Caveolin-1 deficiency exacerbates cardiac dysfunction and reduces survival in mice with myocardial infarction

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Abnormalities in myocardial ischemia (MI)-induced cardiac dysfunction still remain to be determined. We determined the outcome of a permanent left anterior descending coronary artery (LAD) ligation in Cav-1 knockout (KO) mice. Wild-type (WT) and Cav-1 KO mice were subjected to permanent LAD ligation for 24 h. The progression of ischemic injury was monitored by echocardiography, hemodynamic measurements, 2,3,5-triphenyltetrazolium chloride staining, and Western blot analyses. Cav-1 KO mice subjected to LAD ligation displayed reduced survival compared with WT mice. Despite similar infarct sizes, Cav-1 KO mice subjected to MI showed reduced left ventricular (LV) ejection fraction and fractional shortening as well as increased LV end-diastolic pressures compared with their WT counterparts. Mechanistically, Cav-1 KO mice subjected to MI exhibited reduced β-adrenergic receptor density at the plasma membrane as well as decreased cAMP levels and PKA phosphorylation. In conclusion, ablation of the Cav-1 gene exacerbates cardiac dysfunction and reduces survival in mice subjected to MI. Mechanistically, Cav-1 KO mice subjected to LAD ligation display abnormalities in β-adrenergic signaling.

How these different signaling pathways spatially and temporally interact with each other. Caveolae are 50- to 100-nm invaginations of the plasma membrane that compartmentalize numerous signaling molecules such as endothelial nitric oxide (NO) synthase (eNOS), ERK1/2, and tyrosine kinases as well as different heterotrimeric G protein subunits (8, 13, 20, 27, 35, 36). Caveolin (Cav) proteins represent the principal structural components of the caveolar domains (9, 26, 30). The Cav gene family consists of three distinct genes: namely, Cav-1, Cav-2, and Cav-3 (9, 30, 33, 39). Cav-1 and Cav-2 are usually coexpressed and are particularly abundant in endothelial cells, fibroblasts, smooth muscle cells, adipocytes, and epithelial cells, whereas Cav-3 appears to be muscle specific and is expressed in cardiac, skeletal, and smooth muscle cells (32, 33, 37, 39). Although Cav-3 was originally believed to be the only isomorph expressed in cardiomyocytes, Cav-1 and Cav-2 expressions have been recently reported in mouse, rat, and human cardiomyocytes (2, 3, 11, 22, 29).

Interestingly, Cav-1 has recently been involved in the pathogenesis of ischemic injuries (12, 15, 25). For instance, modulations of endogenous Cav-1 expression have been reported in rat models of ischemic acute renal failure, myocardial infarction, and cerebral ischemia-reperfusion (12, 15, 25). Importantly, the generation of Cav knockout (KO) mice strongly supports the role of Cav-1 in the pathogenesis of ischemic injuries (12, 38). Indeed, we and others (12, 38) have previously reported that ablation of the Cav-1 gene in mice increased the extent of ischemic injury in models of cerebral and hindlimb ischemia. Recent evidence has also suggested that Cav-1 and caveolar domains might be involved in the pathogenesis of myocardial ischemic injury (21, 22).

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we determined the outcome of a permanent left anterior descending coronary artery (LAD) ligation in Cav-1 KO mice.

METHODS

Animals. This study was conducted according to guidelines of the National Institutes of Health (NIH) and Thomas Jefferson University Institute for Animal Studies. Cav-1 KO mice were generated as we have previously described (26). All mice used in this study were on the FVB/N genetic background and were housed in a barrier facility at the Thomas Jefferson University.

Materials. Cav-1 and Cav-3 mouse monoclonal antibodies were the generous gifts of Dr. Roberto Campos-Gonzalez (BD-Pharmingen, San Diego, CA). Rabbit polyclonal antibodies to PKA-C and phospho-PKA-C (Thr197) were purchased from Cell Signaling Technology (Danvers, MA). A mouse monoclonal antibody to GAPDH was purchased from Fitzgerald Industries (Acton, MA). Rabbit and mouse horseradish peroxidase (HRP)-conjugated secondary antibodies were purchased from BD-Pharmingen.

