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CLINICAL PERSPECTIVE

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Citation	He, Shun, Benjamin G. Chousterman, Ashley Fenn, Atsushi Anzai, Manfred Nairz, Martin Brandt, Ingo Hilgendorf, et al. 2015. " Lp-PLA 2 Antagonizes Left Ventricular Healing After Myocardial Infarction by Impairing the Appearance of Reparative MacrophagesCLINICAL PERSPECTIVE ." Circ Heart Fail 8 (5) (July 31): 980–987. doi:10.1161/circheartfailure.115.002334.
Published Version	10.1161/CIRCHEARTFAILURE.115.002334
Citable link	http://nrs.harvard.edu/urn-3:HUL.InstRepos:23606069
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Lp-PLA₂ antagonizes left ventricular healing after myocardial infarction by impairing the appearance of reparative macrophages

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Short title: Lp-PLA₂ in myocardial infarction

Key words: monocyte, macrophage, myocardial infarction, healing

Background: Healing after myocardial infarction (MI) involves the biphasic accumulation of inflammatory Ly-6C^{high} and reparative Ly-6C^{low} monocytes/macrophages. Excessive inflammation disrupts the balance between the two phases, impairs infarct healing, and contributes to left ventricle remodeling and heart failure. Lipoprotein-associated phospholipase A₂ (Lp-PLA₂), a member of the phospholipase A₂ family of enzymes, produced predominantly by leukocytes, participates in host defenses and disease. Elevated Lp-PLA₂ levels associate with increased risk of cardiovascular events across diverse patient populations, but the mechanisms by which the enzyme elicits its effects remain unclear. This study tested the role of Lp-PLA₂ in healing after MI.

Methods and Results: In response to MI, Lp-PLA₂ levels markedly increased in the circulation. To test the functional importance of Lp-PLA₂, we generated chimeric mice whose bone marrow-derived leukocytes were Lp-PLA₂-deficient (*bmLp-PLA₂^{-/-}*). Compared to WT controls, *bmLp-PLA₂^{-/-}* mice subjected to MI had lower serum levels of inflammatory cytokines TNF α , IL-1 β and IL-6, and decreased number of circulating inflammatory myeloid cells. Accordingly, *bmLp-PLA₂^{-/-}* mice developed smaller and less inflamed infarcts with reduced numbers of infiltrating neutrophils and inflammatory Ly-6C^{high} monocytes. During the later, reparative phase, infarcts of *bmLp-PLA₂^{-/-}* mice contained Ly-6C^{low} macrophages with a skewed M2-prone gene expression signature, increased collagen deposition, fewer inflammatory cells, and improved indices of angiogenesis. Consequently, the hearts of *bmLp-PLA₂^{-/-}* mice healed more efficiently, as determined by improved left ventricle (LV) remodeling and ejection fraction.

Conclusions: Lp-PLA₂ augments the inflammatory response after myocardial infarction and antagonizes healing by disrupting the balance between inflammation and repair, providing a rationale for focused study of ventricular function and heart failure after targeting this enzyme acutely in MI.

Myocardial infarction (MI) is a leading cause of death worldwide¹. Although the case fatality rate of MI has declined, survival with development of long-term left ventricular dysfunction due to cumulative ischemic myocardial damage has added to the growing epidemic burden of chronic heart failure. The human, social, and economic consequences of chronic ischemic cardiomyopathy present a major challenge and unmet medical need. Patients who initially survive MI must overcome a major obstacle: ischemia damages the heart, and effective cardiac repair likely requires a precise balance between removal of debris and formation of a scar that is compatible with heart function. MI survivors frequently develop heart failure; while many therapeutics in current use have proven beneficial, the high residual morbidity and mortality presents an urgent problem that requires a better understanding of the disease's pathophysiology.

Over the last several years, neutrophils, monocytes and macrophages have emerged as consequential to the inflammatory and healing process that occurs after MI². We now understand that ischemic injury triggers the accumulation of these myeloid cells in the infarcted myocardium^{3, 4}. Shortly after onset of ischemia, large numbers of neutrophils and inflammatory Ly-6C^{high} monocytes infiltrate the infarcted myocardium and produce IL-1 β , IL-6, and TNF α . Within 4-5 days, Ly-6C^{high} monocytes give rise to Ly-6C^{low} reparative macrophages³, which potentiate healing via VEGF, TGF β , and IL-10. The two phases comprising inflammatory Ly-6C^{high} monocyte recruitment and reparative Ly-6C^{low} macrophage differentiation are essential to post-MI recovery; their perturbation (i.e., in the context of co-morbidities) leads to impaired heart function and heart failure^{3, 4}.

Lipoprotein-associated phospholipase A₂ (Lp-PLA₂), a member of the phospholipase A₂ family of enzymes, hydrolyses glycerophospholipids. The ensuing enzymatic reactions frequently generate metabolic signaling molecules with a multitude of biological actions. For example, by hydrolysing phosphatidylcholine at C2 of the glycerol backbone, Lp-PLA₂ produces lysophosphatidylcholine (lysoPC)⁵, which fosters oxidative stress, affects vascular smooth muscle cell proliferation, and increases tissue accumulation of macrophages⁶. A number of observational studies showed that Lp-PLA₂ levels correspond with future cardiovascular events such as acute myocardial infarction and sudden cardiac death.⁷⁻⁹ While preliminary studies reported reduced development of advanced coronary atherosclerosis¹⁰ or stabilization of the necrotic core size¹¹ with selective inhibition of Lp-PLA₂ by the inhibitor darapladib, two recently completed phase III trials did not provide evidence in favor of inhibiting Lp-PLA₂ in cardiovascular disease¹². Neither study focused on left ventricular function nor chronic heart failure endpoints. Moreover, it remains unclear whether Lp-PLA₂ participates in the inflammatory and reparative phases that characterize the innate immune response shortly after MI; these pathways likely influence left

ventricular remodeling and the development of chronic ischemic cardiomyopathy. This study sought to evaluate whether Lp-PLA₂ participates in infarct healing and HF after MI.

