Selecting the Most Appropriate Blood Pressure Measurement Method for Preclinical Research: AHA Recommendations Then and Now

AHA Recommendations: Blood Pressure Measurement in Experimental Animals

When the American Heart Association (AHA) published its recommendations for measuring blood pressure (BP) in experimental animals in 2005, the paper became an important resource for scientists deciding which methods were best for their preclinical studies.

The AHA recommendations[1] compared direct and indirect BP measurement, mainly in rodent models. Direct methods included implantable telemetry and external fluid-filled catheters. The most commonly used indirect method was cuff monitoring (pressure measured in the tail or a limb during a change in blood flow). The publication provided detailed descriptions of the advantages and disadvantages of each method.

Using direct methods, pressure could be continuously monitored, resulting in a nuanced picture of BP changes over an extended period of time. In contrast, indirect methods only measured a small sample of cardiac cycles and generally were not capable of providing an average BP over a 24-hour cycle or over the course of a study. Additionally, indirect cuff measurements were usually performed during the day, which disrupted rodent sleep cycles.

Another important difference between the methods was that the animal handling necessary for performing indirect BP measurement could cause thermal and restraint stress, resulting in confounding cardiovascular effects, even when animals were acclimated to such conditions. Direct telemetric measurement eliminated this variability by making it possible to monitor BP without handling or restraint.

Research also demonstrated that indirect methods were less accurate for many types of studies. Agreement analysis indicated that BP measurements obtained via cuff methods showed poor correlations with direct methods. Also, cuff methods were generally not well suited to measuring diastolic pressure.

According to the AHA publication, the main advantages of indirect BP measurement methods were that they were noninvasive, inexpensive, and could detect frank systolic hypertension or substantial differences in systolic BP over time. The authors also pointed out it could be difficult to check system calibration with an implantable device, requiring tests for baseline drift to be done at the conclusion of a study. An advantage of indirect methods was that sensor could be recalibrated frequently to account for drift.

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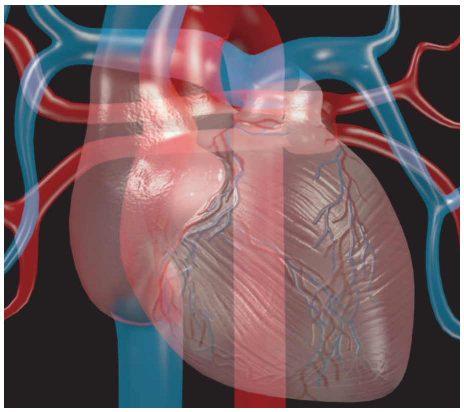
But overall, direct methods were found to be more accurate and reliable than indirect methods for BP measurement. Given the limitations of indirect measurement, the authors advised always using direct methods to quantify relationships between BP and other variables. The authors also pointed out that telemetry had opened the doors to new areas of investigation, such as high-fidelity phenotyping for investigating the genetic determinants of BP regulation. In their discussion of direct methods, the authors asserted that telemetry and externally connected fluid-filled catheters had comparable advantages, but implantable telemetry had an edge because it did not require that animals be restrained.

10 Years Later: Further Considerations

Ten years later, the AHA recommendations remain relevant, but require supplemental information to acknowledge advances in technology and address topics not explored in the original publication. This white paper will cover BP measurement with reference to large animal applications, drift, left ventricular pressure, and hydrostatic pressure.



Large Animal Applications

Because the 2005 recommendations focused mainly on rodent research, this white paper will serve to provide some guidelines for BP measurement in large animal studies. (Examples of large animals commonly used in preclinical research are rabbits, dogs, pigs, and non-human primates.) Precise BP data from large animal studies is essential, in part because large animals are often used for cardiovascular safety testing to determine whether a compound will move on to clinical trials.[2] This white paper will evaluate different methods of large animal pressure sensing based on the findings of several recent studies.

