Selective Vascular Endothelial Protection Reduces Cardiac Dysfunction in Chronic Heart Failure

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To cite this version:

HAL Id: inserm-02296623
https://inserm.hal.science/inserm-02296623
Submitted on 25 Sep 2019

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A large body of experimental and clinical evidence has accumulated to demonstrate that chronic heart failure (CHF) is associated with profound endothelial dysfunction, including impaired endothelial nitric oxide (NO) production. It is also generally assumed that endothelial dysfunction per se contributes to aggravate CHF, as supported by observations that such dysfunction is associated with increased morbidity/mortality in patients with CHF. Indeed, reduced coronary NO production most likely impairs cardiac perfusion, favors inflammation, and affects cardiac contractility and excitation-contraction coupling. In parallel, reduced NO production/bioavailability in peripheral resistance arteries favors vasocostriction thus contributing to the increased peripheral resistance known to aggravate CHF via increased cardiac afterload. Thus, prevention of endothelial dysfunction is considered an important goal of current CHF treatments.

Paradoxically, although the aggravating effects of endothelial dysfunction in CHF have been largely suggested, this has never been directly demonstrated. Conversely, there is no clear evidence that prevention of endothelial dysfunction per se may in turn reduce CHF. Indeed, although many pharmacological treatments of CHF prevent endothelial dysfunction, the contribution of the endothelium to their beneficial effects in CHF is unclear. In fact, reduction of CHF may per se secondarily reduce endothelial dysfunction, as demonstrated for example with heart rate–reducing agents that are devoid of direct endothelial effects but lead to endothelial protection in CHF. Thus, a direct demonstration of these links requires the development of approaches with “selective” endothelial targeting in CHF.

Key Words: bone marrow ■ endothelium ■ heart failure ■ myocardial infarction ■ nitric oxide
Our group discovered a new approach for endothelial protection in CHF, based on inhibition of the protein tyrosine phosphatase 1B (PTP1B). PTP1B is a ubiquitously distributed protein that dephosphorylates various tyrosine kinase receptors, notably insulin, leptin, and vascular endothelial growth factor receptors, modulates immune signaling, and also acts either as tumor suppressor or tumor promoter depending on the cellular context. Thus, although no results have emerged to date from clinical trials, PTP1B inhibitors are currently tested in patients with obesity or type 2 diabetes mellitus and in patients with breast cancer.

Interestingly, we demonstrated that chronic pharmacological inhibition or whole body gene deletion of PTP1B in CHF not only prevented endothelial dysfunction but also improved left ventricular (LV) function and decreased adverse LV remodeling. However, because PTP1B is expressed in many cells other than the endothelium, the exact role of PTP1B-mediated endothelial protection in these beneficial cardiac effects remains unknown. We thus developed a mouse model of selective endothelial PTP1B deficiency to directly assess the role of endothelial protection in CHF.

Methods

Animals and Surgery

All animal experiments were ethically approved by a certified review board according to French and EU legislation (authorization number 01307.01).

Homozygous loxP PTP1B (later referred to as PTP1B<sup>fl/fl</sup>, C57BL/6J strain, CD45.2<sup>+</sup>) were obtained from Dr Neel (University of Toronto, Canada), and were crossed with transgenic mice expressing Cre recombinase under the control of the Tie2 promoter (The Jackson Laboratory, Bar Harbor, ME). These Tie2-Cre<sup>(+)PTP1B <sup>f/f</sup></sup> mice, later named Tie2PTP1B<sup>−/−</sup>, were compared with Tie2-Cre<sup>(−)</sup> PTP1B<sup>f/f</sup> littermates, used as wild-type (WT) controls lacking PTP1B deletion.