Methods

For further details, see the online Supplemental Material.

Animals and animal experiments. 8-10 weeks old Female C57BL6/J (WT) were purchased from the Jackson Laboratory (Bar Harbor, ME). Lp-PLA₂-deficient mice (*Lp-PLA₂^{-/-}*) were kindly provided by Glaxosmithkline Pharmaceuticals Ltd (King of Prussia, PA 19112). All protocols were approved by the Animal Review Committee at Massachusetts General Hospital. C57BL6/J mice were lethally irradiated and reconstituted with WT and *Lp-PLA₂^{-/-}* bone marrow to generate respective chimeric mice. The chimeras had normal leukocyte counts and exhibited no obvious abnormalities, consistent with the Lp-PLA₂-deficient mice¹³. Myocardial infarction (MI) was induced by permanent ligation of the left anterior descending artery. We observed no differences in mortality between the groups.

Lp-PLA₂/PAF acetyl-hydrolase activity assay. The PAF hydrolase activity assay was performed as previously described¹⁴ with modifications using [³H]PAF (Platelet Activating Factor, 1-O-Hexadecyl-[Acetyl-³H(N)]-, Hexadecyl PAF) as a substrate. Unlabeled PAF (1-O-Hexadecyl-2-O-acetyl-sn-glycero-3-phosphorylcholine) was purchased from Enzo Life Sciences, 1-O-Hexadecyl-2-O-[Acetyl-³H(N)]-, Hexadecyl PAF, [acetyl-³H]-, (250μCi (9.25MBq) was purchased from Perkin Elmer, and Bio-Safe II was purchased from Research Products International Corp., Mount Prospect, IL.

Histology. Murine hearts were embedded in Tissue-Tek O.C.T compound (Sakura Finetek) and prepared for sectioning and staining.

Flow cytometry and flow assisted cell sorting. Antibodies used for flow cytometry are listed in the online Supplemental Material. Data were acquired on a BD LSRII and analyzed with FlowJo. Cells were sorted with BD AriaII.

Reverse transcription PCR. RNA was isolated from sorted cells with the RNeasy Micro Kit (Qiagen). Quantitative real-time TaqMan PCR was run on a 7500 PCR thermal cycler (Applied Biosystems).

Magnetic resonance imaging (MRI). MRI was carried out on days 1 and 21 after permanent coronary ligation as described perviously³. We obtained cine images of the left ventricular short axis by using a 7 Tesla horizontal bore Pharmascan (Bruker) and a custom-built mouse cardiac coil (Rapid Biomedical). Late gadolinium enhancement was performed on day 1 to determine infarct size. Acquisition was done as

described previously¹⁵. Images were analyzed using the software Segment (<http://segment.heiberg.se>). The end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), left ventricle volume (LVM), heart rate and cardiac output (CO) were measured.

Statistics: Results are shown as mean \pm SEM. Unpaired Student's t-test was applied to evaluate differences between two groups. One-way ANOVA with post-hoc Tukey's multiple comparisons test was performed when comparing more than two groups between days, because different mice were sacrificed on each time points for organ harvest. P-values of 0.05 and less denote significant changes.

Results

Expression of Lp-PLA₂ after MI and its role on healing

To elucidate whether Lp-PLA₂ participates in healing after MI, we first measured Lp-PLA₂ expression and serum activity in steady state and after MI. Lp-PLA₂ mRNA expression by RT-PCR increased in the infarcts of wild type (WT) mice as early as 1 day after MI (**Fig. 1A**), suggesting Lp-PLA₂ may participate in myocardial ischemic injury. Concordantly, Lp-PLA₂ activity was also increased shortly after MI (**Fig. 1B**). To define the role of Lp-PLA₂ in hematopoietic cells in the pathophysiology of acute MI, we generated chimeric mice by irradiating and reconstituting WT mice with bone marrow either from WT or *Lp-PLA₂^{-/-}* (*bmLp-PLA₂^{-/-}*) mice. In comparison to WT mice, *bmLp-PLA₂^{-/-}* mice had lower Lp-PLA₂ activity at steady state, and this activity did not change after MI (**Fig. 1B**). These findings establish leukocytes as major sources of Lp-PLA₂ in response to MI. We then evaluated infarct healing and demonstrated a significant decrease in infarct size in *bmLp-PLA₂^{-/-}* mice 7 days after MI compared to WT (**Fig. 1C, D**).

Lp-PLA₂ influences systemic inflammation

Coronary occlusion stimulates an inflammatory response characterized by cytokine and chemokine production, and leukocyte recruitment to the heart. Because Lp-PLA₂ participates in inflammation, we assessed the effect of Lp-PLA₂ deficiency after MI. Serum concentrations of inflammatory cytokines TNF α , IL-1 β and IL-6 increased dramatically in WT mice on day 1 after MI, and eventually declined to undetectable amounts on day 7. In contrast, *bmLp-PLA₂^{-/-}* mice showed only moderately elevated TNF α and IL-6, and negligibly increased IL-1 β , demonstrating a diminished inflammatory response in the absence of Lp-PLA₂ (**Fig. 2A**). Time-course profiling of circulating leukocytes after MI revealed that both WT and *bmLp-PLA₂^{-/-}* mice augmented inflammatory myeloid cells (neutrophils and Ly-6C^{high} monocytes), but compared to WT mice, *bmLp-PLA₂^{-/-}* mice had fewer neutrophils and Ly-6C^{high} cells in blood at days 3 and 7, indicating Lp-PLA₂ contributes to the systemic inflammation after MI (**Fig. 2B, C**).

