# Diabetic Complications Consortium

**Application Title:** Neuregulin-1ß for the Treatment of Post-MI Heart Failure in Type 1 Diabetes

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## 1. Project Accomplishments:

We have demonstrated that NRG-1β treatment can mitigate the progression of myocardial infarction (MI)-related heart failure (HF) in streptozotocin (STZ)-diabetic rats by: i) improving left ventricular (LV) systolic function, ii) reducing adverse LV remodeling, and iii) suppression of cardiac fibrosis. We have also demonstrated that these cardioprotective effects of NRG-1β in STZ-diabetic post-MI rats occur independently of blood glucose lowering. We have confirmed and validated the therapeutic efficacy of NRG-1β in mitigating the progression of post-MI HF in STZ-diabetic rats through its administration both pre- and post-MI. In addition, we have also shown that pre-treatment with NRG-1β ameliorates early renal damage in STZ-diabetic post-MI rats.

## 2. Specific Aims:

**Specific Aim 1:** *Determine the efficacy of exogenous NRG-1β to improve residual cardiac function after MI in STZ-diabetic rats.*

**Results:**

**I) Intravenous NRG-1β Therapy Mitigates the Progression of Post-MI HF in STZ-Diabetic Rats**

STZ-diabetic post-MI rats were randomly assigned to receive intravenous vehicle (saline) or NRG-1β treatment (100 μg/kg) twice a week starting 7 days after induction of MI. Echocardiographic asessment of LV systolic function one week after MI (immediately prior to initiation of NRG-1β therapy) in STZ-diabetic rats showed similar LV dysfunction and failure in both groups **(Figure 1A)**. In the vehicle-treated STZ-diabetic post-MI rats, echocardiography showed that LV fractional shortening (FS) and LV ejection fraction (EF) progressively decreased over time **(Figure 1A)**. In contrast, echocardiography showed LVFS and LVEF preservation in the STZ-diabetic post-MI rats that received NRG-1β treatment **(Figure 1A)**. The treatment effects became apparent at 4 weeks of treatment and was maintained throughout the 7 weeks treatment duration **(Figure 1A).**

On the basis of these results, we then performed a pre-treatment study with NRG-1β to determine whether additional benefit could be conferred against the progression of post-MI HF in STZ-diabetic rats. In this pre-treatment study, NRG-1β treatment (same dose and frequency as above) was started in STZ-diabetic rats 2 weeks prior to induction of MI. Echocardiography showed higher LVFS and LVEF among the pre-treated group of STZ-diabetic rats at 2 weeks post-MI **(Figure 1B)**, indicating an earlier onset of the HF-sparing effects of NRG-1β.

NRG-1β-induced cardioprotection and restriction of HF occurred independently of blood glucose reduction when administered either pre-or post-MI (**Figure 2)**.

