Online Data supplement

EFFECT OF LUNG VOLUME REDUCTION SURGERY ON RESTING PULMONARY HEMODYNAMICS IN SEVERE EMPHYSEMA

Gerard J. Criner MD, Steven M. Scharf, MD, Jeremy A. Falk, MD, John P. Gaughan, Ph.D, Alice L. Sternberg, SCM, Namrata B. Patel, MD, Henry E. Fessler, MD, Omar A. Minai, MD and Alfred P.Fishman, MD for the National Emphysema Treatment Trial Research Group

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METHODS AND MATERIALS

Three of the 17 NETT centers performed a cardiovascular substudy which was conducted in eligible patients following screening for the main NETT study. Since the design and methods of the main NETT have been previously described in detail [19], they will only be briefly described. Major enrollment criteria included: bilateral emphysema documented by computed chest tomography to be suitable for LVRS, $FEV_1 \leq 45\%$, (> 15% if 70 years or older), total lung capacity $\geq$ 100% predicted, residual volume $\geq$ 150% predicted, and $PaCO_2 \leq 60$mmHg (55mmHg in Denver). Of special significance for this report, patients were excluded from NETT if mean pulmonary artery pressure (PAM) on right heart catheterization (RHC) was $\geq$ 35 mmHg (38 mmHg in Denver), or peak systolic pulmonary artery (PAS) pressure on RHC was $\geq$ 45 mmHg (50 mmHg in Denver). RHC was undertaken to rule out pulmonary hypertension if PAS pressure on echocardiogram was $\geq$ 45 mmHg. All patients had to be non-smokers for at least 4 months prior to the initial interview and throughout screening, and to be free of significant co-morbidities.

Clinical Assessment

Demographic data and medical histories were collected using standardized instruments [19]. Pulmonary function testing was performed using American Thoracic Society guidelines [20, 21, 22]. The measurements included the Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV_1), and FEV_1/FVC. Thoracic gas volume

was measured using a body plethsymograph, and the diffusing capacity for carbon monoxide (DL_{CO}) was measured using the single breath technique. All data are post-bronchodilator (except for the DL_{CO} which did not have to be) and reported as percentage of predicted normal [23]. Exercise capacity was measured by the standardized 6 minute walk distance test and by standard maximum symptom-limited cycle ergometry using graded exercise loading.

CT Scanning

Radiologists classified the cranio-caudal distribution of emphysema as predominantly affecting the upper lobes (upper lobe predominate), or as predominately involving either the lower lobes, the superior segment of either lower lobes, or the lower lobes. These latter classifications were grouped together and denoted as having a non-upper lobe predominant radiographic pattern of emphysema [24].

Right Heart Catheterization

RHC was performed by experienced cardiologists while the patients were supine at rest prior to rehabilitation (baseline) and 6 months post randomization to treatment. Supplemental oxygen was given as needed to maintain an arterial oxygen saturation $\geq$ 90%. Measurements included right atrial (RA), right ventricular (RV), pulmonary arterial (PA), pulmonary capillary wedge (PCWP), and systemic arterial pressures, as well as arterial (ARTsat) and mixed venous O_2 saturations (MVO_2), and cardiac output (CO) by thermodilution. All pressures were measured at end-inspiration and end-expiration, and

labeled $_{INSP}$ and $_{EXP}$, respectively. Mean PA pressures were calculated as follows: mean PA= PA $_{diastolic}$ + 1/3 of the pulse pressure at end-inspiration and end-expiration. Pulmonary vascular resistance (PVR) was calculated as PVR= [(PAmean-Pw)/ CO] x 79.9 (dynes-sec-cm^{-5}). Systemic vascular resistance (SVR) was calculated as SVR = [(MAP – RAP)/CO] x 79.9 (dynes – sec- cm^{-5}). Stroke volume (SV) was calculated as SV = CO/HR.

Within a few days of RHC, both at baseline and 6 months after randomization to treatment, patients underwent multigated pooled radionuclide angiography (MUGA) while supine at rest for measurement of left and right ventricular ejection fractions. Left ventricular (LV) and right ventricular (RV) ejection fractions (LVEF and RVEF, respectively) were calculated as EF= (end-diastolic – end-systolic counts)/end-diastolic counts.

We assumed that the cardiac output measured at rest during RHC and during gated pool scan were equal for the calculations of stroke volumes, and left-and right-ventricular end-diastolic and end-systolic volumes. Incorporating measurements from RHC and MUGA, the RV and LV end-diastolic volumes (EDV) and end-systolic volumes (ESV) were calculated as EDV=SV/EF and ESV=EDV-SV, respectively. Appropriate cardiovascular parameters were divided by body surface area for the calculation of indices of cardiac function.

STATISTICS

All data are expressed as the mean ± the standard deviation. The differences between the continuous variables in the two treatment groups and between the study groups were analyzed using ANOVA. Binary categorical variables were analyzed using the Fisher's Exact Test. Differences between demographic data in patients who had hemodynamic data both at baseline and 6-month post-randomization were analyzed using unpaired t-tests. Treatment effect was measured using ANOVA followed by pair-wise group comparisons with Bonferroni adjustments. Correlations were done using Pearson correlation coefficients.

We calculated the power to detect changes in the key hemodynamic parameters of interest in the sub-study. These calculations were carried out on PAS, and PAM, the key outcomes of the sub-study. Based on detecting a clinically important difference of 5 mm Hg in PAS and PAM between the groups, the calculated power was 95% and 83% respectively. For a 10 mmHg change in PAS or PAM, the power was >99%. These power calculations support our conclusions that there were no statistically or clinically significant differences between the groups.

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