responders using a discrete left ventricular volumetric value as assessed by any imaging modality. Studies were identified through searching electronic databases from their inception to July 2017.

RESULTS: We identified 2707 citations, of which 23 full-text articles were eligible. Our primary analysis (figure 1.) included four studies (n=1639) and demonstrated that ICD controls experienced lower rates of VAs than CRT non-responders, RR 0.76 (95% CI 0.63,0.92, p<0.01). A secondary analysis included 22 studies (n=5692) and demonstrated that CRT responders have lower rates of VAs than CRT non-responders, RR 0.49 (95% CI 0.41, 0.58, p<0.01).

CONCLUSION: Our primary meta-analysis demonstrates that CRT non-responders have higher rates of VAs compared to the ICD without CRT group. The results of this study suggest that ineffective CRT pacing may be pro-arrhythmic and, disabling CRT function may be a reasonable consideration in non-responders.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ICD Control</th>
<th>CRT Non-Responders</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
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<tr>
<td>Chang et al</td>
<td>13</td>
<td>173</td>
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<td>Gad et al</td>
<td>24</td>
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<td>Thigpen et al</td>
<td>59</td>
<td>113</td>
<td>26</td>
<td>45</td>
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<td>Barthel et al</td>
<td>30</td>
<td>622</td>
<td>62</td>
<td>220</td>
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<tr>
<td>Total (95% CI)</td>
<td>113</td>
<td>316</td>
<td>106</td>
<td>596</td>
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</table>

Figure 1. Forest plot of the four included studies comparing the rates of ventricular arrhythmias between CRT non-responders and ICD only group.

211 RESPONSE TO CARDIAC RESYNCHRONIZATION THERAPY IN PATIENTS ≥75 YEARS OF AGE AND THE EFFECT OF QRS MORPHOLOGY

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BACKGROUND: Cardiac resynchronization therapy (CRT) improves cardiovascular outcomes in patients with heart failure with reduced ejection fraction (HFREF). However, few patients ≥75 years old were included in CRT trials. CRT efficacy is greater in patients with strict left bundle branch block (LBBB). This study aimed to assess the efficacy and safety of CRT in patients ≥75 years of age and to determine if strict LBBB criteria predicts an improved CRT response.

METHODS: We recruited consecutive HFrEF patients with LBBB who received a de novo CRT device at a single tertiary center. Patients were divided into two groups based on age. Group 1 consisted of patients ≥75 years old and group 2 consisted of those <75 years old. The primary endpoint was change in QRS duration after CRT. The secondary endpoints were change in LVEF. Outcomes in patients ≥75 years old were stratified based on if the LBBB met strict or only conventional LBBB criteria.

RESULTS: In 196 consecutive patients with LBBB receiving CRT, 68 were ≥75 years old and 128 were <75 years old. In group 1, the mean age was 81.4±4.2 years and the proportion of males was 75.0%. In addition, 54.5% had ischemic cardiomyopathy, 76.5% had hypertension and 23.5% had diabetes mellitus. In group 2, the mean age was 64.8±7.4 years and the proportion of males was 71.1%. Furthermore, 50.0% had ischemic cardiomyopathy, 76.6% had hypertension and 39.1 had diabetes mellitus. The mean baseline QRS was 160.0±18.0 milliseconds and 160.0±17.5 milliseconds in groups 1 and 2 respectively. Patients ≥75 years old were more likely to receive a CRT pacemaker without defibrillator therapy (CRT-P) compared to those younger than 75 years of age (42.7% vs 9.2%, p<0.0001). The mean change in QRS was -15.0±19.6 milliseconds and -10.1±18.9 milliseconds and the absolute mean change in LVEF was 15.9±14.0 and 13.9±14.4 in groups 1 and 2 respectively. There was no significant difference between the groups. In patients ≥75 years old, those with strict LBBB had a greater reduction in QRS duration, -22.9±14.1, compared to those with conventional LBBB, 4.0±17.9 (p<0.001). In addition, those with strict LBBB had a greater improvement in LVEF 20.0±11.5 compared to those with conventional LBBB, 6.7±15.0 (p=0.001).

CONCLUSION: Patients ≥75 years of age with LBBB undergoing CRT had a similar improvement in QRS duration and LVEF as younger patients. Strict LBBB predicts improved QRS and LVEF response after CRT in patients ≥75 years of age.

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212 ENDOTHELIAL PROGENITOR CELLS ENCAPSULATED IN MATRIX-SUPPLEMENTED MICROGEL IMPROVES CELL RETENTION AND THERAPEUTIC EFFICACY IN PULMONARY ARTERIAL HYPERTENSION

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BACKGROUND: Late outgrowth (L) endothelial progenitor cells (EPC) represent a uniform, highly endothelial-like progenitor cell population; however, their therapeutic benefits in models of pulmonary arterial hypertension (PAH) are limited by poor
cell persistence, due to rapid cell loss by apoptosis (anoikis) and redistribution to non-target organs. Temporary single-cell microencapsulation (i.e., cocooning) provides a portable stem cell niche, that can promote cell survival and retention in animal models of organ lung and heart injury. We hypothesize that microencapsulation of L-EPC with an agarose hydrogel supplemented with integrin-binding proteins will increase survival and retention of L-EPCs injected into the jugular vein and result in greater therapeutic benefits compared to non-cocooned cells in a rat monocrotaline (MCT) model of PAH.