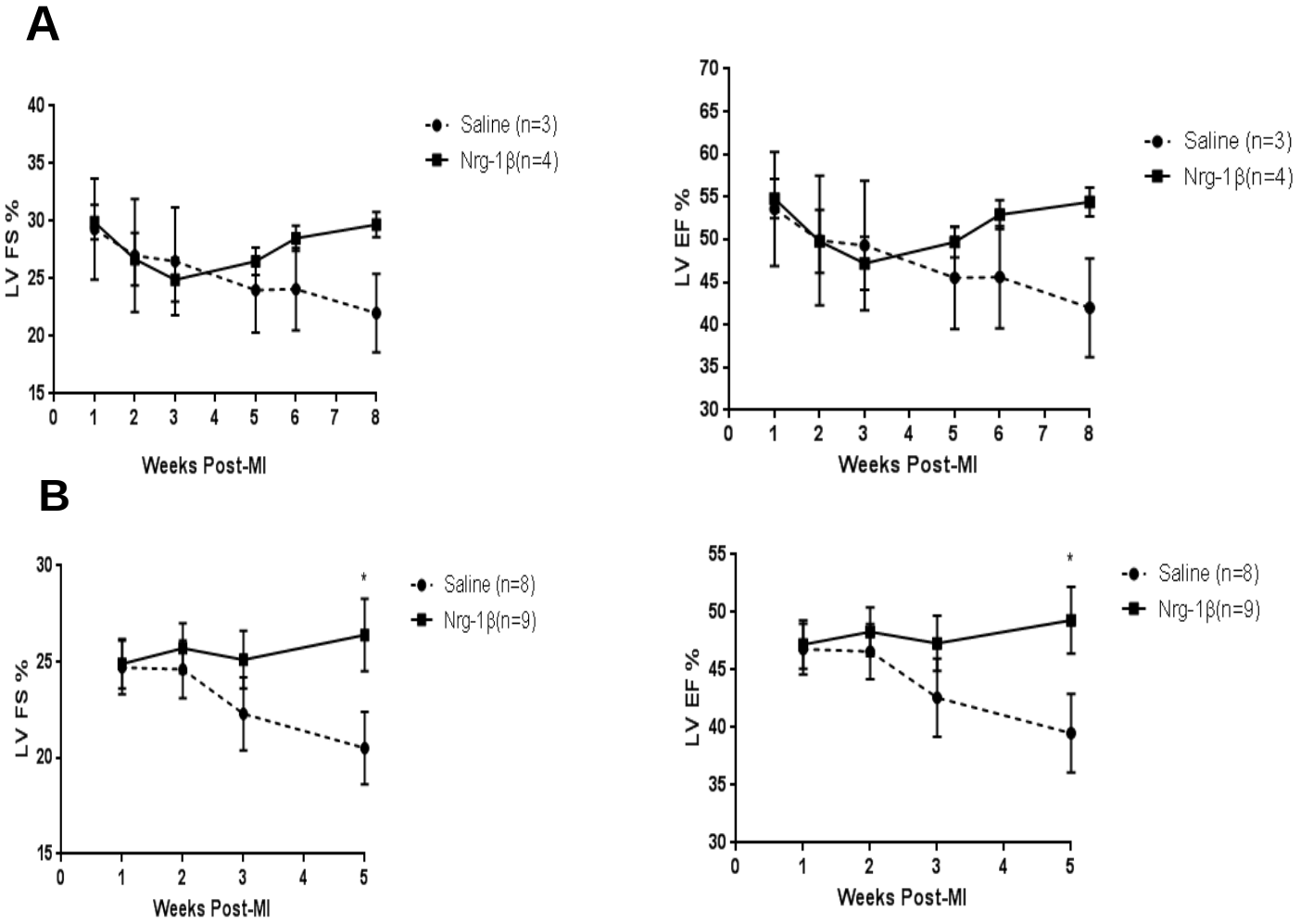



**Figure 1.** Effects of NRG-1β treatment on residual LV function in STZ-diabetic post-MI rats. Top Panel **(A)**, LVFS and LVEF in STZ-diabetic post-MI rats treated with and without NRG-1β beginning 7 days after induction of MI; Bottom Panel **(B)**, LVFS and LVEF in STZ-diabetic post-MI rats pre-treated with NRG-1β.*P<0.05.

