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Editorial

Aging, ischemia and the heart

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1. Introduction

It has long been appreciated that aging is associated with increased susceptibility to myocardial infarction (MI), and more recently, attention has been focused on gender differences and the influence of preconditioning in cardiac ischemic damage. The hallmarks of MI, including tissue necrosis and cell death, scar formation, myocyte hypertrophy, and left ventricular dilation, have been studied extensively to gain further understanding of cardiac remodeling characteristic of MI. In the current issue of the *Journal of Molecular and Cellular Cardiology*, issue 38(2), Willems et al. report the results of a systematic study of a moderate ischemic injury in male and female C57/Bl6 mice from 2 to 28 months of age. This work is important in that the investigators have conducted a comprehensive study of the effect of aging and gender on the response to MI in the mouse, and it provides a foundation for future work employing the many genetic mouse models, which are available, many of which are on the C57/Bl6 background. Utilizing these models to investigate the effects of aging on cardiovascular disease will contribute to our understanding of the myriad of changes that occurs post-MI, and how these are influenced by aging and gender.

This article describes systematically, key elements thought to be crucial in the development of MI in young middle aged to senescent mice. There are a number of interesting findings in this study including:

- Better recovery of developed pressure in young mice compared to all other age groups, and the authors attribute this to less diastolic dysfunction with ischemia/reperfusion in the young mice.
- Coronary blood flow was unaffected by age or gender, infact, the study suggests that coronary flow returns to preischemic levels. Coronary dysfunction as measured by coronary dilation responses to the long acting adenosine 2-chloradenosine appears to be unaffected by age, although following ischemia, coronary dilation is delayed senescent mice.
- A twofold increase in lactate dehydrogenase release in middle aged compared to young mice. However, in the aged population of mice, the levels LDH are not different from those released by young adult hearts.

2. Cardiac changes with aging

In humans, aging is associated with mild–moderate increase in heart size due to ventricular hypertrophy [1]. These changes have been ascribed to increased cardiomyocyte size, and concomitantly there is a decrease in cardiomyocyte cell number. Due to ethical considerations, it is not possible to examine these changes comprehensively in healthy human hearts. Using a murine model, this study describes changes with aging, and also details changes in a number of parameters, previously shown to be involved in MI, in both male and female young to senescent hearts.

3. Gender, aging and ventricular recovery post-MI

Increasing age has been recognized as being associated with increased morbidity and mortality in the setting of MI in animal studies. These findings suggest that the aged myocardium is more susceptible to ischemic injury than the young myocardium [1,2]. Similarly, older patients with acute MI have a poorer outcome than younger ones [1–4]. Willems et al. found that following ischemia ventricular recovery declined with age. Thus, the young adult mice (2–4 months of age) showed better recovery of developed pressure, diastolic pressure, and +dP/dt. There was no difference amongst the oldest groups, and by 8–12 months the recovery was reduced to the same degree as seen with the 24–28-month-old mice. Thus, the degree of recovery in the oldest group was similar to that seen with the "middle aged" mice. This contradicts clinical experience, where the very elderly have the worst outcomes, but this may be influenced somewhat by co-morbidities [4,5]. In the younger groups in the current study, females had somewhat better recovery after ischemia. This benefit disappeared with aging, where the production of estrogen would be expected to decline, and other factors come into play, such as decreased heat shock protein expression and cumulative oxidative stress [6,7].

4. Aging and vascular injury with ischemia

Ischemic injury is not restricted to cardiomyocytes, but also effects vascular tissue as is demonstrated in this article,

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which reports some reduction in reflow post-ischemia in older hearts compared to younger groups (see Fig. 2 of article by Willems et al. in this issue). In contrast to the myocardium, though, vascular function appeared to be relatively preserved with aging. Other studies have shown that the vasculature may indeed contribute significantly to age dependent development of ischemia [1,8,9]. Aging itself is associated with increased expression of adhesion molecules, an increase in plasma nitrites and nitrates, detrimental changes in NO and eNOS levels, and an increase in vessel stiffness [10–12]. These changes and others prime the vessel for injury, and can impair normal vascular relaxation.

