Investigating the Effects of Random Balloon Pulsation on Gas Exchange in a Respiratory Assist Catheter

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We are developing an intravenous respiratory assist catheter, which uses hollow-fiber membranes wrapped around a pulsating balloon that increases oxygenation and CO_2 removal with increased balloon pulsation. Our current pulsation system operates with a constant rate of pulsation and delivered balloon volume. This study examined the hypothesis that random balloon pulsation would disrupt fluid entrainment within the fiber bundle and increase our overall gas exchange. We implemented two different modes for random (rates and delivered volume) versus constant pulsation. The impact on gas exchange was measured in a 3 l/min water flow loop at 37°C. CO_2 gas exchange for randomized beat rate mode was comparable to its corresponding average constant pulsation (*e.g.,* constant 286 beats/min versus randomized 200–400 beats/min was 299.5 ± 0.9 and 302.2 ± 1.4 ml/min/m², respectively). Random volume mode CO_2 exchange was also comparable to constant delivered balloon volume (100% inflation and deflation) (*e.g.,* 294.3 ± 0.6 and 301.1 ± 1.7 ml/min/m², random 50–100% inflation and constant, respectively). Greater active mixing was seen with constant pulsation as compared with randomly changing the parameters of balloon pulsation. *ASAIO Journal* 2006; 52:192–195.

An intravenous respiratory assist catheter is under development by our group[1–5] for treating patients with acute respiratory failure, including acute exacerbations of chronic respiratory failure.[6–9] Our approach differs from that used in the IVOX intravenous catheter, which went into clinical trials in the 1990s,[6–14] in that the device uses a pulsating balloon to enhance gas exchange. A bundle of microporous hollow fibers is wrapped around the centrally located pulsatile balloon. Pure oxygen is pulled through the hollow-fiber membrane (HFM) bundle to oxygenate and remove CO_2 from the blood.[15] Balloon pulsation increases O_2 and CO_2 gas exchange by active mixing of blood flowing past the fibers with blood in the fiber bundle, moving blood past the fiber surfaces at a greater velocity than would otherwise exist in the vena cava.[16] The enhancement of exchange due to balloon pulsation has been evaluated in bench, *ex vivo*, and acute animal studies.[2,4,5,15]

Our current pneumatic drive system pulsates the balloon at a constant beat rate (beats per minute [BPM]) and balloon volume. However, gas exchange levels off at higher beat rates caused by entrainment of fluid elements within the fiber bundle (due to the interaction of balloon-generated flow and longitudinal flow), buildup of fluid oxygen partial pressure, and local decrease in fluid carbon dioxide partial pressure.[16] We hypothesized that we could disrupt entrainment and increase gas exchange by altering our current balloon to create two different random pulsation modes: 1) random balloon pulsation rate, in which a new beat rate within a determined range was randomly varied with each pulsation; and 2) random-delivered balloon volume, in which the volume of gas delivered into the balloon was randomly varied with each pulsation. We compared the gas exchange results for these random pulsation modes to pulsation at a constant rate and volume.

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Materials and Methods

Apparatus

The respiratory catheter used in this study contained a 25 cc pulsating polyurethane balloon centered within a bundle of 600 microporous HFMs (x30-240 Celgard, Membrana GmbH, Wuppertal, Germany).[17] The total surface area of the catheter was 0.17 m² (30-cm-long fiber bundle, 300-μm outer diameter fibers).

The balloon within the fiber bundle was pulsated using a pneumatic drive system (see **Figure 1**), which consisted of positive and negative pressure reservoirs (clear cast acrylic tube 4″ outer diameter, 2.5″ inner diameter, GE Polymershapes, Fairfield, CT),[18] balloon safety chamber, three positive-pressure solenoid valves (0–4 bar range), and three negative-pressure solenoid valves (10^{-5} mm Hg range) (Matrix, Ivrea Italy, P/N: MX751.101C224 and MX751.10VC2JJ).[19] The positive-pressure solenoid valves connected the positive pressure reservoir to the safety chamber. The negative-pressure solenoid values connected the negative pressure reservoir to the other side of the safety chamber.

