regimens used combined nebulised colomycin with either oral ciprofloxacin or intravenous antipseudomonal antibiotics as first line therapy, (Table 1, n = 57; 85%). Overall, first eradication attempts were successful in 52% of cases (35/67). Regimens including nebulised colomycin were more effective (n = 23/38; 60%) than those without it (20%; 2/10) (Fisher`s exact test, $p = 0.04$). Longer courses of ciprofloxacin (>3 weeks) did not improve outcome in comparison with shorter (≤3 weeks) courses (p = NS). Furthermore, intravenous antibiotics were not superior to oral ciprofloxacin (p = NS). Amongst the 32 patients who failed to eradicate *P. aeruginosa* in the first instance, 20 underwent a second attempt. In comparison with first trials, overall success rate of second trials decreased to 35% (n = 7/20). However, this difference did not reach statistical significance (Fisher`s exact test, $p = 0.3$). Nineteen patients, who initially successfully cleared *P. aeruginosa*, required a 2nd eradication trial later during the study period. For those patients, the eradication success was 53%, comparable to the first one.

Abstract S115 Table 1 Frequency and efficacy of antibiotics used as first-line eradication regimens

Treatment	Nebulised colomycin (3 months) &					No nebulised colomycin		
	Cipro (≤3 weeks)	Cipro (>3 weeks)	IVs (2 weeks)	Cipro + IVs	Nil else	Cipro	IVs	Cipro + IVs
Patients, *n*	9	29	13	5	1	6	2	2
Success, *n* (%)	6 (67)	17 (59)	7 (54)	2 (40)	1 (100)	1 (17)	0 (0)	1 (50)

Cipro: Ciprofloxacin; IVs: intravenous antipseudomonal antibiotics.

Conclusions Eradication regimens combining systemic and nebulised antibiotics appear more effective than systemic antibiotics alone to achieve *P. aeruginosa* eradication in non-CF bronchiectasis patients.

Best of basic science advances

S116 GDF-15, THE MIR-542 CLUSTER AND MIR-422A ARE ASSOCIATED WITH MUSCLE WASTING IN INTENSIVE CARE UNIT ACQUIRED PARESIS

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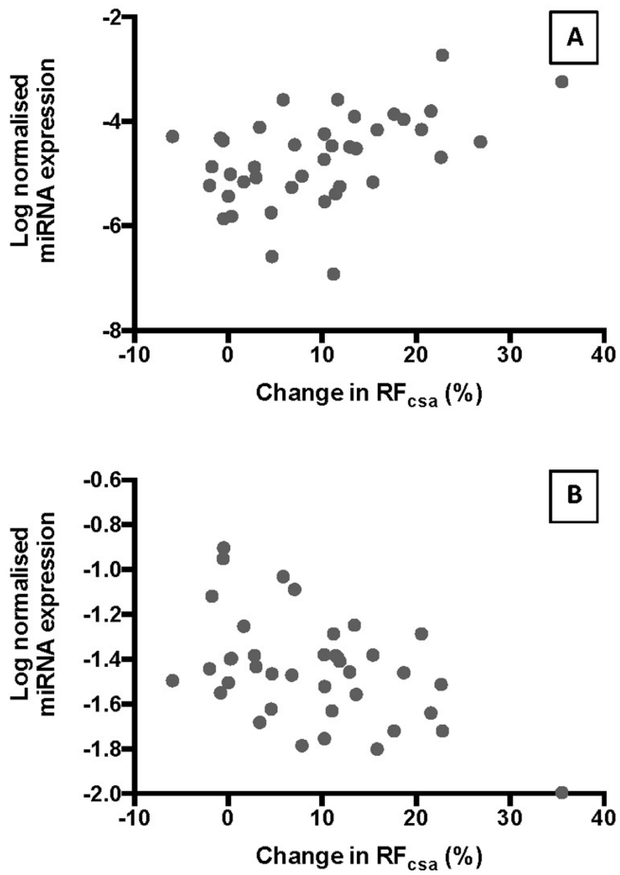
Introduction and aims Intensive care unit acquired paresis (ICUAP) is a common complication of critical illness, associated with significant morbidity and mortality in patients admitted to the ICU. To date, there has been little success in the identification of patients at risk of acute muscle wasting or potential targets for therapeutic intervention.

