Czech Technical University in Prague

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Brachial occlusion method for non-invasive diagnostics of cardiovascular system

Habilitation Thesis

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Abstract

In this interdisciplinary habilitation thesis, several problematics associated with the cardiovascular system (CVS) diagnostics using the innovated brachial cuff occlusion method of measuring pressure pulsations are addressed. The thesis contains a commented overview of the author's published works in this field. The proposals of appropriate methodologies and algorithms based on the signal processing of the blood pressure (BP) pulsations obtained using the technology, with the aim of identification of some CVS pathologies, are introduced and compared with state-of-the art technologies. The presented results indicate the possibilities of successful using the method for blood pressure measurement in patients with heart failure, especially in patients with an implanted continuous flow left ventricular assist devices (CF-LVAD), in whom current standard methods fail. Other promising results have been observed when measuring hemodynamic parameters of CVS, especially pulse wave velocity (*PWV*) and cardiac output (*CO*), where the preliminary results show a high degree of agreement with the gold standard methods, with the great advantages of being non-invasive and easy to use in clinical practice. The proposed diagnostic methodologies could become part of screening medicine and contribute to diagnosis of some cardiovascular diseases (CVDs) and dysfunctions in early stages, such as hypertension or arteriosclerosis. Perspective direction of research in this area are mentioned at the end of the thesis.

Anotace

V této interdisciplinární habilitační práci je řešeno několik problematik spojených s diagnostikou kardiovaskulárního systému (CVS) pomocí inovované okluzivní metody pro měření tlakových pulzací, využívající pažní manžetu. Práce představuje komentovaný přehled publikovaných prací autora v této oblasti. Jsou zde představeny návrhy vhodných metodik a algoritmů založených na zpracování signálů pulzací krevního tlaku (TK), snímaných pomocí této patentované technologie, s cílem identifikace některých patologií CVS, a jsou porovnány s aktuálně používanými technologiemi. Prezentované výsledky naznačují možnosti využití této okluzivní metody pro měření krevního tlaku u pacientů se srdečním selháním, zejména u pacientů s implantovanou levostrannou mechanickou srdeční podporou s kontinuálním tokem (CF-LVAD), u kterých současné standardní metody selhávají. Další slibné výsledky lze pozorovat při měření hemodynamických parametrů CVS, zejména rychlosti šíření pulzové vlny a srdečního výdeje, kde předběžné výsledky ukazují vysokou míru shody s metodami zlatého standardu. Jednotlivé navržené diagnostické metodiky by tak mohly přispět k včasné diagnostice některých kardiovaskulárních onemocnění, jako je hypertenze či arterioskleróza. V závěru práce jsou zmíněny perspektivní směry výzkumu v dané oblasti.

Keywords

Hemodynamics, Cardiovascular system, Arterial stiffness, Blood pressure, Pulse wave velocity, Cardiac output, Left ventricular assist device, Hypertension, Arteriosclerotic vascular disease

Klíčová slova

Hemodynamika, Kardiovaskulární systém, Arteriální tuhost, Krevní tlak, Rychlost šíření pulzní vlny, Srdeční výdej, Levostranná mechanická srdeční podpora, Hypertenze, Arterioskleróza

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I would like to express my special gratitude to all my colleagues and friends, especially to my colleagues Pavol Sajgalik, Bruce D. Johnson from the Human Integrative and Environmental Physiology Laboratory, Mayo Clinic, Rochester, Minnesota, USA and David Zemanek from 2nd Internal Clinic-Cardiology and Angiology, Charles University, General Faculty Hospital, Prague, Czech Republic, who clinically validated and extended my research. Last but not least, I would like to thank to my colleagues Jan Havlik, Martin Dobias and Vaclav Kremen, and to my Ph.D. students Lukas Matera and Yegor Mikhailov, for their diligent cooperation in the development of the technology and methods discussed in this habilitation thesis.

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Content

1. General motivation

Historically, arterial pulse has been perceived as a fundamental sign of life, therefore methods and devices for its non-invasive sensing and evaluation of arterial waveform (texture) and blood pressure (strength) have been developed mainly over the past 150 years (see sphygmograph by Marey in Figure 1). While non-invasive methods of measuring blood pressure have been used constantly (auscultation, oscillometric etc.), the development of non-invasive measurement of the arterial waveform has been dampened, especially with the advent of diagnostic ultrasound. However, it is evident that knowledge of the pressure pulse texture in different parts of the arterial tree can be advantageously used as an added value to the measurement of blood pressure values. Recently, the renaissance of the non-invasive methods of arterial pulse waveform sensing has been obvious. New methods that can evaluate the advanced hemodynamic parameters of the cardiovascular system are being designed [1]. At the same time, it is necessary to mention that even in the field of non-invasive blood pressure measurement, there are still great challenges, especially when measuring people with specific changes in the pressure curve.

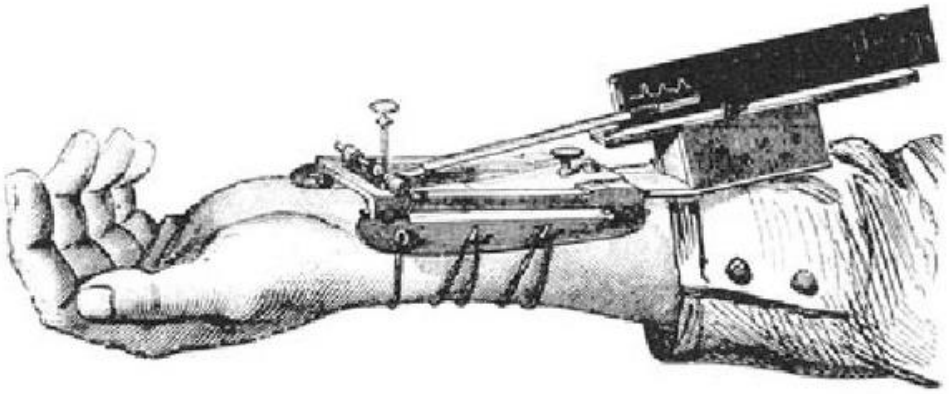

Figure 1: Sphygmograph by Etienne Jules Marey in 1863 [2]

In the onset of the global pandemic of COVID-19, an obvious effort to introduce point of care testing (POCT) methods that could be used directly by patients in the home environment was observed. In combination with telemedicine, it could be a powerful tool of early cardiovascular diagnostics. However, such methods for homecare use must be robust, reliable, and easy to be operated by the end user without the need of an experienced medical professional. In these terms, except for standard automatic electronic sphygmomanometers, which measure only blood pressure and heart rate, there is an obvious lack of homecare methods of advanced hemodynamic parameters monitoring and blood pressure monitors for the specific groups of patients.

Occlusive methods, which most often use an arm cuff to sense pressure pulsations, have been used in medicine for more than 100 years, and during that time they have become a common part of medical care and their use has been adopted by both health professionals and the general public. Non-invasive blood pressure measurement with an arm cuff is a routine procedure which gives fundamental information about the actual status of the cardiovascular system from emergent to preventive indication. It therefore seems advantageous to use these methods also for determining other hemodynamic parameters and thus to expand the diagnostic possibilities of such devices. The arterial

pressure curve is currently obtained standardly and most accurately by the endovascular catheterization technique (direct invasive measurement). It is therefore necessary to obtain a morphologically identical continuous pressure curve using a non-invasive occlusive method. This habilitation thesis discusses the possibilities of using the patented occlusive method for these selected hemodynamic parameters and states of CVS:

- blood pressure measurement in heart failure patients with an implanted CF-LVAD
- arterial stiffness [pulse wave velocity (*PWV*)]
- calculation of circulation parameters [stroke volume (*SV*) and cardiac output (*CO*)]

By determining these parameters using the automatic occlusive method, the diagnosis and thus also the potential risks of CVDs can be determined more accurately, and better managed and targeted follow-up treatment and care is also related to this.

Multidisciplinary research, which is connected to the determination of CVS hemodynamic parameters, is connected to activities in the field of medical HW development, material engineering, digital signal analysis, statistical analysis and, of course, cardiology. The goal is fully automated solutions to obtain quantitative and transparent markers of CVS.

2. Introduction

Over the last several decades, the average life expectancy in the European population has been steadily increasing. Despite the COVID-19 pandemic, which stopped or even reversed this trend in the last two years [3], it can be expected that this indicator will continue to grow in the coming years. This is due to the character of the lifestyle, the increasing efficiency of health care and, last but not least, the hygienic and nutritional level of current life. The result of this is that, coupled with long-term low birth rates, the demographic aging of the population continues to rise [4].

Looking at the attached Figure 2 with the causes of death in EU in 2017, we can find that the highest probability of death was due to cardiovascular diseases. Especially with older age, the probability of dying from cardiovascular disease is safely in the first place for a long time, with a great distance from other causes of death [5].

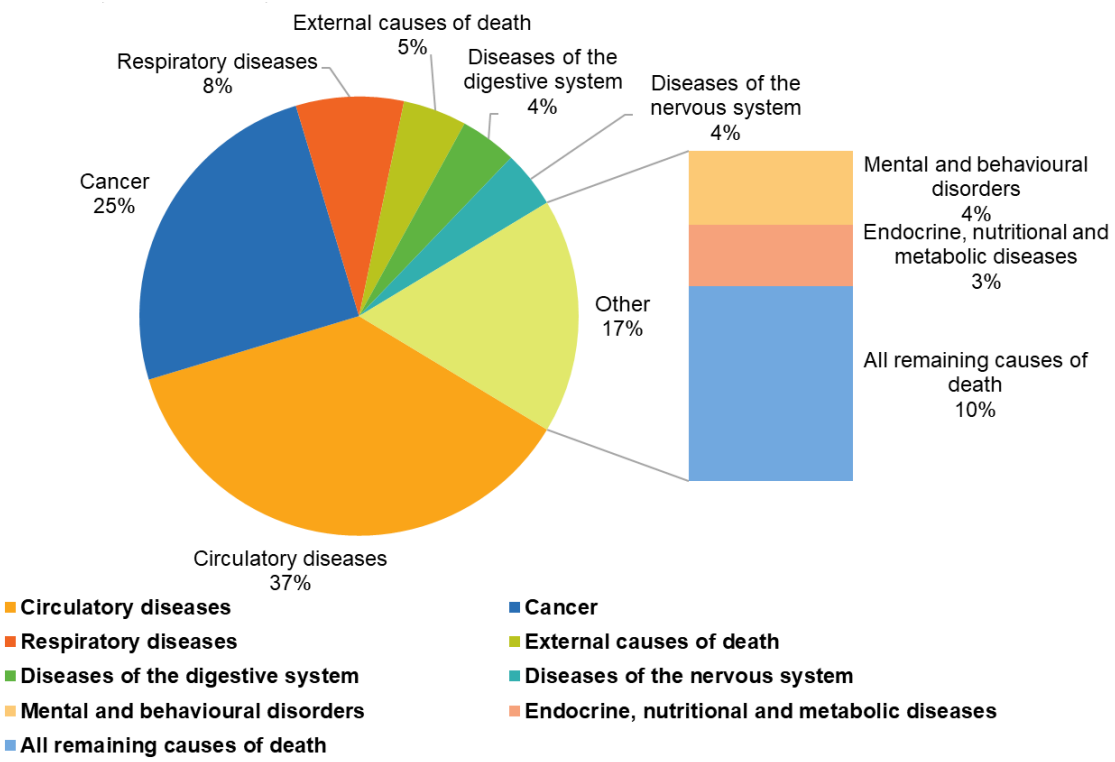

Figure 2: Causes of death by frequency in %, EU, 2017 [6]

Cardiovascular system diseases (CVDs) are, and in the coming years will be, increasingly a burden on the health care system, and it will be necessary to find ways for early and effective diagnosis, which will have a major impact on reducing the costs associated with the treatment of advanced CVDs and heart failure. This situation is far from only affecting the elderly but is affecting people of productive age as well, which makes the whole problem even worse. The need for the development of new or innovative technologies for quick and accurate diagnosis of CVS, which would be feasible even in home care conditions, is thus becoming increasingly clear.

3. General aims of the thesis

Although recently it is possible to observe the rapid development of cuffless devices for non-invasive blood pressure (*BP*) monitoring, classic occlusive methods using a brachial cuff are still the most widespread non-invasive measurement method in clinical practice and deserve attention and research activity for their further development. The great advantage of occlusive methods is their widespread use and acceptance by the professional public, as well as their simple use in home care and in telemedicine. They can be used to evaluate a much wider spectrum of hemodynamic parameters of the cardiovascular system (CVS), moreover, they can find application in specific groups of patients for whom measurement by classical methods is impossible or very difficult.

The presented cumulative thesis comprises 1 US patent [A1] and 5 peer-reviewed journal papers [A2-A6] with the following aims:

i. To design the feasible hardware that are sensitive enough and sufficiently accurate to capture weak pressure pulsations.
ii. To design and validate the feasible algorithms for blood pressure measurement of patients with CF-LVAD.
iii. To design and validate the feasible algorithms and analytical methods for special hemodynamics parameters of CVS.
iv. To improve the possibilities of early diagnostics of CVS and CVS management and thereby reduce the risk of developing CVDs, especially heart failure.

These aims are further supported by the results obtained within the project TH04010173 - Apparatus for non-invasive automatic analysis of hemodynamic parameters (Epsilon program, Technological Agency of the Czech Republic).

4. Basic principles related to the thesis

4.1. Blood pressure

Blood pressure is one of the most important hemodynamic parameters characterizing the mechanical and physiological properties of the bloodstream. Figure 3 shows the record of several blood pressure waves of a healthy resting individual, measured in a. brachialis. Blood pressure levels must be such as to ensure an adequate blood supply to all parts of the body. The highest blood pressure during the cardiac cycle is called the systolic blood pressure (*SBP*). The lowest BP value is called diastolic blood pressure (*DBP*).

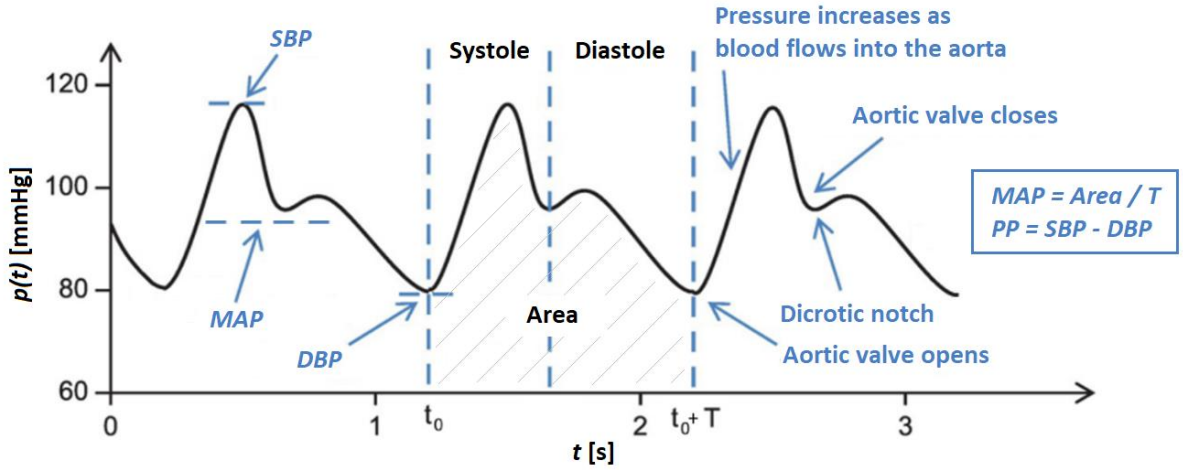

Figure 3: Arterial blood pressure waveform *p(t)*

The mean arterial blood pressure (*MAP*) is the average pressure during one cardiac cycle [7]. Exactly, the *MAP* can be expressed according by the following equation:

$$MAP = \frac{1}{T}\int_{t_0}^{t_0+T} p(t)dt \qquad \text{[mmHg; s, mmHg]} \qquad (1)$$

where *p(t)* represents the course of the blood pressure curve over time.

At resting heart rate, when diastole lasts longer than systole, *MAP* can be roughly expressed as:

$$MAP = DPB + \frac{SBP-DPB}{3} \qquad \text{[mmHg; mmHg, mmHg, mmHg]} \qquad (2)$$

However, with increasing heart rate (increasing load), diastole gradually shortens to less than half (at 100 beats/min and more, so-called tachycardia) of its original value, the duration of systole is almost unchanged. Therefore, also, when the heart rate rises above the critical value (critical rate), the diastolic filling of the ventricles begins to bind and by further increasing the rate, the minute volume does not increase [8].

Mean arterial pressure should be monitored for the following reasons, among others:

- is approximately the same in all places of the arterial part of the cardiovascular system [7]
- is only negligibly affected by the poor transmission characteristics of the measuring device

The difference between *SBP* and *DBP* is the pulse blood pressure *PP*.

$$PP = SBP - DBP \qquad \text{[mmHg; mmHg, mmHg]} \qquad (3)$$

4.2. Heart failure and mechanical circulatory support

Heart failure is a serious life-threatening gradual heart weakening that prevents the heart from blood pumping. Despite modern pharmacotherapy, patients with this chronic condition will reach the final stages of heart failure over time. End-stage heart failure is the most severe form of heart failure. An estimated 64.3 million people are living with heart failure worldwide [9]. Due to a lack of treatment for end-stage heart failure and a limited number of available donors for heart transplantation CF-LVADs became a therapy option for destination therapy as well as a bridge to transplantation [10], [11]. The number of patients treated with LVAD is increasing [10], [12] as durable mechanical support has become widely available.

Left ventricular assist devices (LVAD) or modern continuous-flow left ventricular assist devices (CF LVAD) are implantable medical devices which mechanically support heart function and circulatory system and this durable mechanical support has become widely available allowing patients to be completely ambulatory. The basic principle and implantation site of the CF-LVAD can be seen in Figure 4. LVAD therapy is emerging as a strategy of bridge to transplant (BTT) or as a destination therapy (DT) in patients ineligible for transplantation. In certain cases, ineligible patients can become eligible for transplant after physiologic improvement with LVAD therapy, and a small number of patients with an LVAD may have sufficient recovery of myocardial function to allow device explantation [11]. According to the INTERMACS database annual report 25,551 patients received a CF LVAD support between 2010 and 2019 [13]. Two-years survival on third-generation magnetically levitated centrifugal CF-LVADs is 79.5 % [13].

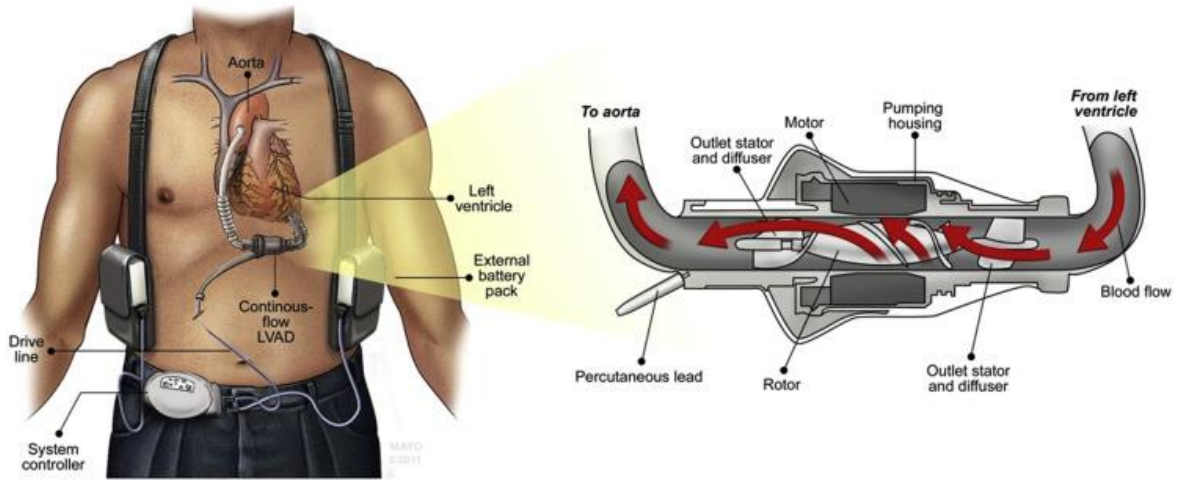

Figure 4: HeartMate II CF-LVAD system (Abbot, USA) (reproduced from [14])

Blood pressure (*BP*) is the essential monitored parameter in end-stage heart failure treated patients. Long-term use of continuous-flow left ventricular assist devices may have negative consequences for autonomic, cardiovascular, and gastrointestinal function. It has thus been suggested that non-invasive monitoring of arterial pulsatility in patients with a left ventricular assist device is highly important for

ensuring patient safety and longevity. The accurately measured *BP*, as well as the hypertension recognition and management in patients with LVADs, is a fundamental component of clinical healthcare [13].

In non-LVAD populations, the arterial blood pressure is easily obtained by auscultation or the oscillometric method, however, in patients supported by CF-LVADs, accurate blood pressure assessment remains challenging because of a reduced pulse pressure *(PP)* [15] and not palpable pulse. Therefore, traditional *BP* measurement by auscultation or automated cuff is less reliable. Variable pressure amplitude in the aorta is given by the ratio of residual contractility of the left ventricle and speed of the device [16]. Commonly used automated devices for non-invasive BP monitoring lead to a remarkably high number of error measurements in patients with CF LVADs [17].

Traditional automated oscillometric *BP* monitors are capable of successfully measuring *BP* in approximately (55–60) % of cases regardless of the measurement accuracy, while manual auscultation allows BP assessment in less than 20 % of LVAD measurements. In the early postoperative period, the invasive intra-arterial catheter (IAC) is considered the most accurate method to measure *BP* in CF-LVAD. However, due to its invasiveness, this method of *BP* measuring is restricted to be used in the operating room and intensive care unit [18]. As this invasive procedure is not feasible to be used in an outpatient routine.

The Doppler blood pressure (DOPBP) technique is often used as a clinical standard to measure *BP* in CF-LVAD patients without an intra-arterial line [15]. In some studies, DOPBP measured *MAP* showed a high correlation with invasive *MAP* (r = 0.97, r = 0.87) in low pulsatility [19], [20]. A study by Lanier et al [21] compared four methods of BP measurement in a cohort of 60 patients supported by HeartMate II. Arterial line, an oscillometric device Terumo Elemano, a standard automated *BP* monitor (GE CARESCAPE TM V100) and Doppler technique. The standard *BP* monitor was successful in 71 % of measurement attempts, Terumo reached 88 %. Importantly, the Terumo device was more accurate, the mean absolute differences compared to arterial line were for *SBP* (4.6±0.6) mmHg and for *MAP* (4.2±0.6) mmHg, respectively. Still, in a significant number of patients there was a difference > 10 mmHg between Terumo and arterial line. This study has shown an important limitation of Doppler technique, which overestimates *MAP* by approximately 9 mmHg and underestimates *SBP* by approximately 4 mmHg depending on the level of residual pulsatility in the peripheral circulation. This limitation is particularly evident with increasing pulse pressure. DOPBP measurement also requires technical expertise and equipment that makes this technique not feasible for simple home *BP* monitoring.

4.3. Oscillometry

The oscillometric method is based on the evaluation of oscillometric pulsations (pressure pulsations), which are sensed by the arm cuff during its inflation or deflation. It is currently the most widespread occlusive method of blood pressure measurement. As can be seen from Figure 5, during the deflation of the cuff, the amplitude of the oscillometric pulsations increases, then its maximum value is reached and further the amplitude of the pulsations gradually decreases. The point of maximum pulsation amplitude is generally considered to be the *MAP* [22]. Then the values of *SBP* and *DBP* are usually determined by applying a mathematical criterion to the envelope of oscillometric pulsations.

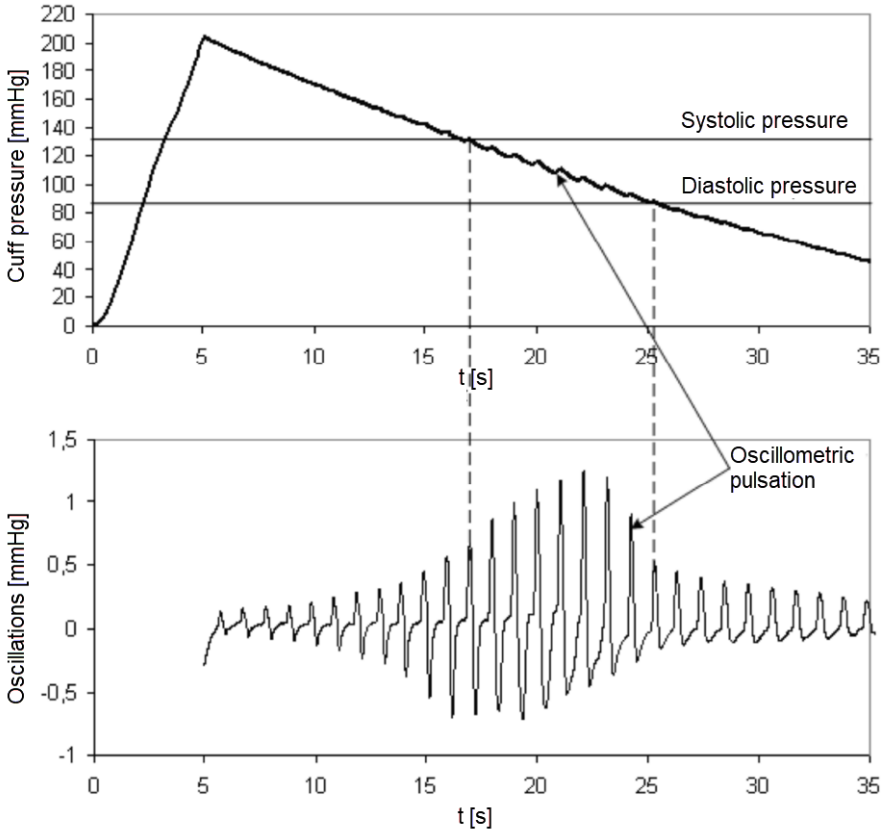

Figure 5: Oscillometric pulsations – (upper part: the oscillometric pulsations superimposed on the cuff pressure; lower part: oscillometric pulsations after filtering and amplification)

Periodically changing pressure in an artery causes its volume pulsations (especially a change in its diameter). These are transferred by the surrounding tissues to the surface of the arm and by the cuff into the pneumatic system of the device. It is flexible and closed, so volume pulsations cause pressure pulsations in the order of tenths to units of mmHg. The amplitude of the oscillations of the arterial wall (changes in its volume) depends on the difference in pressure inside and outside the artery, the so-called transmural pressure. The cause of intra-arterial pressure is blood, hence the heart revolution. The cuff pressure pushes on the artery from the outside. It follows from the course of the volume-pressure dependence that it reaches the greatest steepness at zero transmural pressure. In other words, in the vicinity of zero transmural pressure, its change will cause a maximum change in volume. It corresponds to the vascular unloading condition. The arterial pulsations we observe when slowly inflating or deflating the cuff are maximal if the cuff pressure is equal to *MAP* [22]. This finding represents the only physically or technically derivable and at the same time usable correlation between oscillometric (volume) pulsations of the artery and cuff pressure. It is not possible to directly determine the values of systolic and diastolic pressure from the recorded signal; they are derived empirically from the mean pressure. As already mentioned, specific algorithms are not disclosed by device manufacturers, but in principle there are two ways [22] based on:

i. coefficients – based on numerous measurements, a certain typical course of the blood pressure pulse in the brachial artery is predicted. The coefficients are then empirically derived from it, by which the amplitude of pulsations at *MAP* is multiplied to obtain *SBP* and *DBP* (amplitude at *MAP* A_{max}). Or only one of the pressures is determined by the coefficient and the

other is calculated from it based on the typical pulse oscillation and the shape of the pulses. For example, systolic pressure is defined as a cuff pressure greater than *MAP*, at which the amplitude of the oscillometric pulsations is equal to their value for *MAP* multiplied by the coefficient for systolic pressure ($k_s = A_s/A_{max}$). Analogously, the diastolic pressure is calculated as the cuff pressure less than *MAP*, which corresponds to the amplitude of the oscillometric pulsations A_{max} multiplied by the coefficient characterizing the diastolic pressure ($k_d = A_d/A_{max}$). Both coefficients depend on the flexibility of the cuff, the speed of its blowing, etc. In the literature, e.g. [20] the following ranges can be found for their values: $0.4 < k_s < 0.75$ and $0.6 < k_d < 0.86$. There are, however, a number of pathological circulatory conditions in which the pressure pulse in the arterial bed is altered (e.g. Greater fluctuation in the elderly, less fluctuation in heart failure). Then the pressure values are determined inaccurately, as well as in the presence of movement artifacts in the signal, arrhythmias, or increased arterial stiffness.

ii. first derivative (point of maximum slope) – the cuff pressure corresponding to the point of maximum slope of the curve can be considered as diastolic pressure and, conversely, the minimum slope indicates the value of systolic pressure (these points correspond to the inflection points of the curve). Equivalently, blood pressure values can be obtained from the time derivative of the envelope of oscillometric pulsations – MAP then corresponds to the passage of the derivative zero, DP with its maximum and SP with the minimum.