Surgical procedures. Eight-week-old wild-type (WT) and Cav-1 KO FVB/N male mice were anesthetized with a mixture of xylazine (5 mg/kg) and ketamine (50 mg/kg) (Pfizer Animal Health, Monmouth, NJ), intubated, and ventilated with a small rodent ventilator (Harvard Apparatus, Holliston, MA) at a rate of 110 cycles/min with a tidal volume of 2 ml/min and a positive end-expiratory pressure of 2 cmH2O. A left side thoracotomy was performed, and the pericardium was incised. MI was then induced through permanent ligation of the LAD with a 8-0 silk suture (Fine Science Tools, Foster City, CA) proximal to its bifurcation from the main stem (n = 24 and 31 for WT and Cav-1 KO mice, respectively). The incision was subsequently closed with a 5-0 silk suture (Harvard Apparatus). Sham-operated mice were subjected to the same experimental procedure except for the ligation of the LAD (n = 20 mice/group). WT and Cav-1 KO mice were then allowed to recover in a temperature-controlled environment.

Echocardiography. Transthoracic echocardiography was performed in anesthetized mice [2% (vol/vol) isoflurane] at 24 h post-LAD ligation using the VisualSONICS VeVo 770 imaging system with a 12-MHz scanhead (n = 6–10 mice/group). Two-dimensional targeted M-mode imaging was obtained from the short-axis view at the level of the greatest left ventricular (LV) dimension. We performed three measurements for each animal, and the average was taken in consideration for analysis. All three measurements were highly reproducible. End diastole was determined at the maximal LV diastolic dimension, and end systole was taken at the peak of posterior wall motion. VisualSONICS analysis software was used to calculate LV fractional shortening (FS) and ejection fraction (EF) using previously described formulas (23, 24). The percentage of LV FS was calculated as follows: FS (in %) = (LVEDD − LVESD)/LVEDD × 100, where LVEDD and LVESD are LV end-diastolic and end-systolic diameters, respectively. The percentage of LV EF was calculated as follows: EF (in %) = (LVEDV − LVESV)/LVEDV × 100.
100, where LVEDV and LVESV are LV end-diastolic and end-systolic volumes, respectively.

**Hemodynamic experiments.** Twenty-four hours after LAD ligation, mice were anesthetized with xylazine (5 mg/kg) and ketamine (50 mg/kg) followed by 1,000 units of heparin (Sigma-Aldrich). After stable anesthesia was obtained, the right carotid artery was isolated and incised, and a Millar catheter (SPR-671, Millar Instruments, Houston, TX) was advanced into the LV for hemodynamic measurements (n = 7–12 mice/group). LV pressures were measured and recorded with the Pnomah P3 data-acquisition system (LDS Test and Measurement, Middleton, WI).

**Determination of the area at risk and infarct size.** Twenty-four hours after LAD ligation, mice were anesthetized with xylazine (5 mg/kg) and ketamine (50 mg/kg). Two milliliters of 2% Evans blue dye (Sigma-Aldrich) was then retrogradely injected into the aorta to delineate the in vivo area at risk (AAR; n = 21 and 18 for WT and Cav-1 KO mice, respectively). The heart was then excised, placed in a Z2 Zoom trinocular microscope and photographed with a digital camera (Powershot S31S, Canon). The AAR and infarct area were quantified using NIH ImageJ software. Infarct size was determined using the following previously described equation (17): weight of infarction = (A1 × W1) + (A2 × W2) + (A3 × W3), where A is the percent area of infarction obtained by planimetry of sections 1–3 and W is the weight of the same numbered sections.

**Determination of cardiac NO metabolites.** Measurements of the total nitrate/nitrite concentration in LVs of sham-WT, MI-WT, sham-Cav-1 KO, and MI-Cav-1 KO mice were performed using a Nitrate/Nitrite Colorimetric Assay Kit (Cayman Chemical, Ann Harbor, MI), which is based on the enzymatic conversion of nitrate to nitrite by nitrate reductase, followed by the spectrophotometric quantitation of nitrite levels using Griess reagent (n = 7–8 mice/group).

