From Heart to Head, Thrombi to Emboli, and Inferences to Extrapolation

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Thrombotic and Embolic Consequences of CVD

This issue of JACC presents an excellent study that highlights magnetic resonance imaging (MRI)-verified overt or silent brain lesions in patients with atrial fibrillation (AF) (1). Large and small, cortical and non-cortical infarcts, microbleeds or white matter lesions were detected in as much as 37% of the population. In these patients without a clinical history of stroke or transient ischemic attack, the prevalence of silent brain lesions was also alarmingly high with 15% large and 18% small noncortical infarcts. Although in this study there was a justifiable source of an embolic phenomenon, the MRI-verified infarct prevalence could be as high as 31% even in the general population, men and women aged $\geq$65 years (2), which suggests a possibility of additional sources of embolic insult. Vascular disease and vascular risk factors are common in AF patients. Atherosclerotic disease of carotid arteries, aortic arch and entire length of aorta may contribute to the embolic process. A non-obstructive angioscopy study of the aorta during elective diagnostic coronary angiography or percutaneous coronary intervention, observed spontaneously ruptured aortic plaques presenting as *puff-chandeliers* in 80% patients (3). The gentle sampling of these nude plaques histopathologically revealed the atheromatous cores and fibrin in one-half of the samples, and macrophages and calcific material in another one-quarter.

Atheromatous embolization is an underappreciated multisystem disorder that may lead to structural and functional alterations in vital organs (4). The prevalence of asymptomatic abnormalities on MRI of the brain and their possible relation to vascular risk factors and vascular disease, with no clinical history of focal brain lesions has been reported. In one of the early studies of 77 randomly selected subjects (mean age, 65 years; range, 36-95 years), 62% of subjects had white matter hyperintensities and 9% had deep gray matter hyperintensities

localized in the basal ganglia (5). Age, hypertension and the history of heart disease were found to be independently associated with MRI-based abnormalities. A potential cardioembolic source was detected in 47% of patients upon transthoracic or transesophageal echocardiography. This study alerted that the white matter hyperintensities were frequently present in asymptomatic individuals with vascular risk factors. We have previously systematically reviewed brain changes in 77 imaging studies from patients with vascular risk factors but without clinically manifest cardiovascular, cerebrovascular or peripheral vascular disease and events (6). The vascular risk factors including hypertension, diabetes, obesity, hyperlipidemia, and smoking were independently associated with structural and/or functional brain imaging changes before the clinical manifestation of cardiovascular or cerebrovascular disease. These findings could offer a window of opportunity for treatment of modifiable risk factors and might help prevent development of irreversible brain alterations (6).

The brain or other end organ lesions could result from either thrombotic or embolic processes, and both processes from either atherosclerotic or non-atherosclerotic etiologies (Figure). The thrombotic lesions caused by the plaque rupture and erosion are the commonest cause of the coronary events. On the other hand, larger neurovascular occlusion resulting from plaque rupture or erosion may have devastating effects and are less common. In neurovascular events, emboli arising from the proximal atherosclerotic lesions represent the most frequent mechanism, be it from carotid ulcers or aortic atherosclerotic lesions. The pure embolic lesions arising from cardiac chambers may or may not be a part of atherosclerotic diseases. It is tempting to classify the consequences of atherosclerotic vascular pathology into atherothrombotic and athero-embolic diseases wherein the luminal compromise and major adverse events could result from high-risk plaques locally or where the plaque pathology is responsible for an embolic

episode downstream in the end organs. Athero-embolic process has been recently proposed to be the basis of critical limb ischemia in peripheral artery disease wherein the embolization may occur from abdominal aorta, iliac or femoral artery atherosclerotic lesions (7). On the other hand, erosive pathology in coronary arteries in women not only leads to local vascular compromise but also results in substantial distal bed embolization and microvascular occlusion, and hence poorer outcomes (8).

End-Organ Dysfunction: Thromboembolic Disease and beyond

In the current study (1), the AF patients presented with a high burden of clinically overt or silent brain infarcts, and in a multivariable regression model including all vascular brain lesions, large infarct volume was the strongest predictor for a reduced cognitive function. It remains to be seen whether similar mechanisms could be extrapolated to the patients with abundant vascular risk factors. It is being increasingly recognized that the vascular pathology could contribute in additive or synergistic fashion to cognitive decline (9). Although not so in the study under discussion, microinfarcts and microhemorrhages have been considered to affect cortical cognitive domains (10), or limit connectivity among cognitive networks through white matter pathology (11). Cognitive brain reserve and APOE genotype could alter the threshold for manifest cognitive deficit (11). Further, there might be a direct mechanistic link between vascular risk factors and late-life dementia. For instance, experimental hypertension increases amyloid □ production, and the vascular damage produced by hypertension reduces the clearance of amyloid and tau, promoting neurofibrillary tangles (11). Imaging and autopsy studies have also shown evidence of increased deposition of these proteins with abundant vascular risk factors (12).