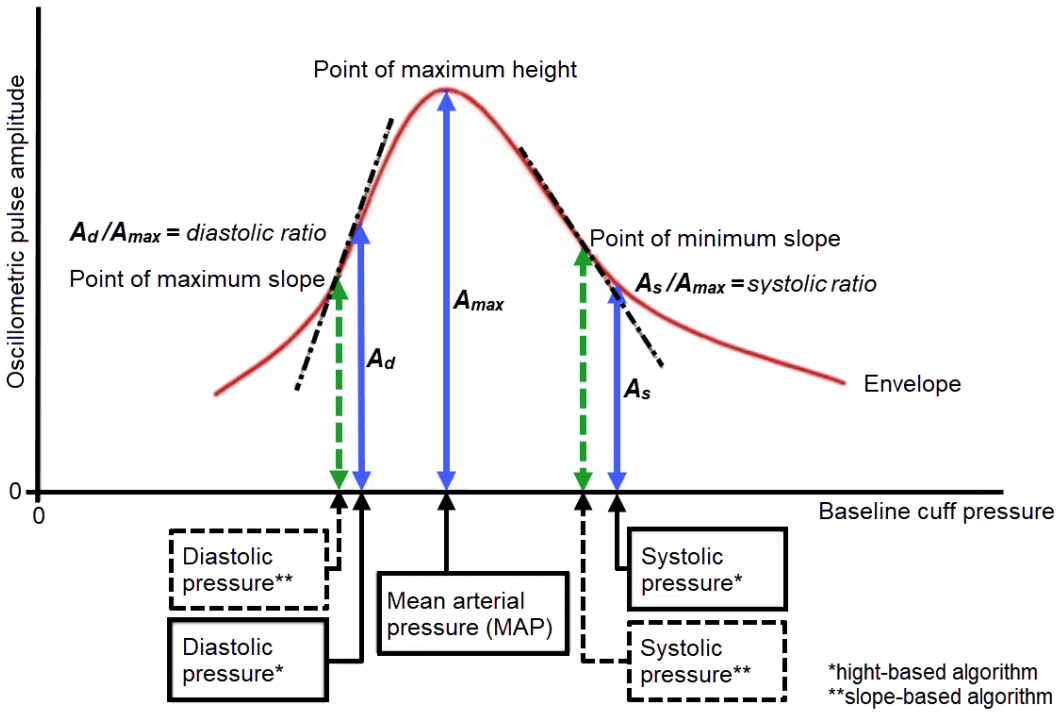

Figure 6: Envelope of oscillometric pulsations with indicated evaluation of SBP and DBP (reproduced from [22])

In both cases we work with a standardized signal envelope of oscillometric pulsations, see Figure 6. Values corresponding to the pressure in the cuff are plotted on the x-axis, the positive amplitude of oscillometric pulsations is most often chosen as the dependent quantity (but it is also possible to use peak-to-peak values of oscillating pulsations or quantities corresponding to area, integral, under the pulsation curve).

4.3.1. Limitation of standard oscillometric method

A much-discussed problem with the oscillometric method is the fact that, unlike the auscultatory method, there is no exact criterion for determining systolic and diastolic pressure. Figure 7 indicates the basic difference between auscultatory and oscillometric methods. Korotkoff sounds become audible at *SBP* and usually disappear at *DBP*, while oscillometric pulsations are evident above *SBP* and continue below *DPB*. The discussed problem is also the determination of the exact value of *MAP*, which is essential for the determination of *SBP* and *DBP* values. As discussed in Article [A2], even the rate of inflation of the cuff itself can affect *MAP* when measured during gradual deflation. Especially in older people with stiffer arteries, this effect is not negligible.

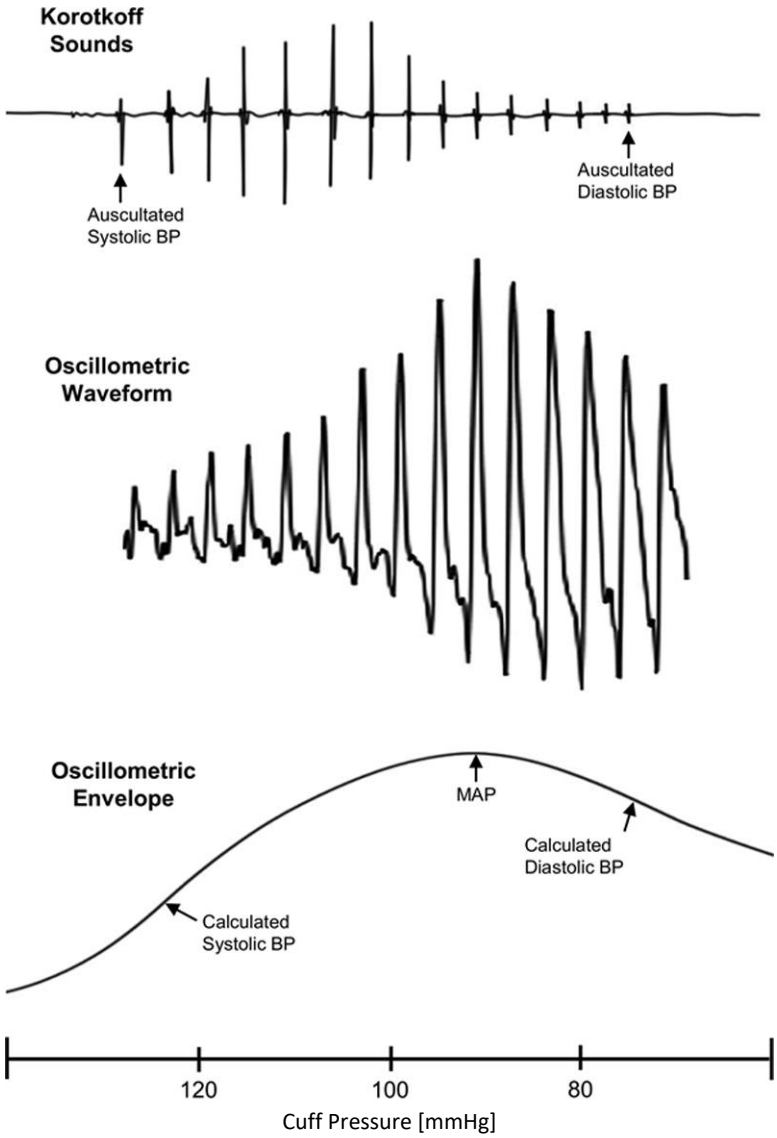

Figure 7: Depiction of manual blood pressure (BP) measurement (with auscultation of Korotkoff sounds) in contrast to automated oscillometric measurement (which derives a mathematical curve called an oscillometric waveform envelope that uses proprietary algorithms to estimate the systolic and diastolic BPs). MAP indicates mean arterial pressure [23].

In the population of patients with an implanted CF-LVAD pump, the situation is even worse, pressure pulsations, i.e. oscillometric pulsations, are an order of magnitude weaker (picture) and standard automatic oscillometric tonometers often do not even pick up such a weak signal and cannot evaluate blood pressure values. This situation occurs because devices designed according to the EN IEC 80601-2-30:2019 [24] standard usually use the same sensor for measuring oscillometric pulsations as for measuring cuff pressure. The measuring range of this sensor is in the order of hundreds of mmHg (standard 300 mmHg according to the [24]), while the maximum amplitude of oscillometric pulsations of patients with an implanted CF-LVAD pump is units of tenths of mmHg, or even less. It is possible to state that the sensitivity of the pressure sensor is insufficient in these cases and even after processing (filtering and amplification) it is often not possible to use such a signal to evaluate blood pressure values [A1].

Another factor that makes it difficult to measure with existing devices is the setting of the CF-LVAD pump. Very often, a situation occurs when once every several heart cycles, the left heart chamber fills up, the aortic valve then opens, and blood is ejected into the aorta. During such a cardiac cycle, blood pressure (especially systolic) is considerably increased compared to previous cardiac cycles, see Figure 8.

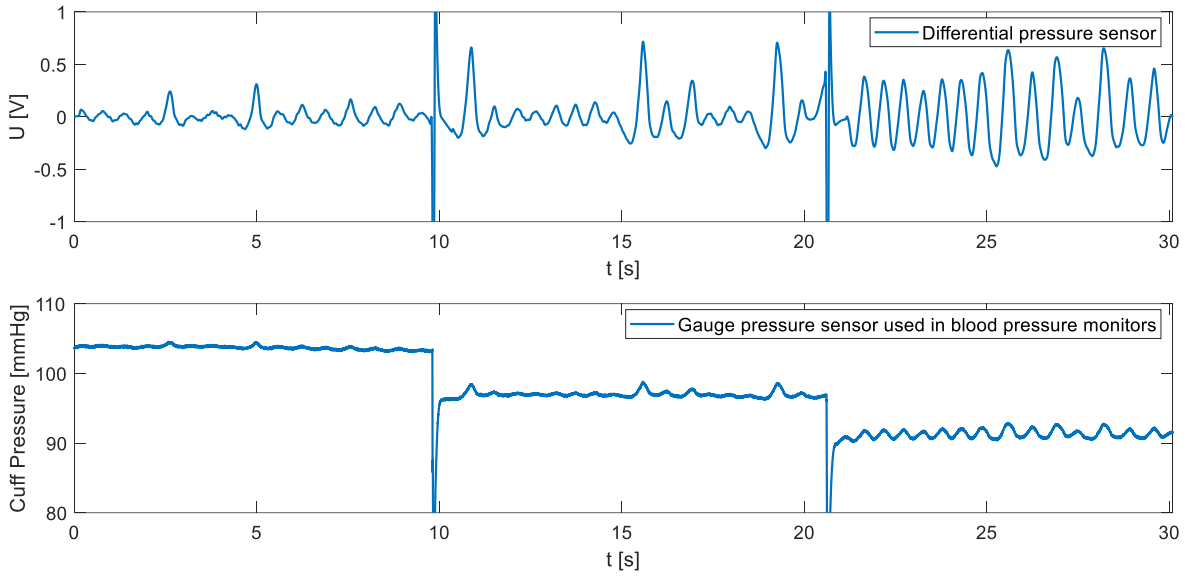

Figure 8: Oscillometric pulsations of a patient with an implanted CF-LVAD (higher amplitudes in the recording correspond to cardiac cycles with blood ejection by the aortic valve open, other pulsations are due to residual heart pulsatility)

4.3.2. Measurement at suprasystolic pressure

Suprasystolic pressure is defined as pressure (35-40) mmHg higher than systolic pressure. At suprasystolic pressure, the artery is completely closed by the arm cuff, and no blood flows through it. The cuff also serves as a pressure pulsation sensor, see Figure 9. It is therefore an extension of the oscillometric method by sensing oscillometric pulsations around suprasystolic pressure. This principle is used for non-invasive measurement of the pulse wave, from which the hemodynamic parameters of the bloodstream are subsequently calculated [25]. The innovative device also works on this principle, see Chapter 5. In this chapter, specific hemodynamic parameters measured by this technology are also described in more detail.

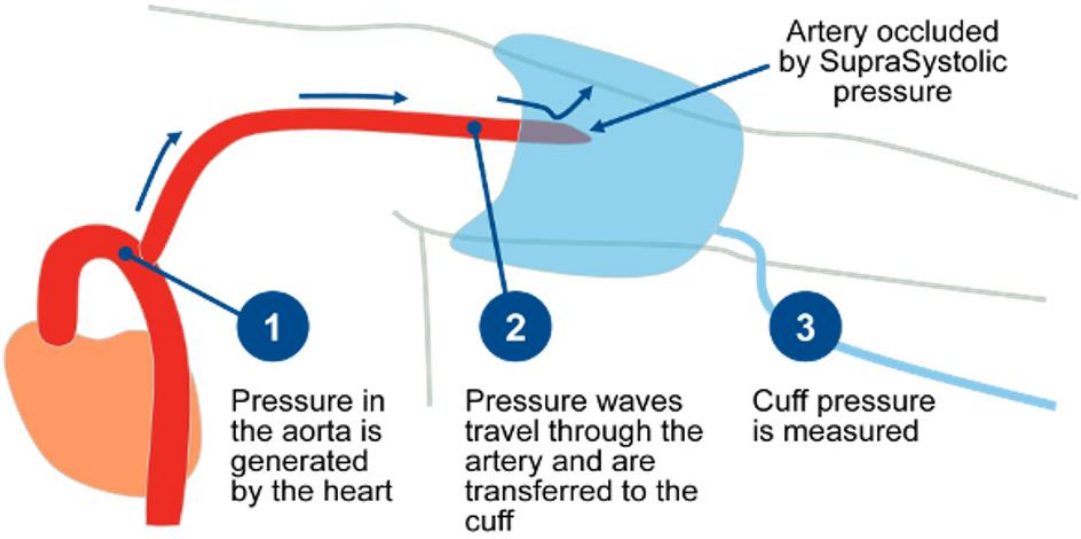

Figure 9: Sensing pressure pulsations at suprasystolic pressure (reproduced from [26])

5. Discussion of the main findings and potential impact of the thesis

5.1. Innovative occlusive method

An idea of accurate non-invasive arterial blood pressure measurement that overcomes the shortcomings of standard blood pressure monitors and doppler method has been resolved by developing a device based on the oscillometric method. This habilitation thesis is focused on possibilities of early cardiovascular diagnostics by a new patented occlusive method for an accurate automated non-invasive measurement of blood pressure waveform based on the occlusive method with arm cuff. The connection of individual elements in the pneumatic part and their control from the electronic part enables, in connection with the arm cuff, up to 100 times more sensitive recording of the pressure curve in comparison with the existing occlusive methods. This type of involvement of arterial pulsation sensing brings completely new possibilities in the diagnosis of certain hemodynamic parameters of the cardiovascular system, or their measurement in patients with weak pressure pulsation, in whom the existing methods fail. This method uses an arm cuff to measure, which a large part of the population knows very well from a routine blood pressure measurement procedure, therefore it appears to be very easy to apply for POCT in home care.

The exact description of the patented device is given in the patent [A1]. The main innovation lies in a special pneumatic connection of the differential pressure sensor according to Figure 10. The individual inputs of this pressure sensor are separated during the measurement by a shut-off valve, and the deflation in the individual branches is feedback-controlled. The difference in static pressures between the individual branches is no greater than ±1 mmHg. Oscillometric pulsations are thus detected by a sensor with a range of ±2 mmHg. This ensures that even very weak oscillometric pulsations with amplitudes in the hundreds to tenths of mmHg (which are common values in CF-LVAD patients) are captured and can be used to evaluation of the blood pressure values (*SBP*, *MAP*, *DBP* and *PP*).

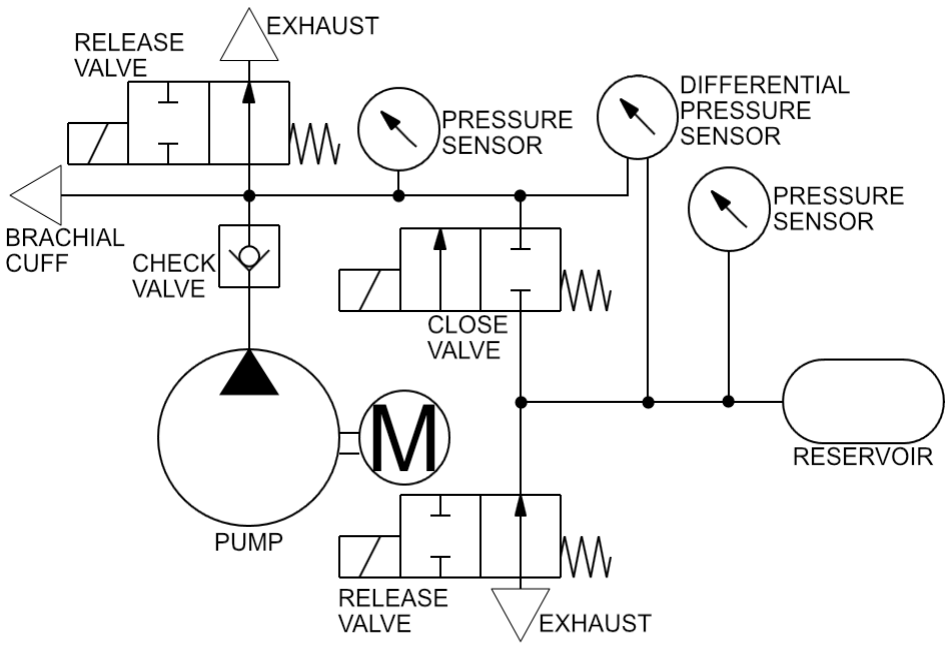

Figure 10: Pneumatic part of the patented device – block diagram

Figure 11 shows a comparison of the record of pressure pulsations taken in a healthy subject at the suprasystolic pressure. In the upper part of the picture there is a record from a standard gauge pressure sensor (upper part of the picture), in the lower part the signal recorded by a differential pressure sensor connected according to the patent [A1]. The differential sensor in such a connection is capable of capturing pressure pulsations, including reflected waves, which is crucial for determining some hemodynamic parameters (see next chapters).

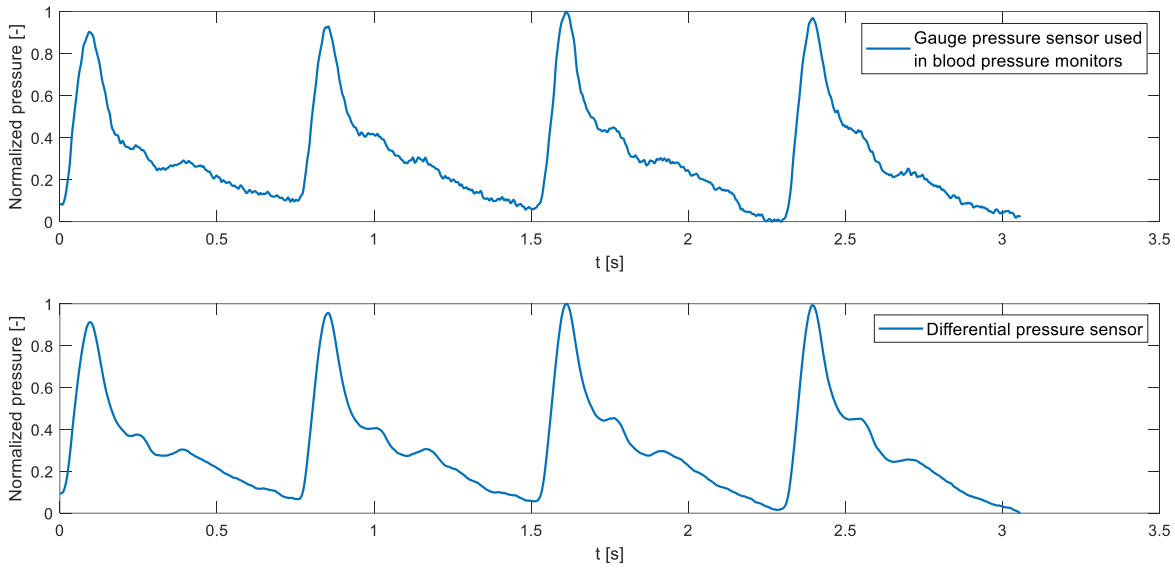

Figure 11: Pressure pulsations at suprasystolic pressure of a healthy subject – comparison standard occlusive method vs. innovative method with differential sensor

5.2. Blood pressure measurement

5.2.1. Mean arterial pressure

The problem of the correct determination of *MAP* is discussed in article [A2]. As mentioned above, the correct determination of *MAP* is essential for the determination of *SBP* and *DBP* values. An oscillometric non-invasive blood pressure (NIBP) monitor was specifically designed according to the patent [A1] to measure oscillometric pulsations and mean arterial pressure (*MAP*) during inflation and deflation of the cuff. Reported data in this article suggest that significantly different *ΔMAP* (difference between the *MAP* during inflation and *MAP* during deflation) between groups of young and elderly people might rather represent different biologic response of the brachial artery and the blood pressure between groups than bias of the measurement system, as one would expect *ΔMAP* to be similar in both groups in the case of system bias. Regulation of systemic arterial blood pressure in general and the level of contraction with actual tonus of smooth muscles in tunica media of arterial wall is balanced by multiple endocrine, paracrine, and autonomic neuronal pathways and can be modulated by antihypertensive drugs. Although, it cannot be completely foreclose a bias of the system because it was not tested against any gold standard method (e.g. intra-arterial catheter), one could speculate that by the given character of a very short pressure stimulus, more likely not causing any regional hypoxia and considering the remarkable age difference between the groups, it is likely that the mechanical properties of the aging arteries [27], [28], [29] contributes to the higher *ΔMAP* difference in elderly group. This could be due to the possibly changing ratio of collagen and elastin in the arterial

wall [28], [30]. Mechanical stress could also potentially activate the age-dependent function of endothelial cells [29] and in turn change the smooth muscle tone [31] by releasing prostaglandins [32], [33], endothelin [34] and other vasoactive agents and theoretically cause a positive *MAP* difference in both groups. Thus, it remains unknown which of the mechanisms plays the dominant role after applying defined pressure on the arterial wall by the cuff and further studies need to be designed to evaluate the method against a gold standard (intra-arterial catheter) and to investigate other biological effects of arteries and endothelial cells to answer questions raised by the presented data. In principle, this could be a supporting method in the assessment of the state of blood vessels.

5.2.2. Systolic and diastolic blood pressure in LVAD population

In the article A3 are discussed the possibilities of *SBP* and *DPB* measurement with device according to the patent [A1]. The device was tested in group of 31 patient with implanted CF-LVAD device (20 HeartMate II and 11 HeartWare) at Mayo Clinic, Rochester, USA. The measured data were compared with simultaneously measured blood pressure values by an invasive technique (I-A BP, on the radial artery) (Bland–Altman plots revealed that the innovated blood pressure (ExpBP) monitor overestimated mean arterial pressure (*MAP*) by 1.2 (4.8) mmHg (mean difference [standard deviation]), whereas the Doppler by 6.7 (5.8) mmHg. The ExpBP *SBP* was overestimated by 0.8 (6.1) mmHg and *DBP* by 1.9 (5.3) mmHg compared with the respective I-A pressures). The tested device monitor was able to assess *SBP*, *DBP*, and *MAP* in the majority of CF LVAD subjects supported either by axial or centrifugal pumps with good agreement to the I-A BP. The independent displaying *SBP* and *DBP* after *MAP* determination may improve overall measurement success rates. (Both techniques achieved similar measurement reliability. In the measurement “success rate” expressed as a frequency (percent) of readable BP values per measurement attempts, Doppler accomplished 100% vs. 97%, 97%, and 94% of successful detections of *MAP*, *SBP*, and *DBP* provided by the ExpBP monitor.) More details are in chapter Results in article [A3].

Automated *BP* monitors specifically designed for the patients supported by CF LVAD might simplify self- and home monitoring of *BP*, contribute to safer use of antihypertensive drugs, and, in turn, may alleviate adverse outcomes associated with poor *BP* control.

5.2.3. Arterial pulsatility index

Long-term use of continuous-flow left ventricular assist devices may have negative consequences for autonomic, cardiovascular and gastrointestinal function. It has thus been suggested that non-invasive monitoring of arterial pulsatility in patients with a left ventricular assist device is highly important for ensuring patient safety and longevity. In the article [A4] is proposed and discussed semi-automated frequency-domain-based index of arterial pulsatility that is obtained during suprasystolic occlusions of the upper arm.

Twenty-three patients with a left ventricular assist device with end-stage heart failure were recruited for this study. Suprasystolic occlusions were performed on the upper arm of the patient’s dominant side, from which the cuff pressure waveform was obtained. Arterial blood pressure was obtained from the radial artery on the contralateral arm. Measurements were obtained in triplicate. The relationship between the cuff pressure and arterial blood pressure waveforms was assessed in the frequency-domain using coherence analysis. A mixed-effects approach was used to assess the relationship between cuff pulsatility index and invasively determined arterial pulsatility (i.e. pulse pressure).

The cuff pressure and arterial blood pressure waveforms demonstrated a high coherence up to the fifth harmonic of the cardiac frequency (heart rate). The cuff pulsatility index accurately tracked changes in arterial pulse pressure within a given patient across repeated measurements.

The cuff pulsatility index shows promise as a non-invasive index for monitoring residual arterial pulsatility in patients with a left ventricular assist device across time.

5.3. Arterial stiffness parameters

The biomechanical properties of the arterial wall can be described using the relationship between the change in pressure *P* and the change in volume *V*. Arterial stiffness is expressed by the instantaneous slope of the *P-V* curve. As arterial stiffness increases, pathophysiological changes in the vascular bed can be observed [35]. The vessels are less capable to adapt to the volume of blood that is ejected from the left ventricle into the circulation and the increase in systolic pressure, leading to left ventricular hypertrophy and fibrosis. Reduced elastic properties, which are ensured in the arterial wall by the ratio of two structural proteins (collagen and elastin), lead to a decrease in diastolic pressure and an increase in *PP*. This results in greater pressure changes in the blood supply to the organs (brain, kidneys) and can lead to their damage [35]. There are already many studies dealing with the measurement of arterial stiffness. These include how invasive and non-invasive methods. Hemodynamic parameters are measured invasively using a catheter. Non-invasively, using ultrasound, MRI, or applanation tonometers· and cuffs, working on different principles. A detailed description of the methods and devices can be found in [36].