Implantable telemetry is considered the gold standard for large animal BP measurement. One example of this is a 2010 toxicology study[3] in which BP was measured in conscious, unrestrained cynomologus monkeys by implanting a miniature transmitter in the right femoral artery. Jacketed external telemetry was used to collect BP and ECG signals. The two-phase study looked at the tolerability and feasibility of the implant as well as the hemodynamic response. BP data were continuously collected for 24 hours following dosing. The result was that signal quality was high (approximately 95% of data points were retained over the 24 hours of data collection) demonstrating that small changes could be detected from continuously collected hemodynamic data. The authors concluded that because undisturbed monitoring is critical for assessing safety margins of pharmaceuticals suspected of having cardiovascular effects, implantable BP telemetry will continue to be a valuable tool for preclinical toxicology studies. The accuracy and reliability of implantable telemetry have been consistently demonstrated in other large animal research as well.[4, 5]

The 2005 AHA recommendations indicated that direct methods of BP measurement were more accurate than indirect methods for rodent model studies. Large animal studies have also been conducted specifically to compare the accuracy of direct and indirect methods of BP measurement. In a study using concious beagles,[6] BP was measured simultaneously with implanted telemetry and tail cuff oscillometry. Ultimately, the results indicated that the indirect tail cuff method could be used to detect changes in BP, but the direct implantable telemetry method showed greater sensitivity. Specifically, when measured directly, the hypertension-inducing drug resulted in BP and pulse pressure increases. In the same situation, indirect measurement showed an increase in BP, but of a shorter duration and reduced magnitude.

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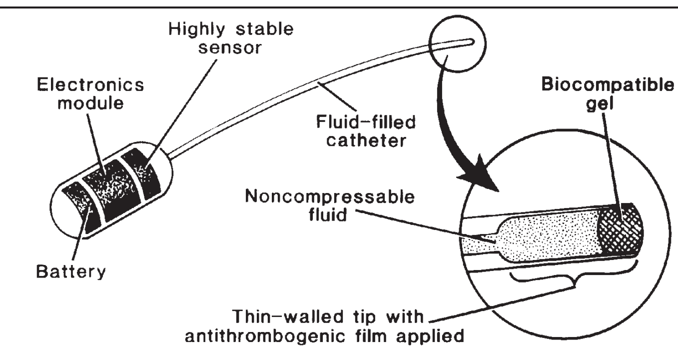
Another notable large animal BP measurement method is high definition oscillometry (HDO). HDO, which was introduced after the publication of the 2005 AHA recommendations, provides measurements of systolic, diastolic, and mean arterial pressures. HDO requires restraint and handling, but is superior to traditional cuff technology because it is faster and allows for real-time measurements that are visible on a computer screen, allowing for immediate assessment of measurement validity.[7]

Some large animal studies have shown that BP measurement with HDO can result in accurate data. For example, in a toxicology study with beagles[8] in which BP was measured simultaneously with a tail root HDO cuff and telemetry implants, the HDO data and telemetry data were closely correlated.

However, there is data variability associated with HDO. A 2010 study[9] comparing simultaneously collected HDO data and telemetry data in conscious beagles found both methods to be precise, but HDO had higher variability for all parameters and a slight positive bias for systolic and diastolic pressure. The authors of this study point out that HDO is subject to animal temperament because of the handling and restraint involved. They recommend acclimating the animals to the restraint to minimize such effects. Because HDO can result in unreliable BP data, the method is most often used for nonrodent repeat-dose toxicology



The first fully implantable pressure telemetry system was developed for rats, but was subsequently adapted for large animals.[10]

studies in which a large number of animals must be screened at once and BP data that are less accurate than implantable telemetry data are acceptable.[7]

Drift (Stability)

