Coronary and Aortic Calcification: Is the Relationship Important?

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Atherosclerosis is a systemic disease with varying presentations. It is important that the attending physician know the extent of the atherosclerotic disease in any patient suffering from or at risk of developing the disease – still the most common cause of death in the western world. Vascular calcifications are considered to be a marker for vascular atherosclerosis regardless of the imaging modality used: calcified aortic arch on chest X-ray, valvular calcifications on echocardiographic examinations, or calcified vertebral and carotid arteries on computed tomography scans during neurological assessment. Nephrologists are also well acquainted with tissue calcifications, which are very common in end-stage kidney disease and in patients on chronic dialysis. This phenomenon is caused by a disturbed mineral balance and high total calcium-phosphate product due to vigorous pharmacological intervention to prevent kidney-related bone disease. Data have shown that the extent of vascular calcification in these patients correlates with adverse clinical outcome [1]. On the vascular wall level, atherosclerotic plaque is one of the targets of excessive calcium accumulation, producing intimal calcification. Indeed, calcified vessels appear to be related to atherosclerotic plaques, and the amount of calcium seems to be associated with the degree of atherosclerotic burden.

Two different pathologic processes related to aortic calcification have been defined. The first is connected to atherosclerosis and is associated with excessive calcium accumulation in the intimal plaque. The second is characterized by medial matrix remodeling, which is directed by different signaling molecules – morphogenes – that convert medial smooth muscle cells into osteogenic cells [1,2]. In this case the stiffness of the aorta impairs diastolic coronary flow and also increases left ventricle afterload, while the intimal process is associated with thrombus formation and embolization.

Calcifications, possessing high contrast, are readily observed by any X-ray modality, especially CT scan. The first CT scans were unable to produce high quality imaging of the moving heart and aorta. But with the introduction in the late 1990s of high speed multi-slice spiral CT, intraaortic and intravascular calcium depositions could be detected, especially when contrast material was added. Fueled by technological improvements, extensive research has been undertaken to clarify the accuracy and clinical relevance of vascular calcifications, and especially, to determine outcome and improve risk assessment and prevention.

The report by Eisen and colleagues [3], published in this issue of *IMAJ*, is yet another important step forward. In their study the authors evaluated patients with proven coronary disease and those who had had a non-invasive test suggesting the presence of coronary disease. All patients underwent double – helical spiral CT – at that time the state-of-the-art modality. Patients were assessed for both coronary and aortic calcification. They found that 91% of this high risk population had coronary calcification (392 of 432), and of these patients 70% also had aortic calcification, indicating diffuse atherosclerosis. As in a similar published work, both aortic and coronary calcifications were closely linked to older age, there were more calcium deposits in the descending than in the ascending aorta, and there was a strong association between the extent of coronary and aortic calcifications. This direct inter-relation between these two processes observed here supports the notion that aortic and coronary calcifications are both expressions of systemic atherosclerosis [4,5]. This study proves the ability of double-helical non-gated spiral CT to detect aortic calcifications accurately, but the evaluation of different coronary segments which may be difficult with this modality was not addressed in their report. The prevalence of left anterior descending calcifications was significantly higher (86.8%) than in other vascular beds (left coronary artery 60%, right coronary artery 62%), which may reflect the limitation of this non-gated modality to accurately evaluate some coronary branches.

The main potential advantage of CT imaging over standard coronary angiography, apart from being non-invasive, is the potential ability of visualization of the coronary artery wall and not only the artery lumen. Image quality depends on device resolution, heart rate and rhythm, and the ability to hold breath.

Since the time Eisen et al. recruited their patients, CT scans have developed considerably and today the cutting-edge devices in the field are capable of 64 slices per rotation [6]. These systems enable high quality true non-invasive coronary angiography. Recent publications indicate that these devices yield a very high negative predictive value for coronary disease (97–100%), rather good sensitivity and specificity (75–95%) and a generally more modest positive predictive value (68–91%) [6-11]. High speed CT permits more detailed morphologic images of the coronary tree within a single short breath-hold duration, overcoming motion artifacts. [6]. Major current limitations include artifacts caused by severe calcifications, the presence of stents, and operation stitches after bypass surgery, especially in older and diabetic patients [6]. Musto et al. [12] assessed the coronary tree in

56 consecutive patients with high probability or documented coronary disease using 64 multi-slice CT. In 22% of their patients the capacity of multi-detector computed tomography was insufficient to accurately assess the coronary arteries. Thus, the actual presence and severity of coronary calcification present a major obstacle for accurate coronary imaging.

Nevertheless, calcium score still has a role in the assessment of coronary atherosclerosis. Pohle and co-workers [13] addressed the prognosis of patients with coronary calcifications. They showed that coronary calcification may provide a reliable risk assessment for future coronary events compared with standard algorithms. They compared the extent of coronary calcifications with the predicted 10 year cardiovascular event risk based on Framingham and PROCAM algorithms in 156 patients with a first myocardial infarction. The evaluation of coronary calcium was performed using electron beam CT during the first 4 weeks after the first acute coronary syndrome. Coronary calcifications were detected in 95% of the patients independent of the patient's age. The presence of calcification was higher than in the Framingham or PROCAM algorithm. Waugh et al [14] reviewed seven studies that included 30,599 subjects and assessed the association between coronary calcification scores on CT and cardiac outcomes in an asymptomatic cohort. Coronary calcification on CT was consistently associated with higher rates of cardiac events with a relative risk of 4.4. An increased coronary calcification score was associated with increased risk of cardiac events.