**Cardiac β-adrenergic receptor density and CAMP measurements.** β-Adrenergic receptor (β -AR) density was measured in isolated cardiac plasma membranes from the viable, healthy portion of the LV free wall by saturation ligand binding with [125I]iodocyanopindolol, as previously described (n = 4–6 mice/group) (14, 28). Nonspecific binding was determined in the presence of 20 μM alpenrodol. Data were analyzed by nonlinear regression analysis using GraphPad Prism (GraphPad software). cAMP levels in cardiac lysates of the viable, healthy portion of the LV free wall were measured with a Cyclic AMP PLUS EIA kit (BioMol, Plymouth Meeting, PA), as previously described (n = 4–6 mice/group) (14, 28).

**Immunoblot analyses.** Whole LVs from sham-WT, MI-WT, sham-Cav-1 KO, and MI-Cav-1 KO mice were homogenized in RIPA lysis buffer containing protease and phosphatase inhibitors (n = 6 mice/group). Lysates were centrifuged at 12,000 g for 10 min to remove the insoluble debris. Bicinchoninic acid reagent was subsequently used to determine the protein concentration of each sample as well as the volume required for 50 μg of protein. Proteins were then separated by SDS-PAGE and transferred to nitrocellulose membranes. Membranes were placed in blocking solution for 30 min and subsequently washed with 10 mM Tris, 150 mM NaCl, and 0.05% Tween 20 (1 × Tris-buffered saline-Tween 20). Membranes were incubated with a primary antibody for 3 h. Finally, HRP-conjugated secondary antibodies were used to detect bound primary antibody using SuperSignal chemiluminescence substrate (Pierce Biotechnology, Rockford, IL). Western blots were quantitated using NIH Imagej software (using the mean gray value for each band). The band intensities were compared using the log-rank test. Differences between other variables were evaluated by either an unpaired Student’s t-test or one-way ANOVA followed by Tukey’s multiple-group comparisons.
RESULTS

Cav-1 KO mice subjected to MI display reduced survival. To gain insight on the role of Cav-1 in the pathogenesis of myocardial ischemic injury, male WT and Cav-1 KO mice were subjected to permanent LAD ligation for 24 h. The mortality rate was then determined as the percentage of mice that initially recovered from surgery but subsequently died within the next 24 h. Interestingly, Cav-1 KO mice show a marked reduction in survival at 24 h postischemia (58.1 ± 2.6%) compared with WT mice subjected to the same procedure (87.5 ± 2.6%) and Cav-1 KO (51.0 ± 1.7%) mice subjected to MI displayed reduced survival at 24 h postischemia (58.1 ± 2.6%) compared with WT mice subjected to the same procedure (87.5 ± 2.6%; Fig. 1). Note that most Cav-1 KO mice died at later time points rather than early after surgery and that dead animals were not used for any of the analyses presented below.

WT and Cav-1 KO mice subjected to MI display similar infarct size. As shown in Fig. 2, Cav-1 KO mice subjected to permanent LAD ligation for 24 h showed similar infarct size/AAR (87.1 ± 1.6%) and infarct size/LV (44.1 ± 1.2%) as WT mice subjected to the same procedure [84.0 ± 1.6% and 43.5 ± 0.9%, respectively, P = not significant (NS)]. Importantly, both WT (52.1 ± 1.6%) and Cav-1 KO (51.0 ± 1.7%) mice subjected to MI displayed comparable AARs (AAR/LV, P = NS; Fig. 2).

Cav-1 KO mice subjected to MI display impaired LV function. As expected, both WT and Cav-1 KO mice subjected to permanent LAD ligation for 24 h displayed reduced LV function as assessed by transthoracic echocardiography (P < 0.05; Fig. 3 and Table 1). However, Cav-1 KO mice subjected to MI show reduced LV EF (24.1 ± 2.2%) and LV FS (11.1 ± 1.1%) compared with WT mice subjected to the same procedure (40.3 ± 1.7% and 19.6 ± 1.0%, respectively, P < 0.05; Fig. 3). Accordingly, Cav-1 KO mice subjected to MI also displayed increased LV end-diastolic pressures (LVEDP) compared with their WT counterparts (P < 0.05; Table 2). Importantly, heart rates were similar in all groups (P = NS; Table 1).