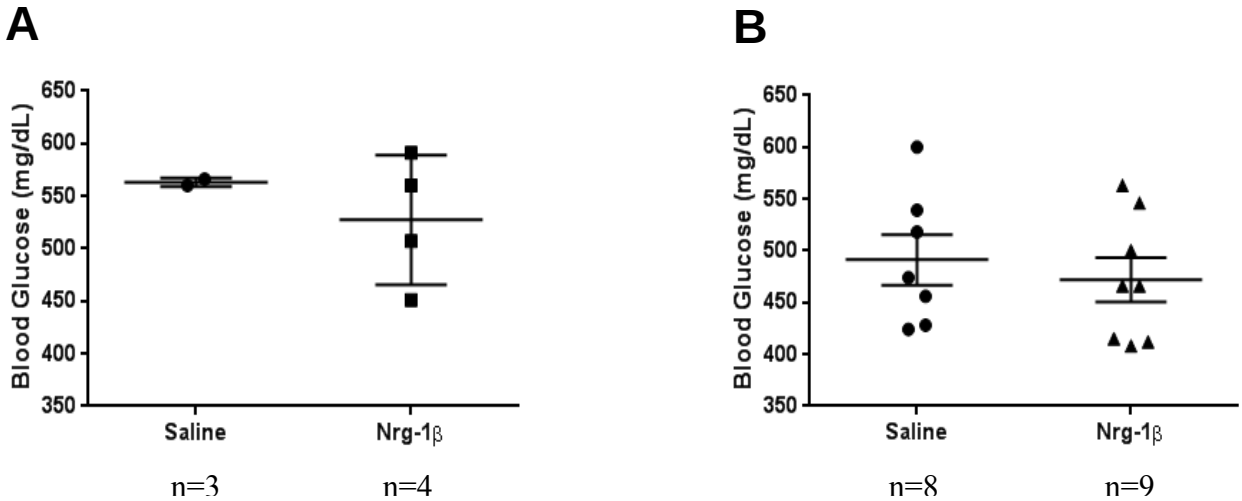
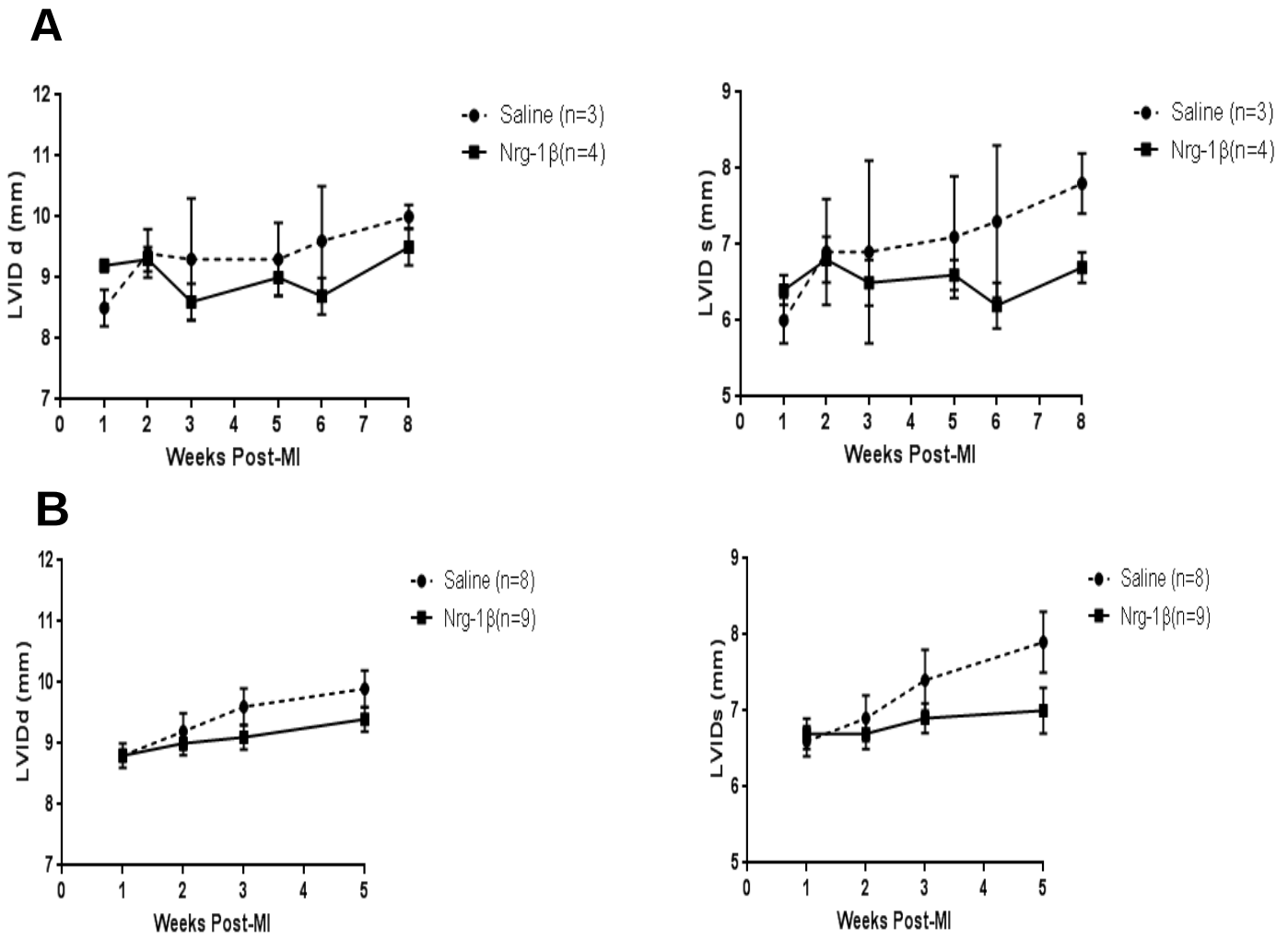