Coronary calcifications coexist with different cardiac and extracardiac calcium deposits such as valvular, aortic and carotid calcifications. The presence of aortic valve and thoracic aortic calcifications was found to be associated with significant coronary arterial stenosis [15]. The correlation of coronary calcium with thoracic descending, abdominal aorta or carotid calcification was more significant in males, while in women the association with aortic arch calcification was more prevalent [16]. In a large study of 60,393 men and 55,916 women aged 30–89 years, the patients' medical files were followed for a median of 28 years. The purpose of the study was to determine whether a correlation existed between aortic arch calcification found on chest radiograph and hospitalization for or death due to coronary heart disease, ischemic stroke, hemorrhagic stroke, or peripheral vascular disease. Aortic arch calcification was associated with an increased risk of coronary heart disease: relative risk 1.27 in men and 1.45 in women. Among women it was also independently associated with a 1.46-fold increased risk of ischemic stroke [17].

In another large cohort of 2618 middle-aged subjects (1345 men and 1273 women) who participated in a mass helical CT screening program for lung cancer and tuberculosis, 28 subjects with previous cerebral infarction were detected. There was a high prevalence of aortic calcification among them, especially in the elderly. The odds ratio of aortic calcifications for subjects with a history of infarction increased as the number of calcified segments increased: 1.82 in men and 2.53 in women. These results suggest that detection of aortic calcifications during chest screening using a mobile helical CT unit is an effective

way to evaluate the risk of cerebral infarction [18]. Two reports by the current investigation team [4,5] also support the correlation between severe aortic calcifications and risk of consequent ischemic stroke. Jayalath and team [19], summarizing the data on abdominal aortic calcification gained from 30 studies, noted a positive correlation between aortic calcification and age, hypertension and smoking history. Calcification of the abdominal aorta was associated with an increased risk of mortality, coronary heart disease and stroke.

The findings of the current study by Eisen et al. [3] are generally in agreement with large clinical data published in this field of research. According to current knowledge, the presence and severity of coronary calcifications are closely related to increased risk of coronary events. On the other hand, the presence of aortic atheromas visualized by CT or even by transesophageal echocardiography increases the risk of brain and coronary ischemic events [20,21]. The statement that the presence of each of these calcifications – whether coronary or aortic – should initiate the clinical workup in the corresponding direction to assess risk is yet to be proven.

Symptomatic patients, particularly young patients, may benefit from high resolution CT as a "rule out" diagnostic tool. However, in view of the risk of radiation and contrast media exposure, CT is not yet ready for coronary screening of asymptomatic patients. Further improvement of coronary imaging will probably reduce the need to assess aortic calcification as the indirect predictor of cardiovascular risk.

Assessment of the degree of aortic calcification may be of practical value with regard to the risk of ischemic stroke. Non-calcified complex and protruding atheromas suggest an increased risk of ischemic stroke, although some publications showed that severe aortic calcifications also increase the risk [22]. Incidental observation of aortic calcifications together with coronary calcium deposits may hint at the presence and extent of systemic atherosclerosis and may be useful in future risk assessment. Further investigation is needed to address the issue of clinical outcome and to define its quantitative predictors.

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Constant kindness can accomplish much. As the sun makes ice melt, kindness causes misunderstanding, mistrust and hostility to evaporate

Albert Schweitzer (1875-1965), Alsatian theologian, musician, philosopher, and physician. He received the 1952 Nobel Peace Prize in 1953 for his philosophy of "reverence for life" expressed in many ways but most famously in founding and sustaining the Lambaréné Hospital in Gabon, Africa.

Capsule

Spliced protein in SMA

Spinal muscular atrophy (SMA) is an inherited disease characterized by the selective death of motor neurons, resulting in generalized muscle weakness that is often fatal in infancy or early childhood. SMA is caused by deletions or mutations in the gene encoding survival motor neuron 1 protein (SMN1), whose function is unclear. SMN1 contributes to the assembly of the pre-mRNA splicing machinery, and loss of SMN1 has been hypothesized to cause disease through disruption of mRNA splicing. However, this cannot readily explain the selective effect of SMN1 loss on motor neurons. An intriguing clue to this selectivity is provided by Setola et al., who identify a truncated form of SMN1 that arises from an alternative spliced SMN1 transcript that is preferentially expressed in the axonal projections of developing motor neurons. Forced expression of this SMN1 variant in cultured non-neuronal cells induces the formation of neurite-like extensions, a change in cell shape reminiscent of that occurring when motor neurons send out axons to their muscle targets. Whether this new variant of SMN1 affects axonal growth *in vivo* and plays a causal role in SMA remains to be investigated.

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