BACKGROUND

- RA is a debilitating disease affecting approximately 1% of the population, which leads to marked disability, considerable pain and fatigue, and early mortality.1
- Although many pharmacologic treatment options are available for RA, three major problems complicate the use of these drugs: many are only marginally successful, have potentially serious side effects, or have exorbitant costs.
- Previous studies have shown that activation of the vagal nerve results in a marked improvement in RA disease activity. Placement of a vagal nerve stimulator had a measurable and significant reduction in RA disease activity in 70% of patients.2
- Vagal nerve stimulation likely has a therapeutic effect in systemic inflammatory disease through two potential mechanisms: activation of the cholinergic anti-inflammatory pathway and enhanced parasympathetic activity.3
- The Valsalva maneuver is often employed to stimulate the vagal nerve and slow the heart rate down, such as with supraventricular tachyarrhythmias.4

OBJECTIVES

We hypothesize that vagal nerve stimulation through non-invasive methods can lower systemic inflammation and improve RA disease. This pilot study will test this hypothesis through the following two specific aims:

1. We will determine if the Valsalva maneuver, which we call non-invasive vagal nerve stimulation (NIVaNS) breathing, is effective in lowering disease activity in RA patients who are on stable but inadequate pharmacologic therapy.
2. We will determine if NIVaNS breathing in RA patients results in measurable decreases in inflammatory cytokines found in the serum.

METHODS

- Double-blind randomized control trial, randomized 1:1 to either NIVaNS breathing (5 min, twice daily) or a placebo intervention (relaxation breathing).
- RA patients must be on stable DMARDs for 3 months.
- 4 week intervention (visits at week 0, 2, 4). At week 4, placebo patients invited to open 4 week NIVaNS breathing extension.
- Data objectively measured using ESR and number of tender/swollen joints on exam. DAS28-ESR, RAPID3, and CDAI scores also measured at each visit.
- Plasma collected and preserved for cytokine analysis.

RESULTS

![Patient enrollment and treatment arms.](image)

Patients with Improvement in DAS28-ESR Disease Activity Category

<table>
<thead>
<tr>
<th>NIVaNS</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>1 patient declined.</td>
</tr>
<tr>
<td>Low</td>
<td>2 patients from the control arm dropped out</td>
</tr>
<tr>
<td>Moderate</td>
<td>8 patients from the test arm NIVaNS group</td>
</tr>
<tr>
<td>High</td>
<td>9 patients from the control arm</td>
</tr>
<tr>
<td>Week 0</td>
<td>7 patients entered into the open extension.</td>
</tr>
<tr>
<td>Week 4</td>
<td>8 patients completed the control arm</td>
</tr>
<tr>
<td>Week 8</td>
<td>9 patients from the test arm (NIVaNS group)</td>
</tr>
</tbody>
</table>

- Of 8 patients originally randomized to NIVaNS breathing, 3 had a significant decrease in RA disease activity, including 1 who went into remission and 1 into low disease activity.
- Of 8 patients originally randomized to control meditative breathing, 2 had a drop in RA disease activity. Seven switched to 4 more weeks of NIVaNS breathing, with 2 having a drop in RA disease activity.
- Thus, 5 patients doing NIVaNS breathing compared to 2 patients doing control breathing had improvement in RA disease activity.
- Several patients expressed some difficulty in understanding instructions in how to do the Valsalva breathing maneuver. This may have been a major limitation in the study.

FUTURE IMPLICATIONS

- Vagal nerve stimulation via the Valsalva maneuver (NIVaNS breathing) requires further study to assess potential symptomatic and anti-inflammatory benefits for the treatment of RA.
- Better clarity with instruction on NIVaNS breathing may improve outcomes.
- We intend to do additional studies to confirm that NIVaNS breathing actually activates vagal nerve activity.
- We intend to perform further studies at this and other institutions with a larger patient population, followed for 8 weeks, and with additional testing to better assess potential impact on vagal nerve activity.

REFERENCES