JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 66, NO. 9, 2015

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jacc.2015.07.019

EDITOR'S PAGE

The Vulnerable Patient

Providing a Lens Into the Interconnected Diseases of the Heart and Brain

Valentin Fuster, MD, PhD

Many philosophers have explored the interconnectedness between the brain and the heart; yet, technological advances in imaging, increased physiological understanding, and a greater appreciation of optimal medical therapy have allowed cardiovascular researchers and clinicians to better comprehend how to assess and treat the vulnerable patient who experiences a systemic disease process across the vasculatures of the heart and brain.

Over the past 10 years, atherosclerosis research has shifted from a local outlook, which utilized invasive imaging techniques to assess vulnerable plaque and high-risk plaques, to a systemic process, focusing on the *vulnerable patient* and the *burden of disease*, which uses various diagnostic and prognostic methods, including biomarkers and optimal medical therapies (1). Because atherosclerosis is a systemic process, it is intuitive that assessing disease at multiple, rather than single, vascular sites may provide greater insight on the overall burden and risk associated with subclinical atherosclerosis (2). As a point of demonstration, in 2 recent bioimaging studies we assessed approximately 10,000 asymptomatic adults >40 years of age, using multimodality vascular imaging of the coronary arteries with electron-beam computed tomography for calcification and of the carotid arteries with 3-dimensional ultrasound was performed (2,3). We found that subclinical atherosclerosis was highly prevalent, detectable in both the coronary and carotid vascular territories in close to 60% of participants (2,3). Thus, we concluded that incorporating detection of subclinical atherosclerosis, irrespective of anatomic territory, in addition to cardiovascular risk factors could be considered in the future for patient management decisions.

As the investigational and the clinical communities have been seeking to better understand the vulnerable patient, it has been increasingly recognized that degenerative brain disease (DBD) is intimately linked to the vasculature and overall burden of disease, on which I have just commented (4–6). This DBD axis is perceptible across a very broad spectrum of disease, from macrovascular large vessel coronary or carotid diseases leading to myocardial infarction or stroke, to microvascular small vessel changes causing dementia (4). Overall, the critical importance of subclinical macrovascular and microvascular diseases with respect to brain, heart, kidney, and other organ function, when examined through the lens of the vulnerable patient, is that they will contribute to the continued progress in fighting these diseases (4). Thus, we must make a transition from primarily considering the coronary vessels to looking at the entire patient in terms of systemic cardiovascular disease (4).

Furthermore, within the context of the burden of disease/DBD axis, one of the most significant risk factors for the vulnerable patient is aging. And, as our population becomes increasingly older, the prevalence of these interconnected disease states will proliferate, in particular DBD. We have already witnessed a tremendous rise in the diagnosis of Alzheimer's disease—the incidence of which doubles every 5 years after 65 years of age, with the diagnosis of 1,275 new cases per year per 100,000 persons older than 65 years of age (7). The prevalence is expected to approach 13.2 to 16.0 million cases in the United States by the midcentury (8). However, this increase in DBD cannot be viewed in a vacuum, because several observations have shown that ischemic microvascular disease affects 60 to 90% of patients

From the Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York.

with Alzheimer's disease (9). Additional research has shown that hypertension and diabetes lead to a decrease in vascular reserve capacity and can cause microvascular disease, stroke, cognitive decline, and dementia (10). Factors other than perfusion, such as genetic predisposition, autonomic failure, and neurodegeneration, also contribute to the progression of Alzheimer's disease and dementia (10).

However, as we continue to learn the mechanisms behind the connection between cardiovascular risk factors and cognitive function, the CARDIA (Coronary Artery Risk Development in Young Adults) study demonstrated that cumulative exposure to cardiovascular risk factors from early to middle adulthood, especially above recommended guidelines, was associated with worse cognition in midlife (11). In this prospective study of 3,381 adults, the primary predictor was 25-year cumulative exposure estimated by areas under the curve for resting systolic and diastolic blood pressures, fasting blood glucose, and total cholesterol (11). The authors concluded that their findings warrant more aggressive treatment of cardiovascular risk factors earlier in life.

Thus, FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) randomly assigned 2,654 individuals with cognitive dysfunction and cardiovascular risk factors—1,260 to the intervention group (n = 631) or control group (n = 629) (12). The authors randomly assigned participants in a 1:1 ratio to a 2-year multidomain intervention, including diet, exercise, cognitive training, and vascular risk modification, or a control group, which consisted of general health advice. Of importance, findings suggest that a multidomain intervention could improve or maintain cognitive functioning in at-risk elderly people from the general population.

In summary, as we are being challenged to not simply focus on treating diseases once they manifest, but rather address risk factors that contribute to those diseases, here is an opportunity where we can investigate, diagnose, and treat an at-risk patient—a vulnerable patient, who could benefit from lifestyle modifications before clinical manifestations affect the heart and the brain.

ADDRESS CORRESPONDENCE TO: Dr. Valentin Fuster, Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, New York 10029. E-mail: valentin.fuster@mountsinai.org.

REFERENCES

1. Tomey MI, Narula J, Kovacic JC. Advances in the understanding of plaque composition and treatment options: a year in review. J Am Coll Cardiol 2014;63:1604–16.

2. Baber U, Mehran R, Sartori S, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the Bioimage Study. J Am Coll Cardiol 2015;65:1065–74.

3. Fernández-Friera L, Peñalvo JL, Fernández-Ortiz A, et al. Prevalence, vascular distribution, and multiterritorial extent of subclinical atherosclerosis in a middle-aged cohort: the PESA (Progression of Early Subclinical Atherosclerosis) Study. Circulation 2015;131:2104–13.

4. Kovacic JC, Castellano JM, Fuster V. Cardiovascular defense challenges at the basic, clinical and population levels. Ann N Y Acad Sci 2012;1254:1–6.

5. Kovacic JC, Fuster V. From treating complex coronary artery disease to promoting cardiovascular health: therapeutic transitions and challenges, 2010–2020. Clin Pharmacol Ther 2011;90:509–18.

6. Kovacic JC, Moreno P, Nabel EG, et al. Cellular senescence, vascular disease, and aging: part 2 of a 2-part review: clinical vascular disease in the elderly. Circulation 2011;123:1900–10.

7. Hirtz D, Thurman DJ, Gwinn-Hardy K, et al. How common are the "common" neurologic disorders? Neurology 2007;68:326–37.

8. Hebert LE, Scherr PA, Bienias JL, et al. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol 2003;60:1119–22.

9. Querfurth HW, LaFerla FM. Alzheimer's disease. N Engl J Med 2010;362:329–44.

10. Novak V, Hajjar I. The relationship between blood pressure and cognitive function. Nat Rev Cardiol 2010;7:686–98.

11. Yaffe K, Vittinghoff E, Pletcher MJ, et al. Early adult to midlife cardiovascular risk factors and cognitive function. Circulation 2014;129:1560–7.

12. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 2015;385:2255–63.