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Radioaerosol Inhalation Lung Scanning: A New Generation

Radioaerosol inhalation lung scanning had its beginnings in the mid 1960's shortly after Drs. George Taplin of UCLA and Henry Wagner of Johns Hopkins independently developed the macroaggregated particles that made the perfusion lung scan possible. It didn't take long to realize that, while the perfusion lung scan could readily show areas of decreased or absent blood flow, it could say virtually nothing about the cause. Because of this shortcoming, Dr. Taplin developed the technique for radioaerosol lung scanning. At the time, about the only thing then available to evaluate lung ventilation was Xenon-133 gas. But because no one had yet developed a delivery/trapping system, its use was limited. Beyond this, the Anger Camera was not yet in wide use and rectilinear scanners could not image a gas that did not remain in the lungs for an extended period. Initially, many isotopes were tried for the creation of the aerosol, but it was finally $Tc99^m$ Sulfur Colloid that became the agent of choice[1]. This isotope worked well with the ultrasonic nebulizers then in use, but its attractiveness disappeared with the advent of the jet nebulizer. This was for the simple reason that jet nebulizers do not aerosolize suspensions readily. These early nebulizers produced a range of particles in the vicinity of 1μ to 5μ, but no one at the time knew very much about the particle size range or distribution. At this time, central deposition was considered diagnostic of COPD and many papers were written to explain why it occurred.

Over the years, efforts were made to overcome the shortcoming of central and tracheal deposition. The results were generally less than fully effective and because of this, the radioaerosol inhalation lung scan languished in just a few centers. While this was happening, the use of Xenon-133 gas was increasing. Systems had been developed to deliver the gas to the patient and charcoal traps had been developed to trap the expired gas, this despite the limitations of single views and poor resolution. Krypton-87^m generators were developed to overcome these problems but, cost and logistics argued against widespread use.

Until the introduction of commercial aerosol systems by Synaco (later Mallinckrodt) and Cadema (later CIS-US), there were only minor improvements in the delivery of the radioaerosol. Taplin, et al, made most of these. They included the use of a large bag downstream from the nebulizer[2] to try to remove the larger particles by gravity, the addition of a light bulb[3] to try to evaporate the larger particles to make them smaller and the addition of a cap over the generator in the nebulizer to cause the larger particles to rain out. Only the latter was successful and it has led to the development of the nebulizers in use today. In the early 1990's, Mishkin developed a system that included a one-way valve at the mouthpiece. In 1997, he modified a commercial nebulizer system to duplicate his original system. It was theorized that without the one-way valve at the mouthpiece, humidified breath would cause the particles to grow beyond the size that would evenly distribute throughout the lung and result in excessive tracheal and bronchial deposition. Testing demonstrated that removal of the one-way valve resulted in a 35% increase in the mass of particles > 1μ, with a corresponding increase in tracheal and central deposition[4]. The system was a fine design, but the necessity of having the exit filter external to the shield created problems with commercial viability. There had to be another way.

Francken, et al, tested a modified commercial system in 1997 that was designed to generate particles almost exclusively < 1μ[5]. The control of particle size and its distribution was accomplished by increasing the diameter of the baffle in the nebulizer so that the particles generated would be required to make two 90° turns before leaving the nebulizer. The first turn would cause larger particles to impact on the baffle and be returned to solution for regeneration. Those that successfully negotiated this turn were of a mass of less than 1μ.

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The system proved quite successful in improving peripheral penetration and reducing tracheal and bronchial deposition. The only problem that came up was slower delivery of the aerosol to the patient. This came about because the extremely small particles could not carry the same amount of radioactivity carried previously by the larger particles and because the generation rate of the nebulizer had been decreased. This was easily compensated for by simply increasing the concentration of the isotope added to the nebulizer reservoir. Still, some thought the breathing time was a little long, especially for patients with breathing difficulties. Hyun, et al, tested a second system which incorporated the same nebulizer (giving the same particle size distribution) but also utilized a holding compartment and a flow control diaphragm[6]. The holding compartment was intended to hold and retain aerosol generated during the time of exhalation in order to make it available during the next inhalation. This would theoretically double the rate of accumulation of aerosol in the lungs. In fact, it more than doubled the accumulation rate. What previously required 5 minutes of breathing now required only 2 minutes. The flow control diaphragm was intended to make certain that the generated aerosol was directed to the holding compartment and also to eliminate or minimize the mixing of humid exhaled breath with the newly generated aerosol.