Pneumatic Drive System Control

A Labview[20] program driving a data acquisition board (NI PCI 6713, National Instruments Corp., Austin, TX)[21] controlled the balloon pulsation rate, solenoid valve timing, delay between solenoid valve opening/closing, and the percentage of time allowed for the balloon inflation, which directly affects the volume delivered to the balloon. The Labview program used for constant balloon pulsation was adjusted to randomly change two parameters: 1) the rate of pulsation (random pulsation rate, RPR); and 2) delivered balloon volume (random balloon volume, RBV). The randomization within the program was achieved through the use of a subroutine utilizing a random number generator function. The RBV was achieved by varying the duty cycle (DC), the percentage of time allowed for

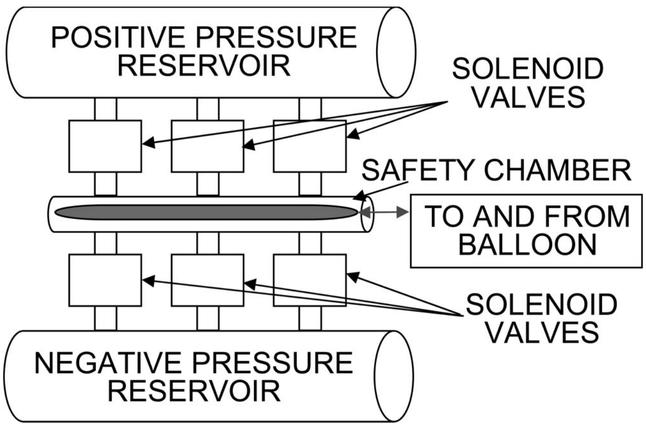

Figure 1. Schematic of pneumatic balloon drive system.

balloon inflation per pulsation. The RBV at a certain DC was determined using a plethysmograph in which the catheter was submerged under water in a sealed chamber with an air pocket at the top. Pressure versus time was measured using a pressure transducer (143SC, Honeywell Sensing and Control, Freeport, IL) and displayed on an oscilloscope (TDS 2014, Tektronix, Inc., Beaverton, OR). Pressure swings were translated into the volume of water displaced by inflation of the balloon, assuming adiabatic compression of air in the chamber.[22]

For RPR, the duty cycle (percentage of time the balloon was inflated per pulsation) was kept constant at 50% inflation and the Labview controller randomly determined a new beat rate after every pulsation. Four different randomized pulsation rate ranges were compared (100–200, 200–300, 100–300, and 200–400 BPM). The randomized rate within these ranges was kept at 20-BPM increments to ensure that the next random pulsation rate was substantially different than the last. Each randomly generated pulsation rate during a given range was recorded. Histograms of the frequency (percentage) of random beat rates during a given time frame were created to assess the distribution of frequencies across the specified minimum and maximum ranges. A sample of 200–400 BPM RPR range is shown in **Figure 2A**; average rate was 286 BPM. Average rates for the other three randomized rate ranges (not shown) were 144, 243, and 176 BPM for the 100–200, 200–300, and 100–300 BPM ranges, respectively. These histograms were used to determine the average beat rate for the constant balloon pulsation tests used to assess the effect of random pulsation rate.

