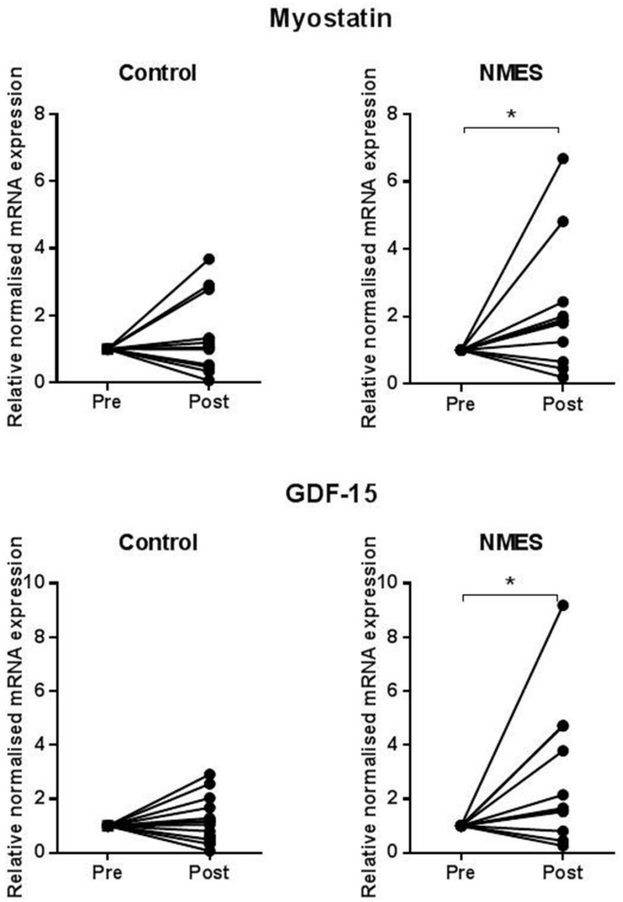
Congenital diaphragmatic hernia (CDH) is a developmental diaphragmatic anomaly resulting in pulmonary hypoplasia and consequent pulmonary hypertension and respiratory failure sequelae. Despite advances in treatment, CDH remains associated with high morbidity and mortality rates. Reduced levels of vascular endothelial growth factor (VEGF) have been implicated in CDH pathogenesis. Animal studies have shown that intrauterine VEGF replacement enhances pulmonary vascularisation and lung epithelial cell proliferation. This study aimed to deliver VEGF through the engineering of a biocompatible and slow releasing nanodiamond (ND) platform, in a rat model of CDH.

NDs were either fluorescently labelled (ND-FL) or conjugated to recombinant VEGF164 (ND-VEGF; 2 μg/mL VEGF164). Nitrofen was administered to pregnant Wistar rats at E9 (term=E22) to induce fetal CDH. At E19, maternal hysterotomy was performed, and NDs (75 μg/mL in 50 μL vehicle/saline) were administered intratracheally followed by fetal tracheal occlusion (TO). Blinded assessment of lung-to-body weight ratio (LBWR) and lung morphometric parameters was performed at E21.5 in CDH offspring.

Prenatal ND administration did not have overt adverse effects. ND-FL biodistribution indicated that NDs localised in type II pneumocytes. ND-VEGF+TO was associated with improved lung growth (LBWR: 5.9 ± 0.2%), which was greater than that observed in VEGF+TO (3.5 ± 0.4%; $p < 0.01$), vehicle+TO (3.9 ± 0.1%; $p < 0.01$), and sham surgery (2.0 ± 0.2%; $p < 0.001$) groups. Moreover, ND-VEGF+TO resulted in thinner alveolar septa (mean transection length/airspace: 18.9 ± 0.5) and increased alveolar size (mean airspace chord length: 31.4 ± 0.6) compared to other treatment groups (p).

This is the first study to show that nanoparticle-mediated prenatal delivery of VEGF induces significant lung growth in CDH and suggests that sustained cargo release is pivotal in mimicking the temporal expression of VEGF in normal lung development.



Abstract S139 Figure 1 Rectus Femoris mRNA expression of Myostatin or GDF-15 in ICU patients (n = 12) relative to baseline (pre) and following 1 week of neuromusclular electrical stimulation (NMES) or control. *$p < 0.05$ Wilcoxon paired analysis of post study comparison relative to baseline

New insights in skeletal muscle wasting and weakness

S139 A PARADOXICAL RISE IN RECTUS FEMORIS MYOSTATIN (GDF-8) AND GDF-15 IN RESPONSE TO NEUROMUSCULAR ELECTRICAL STIMULATION IN CRITICAL CARE

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Introduction Neuromuscular electrical stimulation (NMES) is widely used in rehabilitation and muscle disease. Recently there is increasing interest in its use as a prevention and treatment for intensive care unit acquired weakness (ICUAW). ICUAW is a common and often devastating disease resulting as a consequence of critical illness. The molecular mechanisms are not understood, however early mobilisation and rehabilitation are to date the most effective treatments. NMES has been shown to help prevent muscle wasting in some clinical studies in the ICU setting, however the evidence is inconclusive. We hypothesised that the NMES of a single leg in critical care patients would be associated with reduced muscle wasting and down regulation of molecular pathways involved in muscle breakdown. Specifically myostatin (GDF-8), a potent negative regulator of muscle mass, and GDF-15, a potential novel driver of muscle atropy.

Methods We conducted a single-blinded, single leg, contralateral controlled trial of NMES in patients admitted to a specialist cardiothoracic ICU. Patients were recruited prior to elective high-risk cardiac surgery or during ICU admission. Baseline bilateral rectus femoris cross sectional area (RF_{csa}) was measured by ultrasound and rectus femoris biopsies were taken. 2 × 1 hour sessions of NMES were then conducted for 1 week and ultrasound and biopsies were repeated. Biopsy specimens were examined for mRNA expression of genes of interest and results analysed in paired analysis relative to baseline. (NCT01321320).

Results 12 patients completed the study protocol. Myostatin and GDF-15 mRNA expression were both significantly elevated in NMES legs compared to baseline ($p = 0.03$ and $p = 0.04$ respectively), but remained unchanged in control legs. There was no significant change in RF_{csa}.

Discussion It is believed that NMES will have beneficial effects in the ICU setting in terms of preservation of muscle function. However it is recognised to also have potential to cause muscle damage. In the setting of sedated patients who cannot report pain or those in whom the nutritional and metabolic status of the muscle may be expected to be poor, researchers should be aware that NMES may promote muscle breakdown.