Images in Cardiovascular Medicine

Coronary Bones

Gregor Leibundgut, MD; Philippe Brunner, MD; Annekathrin Mehlig, MD; Michael Ammon, MD

After out-of-hospital resuscitation, a 65-year-old hyperlipidemic patient with a history of smoking was brought to our hospital for early revascularization of an ST-segment-elevation myocardial infarction. Left ventricular function was found to be severely impaired with anterolateral akinesia by transthoracic echocardiography. Coronary angiography showed heavily calcified subtotal stenosis of the proximal left anterior descending and the left circumflex arteries. Immediate percutaneous coronary intervention was performed with stent placement in both affected vessels. Coronary blood flow was fully restored, and the patient was referred to our intensive care unit. Experiencing severe brain damage despite early hypothermia treatment, the patient died 48 hours after percutaneous coronary intervention. Autopsy revealed a large acute anterolateral myocardial infarction including both papillary muscles. On histopathologic examination, cross-sections through the corresponding coronary arteries showed a large atheroma with negative remodeling, formation of mature lamellar bone including fatty bone marrow, and capillary neovascularization within the media of the vessel wall. Bone formation per se was not the main cause of lumen narrowing; however, it directly reflects late atheroma progression and plaque burden. No acute plaque rupture was found in the available cross-sections. The definite mechanism for the large myocardial infarction remains uncertain.

Intimal Calcific Atherosclerosis With Enchondral Ossification

Vascular calcification has long been thought to represent a passive precipitation of calcium phosphate crystals within the vessel wall and is now recognized as an organized pathobiological process sharing many similarities with bone development and metabolism. Accumulation of oxidation-specific epitopes, such as minimally oxidized low-density lipoprotein and oxidized phospholipids, and cytokines, such as tumor necrosis factor-α and interleukin-6, in the subendothelial space of arteries, as well as mechanical and proinflammatory metabolic factors found in atheromatous plaques, represent the initiating process. Subpopulations of endothelial, mesenchymal, and hematopoietic cells become attracted to the lesion and deposit calcium in an attempt to resolve the inflammation in the vascular wall. Activation of osteogenic regulatory genes eventually promotes ectopic ossification and matrix calcification. The origin of vascular calcifying cells remains controversial and may be of both resident cells in the vasculature, as well as of osteogenic progenitors recruited from the circulation. Bone marrow–derived cells infiltrate the plaque via vasa vasorum from the adventitia or directly from the circulation on the luminal side. Circulating vascular smooth muscle cells reprogram their lineage toward osteochondrogenesis and contribute to intimal calcification. Once osteochondrogenic cells are established, mineralization proceeds within the extracellular matrix as a result of a complex and tightly regulated process orchestrated by vascular smooth muscle cells that shares many similarities with the mechanism of calcification in bone. Many common regulatory factors between orthotopic bone formation and extraosseous calcification of atherosclerotic lesions have been identified and described in detail. Apoptotic bodies and matrix vesicle formation at the base of the lipid core in an atherosclerotic plaque act as a nidus for calcium deposition that can cluster together and resemble early changes of plaque ossification. Progressing microcalcifications may then slow down the inflammation process and stabilize the plaque. However, vascular mineral deposition may itself initiate, promote, or perpetuate atherosclerosis by inducing inflammatory cytokines in monocytes that encounter and ingest hydroxypatite crystals.

Like in skeletal tissue, intimal mineralization can propagate by enchondral ossification in which cells of mesenchymal (osteoblasts) and hematopoietic (osteoclasts) origin produce a cartilage matrix eventually leading to mature lamellar bone formation and active bone remodeling.

Chronic exposure to inflammatory stimuli eventually results in enchondral bone formation and angiogenesis within atherosclerotic lesions followed by immigration of peripheral blood stem cells becoming hematopoietic marrow. Mature lamellar bone is an advanced feature of atherosclerotic disease and is found in <10% of human coronary atherosclerotic lesions, often with hematopoietic elements and active bone remodeling (Figure).