WT and Cav-1 KO mice subjected to MI display similar cardiac NO levels. Although there was a trend toward increased cardiac NO metabolites in Cav-1 KO mice subjected to sham surgery compared with their WT counterparts (65.1 ± 12.7 vs. 35.7 ± 6.2 pmol/mg tissue, P = 0.069; Fig. 4), both WT and Cav-1 KO mice subjected to MI displayed similar cardiac NO metabolites (64.5 ± 21.9 vs. 68.3 ± 17.9 pmol/mg, P = NS; Fig. 4).

Cav-1 KO mice subjected to MI display reduced plasma membrane β-AR density. Both WT and Cav-1 KO mice subjected to permanent LAD ligation for 24 h displayed reduced β-AR density at the plasma membrane compared with WT and Cav-1 KO mice subjected to sham surgery (P < 0.05; Fig. 5A). Importantly, Cav-1 KO mice subjected to MI exhibited a marked reduction in plasma membrane β-AR density compared with WT mice subjected to the same procedure (5.3 ± 1.1 vs. 11.5 ± 0.7 fmol/mg, respectively, P < 0.05; Fig. 5A).

Cav-1 KO mice subjected to MI display reduced cardiac cAMP levels and PKA activity. Both WT and Cav-1 KO mice subjected to permanent LAD ligation for 24 h displayed reduced cardiac cAMP levels compared with WT and Cav-1 KO mice subjected to sham surgery (P < 0.05; Fig. 5B). Importantly, Cav-1 KO mice subjected to MI exhibited a greater reduction of cardiac cAMP levels compared with WT mice subjected to the same procedure (14.3 ± 1.2 vs. 23.4 ± 3.1 pmol/mg tissue).

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Fig. 4. Although there was a trend toward increased cardiac nitric oxide (NO) metabolites in Cav-1 KO mice subjected to sham surgery compared with their WT counterparts, both WT and Cav-1 KO mice subjected to permanent LAD ligation for 24 h showed similar cardiac NO metabolites. n = 7–8 mice/group.

Fig. 5. Cav-1 KO mice subjected to permanent LAD ligation for 24 h showed reduced β-adrenergic receptor (β-AR) plasma membrane density (A) and cardiac cAMP levels (B) compared with WT mice subjected to the same procedure. n = 4–6 mice/group. *P < 0.05 vs. sham mice; †P < 0.05 vs. WT mice subjected to MI.
pmol/mg, respectively, \( P < 0.05 \); Fig. 5B). Our Western blot analyses further demonstrated that hearts of Cav-1 KO mice subjected to MI displayed reduced phosphorylation of PKA on the Thr\(^{197}\) residue compared with those of WT mice subjected to the same procedure \( (P < 0.05; \) Fig. 6).

**DISCUSSION**

Caveolar microdomains are particularly abundant in cells of the cardiovascular system such as endothelial cells, smooth muscle cells, cardiac fibroblasts, and cardiomyocytes (32, 33, 37, 39). Interestingly, caveolar microdomains have previously been involved in cardioprotection (21, 22). For instance, a reduction of caveolae number has been reported in the rabbit myocardium after severe anoxia/reoxygenation (6). Moreover, exposure of adult mouse cardiomyocytes to isoflurane before simulated ischemia-reperfusion has been shown to increase the number of caveolae and reduce cell death (22). Disruption of caveolae with methyl-\(\beta\)-cyclodextrin (M\(\beta\)CD) has further been shown to abolish ischemic preconditioning- and opioid-induced cardioprotection in adult rat cardiomyocytes subjected to simulated ischemia-reperfusion (21).

