Journal of Pharmacological and Toxicological Methods 70 (2014) 210–223

Contents lists available at ScienceDirect

Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox

Review

Cardiovascular pressure measurement in safety assessment studies: Technology requirements and potential errors

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ARTICLE INFO

Available online 14 June 2014

Keywords:
Left ventricular pressure
Contractility
Inotropic state
dP/dt_{max}
Frequency response
Hydrostatic pressure
Phase shift
Baseline drift

ABSTRACT

In the early days of in vivo nonclinical pressure measurement, most laboratories were required to have considerable technical/engineering expertise to configure and maintain pressure transducers, amplifiers, tape recorders, chart recorders, etc. Graduate students and postdoctoral fellows typically had some training in the requirements and limitations of the technology they used and were closely engaged in the collection and evaluation of data from their own experiments. More recently, pressure sensing telemetry and data acquisition/analysis systems are provided by vendors as turnkey systems, often resulting in a situation where users are less familiar with the technicalities of their operation. Also, investigators are now more likely to be absent and rely on technical staff for the collection of raw in vivo pressure data from their experiments than in the past. Depending on the goals of an experiment, an investigator may require the measurement of a variety of different pressure parameters, over varying periods of time. A basic understanding of the requirements and limitations that can affect the accuracy and precision of these parameters is important to ensure that the results and conclusions from an experiment are reliable. Factors to consider include the possibility of hydrostatic pressure effects from blood inside the vasculature of the animal, depending on the location of the sensor, as well as from fluid inside a fluid-filled catheter system; long-term stability (lack of drift) of a sensor over time, which can affect the interpretation of absolute pressure changes over a prolonged experiment; frequency response of the sensor and associated electronics; and the phase shift that occurs depending on location of the sensor in the vasculature or because of a fluid-filled catheter system. Each of these factors is discussed, and the particular requirements of frequency response as applied to the measurement of cardiac left ventricular pressure are emphasized. When these factors are understood, a pressure sensing and measurement system can be selected that is optimized for the experimental model being studied, thus eliminating errors or inaccurate results.

1. Introduction

The detection and quantification of drug effects on systemic blood pressure and cardiac function are important for the evaluation of both efficacy in cardiovascular therapeutics as well as undesirable side effects from drugs with other therapeutic indications (Sarazan et al., 2011). Various regulatory guidelines have been developed that support the nonclinical evaluation of the hemodynamic and cardiac function effects of drug candidates prior to testing in humans (Anonymous, 1991, 2000).

In 1628, William Harvey postulated that blood is pumped by the heart in a circular movement through the arteries and veins, and ever since, scientists and physicians have attempted to quantify the process we now call hemodynamics (Geddes, 1991; Harvey, 1931). The first known quantification of arterial blood pressure was provided by Stephen Hales in 1733 using a restrained horse with a cannulated femoral artery connected to a long glass rod. By measuring the maximum and minimum heights of the pulsating column of blood, Harvey was able to measure systolic and diastolic arterial pressures, respectively. In what would now be perceived to be a barbaric animal experiment, Hales went on to characterize the hemodynamics of hemorrhagic shock by measuring the blood pressure while exsanguinating the restrained, conscious horse (Geddes, 1991; Hales, 1738).

Subsequent improvements in technology during the almost 300 years since Hales's experiment include the U-Tube mercury manometer by Poiseuille in 1828 and the strain gauge pressure transducer connected to a fluid-filled catheter by Statham in 1943 (Sarazan & Schweitz, 2009). An implantable version of the strain gauge transducer with externalized wires was developed by Van Citters and Franklin in 1965 (Van Citters & Franklin, 1966) and a totally implantable telemetry device with a miniaturized micro-machined solid state sensor was developed by Brockway and Mills in 1989 (Brockway, Mills, & Miller, 1989).

The popularity of in vivo blood pressure measurement using telemetric signal transmission has dramatically increased during the past two decades, partially due to the development of Safety Pharmacology as a discipline and the implementation of the International Conference

Abbreviations: HR, heart rate; HDO, high definition oscillometry; LVP, left ventricular pressure; dP/dt, first derivative of pressure with respect to time; dP/dt_{max}, peak positive value of dP/dt; FFT, fast Fourier transform.

http://dx.doi.org/10.1016/j.vascn.2014.06.003
1056-8719/

on Harmonization (ICH) S7A Safety Pharmacology guideline in 2000 (Anonymous, 1991; Anonymous S7A, 2000; Kinter & Valentin, 2002; Sarazan et al., 2011). This has resulted in the migration of the practice of nonclinical in vivo cardiovascular assessment from small academic laboratories with considerable engineering and technical expertise to higher throughput pharmaceutical and contract research laboratories with less engineering or technical expertise, relying on automated technology. Also, many of the scientists overseeing these studies are experts in areas other than cardiovascular physiology, such as infectious disease, pulmonary physiology, and molecular biology. Thus, the pros and cons of various technologies and methodologies, and more importantly their limitations, are perhaps less known to those conducting experiments and interpreting the results now than in the past.

In response to these trends, this review will provide an overview of basic hemodynamics, the blood pressure measurement technologies available today, potential sources of error associated with these technologies, and will provide specific guidance to ensure that cardiovascular pressure measurements performed in nonclinical safety assessment studies have adequate methodological and scientific rigor, thus facilitating well-informed drug development decisions.