Lp-PLA₂ impairs the appearance of reparative macrophages

The myocardium displays a biphasic monocyte and macrophage response during MI^{3,4}. In the first phase, inflammatory Ly-6C^{high} monocytes infiltrate the ischemic myocardium from the blood and participate in inflammation. In the second phase, reparative Ly-6C^{low} macrophages contribute to collagen deposition and scar formation. We profiled leukocytes in the myocardium in the steady state and 1, 3 and 7 days after MI in both WT and *bmLp-PLA₂^{-/-}* mice. The infarcts of both strains accumulated neutrophils, which peaked on day 1, Ly-6C^{high} monocytes, which peaked on day 3, and Ly-6C^{low} macrophages, which peaked on day 7 (**Fig. 3A, B**). This finding agrees with our previous observations^{3,4}. Yet, for nearly every peak, infarcts of *bmLp-PLA₂^{-/-}* mice accumulated only half the number of cells (neutrophils on day 1 and Ly-6C^{high} monocytes on day 3) compared to WT controls, consistent with our observations in the blood (**Fig. 2**), and affirming that Lp-PLA₂ aggravates inflammation.

Aside from determining the number of cells that accumulate (quantity), macrophage activity (quality) is an essential measure of the cells' impact on inflammation and repair. We asked whether Lp-PLA₂ shapes macrophage function by measuring expression of signature M1/M2 genes in sorted cardiac macrophages. In comparison to WT macrophages, *Lp-PLA₂^{-/-}* macrophages exhibited higher expression of mRNAs that encode M2-associated genes (Arg, IL-10, CD36, Fizz) and lower levels of those corresponding to M1-associated genes (MMP-3, MMP-9, TLR9, TLR4) (**Fig. 3C**). These data are consistent with the idea that lysophosphatidylcholine, a product of Lp-PLA₂, potentiates an M1-like macrophage phenotype.¹⁶ Together, these data show that Lp-PLA₂ promotes recruitment of inflammatory myeloid cells and delays the appearance of reparative macrophages in the ischemic myocardium.

Lp-PLA₂ retards healing after myocardial infarction

The differences in leukocyte recruitment between WT and *bmLp-PLA₂^{-/-}* mice prompted us to determine whether the absence of Lp-PLA₂ affects the repair of the ischemic myocardium. To this end, we profiled myeloid cell infiltration, extracellular matrix deposition, neovascularization, and smooth muscle cell accumulation by immunohistochemistry (**Fig. 4**). Compared with WT controls, the myocardium of *bmLp-PLA₂^{-/-}* mice accumulated fewer myeloid CD11b⁺ cells, indicating less severe inflammation. Infarcts of *bmLp-PLA₂^{-/-}* mice also had larger regions of extracellular matrix deposition, as evidenced by higher percentage of collagen I⁺ areas (24% versus 32%), larger CD31⁺ areas (5% vs 11%), suggesting improved neovascularization of the heart, but no changes in the number of smooth muscle actin⁺ myofibroblasts (α -SMA⁺ area). Collectively, the results of histologic examination demonstrate more effective healing in the absence of Lp-PLA₂. These results demonstrate that Lp-PLA₂ inhibits the resolution of inflammation after MI.

Improved heart function in the absence of Lp-PLA₂

To test whether inflammation mediated by Lp-PLA₂ after MI translated to impaired heart function, we performed magnetic resonance imaging (MRI) *in vivo* in WT and *bmLp-PLA₂^{-/-}* mice. In the steady state, we detected no differences in cardiac function between WT and *bmLp-PLA₂^{-/-}* mice. After permanent coronary artery ligation, the end-diastolic volume (EDV) and end-systolic volume (ESV), ejection fraction (EF), left ventricle volume (LVM), heart rate and cardiac output (CO) were measured in individual mice on day 1 and day 21 after MI. Late gadolinium enhancement was performed on day 1 to determine infarct size (**Fig. 5A, B and Table 1**). The infarct sizes were similar on day 1 in both groups, excluding a potential surgical bias (**Fig. 5B**). Although LVM increased similarly between the two groups on day 21, increased EDV was only observed in WT mice, indicating more favorable remodeling in mice lacking Lp-PLA₂. Moreover, compared with day 1, EF at day 21 diminished in WT mice but increased modestly in *bmLp-PLA₂^{-/-}* mice, suggesting improved recovery of heart function in the absence of Lp-PLA₂. Overall, the data show that Lp-PLA₂ aggravates LV remodeling and impairs LV function after MI.

Discussion

Recruitment of neutrophils and Ly-6C^{high} monocytes into the infarcted myocardium and the subsequent generation of reparative macrophages from Ly-6C^{high} monocytes contribute to necrotic debris clearance, matrix deposition, granulation tissue formation, and angiogenesis. Perturbations in the inflammatory response impair infarct healing and promote heart failure¹⁷⁻¹⁹. This study shows that deficiency of Lp-PLA₂ on hematopoietic cells attenuates systemic inflammation after MI, impairs leukocyte infiltration into infarcts, and enhances generation of reparative Ly-6C^{low} macrophages, leading to less adverse LV remodeling and improved recovery of LV function. Together, the data show that Lp-PLA₂ modulates inflammation after MI and suggest that targeting of Lp-PLA₂ might lessen LV dysfunction and the development of chronic heart failure following myocardial infarction.