For RBV, the duty cycle was randomly changed from 25–65%, 25–50%, or 50–65% inflation, at 5% increments at a constant pulsation rate of 300 BPM. These random duty cycles created a RBV of 12.7–24.4 cc (maximum balloon volume = 24.4 cc), as determined using the plethysmograph method. A constant duty cycle of 50% and constant 300 BPM were used as the control for comparison to the randomized RBVs (constant 24.4 cc delivery). A sample histogram of RBV using 25–65% duty cycle with 5% increment is shown in **Figure 2B**, where delivered balloon volume (DBV) ranged from 24.4 cc fully deflated balloon to 14.3 cc inflated and 24.4 cc fully inflated balloon to 12.7 cc deflated (with an average of 20.2 cc DBV). Average DBV for 14.3 cc deflated to 24.4 cc RBV mode

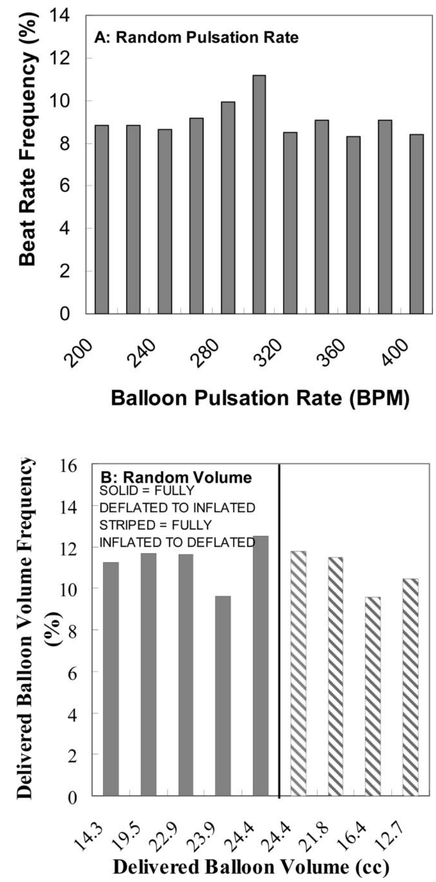

Figure 2. Typical histograms for frequency of (A) random balloon pulsation rate and (B) random delivered balloon volume normalized to sample period. (Constant averages = 286 BPM and 20.2 cc delivered volume.)

was 21.6 cc and 18.8 cc for the 12.7 cc inflated to 24.4 cc RBV mode.

Gas Exchange Evaluation

Gas exchange for all pulsation modes (constant, RPR, and RBV pulsation) were characterized in a mock vena cava test loop with de-ionized water circulating at 3 l/min at 37°C. The catheter was placed in a 1¼″ rigid test section with internal spacers to keep the device centered. Pure oxygen sweep gas was pulled through the device at 3 l/min, then flowed through a moisture trap, thermal mass flow meter (GR-116-A-PV-O2, Fathom Technologies, Round Rock, TX), and a sealed vacuum pump (400-3910, Barnant Company, Barrington, IL). A CO_2 analyzer (CO2-44B, Physio-Dyne Instrument Corporation, Quogue, NY) was used to measure the percent CO_2 exiting the device. Sweep gas pressure drop across the device was measured using a pressure transducer (143SC, Honeywell Sensing and Control, Freeport, IL).

Carbon dioxide (V_{CO2}) and oxygen (V_{O2}) gas exchange were calculated from gas side and liquid side measurements, respectively. V_{CO2} was calculated using the following formula:

$$V_{CO2} = Q_{OUT}^{STP} F_{CO2} \quad (1)$$

where Q_{OUT}^{STP} is the sweep gas flow rate and F_{CO_2} is the CO_2 fraction exiting the catheter. This was then normalized (V_{CO2}^{*})

to our target inlet pCO_2 of 50 mm Hg using the following formula:

$$V^*_{CO2} = V_{CO2}\frac{50}{pCO_2^{INLET}} \quad (2)$$

to adjust for changes in V_{CO2} due to small fluctuations in inlet pCO_2 ($< \pm 5$ mm Hg).

The value of V_{O2} was determined using:

$$V_{O2} = \left(pO_2^{OUTLET} - pO_2^{INLET}\right) \cdot Q \cdot \alpha^{37C}_{WATER} \quad (3)$$

where pO_2^{OUTLET} is the oxygen partial pressure after the device, pO_2^{INLET} is the O_2 partial pressure before the device, Q is the water flow rate, and α^{37C}_{WATER} is the solubility of oxygen in water at 37°C [0.000317 ml O_2 /100 ml blood / mm Hg]. CO_2 and O_2 gas exchange levels were normalized to the surface area of the catheter.