The innovated occlusive method can be used especially when determining Pulse wave velocity (*PWV*). The *PWV* parameter is defined as the speed at which the pulse wave generated during systolic contraction propagates through the arterial tree. According to the methodology of the European Hypertension Society, the evaluation of the *PWV* parameter is taken as one of the basic indicators of arterial stiffness. It points to the elastic properties of blood vessels. The greater the PWV, the less the compliance of the vessels, and this leads to greater arterial stiffness. [19] The velocity of pulse wave propagation between the carotid and femoral artery (*cfPWV*), which describes the velocity of pulse wave propagation in the aorta, is considered as a valid predictor of cardiovascular diseases such as hypertension, diabetes, etc. [19]

5.3.1. Pulse wave velocity assessment

The analysis of weak pressure pulsations can also be advantageously used to determine other CVS hemodynamic parameters. When creating an occlusion using an arm cuff, i.e. inducing suprasystolic pressure, which is a pressure safely above the *SBP* value (at least by 30 mmHg), the cuff serves as a pressure pulsation sensor. Using the above-mentioned differential sensor and a cuff with a tube, which have suitable material properties, it is possible to detect a morphologically identical signal, as during invasive catheterization [37]. Based on such recorded data, the pulse wave velocity, see article [A5].

A total of 21 subjects were included in the study, in which the PWV values obtained by the non-invasive method of the gold standard (SphygmoCor VX) and the cuff-based device according to the patent [A1] were compared. The results confirmed that the novel design of single brachial-cuff technique generating high fidelity signal compares very closely with the current gold standard method SphygmoCor VX for *PWV* assessment. The correlation between methods using a Pearson's correlation coefficient was $r = 0.88$ ($p < 0.001$), see chapter results in the article [A5]. Results have also shown that

PWV is an age-dependent parameter, where the *PWV* is increasing with the age because of the loss of the elasticity of aortic walls and their calcification. Since the clinical need is to recognize the alterations of cardiovascular system prior developing organ complications, the presented technique can be used in the home monitoring and primary care setting.

Additional supporting data were obtained within the Epsilon project TH04010173 (Technology Agency of the Czech Republic). As part of this project, the developed device prototype was compared with the SphygmoCor VX device. A total of 145 people were measured, of which 95 were men and 50 were women. The age of the measured persons was (35.7±15.5) years (mean ± standard deviation). The height of the measured persons was (176.9±8.9) cm, and the weight was (76.6±15.5) *kg*. The body mass index (*BMI*) in the measured population was (24.4±4.0) $kg \cdot m^{-2}$. The criteria for excluding subjects from the study and statistical processing were as follows: *SBP* > 180 mmHg, *DBP* > 120 mmHg, second degree obesity (*BMI* > 35 $kg \cdot m^{-2}$) and arm circumference greater than 32 *cm*. Based on these criteria, 10 subjects were excluded from statistical processing. Another 4 subjects were also excluded due to the impossibility of recording *PWV* using the SphygmoCor VX device, and in 5 subjects it was not possible to process suprasystolic pulsations using the developed prototype. The resulting set for the comparative analysis of non-invasive methods between the new prototype and the SphygmoCor VX was 113 subjects. For measured data using a prototype, a model of the dependence of *PWV* on individual basic parameters determined from information and measurements from patients was created. The model is dependent on age, diastolic pressure, pulse wave propagation speeds between the jugulum and symphysis, or navel (umbilicus) and their distances. This the model was also used for invasive comparative analysis. The correlation analysis for the resulting model is as follows: $r = 0{,}74$, $p = 4 \cdot 10^{-21}$. The dependencies are then shown by linear regression graphs and the Bland-Altman graph, see Figure 12.

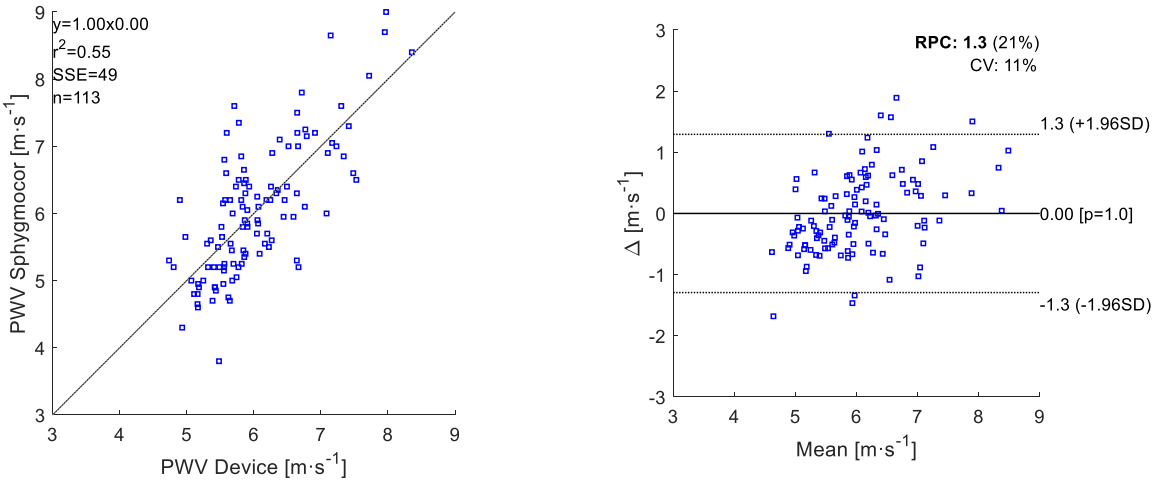

Figure 12: Comparison of *PWV* values of the prototype device and the SphygmoCor. Linear regression graph, where the x-axis represents the *PWV* model values from the device prototype, and the y-axis the *PWV* values from the SphygmoCor (left). Bland-Altman plot showing differences and means of individual measurements between methods (right).

5.4. Circulation parameters

Circulation parameters describe the dynamics of CVS blood flow, especially the flow rates and speeds of blood flow through individual areas of the vascular bed. In this work, attention is paid to cardiac output, which can be measured by the occlusive method. Cardiac output (*CO*) describes the volume of blood that is ejected by the left ventricle into the bloodstream in one minute, see equation 4. The rest value of the *CO* is in the range (4 to 8) l.min^{-1}, during load and then you can go up to 20 l.min^{-1} [38].

$$CO = SV \,.\, HR \qquad [\text{l.min}^{-1};\ \text{l},\ \text{min}^{-1}] \tag{4}$$

where *SV* is stroke volume and *HR* is pulse rate.

Cardiac output is one of the basic hemodynamic parameters and is part of advanced hemodynamic monitoring during perioperative examinations and intensive care. Except Fick's method, which is considered the "gold standard" of *CO* measurement, there are also other methods [39], [40]:

- Invasive methods
  - Thermodilution principle (continuous, intermittent bolus)
- Minimally invasive methods
  - Dilution principle (most often lithium salts, esophageal Doppler)
- Non-invasive methods
  - Bioimpedance and bioreactance, ECOM, Doppler principle, plethysmography, Cuff-occlusion method

5.4.1. Cardiac output assessment

The study in article [A6] provides an initial assessment of a new non-invasive technique for estimating cardiac output. There is a comparison of cardiac output derived from a novel formula adapted for the new brachial occlusion method to the previously validated open circuit acetylene method. Thirteen healthy adult subjects with no history of tobacco use were recruited from the surrounding community of Mayo Clinic in Rochester, MN, USA, and provided written informed consent. With one exception, all subjects maintained various levels of physical activity, mostly recreational, during the time of the study. Both techniques provided similar estimates of cardiac output at rest and during exercise, see chapter results in article [A6]. Accordingly, this technique may provide an alternative method to non-invasively assess cardiac output in a wide range of environmental conditions.

Based on this article, part of the Epsilon TH04010173 project was also focused on the non-invasive determination of cardiac output (*CO*) using precise sensing and evaluation of suprasystolic pressure pulsations. As a reference method for determining cardiac output, the thermodilution method [36]. The calculation of *CO* using non-invasive measurement was based on the above-mentioned publication [A6], and mainly on the decomposition of the suprasystolic pressure curve into individual parts. First, the suprasystolic pressure curve was divided into systolic and diastolic parts. The systolic part is subsequently important for the calculation of cardiac output. It was further divided into the primary and reflected wave (the latter, with its simplified form, reflects the approximate sum of reflected waves within the systolic phase of the heart cycle), see Figure 13. A total of 14 patients were measured, 2 subjects were excluded due to a problem with the assessment of cardiac output by a non-invasive method. In total, 12 patients (10 women, 2 men) were evaluated, who were measured using the device prototype and the thermodilution method. The age of these measured persons was (62.4±12.0) years.

The height of the measured persons was (166.3±7.9) cm, and the weight was (71.7±18.7) kg. The body mass index (*BMI*) in the measured population was (25.7±5.5) $kg \cdot m^{-2}$. Systolic blood pressure was (135.5±27.9) mmHg and diastolic blood pressure was (76.8±7.6) mmHg.

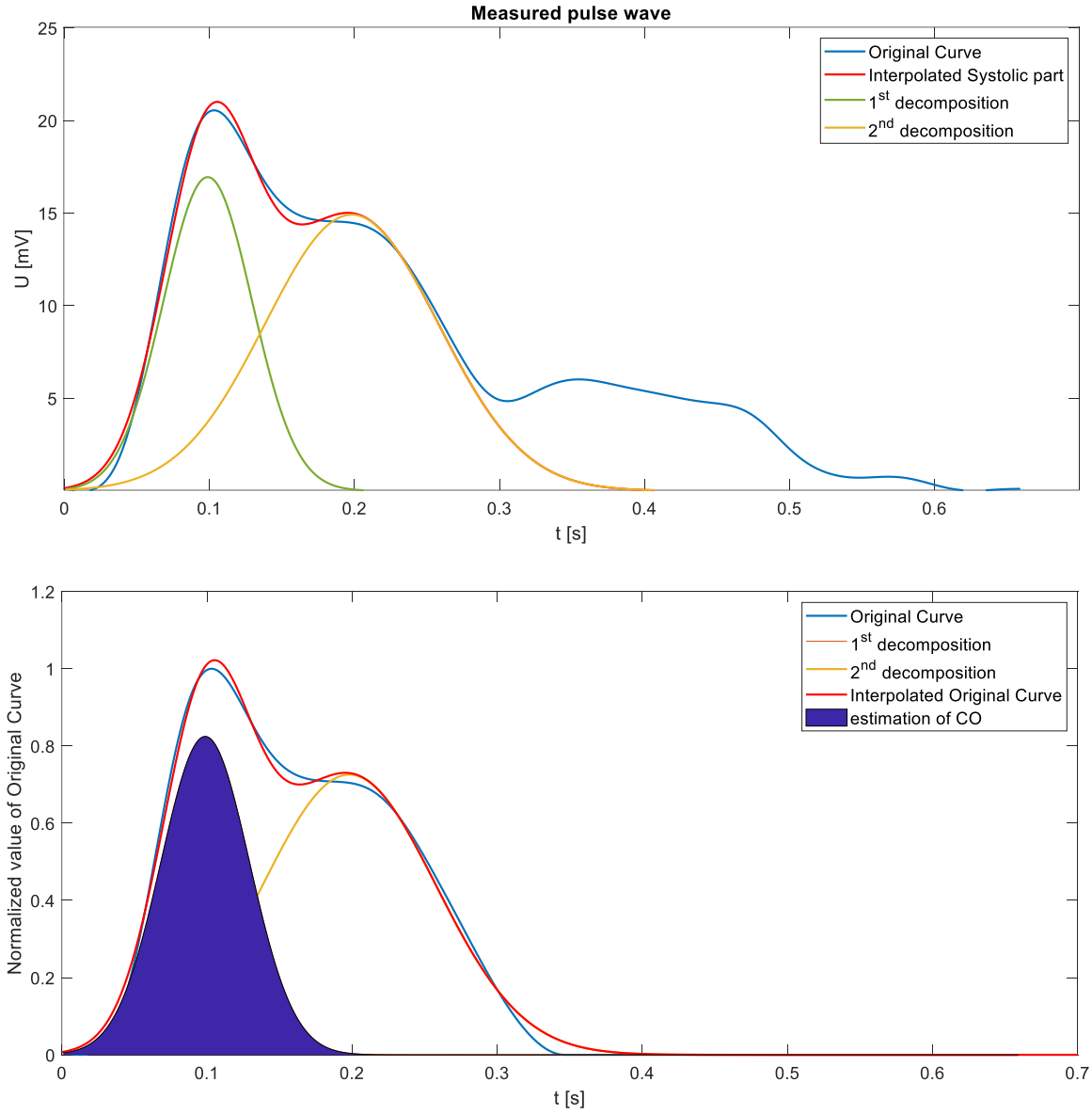

Figure 13: Demonstration of decomposition of suprasystolic pressure pulsation (upper part) and subsequent calculation of cardiac output (*CO*) using the acquired primary wave (lower part).

The comparison of the non-invasive method with the validated standard in the form of the thermodilution method is again expressed using linear regression and Bland-Altman graphs, Figure 14 and Figure 15.

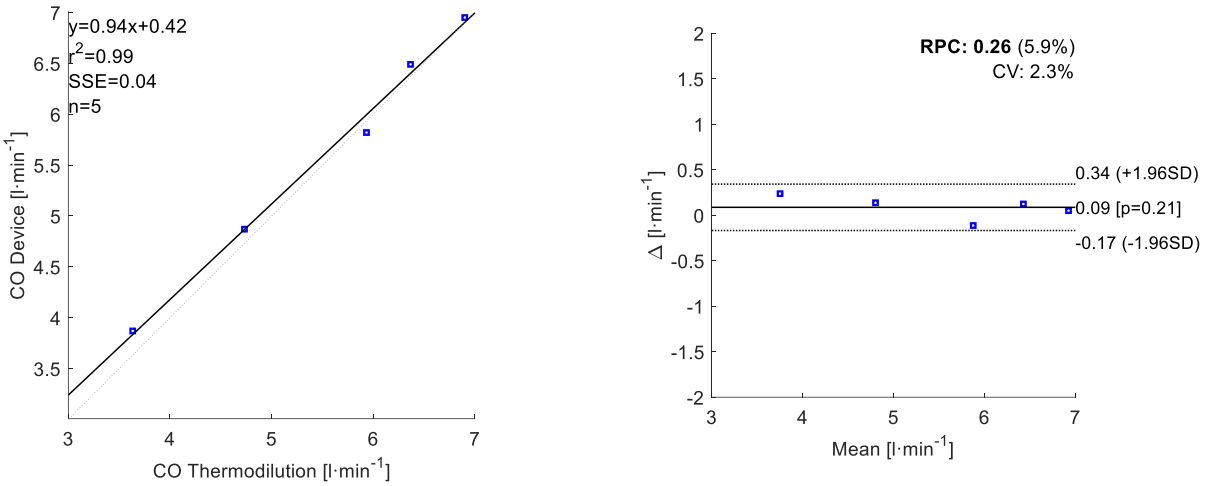

Figure 14: Comparison of *CO* values of the device prototype and the thermodilution method for patients with unequivocal detection (5). Linear regression graph, where the x-axis represents the *CO* values from the thermodilution method, and the y-axis the *CO* value from the device (left). Bland-Altman plot showing differences and means of individual measurements between methods (right).

As part of the correlation analysis, the Pearson correlation coefficient was $r = 0.9966$; $p < 0.001$. These model results corresponded to subjects (5) with a low amplification index and a clear decomposition, see Figure 14. For the others (7), the model value was approximately half of the calculated one, and the overall correlation analysis was as follows ($r = 0.8190$; $p < 0.01$), see Figure 15. These were patients with very low *BMI* and blood pressure, but the resulting model was unable to determine the exact criteria as to why this is the case and what causes it due to the smaller total number of subjects.

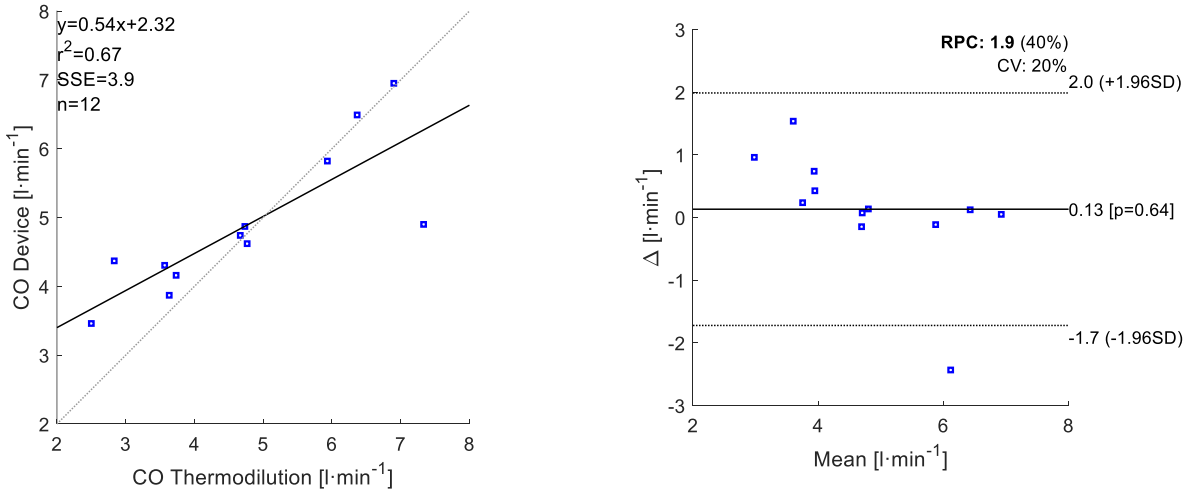

Figure 15: Comparison of *CO* values of the device prototype and the thermodilution method for all (12) patients. Linear regression graph, where the x-axis represents the *CO* values from the thermodilution method, and the y-axis the *CO* values from the device (left). Bland-Altman plot showing differences and means of individual measurements between methods (right).

6. Conclusion

In this habilitation thesis, the problem of non-invasive measurement of CVS hemodynamic parameters was solved using an innovative brachial cuff occlusion method. The vitality of this concept and its potential benefit for clinical practice were demonstrated. Based on the patented technology, methodologies for measuring *MAP*, blood pressure in patients with CF-LVAD, measuring arterial stiffness (*PWV*) and cardiac output (*CO*) resp. stroke volume (*SV*) were gradually designed and tested. All these areas bring promising results for application in clinical practice.

6.1. General contribution of the thesis

The main contribution of the research, hereby disclosed as the habilitation thesis, can be summarized into four points according to the general aims:

i. A new method of sensing weak pressure pulsations was developed, based on the use of a differential pressure sensor. This patented connection enables up to 100 times more sensitive recording of the pressure curve in comparison with the existing occlusive methods. In addition, it has been demonstrated that scanning can be performed using a standard arm cuff and tubing with which both medical personnel and the general public have experience, which could facilitate the deployment of such a device in clinical practice.

ii. The potential for the use of the developed device in measuring blood pressure in persons with weak pressure pulsations was shown. This is mainly a population of patients with an implanted CF-LVAD. In these patients, non-invasive blood pressure monitoring using existing methods is very difficult and may result in poorer blood pressure management. The use of the device in clinical practice and in home care would be very beneficial for this group from the point of view of blood pressure management and could contribute to the quality and extension of survival time.

iii. The results confirmed that the innovative design of the single brachial-cuff technique captures a high-fidelity signal that is comparable to the current gold standard method SphygmoCor VX for *PVW* assessment. Since the clinical need is to recognize the alterations of cardiovascular system prior developing organ complications, the presented technique can be used in the home monitoring and primary care setting. A proprietary hardware solution allows for building the presented design in a standard non-invasive brachial cuff blood pressure monitor. The simplicity of use, yet ability to provide consistent results strongly supports feasibility of the proposed solution in preventive care and can be translated into clinical practice.

iv. Preliminary data also confirm the feasibility of this novel, non-invasive principle for CO measurement. Unlike the most similar technique, the volume clamp method, the occlusion technique eliminates the need for technically challenging servo-regulated cuff pressure to record the BP curve. Furthermore, the pressure signal obtained from the brachial artery might be less likely affected by peripheral vasoconstriction. Thus, the occlusion principle has the potential to be developed into an easy-to-perform, accurate, and relatively mobile method for the non-invasive assessment of *CO* at rest and during exercise.

The above-mentioned points lead to the main contribution of the problem solved in the habilitation thesis, which is the timely diagnosis of the development of CVS diseases, especially heart failure. The diagnostic and monitoring possibilities described in this work demonstrate the very promising

potential of the developed technology for this main purpose. Whether it is blood pressure, pulse wave velocity, cardiac output, or other hemodynamic parameters, these are parameters that are very important for early diagnosis. The simplicity and familiarity of the established measurement methodology promises the possibility of rapid expansion in clinical practice.

6.2. Future work

There are several aspects and goals related to the investigation of CVS diagnostics with occlusive methods that are necessary to be solved in future research:

i. Development of a fully automated system for blood pressure measurement in patients with weak pressure pulsations, including smooth pressure deflation feedback control on both sides of the differential sensor. This will enable the continuous recording of oscillometric pulsations compared to step-deflation technique, which may result in more accurate determination of SBP and DBP values.
ii. Improvement of methodologies for obtaining clinical data for individual hemodynamic parameters and development and refinement of current algorithms. So far, data has been obtained on small sets of subjects. To improve the evaluation algorithms, it will be necessary to obtain a larger amount of clinical data on different sets of people.
iii. Extension of existing algorithms to measure central blood pressure resp. determination of appropriate transfer function between brachial and central pressure. This issue has already been partially resolved within the project TH04010173 and additional data collection is currently underway.
iv. Development of new diagnostic possibilities of the proposed technology. One of the promising ways is the measurement of hemodynamic parameters during breathing maneuvers (i.e. Valsalva) with oral pressure control, which could be beneficial in the early diagnosis of heart failure, especially diastolic dysfunction.
v. Another interesting problem, for which the use of the occlusive technique could be appropriate, is the measurement of endothelial dysfunction. Designing appropriate methodology and algorithms for the evaluation of pulsatile data.

For all these research activities, it would be necessary to expand the current research team and continuously involve new Ph.D. as well as undergraduate students in the solution of ongoing projects within this research field.

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List of selected author's publications related to the thesis

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APPENDICES

APPENDIX A1

FABIAN, V., KREMEN V., DOBIAS, M. (CTU in Prague). *Method for an accurate automated non-invasive measurement of blood pressure waveform and apparatus to carry out the same.* United States Patent and Trademark Office, US Patent US10251567. 2019-04-09.

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(54) METHOD FOR AN ACCURATE AUTOMATED NON-INVASIVE MEASUREMENT OF BLOOD PRESSURE WAVEFORM AND APPARATUS TO CARRY OUT THE SAME

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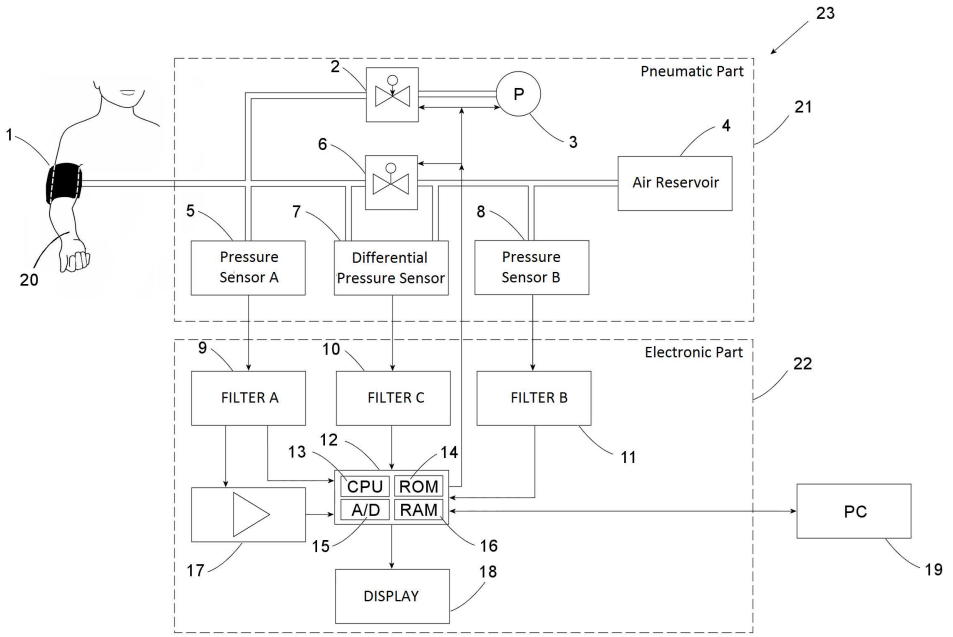
(52) **U.S. Cl.**

CPC ***A61B 5/02108*** (2013.01); ***A61B 5/02233*** (2013.01); ***A61B 5/0235*** (2013.01); ***A61B 5/6824*** (2013.01); ***A61B 5/7203*** (2013.01)

(57) **ABSTRACT**

An apparatus for an accurate automated non-invasive measurement of blood pressure waveform using brachial (occlusion) cuff pressurized above systolic pressure and using differential pressure sensor. The methodology involves measurement in suprasystolic mode and in utilization and construction of the device followed by algorithms for processing and analysis of measured blood pressure pulse waves and assessment of hemodynamic parameters of human cardiovascular system. The device includes an electro-pump connected to the collar device, a differential pressure sensor, pressure senor A, pressure sensor B, valve, closing a valve and the air reservoir. The cuff is wrapped around a person's arm. The values of the instantaneous pressure in the pneumatic portion of the device are converted into an electric signal by the pressure sensor A, pressure sensor B and the differential pressure sensor. These signals are then filtered using a set of passive RC elements for filtering out high frequency interference, and fed to the microprocessor with a computing unit, analog to digital converter. The sampling frequency is sensed signal at least 200 Hz. The control algorithm in the microprocessor, according to signals from the pressure sensor A further controls the course of cuff pressurization, controls the control valve, and finally determines the closing and opening of the closing valve. A microprocessor further controls a display and the data may be transmitted to the PC.



