

BIOLOGIC CONTROLS FOR THE PF LAB

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Has this ever happened in your lab: three consecutive subjects who have normal spirometry and normal lung volumes all show decreased DL_{CO} values? Is this a chance occurrence or is there an equipment problem?

What is a control?

In generic terms, a control is a test signal that can be applied to a measuring system to assess accuracy and/or precision. In the pulmonary function laboratory the measuring system consists of transducers (spirometers, gas analyzers, etc.), a computer with its application software, and an interface connecting the two. There are several types of controls available to assess the integrity of pulmonary function testing systems. It is important to note that controls and calibration are really two separate functions. Calibration provides for *adjustment* of the output of the measuring system to match a known signal. Control (or quality control) *tests* the output of the device to ascertain how accurate or precise the system is.

Controls for use in PFT labs include devices such as the 3-Liter syringe, lung analogs, and lung simulators. A unique type of control is the biologic control, or normal subject. An important difference between the mechanical devices & biologic controls is that the former can be used to assess accuracy and precision, while the latter measures the precision of the system. This is not as big a drawback as it might appear. Biologic controls, unlike a syringe or simulator, cannot typically produce the same signal (FVC, FEV₁, etc.) on demand. They do however allow us to test all the components of our PFT systems in the same way that patients are tested.

Biologic controls for PFT

The requirements for a biologic control for pulmonary function testing are relatively simple. The subject should be a non-smoker with normal lung function – no asthma or other respiratory disease. Ex-smokers may be acceptable as control subjects if their pack-year history is small (e.g. less than 5 pack-years) and they have been non-smokers for 10 years or more. The subject needs to be available for repeat testing; hospital or laboratory staff usually fulfills this requirement. For most laboratories, a range of control subjects is recommended (male/female, tall/short, young/old). This may not be practical for small labs, but one biologic control is better than none. Ideally, the controls should be representative of the patient population served by the lab.

How to implement a biologic control program

Testing of healthy subjects for quality control should be done in the same way as patient testing. Repeat testing on non-naive subjects should result in tight standards for detecting problems.

1. Calibrate all equipment normally as for patient testing, including any maintenance procedures that might be required.
2. Test *control* subjects using the same standardized methods recommended for *patient* testing. The control subject should meet all of the acceptability and repeatability criteria for spirometry, lung volumes, and DL_{CO} recommended by ATS/ERS guidelines.
3. Repeat the measurements on different days on a schedule commensurate with the goals of the quality control program (see 'What are biologic controls useful for' below). If the goal is to determine bias between different systems, it might be appropriate to test the control subject on all systems on the same day. A small laboratory with a single system might check their control subjects weekly or monthly if their goal is to establish day-to-day variability. Published ATS/ERS guidelines recommend weekly biologic controls (or simulator) for DL_{CO} and monthly biocontrols for lung volumes systems. Ideally controls subjects should be tested at about the same time of day to minimize the effects of diurnal variations in lung function.
4. Calculate the necessary statistics; this includes the mean, standard deviation (SD), and coefficient of variance (CV). Assuming that the lung function parameters vary in a normal fashion from day to day, low and high limits can be estimated by ± 2 SD around the mean. Spreadsheet software is useful for recording control data and performing simple statistical calculations. The control data can also be represented graphically. A min. of 10 tests is a basis for establishing means and SDs; 20-30 repetitions produce a valid sample.
5. Formulate an action plan to be used when the results of control studies indicate a problem. For parameters such as the FVC and FEV₁, the coefficient of variation (SD/mean) may be 0.05 or less. For lung volumes (TLC, FRC) and DL_{CO} day-to-day variations of less than 10% are typical. Control values greater than these ranges suggest equipment problems or procedural errors. The plan should include criteria for defining an 'out-of-control' situation and the steps to be taken to resolve the issue. In most situations, repeating the biologic control can be used to document resolution of the problem.

What are biologic controls useful for?

