

## EDITORIAL COMMENT

# Age-Associated Cardiovascular Changes Are the Substrate for Poor Prognosis With Myocardial Infarction\*

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Advanced age is a powerful independent predictor of short-term mortality and morbidity in post-infarct patients (1–3). Randomized studies, including thousands of patients, indicate 10-fold increases in death, clinical heart failure (HF), and cardiogenic shock as age increases from <60 to >85 years (1). Although age differences in complications and mortality may relate in part to delayed and atypical presentations and the increased likelihood of contraindications and complications from thrombolytic and beta-blocker therapies (2), the pre-existing age-associated changes in vascular and ventricular properties alter the substrate upon which the infarction occurs and probably play a crucial role in the poor prognosis of elderly patients with acute myocardial infarction (MI). In this issue of the *Journal*, Kurotobi et al. (4) illustrate another example of the interaction

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between age-related cardiovascular changes (endothelial dysfunction) and disease (MI) and how this relationship has a negative impact on older patients with acute MI.

## CARDIOVASCULAR CHANGES WITH PHYSIOLOGIC AGING

There are several cardiovascular changes associated with physiologic aging that contribute to the poor prognosis in older patients with acute MI. These include decreased beta-adrenergic sympathetic responsiveness (5,6), slowed and delayed early diastolic filling (7,8), increased vascular stiffness (9,10), and endothelial dysfunction (11,12). Decreased inotropic beta-adrenergic responsiveness may affect cardiovascular function in the post-infarction period by limiting contractile reserve in the region remote from the infarct and thereby the ability of that myocardium to compensate for the contractile performance lost as the result of the infarct itself. Age-associated decreased early filling,

on the order of 6% to 7% per decade (8), increases the dependence of end-diastolic left ventricular (LV) volume on atrial contraction and is thought to result in higher left atrial and pulmonary pressures for any given stroke volume (13). Higher diastolic LV pressures may impair coronary perfusion and contribute to adverse outcomes after infarction in older patients.

The age-associated increased arterial stiffness result from several factors, including fragmentation of the elastic membrane, intimal thickening, increases in collagen content and linking, decreased baroreflex sensitivity, and diminished endothelium-dependent vasorelaxation (5). These changes increase the vascular load faced by the LV and exert a significant influence on cardiovascular performance in healthy subjects (14–16). A relationship between arterial stiffness, as indexed by sphygmomanometry-determined pulse pressure and increased risk of future coronary heart disease, congestive HF, and death, has been demonstrated in elderly populations previously free of symptomatic heart disease (17–19). In addition, elevated pulse pressure is an independent predictor of mortality in patients with chronic HF and LV dysfunction after MI (20,21).

Aging is also associated with endothelial dysfunction. Studies in subjects free of coronary artery disease and the classic risk factors for atherosclerosis demonstrate a significant inverse linear relationship between age and percent change in coronary and brachial arterial diameters and blood flow responses to the intra-arterial administration of the endothelial-dependent vasodilator acetylcholine (11,12). There is no age relationship for intra-arterial papaverine and nitroprusside, endothelial-independent vasodilators. Furthermore, the inhibition of nitric oxide (NO) synthase with L-NMMA reduces forearm blood flow significantly less in older subjects than in younger subjects (22). These studies suggest that in healthy subjects, the basal release of NO from vascular endothelium is reduced in the elderly, and the age-associated reduction in the vascular responsiveness to endothelium-dependent vasodilation in both the coronary and forearm circulation suggests a general diminution in NO vasodilation in all vascular beds (23).

## CURRENT STUDY

This important study by Kurotobi et al. (4) demonstrates how age-associated endothelial dysfunction has a negative impact on older patients with acute MI. Angiographic collateral blood flow was assessed in 1,934 patients with acute MI and an occluded infarct vessel. The presence of collaterals decreased progressively with the increasing age of the patient, and on multivariate analysis, age was independently associated with a lesser prevalence of angiographic collaterals. As previous studies also have demonstrated, preinfarction angina, a history of angina, and time to catheterization were also related to the presence of collaterals. Unexplained, patients with circumflex infarcts were

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less likely to have collateral blood flow. In older patients, the lack of angiographic collaterals to the infarct vessel was an independent predictor of mortality. Unanswered in this study is whether older patients have a decreased ability to develop collaterals, or similar to many animal models, the development of collaterals is just delayed. Furthermore, a decreased ability to form collaterals in chronic coronary disease may, a priori, put the elderly at increased risk to develop an MI.

Although the primary stimulus for collateral growth is controversial, angiogenesis requires the proliferation and migration of endothelial cells (24,25). With increasing age, endothelial dysfunction in collateral arterioles caused by a reduction in endothelial NO synthase expression contributes to a decline in angiogenesis (25-27). Nitric oxide bioavailability also is reduced in aged collateral arterioles because of significantly greater amounts of superoxide and nitrated tyrosine residues of proteins (27). In addition to endothelial dysfunction, there is an age-related decrease in endothelial progenitor cells from the bone marrow (28) that likely limits the ability to form new blood vessels in response to ischemia.

Another important link between age-associated endothelial dysfunction and impaired collateral vessel growth is the decreased endothelial release of growth factors crucial for angiogenesis (26,29,30), including platelet-derived growth factor-B (PDGF-B). The release of this growth factor stimulates the endothelial expression of several other growth factors, including vascular endothelial-derived growth factor (VEGF) (29). Animal models show that the endothelial expression of PDGF-B is down-regulated in the senescent heart, also resulting in the reduced expression of VEGF (29). In animal models of ischemia, VEGF messenger ribonucleic acid and protein are reduced in aged animals, resulting in significantly less perfusion pressure, angiographic collateral vessel development, and capillary density than in young animals (26). Pre-treating aged ischemic animals with VEGF protein, PDGF-AB, or bone marrow-derived endothelial precursor cells from young animals results in an increase in angiographically visible collaterals, improved perfusion pressure, improved angiogenesis, and a reduction in myocardial infarct size (26,29,30). These studies suggest that age-associated endothelial dysfunction results in reduced elaboration of endothelial-derived growth factors in response to ischemia and impaired angiogenesis.

## CLINICAL IMPLICATIONS

The excess morbidity and mortality in older patients with acute MI is an increasing challenge as the population ages. The data from Kurotobi et al. (4) suggest that the establishment of normal coronary and myocardial blood flow in an expeditious fashion is particularly important in older patients with acute MI because the infarct vessel is less likely to receive collateral flow than it is in younger patients. This finding may help explain the impressive survival advantage

for acute percutaneous coronary intervention compared with thrombolytic therapy in the elderly (31). Whether therapies that enhance angiogenesis are particularly beneficial in the older patients with coronary disease awaits further study.

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