2. Basic circulatory physiology and hemodynamics

The mammalian circulatory system is divided into two components that operate in series, with the heart as the common connection. The systemic circulation originates in the cardiac left ventricle[1] and perfuses the entire body with blood ejected from the heart under relatively high pressure through the aorta. After perfusing the systemic microcirculation, the blood returns to the right atrium of the heart through the venous system, under very low pressure. The pulmonary circulation originates in the cardiac right ventricle and perfuses only the lungs through the pulmonary artery under much lower pressure than the systemic arterial circulation. After perfusing the pulmonary circulation, the blood returns to the left atrium through the pulmonary veins. This also occurs under very low pressure, similar to the systemic venous return to the right atrium. The dramatic difference in the pressure of the blood leaving the left ventricle into the aorta compared to the blood leaving the right ventricle into the pulmonary artery is important and has implications for its accurate measurement with pressure sensing instrumentation systems.

Blood flow into and out of both sides of the heart is maintained in a forward direction by the presence of one-way valves. Through the contraction and relaxation of the ventricles, in combination with the closing and reopening of the valves, low pressure blood entering the heart is ejected under higher pressure into the respective artery (pulmonary artery or aorta). The temporal relationship between pressures in the ventricles and their outflow arteries is often visualized in what's known as a Wiggers' diagram (Fig. 1).

Blood pressure measurements in nonclinical safety assessment studies often occur in the systemic arterial system, typically the aorta and the cardiac left ventricle. Right ventricular pressure and pulmonary arterial pressure are also sometimes measured, although this typically occurs in focused efficacy studies to evaluate pulmonary hypertension.

2.1. Tonic and phasic pressure parameters

Arterial blood pressure is a periodic signal that is tonic and phasic. Derived parameters commonly calculated from in vivo cardiovascular pressure measurements contain either tonic or phasic information, or both (Table 1).

The tonic component of an arterial blood pressure signal does not change rapidly and is typically represented by mean arterial pressure and it contains no frequency information under normal circumstances. Mean arterial pressure is calculated by measuring the area under the blood pressure curve for a specified time, typically one cycle, and dividing by that time.[2] The tonic component of arterial or ventricular pressure measurement is affected by slow changes in the amplitude of the signal, typically due to changes in atmospheric pressure, hydrostatic (head) pressure and sensor drift (change in offset). The phasic, or pulsatile, component of an arterial pressure signal is primarily affected by the frequencies, as opposed to the amplitudes, of the information in the signal. A more complete explanation of analysis of the frequency content of a signal will be presented in the "Frequency Response" section later in this manuscript. Parameters derived from the phasic component of an arterial blood pressure signal include pulse rate and pulse pressure while the phasic component of a ventricular signal provides the very important dP/dt_{max} and dP/dt_{min} parameters used to study inotropic and lusitropic changes. Both tonic and phasic information is contained in the systolic and diastolic pressure parameters. The phasic component of an arterial or ventricular pressure signal is primarily defined by the frequency response of the sensing/measurement system. Frequency response will be discussed in greater depth in a later section.

The phasic component of a systemic arterial blood pressure signal is created from the pulsatile ejection of blood from the left ventricle into the elastic aorta during systole. Blood pressure immediately beyond the aortic valve exhibits a rapid rise to a relatively constant pressure during systolic left ventricular ejection, the dicrotic notch signifying closure of the aortic valve, and then an exponential decline of aortic pressure during diastole. As the site of pressure measurement is relocated farther downstream from the aortic valve, the morphology of the pressure waveforms changes. When blood flow through the arterial vascular tree is driven by the local pressure gradient, mean arterial pressure decreases, the peak systolic pressure increases, and the minimum diastolic pressure decreases, resulting in a pulse pressure increase. This is known as distal pulse amplification and is largely due to the summation of the downstream pressure pulse with reflected waves from the distal aorta and iliac arteries (Remington & Wood, 1956) (Fig. 2). As the pressure pulse reaches the resistance vessels (arterioles and capillaries), the pulsatile component of pressure is removed (dampened) and the signal becomes primarily tonic. Mean arterial pressure is reduced due to a major pressure drop across the resistance bed. A thorough understanding of distal pulse amplification is important, depending on the measurements that are taken. For example, analysis of just systolic pressure would lead an investigator to falsely conclude that blood pressure increases as blood flows down the aorta.

The performance requirements for instruments used to measure in vivo blood pressure in the different components of the circulatory system vary with the signal type. These differences will be explored in subsequent sections of this document.

3. Pressure sensing technology

Blood pressure measurement systems fall into two major categories, direct and indirect. Direct is typically more precise and accurate than indirect but is also more invasive. Indirect pressure measurement will be discussed first, followed by direct.

3.1. Indirect

The most common application of indirect blood pressure measurement, sphygmomanometry, is used by medical professionals to measure a human patient's blood pressure with a cuff on the upper arm (at the

[1] The transitions from one circulatory system to the other have been arbitrarily defined as the atrioventricular valves.

[2] This is the only valid method of calculating mean arterial pressure. Simplified methods such as adding 1/3 of the pulse pressure to the diastolic pressure are inaccurate and should only be used when only two data points (systolic and diastolic pressures) are known, such as in the case with sphygmomanometry. Whereas this estimate may be moderately accurate in some cases, it is extremely sensitive to changes in heart rate when the relative time in systole and diastole varies.