The Tie2-Cre approach induces gene deletion not only in endothelial but also in hematopoietic cells. Thus, to assess the respective roles of PTP1B deletion in the endothelial versus hematopoietic cells and especially restrict the ablation of PTP1B to the endothelium, Tie2PTP1B<sup>−/−</sup> mice were lethally irradiated (10 Gy, Faxitron) 2 months before induction of myocardial infarction (MI) and grafted with 20 million bone marrow (BM) cells from CD45.1 C57/B6 mice (Jackson Laboratory; for chimerism monitoring, see below), to obtain mice with selective endothelial PTP1B deficiency (endoPTP1B<sup>−/−</sup>). They were compared with 3 groups: (1) mice with selective deletion of PTP1B in the hematopoietic compartment (CD45.1 C57/B6 mice irradiated and grafted with BM from Tie2PTP1B<sup>−/−</sup> mice, referred to as Tie2-BM-PTP1B<sup>−/−</sup>), (2) mice without PTP1B deletion (CD45.2 irradiated and grafted with BM from CD45.1 mice referred to as BM-WT, and (3) Tie2PTP1B<sup>−/−</sup> irradiated and grafted with BM from Tie2PTP1B<sup>−/−</sup> mice.

At the end of the experiment, BM cell suspensions from transplanted mice were stained with anti-CD45.1 and anti-CD45.2 (APC-Cy5.5; Becton Dickinson, Franklin Lakes, NJ). The percentage of BM chimerism was evaluated by flow cytometry (FACS Canto II; Becton Dickinson).

MI was induced by left coronary artery ligation in male mice (body weight, 22–25 g), anesthetized with 3.6 mg/kg xylazine IP followed by continuous isoflurane 2% inhalation (1.5 mL/min; Baxter) during artificial ventilation, and sedated with buprenorphine (0.5 mg/kg). Anesthesia and sedation were controlled by monitoring heart rate, and by performing paw pinch reflex and corneal reflex tests.

Procedures for evaluation of cardiac function, remodeling and perfusion, as well as endothelial function, western blotting, polymerase chain reaction (PCR), and immunohistochemistry are described in the Data Supplement.

Statistical Analysis

Data are presented as mean±SEM. For vascular functional studies, comparisons were performed using 2-factor repeated measurement ANOVA. Survival was analyzed by Mantel Cox test. All other comparisons were performed by nonparametric Kruskal–Wallis analysis followed by Dunn post hoc test. P<0.05 was considered significant.

Results

Endothelial PTP1B Deletion

In mesenteric arteries, Tie2PTP1B<sup>−/−</sup> mice displayed significant mRNA expression of the Cre-truncated form of PTP1B, whereas the corresponding reverse transcriptase-PCR signal was low in WT mice. Tie2PTP1B<sup>−/−</sup> mice also displayed a markedly decreased expression of the WT form of PTP1B (Table 1). Immunohistochemistry showed that PTP1B was present in the mesenteric artery endothelium of WT but not in the Tie2PTP1B<sup>−/−</sup> mice (Figure 1A).

Vascular Function

In WT sham mice, the stepwise increase in intraluminal flow induced a progressive increase in mesenteric artery diameter (ie,
marked in Tie2PTP1B−/− than in WT, whereas in both cases, however, the inhibitory effect of L-NNA appeared slightly less
relaxation. In Tie2PTP1B−/− mice with CHF, FMD was mark-
ificantly increased compared with WT CHF, this effect was absent
in Tie2PTP1B−/− mice with CHF (Figure 1D), suggesting that
impaired FMD was entirely because of reduced NO
bioavailability (Figure 1C). Furthermore, arteries from WT CHF
displayed an almost complete abolition of eNOS Ser1177 phos-
phorylation, in the absence of changes of total eNOS (Figure 1E).

In sham mice, FMD was similar in WT and Tie2PTP1B−/−; however, the inhibitory effect of L-NNA appeared slightly less
marked in Tie2PTP1B−/− than in WT, whereas in both the cases,
the L-NNA-resistant response was abolished by MS-PPOH,
suggesting that endothelial PTP1B deficiency tended to
increase the epoxyeicosatrienoic acids–mediated component of
relaxation. In Tie2PTP1B−/− mice with CHF, FMD was mark-
edly increased compared with WT CHF, and was comparable
to that observed in sham (Figure 1B). This was accompanied
by a restored inhibitory effect of L-NNA (Figure 1C) and of
phosphorylated eNOS (Figure 1E), suggesting that it was asso-
ciated with a restoration of the impaired NO production.