Biologic controls offer an elegant solution to establishing precision and detecting problems, even in systems as simple as a bedside

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Health Professionals, and for hunters. These are pretty much linked lists to within the HHS site and to other government agency web pages. The next topic is "Bird and Animal Issues". There is basic information and information on protecting poultry, protecting people exposed to animals, protecting your pets, and links to sites for monitoring global progress of the disease in birds and humans. In "Global Activities" you can view global efforts to survey and monitor avian flu. This effort supports the government's national strategy to detect and contain outbreaks before they spread around the world. "Travel" provides information to travelers and the travel industry to help reduce the risk of exposure and spread of avian flu through traveling should it become pandemic. Lastly, the section titled "Research" looks at the strides that researchers are making in understanding the H5N1 virus. It also looks at progress in developing a vaccine and in evaluating antiviral medications as they relate to avian flu.

As the homepage banner reads "GET INFORMED. BE PREPARED". This will affect Respiratory Professionals in a profound manner. Supplanted only by the manufacturers of the vaccines and antivirals, we will be the highest priority group to receive a vaccine. Mechanical ventilation will be required by 745,000 patients in the worst case pandemic scenario. Health care providers are under equipped and under manned to handle such a pandemic. So being informed and preparing as best we can is crucial. This is the place to start. Go to: (no "www") <http://pandemicflu.gov> OR <http://avianflu.gov>. Or type "Pandemic Flu" at Yahoo.com (it will be first on the hit list) or at Dogpile.com (it will be second on the hit list).

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spirometer. Repeated measurements of important parameters allow valid statistical limits to be set for each piece of equipment. A similar rationale can be applied to other devices used for pulmonary diagnostics, such as metabolic carts for exercise or nutritional studies.

Table 1 Spirometric variables in a control subject

Control A 37 y/o Female, 65 inches

	FVC	FEV ₁	FEF _{25-75%}
Mean	3.81	2.84	2.19
SD	0.06	0.07	0.11
CV	1.6%	2.4%	5.1%
N	27	27	27

As noted above, repeated measurements on normal subjects provide a method for estimating the precision of the test in question. Precision is another way of saying "How variable is this measurement from day to day?" Table 1 shows the mean, SD, and CV along with the number of control tests (N) for some simple spirometric variables in a healthy subject. In this control subject the coefficients of variation for FVC and FEV₁ are much less than 5%, and just slightly greater than 5% for FEF_{25-75%}. The day-to-day FEV₁ variability that might be expected for a similar subject on this spirometer would be approximately 2* SD, or about 140 ml. From a clinical perspective this would be the smallest change that could be detected in a similar subject. This type of precision data can be useful for test interpretation. For example, in a female patient of similar age and height, a change in FEV₁ of less than 140 ml on serial testing would not be considered significant.

For labs that have several systems, testing control subjects on each system can identify bias between instruments. This concept can be applied in PFT labs that use the multiple PFT systems from a single manufacturer, or to systems that use different methodologies. For example, PFT Lab A uses three DL_{CO} systems from the same manufacturer, while PFT Lab B uses one DL_{CO} system with the traditional CO and He analyzers and a second system with a rapid responding multigas analyzer. Both Lab A and Lab B could use biologic controls to detect differences between their systems. Lab A might expect small and insignificant differences in DL_{CO} among the three systems. Lab B would also expect little difference between the two methods, but could identify the magnitude and direction of any differences. In these examples, separate statistics would be maintained for systems so that the means and SD values could be compared.

Biologic controls can be useful for trouble-shooting suspect equipment. In the scenario at the beginning of this discussion, consecutive low DL_{CO} measurements were observed in subjects with normal spirometry and lung volumes. By testing the DL_{CO} of a control subject, lab personnel can determine whether the observed discrepancies are real or the result of equipment malfunction. Values that fall outside of the range defined by the mean and SD can be taken as evidence that corrective action is needed.

A well established mean (and SD) in one or more control subjects may also be useful for evaluating new equipment or software changes. A lab considering new equipment can compare important parameters as measured by the existing and the proposed systems. Similarly, biocontrols offer a defined method of evaluating software or hardware upgrades to existing equipment.

Biologic controls should be a part of a PFT lab's quality assurance program because they are easy to implement (and relatively inexpensive), test all aspects of system performance (hardware, software, procedures), are useful for monitoring & trouble-shooting PFT equipment and can be used for equipment evaluation and comparison.