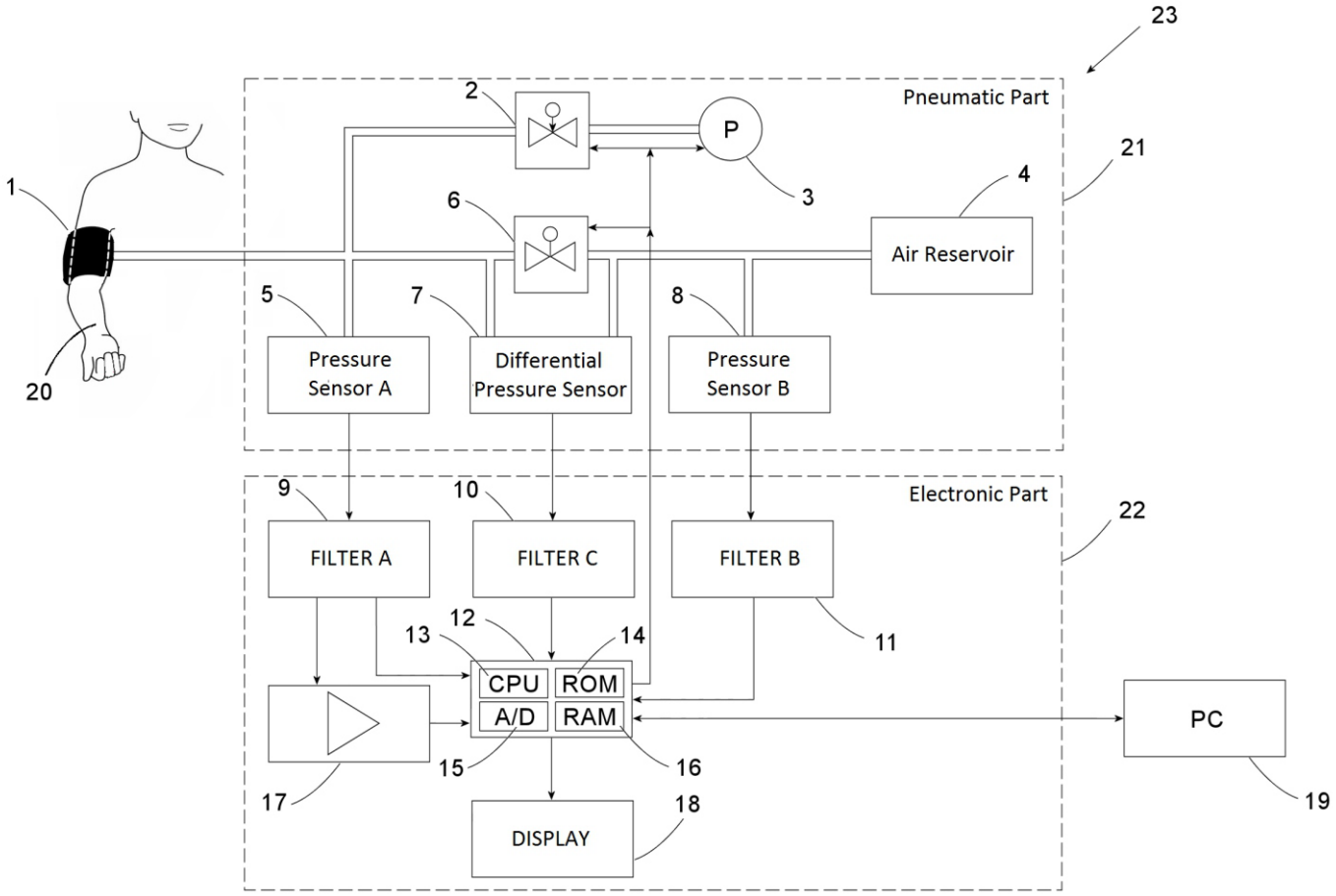

23
Pneumatic Part
2
P
3
21
4
6
Air Reservoir
1
5
7
8
Pressure Sensor A
Differential Pressure Sensor
Pressure Sensor B
20
Electronic Part
22
9
10
FILTER A
FILTER C
FILTER B
11
12
13
14
CPU
ROM
A/D
RAM
PC
15
16
17
18
19
DISPLAY

FIG. 1

METHOD FOR AN ACCURATE AUTOMATED NON-INVASIVE MEASUREMENT OF BLOOD PRESSURE WAVEFORM AND APPARATUS TO CARRY OUT THE SAME

BACKGROUND AND SUMMARY

[0001] The present application claims priority to Czech Republic Patent Application PV 2016-6, filed Jan. 7, 2016, which is incorporated by reference. The technical solution concerns a method for accurate automated non-invasive measurement of blood pressure waveform and the apparatus to carry out the method. By using the device and the method, and based on measured signals processed by developed algorithms it is possible to effectively determine important hemodynamic parameters of cardiovascular system. This device is intended for use in human and veterinary medicine, especially in the investigation of the state of cardiovascular system, i.e. hemodynamic parameters of bloodstream.

[0002] Devices for determination of hemodynamic parameters of cardiovascular system based on measurement of pressure waves are widely used in human medicine. They enable to determine many advanced hemodynamic parameters that enable complex assessment of cardiovascular system including pulse wave velocity (PWV), augmentation index (AIx) that servers as basic parameters for assessment of Arterial Stillness (AS) and risk of development and progression of arteriosclerosis and associated comorbidities.

[0003] Superior and most precise method for assessment of above-mentioned parameters still remains invasive measurement by catheter introduced to aortic root. This is still invasive operating procedure associated with certain known health risks and high price. The examination can't be performed under ambulatory conditions and have to be performed by certified interventional cardiologist in specially equipped operating room for angiology including catheter and other equipment to perform this type of surgery.

[0004] Non-invasive substitution of the invasive method is described in patent U.S. Pat. No. 6,117,087 and uses contact pressure sensor and sophisticated mathematical models derived from limited amount of data measured of patients with indications of several cardiovascular diseases. Learning models under such circumstances introduces high infidelity into the method.

[0005] Another solution is described in Czech patent number 295119, where measurement of blood pressure pulse wave is accomplished by contact pressure sensor connected to differential pressure sensor that increases sensitivity of measured pressure curve. This solution enables to measure very small blood pressure pulse waves from the surface of pressurized arteries at radial arteries with option of PWV analysis using special setup of device and utilization of two sensors, while there is no constriction of measured artery by the device. Placement of the device at radial artery is main limitation of the method to assess central aortic pulse wave as well as brachial pulse wave. This is because of known physiological phenomenon that describes change of pattern and amplitude of pulse wave in a particular place if measured from the aortic root distally along arm compare to pulse wave measured in the aortic root. This phenomenon applied to the method suggests that the method has substantial inaccuracy as well.

[0006] Main disadvantages of devices that use contact pressure sensor (e.g. Sphygmocor CVMS by AtCor) are changes of sensed pulse wave that are introduced by movements of examiner (physician) and by patient during measurement. These changes generate inaccuracies. Another main disadvantage of the method is that measurement can't be carried out automatically and it needs trained medical personnel.

[0007] SphygmoCor XCEL (AtCor), Arteriograph (TensioMed) BP+ (Uscom) that determine hemodynamic parameters of cardiovascular system from pattern of suprasystolic pressure pulse waves doesn't offer solution of above-mentioned disadvantages. Measurement is carried out automatically and by using arm cuff for measurement of suprasystolic pressure pulse waves. As described in patent WO 2005077265 A1, these pulsations are sensed using suprasystolic pressure (preferred is a systolic pressure +35 mmHg) by standard pressure sensor used in devices for blood pressure measurement by standard oscilometric principle. Typical dynamic range of these sensors is usually min 40 kPa, and relative overpressure ~300 mmHg. Because of small amplitudes of suprasystolic pressure pulse waves device in patent WO 2005077265 A1 uses compensation filter ("reverse filter") that a circuit that compensates for pattern of the signal during measurement. This is method is burdened by inaccuracy and under discussion in scientific press—e.g. discussed in Validation of the Arteriograph working principle: questions still remain. Bram Trachet et al. Journal of Hypertension, 29:619-622, 2011. This remains similar also for patents US 2014135632 A1 and US 2010256507A1. Another disadvantage of above-mentioned devices is a complexity of mathematical models for assessment of hemodynamic parameters. These models are derived from limited set of the data and highly multivariate. They also need certain high amount of input parameters they use together with measured pressure pulse wave to be able to calculate a result. Other several sensors often supply these input parameters. Used models were often tested using limited sizes of study populations and limited types of cardiovascular diseases, which can introduce certain instabilities and inaccuracies into models and thus into the whole measurement system.

[0008] In an aspect of the present invention, accurate automated non-invasive measurement of blood pressure waveform according to the invention is provided. Its essence consists in the following method of measurement and in the following apparatus embodiment. The device consists of an electromechanical pump connected to an arm cuff, a differential pressure sensor, a pressure sensor A, a pressure sensor B, a control (decompression) valve, a closing valve and an air reservoir, with a minimal volume of 50 ml. Arm cuff is wrapped around the arm of the examined person and just tightened. Actual values of the pressures in the pneumatic components of the apparatus are converted into an electrical signal by the pressure sensor A, the pressure sensor B and the differential pressure sensor. These signals are then filtered using a set of passive RC low pass filters to remove high frequency interference, and thereafter through analog to digital converter (at least 12-bit) they are digitized and ready for further computer processing. The signal from pressure Sensor A is after filtration amplified by an amplifier, approximately 50 to 100 times. The sampling frequency of the signal is at least 200 Hz. The control element, based on the current sensed values from the pressure sensor A and by casing the electromechanical pump, and the control and closing valves, controls and monitors the course of the cuff

inflation during measurement. The control element (e.g. a microprocessor) senses, processes and evaluates the measured data that can be displayed directly on the display, or may be transferred to a PC for further processing.

[0009] In the first phase of measurement, the apparatus device according to the invention begins to inflate the arm cuff bladder via electromechanical pump, at a rate controlled by the control element, e.g. a microprocessor. The cuff inflation speed is gradually slowed down so that the pneumatic system reaches a specified value of suprasystolic pressure. Through the closing valve, which is located between the inputs of the differential pressure sensor, and which is at this phase of measurement in open position, is inflated the air reservoir, which serves to minimize pressure variations in the pneumatic system. During the controlled inflation of the pneumatic system, the processor continually evaluates oscillometric pulsations obtained by digitalization of filtered and amplified signal from the pressure sensor A. Based on measured oscillometric pulsations during cuff inflation and cuff pressure signal from unamplified pressure sensor A, the value of suprasystolic pressure is determined by the control element (e.g. a microprocessor). The value of suprasystolic pressure is at least 30 mmHg higher than a systolic pressure of measured person. Pneumatic system is inflated to the suprasystolic pressure by an electromechanical pump before starting the measurement of blood pressure waveform.

[0010] A necessary condition for quality measurement of the pulse pressure wave by the apparatus according to the invention is to achieve suprasystolic pressure in the cuff placed on the arm over the brachial artery. After reaching the suprasystolic pressure and its stabilization, i.e. the pressure drop in the pressure sensors A and B is less than 1 mmHg/min, there is a signal from the processor to trigger the closing valve, i.e. the valve is closed. This separates the inputs of differential pressure sensor, i.e. separation of the static cuff pressure from pressure with superimposed pressure pulsations. At output of the differential sensor with a range of hundreds of Pa—preferred±250 Pa or±500 Pa, i.e. approx.±1.88 mmHg, respectively±3.75 mmHg, appears blood pulse wave signals—pressure pulsations, separated from the static pressure cuff. Next phase of measurement is suprasystolic pressure pulsations measurement. During this phase, the tightness in separate parts of a pneumatic system is monitored using the signals from the pressure sensors A and B. This procedure yields a signal that is up to 100 times more sensitive compare to existing methods of suprasystolic pressure pulsations measurement. This thus eliminates disadvantages of existing devices for the automatic measurement suprasystolic pressure pulsations, in particular the need of using a compensation filter or derived complex multivariate models.

[0011] After suprasystolic pressure pulsations measurement is finished, a control element (e.g. a microprocessor) opens the closing valve and by regulation (decompression) valve gradually releases the cuff pressure, and pressure throughout the whole pneumatic system. During the controlled deflation the oscillometric pulsations from pressure sensor A are measurement and therefore it is possible to measure blood pressure—systolic, diastolic, mean arterial, using standard oscillometric method.

[0012] System automatically determines actual heart rate of the person using analysis of measured data. Other hemodynamic parameters of cardiovascular system of examined person are automatically determined from the pattern of the signal, e.g. systolic and diastolic blood pressure of each heartbeat, pulse wave velocity (PWV), augmentation index (AIx), central aortic pressure, area under the curve and the maximum pressure amplitude, which reflects the instantaneous stroke volume, and others.

[0013] The measured pressure curve is accurate and corresponds to the brachial pulse wave otherwise invasively measured by a catheter placed in patient's arm. The apparatus according to the invention is accurate, portable, and inexpensive and is usable even in individuals with cardiovascular disease, or cardiovascular system status changes. To operate the device is simple and it is easy to learn. Patient themselves are able to perform the measurement after a short learning practice period. It allows carrying out measurements in outpatient settings, such as surgery cardiologists, internists and general practitioners, but also at home environment. The whole one trial of scanning procedure takes at maximum mo minutes and it does not burden or harm the patient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] The invention is illustrated using the attached drawing, wherein FIG. **1** is a block diagram of an exemplary apparatus according to the invention.

DETAILED DESCRIPTION

[0015] There is a block diagram of device **23** according to the invention in the FIG. **1**. The device for non-invasive measurement of suprasystolic pressure pulsations of the invention implemented by a microprocessor **12** with a 24-bit A/D converter **15** with a sampling frequency of 200 Hz. Inflating the pneumatic part **21** of the device **23**, including the occlusive cuff **1**, which is located in the patient arm **20** and the air reservoir **4** of 100 ml volume, is carried out by electromechanical pump **3**. Control (decompression) valve **2** is located between the inputs of the differential pressure sensor **7** and is controlled, as well as the process of inflating the pneumatic part **21**, by computing unit **13** of the microprocessor **12**, according to an algorithm stored in the program memory of the microprocessor (ROM) **14**. Signals measured from the pressure sensor A **5**, pressure sensor B **8** and the differential pressure sensor **7** are preprocessed using a filter A **9**, filter B **10** and filter C **11**—RC low pass filters to eliminate high frequency interference, and an amplifier of oscillometric pulsations **17** and are stored in the data memory (RAM) **16** of the microprocessor **12**. Digitalized data can be transmitted to the PC **19** for additional processing and simultaneously displayed on the display **18**. Electronic part **22** of the device **23**, the differential pressure sensor **7**, the pressure sensor A **5**, pressure sensor B **8**, the electromechanical pump **3**, the control (decompression) valve **2** and the closing valve **6** are powered by batteries.

[0016] In the device for an accurate automated non-invasive measurement of blood pressure waveform using brachial (occlusion) cuff pressurized above systolic pressure and using differential pressure sensor. Methodology involves measurement in suprasystolic mode and in utilization and construction of the device followed by algorithms for processing and analysis of measured blood pressure pulse waves and assessment of hemodynamic parameters of human cardiovascular system. The device comprises an electro-pump (**4**) connected to the collar device (**1**), the

differential pressure sensor (**7**), pressure sensor A (**6**), pressure sensor B (**8**), valve (**2**), closing a valve (**6**) and the air reservoir (**4**). Cuff (**1**) is wrapped around the arm persons under investigation (**20**). The values of the instantaneous pressure in the pneumatic portion (**21**) of the device (**23**) are converted into an electric signal by the pressure sensor A (**6**), pressure sensor B (**8**) and the differential pressure sensor (**7**). These signals are then filtered using a set of passive RC elements (**9**), (**10**), (**11**) for filtering out high frequency interference, and fed to the microprocessor (**12**) with a computing unit (**13**), analog to digital converter (**15**). The sampling frequency is sensed signal at least 200 Hz. The control algorithm in the microprocessor (**12**), according to signals from the pressure sensor A (**6**) further controls the course of cuff pressurization, controls the control valve (**2**), and finally determines the closing and opening of the closing valve (**6**). A microprocessor (**12**) further controls a display (**18**) and the data may be transmitted to the PC (**19**).

[0017] The device according to the invention finds an application in civilian use of individual care for non-invasive monitoring of hemodynamic parameters of the cardiovascular system and for a prognosis of cardiovascular diseases, in the area of medical care and postoperative monitoring of patients, but also in preventive medical care, and thereby preventing cardiovascular disease and its comorbidities.

What is claimed is:

1. A method for accurate automated non-invasive measurement of blood pressure pulse waves, comprising:

wrapping an arm cuff around an arm of a person to be examined person;

inflating the arm cuff and slowing a speed of cuff inflation so that a value of a suprastolic pressure at least 30 mmHg higher than the systolic pressure of the person is reached in a pneumatic part comprising the arm cuff,

sensing suprasystolic pressure pulsations,

converting sensed suprasystolic pressure pulsations into electrical signals,

filtering the electrical signals to eliminate high frequency interference and provide filtered electrical signals,

digitizing the filtered electrical signals for computer processing.

2. The method according to claim **1**, comprising, after inflating the arm cuff, performing a controlled deflation of the arm cuff, and detecting oscillometric pulsation during the controlled deflation for measurements of systolic, diastolic and mean pressure using a standard oscillometric method.

3. A device for performing the method according to claim **1**, comprising a pneumatic part comprising the arm cuff and an air reservoir, the arm cuff and the air reservoir being connected with an electromechanical pump, a differential pressure sensor, a first pressure sensor, a second pressure sensor, a control valve, and a closing valve, which are connected to an electronic part comprising a control element comprising computing unit, program memory, data memory, and analog-digital converter.

4. The device according to claim **3**, wherein a sampling frequency of signals in the control element is 180 Hz to 220 Hz.

5. The device according to claim **3**, wherein the closing valve is controlled by the control element to pneumatically separate, after reaching the supraystolic pressure, pressure in the air reservoir from pressure superposed suprasystolic blood pressure pulsations in the arm cuff.

6. The device according to claim **3**, wherein the first and second pressure sensors are arranged to monitor pressure drop in the pneumatic part during measurement of suprasystolic pressure pulsations.

* * * * *

APPENDIX A2

FABIAN, V., HAVLIK, J., DVORAK, J., KREMEN, V, SAJGALIK, P., BELLAMY, V., SCHIRGER, J., A., SOVKA, P., JOHNSON B., D. Differences in mean arterial pressure of young and elderly people measured by oscillometry during inflation and deflation of the arm cuff. *Biomedical Engineering/Biomedizinische Technik*, 2016, 61.6: 611-621. ISSN 0013-5585. DOI 10.1515/bmt-2015-0098.

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Differences in mean arterial pressure of young and elderly people measured by oscilometry during inflation and deflation of the arm cuff

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Abstract: Systemic arterial blood pressure (BP) is one of the most important parameters of the cardiovascular system. An oscillometric NIBP monitor was specifically designed to measure oscillometric pulsations and mean arterial pressure (MAP) during inflation and deflation of the cuff. Nineteen healthy young (age 23.1±1.7 years; mean±SD) and 35 elderly (83.9±7.9 years; mean±SD) subjects were studied. Differential analysis of MAP during inflation and deflation show mean |ΔMAP|=2.9±2.6 mm Hg in the young group (mean±SD) and |ΔMAP|=6.3±5.2 mm Hg for seniors (mean±SD). There was a significant difference ($p<0.05$) in means of |ΔMAP| measured during cuff inflation and cuff deflation between both groups. In about 50% of elderly subjects |ΔMAP| was higher than 5 mm Hg. Potential clinical relevance of the method needs to be further evaluated.

Keywords: blood pressure measurement; mean arterial pressure; oscillometric method.

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Vaclav Kremen: Czech Institute of Informatics, Robotics, and Cybernetics, Czech Technical University in Prague, Czech Republic
Pavol Sajgalik: Faculty Hospital, 1st Department of Internal Medicine, Cardio-Angiology/International Clinical Research Center, St. Anne's University, Brno, Czech Republic; and Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic, Rochester, NY, USA
John A. Schirger and Bruce D. Johnson: Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic, Rochester, NY, USA

Introduction

Systemic arterial blood pressure (BP) is one of the most important parameters of the cardiovascular system. Worldwide, BP measurement is part of a routine procedure which gives healthcare givers fundamental information about the actual status of the circulation from emergent to preventive indications. High blood pressure has become one of the most common reasons for medical office visits. Essential arterial hypertension (HT) with prevalence at about 44% in European countries, being highest in Germany, and about 30% in US, is at the same time the most treatable risk factor of cardiovascular diseases. With age, prevalence of hypertension is much higher and exceeds 65% in those older than 60 years [70, 71]. Furthermore, aging of populations in developed Western countries is well documented [18]. In an ambulatory setting, the value of BP modulates antihypertensive therapy usually for longer periods of time. Poor BP control carries specific risks for every age group. In the elderly, low BP can lead to falls of patients with often severe consequences impairing their quality of life. Importantly, optimized therapy reduces mortality even in patients older 80 years [67]. Optimal therapy of HT relies on accurate BP measurements. Even though the gold standard for non-invasive BP measurement is the ausculatory method by a trained observer, BP monitors are used on a daily basis even in such a challenging situations like in obese and elderly patients and are the only option for 24 h ambulatory monitoring, being important for better prediction of cardiovascular risk than measurements made at a doctor's office [55]. Thus, improvement of measurement accuracy of BP monitors remains clinically important.

BP monitors have undergone significant changes in the last 20 years. Mostly either an auscultatory or oscillometric method, or combination of both methods is used [9, 36] as the core of blood pressure measurement devices used in ambulatory or home conditions [29]. The oscillometric compared with the auscultatory technique has the advantage of being less expensive from a manufacturing point of

view and requires less complex algorithms. Oscillometry can be used in noisy surroundings and provides readings when an auscultatory gap is present; when the Korotkoff sounds persist until zero pressure, such as in patients with hyperkinetic circulation [52]; or when the sounds are faint, such as in obese subjects [61]. Standardized protocols for validating the clinical accuracy of noninvasive BP monitors have been available since 1987 [15, 16, 35, 40, 42, 43, 46–48, 60, 62]. As Ng reviewed in [39], some of them claimed to use manual auscultatory BP as a reference [16, 47, 48, 62], whereas others allow use of intra-arterial pressure, in addition to manual auscultatory BP, as a reference [11, 14, 15, 19, 38, 40, 42, 43, 46, 54, 57, 60]. Performance analysis of current ambulatory BP monitors (ABPM) showed a decrease of accuracy in single measurements when measured in the elderly or in diseases influencing cardiovascular system. BP variability increases with advancing age and higher pressure [34, 65], which makes ABPM devices less accurate in the elderly [6, 37, 44] and hypertensive subjects [6, 37, 45, 53]. Pagonas [51] and Verberk [66] showed that ABPM measures with a higher error rate in atrial fibrillation. In that case, a minimum of three consecutive oscillometry BP measurements must be performed to overcome this pitfall [51, 66]. The performance of ABPM in truly ambulatory conditions and during exercise remains a matter of controversy [39]. It is therefore crucial to ensure that a particular ABPM device is suitable for the specific study and subject. Oscillometric determination of BP during cuff inflation may be advantageous [1, 49]. Cuff inflation requires lower cuff pressure and shorter duration than deflation [1]. Alpert showed in [1] that inflation based algorithm can be incorporated into ABPM and pass the Association for the Advancement of Medical Instrumentation standard requirements and achieve an A/A grading according to British Hypertension Society protocol [1]. This study evaluates the differences between mean arterial pressure (MAP) detected during gradual cuff inflation and gradual cuff deflation while both inflation, and deflation are taken consecutively without delay on the human subject. The main aim of the study is to show differences between MAP measured in inflationary and deflationary oscillometry for groups of young and elderly healthy humans.

Materials and methods

Non-invasive blood pressure measurement device

An oscillometric non-invasive BP (NIBP) measurement system was specifically designed for the experiment. It was used to measure oscillometric pulsations during inflation and deflation of the cuff, respectively. The device was designed to obtain maximum linear course pressure in the cuff, and to minimize artifacts caused by active elements, in particular control valves and the air pump. The device uses a pressurized container, a 5-l tank, which stores compressed air. The air is then passed with a maximum linearity into cuffs. Initial pressure in the container was inflated to 350 mm Hg prior to each measurement. In extreme cases, where pressure decreased rapidly, the container was inflated during this particular measurement too. The input valve, which controls the flow of air to the cuff, was designed to be feedback-controlled so it achieves maximum possible linearity of the cuff inflation.

The NIBP device contains a standard pressure sensor that receives the pressure in the cuff. Oscillometric pulsations are obtained by filtering through the high-pass filter (see section Algorithm for Mean Arterial Pressure Detection).

A repeatability of MAP measurement was performed on 32 healthy individuals (16 men, 16 women, age 24±6 years; mean±SD) in standard clinical settings in resting (15 min resting, three repeated measurements in interval 30–60 s). The results of these measurements showed average ΔMAP=1.0±2.1 mm Hg (average MAP=87±12 mm Hg; mean±SD). Another test of ΔMAP variance to prove repeatibility of measurements was performed (by the same methodology as on the group of 32 healthy individuals) on two preselected cohorts of 10 healthy young subjects (seven men, three women, age 22.1±0.9 years; mean±SD) and 10 elderly subjects (four men, six women, age 83.8±6.8 years; mean±SD). The results of ΔMAP variance analysis showed variance of ΔMAP 1.0±0.6 mm Hg (mean±SD) in the young group, and 1.2±0.6 mm Hg (mean±SD) in the elderly group. There was no statistically significant difference between means of both ΔMAP variance analysis groups ($p<0.05$).

Described NIBP measurement device was connected to a measurement system. The system is equipped with electronics controlling measurements of oscillometric pulsations in both inflation, and deflation of the cuff, respectively.

Study population

Measurements were performed at the Faculty of Electrical Engineering, Czech Technical University in Prague, and at retirement home in Prague – Malešice, both in the Czech Republic. The first group consisted of healthy individuals, students ranging in age from 20 to 26 years (average age 23.1±1.7 years; mean±SD). The second group consisted of senior citizens in age ranging from 53 to 94 years (average age 83.9±7.9 years; mean±SD). The average body mass index (BMI) of the people in the young group was 22.0±1.8 $kg \cdot m^{-2}$ (mean±SD). In the group of elderly people the overall average BMI was 27.8±6.4 $kg \cdot m^{-2}$ (mean±SD).

All subjects reporting signs of cardiac arrhythmias during measurements were excluded from the analysis (one young man and five elderly people). All signals affected by motion artifacts were also excluded from an analysis (one young man and three elderly people). Subjects who had previously reported cardiac or cerebral events and subjects with an arm circumference that was outside the range of 23–32 cm were excluded (five elderly people). In total of 19 students and 35 seniors were analyzed.

Measurement protocol

All measurements were carried out with the patient in a seated position. The cuff (standard OMRON CM2 cuff, OMRON Healthcare

Europe B.V., The Netherlands) was placed on the left arm. First, a systolic blood pressure (SBP) was measured by the auscultatory method about 30–60 s prior experiment. Based on measured SBP the cuff was inflated 30 mm Hg above the SBP of measured subject according to BHS evaluation protocol for oscillometric blood pressure measurement devices [47]. The pressure in the cuff was recorded, and measured values were continuously stored in the memory of the device (sampling frequency FS=400 Hz). A one measuring sequence consisted of cuff inflation at a rate of 3 mm Hg/s up to 30 mm Hg above SBP, pause for 5 s, the cuff deflation at rate of 3 mm Hg/s, and then recorded data were processed on a PC. All measurements were performed by an identical qualified technician.

Algorithm for mean arterial pressure detection

The described oscillometric BP method was applied to obtain MAP values. There is a transmission of mechanical oscillations of the vessel wall to the cuff when the tourniquet is applied to the artery underneath the cuff, both during inflation or deflation, respectively. This causes rapid changes of the pressure in the cuff. These pressure changes are superimposed on slow changes of a pressure produced by inflation or deflation of the cuff.

The raw oscillometric signal is filtered by a third order high pass Bessel filter with cut-off frequency set to 0.4 Hz for removing the slowly varying component. There is also applied first-order anti-aliasing filter with cut-off frequency of 140 Hz. Superimposed rapid pressure oscillations (at range about mm Hg) are therefore extracted and then analyzed.