Furthermore, although acute in vitro PTP1B inhibition mark-
edly increased FMD in WT CHF mice, this effect was absent
in Tie2PTP1B−/− mice with CHF (Figure 1D), suggesting that
the beneficial arterial effect of this inhibition is indeed because
of blockade of the endothelial PTP1B. Compared with WT,
Tie2PTP1B−/− CHF mice did not show any changes in the di-
latory response to acetylcholine (Figure 2A) or to the NO donor
SNP (Figure 2B). Neither CHF nor PTP1B deletion affected the
arterial expression of inducible nitric oxide synthase, neuronal
nitric oxide synthase, CD45, ICAM-1, and VCAM-1 (Table 1).

**Echocardiography**

In WT mice, CHF was associated with a marked and progres-
sive LV dilatation (Figure 3A–3C), and a 70% decrease in LV
fractional shortening (FS, Figure 3D), accompanied by an
inverted E/A ratio (<1) suggestive of impaired LV diastolic
function (Figure 3E).

PTP1B deletion did not affect LV diameters, FS, or E/A
ratio in sham mice. In contrast, compared with sham CHF
mice, Tie2PTP1B−/− CHF displayed a marked reduction in LV dilatation (Figure 3A–3C), a 75% increase in FS (Figure 3D), and a normalization of E/A ratio (Figure 3E) showing a significant improvement of both LV systolic and diastolic functions.

**LV Hemodynamics**

In WT, CHF decreased diastolic and systolic arterial pressures (Figure 4A and 4B), as well as LV end-systolic pressure and end-systolic pressure/volume relationship (Figure 4D–4F), demonstrating impaired LV systolic function. In parallel, these CHF WT displayed a significant increase in LV end-diastolic pressure and a nonsignificant increase in end-diastolic pressure/volume relationship (Figure 4C–4E), demonstrating diastolic dysfunction.

In sham mice, Tie2PTP1B−/− did not show any differences with WT in arterial or LV pressures. In contrast, compared with WT CHF, Tie2PTP1B−/− CHF displayed an increase in arterial pressures (significant only for systolic pressure, Figure 4A and 4B), a nonsignificant increase in LV end-systolic pressure

**Figure 2.** Effect of chronic heart failure (CHF) and protein tyrosine phosphatase 1B (PTP1B) deletion on (A) acetylcholine-mediated and (B) sodium nitroprusside–mediated vasodilatation of mesenteric arteries (n=9–12). Values are mean± SEM.

**Figure 3.** A, Representative echocardiographic tracings obtained in wild-type (WT) sham, WT chronic heart failure (CHF), and Tie2PTP1B−/− mice. B–D, Evolution with time of left ventricular (LV) systolic diameter (B), LV diastolic diameter (C), and LV fractional shortening (D), evaluated by echocardiography. E, E/A ratio evaluated by transmitral pulsed Doppler at 4 months post-myocardial infarction (MI). Values are mean±SEM (n=8–14 per group). **P<0.01 and ***P<0.001 vs WT sham; †P<0.05, ††P<0.01, and †††P<0.001 vs WT CHF.
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(Figure 4D), and a significant decrease in LV end-diastolic pressure (Figure 4C). Furthermore, Tie2PTP1B<sup>−/−</sup> mice were partly prevented against the CHF-induced decrease in LV end-systolic pressure/volume relationship (Figure 4F) and the increase in LV end-diastolic pressure/volume relationship (Figure 4E); however, these effects did not reach statistical significance.

**Cardiac Remodeling, Perfusion, and Gene Expression**

Infarct size was not significantly different between WT (17.9±0.1% of LV, n=8) and Tie2PTP1B<sup>−/−</sup> mice (20.7±0.1% of LV, n=8). Compared with sham, CHF WT mice displayed significant increases in both LV and RV weights (Figure 5A.
and 5H), LV cardiomyocyte sizes (Figure 5B and 5E), and collagen density (Figure 5C). CHF also increased LV mRNA expression of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP; Figure 5F and 5G; Table 2) as well as matrix metalloproteinase 2 (MMP2), matrix metalloproteinase 9 (MMP9), and neuronal nitric oxide synthase (nNOS) in the absence of detectable changes in tumor growth factor β (TGFβ; Figure 5D; Table 2), eNOS, inducible nitric oxide synthase, CD45, F4/80, α myosin heavy chain, and β myosin heavy chain (Table 2).