GDF-15, a TGF-B family member, has been shown to be a potential driver of acute muscle wasting in ICUAP (Crit Care Med 2013;41:982). From previous analyses in ICUAP and other wasting conditions, we hypothesised that pre-surgery expression of microRNAs from the miR-542 family would be higher in patients who would lose significant muscle bulk following surgery, whereas expression of miR-422a would be lower.

Methods A prospective observational study of 40 patients undergoing high-risk cardiothoracic surgery with cardiopulmonary bypass was conducted. Patients underwent pre- and post-operative paired rectus femoris biopsies and blood sampling. Muscle wasting was assessed by ultrasound pre-operatively and at day 7 post surgery. Plasma GDF-15 protein was quantified by ELISA and mRNA and microRNA expression in muscle specimens by RT-PCR.

Main results 52% (21 of 40) patients developed muscle atrophy. Plasma GDF-15 concentration was significantly raised at all sampling time points in patients with significant muscle wasting (wasters) compared to those that did not (non-wasters). miR-542–3p (median 1.9-fold, p = 0.0029), miR-542–5p (median 4.5-fold, p = 0.0346) and miR-424 (median 4.2-fold, p = 0.0040) were higher in pre-operative muscle specimens of wasters compared to non-wasters, whilst miR-422a was lower (median 1.2-fold, p = 0.0176). Expression of these miRNAs significantly correlated with change in rectus femoris cross-sectional area over time (see Figure 1).



Abstract S116 Figure 1 Correlation between change in rectus femoris cross-sectional area (RF_{csa},%) and pre-operative; A) miR-542-5p expression (n = 40). Pearson r = 0.47, p = 0.0022 and B) miR-422a expression (n = 40) Pearson r = 0.55, p = 0.0003

Discussion Pre-operative expression in muscle of these miRNAs correlates significantly with reductions in muscle bulk after major surgery and cardiopulmonary bypass suggesting that the pre-existing status of the muscle is important in the susceptibility to muscle wasting. Furthermore, as both miR-542–3p/-5p and miR-422a are predicted to regulate p53 activity in opposite directions, these data imply that the p53 stress pathway

contributes to this susceptibility. This study identifies these microRNAs as potential therapeutic targets in ICUAP.

S117 RSIV. F/HN-MEDIATED GENE THERAPY ENABLES LUNGS TO PRODUCE THERAPEUTICALLY RELEVANT LEVELS OF FVIII

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We have previously shown that lung when treated with Sendai virus-mediated gene transfer can produce secreted proteins and release them into the circulation (Griesenbach *et al*., Mol Therapy 2002). Despite the high levels of transduction efficiency the gene expression is transient and repeated administration is not feasible due to induction of immune responses. To overcome these barriers we developed a lentiviral vector specifically pseudotyped with the Sendai virus envelope proteins F and HN (rSIV. F/HN) to allow efficient transduction of the airways. Stable expression for >20 months after a single dose and efficient transduction after repeated administration despite detection of anti-rSIV. F/HN neutralising antibodies make the vector an attractive candidate for a large range of disease indications. Here, we first transduced mouse lung with rSIV. F/HN carrying the secreted reporter gene Gaussia luciferase (GLux) or a control virus by nasal instillation (1e6 transduction units (TU)/mouse, n = 5–6/group). Persistent levels of GLux expression were detectable in lung (3 logs above control) and broncho-alveolar lavage fluid (BALF, 4 logs above control) for at least 12 months. Importantly, even this modest dose of virus lead to significant ($p < 0.01$) levels of GLux in serum (274 ± 72 RLU/ul, control: 41 ± 6 RLU/ul) which persisted for at least 12 months further supporting the hypothesis that the lung is a suitable, non-invasive factory for production of secreted proteins. Gene therapy strategies for haemophilia have focussed on intravenous or intramuscular delivery of the gene transfer agent. Here, we treated the murine lung with rSIV. F/HN carrying the FVIII cDNA (1.6e8–3.4e8 TU/mouse,) or placebo and assessed whether therapeutically relevant levels of FVIII can be produced. Significant ($p < 0.05$) and dose-related levels of FVIII were detectable in lungs and BALF 10 and 28 days post-transduction. Dose-related levels of FVIII were also detectable in plasma, which reached a therapeutically relevant level of 3% of normal 1 month after gene transfer. These data support the concept that rSIV. F/HN-mediated transduction of lungs can produce therapeutically relevant and persistent levels of recombinant protein in blood.