A Student's *t*-test assuming equal sample variance was used to determine *p* values and assess any statistically significant differences between constant pulsation and the randomized pulsation modes. Statistically significant differences were defined as $0.01 \leq p < 0.05$. Highly significant differences were defined as $0.001 \leq p < 0.01$. Very highly significant differences refer to $p < 0.001$. *P* values > 0 .05 were not considered significantly different, but trending toward significance when $0.05 \leq p < 0.10$.

Results

Gas exchange for random pulsation rate and average constant pulsation rate are shown in **Figure 3**. Carbon dioxide exchange (**Figure 3A**) for all random pulsation was not statistically different from their average constant pulsation ($p >$ 0.15). The 100–300 BPM range yielded a small, but inconsequential trend toward a statistically significant difference ($p =$ 0.09) in gas exchange. Oxygen exchange (**Figure 3B**) for the 200–300 and 200–400 BPM random pulsation ranges versus their respective values for average constant rate showed no statistically significant differences ($p > 0.4$). Gas exchange for the 100–200 BPM random pulsation range was 27.4% lower than its respective value for average constant pulsation ($p =$ 0.03, statistically different). For the 100–300 BPM range, gas exchange was 19.5% lower than its respective value for average constant pulsation ($p = 0.009$, highly statistically different).

Gas exchange for the random balloon volume mode at various DBVs is shown in **Figure 4**. Carbon dioxide exchange (**Figure 4A**) for random fully inflated and fully deflated 12.7–24.4 cc mode and for 12.7–24.4 cc fully inflated to deflated DBV mode versus 24.4 cc delivered constantly was statistically significantly different ($p = 0.03$ and 0.04, respectively). However, these random ranges were 2.3% and 6.7% (inflated/deflated and inflated to deflated, respectively) lower than the constant mode. For fully deflated to inflated 14.3–24.4 cc mode versus constant delivered volume, gas exchange was not statistically different ($p = 0.18$). Oxygen exchange (**Figure 4B**) for fully inflated and deflated 12.7–24.4 cc DBV range versus constant 24.4 cc delivered mode was not statistically different ($p = 0.34$). For fully deflated to inflated 14.3–24.4 cc range, gas exchange was 11.7% lower than constant DBV ($p = 0.67$, trend towards statistical difference). For 12.7–24.4 cc fully inflated to deflated random range, gas exchange was not statistically different ($p = 0.04$).

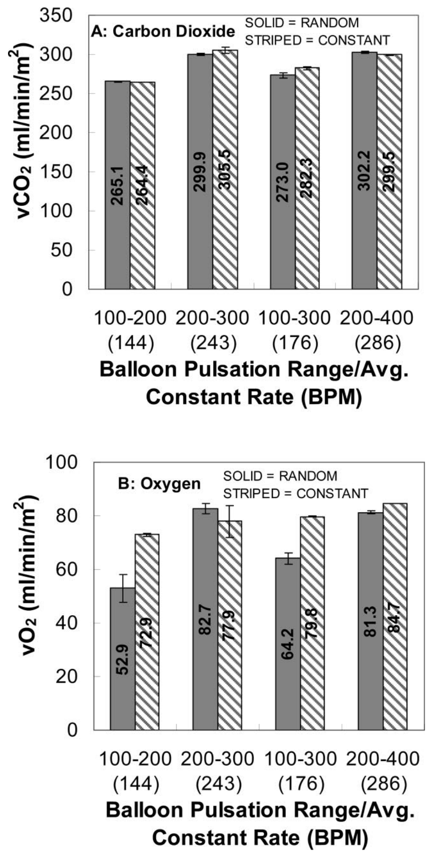

Figure 3. Gas exchange for random pulsation rate ranges compared to their corresponding constant average pulsation rates for (A) carbon dioxide and (B) oxygen.