Monocyte-derived macrophages can produce substantial Lp-PLA₂²⁰, and in the mouse Lp-PLA₂ is expressed almost exclusively by myeloid cells (www.immgen.org). Previous studies have identified macrophage Lp-PLA₂ expression at both the mRNA and protein levels in human and rabbit aortic lesions²¹. Plaques with characteristics of vulnerable and ruptured atheromata, but not early lesions, contain abundant Lp-PLA₂²². Therefore, extensive efforts have been taken to prevent atherosclerosis-related coronary heart disease by inhibiting Lp-PLA₂ and thus promoting plaque stability¹². But Lp-PLA₂ may participate in coronary heart disease by modulating inflammation independent of effects on the plaque itself. For example, our data showed that Lp-PLA₂ rose dramatically during MI. As a phospholipase, increased Lp-PLA₂ hydrolyzes phospholipids of oxidatively damaged cells or lipoproteins. Lp-PLA₂ hydrolyzes oxidized phosphatidylcholine, generating lysoPC and oxidized fatty acids that are capable of acting as monocyte chemoattractants as well as maintaining macrophages in a pro-inflammatory phenotype^{6, 16, 23}. Lp-PLA₂ can also contribute to inflammation by interfering with

phagocytic clearance of apoptotic cells, e.g. neutrophils, via cleavage and removal of oxidized phosphatidylserine, a known “eat-me” signal²⁴. Consistent with this hypothesis, we found that *bmLp-PLA₂^{-/-}* mice had milder inflammatory responses as well as fewer neutrophils and Ly-6C^{high} monocytes accumulating in the myocardium. This reduced number of inflammatory leukocytes ameliorated adverse LV remodeling and improved heart function recovery. Therefore, our data strongly support a role for Lp-PLA₂ in increased risk of heart failure by directly promoting systemic and local myocardial inflammatory responses after MI, functions distinct from effects on the atherosclerotic plaques. Our experiments, performed with bone marrow chimeras, demonstrate an effect on MI healing with a ~80% knockdown of Lp-PLA₂, indicating this is a sufficient reduction to elicit positive effects. Future studies will need to elucidate in more detail the full scope of Lp-PLA₂ function not only on leukocyte behavior, but also on effects attributed to other cells in the heart, such as fibroblasts and endothelial cells.

Recently, two large multi-center phase III trials completed evaluation of the Lp-PLA₂ inhibitor darapladib on the reduction of cardiovascular adverse events in over 28,000 patients with documented coronary heart disease. These two complementary trials covered both chronic and acute coronary heart disease and evaluated traditional coronary heart disease endpoints. Thus, these studies did not formally focus on LV function or long-term development of heart failure^{25, 26}. The *Stabilization of pLaques us/Ing Darapladib-Thrombolysis in Myocardial Infarction (SOLID-TIMI 52)* trial enrolled patients within 30 days of acute coronary syndrome (ACS) and the *STabilization of Atherosclerotic plaque By Initiation of darapLad/b TherapY (STABILITY)* trial enrolled patients with stable chronic coronary heart disease. Despite promising preclinical results¹⁰, both clinical trials concluded that direct inhibition of Lp-PLA₂ with darapladib failed to reduce major adverse cardiovascular events^{12, 27}. Crucially, the trials did not test whether blockade of Lp-PLA₂ *per se* was beneficial: patients receiving darapladib or placebo were already receiving up to 4 different therapeutics against heart disease, including statins and ACE inhibitors. The trials therefore showed that under the specific parameters of the study, darapladib did not provide benefit above that afforded by current treatment regimens.

Our results provide an alternative explanation as to why the clinical trials might not have improved the tested end-points. Our data show that, as early as day 1 after MI, expression of Lp-PLA₂ was increased. In the absence of Lp-PLA₂, inflammatory leukocyte recruitment was blunted, yielding a smaller inflammatory response that correlated with improved healing and heart function 7 and 21 days later, respectively. Lp-PLA₂ might elicit its most detrimental effects in the acute phase after MI. If so, blocking the enzyme earlier than the SOLID or STABILITY trials might benefit endpoints related to LV function. Several human studies have shown data in support of the idea that healing of the infarcted myocardium involves the biphasic accumulation of monocytes and macrophages. In one study, a cohort of 36 patients monitored over two weeks after MI demonstrated a peak of circulating inflammatory CD16⁻ monocytes

on day 2.6 after MI, followed by another peak of CD16⁺ monocytes on day 4.8.¹⁹ Because CD16⁻ monocytes resemble inflammatory Ly-6C^{high} monocytes whereas CD16⁺ monocytes (and in particular CD16⁺ CD14^{dim}) resemble Ly-6C^{low} monocytes, these findings suggest that acute inflammation may likewise peak in humans within one week after MI. Immediate inhibition of Lp-PLA₂ might be the optimal time window for improving outcomes related to LV function. The SOLID trial, which enrolled patients within 30 days, did not test whether patients receiving darapladib within the first 3 days post MI benefited from treatment. Hence, the clinical trial findings do not argue against the role of Lp-PLA₂ in inflammation after MI.