To evaluate whether midlife vascular risk factors were associated with brain amyloid deposition, Gottesman and colleagues employed amyloid-seeking fluorinated radiotracer imaging in the participants of the Atherosclerosis Risk in Communities study (12). Almost 350 participants who were enrolled for vascular risk factor assessment between 1987-1989, underwent brain positron emission tomography imaging 2 decades later. A greater number of midlife risk factors including body mass index ≥30, current smoking, hypertension, diabetes, and total cholesterol ≥200 mg/dL at baseline in enrollees, then aged 45-64 years, was associated with elevated radiotracer uptake upon follow-up; compared with no risk factors the odds ratio for elevated uptake in association with 1 historical vascular risk factor was 1.88 and for ≥2 risk factors was 2.88. These findings are consistent with a role of vascular disease in the development of Alzheimer disease. A tight control of modifiable vascular risk factors at midlife (e.g. sedentary lifestyle, smoking, hypertension, obesity, and diabetes) might reduce the incidence of late life dementia (13). The possibility of modifying the evolution to cognitive decline could be stronger in APOE ε4 carriers with high genetic risk of Alzheimer's disease (14).

Inferences to Extrapolation

This study highlights that the end organs bear the brunt of damage associated with cardiovascular diseases. The process may be subclinical and could lead to long-term deficit in the recipient organs. For instance, cognitive function is predominantly associated with cortical or noncortical infarcts, majority of which might be silent. Although these findings invoke the necessity of more extensive imaging work up for the patients with cardiovascular disease, the cost-effectiveness of such a presumption would need to be established. The major motivation for a more extensive assessment is the potential for therapeutic intervention. Although the evidence of the association of cardiovascular risk factors with cognitive dysfunction is convincing and a

strategy for prevention is intuitive the clinical trial data demonstrating the benefit of prevention of cardiovascular risk factors needs confirmation (11,13-16). Intervention studies are needed to address the potential benefit of risk factor containment and hence the relevance of advanced imaging studies. In addition, it is quite convenient to believe that the atheroembolic diseases would draw additional benefit from anti-thrombotic agents with or without anti-platelet agents. The sub-analyses of CAMPUS trial (17,18) has revealed that the success of anti-coagulants was predominantly driven from the diseases of atheroembolic basis than the coronary artery disease itself. Conversely, in the study of Conen et al. in the AF patients, the silent infarcts were seen in a population with a high prevalence of oral anticoagulation at the time of brain MRI. It is also not yet clear as to the extent of brain lesions (and for that matter peripheral artery disease compromise) that would lead to end organ limitation or adverse events. Although the study of Conen et al. suggests that only large infarct volume is evidently associated with cognitive dysfunction, intuitively all cortical and noncortical lesions should affect the regions that subserve cognition or those which connect these regions to regions of execution. This field of heart-to-head interaction, and thrombotic or embolic processes would remain to be one of the most fertile area of investigation so that inferences drawn from the association studies should not need extrapolation.

REFERENCES

(1). Conen et al. J Am Coll Cardiol. 2019;XXX

(2). Price TR, Manolio TA, Kronmal RA et al. Silent brain infarction on magnetic resonance imaging and neurological abnormalities in community-dwelling older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. Stroke 1997;28:1158-64.

(3). Komatsu S, Yutani C, Ohara T, et al. Angioscopic evaluation of spontaneously ruptured aortic plaques. J Am Coll Cardiol 2018;71:2893-902.

(4). Kronzon I, Saric M. Cholesterol embolization syndrome. Circulation 2010;122:631-41.

(5). Lindgren A, Roijer A, Rudling O, et al. Cerebral lesions on magnetic resonance imaging, heart disease, and vascular risk factors in subjects without stroke. A population-based study. Stroke. 1994;25(5):929-34.

(6). Friedman JI, Tang CY, de Haas HJ, et al. Brain imaging changes associated with risk factors for cardiovascular and cerebrovascular disease in asymptomatic patients. JACC Cardiovasc Imaging. 2014;7(10):1039-53.

(7). Narula N, Dannenberg AJ, Olin JW, et al. Pathology of Peripheral Artery Disease in Patients With Critical Limb Ischemia. J Am Coll Cardiol. 2018;72:2152-2163.

(8). Burke AP, Farb A, Malcom GT, Liang Y, Smialek J, Virmani R. Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. Circulation. 1998;97:2110-6.

(9). Kovacic JC, Fuster V. Atherosclerotic risk factors, vascular cognitive impairment, and Alzheimer disease. Mt Sinai J Med. 2012;79:664-73.

(10). Biesbroek JM, Weaver NA, Biessels GJ. Lesion location and cognitive impact of cerebral small vessel disease. Clin Sci. 2017;131:715–728.