There is a gradual increase in the amplitude of the oscillations and then a fall back. It has been shown that the maximum amplitude of oscillations occurs when the cuff pressure corresponds to the MAP [56, 73]. Rapid pressure changes measured when the cuff is inflated and deflated are typical, and have been described many times in the past, for example, by Drzewiecki and Bronzino [12] and by Sorvoja [59].

Our approach to MAP detection uses the peak detector to find positive and negative peaks in the oscillation signal. The detected peaks in the time-based signal are converted to the table, where one parameter is the relative amplitude of the peak and the second parameter is the corresponding pressure in the cuff. Then 16-order polynomial equations separately for positive and negative peaks are found. On these calculated upper and bottom envelopes, we can find the maximum difference, which corresponds with the MAP. Finally, the labeled signal is checked manually for excluding faults. A similar method has been thoroughly tested in [73].

Data evaluation

MAP during inflation and deflation of the cuff was measured. Differences between MAP in deflation and inflation were evaluated. This difference is indicated as

$$\Delta MAP = MAP_{inflation} - MAP_{deflation}. \quad (1)$$

The ΔMAP comparative study was carried out in accordance with Bland-Altman [2]. The ΔMAP data in the two groups (young and elderly) were statistically compared. First, the normality of the distribution of the data (separately for young people and for the elderly) was proved using both the Lilliefors test [32] and the Jarque-Bera test [30]. Consecutively, the two-sample F-test was used for an investigation of the variance of the samples in both groups to prove that variances are different. Finally the two-sample t-test for data with unequal variance was used for a comparison of the ΔMAP mean values.

Results

An example of MAP evaluation by the oscillometric principle taken from measured data is shown in Figure 1. It shows that there is an increase in the amplitude of the (oscillometric) pressure pulsations during inflation/deflation of the cuff, respectively. A maximum value is reached, and then the amplitude of the pulsations gradually

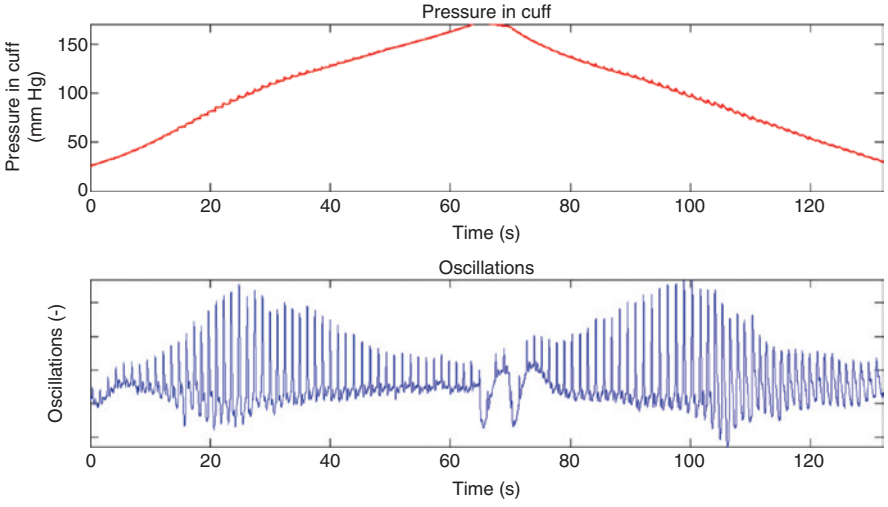

Figure 1: Temporal characteristics of cuff pressure vs. measured oscillometric BP pulsations during cuff inflation and deflation, respectively.

decreases. The point of maximum amplitude of the pulsations is considered to be the MAP [56].

The ΔMAP values for both groups are shown in Figure 2. The average value of ΔMAP=1.7±3.6 mm Hg (mean±SD) for the young group, and ΔMAP=4.6±6.8 mm Hg (mean±SD) for the elderly, respectively. The MAP value is often higher during inflation than deflation (Figure 2 – a positive ΔMAP values). It is 74% in young people and 80% in the elderly. In absolute values, ΔMAP resulted in |ΔMAP|=2.9±2.6 mm Hg (mean±SD) for the young group and |ΔMAP|=6.3±5.2 mm Hg (mean±SD) for the elderly, respectively. |ΔMAP|>5 mm Hg in 48% in the group of seniors, and only 11% in the young. The relative frequencies of the |ΔMAP| occurrence and the given box plots for both groups are shown in Figure 3.

Raw data of ΔMAP for the groups of young and senior people including baseline characteristics are shown in Tables 1 and 2, respectively.

A correlation plot and the Bland-Altman plot for MAP obtained in the groups of young and elderly are shown in Figures 4 and 5, respectively. The upper pictures show a relation between MAP measured during cuff inflation and deflation, respectively. The bottom pictures show the Bland-Altman plot, a dependency of ΔMAP on the mean value obtained from both methods inflation and deflation – mean ($MAP_{inflation}$, $MAP_{deflation}$).

ΔMAP is independent from the mean ($MAP_{inflation}$, $MAP_{deflation}$) value in young people (see Figure 4) and both methods measure similarly (obtained points in the upper figure lie around the axis of the quadrant – dotted line – and close to zero in the bottom figure). However, in the elderly, ΔMAP is dependent on the mean ($MAP_{inflation}$, $MAP_{deflation}$) value (see Figure 5, for lower mean ($MAP_{inflation}$, $MAP_{deflation}$) values the ΔMAP is higher than for higher values) and overall differences of MAP measurements for both methods are significant ($p<0.001$).

Both groups (young and elderly) have normal distribution ($p<0.05$) with different variance ($p<0.05$) and different means ($p<0.05$). The mean value of ΔMAP in the group of young people is significantly different ($p<0.05$) than in the group of elderly people.

Discussion

The oscillometric principle does not define clearly a determination of SBP and DBP. SBP and DBP are frequently determined using the ratiometric (height-based) method [69]. This means that SBP and DBP is determined when the amplitude of oscillation reaches 55% or drops down to 85% of the maximum amplitude of oscillations, respectively. These thresholds were determined empirically on the basis of earlier measurements [39]. In this case, thresholds are not fixed, and may vary from device to device. This has been discussed many times in the past, for example in [22].

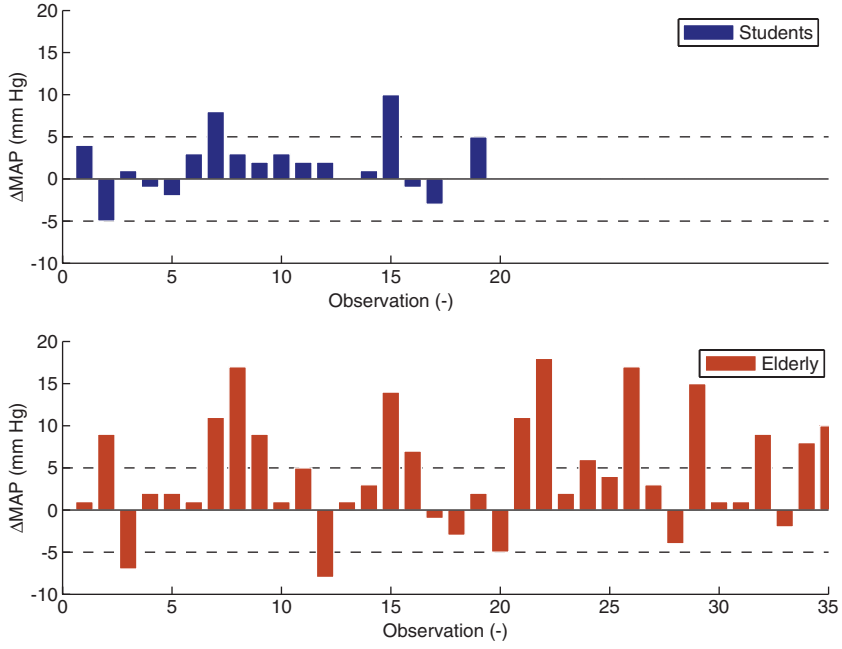

Figure 2: ΔMAP values observed in group of young people (upper) and in the elderly (bottom). ΔMAP is calculated as difference of MAP measured during inflation and deflation, respectively.

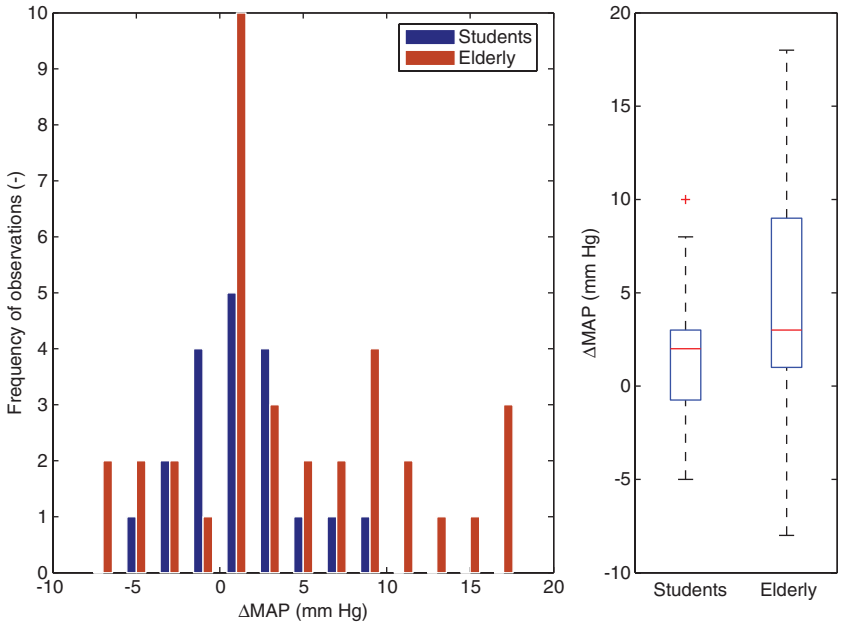

Figure 3: Frequencies of the occurrence of ΔMAP values for group of young people and in the elderly (left), and corresponding box plots for both groups (right).

Table 1: The raw data for group of young people (age, height and sex are obtained from anamnestic questionaire).

Subject	Age (year)	Height (cm)	Weight (kg)	BMI (kg·m^{-2})	Sex	MAP_{inf} (mm Hg)	MAP_{def} (mm Hg)	ΔMAP (mm Hg)
1	23	178	71	22.4	F	99	95	4
2	23	182	78	23.5	M	100	105	-5
3	20	186	70	20.2	M	98	97	1
4	24	170	55	19.0	F	97	98	-1
5	23	167	57	20.4	F	88	90	-2
6	24	169	67	23.5	F	100	97	3
7	23	182	77	23.2	M	92	84	8
8	22	177	58	18.5	M	92	89	3
9	20	182	69	20.8	M	112	110	2
10	23	180	77	23.8	M	105	102	3
11	25	173	65	21.7	M	100	98	2
12	25	160	56	21.9	F	90	88	2
13	21	162	62	23.6	F	93	93	0
14	22	163	62.5	23.5	F	90	89	1
15	25	170	70	24.2	M	108	98	10
16	26	185	76	22.2	M	82	83	-1
17	23	182	75	22.6	M	93	96	-3
18	25	175	73	23.8	F	95	95	0
19	22	170	57	19.7	F	95	90	5

Sometimes, and frequently in clinical practice, the MAP value is determined as one third of a SBP and DBP difference plus DBP.

$$MAP = \frac{SBP\text{-}DBP}{3} + DBP \quad (2)$$

However, this equation is only an approximate relation and is valid only for the universal patient and in quiescent conditions when the duration of diastole is about two times longer than the duration of systole. It means that the SBP and DBP values are not useful for determination of MAP and limit the ability to compare SBP and

Table 2: The raw data for group of seniors (age, height and sex are obtained from anamnestic questionaire).

Subject	Age (year)	Height (cm)	Weight (kg)	BMI (kg·m^{-2})	Sex	MAP_{inf} (mm Hg)	MAP_{def} (mm Hg)	ΔMAP (mm Hg)
1	86	156	60	24.7	F	114	113	1
2	75	165	90	33.1	F	119	110	9
3	90	158	59	23.6	F	111	118	-7
4	87	162	62	23.6	F	100	98	2
5	88	163	64	24.1	F	117	115	2
6	91	165	65	23.9	F	93	92	1
7	94	156	62	25.5	F	102	91	11
8	81	160	60	23.4	F	98	81	17
9	87	152	64	27.7	F	99	90	9
10	86	168	85	30.1	F	90	89	1
11	74	168	64	22.7	F	85	80	5
12	83	162	78	29.7	F	102	110	-8
13	85	165	85	31.2	F	99	98	1
14	85	159	51	20.2	F	94	91	3
15	80	174	115	38.0	F	118	104	14
16	83	140	102	52.0	F	120	113	7
17	85	168	63	22.3	F	108	109	-1
18	90	150	75	33.3	F	111	114	-3
19	84	168	87	30.8	F	113	111	2
20	89	168	62	22.0	F	112	117	-5
21	82	156	90	37.0	F	105	94	11
22	86	160	66	25.8	F	108	90	18
23	84	158	80	32.0	F	93	91	2
24	63	163	63	23.7	F	78	72	6
25	89	162	61	23.2	M	113	109	4
26	79	152	62	26.8	F	103	86	17
27	85	162	58	22.1	F	105	102	3
28	84	156	80	32.9	F	95	99	-4
29	91	158	48	19.2	F	107	92	15
30	87	162	78	29.7	F	127	126	1
31	90	162	58	22.1	F	114	113	1
32	53	170	90	31.1	M	120	111	9
33	88	155	60	25.0	F	115	117	-2
34	90	168	88	31.2	F	100	92	8
35	82	172	86	29.1	M	103	93	10

DBP obtained by the auscultatory method and the MAP value obtained by the oscillometry method. These values cannot be directly compared definitely.

The correct relationship between MAP, SBP and DBP is based on a definition of the mean value

$$\mathrm{MAP}=\frac{1}{T}\int_{t_0}^{t_0+T}p(t)\,dt, \tag{3}$$

where $p(t)$ is an immediate pressure value, t_0 is an arbitrary moment and T is a heart period. Unfortunately, this relationship requires knowledge of the instantaneous pressure values which cannot be obtained non-invasively.

These reasons for inconsistent determination of SBP and DBP from device to device and the inability to compare non-invasively measured SBP, DBP and MAP have led us to the decision to focus on MAP values only and omit SBP and DBP analysis during this study.

The definition of the auscultatory method according to EN 1060-3:1997+A2:2009 Non-invasive sphygmomanometers – Part 3: Supplementary requirements for electro-mechanical blood pressure measuring systems [41] indicates that Korotkoff sounds evaluation is carried out only in the slow release of cuff pressure. Evaluation of Korotkoff sounds while gradually inflating was not performed in our study because it is contrary to the definition of the method. Korotkoff sounds evaluation has also other important limitations and could not be used for our study. The method is unable to measure MAP, it only measures SBP and DBP. For these reasons, we were not focused on comparing the values of blood pressure between auscultatory and oscillometric method and its gradual differences in

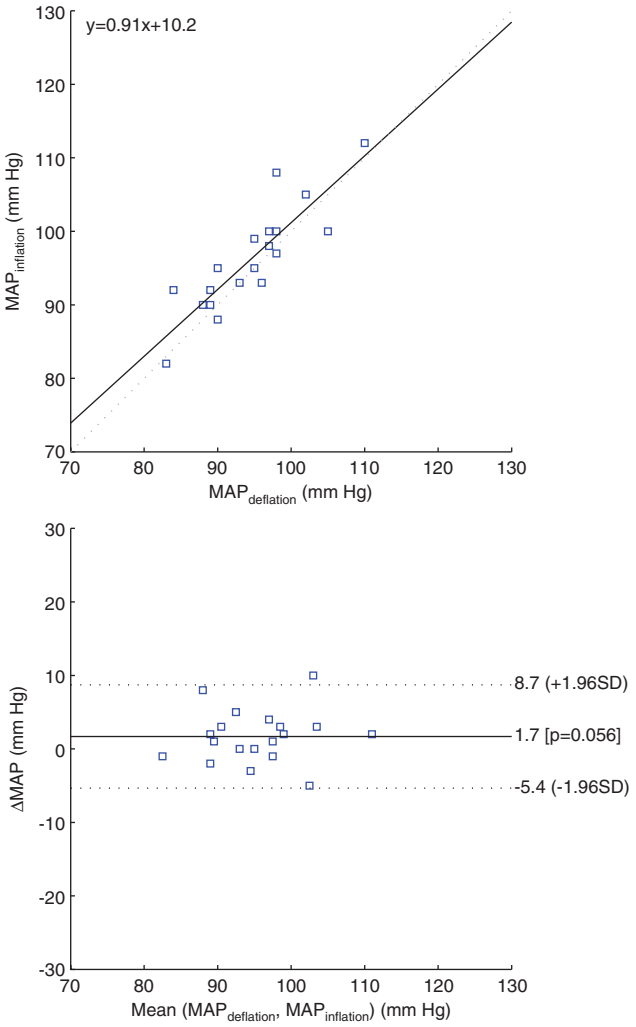

Figure 4: Young people group.
Upper picture shows correlation between MAP measured during inflation and deflation of the cuff. Bottom picture shows the Bland-Altman plot of ΔMAP dependency on mean MAP during deflation and inflation, respectively.

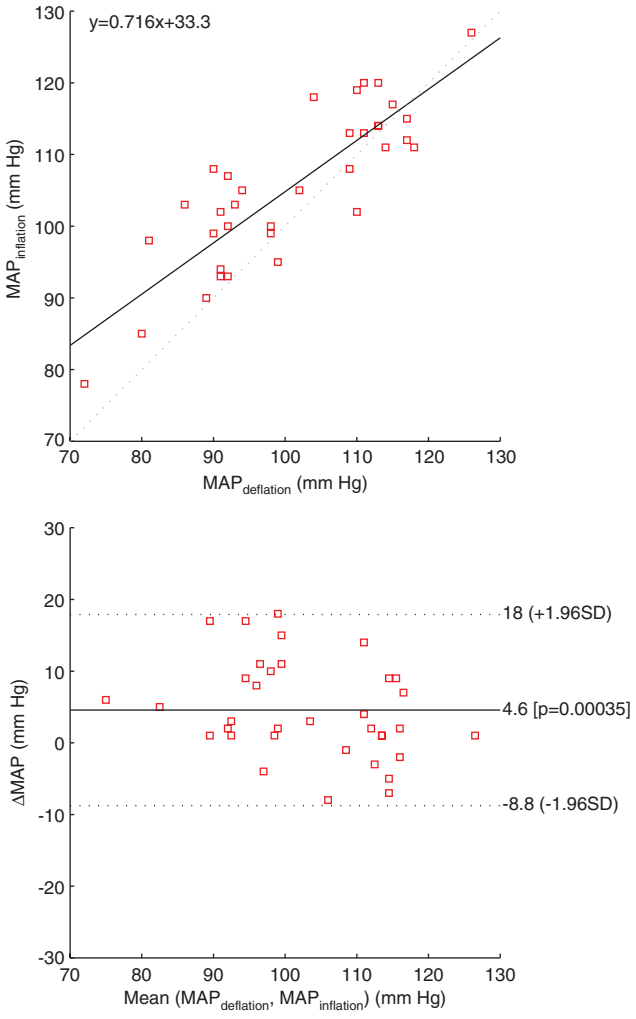

Figure 5: Elderly group of people.
Upper picture shows correlation between MAP measured during inflation and deflation of the cuff. Bottom picture shows the Bland-Altman plot of ΔMAP dependency on mean MAP during deflation and inflation, respectively.

inflation and deflation of the cuff in this study. On the contrary, the auscultatory method, the oscillometric method during the inflation phase is well defined and enables MAP to be measured, as indicated in paragraph 3.4 of the cited standard. Therefore, the presented study was focused only on differences of MAP (assessed by oscillometric method) during the gradual inflation and deflation of cuff pressure.

Figure 1 shows our case of an increase in the amplitude of measured oscillometric pressure pulsations during inflation and deflation of the cuff. A maximum value is reached, and then the amplitude of the pulsations gradually decreases. The point of maximum amplitude of pulsations was generally considered to be the MAP for deflationary oscillometry [56]. This might not be true for certain situations [3]. Many ABPM manufacturers assume that MAP occurs during maximum oscillometric pulse of amplitude envelopes, and use this assumption to determine systolic and diastolic BP using empirical algorithms. The algorithms used are based, for example, on a height-based criterion or on finding the maximum slope of the envelope of measured pressure pulsations, etc. [13, 22, 33, 39]. In contrast to the auscultatory method, no clear criterion exists in the oscillometric method that defines the systolic and diastolic BP [69] and exact detection of the point of maximum pressure pulsation is therefore one of the most important parameters in ABPM using the oscillometric method. The device uses the above mentioned height-based method ratios.

The oscillometric method is based on the analysis of pressure pulsations that arise in an artery while the

pressure is being increased or decreased in the inner air hose of the cuff wrapped around a limb. The most commonly available ABPM devices are based on the oscillometric principle measure of oscillometric pulsations during deflation of the cuff only. There are also several devices based on inflationary oscillometry – the oscillometric principle for BP measurement during cuff inflation, for example, the OMRON-MIT Elite BP monitor (OMRON Healthcare Europe B.V., The Netherlands). Precision of the OMRON device has been evaluated for measurements in pregnancy and pre-eclampsia [8, 10, 23] and also for general use in the adult population [24]. Another NIBP device using inflationary oscillometry is the Criticare 8100E nGenuity vital signs monitor (Criticare Systems, Inc., USA). This device was evaluated in a comparative study with the Datex Ohmeda GE S/5 (GE Healthcare, UK) vital signs monitor (standard deflationary oscillometry measurement of NIBP) [27]. All mentioned studies showed reliability of inflationary oscillometry compared to the so far standardly used deflationary oscillometry. The device presented in our study has an ability to measure MAP by inflationary and deflationary oscillometry by inflation and deflation of the cuff during one measurement period consecutively. To the best of our best knowledge, none of ABPM devices available on the market have an option to measure and compare MAP measured by the oscillometric principle during inflation and deflation, respectively.

A technical limitation of the study is that the inflation speed (3 mm Hg/s) is at the lower limit of standard inflation/deflation speed used in ABPM devices. This can cause more venous filling in the arm resulting in measurement bias. However, the measurement protocol was identical for both groups (young and elderly) and it can be argued that this effect does not affect statistical analysis and the conclusions of the study.

These very interesting results may attract the attention of the clinicians to the problem of technical limitations of particular devices used especially in aged subjects and how such obtained data could be influenced by different algorithms of BP monitors. This study shows that in about 50% of elderly subjects the $|\Delta MAP|$ is higher than 5 mm Hg and the difference can reach 11 mm Hg in MAP, thus becoming clinically relevant, this might affect further therapy. The innovative principle of BP measurement introduced in this article may increase the discussion if one could acquire more information about the cardiovascular system in a given setting than the accurate BP values. ΔMAP during inflation/deflation is significantly lower in the group of young subjects than in group of seniors and one could speculate if this is due to atherosclerosis, arterial stiffness, endothelial dysfunction or other reasons. This factor may cause greater differences in MAP.

As the prevalence of arterial stiffening increases with age [63], higher arterial stiffness of brachial artery in the elderly group can cause the higher MAP during inflation than during deflation presented at the maximal oscillometric pulsation amplitude (indicating MAP by oscilometric method) when compared to young subjects with no significant difference between ΔMAP during inflation and deflation. The arterial stiffness has been proposed as being the primary cause of pseudo-hypertension (discrepancy between invasive and non-invasive BP reading) [50]. Non-invasive detection of pseudo-hypertension requires further research. Speculation has increased about transmural pressure and the cross-sectional area of the brachial artery as it closes under the influence of the pressure cuff [50]. Assessment of arterial stiffness using pulse wave velocities (PWV) in those subjects, with high $|\Delta MAP|$ could better clarify the interpretation of measured data in future studies [5, 64]. Our results might potentially contribute to the development of a novel simple screening tool for the arterial stiffness in the future.

Subject selection was chosen on the basis of a clear differentiation between the two age groups. This outcome seems in good accordance with previous physiological studies, e.g. [20, 68] and [74], which shows differences in arterial characteristics during inflationary and deflationary tests. The authors speculate that for oscillometric measurements based on the ratiometric (height-based) method, the change in MAP during blood pressure measurements may result in a change in the assessed values of SBP and DBP. Based on the results presented here, this situation occurs more often in the elderly. This may have negative consequences for the treatment of hypertension. From this perspective, it is very important to choose a measurement method that is suitable for the individual person. Essential hypertension is a well-proven risk factor of multiple cardiovascular diseases like myocardial infarction, heart failure, renal failure, cerebrovascular complications and is one of the leading causes of mortality in the Western world [31]. The impact of not optimally controlled BP has significant health and economic impacts on society, most importantly; lowering high blood pressure significantly reduces cardiovascular morbidity and mortality [17]. Therefore, the effort in developing highly accurate BP monitors available even for specific subpopulations is needed.

The auscultatory method is generally considered to be the gold standard for NIBP measurements, but it is very difficult to use this method for automatic measurements. For many reasons, mainly because of its simple implementation from both the technological and the signal processing point

of view, oscillometry is the most widely used automatic method for NIBP measurements. It follows from the description of the oscillometric method that the results are highly dependent on a precise determination of MAP. However, it cannot be clearly stated whether the determination of MAP is more precise in inflationary oscillometry or in deflationary oscillometry. The results of our study show a significant difference ($p<0.001$) between MAP measured during cuff inflation and during cuff deflation, mainly in the elderly.

Reported data suggest that significantly different ΔMAP between groups of young and elderly people might rather represent different biologic response of the brachial artery and the blood pressure between groups than bias of the measurement system, as one would expect ΔMAP to be similar in both groups in the case of system bias. Biologic interpretation of results exceeds the intention and design of this study and opens questions about potentially novel applications of oscillometric BP measurement technique during inflation and deflation. Regulation of systemic arterial blood pressure in general and the level of contraction with actual tonus of smooth muscles in tunica media of arterial wall is balanced by multiple endocrine, paracrine and autonomic neuronal pathways and can be modulated by antihypertensive drugs. Although, we cannot completely foreclose a bias of the system because it was not tested against any gold standard method (e.g. intra-arterial catheter), one could speculate that by the given character of a very short pressure stimulus, more likely not causing any regional hypoxia and considering the remarkable age difference between the groups, it is likely that the mechanical properties of the aging arteries [7, 28, 58] contributes to the higher ΔMAP difference in elderly group. This could be due to the possibly changing ratio of collagen and elastin in the arterial wall [4, 28]. Mechanical stress could also potentially activate the age-dependent function of endothelial cells [58] and in turn change the smooth muscle tone [26] by releasing prostaglandins [21, 25], endothelin [72] and other vasoactive agents and theoretically cause a positive MAP differences in both groups. Thus, it remains unknown which of the mechanisms plays the dominant role after applying defined pressure on the arterial wall by the cuff and further studies need to be designed to evaluate the method against a gold standard (intra-arterial catheter) and to investigate other biological effects of arteries and endothelial cells to answer questions raised by the presented data.