Compared with WT, Tie2PTP1B−/− CHF mice showed significantly smaller increases in these parameters of LV and RV hypertrophy and fibrosis, demonstrating reduced adverse cardiac remodeling, associated with reduced LV mRNA expression of ANP, BNP, MMP2, and MMP9 (although not significant for MMP2), in the absence of changes in the expression of the other genes tested (Table 2).

Neither CHF nor PTP1B deletion affected LV capillary density (capillary/myocyte ratio: WT sham 1.09±0.08, n=11; Tie2PTP1B−/− sham: 1.12±0.05, n=11; WT CHF 1.29±0.06, n=10; Tie2PTP1B−/− CHF 1.31±0.06, n=11) or LV perfusion (mL·min⁻¹·g⁻¹: WT sham 11.0±0.7, n=8; Tie2PTP1B−/− sham: 11.2±0.6, n=9; WT CHF 9.7±0.5, n=11; Tie2PTP1B−/− CHF 9.7±0.5, n=16).

**Bone Marrow Transplantation**

In Tie2PTP1B−/− CD45.2 mice irradiated and grafted with CD45.1 (WT) BM, 95±3% of hematopoietic cells were CD45.1 positive, whereas in CD45.1 mice irradiated and grafted with Tie2PTP1B−/− CD45.2 BM, 96±2% of hematopoietic cells were CD45.2 positive demonstrating the excellent efficacy of the transplantation (Figure 6A).

WT (CD45.2) mice reconstituted with CD45.1 BM (WT-BM) displayed similar vascular and cardiac responses to CHF than nonirradiated WT CHF mice, including a near complete abolition of FMD (Figure 6B), similar LV hypertrophy (Figure 6C) and fibrosis (Figure 6E), and similar decrease in LV FS (Figure 6D). Importantly, WT mice reconstituted with BM from Tie2PTP1B−/− mice also did not differ from WT CHF mice in terms of these endothelial and cardiac responses.
In contrast, Tie2PTP1B−/− mice grafted with BM from WT mice (ie, selective endothelial deficiency) displayed signs of cardiovascular protection similar to those of nonirradiated Tie2PTP1B−/− mice described above, including fully restored mesenteric FMD (Figure 6B), markedly and significantly increased LV FS (Figure 6D) as well as decreased LV hypertrophy (Figure 6C) and fibrosis (Figure 6E). These effects were virtually identical to those observed in Tie2PTP1B−/− mice. Together, these results demonstrate that the protective endothelial and cardiac effects observed in Tie2PTP1B−/− mice were entirely because of deletion of PTP1B in vascular endothelial cells and not in hematopoietic cells.

Survival
In WT, CHF markedly decreased survival (46% at 4 months). Mortality occurred essentially between 1 week and 2 months post-MI. Compared with WT, Tie2PTP1B−/− had markedly reduced mortality (86%, Figure 7A). A similar effect on survival was observed in endoPTP1B−/− mice (Figure 7B).

Discussion
The present study, performed in mouse model of MI-induced CHF, shows that selective deletion of PTP1B in the endothelium is not only associated with markedly reduced endothelial dysfunction (ie, restored flow-dependent, NO-mediated dilation, and eNOS phosphorylation in mesenteric arteries) but is also accompanied by reduced CHF as shown by the improved LV function, hemodynamics, and remodeling, as well as a markedly increased survival. To the best of our knowledge, this is the first direct demonstration that prevention of endothelial dysfunction per se leads to a reduction of CHF.