METHODS: L-EPCs were encapsulated by vortex-emulsion using various concentrations of agarose, together with fibronectin and fibrinogen, and capsule size and initial cell viability were assessed. Encapsulated and non-encapsulated L-EPCs were transduced with luciferase and administered to SD rats three days after injection of MCT. L-EPCs were tracked in vivo by bioluminescence imaging (BLI) to assess cell persistence and bio-distribution for up to three weeks post cell injection. At end-study, right ventricular systolic pressure (RVSP) and right ventricular hypertrophy (RVH) were assessed for therapeutic efficacy.

RESULTS: The initial BLI signals at 15 minutes after delivery were similar in non-cocooned and cocooned L-EPCs; however, only cocooned cells could be detected by BLI after four and 24 hours (28±12% and 12±8% of baseline signal, respectively; p<0.0001 and 0.05, n=11). Microencapsulation of L-EPCs led to significant improvement in RVSP three weeks after delivery compared to MCT alone (56±24 vs. 80±7 mmHg, respectively; p<0.05), whereas no improvement in pulmonary hemodynamics was seen with delivery of non-encapsulated cells.

CONCLUSION: These results demonstrate that single-cell cocooning can significantly increase retention of L-EPCs within the lungs. Furthermore, even a modest increase in L-EPC persistence over 24 hours can provide an important therapeutic benefit, not seen with non-encapsulated L-EPCs in the rat MCT model of PAH.

![Figure 1: Encapsulated L-EPC were retained significantly longer than non-encapsulated L-EPC. (A) Representative images of the bioluminescent signal emitted by luciferase-transfected L-EPC at baseline, 4h, and 24h post cell injection, including ex vivo images of lungs. The encapsulated L-EPC were detectable in the lungs up to 24h whereas non-encapsulated L-EPC were cleared after 4h and not detectable. (B) Retention of the cells is shown as a proportion of the baseline signal, indicating the significantly improved retention of the encapsulated compared to the non-encapsulated L-EPC. Data represent mean ± SD.](image-url)

213 ENDOTHELIAL-TARGETED CELL APOPTOSIS LEADS TO TRANSIENT PULMONARY HYPERTENSION FOLLOWED BY RAPID REPAIR AND RESOLUTION

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BACKGROUND: Endothelial cell (EC) apoptosis is increasingly recognized as a central trigger for pulmonary arterial hypertension (PAH), although the mechanisms by which endothelial injury leads to the development of the hemodynamic and pathological features of this disease are not well understood. Therefore, we developed a transgenic model to induce targeted endothelial injury in response to diphtheria toxin (DT) in mice by driving expression of the DT receptor, which is not normally expressed in rodents, using an EC specific promoter. This model was used to test the hypothesis that EC apoptosis is sufficient to induce PAH, and to explore the mechanisms responsible for both the onset and resolution of this phenotype.

METHODS AND RESULTS: Mice expressing CRE under the VE-Cadherin promoter were crossed with animals harboring the human DT receptor (DTR) gene flanked by LoxP sites. Administration of 10 ng DT led to an increase in RVSP within 72 hours in BT animals (n=18) 34.74 ± 1.26 mmHg when compared to saline treated controls (n=13) 23.78 ± 0.46 mmHg (p<0.0001) but no change in right ventricle hypertrophy (RVH) at this early nor in systemic arterial pressure. Interestingly, after a single injection of DT, the increase in RVSP was transient and returned to control levels within one-week (24.12 ± 1.43 mmHg, n=11). Despite a recovery in RVSP, DT treated animals displayed a delayed increase in RVH at one week (0.2656 ± 0.006, n=14) when compared to controls (0.2444 ± 0.004, n=12; p=0.009). In addition, older animals (25 weeks) (n=10) that received the DT treatment had an increased mortality rate (6/10) within the first week when compared to younger animals (12 weeks) (n=17) (1/17). Micro-CT of DT-treated animals showed a 20-percent decrease in total vasculature volume when compared to saline controls. This was associated with a loss in both CD144+ECs and AN2+pericytes assessed by flow cytometric analysis, while there was an increase in the CD11b+ macrophage population at 72 hours post treatment.

CONCLUSION: We have demonstrated that direct EC injury and apoptosis is sufficient to induce a transient PAH phenotype in BT-DTR mice. This model will be used to define the role of EC loss and microvascular degeneration in the development of PAH, as well the mechanisms responsible for vascular repair. This work provides novel insights into mechanisms and potential therapeutic targets for the treatment of this disease.