domain analysis is required, bottom line is that frame rate and heart rate in both views should be the same. To accomplish this, we always acquired both level of images with the same depth and the sector size to ensure frame rate is identical. In addition, we are very keen about the heart rate when we acquired images. If the differences of heart rate from both level were than > 5 b.p.m., we tried to obtain another image to reduce the difference in heart rate. Because held respiration during image acquisition often makes heart rate slow, it is not always easy to obtain the same heart rate in both images. However, minor differences in heart rate between the two images produce only two or three frames more in one view. This does not tremendously affect the calculation of LV twist, because the number of frames during systole is usually the same, and only differences would be occurred in the later part of diastole, which does not affect our calculation of untwisting and untwisting rate. Although Dr Burns claimed cubic spline interpolation of the temporally normalized apical and basal rotation data might overcome this issue, careful acquisition of images could alleviate this problem.

Left ventricular untwisting, which is thought to contribute diastolic LV suction, is predominantly observed during isovolumic relaxation period in normal heart. Thus, untwisting should be evaluated from aortic valve closure to early diastolic phase. A negative value of untwisting at \( t = 5\% \) in our study (Table 3) reflects the presence and severity of delayed onset of untwisting after the aortic valve closure, and it also suggests that LV still continuously twists for the first 5% of diastolic period, resulting in the adverse impact on LV early diastolic filling.

Finally, we apologize the unit of untwisting is not degree/ns but %/ms as the authors suggested. Although 2D STI assessment of LV untwisting is a promising method for providing new indices in the evaluation of early diastolic function, further technological refinements and more user-friendly software is mandatory to expand this technology in the daily clinical practice.

References

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As one of the cohorts for recent genome-wide association studies, we have experienced first hand the difficulty with accurate phenotyping, especially for CAD. Atherosclerosis is a diffuse process, and coronary angiography may not always reveal the true burden of disease, especially if the vessel has undergone Glagov remodelling.

The authors comment on and analyse LMD as a discrete entity, but clinical experience suggests that LMD is rarely an isolated phenomenon. More commonly, LMD occurs with significant CAD elsewhere in the coronary circulation. In our genetic registry of all patients passing through the catheter laboratory, we have over 2000 coronary angiograms available for analysis. Of the patients who had had an MI, we found 64 patients with LMD > 50% diameter stenosis. Of these patients, those with LMD, in addition to one-vessel disease (VD), two-VD, and three-VD were 22%, 28%, and 45%, respectively (unpublished data). Only 5% had LMD alone. Fischer et al. do not address this distinction and in the absence of that data, we would argue that the heritability of LMD is actually a surrogate of heritability of severe CAD as manifested by the number of vessels involved. This would also explain the finding that relatives of LMD patients have a higher risk of developing an event, as they would have inherited a more severe underlying atherosclerotic process.

This paper raises important questions about the inheritance of CAD. The notion that disease is, in part, genetically driven to occur primarily in certain sites in families defies current evidence and our current understanding of the atherosclerotic process. Alternative explanations include the role of flow mechanics in the development of lesions especially in the proximal coronary tree. We know from an expanding evidence base that low-wall shear stress (WSS) contributes to plaque development in anatomically predisposed sites. It seems plausible then, that low WSS in anatomically identical vascular regions would lead to plaque development in the same sites. However, coronary anatomy is rarely identical, even in monozygotic twins and so this theory also fails to fully explain the rationale for site-specific coronary lesion inheritance.

In conclusion, we congratulate the authors on their important attempt to narrow the phenotype of coronary disease in order to make genetic studies more meaningful. However, we would argue from a pathophysiological perspective that a hereditary basis is more likely to explain underlying processes leading to atherosclerosis rather than a site-driven mechanism, which is difficult to link.

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Familial aggregation of left main coronary artery disease and future risk of coronary events in asympomatic siblings of affected patients

We read with interest Fischer et al’s recent paper on the heritability of angiographically diagnosed left main disease (LMD). They concluded that the presence of LMD in an index patient confers a three-fold increased risk of LMD in a sibling, confirming earlier findings of familial aggregation of location-specific coronary lesions. They further concluded that LMD, in a patient with myocardial infarction (MI), offers prognostic information on unaffected siblings over and above a family history of coronary artery disease (CAD).
with established and accepted models of atherosclerosis.

References

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Familial aggregation of left main coronary artery disease and future risk of coronary events in asymptomatic siblings of affected patients: reply

We thank Dr Patel et al. for their kind interest in our manuscript. Indeed, we agree with the authors that manifestation of atherosclerosis is anatomically diffuse and as such modulated by several, including heritable, risk factors. Also, their notion that left main disease (LMD) is rarely an isolated phenomenon but rather occurs in addition to disease manifestation at other branches of the coronary tree is concordant with our results. Based on their clinical observations, Dr Patel et al. argue that the heritability of LMD is a surrogate of heritability of severe coronary artery disease (CAD) rather than a result from distinct heritable predisposition. They further conclude that coincidence of LMD and severe CAD may explain our finding that relatives of LMD patients have a higher risk of severe coronary artery disease (CAD) rather than a result from distinct heritable predisposition. Indeed, the group used for comparison consisted of individuals who had at least two siblings with evidence of CAD including one with myocardial infarction—but no family history of LMD.1 Moreover, with the exception of LMD, there was no difference in the distribution of the number of vessels involved in relatives of siblings with known coronary morphology, who experienced myocardial infarctions during follow-up when compared with those relatives of siblings who remained asymptomatic (data not shown). Regrettably, we have no evidence of disease localization in prospectively observed, initially unaffected siblings of CAD patients, of whom many died suddenly.

Finally, Dr Patel et al. consider alternative explanations for the heritability of LMD including flow mechanics in the development of lesions, i.e. arterial wall shear stress. Indeed, it may be plausible that low shear stress in anatomically identical vascular regions would lead to plaque development in such sites. Our previous analysis revealed low if not absent concordance rates for the predominance of coronary blood supply even in monozygotic twins.2 Thus, as already mentioned by Dr Patel et al., this theory does not explain the relatively high LMD inheritance. Of interest in this regard might be the particular ontogenetic determination of this proximal site that is distinct from more distal parts of the coronary artery.2

Future studies including genome-wide associations may shed further light on the inherited factors for CAD in general and LMD in particular. From our perspective, we kindly invite Dr Patel and coworkers for combining their and our respective analyses for addressing these pertinent questions.3

References