**Figure 2.** Effects of NRG-1β treatment on terminal blood glucose in STZ-diabetic post-MI rats. **(A)**, Blood glucose in STZ-diabetic post-MI rats treated with and without NRG-1β beginning 7 days after induction of MI **(B)**, Blood glucose in STZ-diabetic post-MI rats treated with and without NRG-1β prior to MI.

**II) <u>Intravenous NRG-1β Therapy Reduces Adverse LV Remodeling in STZ-Diabetic Rats with MI</u>**
Echocardiography showed that administration of NRG-1β to STZ-diabetic rats either pre- or post-MI attenuated LV remodeling as evidenced by less LV end-diastolic and systolic dilatation **(Figure 3).**




**<u>Figure 3.</u>** LV internal dimension, diastolic (LVIDd) and LV internal dimension, systolic (LVIDs) in STZ-diabetic post-MI rats that received NRG-1β starting 7 days post-MI **(A)** and in STZ-diabetic post-MI rats that were pre-treated with NRG-1β two weeks prior to induction of MI **(B)**.

**III) <u>Intravenous NRG-1β Therapy Suppresses Cardiac Fibrosis in STZ-Diabetic Post-MI Rats</u>**
Cardiac Fibrosis evaluated by Masson trichrome staining was dramatically less in the NRG-1β-treated STZ-diabetic post-MI rats compared to the vehicle-treated STZ-diabetic post-MI rats at the end of 7 weeks therapy beginning 7 days post-MI **(Figure 4).**

**Vehicle** **NRG-1β**

**<u>Figure 4.</u>** Cardiac fibrosis in LV.

**Specific Aim 2:** *Determine the efficacy of exogenous NRG-1β to improve distant end-organ complications such as vascular, kidney, and peripheral nerve function in STZ-diabetic post-MI rats.*

**Results:**

**I) Intravenous NRG-1β Pre-Treatment Ameliorates Early Renal Damage in STZ-Diabetic Post-MI Rats**

Vehicle-treated STZ-diabetic post-MI rats exhibited significantly higher urinary excretions of creatinine compared to the NRG-1β-treated STZ-diabetic post-MI rats (**Table 1**), suggesting attenuation of glomerular hyperfiltration by NRG-1β, a characteristic functional abnormality induced by type 1 diabetes and distinctive feature of early diabetic nephropathy. Urine protein levels in vehicle-treated versus NRG-1β-treated STZ-diabetic post-MI rats were not statistically different (**Table 1**).

**Table 1. Animal Characteristics and Biochemical Parameters**

| Parameter | DM + MI + Saline | DM + MI + NRG-1β |
|---|---|---|
| Body Weight (g) | 231 ± 7.8 | 228 ± 7.3 |
| Blood Glucose (mg/dL) | 491 ± 24 | 472 ± 21 |
| Urine Creatinine (mg/dL) | 10.8 ± 0.7 | 8.7 ± 0.5* |
| Urine Protein (mg/ml) | 7.0 ± 0.6 | 8.3 ± 0.4 |

N= 4-9 rats per group. *$P$<0.05 versus saline-treated STZ-diabetic post-MI rats.

## 3. Publications:

None during this initial funding period.