We and others previously revealed that PTP1B is a target for the prevention of endothelial dysfunction, in the context of diabetes mellitus, obesity, and CHF. Many mechanisms may indirectly contribute to this protective effect, especially in the context of chronic in vivo inhibition or gene deletion. However, the fact that in CHF, endothelial function (FMD) and eNOS phosphorylation may be improved by acute in vitro incubation of isolated arteries with a PTP1B inhibitor strongly suggested that a large part of the protective effects directly involve the endothelium (eg, restoration of phosphorylation pathways of eNOS activation) and is not the indirect consequence on the endothelium of improved CHF. In this context, the fact that in the present study, selective endothelial PTP1B deficiency restored endothelial function and flow-induced eNOS phosphorylation to the same extent as that observed after long-term pharmacological inhibition or global gene deletion reinforces the view of the crucial role of endothelial PTP1B in the aggravation of endothelial dysfunction. It must be noted that under some conditions, reduced endothelial dysfunction may also be indirectly caused by nonendothelial PTP1B deletion, as shown for example in obese mice with hepatic PTP1B deficiency, in which the endothelial protective effects are most likely directly caused by nonendothelial PTP1B deletion, as shown for example in obese mice with hepatic PTP1B deficiency, in which the endothelial protective effects are most likely secondary to the simultaneously improved glucose and lipid homeostasis and increased insulin sensitivity. In any case, the markedly reduced endothelial dysfunction observed here in endoPTP1B−/− mice provides a unique situation to assess the cardiac consequences of selective endothelial protection in the context of CHF.

Endothelial protection observed in mice with endothelial PTP1B deficiency was associated with a potent reduction in the severity of CHF. This was observed in terms of echocardiography (increased LV FS and normalized E/A ratio) and invasive LV hemodynamics. In parallel, endothelial protection also triggered profound beneficial effects on LV remodeling, demonstrated by the decreased LV dilatation assessed by

| Table 2. Left Ventricular Expression of Various Genes Assessed by Reverse Transcriptase-Polymerase Chain Reaction |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| WT Sham (n=6) | Tie2PTP1B−/− Sham (n=5) | WT CHF (n=8) | Tie2PTP1B−/− CHF (n=9) |
| eNOS | 1.21±0.04 | 1.07±0.09 | 0.90±0.07 | 1.12±0.03 |
| iNOS | 1.05±0.09 | 1.09±0.10 | 0.76±0.09 | 1.06±0.06 |
| nNOS | 1.13±0.09 | 1.21±0.13 | 0.78±0.06* | 0.93±0.13 |
| CD45 | 0.83±0.07 | 1.30±0.21 | 1.36±0.33 | 1.60±0.19 |
| F4/80 | 0.90±0.05 | 0.93±0.07 | 1.24±0.17 | 1.54±0.14 |
| αMHC | 1.36±0.09 | 1.53±0.07 | 1.04±0.17 | 1.08±0.04 |
| βMHC | 1.11±0.05 | 1.22±0.12 | 0.99±0.11 | 1.07±0.03 |
| ANP | 1.04±0.10 | 1.05±0.21 | 1.98±0.30† | 1.07±0.26§ |
| BNP | 0.73±0.29 | 1.04±0.19 | 3.15±0.42† | 1.63±0.54§ |
| MMP2 | 0.66±0.05 | 0.73±0.06 | 1.64±0.19‡ | 1.17±0.09 |
| MMP9 | 0.45±0.14 | 0.96±0.13 | 1.31±0.14† | 0.71±0.11§ |
| TGFβ1 | 0.81±0.10 | 0.83±0.05 | 1.03±0.08 | 1.01±0.12 |

αMHC indicates α myosin heavy chain; βMHC, β myosin heavy chain; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CHF, chronic heart failure; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; LV, left ventricular; MMP2, matrix metalloproteinase 2; MMP9, matrix metalloproteinase 9; nNOS, neuronal nitric oxide synthase; PTP1B, protein tyrosine phosphatase 1B; TGF, transforming growth factor β; and WT, wild-type.

*P<0.05, †P<0.01, ‡P<0.001 vs WT sham; §P<0.05 vs WT CHF.
echography, together with decreased cardiac hypertrophy and fibrosis, and reduced cardiac ANP and BNP.

