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| ***Online Supplement Table E1.*** Enhanced TLD Procedure  Targeted lung denervation (TLD) is a novel bronchoscopic therapy that interrupts parasympathetic nerve input to the lungs. Prior to the procedure, the physician inspects the airways to ensure procedure compatibility and suctions excess mucus from the mainstem bronchi. The catheter is then positioned in the distal mainstem bronchus with a flexible bronchoscope used for visualization. Once placed in the appropriate position, coolant flows through the conduit and balloon with their inflation pressing the electrode against the airway wall. The physician then confirms both the electrode and the balloon are contacting the airway wall and that there is sufficient separation of the electrode from branching airways. If all these safety checks are satisfied, the physician will then begin the activation delivering radio frequency energy from the electrode to disrupt the parasympathetic nerves that run along the outside of the mainstem bronchus. After the energy has been delivered in one position, the balloon is deflated and rotated into the next position. This series of safety checks and activations is continued until circumferential treatment is achieved in the main bronchus before treating the other main bronchus in the same manner. |

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| ***Online Supplement Table E2.*** Frequency domain analysis of heat rate variability and Kubios software  Oscillations in heart rate occur at multiple frequencies simultaneously. Oscillations are often divided into three main frequency bands where these components of heart rate variability (HRV) each have physiologic origins. The very low frequency (VLF) band typically spans from 0 to 0.04 Hz and information of physiologic origins of oscillations at these frequencies is currently limited. The low frequency band (LF) includes frequencies from 0.04 to 0.15 Hz and is influenced by both parasympathetic and sympathetic input. Finally, the high frequency (HF) band is defined as 0.15 to 0.4 Hz and oscillations in this band are attributed primarily to parasympathetic signaling. A distinct component of HRV, respiratory sinus arrhythmia (RSA), is the cyclic variation in heart rate that follows respiration. RSA oscillations follow typical respiratory frequency which matches the HF band [[1-3](#_ENREF_1)].  HRV is evaluated by examining how the inter-beat interval (IBI) or the time between each heartbeat changes over time. Because the most distinct feature on an electrocardiogram (ECG) is the R-wave, the time elapsed between successive R-waves is used to measure IBIs. As a result, these IBIs are also known as RR intervals. A series of consecutive RR intervals is often analyzed using either time-domain methods or frequency-domain methods. With time-domain methods, operations are performed directly on the RR interval series and result in outcome measures such as mean RR interval, mean heart rate, standard deviation of RR intervals, etc. Frequency domain methods estimate a power spectrum for the RR interval series. This allows for separating the overall HRV into the VLF, LF and HF frequency bands where special attention can be paid to variability attributed to RSA. The amount of power contained in each band describes how much of the overall HRV occurs at this frequency. Power in each band is calculated by integrating the power spectrum between the limits of each band.  Before estimating the power spectrum of an RR interval series, the dataset is manually checked for artifacts to ensure analysis is not affected. Preventable artifacts caused by things like improper recording setup and patient movement often affect many consecutive data points and have potential to drastically skew analysis. These artifacts are avoided by simply not analyzing datasets which contain them. Unpreventable artifacts like ectopic beats typically occur much less often and can be manually removed leaving a dataset suitable for analysis.  As the RR interval describes the time between two beats, each datapoint in the series is a function of two beats. For example, the second datapoint in an RR interval series is a function of the third and second heartbeat and calculated as the difference between the time of their occurrences. If this dataset is treated as a time series, it will be inaccurate as each datapoint was not sampled equidistantly with time. Before a power spectrum is estimated, the RR interval series is typically interpolated to make it an evenly sampled time series. Both this interpolation and the following estimation of the power spectrum are typically done using a specialized software.  Kubios HRV Premium is a software that is commonly used for both HRV research and personal exercise training. The software has been scientifically validated and has a user-friendly interface [[3](#_ENREF_3)]. This software allows for the user to input heart rate data and perform a variety of well-established analyses on the data. For this study, Kubios HRV premium was used to perform a cubic spline interpolation on each artifact free RR interval series converting it into an evenly sampled time series. The software then estimated the power spectrum of the series and integrated the power contained within the HF band. The amount of power contained within the HF band was equated to presence of RSA and this was compared per subject before and after targeted lung denervation. For the human subjects, there were multiple RR interval series evaluated before and after TLD which were averaged. For more information about Kubios HRV Premium software, visit the following link: <https://www.kubios.com/>.  ***References:***  1 Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. European heart journal 1996;17:354-381.  2 Pumprla J, Howorka K, Groves D, Chester M, Nolan J: Functional assessment of heart rate variability: physiological basis and practical applications. International journal of cardiology 2002;84:1-14.  3 Tarvainen MP, Niskanen JP, Lipponen JA, Ranta-Aho PO, Karjalainen PA: Kubios HRV--heart rate variability analysis software. Computer methods and programs in biomedicine 2014;113:210-220. |