The pathogenesis of ectopic ossification and eventually lamellar bone formation remains a rare event, only occurs in areas with heavy calcifications, and is an active, cell-mediated process. Although macrovascular compliance becomes progressively impaired, a putative biological benefit of vascular mineralization lies in encapsulation of inflammatory stimuli and mechanical stabilization of the vulnerable plaque. The former is supported by the observation that coronary calcium is inversely related to heavy calcifications, and the latter is supported by the observation that coronary calcium is inversely related to heavy calcifications, and the latter is supported by the observation that coronary calcium is inversely related to heavy calcifications, and the latter is supported by the observation that coronary calcium is inversely related to heavy calcifications, and the latter is supported by the observation that coronary calcium is inversely related to heavy calcifications, and the latter is supported by the observation that coronary calcium is inversely related to heavy calcifications, and the latter is supported by the observation that coronary calcium is inversely related to heavy calcifications, and the latter is supported by the observation that coronary calcium is inversely related to heavy calcifications, and the latter is supported by the observation that coronary calcium is inversely related to heavy calcifications, and the latter is supported by the observation that coronary calcium is inversely related to heavy calcifications, and the latter is supported by the observation that coronary calcium is inversely related to heavy calcifications.
associated with more extensive and diffuse coronary atherosclerosis and accelerated disease progression.\(^4\) Finite element analyses revealed that, in contrast to a large lipid core, which dramatically increases vessel wall stress, calcification does not increase fibrous cap stress.\(^5\) Risk of plaque rupture eventually decreases as calcified plaques begin to coalesce. Microcalcifications resemble spots of dead calcified macrophages or vascular smooth muscle cell, which may facilitate plaque rupture through local stress concentrations and interfacial debonding, and are distinct from lamellar bone, which is synthesized through an active and well-organized process and mechanically stabilizes the atherosclerotic lesion. Severe coronary calcifications were found to be more frequent in stable lesions compared with ruptured or vulnerable plaques, which further supports a stabilizing effect and may identify a subset of patients with benign plaque histology. Characteristics of unstable lesions are distinct from stable plaques, including positive vascular remodeling, a lower calcium score in computed tomography scans, and spotty calcification. It is well accepted that coronary calcium identifies high-risk patients and adds incremental value to the Framingham risk score. Atherosclerotic plaque burden is higher and calcifications are more extensive in patients with acute myocardial infarction compared with age-matched control subjects. A recent study, however, did not identify coronary calcification as an independent predictor of unstable plaques in a multivariate analysis.\(^6\) Coronary calcification identifies the vulnerable patient with higher plaque burden rather than the vulnerable plaque.

The well-controlled process of lamellar bone formation in the vasculature provides opportunities for preventive or therapeutic interventions. Heterotopic ossification is a sequela of atherosclerosis for which no specific therapy is available thus far. Prevention of inflammation as a key inductive component to vascular mineralization at an early stage, and treatment of classic atherosclerotic risk factors remains the only therapeutic option. New therapeutic strategies may be developed to target cell differentiation into osteoclasts to mitigate atherosclerotic calcification.

**Disclosures**

None.

**References**


**Figure.** Heterotopic enchondral ossification with mature lamellar bone formation and active bone remodeling in an atherosclerotic lesion. **Left,** Cross-section through the left anterior descending coronary artery (LAD) showing a large atheroma causing subtotal lumen obstruction. The arterial media below the atheroma is partially destructed and contains a large trabecula normally found in spongiosa of skeletal bone. Asterisk indicates remaining true lumen of the vessel. The plaque shows distinct layers of dense collagen and neovascularization (black arrowhead). Ectopic enchondral ossification forms a true trabecula in the atherosclerotic lesion consisting of mature lamellar bone formation and active bone remodeling. **Right,** Magnified view of the black box in the left panel with the trabecular bone structure. The space between the trabeculae contains fatty bone marrow including histiocytes, foamy cytoplasm (black arrowhead), and capillaries (asterisk) resembling bone marrow.
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