Conclusion

A proposed ABPM device was able to measure and determine MAP during inflation and deflation of the cuff. The results of our study show a significant difference between MAP measured during cuff inflation and during cuff deflation, mainly in the elderly group of people ($\Delta MAP=1.7\pm3.6$ mm Hg, $|\Delta MAP|=2.9\pm2.6$ mm Hg (mean±SD) for the young group and $\Delta MAP=4.6\pm6.8$ mm Hg, $|\Delta MAP|=6.3\pm5.2$ mm Hg (mean±SD) for the elderly). $|\Delta MAP|$ during inflation/deflation is significantly lower in the group of young subjects than in the group of seniors. The study shows that in about 50% of elderly subjects is the $|\Delta MAP|$ higher than 5 mm Hg and the difference can reach 11 mm Hg in MAP.

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APPENDIX A3

SAJGALIK, P., KREMEN, V., FABIAN, V., MALTAIS, S., STULAK, J., M., KUSHWAHA, S., S., JOYCE, L., D., SCHIRGER, J. A., JOHNSON, B., D. Non-invasive Blood Pressure Monitor Designed for Heart Failure Patients Supported with Continuous-flow Left Ventricular Assist Devices. *ASAIO journal (American Society for Artificial Internal Organs: 1992)*, 2019, 65.2: 127. ISSN 1058-2916. DOI 10.1097/MAT.0000000000000775.

Noninvasive Blood Pressure Monitor Designed for Patients With Heart Failure Supported with Continuous-Flow Left Ventricular Assist Devices

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The gold standard for noninvasive blood pressure (BP) measurement, the Doppler technique, does not provide systolic blood pressure (SBP) and diastolic blood pressure (DBP) and may limit therapy outcomes. To improve patient care, we tested specifically designed experimental BP (ExpBP) monitor and the Doppler technique by comparing noninvasive measures to the intraarterial (I-A) BP in 31 patients with end-stage heart failure (4 females) 2.6 ± 3.4 days post-LVAD implantation (20 HeartMate II and 11 HeartWare). Bland–Altman plots revealed that the ExpBP monitor overestimated mean arterial pressure (MAP) by 1.2 (4.8) mm Hg (mean difference [standard deviation]), whereas the Doppler by 6.7 (5.8) mm Hg. The ExpBP SBP was overestimated by 0.8 (6.1) mm Hg and DBP by 1.9 (5.3) mm Hg compared with the respective I-A pressures. Both techniques achieved similar measurement reliability. In the measurement "success rate" expressed as a frequency (percent) of readable BP values per measurement attempts, Doppler accomplished 100% *vs.* 97%, 97%, and 94% of successful detections of MAP, SBP, and DBP provided by the ExpBP monitor. The ExpBP monitor demonstrated higher accuracy in the MAP assessment than the Doppler in addition to providing SBP and DBP in majority of subjects. Improved BP control may help to mitigate related neurologic adverse event rates. *ASAIO Journal* 2019; 65:127–133.

Key Words: systolic, diastolic, noninvasive, monitor, LVAD

Continuous-flow (CF) left ventricle assist device (LVAD) therapy, an established treatment modality for advanced heart failure (HF), is experiencing exponential growth because of increased durability and progressive engineering of the pumps.[1–3] In non-LVAD populations, the arterial blood pressure (BP) is easily obtained by auscultation or the oscillometric method, but in patients supported by CF LVAD, accurate BP assessment remains challenging because of a reduced pulse pressure (PP).[4] Despite advancements in LVAD technology, a specific, clinically validated LVAD BP monitor is not currently available. Traditional automated oscillometric BP monitors are capable of successfully measuring BP in approximately 55–60% of cases regardless of the measurement accuracy, whereas manual auscultation allows BP assessment in less than 20% of LVAD measurements.[4] Currently, clinical management of patients supported by LVAD relies on a Doppler BP method, which significantly overestimates mean arterial pressure (MAP).[5] Intracranial bleeding, one of the major adverse events of LVAD therapy, is associated with poor BP control.[3,6] Limited availability of Doppler-derived BP could also compromise adequate therapeutic response and negatively influence clinical outcomes.[7,8] Conversely, in patients with hypertension, the overestimation of MAP may contribute to antihypertensive drug overdosing with subsequent, impaired renal perfusion and a higher risk of falls caused by underlying orthostatic hypotension.

In response to this clinical need, an experimental, noninvasive, brachial cuff blood pressure (ExpBP) monitor has been developed with algorithms customized for the altered hemodynamics of patients supported by LVAD. Accordingly, we studied the validity, repeatability, and measurement "success rate" of the ExpBP monitor compared with the intraarterial (I-A) BP. Second, we compared the noninvasive LVAD ambulatory "gold standard" Doppler technique to the I-A BP in the same population.

Materials and Methods

Patients

A total of 31 patients with end-stage HF (4 females; age, 63 ± 10 years; body mass index, 28.6 ± 6.0 kg/m^2) indicated for durable mechanical cardiac support with an LVAD implanted at Mayo Clinic, Rochester, Minnesota, were included in the study.

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Off-label use/unapproved drugs or products: This article includes data from investigational use of the device (experimental blood pressure monitor). Use of the non–Food and Drug Administration–approved device was approved by the Mayo Clinic Ethic Committee (Institutional Review Board) for purpose of this study.

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The patients' demographic information including medical history, cardiac risk factors, and related blood markers is illustrated in **Table 1** with the pump characteristics displayed in **Table 2**.

Study Design

The present single-center prospective, nonrandomized study was approved by the Mayo Clinic Institutional Review Board. To achieve the goal of the study, BP was measured in patients supported by a CF LVAD Heart Mate II (HM II; Thoratec Corporation, Pleasanton, CA) or HeartWare (HW Corp., Framingham, MA) device at the intensive care unit, 2.6 ± 3.4 days after device implantation. Blood pressure was assessed in patients in a stable, supine position. The invasive BP was recorded continuously via the critical care monitor, Philips IntelliVue MP 50 (Phillips, Eindhoven, the Netherlands) connected to a 20 Fr I-A catheter placed in the radial artery through disposable pressure transducer TruWave PXMK2064 (Edwards Lifesciences, Irvine, CA). Before each recording, the system was flushed, zeroed, and the transducer was leveled at the phlebostatic axis.[9,10] For the noninvasive BP assessments, appropriately sized cuffs were chosen with the cuff placed either on the ipsilateral or contralateral arm based on clinical restrictions; however, BP was assessed noninvasively by the ExpBP monitor and the Doppler technique from the same extremity.[11] Doppler Flow Detector, model 811-BTS (Parks Medical Electronics Inc., Aloha, OR) with a calibrated sphygmomanometer, Model Baum Pocket Aneroid (W. A. Baum Co. Inc., Copiague, NY) was used for detecting the Doppler BP as previously described.[4] Blood pressure was assessed in triplicate for each measurement method within 1 minute between measurements, obtaining I-A records from the continuous BP monitoring, followed by a noninvasive measurement using the ExpBP monitor, and finally, Doppler ultrasound.

Table 1. Demographic Characteristics of Studied Cohort

Variable	Mean ± SD or n (%)
n = 31	
Age (years)	63 ± 10
Male sex	27 (84)
Weight (kg)	88.8 ± 24.5
Height (m)	1.75 ± 0.11
Body mass index (kg/m^2)	28.6 ± 6.0
Nonischemic dilated CMP	17 (55)
Ischemic CMP	13 (41)
Complex CHD	1 (3)
Diabetes	14 (44)
Hypertension	15 (47)
COPD	7 (22)
Obstructive sleep apnea	11 (34)
Chronic kidney disease	18 (57)
Hyperlipidemia	11 (34)
Atrial fibrillation	4 (13)
Smoking	6 (19)
HeartMate II	20 (62)
HeartWare	11 (34)
Erythrocytes (×10[12]/L)	3.5 ± 0.8
Hemoglobin (g/dl)	10.4 ± 2.2
Platelets (×10[9]/L)	185 ± 84
Creatinine (mg/dl)	1.6 ± 0.9
Blood urea nitrogen (mg/dl)	33.9 ± 19.3
Potassium (mmol/L)	4.3 ± 0.5

CHD, congenital heart disease; CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disease.

Table 2. Device Types Implanted and Settings at the Time of BP Assessment

	HeartMate II	HeartWare
	n = 20	n = 11
Variable	Mean ± SD or n (%)	Mean ± SD or n (%)
Age (years)	67.2 ± 8.0	56.7 ± 9.1
Male (%)	19 (95)	8 (73)
Ischemic etiology (%)	11 (55)	2 (18)
LVAD speed (RPM)	9010 ± 382	2667 ± 198
LVAD power (W)	5.2 ± 0.9	4.1 ± 1.3
Pulsatility index	5.7 ± 1.0	N/A

BP, blood pressure; LVAD, left ventricle assist device; SD, standard deviation.

The Noninvasive BP Measurement System

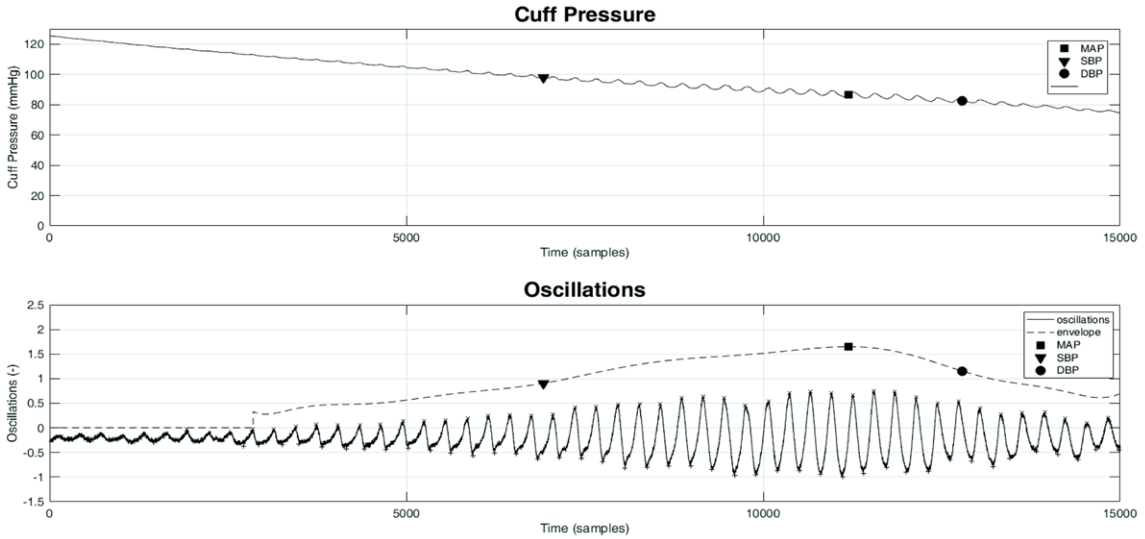
The prototype of the noninvasive BP measurement system was specifically designed for the LVAD population, consisting of the ExpBP monitor operated via the attached computer. The device was developed on a standard oscillometric principle for noninvasive BP measurement[12] with customized hardware and software to adapt for lower BP pulsatility (see Figure 1, Supplemental Digital Content, http://links.lww.com/ASAIO/A258). The device automatically measured oscillometric pulsations during cuff deflation at a speed of 2 mm Hg/second and was programmed to generate the most linear cuff deflation course, while minimizing artifacts caused by control valves. A standard pressure sensor (Freescale Semiconductor, type: MPXV5050GP) was used to measure the pressure in the cuff. The pressure signal from the sensor was filtered by an analog first-order low-pass antialiasing filter with a cutoff frequency of 140 Hz. Data were then digitized with a sampling frequency of 400 Hz.

Algorithms for Arterial Pressure Detection

The standard oscillometric BP method was applied to obtain MAP values.[12] In the device, the raw digitized pressure signal with oscillometric pulsations was filtered by a third-order high-pass Bessel filter with a cutoff frequency of 0.4 Hz to remove a slowly varying component of deflating cuff pressure. As a result, the filtered signal contained only the superimposed rapid pressure oscillations (at a range about mm Hg). During the cuff deflation, peak-to-peak oscillation amplitude changes gradually increased, reaching a maximum and then decreasing (**Figure 1**). It has been shown that the maximum peak-to-peak amplitude of oscillations occurs when the cuff pressure corresponds to the MAP.[12–15] The device used a MAP detection algorithm that employed a peak detector to find positive and negative peaks of oscillations based on polynomial fitting (**Figure 1**).[16] At the time of a maximum absolute difference of envelopes, the cuff pressure corresponded to MAP, as described previously.[13,16] The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained using height-based criteria.[17] The successful measurement was considered when the BP value was displayed for a given measurement attempt. The PP was calculated as the difference between SBP and DPB.

Statistical Analyses

According to the recommendations of American Heart Association for BP assessment, the average of the second and the third measurement was considered as a representative value



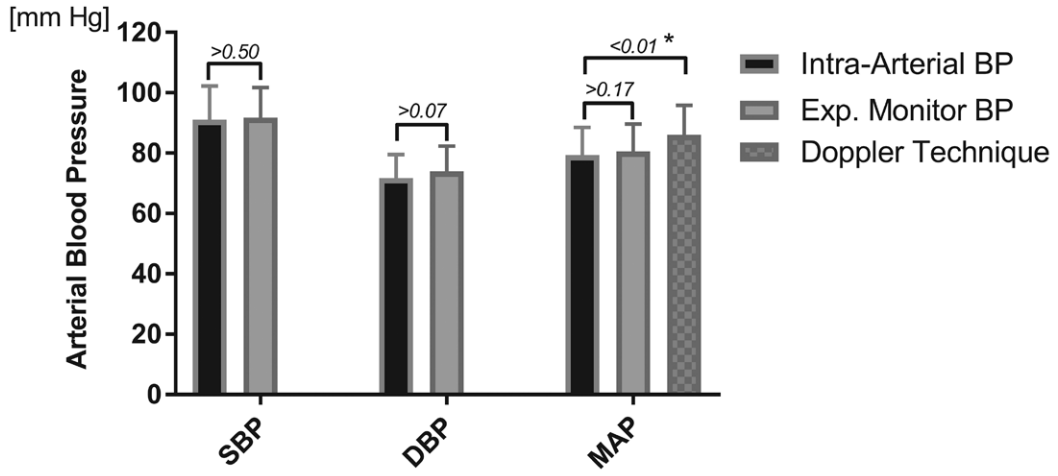
SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure, MAP= Mean Arterial Blood Pressure. Example of BP values assessed by the ExpBP monitor: SBP = 98mm Hg, DBP = 84mm Hg, MAP = 87mm Hg

Figure 1. Temporal characteristics of cuff pressure *vs.* measured oscillometric BP pulsations.

for the calculation of noninvasive BP measures.[11] For the I-A BP measures, 30 second average values were used. Where appropriate, variables were summarized as mean (standard deviation [SD]) and frequency (percent) for continuous and categorical measurements, respectively. The Bland–Altman (B-A) plots were constructed for the evaluation of the methods agreement between the ExpBP monitor versus I-A BP and Doppler BP versus I-A, respectively, with the bias of ±95% confidence intervals. Also, mean absolute difference (MAD) and Pearson correlations were used to compare between methods. For the repeatability assessment, MAD between the second and third BP measurement for each pressure (MAP, SBP, DBP, and PP) of a given method was performed with Pearson correlation coefficient calculated between obtained values. In addition, the "measurement success rate" was expressed as a percent of total measurement attempts. Data was analyzed using JMP Pro 10 (SAS Institute, Cary, NC) statistical software package, and B-A plots were carried out in GraphPad Prism version 7.00 (GraphPad Software, La Jolla, CA). Significance was considered present when $p < 0.05$.

Results

The general overview of results, demonstrating means of BP values from all three methods, is illustrated in **Figure 2**. SBP, DBP, and MAP were assessed by using the ExpBP monitor with an additional calculation of the PP, compared with the Doppler technique, which generated only a single BP value.



Means of BP values. SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure, MAP= Mean Arterial Pressure

Figure 2. Comparison of blood pressure values between techniques.

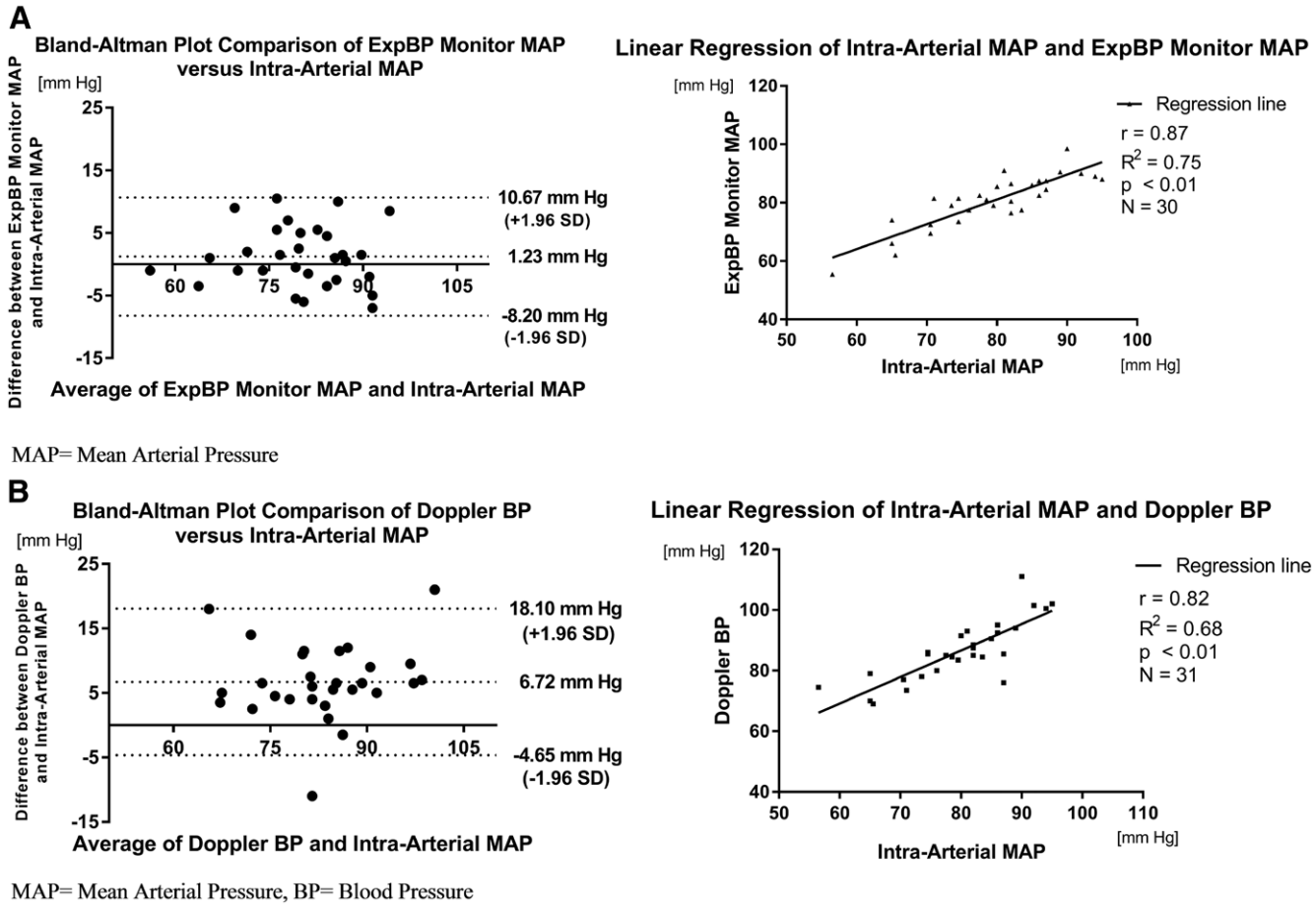


Figure 3. Comparison of non-invasive methods for blood pressure assessment with the invasive blood pressure. **A**: Agreement of methods for mean arterial pressure assessment delivered via the arterial line and the experimental blood pressure monitor in Bland–Altman analysis and Pearson correlation coefficient. B: Agreement of methods for mean arterial pressure assessment delivered via the arterial line and the Doppler Technique in Bland–Altman analysis and Pearson correlation coefficient.

Validation Analysis of the Experimental BP Monitor and Doppler Technique Referenced to I-A Pressures

The B-A analyses revealed a closer agreement of methods in the assessment of MAP between the ExpBP monitor and I-A pressure compared with the agreement in the MAP derived by the current gold standard, Doppler technique, and I-A MAP (**Figure 3, A** and **B**). Mean absolute differences between ExpBP monitor MAP *versus* I-A MAP and Doppler BP *versus* I-A MAP, respectively, were 3.9 ± 1.1 and 7.5 ± 1.0 mm Hg.

Additionally, there were strong Pearson correlations between I-A *versus* ExpBP monitor SBP, DBP, and PP ($r = 0.84$, $p < 0.01$; $r = 0.80$, $p < 0.01$; and $r = 0.73$, $p < 0.01$). Compared with corresponding I-A pressures, B-A plots displayed that the ExpBP monitor overestimated SBP by 0.8 (−11.3 + 12.8) mm Hg and DBP by 1.9 (−8.5 + 12.3) mm Hg and underestimated PP by 1.3 (−13.3 + 10.8) mm Hg (see Figures 2 and 3, Supplemental Digital Content, http://links.lww.com/ASAIO/A259).

Measurements Repeatability

The I-A technique achieved the highest reliability expressed in Pearson correlations and MAD between second and third measurements: $r = 0.99$ ($p < 0.01$) and 1.0 ± 1.2 mm Hg for MAP; $r = 0.98$ ($p < 0.01$) and 1.3 + 1.9 mm Hg for SBP; $r = 0.99$ ($p < 0.01$) and 0.7 ± 0.8 mm Hg for DBP; and lastly $r = 0.98$ ($p < 0.01$) and 1.0 ± 1.7 mm Hg for PP.

For the ExpBP monitor, analyses have revealed the Pearson correlation of $r = 0.98$ ($p < 0.01$) with MAD of 1.5 ± 1.2 mm Hg between the second and the third measurement for MAP, $r = 0.95$ ($p < 0.01$) with MAD of 2.4 ± 2.1 mm Hg for SBP; $r = 0.94$ ($p < 0.01$) with MAD of 1.9 ± 2.4 mm Hg for DBP; and $r = 0.84$ ($p < 0.01$) with MAD of 2.9 ± 3.1 mm Hg for PP.

The Doppler technique has displayed correlation between the second and the third measurement of $r = 0.98$ ($p < 0.01$) with a 1.5 ± 1.1 mm Hg of MAD between measurements, when rigorously performed by a single, trained observer.

Measurement Success Rate

In the CF LVAD population, problems commonly associated with the BP assessment using automated devices lead to remarkably a high number of "error" readings, when no values are provided by the BP monitor. In our study, an original approach was applied, allowing for an independent assessment of SBP and DBP from the ExpBP monitor after MAP was positively determined by the algorithm. This allowed for higher success rates for the MAP and SBP compared with DBP values. The Doppler technique achieved a high success rate in a critical care setting (**Table 3**).

Table 3. Measurement Success Rates Overview

	Percent of Total Successful Blood Pressure Measurement Attempts (%)	Percent of Patients with Three Successful Blood Pressure Measurement Attempts (%)	Percent of Patients with Successful Second and Third Blood Pressure Measurement Attempts (%)
Intraarterial BP			
MAP	100	100	100
SBP	100	100	100
DBP	100	100	100
Experimental BP monitor			
MAP	95	86	97
SBP	89	78	97
DBP	87	74	94
Doppler technique			
Doppler BP	99	97	100

BP was assessed three times by each method for a total of 31 subjects resulting in 93 measurement attempts by each method.
BP, blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.

Subanalysis of Doppler BP According to the I-A PP

By analyzing the accuracy of Doppler measurements, the data revealed a significant positive relationship between the I-A MAP to Doppler BP difference and the I-A PP ($r = 0.55$; $p < 0.01$). Also, this relationship between the I-A MAP and the Doppler BP was significant if calculated for I-A SBP to I-A MAP pressure difference ($r = 0.57$; $p < 0.01$; **Figure 4, A** and **B**).

Discussion

In the presented work, we tested the performance of an experimental BP monitor specifically designed to overcome the challenging hemodynamic characteristics of patients supported by CF LVADs. The design allowed for the noninvasive measurement of the MAP, SBP, and DBP in majority of patients supported by CF LVAD at early postimplantation stage using the ExpBP monitor. Acquired BP values were in close agreement to the respective invasive BP values. In addition, the accuracy and reliability of the Doppler technique was tested by a single operator under rigorous conditions.

Performance of the Experimental BP Monitor in Respect to Regulatory Standards for BP Monitors

The narrowest ±95% limit of agreement in the B-A analysis was achieved by comparing the I-A to the ExpBP monitor MAP, followed by DBP and SBP. The unique algorithm used in the ExpBP monitor also allowed for the low bias of 1.2 (4.8) mm Hg (mean [SD]) in the MAP assessment, 0.8 (6.1) mm Hg for the SBP, and 1.9 (5.3) mm Hg for the DBP, respectively. According to the Revised British Hypertension Society (BHS) protocol defining procedures for validation of BP monitors for special groups and in special circumstances (pregnant, children, elderly subjects, *etc.*), BP is required to be assessed in 30 subjects from the particular studied population and evaluated against a reference method (including ausculatory method). To achieve the highest degree of accuracy (grade A), the difference in BP values obtained by a tested method and a reference method must be ≤15 mm Hg in at least 95% of measurements, ≤10 mm Hg in at least 85%, and at least ≤5 mm Hg in at least 60% of measurements.[18] In categories, ≤15 mm Hg, ≤10 mm Hg, and ≤5 mm Hg, the ExpBP monitor achieved 99%, 93%, and 65% for SBP and 100%, 95%, and 57% for DBP. The existing standard of the International Organization for Standardization ISO 81060–2:2013 allows for BP monitors validation in groups with special conditions. The norm defines pass/fail criteria based on BP mean difference between tested and invasive reference method ≤5 mm Hg with SD ±8 mm Hg from all measurements (minimum of 150 measurement on 15 patients).[19]

Further improvement of the accuracy using oscillometric principle in patients supported by CF LVAD may be challenging because of a diminished PP, where movement artifacts and particularly the low-frequency respiratory-synchronous BP modulation, have relatively higher impact on the recorded

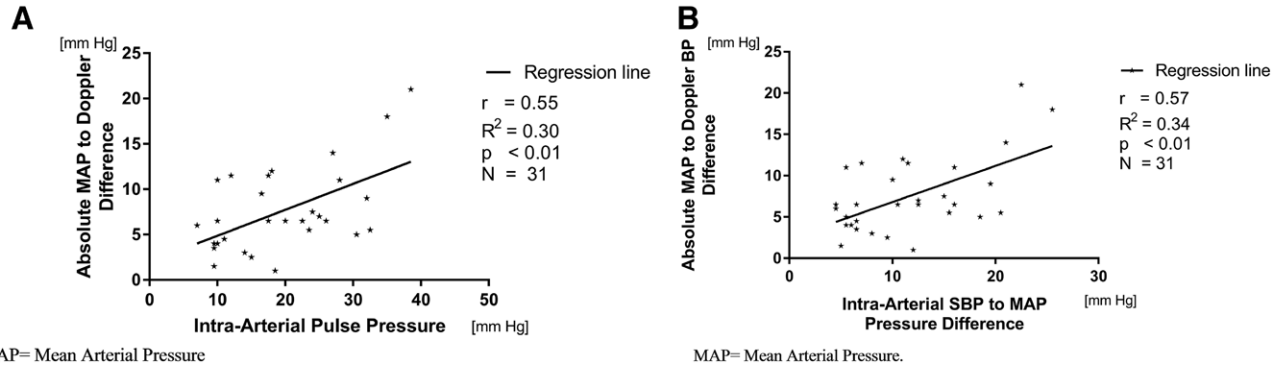


Figure 4. Effect of invasively assessed arterial pulsatility on accuracy of Doppler blood pressure. **A**: Linear relationship between intraarterial pulse pressure and absolute mean arterial pressure to Doppler pressure difference. B: Linear relationship between intraarterial systolic blood pressure to mean arterial pressure and absolute mean arterial pressure to Doppler pressure difference.

signal compared with the non-LVAD population. This may generate a flatter oscillometric envelop (**Figure 1**), which in turn increases the level of uncertainty in the detection of the maximal peak. In response, this may negatively affect the accuracy of MAP assessment, and consequently, also impact calculations of SBP and DBP. Paradoxically, artifacts traditionally perceived to be challenging for the oscillometric method in non-LVAD population (arrhythmias, mainly atrial fibrillation) may have smaller effect on the accuracy or measurement success rate in the LVAD population because of the position of the pump by-passing the left ventricle (LV). In this setting, the atrial contribution to the final stroke volume is diluted between the pump and the LV output, which may be seen in a relatively less pronounced beat-to-beat stroke volume variability during uneven LV filling. Our data suggest that the BP assessment should not be significantly affected when the residual PP exceeds approximately 5 mm Hg. This may have positive clinical implications also for the aortic valve closure post-LVAD implantation, surgical procedure performed in indicated cases to prevent progression of the aortic insufficiency.