An incidental finding was that the image quality had been markedly improved[7]. To explain this improvement we must return to Washington, et al. The flow control diaphragm functions in a manner somewhat similar to the one-way valve at the mouthpiece in the Mishkin system in that it tends to prevent saturated breath from the patient exhalation from mixing with the newly generated aerosol. This, in turn, prevents some of the growth of the particle that occurs as they absorb moisture. The primary difference between the two systems (Washington/Mishkin and Hyun) is that the Mishkin device allows the one-way valve to strip the larger particles from the airstream while the Hyun device does not generate the larger particle in the first place. The increased breathing restriction in the Mishkin device caused by the one-way valve is absent in the Hyun device. This lack of breathing restriction acts to increase both patient comfort and compliance.

Classical knowledge such as O.C. Raabe, published in 1982, state that particle sizes from 0.2 to 1.0μ are the least likely to stay in the lungs[8]. This was taken from the literature then available and the measurements were made with monodisperse particles. These particles were most likely inorganic microspheres. As such, their size would be unlikely to change during the respiratory cycle. More recently Toporkov reported that water soluble particles in the respiratory tract, under 100% humidity, can grow as much as 4-5 times their original size[9]. Washington reported a particle size increase of 35% for particles greater than 1μ. Further, Clark states that there seems to be a trend toward regarding particle sizes of 1 to 3μ as being ideal for deep lung penetration[10]. We believe, and our studies and observations seem to support, the contention that the ideal initial particle size for deep lung penetration with minimal upper respiratory tract deposition is less than 1μ for modern water-soluble drugs. While this in no way invalidates Rabbe, it makes his conclusions irrelevant. Clark stops short in that he states the trend is toward 1 to 3μ without taking growth into account. It is for these reasons that we have worked to develop a nebulizer which generates particles almost exclusively below 1μ.

At this point it is worth noting that mass relative to particle diameter is not linear, but is in proportion to volume. The volume of a sphere is determined by the formula:

$$V = \frac{4\pi r^3}{3}$$

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Therefore, if a sphere of 1μ diameter has a mass of 1, then a sphere of 3μ diameter has a mass of 27.15 and a sphere of 5μ has a mass of 125.66. From this it can be seen that a 5μ particle is capable of carrying 125 times the radioactivity of a 1μ particle. If we accept that through moisture absorption, aerosol particles do grow in size as they penetrate the passageways of the lung, and that final particle size must be no greater than 1μ to 3μ to reach and deposit in the deep lung, then we must start with very small particles in order to allow for size growth. Even so, the deposited particles will have carried no more drug (radioactivity) than they contained originally. At the same time, any particles larger than 1u which are generated by the nebulizer will contain the much greater amount of activity related to their mass. Because the larger particles are unable to negotiate the upper respiratory tract, they are most likely to deposit in the trachea and main stem bronchus, thus adding to the count rate in a much larger proportion than their numbers alone would indicate.

In designing a nebulizer to deliver particles largely less than 1u, it became clear that a very small percentage of particles greater than 1μ could produce a noticeable difference in image quality. Our first nebulizer produced 35% of particles in the 1μ to 5μ range. The first modification reduced the percentage of particles in the 1μ to 5μ range to 8.2% and the second modification reduced this number to less than 3%. It was this second modification that yielded the best results in terms of overall image quality in a blind reading of 43 consecutive studies. This unit then moved into production.