(11). Iadecola C, Gottesman RF. Cerebrovascular Alterations in Alzheimer Disease. Circ Res. 2018;123:406-408.

(12). Gottesman RF, Schneider AL, Zhou Y, et al. Association between midlife vascular risk factors and estimated brain amyloid deposition. JAMA. 2017;317:1443–1450.

(13). Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol 2014;13:788–94

(14). Bangen KJ, Beiser A, Delano-Wood L, et al. APOE genotype modifies the relationship between midlife vascular risk factors and later cognitive decline. J Stroke Cerebrovasc Dis. 2013;22:1361-9.

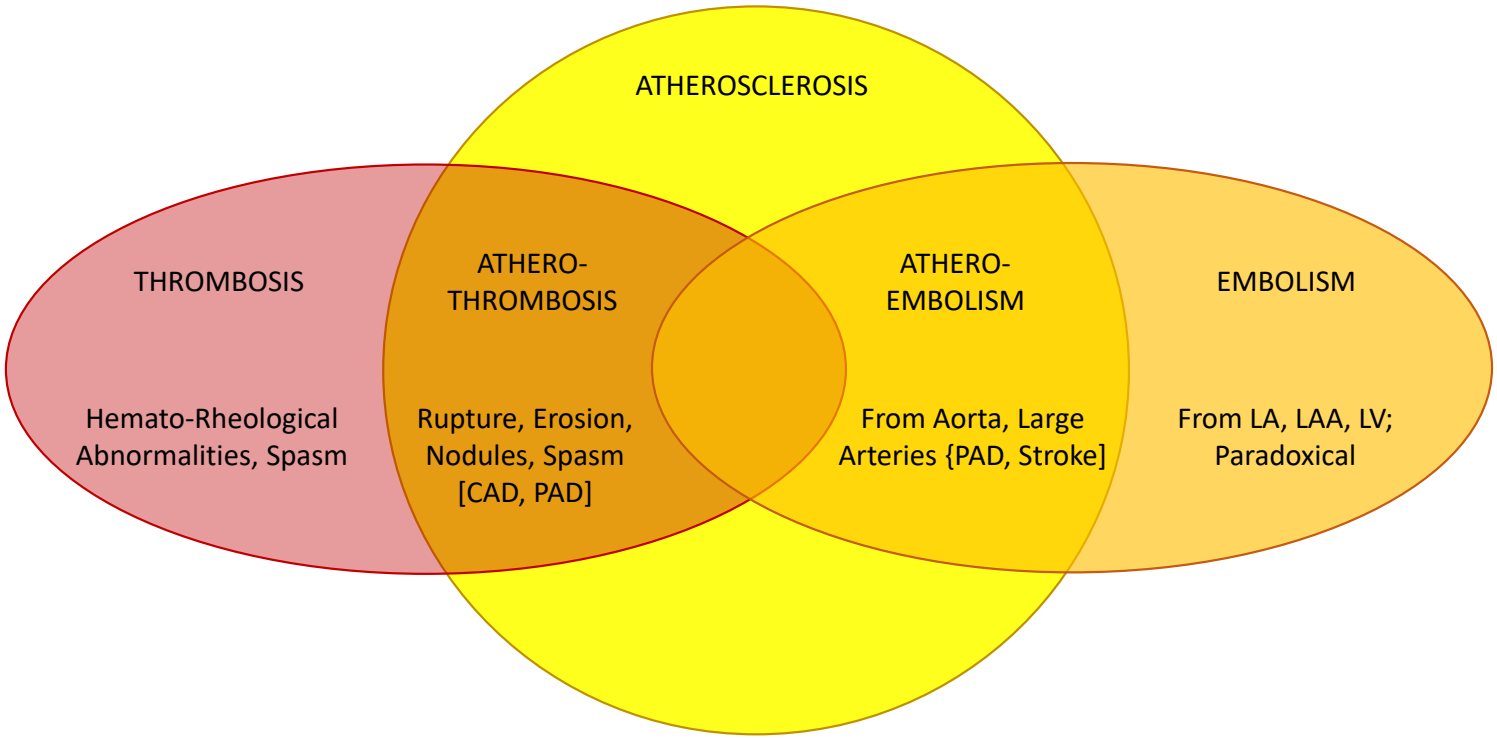
(15). Forette F, Seux ML, Staessen JA et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet. 1998;352:1347–1351.

(16). Wright JT, Williamson JD, Whelton PK et al. SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373:2103–2116.

(17). Anand SS, Bosch J, Eikelboom JW, et al. COMPASS Investigators. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet. 2018;391:219-229.

(18). Connolly SJ, Eikelboom JW, Bosch J, et al. COMPASS investigators. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet. 2018;391:205-218.

Figure Legend: Atherothrombotic and atheroembolic diseases.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Nodules, Spasm
[CAD, PAD]
From Aorta, Large
Arteries {PAD, Stroke]
From LA, LAA, LV;
Paradoxical