In summary, the data demonstrate that Lp-PLA₂ regulates the host response after MI through modulation of inflammation. By enhancing inflammation and impairing repair, the induced Lp-PLA₂ negatively regulates recovery of LV function. In addition to stimulating atherosclerotic plaque vulnerability, the effect of Lp-PLA₂ after MI reveals a novel role of this enzyme in modulating the myocardial response to ischemic injury. These mechanistic insights have implications for developing effective therapeutics against ischemic cardiomyopathy and chronic heart failure post MI.

Acknowledgements

The authors thank Michael Waring and Nathalie Bonheur for sorting cells.

Sources of Funding

This work was supported in part by GSK funding (GlaxoSmithKline: Targeting Lp-PLA₂ in Inflammatory Cardiovascular Disease) and by NIH grants 1R01HL095612 and R56AI104695 (to F.K.S.).

Disclosures

None.

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Figure Legends

Figure 1: Lp-PLA₂ activity and mRNA expression during myocardial infarction. **A**, mRNA levels quantified by Realtime PCR in wild-type (WT) mice at the indicated time points after MI. Day 0 represents the steady state mice. Results are presented as mean \pm SD, ** $p \leq 0.01$, $n = 5-10$ per group. **B**, Plasma Lp-PLA₂ activity in chimera WT and *bmLp-PLA₂^{-/-}* mice at steady state and in *bmLp-PLA₂^{-/-}* mice at indicated time points after MI. ** $p \leq 0.01$, $n = 5-10$ per group. **C**, Quantification of infarct size on day 1 and 7 after MI in WT and *bmLp-PLA₂^{-/-}* mice (left). * $p \leq 0.05$, $n = 4-6$ per group. **D**, Representative images of infarct size on day 7 after MI were shown in both WT and *bmLp-PLA₂^{-/-}* mice.

Figure 2: LP-PLA₂ moderately affects systemic inflammation. **A**, ELISA analysis of plasma levels of TNF α , IL-1 β and IL-6 in wild-type (WT) and *bmLp-PLA₂^{-/-}* mice at the indicated time points after MI. **B**, Representative flow cytometric images of leukocyte profiling of blood in wild-type (WT) and *bmLp-PLA₂^{-/-}* mice, **C**, Quantification of total leukocytes, neutrophils, Ly-6C^{high} monocytes, Ly-6C^{low} monocytes in the blood. Results in one of three experiments with similar patterns are presented as mean \pm SEM, * $p \leq 0.05$, ** $p \leq 0.01$ (WT vs. *bmLp-PLA₂^{-/-}*) vs. $n = 5$ per group.

Figure 3: Attenuated inflammatory response in *bmLp-PLA₂^{-/-}* myocardial infarct tissue. **A**, Representative images for flow cytometric analysis of MI tissue cell suspensions at the indicated time points after MI in WT and *bmLp-PLA₂^{-/-}* mice. **B**, Flow cytometry based quantification of neutrophil, monocyte and M Φ (macrophage) numbers in MI tissue of WT versus *bmLp-PLA₂^{-/-}* mice before and 1, 3, and 7 days post MI. Results in one of three experiments with similar patterns are presented as mean \pm SEM, * $p \leq 0.05$, $n = 4$ per group. **C**, Gene expression profiling of WT and *bmLp-PLA₂^{-/-}* macrophages sorted from MI tissue 7 days after permanent LAD ligation. Results are presented as mean \pm SEM percent change of marker expression in *Lp-PLA₂^{-/-}* compared to WT control mice, * $p \leq 0.05$, ** $p \leq 0.01$, $n = 5$ per group.

Figure 4: Improved cardiac remodeling in *bmLp-PLA₂^{-/-}* mice 7 days after myocardial infarction. Immunohistochemical staining of MI tissue for CD11b, Collagen 1 (Col1), CD31, and non-vascular smooth muscle alpha actin (SMA) in wild-type (WT) and *bmLp-PLA₂^{-/-}* chimeric mice 7 days post MI. Quantification of 10 randomly selected fields of view per mouse (5 mice). Results are presented as mean \pm SEM, * $p \leq 0.05$, *** $p \leq 0.001$, $n = 50$ fields of view per group.

Figure 5: Lp-PLA₂ aggravates LV dysfunction after myocardial infarction.

A, Representative MRI images with late gadolinium enhancement (left panels) on day 1 after permanent LAD ligation, and end-systole (middle panels) and end-diastole (right panels) on day 21 of infarcted hearts from WT and *bmLp-PLA₂^{-/-}* mice, respectively. **B**, Quantification of individual changes (Δ) in heart parameters from day 1 to day 21 post MI (day 21 – day 1). Results are presented as mean \pm SD percent change of marker expression in WT and *bmLp-PLA₂^{-/-}* mice, respectively. * $p \leq 0.05$, $n \geq 7$ per group.