We used the Tie2-Cre approach as it is known to be effective and potent for targeted gene deletion in the endothelium. Indeed, it was associated with a profound reduction in the mRNA expression of native (WT; nontruncated) PTP1B in mesenteric arteries. Its expression was not abolished, however, most likely because of the maintained expression of PTP1B in nonendothelial vascular cells, for example, smooth muscle cells. We, however, confirmed by immunohistochemistry using an antibody directed toward the deleted (catalytic) part of the protein that the full-length PTP1B was absent from endothelial cells. This was accompanied by a strong expression of the Cre-truncated form of PTP1B assessed by reverse transcription-PCR. These results show that the Tie2-Cre approach indeed resulted in a profound PTP1B deletion in the

**Figure 6.** A. Flow cytometry analysis of cells expressing CD45.1 (left) and CD45.2 (right) in CD45.2 mice transplanted with CD45.1 bone marrow (BM) (top) or CD45.1 mice transplanted with CD45.2 BM (bottom). B–E, Mesenteric artery flow-mediated dilatation (FMD; B), left ventricular (LV) cardiomyocyte size (C), LV fractional shortening (FS; D), and LV fibrosis (E) in irradiated and transplanted chronic heart failure (CHF) mice. Values are means ± SEM from 5 to 8 animals per group. †P<0.05, ††P<0.01, and †††P<0.001 vs CD45.2 transplanted with CD45.1 BM; §P<0.05, §§P<0.01, and §§§P<0.001 vs CD45.1 transplanted with Tie2PTP1β-/- BM.

**Figure 7.** Evolution of survival for 4 months after myocardial infarction (MI), (A) in sham and chronic heart failure (CHF) wild-type (WT) or Tie2PTP1β-/- mice, and (B) in CHF mice subjected to irradiation and bone marrow (BM) transplantation. †††P<0.001 vs CD45.2 transplanted with CD45.1 BM; §§§P<0.001 vs CD45.1 transplanted with Tie2PTP1β-/- BM.
endothelial cells. However, although commonly used because of its potency, the Tie2 approach has the limitation that it is also associated with gene extinction in hematopoietic Tie2-expressing cells.\textsuperscript{18,19} This was verified in our study (PTP1B mRNA expression in BM cells: WT 1.01±0.05; Tie2PTP1B\textsuperscript{−/−} mice 0.05±0.05). Thus, to separate the effects between endothelial versus hematopoietic PTP1B deletion, and to obtain a model with selective endothelial PTP1B deficiency, we performed additional irradiation/BM transplant experiments. With this technique, we reached a high efficacy of the irradiation/BM transplantation with >95% chimerism. Importantly, we verified that this protocol did not affect endothelial or cardiac function, or the effects of CHF on these parameters. Indeed, WT mice irradiated and transplanted with WT BM had values similar to nonirradiated mice in terms of FMD, LV FS, hypertrophy, and fibrosis, both in sham and CHF mice.

Next, we demonstrated that mice with PTP1B deletion restricted to BM cells displayed no reduction in endothelial dysfunction and no improvement in cardiac function and remodeling. In contrast, mice with PTP1B deletion restricted to the endothelium (endoPTP1B\textsuperscript{−/−}) showed potent endothelial protection and reduction of cardiac dysfunction and remodeling, and these effects were similar to those observed in mice with deletion both in the endothelium and hematopoietic compartments. Thus, importantly, this demonstrates that the observed reduction of CHF is indeed entirely the consequence of PTP1B deletion in the vascular endothelium.

Immunohistochemical and PCR data obtained in arteries with endothelial PTP1B deficiency suggested that PTP1B is also present in arterial smooth muscle cells, although with a lesser expression than that of endothelial cells, as demonstrated by the two third decrease in arterial gene expression in Tie2PTP1B\textsuperscript{−/−} mice. The exact roles of this smooth muscle form of PTP1B are unclear; however, it is unlikely to modulate arterial relaxation as suggested by the absence of changes in the responses to sodium nitroprusside in Tie2PTP1B\textsuperscript{−/−} mice (this study) as well as in mice with global PTP1B deficiency or after pharmacological PTP1B inhibition.\textsuperscript{16}

Increased myogenic tone of resistances arteries (possibly secondary to endothelial dysfunction) is known to contribute to increased peripheral resistance in CHF\textsuperscript{23,24} and thus probably is an aggravating factor this disease. Thus, although we have not addressed this question, it is possible that endothelial PTP1B deletion positively modulates myogenic tone and that this contributes to the overall reduction of CHF. This hypothesis deserves to be tested in subsequent experiments.