Although Cav-3 was originally believed to be the only caveolin isoform present in cardiomyocytes, it is now well recognized that Cav-1 is expressed in all cardiac cell types including cardiomyocytes (2, 3, 11, 22, 29). For instance, coimmunoprecipitation of Cav-1 with Cav-3 was observed in lysates of adult mouse and rat cardiomyocytes (11). Western blot and immunofluorescence analyses also revealed the expression of Cav-1 in adult mouse cardiomyocytes (2, 3, 22). Moreover, freeze-fracture electron microscopy combined with immunogold labeling recently demonstrated the expression of Cav-1 in human cardiomyocytes (29). Importantly, Cav-1 was also recently involved in the pathogenesis of myocardial ischemic injuries (22, 25). For instance, although its total protein expression remained unchanged, a dissociation of Cav-1 from caveolae to the cytosol was reported in hearts of rats subjected to MI (25). This dissociation was suggested to increase cytosolic Cav-1/eNOS complexes and to, consequently, reduce NO.
production (25). Furthermore, the phosphorylation of Cav-1 has been suggested to contribute to ischemic preconditioning-induced cardioprotection (22). Indeed, Patel et al. (22) reported an increased phosphorylation of Cav-1 in hearts of WT mice after isoflurane exposure and ischemic preconditioning. Mechanistically, the phosphorylation of Cav-1 appears necessary for the recruitment of COOH-terminal Src kinase and the subsequent deactivation of Src (1, 22). Accordingly, Cav-1 KO mice have been shown to be resistant to isoflurane-induced cardiac protection (22). However, although it appears to be involved in ischemic preconditioning, the role of Cav-1 in MI-induced cardiac dysfunction remains unclear. Our present results demonstrate that Cav-1 KO mice subjected to permanent LAD ligation for 24 h displayed reduced survival compared with their WT counterparts. Interestingly, despite similar AAR and infarct sizes, hearts of Cav-1 KO mice subjected to MI displayed impaired cardiac function, as indicated by reduced LV FS and EF and increased LVEDP compared with their WT counterparts.

Mechanistically, Cav-1 is particularly well known for its negative regulation of eNOS activity (7, 8). Indeed, direct interaction of eNOS with the Cav-1 scaffolding domain (residues 82–101) has previously been shown to inhibit eNOS activity (7, 8). Accordingly, Cav-1 KO mice display decreased vascular tone and microvascular hyperpermeability secondary to eNOS hyperactivation (26, 34). Therefore, to evaluate if increased NO production could be involved in the impaired cardiac function observed in Cav-1 KO mice subjected to MI, we subsequently determined the cardiac NO metabolites in hearts of WT and Cav-1 KO mice subjected to either sham surgery or LAD ligation. Interestingly, although there was a trend toward increased cardiac NO metabolites in Cav-1 KO mice subjected to sham surgery compared with WT mice subjected to the same procedure, both WT and Cav-1 KO mice subjected to LAD ligation displayed similar cardiac nitrate/nitrite levels. Thus, the impaired cardiac function observed in Cav-1 KO mice subjected to LAD ligation is unlikely to be ascribed to increased NO production. However, further studies with NO inhibitors are warranted to confirm such a conclusion.

Activation of the β-adrenergic signaling pathway also plays an important role in the regulation of cardiac function. The β-adrenergic signaling pathway consists of β-ARs activating the G protein subunit, Gsα, which, in turn, stimulates the effector, adenylyl cyclase (AC). AC is then responsible for the production of the second messenger cAMP, which activates PKA. PKA subsequently phosphorylates different proteins involved in cardiac inotropy, chronotropy, and lusitropy, such as L-type Ca2+ channels, phospholamban, and troponin I. Importantly, caveolar domains have previously been shown to compartmentalize several molecules involved in the β-adrenergic signaling pathway, such as β-AR, Gsα, AC, cAMP, and PKA (20, 27, 35, 36). Caveolar domains may thus serve as platforms to optimize cardiac β-adrenergic signaling. Accordingly, disruption of caveolar domains with MβCD has previously been shown to inhibit forskolin- and isoproterenol-stimulated cAMP production in cultured rat neonatal cardiomyocytes (18). On the other hand, Cav proteins may also promote signaling via enhanced receptor-effector coupling. In fact, Cav-3 has been shown to directly interact with β-AR, Gsα, and AC in rat cardiomyocytes (10, 19, 31). However, although previous reports have investigated the function of caveolae and Cav-3 in β-adrenergic signaling, the role of Cav-1 in the modulation of cardiac β-adrenergic signaling still remains elusive. Interestingly, our present results demonstrate that hearts of Cav-1 KO mice subjected to MI exhibit reduced plasma membrane β-AR density. In addition, hearts of Cav-1 KO mice subjected to permanent LAD ligation displayed reduced cAMP levels as well as reduced PKA activity, as assessed by the phosphorylation of PKA on the Thr197 residue, compared with their WT counterparts. The impaired LV function observed in Cav-1 KO mice subjected to MI could thus be attributed, at least in part, to reduced β-adrenergic signaling (Fig. 7). Importantly, as Cav-1 KO cardiomyocytes retain caveolae formation (4), the defects in β-adrenergic signaling observed here are likely to be ascribed to a lack of Cav-1 protein expression. Cav-1 might thus act as a chaperone or scaffolding protein that spatially and temporally facilitates the interactions of the different members of the β-adrenergic signaling pathway. Accordingly, decreased responses to the AC agonist forskolin as well as reduced cAMP levels in response to the β3-AR agonist CL-316,243 were recently reported in primary adipocytes derived from Cav-1 KO mice (16). Furthermore, ablation of the Cav-1 gene has been shown to alter β-AR function and reduce PKA activity in the mouse small intestine (5).