Figure 1

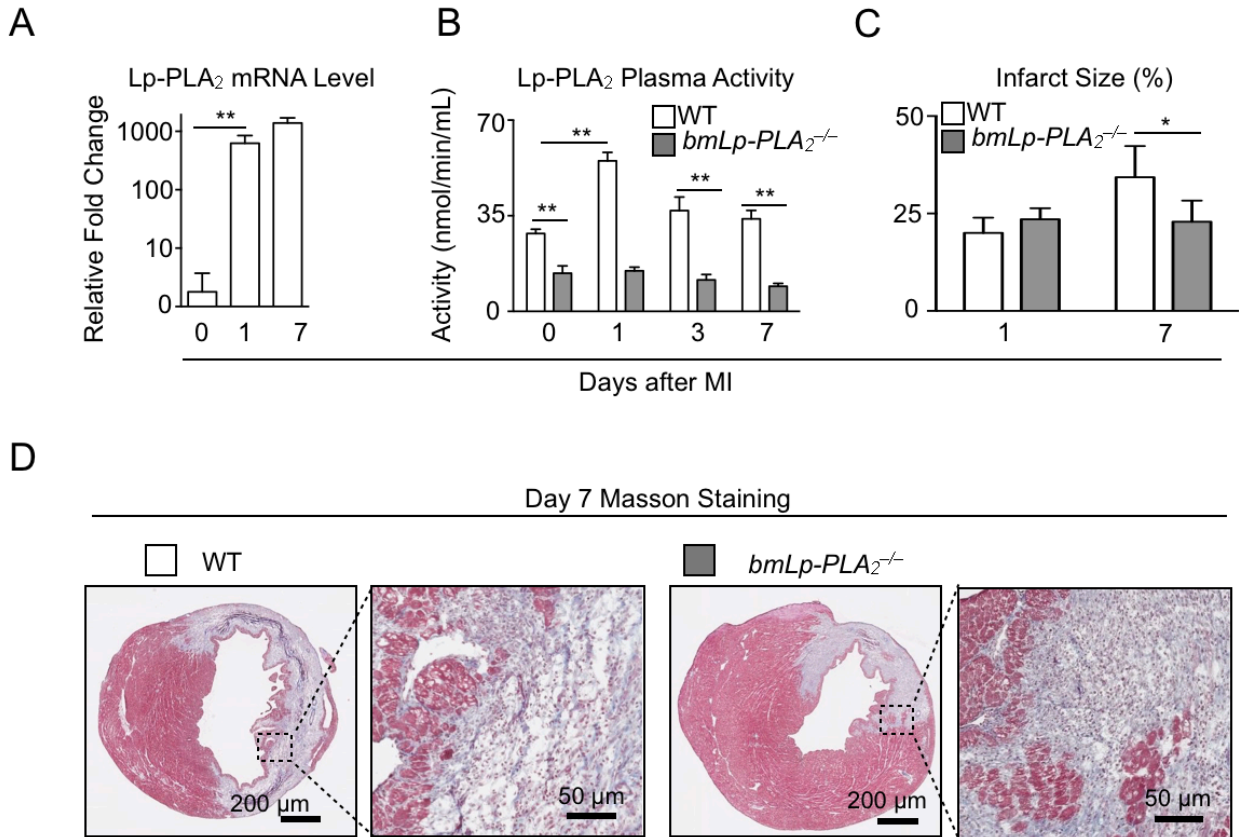


Figure 2

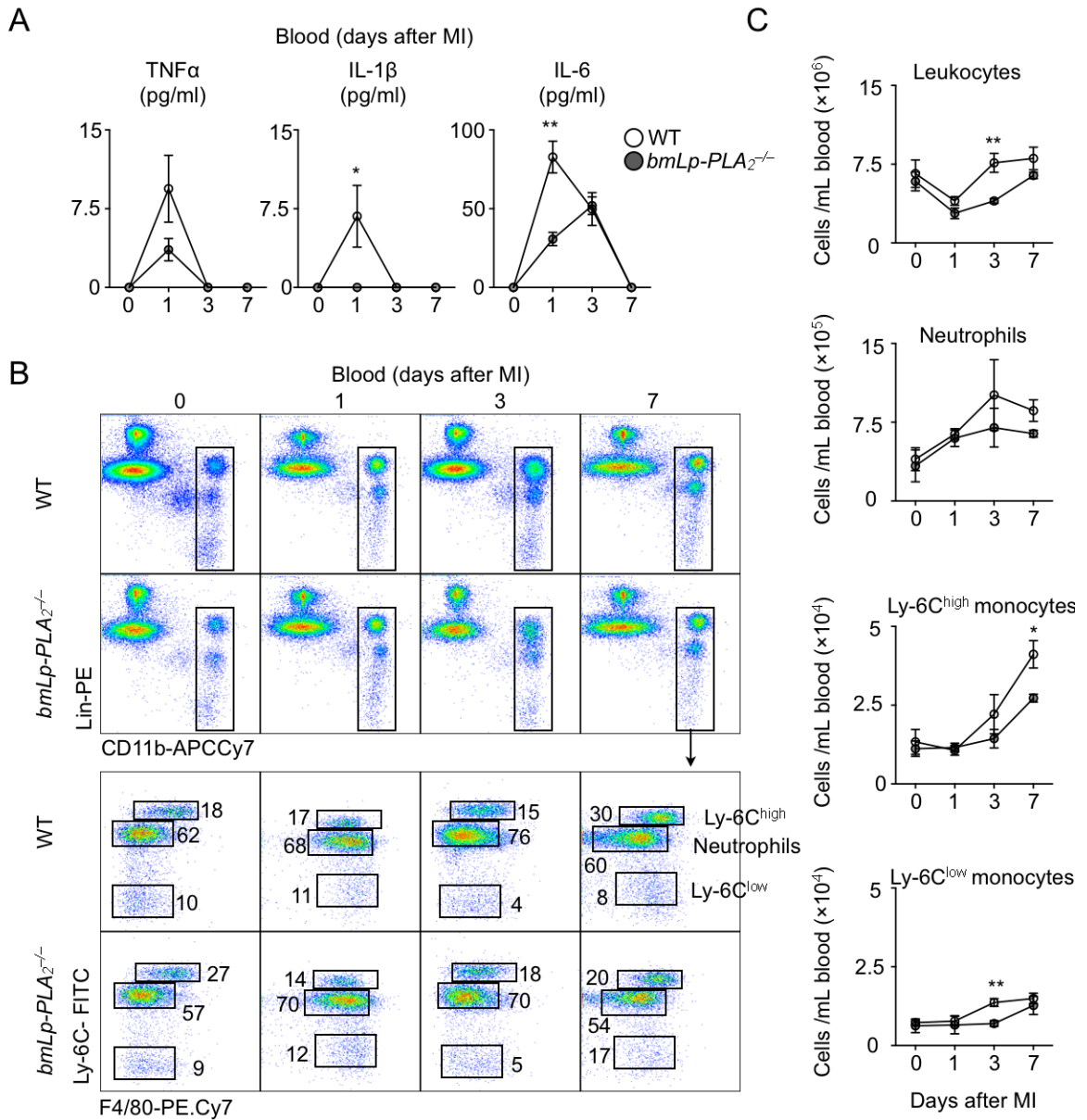