REFERENCE

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S118 CIRCADIAN GLUCOSE PATTERNS IN ADULT CARDIOTHORACIC TRANSPLANT RECIPIENTS

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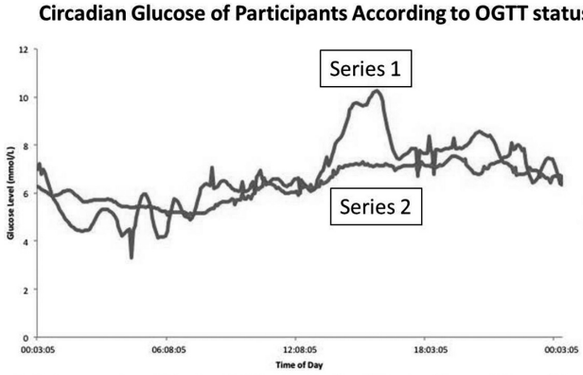
Introduction New onset diabetes after transplantation (NODAT) is a well-known complication of immunosuppressive therapy and is associated with excess morbidity and mortality. Early identification and treatment of impaired glucose regulation (IGR) is crucial to help prevent or delay the development of NODAT and its associated complications.

Aim To define circadian glucose patterns of cardiothoracic transplant (CTTx) recipients using a continuous glucose monitoring system (CGMS) and compare the findings with conventional tests for diabetes.

Method Cross-sectional study in a CTTx outpatient clinic. CGMS was used to construct circadian glucose profiles. Those with CGMS values in excess of 7.7 mmol/l were asked to complete oral glucose tolerance tests (OGTT) and HbA1c.

Participants Convenience sampling was used to identify 12 stable CTTx recipients (2 heart, 3 single lung and 7 double lung Tx; 9 male; mean [SD] age 58 [8] years, BMI 28.6 [4.9] kg/m^2, daily prednisolone dose 11.5 [2.2] mg; 4 on tacrolimus vs 8 on cyclosporine; median 477 days since Tx).

Results None had symptoms of hyperglyaemia. CGMS duration range: 37 to 183 hrs/patient. A significant difference was seen between mean morning (06.00–12.00 hrs) and evening (14.00–20.00 hrs) glucose values (5.8 [1.2] vs 7.6 [1.4] mmol/l; $p < 0.001$, Figure 1). On CGMS data all participants had glucose values >7.7 mmol/l. Three (25%) had glucose values >11.1 and <3.5 mmol/l on CGMS and were diagnosed with impaired glucose tolerance on OGTT. Compared with 9 normal OGTT patients, the IGT group displayed a higher number of hyperglycaemic episodes/day and a greater% of time above 7.8 mmol/l. No cases of impaired fasting glycaemia or NODAT were identified using OGTT or HbA1c.



Abstract S118 Figure 1

Conclusion Findings of this pilot study emphasise the importance of improving screening for IGR in CTTx recipients. We identified diurnal variation in glucose patterns, with higher glucose values in the afternoon and evening than morning, which has implications for timing of random glucose sampling in clinic. Poor correlation was found between CGMS and conventional diagnostic tests for diabetes which may not be sensitive enough to identify IGR in CTTx recipients. This merits further investigation in a larger cohort.