To the editors:

Thrombin is believed to play a role in the pathogenesis and progression of atherosclerosis (1, 2). To elucidate this role the relationship between thrombin generation and carotid intima-media thickness (CIMT), supposed to be a marker of atherosclerosis, was investigated by Bernhard et al. (2) in 163 consecutive healthy persons (mean age: 59.8 years). All patients underwent ultrasound examination for CIMT measurement, thrombin generation was measured by means of a calibrated automated thrombogram (CAT). The authors observed in adults younger than 45 years without clinically overt atherosclerotic disease a significant association between endogenous thrombin potential (ETP), a marker of the individual potential of thrombin generation and CIMT. Given the significant association between ETP and CIMT the authors concluded that ETP may serve as an index for subclinical atherosclerosis in subjects younger than 45 years.

There are several critical points concerning the relationship between CIMT, thrombin and atherosclerosis.

Is CIMT a marker of preclinical atherosclerosis?

According to Bernhard et al. (2) ’intima-media thickness (IMT) of the carotid artery is a marker of preclinical atherosclerosis’. This statement is incorrect. Expert opinion continues to divert significantly on whether increased IMT is a marker of preclinical atherosclerosis (3, 4). CIMT is a combined ultrasound measure of the intimal and medial layers of the arterial wall (5), while atherosclerosis is primarily a disorder of the intima (6). Non-atherosclerotic conditions that affect the intima or the media may as well account for an increased CIMT. Intimal hyperplasia and intimal fibrocellular hyper trophy in tensile wall stress (7, 8), medial hypertrophy in hypertension (9) and extracellular matrix glycosylation and calcification of the media in diabetes (10) result in an increased CIMT. It is surprising that Bernard et al. (2) while conceding that a ’multiple linear regression analysis is also necessary to check the influence of relevant covariates of development of arteriosclerosis like blood pressure, cholesterol and blood glucose level’ failed to mention any relevant covariates vital in the analysis of the obtained IMT results.

I Single or composite CIMT measurement?

Bernhard et al. (2) measured the far and near wall IMT at the common carotid artery 10 mm proximal from the flow divider. IMT measurement at a single, pre-established carotid section can coincide with a normal IMT segment, while missing pathologically altered carotid artery regions, i.e. outside of the pre-established measurement area, considering that atherosclerotic alterations are asymmetric in nature (11, 12). Noteworthy is that early atherosclerotic lesions appear more frequently in the distal parts of the carotid bed (13), mainly in areas subject to high wall stress, such as the carotid artery bifurcation (14, 15). Differences in pressure-induced wall stress across the carotid artery may also account for specific segment distribution patterns of IMT in healthy subjects (15, 16). Lim et al. (16) observed in a healthy population significantly lower IMT at the common carotid artery as compared with the IMT at the carotid bifurcation. A multiple site, i.e. composite CIMT measurement, including the common carotid artery, the carotid bifurcation and the internal carotid artery, as performed in the Rotterdam study (17) and Atherosclerosis Risk in Communities (ARIC) study (15, 18), provides consequently a more accurate estimate of the actual carotid IMT.

I Which are CIMT cut-off values?

Thresholds to define a pathologically increased IMT and an atherosclerotic plaque lack scientific justification. Several cut-off values were reported for pathologically increased IMT: >0.60 mm (19), >0.80 mm (20), ≥0.90 mm (21) and ≥1.0 mm (22). Several IMT cut-off values were suggested for atherosclerotic plaque: ≥1.1 mm (23) and ≥1.5 mm (24). The absence of a consensus on IMT cut-off values underlines the difficulties to compare and to draw definite conclusions from IMT studies based on different methodologies (24, 25). Bernhard et al. (2) did not report their selected IMT cut-off values.

Conclusion

In light of the controversy related to the validity of CIMT as surrogate marker (3, 4) and the lack of standardized CIMT measurements (24, 30), at the current stand of research it may be sensible not to use CIMT as a proxy measure of generalized atherosclerosis. The conclusion that ETP may serve as an index for subclinical atherosclerosis in subjects ≤45 years should be considered consequently with great caution.

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References