Figure 3

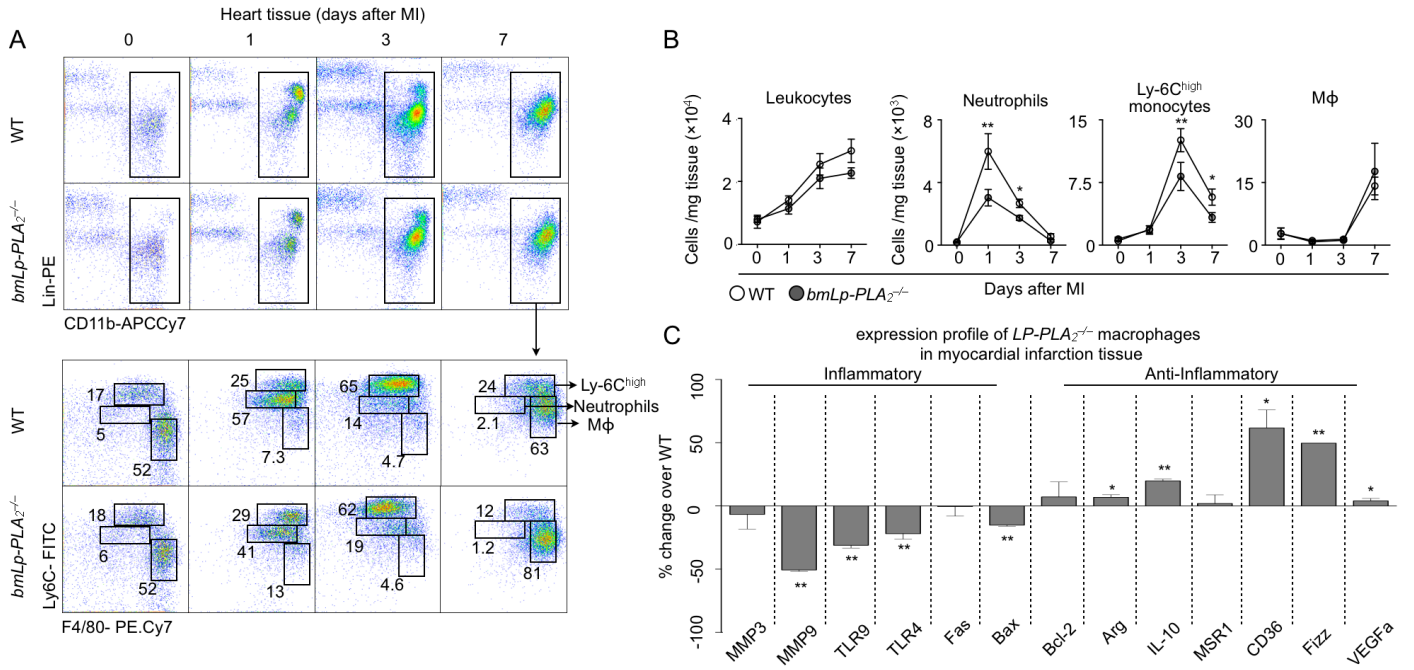


Figure 4