Study limitations. In the present study, we used a mouse model of permanent LAD ligation. However, permanent coronary occlusion is relatively rare clinically compared with occlusion/reperfusion. Importantly, Patel et al. (22) previously reported similar infarct sizes in WT and Cav-1 KO mice subjected to LAD ligation for 30 min followed by 2 h of reperfusion. Mechanistically, we show that ablation of the Cav-1 gene reduces cardiac β-adrenergic signaling, the role of Cav-1 in the modulation of cardiac β-adrenergic signaling still remains elusive. Interestingly, our present results demonstrate that hearts of Cav-1 KO mice subjected to MI exhibit reduced plasma membrane β-AR density. In addition, hearts of Cav-1 KO mice subjected to permanent LAD ligation displayed reduced cAMP levels as well as reduced PKA activity, as assessed by the phosphorylation of PKA on the Thr197 residue, compared with their WT counterparts. The impaired LV function observed in Cav-1 KO mice subjected to MI could thus be attributed, at least in part, to reduced β-adrenergic signaling (Fig. 7). Importantly, as Cav-1 KO cardiomyocytes retain caveolae formation (4), the defects in β-adrenergic signaling observed here are likely to be ascribed to a lack of Cav-1 protein expression. Cav-1 might thus act as a chaperone or scaffolding protein that spatially and temporally facilitates the interactions of the different members of the β-adrenergic signaling pathway. Accordingly, decreased responses to the AC agonist forskolin as well as reduced cAMP levels in response to the β3-AR agonist CL-316,243 were recently reported in primary adipocytes derived from Cav-1 KO mice (16). Furthermore, ablation of the Cav-1 gene has been shown to alter β-AR function and reduce PKA activity in the mouse small intestine (5).
reperfusion. Nevertheless, future studies should determine the effect of a genetic ablation of Cav-1 on cardiac function and activation of the β-adrenergic signaling pathway in models of coronary occlusion/reperfusion.

The exclusion of dead animals from the AAR and infarct size measurements could have created a potential selection bias as Cav-1 KO animals that died could have had larger infarcts. However, as mentioned above, similar infarct sizes have been reported in WT and Cav-1 KO mice subjected to coronary occlusion/reperfusion (22). Nonetheless, our results demonstrate the importance of exacerbated contractile dysfunction in the absence of infarct alterations. Indeed, despite similar AAR and infarct sizes, hearts of Cav-1 KO mice subjected to MI displayed impaired cardiac function, as indicated by reduced LV FS and EF and increased LVEDP compared with their WT counterparts. Exacerbated contractile dysfunction could thus contribute to the reduced survival observed in Cav-1 KO mice subjected to MI.

Conclusions. Ablation of the Cav-1 gene exacerbates cardiac dysfunction and reduces survival in mice subjected to myocardial ischemic injury. Mechanistically, Cav-1 KO mice subjected to permanent LAD ligation display abnormalities in β-adrenergic signaling.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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