The endothelial and cardiac effects of endothelial PTP1B deletion were associated with a significant increase in 4-month survival. This beneficial effect was observed a clinically relevant setting, because in contrast with many mouse studies in which marked mortality occurs within the first week and is low thereafter, virtually all mortality occurred in the present study after the first week post-MI. We think that this low immediate mortality is because of improved postoperative care of the animals.

We hypothesized that the reduction of CHF observed in Tie2PTP1B\textsuperscript{−/−} mice was the consequence of the reduced endothelial dysfunction. One alternative hypothesis would be that it may be partly the consequence of a proangiogenic effect of the deletion. Indeed, we showed previously that global (whole body) PTP1B deletion in mice with MI increased cardiac vascular endothelial growth factor signaling, angiogenesis, and perfusion at 8 days post-MI.\textsuperscript{25} Similarly, mice with endothelial PTP1B deficiency also showed increased vascular endothelial growth factor signaling, together with increased angiogenesis and arteriogenensis in a model of hindlimb ischemia, although cardiac ischemia was not studied in this study.\textsuperscript{26} In contrast, in this study, we found no change in cardiac capillary density or MRI-based LV perfusion at 4 months post-MI. Thus, although we cannot exclude that early changes in angiogenesis or perfusion may have occurred in our study, this would suggest that the reduced CHF severity that we observed is to a large extent independent of changes in cardiac angiogenic responses.

To the best of our knowledge, our study is the first to directly address the consequences of selective reduction of endothelial dysfunction on CHF. Several studies reported the beneficial effects of eNOS overexpression in CHF;\textsuperscript{27} however, this does not fully reproduce reduction of endothelial dysfunction, and in fact cardiac-specific eNOS overexpression is also beneficial in this setting.\textsuperscript{28} A recent study reported reduced cardiac fibrosis and CHF in mice with endothelial P53 deficiency;\textsuperscript{29} however, this study did not evaluate endothelial function and further was performed in a model of transverse aortic constriction that does not recapitulate all the characteristics of changes in endothelial function that can affect CHF (especially changes in cardiac afterload).

In conclusion, using mice with selective endothelial PTP1B deficiency, we demonstrated a direct link between endothelial dysfunction and aggravation of CHF. This not only further supports the concept that PTP1B inhibition is a promising target of this disease but also clearly reinforces the importance of targeting the endothelium in the treatment of CHF.

Acknowledgments

We thank Benjamin Neel for providing the PTP1B\textsuperscript{−/−} mice, Ebba Brakenhielm and Pierre-Alain Thiebaut for useful scientific discussions and manuscript drafting, and Annie Lejeune, Anaïs Dumesnil, and Sylvanie Renet for expert technical assistance.

Sources of Funding

This study was supported by a grant from the Fondation de France. Julie Maupoint was supported by Allocation Region Haute Normandie, Elodie Gomez was supported in part by a grant from the Groupe de Réflexion sur la Recherche Cardiovasculaire.

Disclosures

None.

References


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Although it is usually accepted that endothelial dysfunction contributes to symptoms and progression of chronic heart failure (CHF), the direct deleterious effect of endothelial dysfunction in this setting has not been established. Using a novel approach of selective endothelial protection (endothelial specific deletion of protein tyrosine phosphatase 1B) in a mouse model of CHF postmyocardial infarction, we demonstrated that such selective endothelial protection was sufficient to improve left ventricular function and reduce adverse remodeling. Such a direct demonstration that endothelial protection per se reduces the propensity to develop CHF suggests a causal role for endothelial dysfunction in CHF development. Thus, the endothelium should be considered as a potential target in the treatment to prevent CHF post infarction.