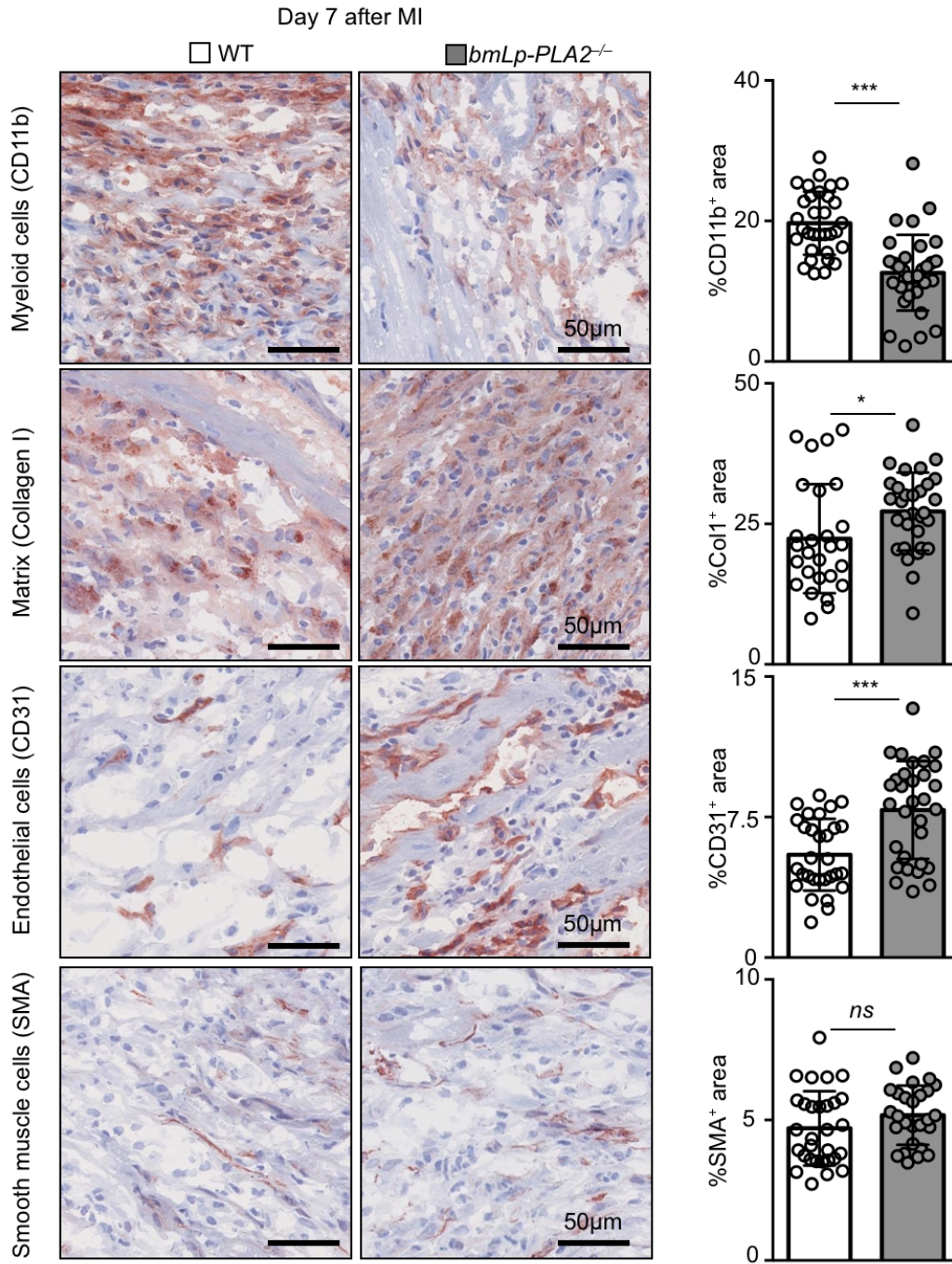
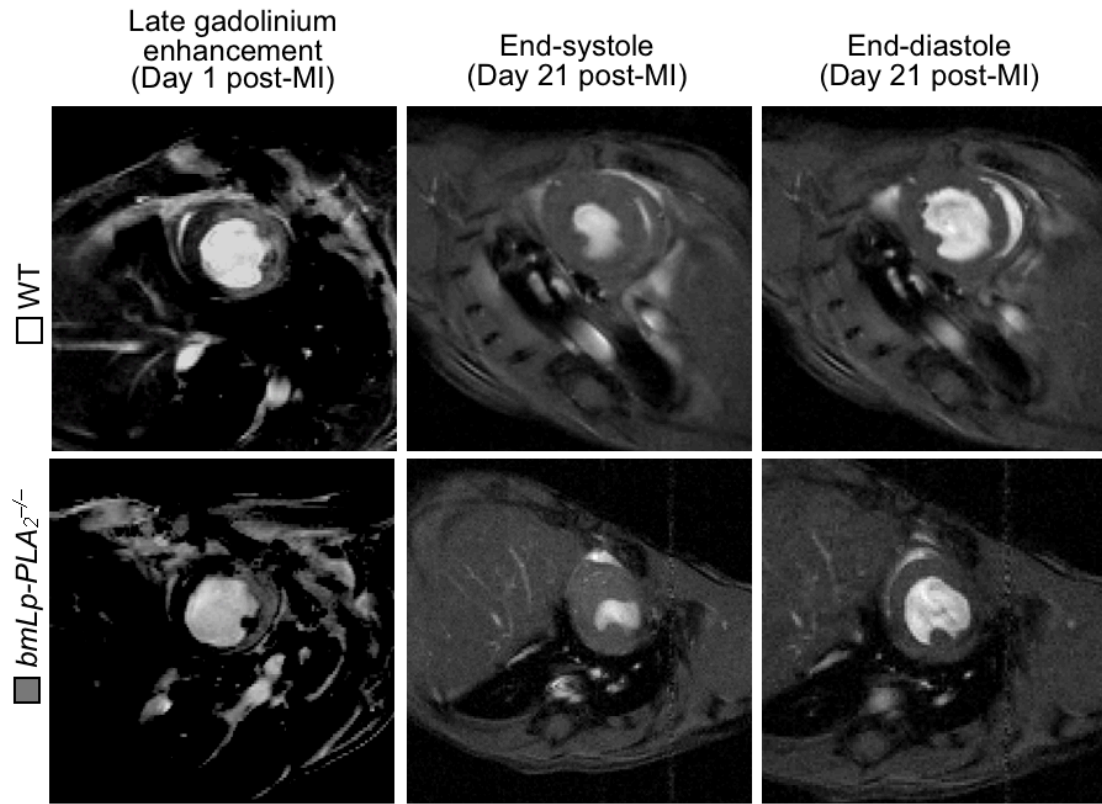


Figure 5

A



B