As in all things, there were compromises. The compromise in this case being decreased aerosol generation efficiency. It now required 2-4 times longer breathing to obtain the same count rate as the original system. This was compensated for by increasing the concentration of isotope placed in the nebulizer reservoir. This brought breathing times into a reasonable range for a pre-perfusion study, but post-perfusion aerosol studies remained somewhat difficult. The difficulty being either patient compliance because of excessive breathing time, or a lack of an adequate concentration of isotope in the evening and early morning hours.

To overcome the lack of efficiency accompanying the smaller particles, a new unit was developed which returned breathing times to previous levels while still providing the very small particles needed for superior image quality. This new unit provides a holding chamber and flow control diaphragm. The holding chamber enables the unit to retain the aerosol generated during the time of patient exhalation, so that upon inspiration, the patient inhales both the aerosol generated during inspiration and that generated during the preceding exhalation. The flow control diaphragm directs the breath to an exit filter during exhalation and opens during inhalation to give access to both the currently generated aerosol and the previously generated and stored aerosol. Where the flow control diaphragm differs from a one-way valve is in its ability to open completely without restricting the stream of the aerosol and to do so without increasing the breathing resistance. These two characteristics together prevent pooling of the aerosol at the valve with a consequent loss of efficiency.

TESTING

Particle size measurements were performed using a Quartz Crystal Microbalance, 10 Stage Cascade Impactor, manufactured by California Measurements, Sierra Madre, CA. This device has been criticized for its inability to handle high concentrations of aqueous aerosols (9). We have been using this unit for 10 years and are very pleased with its reproducibility over this period. The only qualifier being that it must be used properly, i.e., short sampling times. The industry standard unit is the Anderson 8 Stage Cascade. We have tested both the PC-2 and the Anderson simultaneously and found that in our hands there is no essential difference. We have also had our aerosol tested by TSI Inc., St. Paul, Minn., using their Model 3934 Scanning Mobility Particle

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Sizer and obtained the same results. Testing was conducted using Oxygen as the driving gas at a flow rate of 10L/min., the aerosol was drawn past an isokinetic intake orifice at 14L/min. and the aerosol was drawn through the cascade stages at 0.24L/min. Sampling times varied from 1sec. To 5 sec., and settling time in the cascade was 90sec.

Aerosol generation rate, expressed as mL/min., was obtained by determining weight loss per unit of time. Weights were obtained using a Mettler Analytical Balance reading to 0.001g. All tests were conducted using Oxygen as the driving gas at a flow rate of 10L/min. as determined with a calibrated Gilmont Flow Tube. The aerosol generation rate for our original nebulizer (Medi/Nuclear® Corp., NEB-3A) was 0.28mL/min. and for nebulizer modification 2 was 0.14mL/min. The latter is now in production as Medi/Nuclear® Corp., NEB-3A+.

TESTING SUMMARY

Nebulizer	*Particle Size Range*	*Distribution %*
NEB-3A	< 0.2µ	3.3
	0.2µ to 1.0µ	58.2
	1.0µ to 5.0µ	37.1
	> 5.0µ	1.4
Modification #1	< 0.2µ	16.8
	0.2µ to 1.0µ	75.0
	1.0µ to 5.0µ	8.2
	> 5.0µ	0
Modification #2	< 0.2µ	6.9
	0.2µ to 1.0µ	90.2
	1.0µ to 5.0µ	2.9
	> 5.0µ	0
NEB-3A+	< 0.2µ	40.8
	0.2µ to 1.0µ	57.1
	1.0µ to 5.0µ	2.1
	> 5.0µ	0

As can be seen from the above summary, the primary concern is to limit the particles >1µ to as low a percent as possible. While it may seem insignificant, the 8.2% of particles >1µ in Modification #1 resulted in greater central deposition than the 2.9% of Modification #2 and the further reduction of particles >1µ to 2.1% in NEB-3A+ further decreased central deposition. The NEB-3A+ is the nebulizer currently in production.

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September 3, 1998

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