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Original Article

Development of an experimentally useful model of acute myocardial infarction: 2/3 nephrectomized triple nitric oxide synthases-deficient mouse

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ABSTRACT

We investigated the effect of subtotal nephrectomy on the incidence of acute myocardial infarction (AMI) in mice deficient in all three nitric oxide synthases (NOSs). Two-thirds nephrectomy (NX) was performed on male triple NOSs$^{-/-}$ mice. The 2/3NX caused sudden cardiac death due to AMI in the triple NOSs$^{-/-}$ mice as early as 4 months after the surgery. The 2/3NX triple NOSs$^{-/-}$ mice exhibited electrocardiographic ST-segment elevation, reduced heart rate variability, echocardiographic regional wall motion abnormality, and accelerated coronary arteriosclerotic lesion formation. Cardiovascular risk factors (hypertension, hypercholesterolemia, and hyperglycemia), an increased number of circulating bone marrow-derived vascular smooth muscle cell (VSMC) progenitor cells (a pro-arteriosclerotic factor), and cardiac up-regulation of stromal cell-derived factor (SDF)-1α (a chemotactic factor of the progenitor cells) were noted in the 2/3NX triple NOSs$^{-/-}$ mice and were associated with significant increases in plasma angiotensin II levels (a marker of renin–angiotensin system activation) and urinary 8-isoprostane levels (a marker of oxidative stress). Importantly, combined treatment with a clinical dosage of an angiotensin II type 1 receptor blocker, irbesartan, and a calcium channel antagonist, amlodipine, markedly prevented coronary arteriosclerotic lesion formation and the incidence of AMI and improved the prognosis of those mice, along with ameliorating all those pro-arteriosclerotic parameters. The 2/3NX triple NOSs$^{-/-}$ mouse is a new experimentally useful model of AMI. Renin–angiotensin system activation, oxidative stress, cardiovascular risk factors, and SDF-1α-induced recruitment of bone marrow-derived VSMC progenitor cells appear to be involved in the pathogenesis of AMI in this model.

1. Introduction

Acute myocardial infarction is a disorder in which cardiac myocytes undergo necrosis as a consequence of interrupted coronary blood flow [1]. Acute myocardial infarction is a major cause of morbidity and mortality worldwide, with more than 7 million people in the world suffering from acute myocardial infarction each year [1]. Over the past two decades, the in-hospital mortality rate after admission for acute myocardial infarction has substantially declined to less than 10%, owing to

Abbreviations: ACE, angiotensin-converting enzyme; ADMA, asymmetric dimethylarginine; AMI, acute myocardial infarction; APC, activated protein C; apo E, apolipoprotein E; AT_1, angiotensin II type 1; CKD, chronic kidney disease; ECG, electrocardiography; FITC, fluorescein isothiocyanate; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HDL, high-density lipoprotein; mAb, monoclonal antibody; NO, nitric oxide; NOS, NO synthase; NX, nephrectomy; Sca-1$^+$, stem cell antigen-1$^+$; SDF-1α, stromal cell-derived factor-1α; VSMC, vascular smooth muscle cell; WHHL, Watanabe heritable hyperlipidemic; WT, wild-type.