LVAD-Specific Performance Assessment of the Experimental BP Monitor

Apart from the accuracy and reliability of BP assessment, a common problem of BP monitors not specifically designed for the patients supported by LVAD is a remarkable rate of error readings, when no BP value is provided by an automated monitor.[4,5] In this study, the ExpBP monitor achieved more than 90% of successful BP readings for the second and third measurement attempts for MAP, SBP, and DBP (**Table 3**), despite the majority of subjects receiving vasopressors at the time data collection. The success rates were maximized because of a unique feature to provide each of the BP values independently, even if the SBP or DBP was a missing value. Authors speculated that the ExpBP monitor might possibly achieve an even higher success rate in a stable CF LVAD population with a longer time post-LVAD implantation and no pharmacologically induced peripheral vasoconstriction. This needs to be confirmed in further studies.

Arterial PP and Pulsatility Index

Interpretations of calculated PP (PP = SBP − DBP) should be used with caution in potential attempts to use this information for the pump setting evaluation. The extrapolation of the value of pulsatility index (PI) provided by HeartMate pumps to the calculated PP remains challenging because no significant correlation was found between the ExpBP monitor PP and PI (r = 0.35; p = 0.15; n = 20) and also between the I-A PP and PI (r = 0.28; p = 0.23; n = 20) in the dataset collected on subjects very shortly after the LVAD placement. Hence, further effort is required in technological research focused on developing more reliable methods for a precise assessment of the residual pulsatility to enable its clinical utilization beyond the traditional PI value provided by the HM device controllers, as stressed by Cheng *et al*.[20] and Edwards *et al*.[21] Promising improvements in hemodynamic monitoring of patients supported by LVAD may be seen in future with clinical implementation of implantable hemodynamic sensors.

Overall, the current results suggest excellent performance of the ExpBP monitor in the assessment of SBP, DBP, and MAP compared with recently published data focused on testing monitors for BP measurement in the CF LVAD population.[5,22] Present work is in consideration with the idea of implementing automated BP monitors suitable to patients with CF physiology into clinical practice.[23]

Accuracy of the Doppler BP in Respect to the Arterial PP and Clinical Implications

The Doppler technique achieved very high measurement success rate and repeatability, in concordance with published literature.[4,5,8] Although the Doppler BP showed strong correlation with the I-A MAP, overall Doppler overestimated I-A MAP in average by 6.7 (5.8) mm Hg (**Figure 3B**) and underestimated SBP by 5.0 (6.6) mm Hg. Furthermore, the data revealed a positive relationship between the I-A PP and the I-A MAP to Doppler BP difference (**Figure 4, A** and **B**). This data supports previous observations by Lanier *et al*.[5] that the accuracy of MAP assessment by the Doppler technique decreases with increased pulsatility. Thus, in patients with a higher PP, the Doppler may determine more closely I-A SBP rather than I-A MAP. This relationship may have an important clinical implication in managing post-LVAD hypertension based on the recommendation to maintain the Doppler BP between 70 and 80 mm Hg and not to exceed 90 mm Hg.[24–26] Thus, with increased pulsatility, there is a risk of overdosing antihypertensive therapy because of significantly higher differences between the true MAP *versus* the measured Doppler BP. In turn, potential chronic hypoperfusion may contribute to impaired glomerular filtration pressure, increasing risk of orthostatic hypotension with syncope and higher risk of cranial trauma. Other than the inability to provide SBP and DBP, the limitation of the Doppler technique is in the need for a trained person to perform a measurement. Yet, despite the clinical importance, this limitation of the Doppler technique will remain unsolved until either another physiologic surrogate for the peripheral arterial pulsatility assessment will be implemented in the Doppler technique or until an LVAD-specific automated BP monitors will overcome the limitations of the Doppler to provide only a single BP value. However, the remarkable success rate of Doppler technique may reserve a continuing position of this technique in the setting of hemodynamically challenging conditions (*e.g.*, circulatory shock).

Study Limitations

In the current study, we tested the performance of the ExpBP monitor prototype. For clinical use, the final design of the monitor will require extended clinical validation. The BHS validation protocol requires specific distribution of BP values in the tested population, which was not appreciated in current study.[18] Because the ExpBP monitor was tested on critically ill subjects, the methodology was limited by certain inconsistency in noninvasive BP measurements being acquired on either ipsilateral or contralateral arm from the reference method (because of vein thrombosis, *etc.*). However, none of the subjects included in the study were to be found with a significant lateral BP difference. Moreover, although the BHS protocol does not recommend the BP to be assessed on the contralateral arm, the newer internationally valid ISO standard 81060–2 allows this approach after the lateral difference determination.[18,19] Finally, the results from the Doppler technique could be positively or negatively biased, because the Doppler BP assessment was not blinded from the invasive BP.

Conclusions

The ExpBP monitor was able to assess SBP, DBP, and MAP in the majority of CF LVAD subjects supported either by axial or centrifugal pumps with good agreement to the I-A BP. The independent displaying SBP and DBP after MAP determination may improve overall measurement success rates. Automated BP monitors specifically designed for the patients supported by CF LVAD might simplify self- and home monitoring of BP, contribute to safer use of antihypertensive drugs, and, in turn, may alleviate adverse outcomes associated with poor BP control.

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APPENDIX A4

CROSS, T., J., SAJGALIK, P., FABIAN, V., MATERA, L., KUSHAWA, S., S., MALTAIS, S., STULAK, J., M., SCHIRGER, J., A., JOHNSON, B., D. Non-invasive assessment of arterial pulsatility in patients with continuous-flow left ventricular assist devices. *The International Journal of Artificial Organs*, 2020, 43.2: 99-108. ISSN 0391-3988. DOI 10.1177/0391398819868236.

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Abstract

Introduction: Long-term use of continuous-flow left ventricular assist devices may have negative consequences for autonomic, cardiovascular and gastrointestinal function. It has thus been suggested that non-invasive monitoring of arterial pulsatility in patients with a left ventricular assist device is highly important for ensuring patient safety and longevity. We have developed a novel, semi-automated frequency-domain-based index of arterial pulsatility that is obtained during suprasystolic occlusions of the upper arm: the 'cuff pulsatility index'.

Purpose: The purpose of this study was to evaluate the relationship between the cuff pulsatility index and invasively determined arterial pulsatility in patients with a left ventricular assist device.

Methods: Twenty-three patients with a left ventricular assist device with end-stage heart failure (six females: age = 65 ± 9 years; body mass index = 30.5 ± 3.7 kg m^{-2}) were recruited for this study. Suprasystolic occlusions were performed on the upper arm of the patient's dominant side, from which the cuff pressure waveform was obtained. Arterial blood pressure was obtained from the radial artery on the contralateral arm. Measurements were obtained in triplicate. The relationship between the cuff pressure and arterial blood pressure waveforms was assessed in the frequency-domain using coherence analysis. A mixed-effects approach was used to assess the relationship between cuff pulsatility index and invasively determined arterial pulsatility (i.e. pulse pressure).

Results: The cuff pressure and arterial blood pressure waveforms demonstrated a high coherence up to the fifth harmonic of the cardiac frequency (heart rate). The cuff pulsatility index accurately tracked changes in arterial pulse pressure *within* a given patient across repeated measurements.

Conclusions: The cuff pulsatility index shows promise as a non-invasive index for monitoring residual arterial pulsatility in patients with a left ventricular assist device across time.

Keywords

Left ventricular assist device, pulsatility index, non-invasive

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Introduction

Continuous-flow left ventricular assist devices (LVADs) are an established treatment modality for patients with end-stage heart failure. Given that the durability of modern pumps has increased significantly in recent years, there is a growing need for research to examine the longer-term consequences of LVAD therapy on the occurrence of adverse events, quality of life and survival.[1–3] It is well known that continuous-flow LVADs adversely impact on the arterial pulse waveform, wherein arterial pulsatility

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declines the further that pump speed is increased.[3] Unfortunately, low arterial pulsatility may increase the risk of several negative outcomes, such as long-term end-organ dysfunction,[4–7] gastrointestinal bleeding,[8–10] endothelial dysfunction,[11] autonomic dysregulation and impaired renal function[4–6,12] and may also impair pulmonary function and gas exchange.[7,13,14] With these associated risks in mind, the question arises: Is monitoring of arterial pulsatility in LVAD patients important for ensuring their safety and longevity?

At present, there is little data available to support or refute the clinical usefulness of monitoring arterial pulsatility in LVAD patients. The relative paucity of such data may be due to our present lack of a convenient, non-invasive and accurate technique to measure arterial pulsatility in this clinical population. Certainly, the arterial pulse waveform may be obtained using finger arterial photoplethysmography in LVAD patients using a servo-controlled, volume-clamp method.[15–17] In addition, Doppler ultrasound has demonstrated a strong promise for determining arterial pulsatility under different LVAD pump settings.[18,19] However, these methods are neither simple nor convenient, insofar as each method requires expensive equipment and a high degree of technical skill for valid/reliable measurements – issues which do not favour their frequent use in longitudinal or remote monitoring. It is of note that some recent generations of LVADs offer indirect measurements of arterial pulsatility – these indices of arterial pulsatility are typically derived from 'pulsatile-like' changes in LVAD pump power.[20] Notwithstanding the many studies that have demonstrated an association between LVAD pump-derived indices of pulsatility and adverse clinical outcomes,[6,8,9,11,21] these measures of arterial pulsatility correlate poorly with that invasively determined from arterial blood pressure (ABP).[22] Thus, while it cannot be denied that pulsatility index (PI), pump speed and power may provide useful information for the monitoring and prevention of serious adverse outcomes, such as pump thrombosis,[23] it remains to be seen whether more accurate measures of arterial pulsatility may confer additional benefits for the clinical management of LVAD patients. And while it is true that current (and future) generations of LVAD pumps may offer indirect measures of arterial pulsatility, it must be remembered that there remains a long-standing population of LVAD patients who survive on older generation devices. What is needed, therefore, is a simple non-invasive method for determining arterial pulsatility that can be applied to all patients with LVAD irrespective of their pump's technology.

We have recently developed a simple non-invasive device which uses brief suprasystolic occlusions (< 30–40 s) of the upper arm to resolve an arterial pulse waveform; this device is similar to that described by Horváth et al.[24] This method yields a continuous non-invasive arterial pressure curve during the period of suprasystolic occlusion and is highly correlated with systolic blood pressure, augmentation index and pulse-wave velocity determined from invasively obtained arterial pressures. Certainly, this method shows promise for the non-invasive monitoring of arterial pulse characteristics in LVAD patients. However, this method necessitates the precise identification of cardiac beat intervals in the time-domain to perform its calculations. Moreover, measurement artefacts induced by motion, breathing, muscle contraction, and so on will decrease the accuracy with which beat intervals may be detected from the pressure waveform in the time-domain. As such, the validity of this method depends critically on capturing a pressure waveform with a high signal-to-noise ratio – a condition that is especially challenging in LVAD patients with close to zero pulsatility. To overcome these limitations, we have developed a 'cuff pulsatility index' (CPI) which uses a semi-automated frequency-domain approach – a method that obviates the need for precise detection of beat intervals in the time-domain.

Therefore, the aims of this study were twofold. First, we sought to determine the relationship between the intra-arterial pressure waveform and the arterial pulse curve obtained from the non-invasive 'occlusion' method described by Horváth et al.[24] Second, we evaluated whether the frequency-domain measure of arterial pulsatility, the CPI, could be used as a valid surrogate for intra-arterial pulse pressure in patients with LVAD. We hypothesized that not only would the two waveforms demonstrate a correlation with one another, but that our novel measure of arterial pulsatility, the CPI, would strongly correlate with pulse pressure determined from invasive measurements of blood pressure.

Methods

Patients and ethical approval

A total of 23 end-stage heart failure patients (four females: age $= 63 \pm 10$ years; body mass index (BMI) $= 28.6 \pm 6.0$ kg m^{-2}) with an LVAD implanted at Mayo Clinic, Rochester, Minnesota, USA, were included in the study. Patients were included in the study if they received LVAD therapy from either the HeartMate II (Abbott Laboratories, Chicago, IL, USA) or HeartWare (Medtronic, Minneapolis, MN, USA) devices. There were no exclusion criteria. The study was approved by Mayo Clinic Institutional Review Board (IRB) and all subjects signed written informed consent prior the study was performed.

Experimental devices

ABP was invasively determined via a 20 Fr intra-arterial catheter placed in the radial artery and a disposable pressure transducer (TruWave™PXMK2064, Edwards Lifesciences, Irvine, CA, USA). The intra-ABP waveform

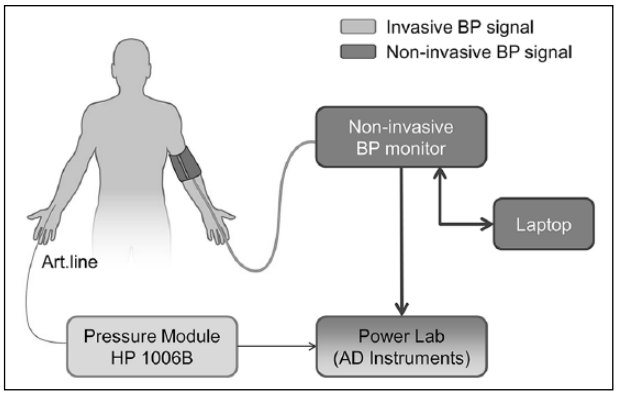

Figure 1. Schematic illustration of experimental design.
BP: blood pressure.

was continuously recorded on a critical care monitor (IntelliVue MP 50 and HP 1006B, Phillips, Amsterdam, the Netherlands). Prior to each recording, the system was flushed with saline and zeroed at the phlebostatic axis.[25,26] The non-invasive blood pressure waveform was obtained using the suprasystolic occlusion principle as previously described.[24,27] An appropriately sized inflatable pneumatic cuff (CM2, Omron Healthcare, Inc., Lake Forest, IL, USA) was positioned on the upper arm such that a 5 cm overlap of the cuff was present at 3 cm above the cubital fossa. The brachial cuff was interfaced with our experimental blood pressure monitor.[22,28] A differential pressure sensor (±2 kPa, MPXV7002DP, NXP Semiconductors, Eindhoven, Netherlands) was used to measure the pressure inside the brachial cuff during the measurement at suprasystolic pressure.[29] The raw pressure signal was passed through an analog low-pass noise filter with a cut-off frequency of 650 Hz. The ABP waveform from the IntelliVue unit, and the brachial cuff pressure obtained from the experimental monitor was digitized at a sampling frequency of 1000 Hz (PowerLab 16/30, ADInstruments, Bella Vista, NSW, Australia). It should be noted that the analog voltage from the IntelliVue unit is output at approximately 40 Hz with 8-bit resolution (~2.0 mmHg·bit-1 sensitivity). By oversampling this signal at 1000 Hz, and passing the signal through a low-pass third-order Butterworth filter (500 Hz cut-off frequency), we increased the resolution of the ABP signal to 10.3-bit (~0.4 mmHg·bit-1 sensitivity).[30]

Experimental procedures

The present investigation was a single-centre, prospective non-randomized study. Patients were entered into the study 2.6 ± 3.4 days after LVAD implantation. Intra-ABP was recorded from the radial artery, and non-invasive brachial cuff pressures were measured from the contralateral arm. A schematic illustration of the experimental setup is displayed in Figure 1. Data were collected in the intensive care unit while patients were stable and in the supine position. After 10–20 min of quiet rest (baseline), the brachial cuff was inflated to approximately 35 mmHg above systolic pressure (suprasystolic pressure) for a duration of ~30 s. During this period, the ABP signal and cuff pressures were recorded. These measurements were repeated 2 to 3 times, separated by 1-min periods of rest with the brachial cuff deflated. Patients were encouraged to remain still, avoid coughing and relax their arm to minimize motion artefacts during the recordings.

Data analyses

Data were transferred to MATLAB (R2016a, MathWorks, Natick, MA, USA) for signal analysis. The ABP and brachial cuff pressure signals were detrended, and bandpass filtered with a third-order Butterworth filter between 0.2 and 24.0 Hz. Data were subsequently downsampled to 256 Hz. The middle 20 s of each recording was analysed to avoid edge effects introduced by the filtering process. Heart rate (HR) was calculated from the filtered ABP signal via a simple peak-detection algorithm. Pulse pressure of the filtered ABP pressure waveform was taken as the difference between the maximum and minimum pressures observed throughout each cardiac cycle. The spectral power of the ABP and cuff pressure signals were computed using a 2048-point (*nfft*) Welch-periodogram.[31] A rectangular windowing function of 1024 points long was used with 50% overlap. The magnitude-squared coherence (*Coh*) between ABP and cuff pressure waveforms was calculated using Welch's averaged, modified periodogram. *Coh* ranges from 0 to 1 and indicates the strength of the linear relationship between two signals at a given frequency (e.g. ABP and cuff pressure). The frequency basis of each spectral function was transformed onto a relative scale by normalizing to the individual's cardiac frequency (f_c) during each measurement period, where $f_c = HR \cdot 60^{-1}$. This transformation allowed us to compare spectral powers and coherences at each multiple (harmonic) of f_c between patients. The ABP and cuff pressure power spectrums, and the computed *Coh* functions were averaged across repeated trials for each subject.

It was necessary to evaluate the statistical significance of coherence estimates at each frequency. To achieve this goal, we used the randomized shuffle/permutation test.[32] In brief, this method is performed by completing the following steps:

1. Obtain the *Coh* value on a pair of ABP and cuff pressure waveforms from a given subject at a given measurement period.
2. Randomly resample the ABP waveform without replacement (i.e. random shuffle) to obtain a replicate dataset.
3. Perform the same randomized shuffle on the cuff pressure waveform.

4. Compute the *Coh* at each frequency using this randomly reshuffled pair of ABP and cuff pressure waveforms.
5. Repeat steps 2 through 4 to generate 500 permuted datasets.

The above procedure destroys any structural relationship between the ABP and cuff pressure waveforms, producing a distribution of *Coh* values that one might expect if ABP and cuff pressure waveforms were uncorrelated. The upper 95th confidence limit of the randomly permuted *Coh* values ($Coh_{95\%}$) is obtained at each frequency. If the *Coh* value obtained in step 1 is larger than $Coh_{95\%}$ at a given frequency, the observed spectral relationship was significantly greater than that obtained from a background of random, uncorrelated noise. It is emphasized that this permutation test was performed separately on each pair of ABP and cuff pressure waveforms for each measurement window, per patient – data were not mixed between repeated observations and patients.

The cuff pulsatility index (CPI) was computed as the integrated spectral power between the f_c and its fifth harmonic (i.e. $5{\cdot}f_c$). This range was extended by 0.5 Hz in both directions (i.e. f_c – 0.5 Hz and $5{\cdot}f_c$ + 0.5 Hz) to ensure that spectral peaks corresponding to each harmonic were captured in the calculation of CPI.

Statistical analyses

The spectral powers for ABP and cuff pressure signals, and the computed *Coh* values were averaged across patients at each multiple of f_c up to $10{\cdot}f_c$. The proportion of patients (%) displaying a significant *Coh* at each multiple of f_c was also reported (i.e. where $Coh > Coh_{95\%}$). A linear mixed-effects model was used to determine linear relationship between the computed CPI and the invasively determined pulse pressure measured from the ABP waveform. This model was built in all the available data, including the repeated observations for CPI and arterial pulse pressure within each patient. Preliminary analysis of the data indicated that a mixed-effects model with a random intercept and slope yielded the best model-fit as evidenced by the lowest Akaike information criterion (AIC). That is, not only was a group-level slope and intercept fit by the model, but also an individual intercept and slope was fit to each patients' repeated observations. The marginal coefficient of determination (R^2_{marginal}) and root mean square error ($\text{RMSE}_{\text{marginal}}$) were computed based on the overall 'population-level' intercept and slope, ignoring the individual patient relationships between CPI and arterial pulse pressure (i.e. fixed effects only). Conversely, the conditional coefficient of determination ($R^2_{\text{conditional}}$) and root mean square error ($\text{RMSE}_{\text{conditional}}$) were computed based on the *combined* 'population-level' and individual patient relationships between CPI and arterial pulse pressure (i.e. fixed and random effects). By comparing the marginal and conditional R^2 and RMSE, one is able to determine whether the CPI may be a useful marker of absolute arterial pulsatility, or whether the CPI is better used to track changes in arterial pulsatility within LVAD patients. Results are presented as means ± standard error of the mean (SEM). Statistical analyses were performed using R Statistical Software (version 3.4.3) and were considered significant if $p < 0.05$.

Results

Patient demographic and clinical characteristics are reported in Tables 1 and 2. The group-averaged HR and f_c were 96 ± 10 beats min^{-1} and 1.60 ± 0.17 Hz, respectively.

Figure 2 illustrates the spectral powers of the ABP and cuff pressure signals, and the computed *Coh* between the two signals. For both the ABP and cuff pressure waveforms, spectral power tended to decrease exponentially at higher multiples of the patients' f_c. The observed *Coh* at the first and second multiples of f_c were very high (> 0.80), indicating a strong level of association between the ABP and cuff pressure signals at these harmonic frequencies. Indeed, the majority of patients (> 50%) displayed significant *Coh* values ($> Coh_{95\%}$) up to the fifth harmonic of the cardiac frequency. Figure 3 displays the relationship between the CPI obtained from the brachial cuff and the invasively determined arterial pulse pressure via the ABP waveform. The R^2_{marginal} and $\text{RMSE}_{\text{marginal}}$ for the best-fit mixed-effects model was 0.15 and 5.5 mmHg, respectively. On the contrary, the $R^2_{\text{conditional}}$ and $\text{RMSE}_{\text{conditional}}$ were 0.99 and 0.5 mmHg, respectively. The observation that $R^2_{\text{conditional}}$ was higher than R^2_{marginal}, and $\text{RMSE}_{\text{conditional}}$ was lower than $\text{RMSE}_{\text{marginal}}$, indicates that CPI may be better used to track within-patient changes in arterial pulsatility, rather than to compare arterial pulsatility between patients (cross-sectionally) or against an arbitrary absolute reference level.

Discussion

The central purpose of this work was to, first, examine whether the pressure waveform obtained via the brachial 'occlusion' method reflected the arterial pulse waveform as measured invasively from the radial artery (i.e. ABP) and to, second, determine whether the CPI could be used as a surrogate for intra-arterial pulse pressure in LVAD patients. Our findings demonstrate that the cuff pressure and ABP waveforms are linearly associated with one another up to the fifth harmonic of the cardiac frequency (i.e. f_c). We are thus highly confident that the cuff pressure waveform, as obtained via the brachial 'occlusion' method, provides a reasonable approximation of the pulsatile characteristics of the underlying 'true' arterial waveform.

Table 1. Patient characteristics.

Variable	
Age (years)	65 ± 9
Male (N, %)	17 (74)
Mass (kg)	85.3 ± 18.2
Height (m)	1.75 ± 0.12
Body mass index (kg/m^2)	30.5 ± 3.7
Non-ischemic dilated CMP (N, %)	11 (48)
Ischemic CMP (N, %)	12 (52)
Diabetes Mellitus (N, %)	8 (34)
Hypertension (N, %)	15 (65)
COPD (N, %)	4 (18)
Obstructive sleep apnea (N, %)	8 (34)
Chronic kidney disease (N, %)	19 (83)
Hyperlipidaemia (N, %)	14 (61)
Smoking (N, %)	8 (34)
HeartMate II (N, %)	11 (48)
HeartWare (N, %)	12 (52)
Erythrocytes (× 10(12)/L)	3.6 ± 0.8
Haemoglobin (g/dL)	11.2 ± 2.4
Platelets (× 10(9)/L)	198 ± 112
Creatinine (mg/dL)	1.7 ± 1.3
Blood urea nitrogen (mg/dL)	34.9 ± 21.0
Potassium (mmol/L)	4.2 ± 0.5

Values are reported as means ± standard deviations, or counts and proportions where specified.
N: count; CMP: cardiomyopathy; COPD: chronic obstructive pulmonary disease.

Table 2. Device types implanted and settings at the time of BP assessment.

Variable	HeartMate II (n = 11)	HeartWare (n = 12)
Age (years)	69 ± 8	55 ± 10
Male (N, %)	11 (100)	6 (50)
Ischemic aetiology (N, %)	9 (82)	3 (25)
LVAD speed (r/min)	9065 ± 308	2618 ± 167
LVAD power (W)	5.4 ± 0.7	4.0 ± 1.2
Pulsatility index	6.4 ± 1.1	N/A

Values are reported as means ± standard deviations, or counts and proportions where specified. The pulsatility index displayed here is that obtained from the HeartMate II.
N: count; LVAD: left ventricle assist device.

Furthermore, our results indicate that our frequency-domain index of arterial pulsatility, the CPI, may be used to track changes in arterial pulsatility *within* an LVAD patient across repeated measurements.