One potential issue with pressure sensors is drift, or lack of stability, which occurs when the offset and/or sensitivity of the sensor fluctuates, causing the measured BP to change over time or with temperature changes. With external fluid-filled catheters, the sensor could be calibrated against a known standard, such as a mercury manometer, before every measurement. The device could also be recalibrated before and after an experiment to identify any possible inaccuracies. Drift was problematic when the first implantable sensors were developed because there was no way to access and recalibrate the sensor. Also, *in vivo* transducers could not be vented to the atmosphere, thus introducing changes in barometric pressure due to weather. For these reasons, the 2005 AHA recommendations pointed to drift as a potential problem with implantable telemetry. However, in the intervening decade, stability has steadily improved due to advances in implantable telemetry technology and methodology. Today, long-term studies using implantable telemetry can be conducted with negligible drift,[7] making it unnecessary to recalibrate the sensor over the course of the study.

Left ventricular pressure

Measurement of cardiac left ventricular pressure (LVP) was not discussed in the 2005 AHA recommendations. Cardiac contractility is an important endpoint when assessing the safety of a potential new drug because an increase or decrease can be very harmful in certain clinical conditions. Contractility can be assessed based on LVP, which is the pressure generated inside the left ventricular chamber of the heart. Several cardiovascular parameters are needed to accurately measure contractility. One of those parameters is dP/dt_{max}, the peak positive rate of pressure change inside the left ventricle after systolic contraction starts but before the aortic valve opens and injection into the aorta occurs.

In order to accurately measure dP/dt_{max}, the LVP measurement system must have a high signal-to-noise ratio and a higher frequency response compared to other cardiovascular parameters.

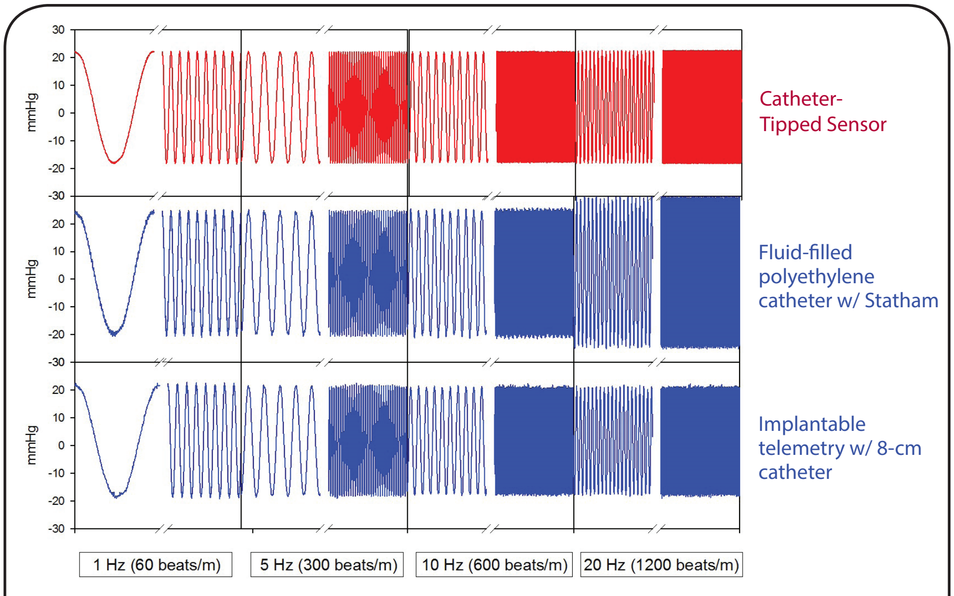
Too much frequency response can cause signal noise, resulting in inaccurate data if the signal is not artificially decreased through a low pass filter.

Frequency response (also referred to as bandwidth) is a quantified comparison of a system's output compared to its input at various frequencies. In dogs, non-human primates, and rats, all of the important signal information occurs at frequencies below approximately 100 Hz. Therefore, frequency response to adequately measure dP/dt_{max} should be at least 100 Hz. Frequency response values significantly higher than 100Hz may imply greater signal fidelity, however, this isn't necessarily the case. Too much frequency response can cause signal noise, resulting in inaccurate data if the signal is not artificially decreased through a low pass filter. In most cases, a frequency response of approximately 100 Hz is more than adequate for measuring cardiac contractility.