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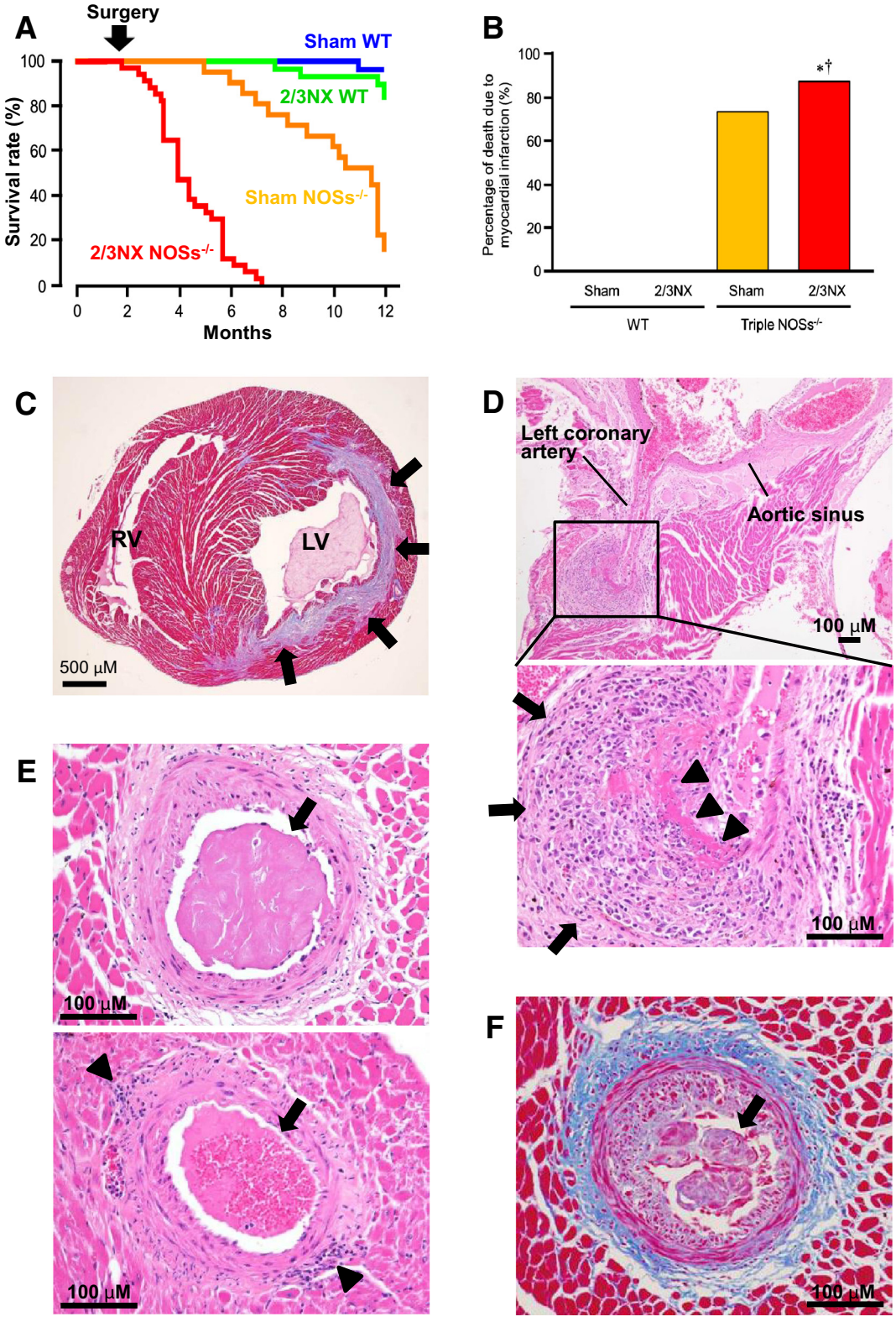

Fig. 1. Sudden cardiac death due to spontaneous myocardial infarction in 2/3 nephrectomized (NX) male triple nitric oxide synthases (NOSs)-deficient mice. (A) Survival rate ($n = 28$–49). NOSs$^{-/-}$, triple NOSs$^{-/-}$ mice; WT, wild-type mice; sham, sham-operated. (B) Percentage of death due to myocardial infarction in the total causes of death ($n = 2$–32). Sham, sham operation. (C) Lateral wall myocardial infarction (arrows) (Azan staining). LV, left ventricle; RV, right ventricle. (D) Marked infiltration of inflammatory cells (arrows) and fibrinoid necrosis (triangles) at the adventitia of the left coronary artery (hematoxylin-eosin staining). (E) Intracoronary thrombi (arrows) and adventitial infiltration of inflammatory cells (triangles) (hematoxylin–eosin staining). (F) Intimal thickening, perivascular fibrosis (blue color), and intracoronary thrombus (arrow) (Azan staining). (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.)