Discussion

This study evaluated the potential for random balloon pulsation to further enhance gas exchange in our pulsating balloon respiratory catheter. We hypothesized that random pulsation would disrupt fluid entrainment within the fiber bundle and improve gradients for gas exchange. We investigated random balloon pulsation rate and random balloon volume. Overall, random balloon pulsation did not meaningfully impact gas exchange in our respiratory catheter. Gas exchange with random pulsation was comparable and lower in some cases than our conventional constant balloon pulsation.

Random balloon pulsation rates were achieved by our pneumatic drive system, but due to the nature of the system, each pulsation rate had the same balloon inflation rate (*i.e.,* it took the same amount of time to fill the balloon at 200 BPM as it did for 400 BPM). Therefore, in reality we were only able to vary the "quiet time" before the balloon deflated. Any flow generated by the balloon's inflation (or deflation) occurred at the same rate for each random pulsation rate. This may explain why gas exchange at the constant rates were equal to (if not higher) than their corresponding average random pulsation rate ranges. A system (such as a bellows or voice coil) that would allow for changes in balloon filling rate would poten-

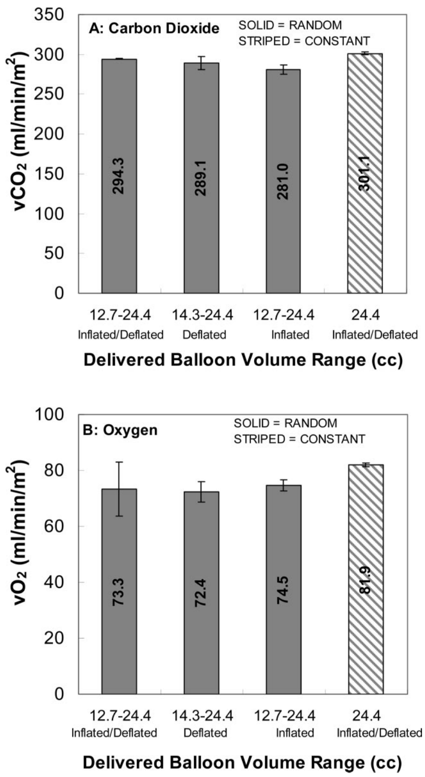

Figure 4. Gas exchange for random delivered balloon volume compared to constant delivered volume for (A) carbon dioxide and (B) oxygen.

tially increase gas exchange due to disruptions of entrained fluid within the fiber bundle.

We compared all of the random delivered balloon volume ranges to our maximum available delivered volume of 24.4 cc at constant pulsation. We could have compared the gas exchange to each random range's respective average delivered volume. For example in **Figure 2B**, the average volume was only 20.2 cc, as compared with 24.4 cc at constant pulsation. We knew from work with our conventional constant pulsation rate, a volume of 20.2 cc would achieve lower gas exchange than one with 24.4 cc because of the lower balloon generated flow (as measured by the plethysmograph method; see Materials and Methods) created by the lower volume. As seen in the sample histogram (**Figure 2B**), random mode included the maximum delivered volume and would contribute to overall increased gas exchange over only 20.2 cc delivered at constant mode. Comparing the random pulsation ranges to a constant rate with the highest available delivered volume allowed for a fair determination as to whether gas exchange was increased due to the random delivered volumes.

Further advancements in our balloon pulsation system, such as incorporating a bellows system into the Labview-controlled program, could potentially disrupt entrained fluid more efficiently than our current pneumatic system by allowing for changes in the rate at which the balloon fills and empties. Changes in balloon fill rates coupled with varying the "quiet time" between pulsations could further increase the maximum gas exchange seen with our respiratory catheter under conventional constant pulsation rates.

Acknowledgments

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