Frequency response characteristics vary depending the type of transducer technology used. Traditional fluid-filled catheters (such as those in external Statham-type transducers) can provide modest frequency response. However, they are often constructed out of compliant materials and have a relatively long catheter length extending into the transducer, which can result in inadequate frequency response and/or phase shift in the pressure signal. Also, traditional fluid-filled catheters can develop air pockets that can compromise frequency response. Another disadvantage of traditional fluid-filled catheters (as well as implantable transducers with externalized wires) is that infections can occur at the exit site.[2]

Solid-tipped transducers are implantable devices for acute scenarios. These devices can suitably measure BP, but generally have high drift and much more frequency response than is required for cardiovascular signals, thus requiring low pass filtering of signals.

There are also hybrid transducers that use an *in vivo* fluid-filled catheter. The most advanced devices have a thin-walled sensing region at the tip containing a gel that interfaces between the fluid in the catheter and the surrounding body fluid, promoting excellent transfer of frequency content. This type of implantable telemetry technology results in an appropriate amount of frequency response for the most accurate pressure measurement.[7]



Output signals from laboratory tests of three pressure sensing systems using mechanical stimulation with a sine wave at increasing frequencies. Note that at 20 Hz, the Statham catheter had a frequency higher than the actual input.[7]

Hydrostatic Pressure

Another factor that was not discussed in the 2005 AHA recommendations is hydrostatic pressure. Hydrostatic (head) pressure is the pressure at a certain depth in liquid resulting from the weight of the fluid at equilibrium. In an animal model, hydrostatic pressure can become problematic when the site of interest and the location of the pressure sensor are at different heights and the distance in between is filled with liquid. In the context of pressure measurement, hydrostatic pressure could result in compromised data if the tip of a fluid-filled catheter is at a different height than the sensor. When an external transducer is used to measure BP, the transducer is held at the level of the base of the animal's heart to prevent this effect.

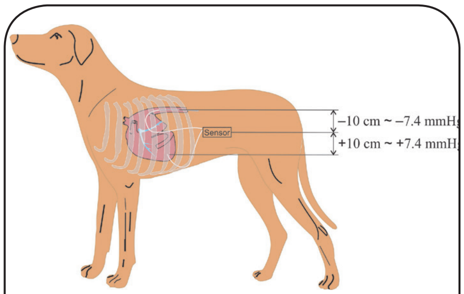


Illustration of the impact of hydrostatic pressure on a laboratory dog. The height difference between the top and the bottom of the thorax is approximately 20 cm. When the aortic valve is open and the two compartments are connected, the measured pressure would be 7.4 mm Hg lower than the sensor positioned at midlevel and the pressure in the left ventricle would be 7.4 mm Hg higher (ignoring the kinetic effects of moving blood).[7]

But catheter-tipped pressure sensors measure pressure at the site of the probe, rather than the heart. This may result in higher mean arterial pressure when it is measured closer to the ground. This effect is negligible in most small animals because head height is similar to the height of other points of interest in the body. However, it becomes a concern in larger animals. This problematic hydrostatic pressure effect can be minimized by using a short fluid-filled catheter connecting the site of interest in the cardiovascular site to a sensor that is implanted near the height of the heart.[9]

Final Thoughts

Accurate BP measurement is vitally important for preclinical cardiovascular research. The 2005 AHA recommendations for BP measurement provided an excellent foundation for scientists deciding which methods were most appropriate for their research. This white paper expands on the information provided by the AHA, summarizing pressure measurement methods used for large animal applications and LVP measurement, and describing other factors that can affect pressure sensing, including drift, hydrostatic pressure, and special considerations for the measurement of cardiac contractility.

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By and large, scientific research shows that implantable telemetry provides the most precise, reliable BP data because it allows for direct sensing and can also offer safeguards against the difficulties associated with pressure measurement.

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