5. LDH, aging and necrosis

In the current study, the release of LDH following ischemia increased from young adult to middle age, and then declined in the aged and senescent male mouse hearts, such that the LDH release by senescent and young hearts was the same. Similar LDH patterns for LDH release by young and senescent mouse hearts have been reported by others [13]. Although the authors interpret LDH release as reflecting a change in degree of injury with aging, it also could reflect differences in the amounts of LDH present in the myocardium. The effect of age and gender on myocardial LDH levels has not been well-studied. In one report, the LDH content was greater for 2 vs. 12-month-old female Wistar rats [14]. LDH levels have been found to decline with aging in the vasculature [15]. Thus, the observed changes in LDH release, rather than reflecting only differences in injury may represent differences in the total LDH present in the heart. In other words, the reduction in LDH release seen in the aging heart may be a sign of less total LDH, rather than less injury. Alternatively, apoptosis may be a greater cause of cell death in senescent heart, and this would not cause rapid release of LDH, like necrosis. Future work needs to address mechanisms of cell death with ischemia over the aging spectrum, from young adult to senescent, as well as changes in other key proteins, including LDH. Already there is evidence that aging is associated with reduction in expression of SERCA2A and $-adrenergic receptors, among other proteins [11,16,17].

6. The extracellular matrix, aging and diastolic dysfunction

Willems et al. found that collagen content increased significantly in the both the aged and senescent hearts in the absence of ischemic injury. Here the mouse heart shows the same change observed in other established models—that collagen increases with aging due primarily to collagen I [18]. In addition, aging is associated with an increase in collagen cross-linking, which further contributes to stiffness. There was no overall difference with aging for $-dP/dt$ in the current study. Other indices of ventricular relaxation and diastolic function were not measured. Research has focused on fibrosis and increased collagen as leading to increased stiffness, but other factors need to be considered, such as changes in titin, as all abnormalities of diastolic function do not necessarily arise from the extracellular matrix [19–21]. For example, recent work suggests that aging is associated with increased stiffness of the myocyte, itself [22].

7. Cardiac rupture after MI

Coronary ligation to produce MI in the mouse is associated with a very high incidence of cardiac rupture compared to MI in humans. Willems et al. studied the isolated perfused heart, which is an excellent model for hemodynamic studies, but does not provide information with regards to remodeling after coronary occlusion. Cardiac rupture is common in mice after coronary ligation, and in one study of 3-month-old mice occurred predominantly in male mice [23]. In contrast, in humans, rupture occurs predominantly in females, and is more common in patients over 65. The incidence of rupture in acute MI is estimated to be between 2% and 7% [24]. Rupture usually occurs within 5 days of MI, and accounts for about 15% of in-hospital deaths from MI [25–27]. Similarly, in mice, rupture occurred predominantly between 3 and 5 days post-infarction [23]. Other commonly used models of MI, including rat, rabbit, and pig, rarely, if ever have cardiac rupture. Thus, the mouse model may provide important insights into the etiologies and possible treatments for this major cause of mortality with acute MI.

8. Hormones and cardiac remodeling

Whereas estrogen appears to have protective effects, some studies suggest that testosterone may be detrimental to myocardial remodeling following MI [28]. Much more research is needed on the effects of estrogen and testosterone on the heart, and changes that occur with aging. Clearly, clinical trials of estrogen do not provide definitive answers on the role of estrogen replacement in the absence of a sound understanding of the underlying basic mechanisms of action and cellular targeting [29].

9. Preconditioning and aging

Although MI has been studied extensively, efforts have focused much less on the aging myocardium, even though, the majority of MI's occur in individuals from mid-life to aged. A major focus of ischemia research has been preconditioning. Although there have been reports of species differences, ischemic preconditioning with brief periods of ischemia protects both animal and human myocardium from a subsequent ischemic injury [30]. Whether the aging heart can be preconditioned, and the possible pathways to preconditioning in the aged heart, remain controversial [31–35].

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