter pattern of hospitalizations for acute myocardial infarction (+11% in winter vs summer).[5] Interestingly, the significant peak in January was found for total cases, fatal cases (death during hospitalization), and cases occurring in women. Thus, taking into account that a 1 mmol/L (39 mg/dl) cholesterol reduction has been associated with a 12% decrease in all-cause mortality and 19% decrease in coronary mortality,[6] the data reported by Tung et al[1] deserve close attention.

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QRS Fragmentation in Patients With Repaired Tetralogy of Fallot

Advancements in surgical strategies for patients with tetralogy of Fallot (TOF) have had a significant impact on their survival; the long-term survival rate (over a mean follow-up period of 25.5 years) has increased to almost 90%.[1] Nevertheless, clinical events such as life-threatening arrhythmias and sudden cardiac death are known to occur in this population. Potential risk factors for such outcomes include delayed intracardiac repair, increased right ventricular systolic pressure, severe pulmonary regurgitation, ventricular dysfunction, transannular right ventricular outflow tract patch, frequent ectopics, and increased cardiopulmonary bypass time. However, the anatomic modifications and remodeling secondary to the corrective surgery, mechanical events such as ventricular dilatation and stretch,[2] damage of impulse-generating and impulse-conducting tissue because of surgical incision, cannulation or suture,[3] and the presence of areas of fibrotic tissue around infundibular resection and interventricular patches proved by imaging studies all point to the anatomic substrate for abnormal depolarization and repolarization prone to ventricular arrhythmias and sudden cardiac death.

In a recent issue of *The American Journal of Cardiology*, Tzemos et al[4] showed that QRS duration was associated with abnormal intra- and interventricular mechanics and may explain the adverse outcomes in patients with corrected TOF. Traditionally, electrocardiographic parameters, including right bundle branch block, left-axis deviation, left anterior hemiblock,[5] QT dispersion, and QRS duration, have been studied as independent predictors of clinical outcomes in patients with TOF. Although some studies have shown contradictory results,[6] QRS duration has evolved as a more reliable predictor.[7]

Fragmented QRS (FQRS) is the alteration of QRS morphology leading to a terminal conduction delay or a fragmentation of QRS complexes on 12-lead electrocardiography and has been associated with myocardial electrical instability. FQRS has been proved to be an independent predictor of cardiac events in patients with coronary artery disease.[8] The arrhythmic substrate in TOF has been likened to postinfarction scar-related ventricular tachycardia.[9] Hence, it is reasonable to postulate that there may be a stronger correlation between the presence of FQRS and ventricular dyssynchrony and dysfunction in patients with corrected TOF, and FQRS on 12-lead electrocardiography might be a better predictor of adverse clinical outcomes in these patients. The ability of FQRS to be observed on routine 12-lead electrocardiography makes it a powerful tool of prediction. Because right bundle branch block pattern is almost always seen in patients with TOF, the presence of FQRS may be seen in >2 contiguous leads, and the number of leads showing FQRS may correlate with the extent of electrical instability and may be associated with left ventricular dysfunction and dyssynchrony. Therefore, FQRS may be a better predictor, independently or in combination with QRS duration, of adverse clinical outcomes in patients with repaired TOF, and further studies are warranted.

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