Advantages of the CPI

There is growing concern over the potential for continuous-flow LVAD therapy to increase the risk of end-organ dysfunction,[6] gastrointestinal bleeding,[8–10] endothelial dysfunction,[11] autonomic dysregulation and impaired renal function[4–6,12] and pulmonary gas-exchange impairment.[7,13,14] As such, it is conceivable that longitudinal monitoring of arterial pulsatility in LVAD patients may also hold prognostic value. For example, at a given pump speed, an increase in arterial pulsatility over time may indicate partial recovery and therapeutic benefit of the LVAD, whereas, on the contrary, a gradual decline in arterial pulsatility in LVAD patients may portend worsening heart failure. There are, of course, several methods available to assess and monitor arterial pulsatility in LVAD patients. For example, arterial pulse pressure may be obtained via the 'oscillometric' method[22] or from a finger photoplethysmograph.[16] Yet, although the former method is easily implement using an automated cuff inflator, the latter requires expensive hardware to implement the 'volume-clamp' method to reconstruct the arterial pulse wave.[15] Recently, Doppler ultrasound velocimetry of the middle-cerebral artery has been used to quantify the transmission of arterial pulsatility to the brain in LVAD patients.[18,19] And while promising, this method is not suitable for routine, potentially home-based, monitoring of arterial pulsatility in LVAD patients. Further to the above, these methods all require a 'minimum pulse pressure' to be present in the arterial pulse waveform, from which salient features are extracted in the *time-domain* (i.e. systolic and diastolic pressures/flows). As such, these current methods are likely to fail in those LVAD patients with little to no residual arterial pulsatility. It is with the above in mind that we developed the cuff pulsatility index (CPI).

The CPI is a frequency-domain-based method of quantifying arterial pulsatility from a pressure waveform obtained via a brachial cuff using the 'occlusion' method.[24,27] In essence, it measures the spectral power of the cuff pressure waveform at harmonics directly related to the cardiac frequency. This index of arterial pulsatility offers several advantages over existing methods. For instance, the CPI does not require any salient feature extraction from the time-domain pressure waveform *per se* and, as such, does not necessitate that a 'minimum pulse pressure' be evident in the arterial waveform. Notwithstanding this advantage, we emphasize that one still requires knowledge of the average cardiac frequency (f_c) during the measurement period. In this study, we determined f_c from the ABP waveform. In practice, however, it is envisioned that f_c can be measured directly from the R-waves of an ECG (electrocardiogram) waveform obtained from bipolar electrodes underneath the brachial cuff. A further advantage of the CPI is that it is relatively simple to implement in the home-based setting by its incorporation into existing automated blood pressure monitors. Finally, the frequency-domain approach which yields the CPI may be applied to any signal that purports to represent the arterial pulse waveform (ABP, finger photoplethysmography, etc.). In this manner, the CPI is not

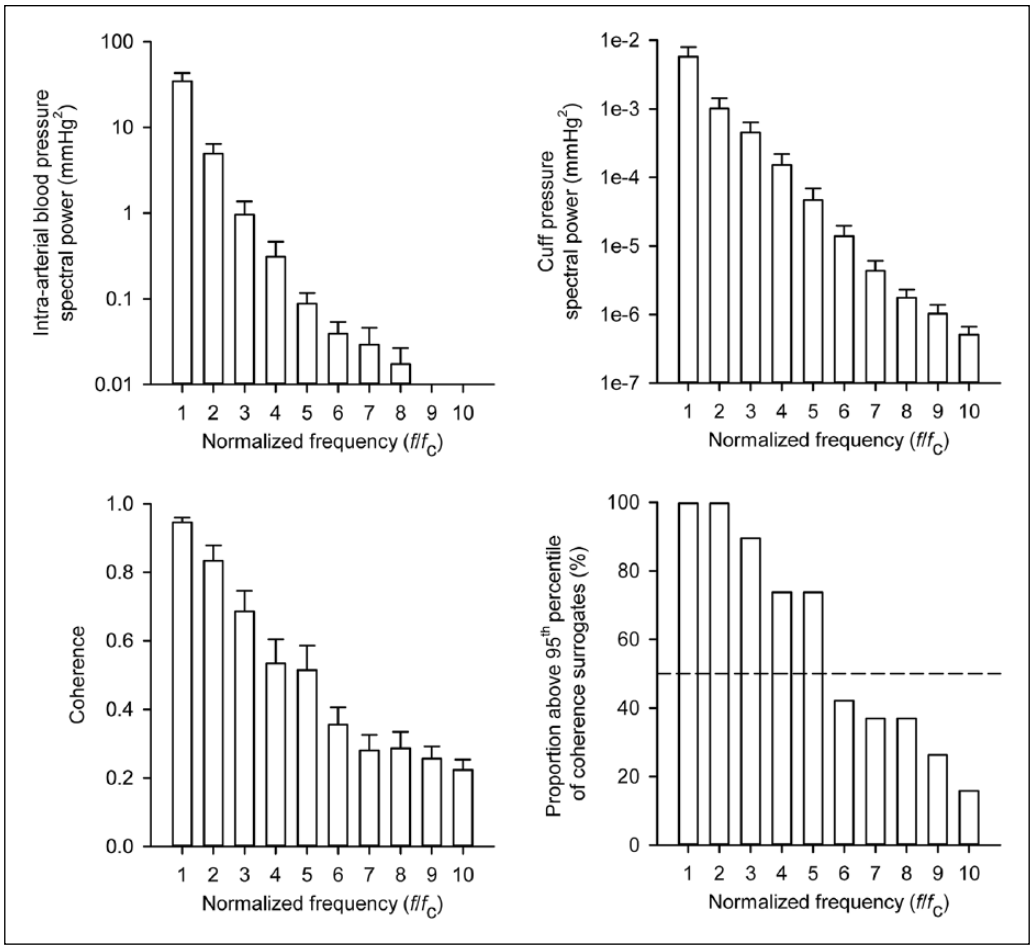

Figure 2. Spectral powers of and coherence between intra-arterial and cuff pressure signals during suprasystolic occlusions. Values represent means ± SEM. The dashed line in the lower right panel indicates a 50% cut-off whereby mean values above this line indicate that the majority of patients displayed significant coherence between intra-arterial and cuff pressure signals at the corresponding harmonic of the cardiac frequency.
f/f_c: spectral frequency normalized to the cardiac frequency.

confined to data obtained from the brachial cuff 'occlusion' method. With these advantages in mind, it is encouraging that our findings indicate that the CPI may be used to track changes in arterial pulse pressure *within* a given LVAD patient across repeated observations (Figure 3). To demonstrate this point further, we performed a series of brachial cuff occlusions in one of our recruited LVAD patients while their device was adjusted to two separate speeds, 2500 and 2640 r/min. Figure 4 illustrates that upon an increase in pump speed, both the invasively determined arterial pulse pressure (PP) and our non-invasive index of arterial pulsatility, the CPI, declined by roughly 25%.

A further advantage of the CPI is that several other clinically relevant variables may be derived from the same measurement technique (i.e. 'occlusion' method). For example, we have recently shown that the 'occlusion' method provides a valid measure of systemic blood pressure in LVAD patients[22] – a clinically important variable that holds a strong prognostic value in this population. Furthermore, we have demonstrated that specialized analysis of the cuff pressure waveform provides an accurate estimate of cardiac output.[27] Thus, it is possible that with future developments of the method, one may be able to obtain a comprehensive assessment of hemodynamic status (cardiac output, arterial pulsatility, systemic blood pressure) from a single period of suprasystolic cuff occlusion in LVAD patients.

Disadvantages of the CPI

Although the CPI may be a promising new approach to monitoring arterial pulsatility *within* a given LVAD patient, it is emphasized that this index does not provide an accurate measure of intra-arterial pulse pressure *between* subjects (Figure 3). Thus, the CPI, in its current form, should not be used to compare the absolute level of arterial pulsatility between any two LVAD patients. In addition, it must be said that the CPI is not immune to extraneous pressure

artefacts produced by motion, muscle contractions and so on. This point reduces the likelihood of using the CPI in the ambulatory state; patients must remain still during the measurement period. Finally, it is probable that newer generation LVAD pumps, specifically those designed to induce a certain degree of artificial pulsatility (see 'Future directions' section), will contribute a significant amount of spectral power in the cuff pressure waveform at the frequency of the pump speed oscillation. Importantly, this additional spectral content may be close to or perhaps even centred on the cardiac frequency, in which case the CPI, as presently described, would not be able to differentiate between the pulsatility generated by the heart and the LVAD pump. To address this issue, it is conceivable that future implementations of our CPI method could incorporate joint time-frequency analyses, whereby the spectral power in the cuff pressure waveform may be analysed only during those sections of time where the pump was not performing a 'Lavare' cycle, or attempting to induce pulsatility via rapid changes in impeller speed.

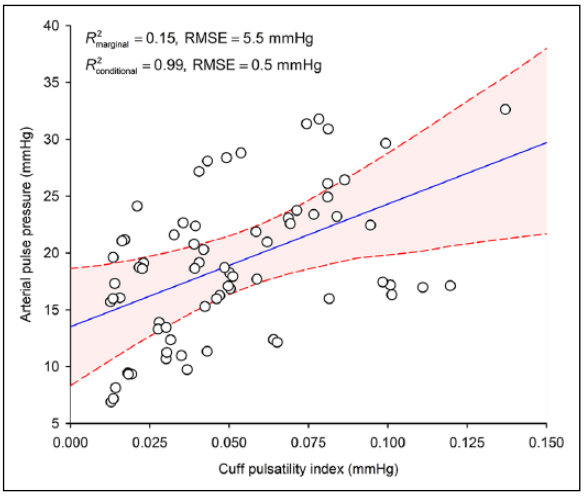

Figure 3. Linear mixed-effects model illustrating the relationship between the CPI and arterial pulse pressure.
The solid blue line represents the overall significant ($p < 0.05$) fixed-effect of CPI on arterial pulse pressure. The red dashed lines and shaded interval denote the 95% confidence band of the marginal fixed-effect of CPI on arterial pulse pressure. $R^2_{marginal}$ and $R^2_{conditional}$: the coefficient of determination for the marginal (group-level effects only) or the conditional (group-level + participant effects) representations of the linear mixed-effects model. This figure demonstrates that the relationship between CPI and arterial pulse pressure is strongest when intra-patient variability is considered (i.e., $R^2_{conditional} >> R^2_{marginal}$).
CPI: cuff pulsatility index; RMSE: root mean square error.

Methodological considerations

The lack of significant coherence values beyond the fifth harmonic of f_c may have been due to inter-individual differences in upper arm anthropometry which may have, in turn, impacted the signal quality of the recorded cuff pressure waveform. Importantly, however, Horváth et al.[24] reported that upper arm dimensions and fat-to-muscle ratio do not appear to affect the signal quality of the cuff pressure waveform during suprasystolic occlusions. Instead, the reduction in coherence between the arterial and cuff pressure waveforms at the higher harmonics may be more likely the result of sampling arterial and cuff pressures at

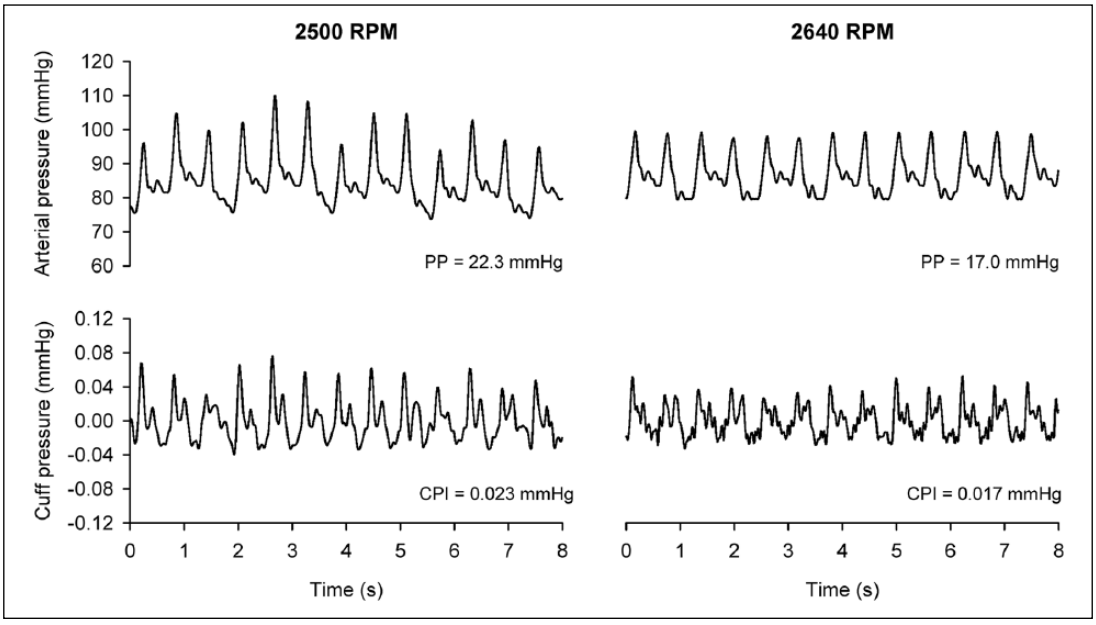

Figure 4. Intra-arterial and cuff pressure waveforms during the brief suprasystolic occlusions in a single patient whose left ventricular assist device pump speed was adjusted from 2500 (left panels) to 2640 r/min (right panels).
Note that both CPI and PP decreased by a similar order of magnitude as pump speed was increased.
CPI: cuff pulsatility index; PP: pulse pressure determined from intra-arterial waveform.

different sites and under different conditions. For example, intra-ABP was continuously monitored in the contralateral arm (with respect to upper arm cuff) with no obstruction to blood flow ('free-flow' condition), whereas cuff pressure was measured under 'stop-flow' conditions during suprasystolic occlusion. Any differences in arterial waveform morphology due to 'free-flow' versus 'stop-flow' conditions may have therefore reduced coherence between these two signals, particularly at higher harmonics. Furthermore, it must be considered that arterial pressure was obtained from the radial artery – a site more distal from the heart than that where cuff pressure was obtained (i.e. upper arm/brachial artery). Given that the arterial pulse wave changes in morphology as measurement site proceeds distally along the arterial vascular tree,[33] it is perhaps not surprising that the cuff (*brachial*) arterial pressure waveform did not cohere with the *radial* arterial pressure waveform at these higher harmonics. Finally, while we are confident that our intra-arterial catheter-transducer system displayed adequate frequency response characteristics (i.e. natural frequency > 14 Hz), we cannot rule out the possibility that the mechanical properties of the system may have dampened the higher frequency spectral content of the ABP waveform. This point may also explain why it became difficult to observe significant *Coh* values at the higher frequencies, particularly at the 9th and 10th harmonics of f_c (see upper left panel in Figure 2).

Implications of our findings

Despite the promise in using the CPI to monitor arterial pulsatility in LVAD patients, the following questions arise: (i) What is the Clinician to do if the CPI of an LVAD patient changes over a given period of time? (ii) How might pump speed be adjusted in response to a rise or fall in CPI? (iii) What is the prognostic value of CPI? Unfortunately, the present data do not allow us to make any firm recommendations on how CPI may be used to guide/alter the clinical management of LVAD patients. Rather, it was the express purpose of this study to develop a non-invasive method of measuring arterial pulsatility in this cohort of patients, such that longitudinal studies may then be conducted, from which recommendations may eventually be afforded. We do, however, anticipate that the CPI may demonstrate its clinical utility, not through the ability to classify LVAD patients as having 'low' or 'high' pulsatility, but through its ability to monitor directional changes over time (e.g. is CPI increasing, decreasing or stable?). Whether a rise, a fall or a plateau in CPI is indicative of good/poor clinical status remains to be seen with future investigations.

Future directions

It is worth noting that central haemodynamics can be monitored in LVAD patients via implantable devices, such as the wireless measurement of pulmonary artery pressure via the CardioMEMS system (CardioMEMS Heart Failure System, St. Jude Medical Inc., Atlanta, GA, USA). Certainly, these systems may prove cost-effective in the management of heart failure patients, and possess a strong potential for the benefit of patients with LVADs.[34] However, it is emphasized that non-invasive haemodynamic assessments, such as that provided by the CPI in this study, provide no additional risk to patients, and can be implemented conveniently, at low cost in the home environment. Further to this point, not only may the CPI be useful for home-based haemodynamic monitoring of LVAD protocols, but may also show potential for use in weaning protocols and non-echocardiographic monitoring of aortic regurgitation progression post-LVAD implantation. Importantly, new assist devices that provide artificial pulsatility (e.g. HeartMate III, St. Jude Medical Inc., Atlanta, GA, USA) may lower the rates of serious adverse outcomes in LVAD patients.[35] These findings contribute to the growing discussion of whether the incorporation of artificial pulsatility into LVADs will improve post-implantation rates of aortic regurgitation, left ventricular recovery, pulmonary vascular remodelling, and so on.[36–38] Moving forward, we foresee that the CPI developed in this study may serve as a practical and convenient research tool to be used in future studies that require longitudinal tracking of residual arterial pulsatility across various modes of pump operation in these new assist devices (i.e. synchronous vs asynchronous modes). Certainly, it would be prudent to next examine whether the CPI accurately tracks larger, more longer-term changes in arterial pulsatility within a given LVAD patient (e.g. across weeks/months), as opposed to the relatively small temporal window used in the present investigation (< 30 min).

Conclusions

The present study provides details on a non-invasive method of extracting a 'pulsatility index' (the CPI) from a cuff pressure waveform during suprasystolic occlusion of the upper arm in LVAD patients. The CPI appears to accurately track changes in invasively determined arterial pulsatility *within* a given LVAD patient. However, further studies are needed to improve the method such that comparisons can be made *between* LVAD patients, and later be used to explore relationships between CPI and other relevant clinical outcomes (e.g. gastrointestinal bleeding, right heart failure, maximal aerobic capacity, etc.).

Off-label use/unapproved drugs or products

This article includes data from investigational use of the device. Use of the non-FDA (Food and Drug Administration) approved device was approved by the Mayo Clinic ethic committee (Institutional Review Board) for purpose of this study.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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APPENDIX A5

FABIAN, V., MATERA, L., BAYEROVA, K., HAVLIK, J., KREMEN, V., PUDIL, J., SAJGALIK, P., ZEMANEK, D. Noninvasive Assessment of Aortic Pulse Wave Velocity by the Brachial Occlusion-Cuff Technique: Comparative Study. *Sensors*, 2019, 19.16: 3467. ISSN 1424-8220.
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Noninvasive Assessment of Aortic Pulse Wave Velocity by the Brachial Occlusion-Cuff Technique: Comparative Study

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Abstract: Cardiovascular diseases are one of most frequent cause of morbidity and mortality in the world. There is an emerging need for integrated, non-invasive, and easy-to-use clinical tools to assess accurately cardiovascular system primarily in the preventative medicine. We present a novel design for a non-invasive pulse wave velocity (PWV) assessment method integrated in a single brachial blood pressure monitor allowing for up to 100 times more sensitive recording of the pressure pulsations based on a brachial occlusion-cuff (suprasystolic) principle. The monitor prototype with built-in proprietary method was validated with a gold standard reference technique SphygmoCor VX device. The blood pressure and PWV were assessed on twenty-five healthy individuals (9 women, age (37 ± 13) years) in a supine position at rest by a brachial cuff blood pressure monitor prototype, and immediately re-tested using a gold standard method. PWV using our BP monitor was (6.67 ± 0.96) m/s compared to PWV determined by SphygmoCor VX (6.15 ± 1.01) m/s. The correlation between methods using a Pearson's correlation coefficient was r = 0.88 ($p < 0.001$). The study demonstrates the feasibility of using a single brachial cuff build-in technique for the assessment of the arterial stiffness from a single ambulatory blood pressure assessment.

Keywords: arterial stiffness; pulse wave velocity; suprasystolic blood pressure; single-cuff

1. Introduction

Cardiovascular diseases are one of the most important causes of morbidity and mortality in the world. Known risk factors include smoking, arterial hypertension, hyperlipidemia, diabetes, metabolic syndrome, etc. Although cardiovascular mortality has declined in developed countries as a result of better treatment and prevention in recent decades, the identification of individuals with higher risk is very important and can prevent severe consequences [1]. Early preventive intervention can lead to delaying or even averting their manifestations. Besides the blood pressure (BP), arterial stiffness is one of options to assess the risks since it is associated with pathophysiology of arterial hypertension and is often evaluated by measuring pulse wave velocity (PWV). In particular, the aortic stiffness is one of determinant of the absolute central versus peripheral BP (e.g., arm) difference; it has been recognized

as a significant factor of cardiovascular health, and as an important index for prediction of arterial hypertension and a high BP [2]. In general, arterial stiffness quantifies mechanical properties of the arterial wall is an independent predictor for fatal and non-fatal cardiovascular events in hypertensive patients. Ultimately, it provides an added value above and beyond traditional risk factors, which was recognized in a number of studies [3,4]. Although the relationship between aortic stiffness and events is continuous, a threshold value is 10 m/s in middle-aged hypertensive patients can differentiate those with higher cardiovascular risk [5].

The most common equation which describes the arterial stiffness is the relationship between change in pressure (ΔP) and change in volume (ΔV). Structurally, elastin, collagen and smooth muscles are the main components of the large conduit arteries and this composition is changing during ageing, which is closely associated with developing the arterial stiffness and hypertension.

Aortic higher PWV represents a consequence of arterial stiffness. The PWV is related to the wall stiffness, vessel geometry and blood density. These relationships are described by Moens-Korteweg equation [6,7]. A carotid-femoral PWV is often considered as a gold standard for a non-invasive measurement of PWV [8]. Nowadays, it is the only method, which is accurate enough to be considered as a diagnostic method and describes the PWV in the aorta. The PWV is calculated as a ratio of a distance between carotid and femoral artery and pulse transit time between these two points.

There are few non-invasive methods for the evaluation of arterial stiffness and PWV. In the current clinical practice, the SphygmoCor technology (AtCor Medical, Australia), and VaSera (Fukuda, Japan) devices are the most frequently used. The SphygmoCor technology uses applanation tonometry for obtaining the pulse wave from the carotid and femoral arteries and estimates PWV from the delay between pulse waves on the carotid and femoral arteries with respect to ECG [9–12]. The VaSera device uses the four-cuff oscillometric system with the ECG recording and an amorphous pulse wave sensor placed on the carotid and the femoral arteries. The device estimates several parameters correlated with arterial stiffness, especially the PWV and CAVI index [13–17]. These devices are relatively expensive and requires trained technician for accurate results, which is disadvantageous for implementing in the wider general internal, and preventative offices. Another method for PWV estimation is Arteriograph (Tensiomed, Hungary). The Arteriograph technology uses a different approach than the SphygmoCor technology and VaSera devices in principle. The Arteriograph technology uses an analysis of oscillometric pulsations detected in the brachial artery for indirect estimation of PWV by the difference in time between the beginning of the first (forward) and the second (reflected) pulse wave. This delay corresponds to the distance between the jugulum and the symphysis. The method does not use ECG recording [9]. Since the Arteriograph uses a single cuff for data acquisition, the practical use is remarkably higher, however the signal processing requires sophisticated signal processing for obtaining required parameters.

For the purpose of this study we utilized a newly developed proprietary principle [18] for non-invasive recording of highly accurate raw signal of blood pressure waveform requiring minimal filtering without introducing a potential bias in the PVW assessment. This technique stands out as a single brachial cuff technique and a viable platform for development an easy-to-operate complex hemodynamic monitor, which could deliver information about peripheral BP, PWV, and estimate central blood pressure during a one short patient visit. As such, this technique will be well suitable in the preventive and family care medicine. We hypothesize that the below proposed concept of integrated hemodynamic monitor will overcome practical disadvantages of gold standard methods (requiring more than one signal from the human body for PWV analysis) and yet delivering reliable and validated results in a user-friendly design.

2. Materials and Methods

2.1. Amended Brachial Occlusion-Cuff Technique

For the purpose of the study, we have developed a prototype of BP monitor using unique hardware and software features. In principle, the device is based on settle detection of pressure pulsations from brachial arm cuff, which is pressurized (35–40) mm Hg above systolic pressure. This pressure is called a 'suprasystolic' or 'stop flow'. During this pressure, the brachial artery is completely occluded and the propagating pulse waves, created by contraction of the left ventricle and the ejection of blood into the aorta, are completely transmitted through arm cuff to pressure sensors.

Very sensitive differential pressure sensor (range ± 3.8 mm Hg) enables to detect even very weak pressure pulsations. The block diagram of the pneumatic part of the device is shown in Figure 1. Upon reaching the suprasystolic pressure, the closing valve is closed, and the reservoir is pneumatically separated from the cuff. Thus, at the differential sensor output we see only superimposed pressure pulses from the cuff. Conventional devices use gauge pressure sensors with a range of at least 300 mm Hg to detect pressure pulses. With this differential pressure sensor is our method 40 times more sensitive compared to these conventional devices. It eliminates the disadvantages of existing devices, in particular the necessity of using a compensation filter or derived models [18].

The typical pulse wave obtained by averaging of several acquired cardiac cycles is shown in Figure 2. During the data evaluation, the signal of each cardiac cycle is divided into segments separated by significant peaks. The first one is a systolic peak (S), which corresponds to contraction of the left ventricle. The consequent peaks detected by differential pressure sensor are systolic peak reflected from iliac bifurcation (R) and a delayed diastolic peak reflected from the lower body (D).

The time interval between S and R is ΔT and it is the time, which takes the pulse wave to travel from the arch of aorta to iliac bifurcation and back to brachial artery, where is the pulse wave detected. The iliac bifurcation is known as a main source of the reflection of the systolic peak.

The distance, which traveled the measured pulse wave, was determined as a distance between the jugulum and the half of distance between umbilicus and symphysis.

The developed device consists of 3 pressure sensors (two gauge pressure sensors, one differential pressure sensor), an electric pump, a brachial arm cuff, two valves and electronic circuits.

The analog outputs from pressure sensors are amplified and digitized by the BIOPAC MP36 system, which uses 24-bit sigma-delta A/D converter (SNR: > 89 dB min Tested at lowest Gain at 1000 s/s with grounded front end, CMRR: 110 dB minimum at 50/60 Hz) with a sampling frequency 200 Hz. The BIOPAC MP36 system was used because it meets the high medical regulations for medical devices.

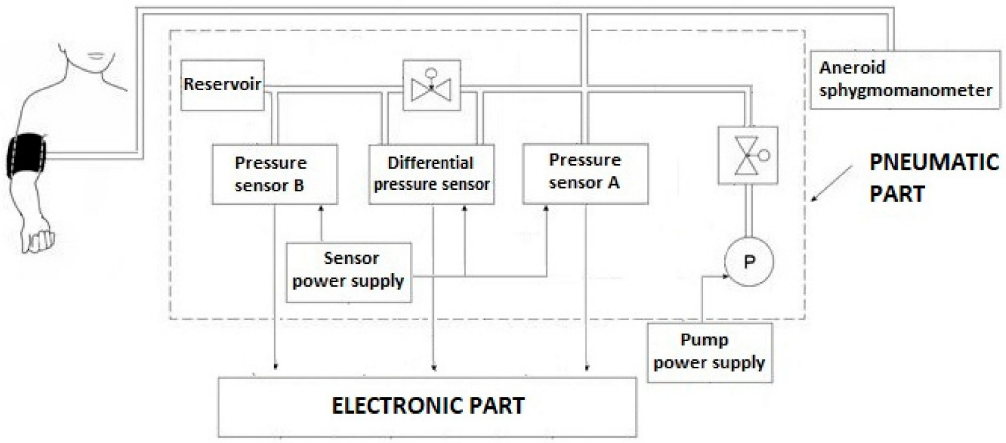

Figure 1. Pneumatic part of experimental device [18].

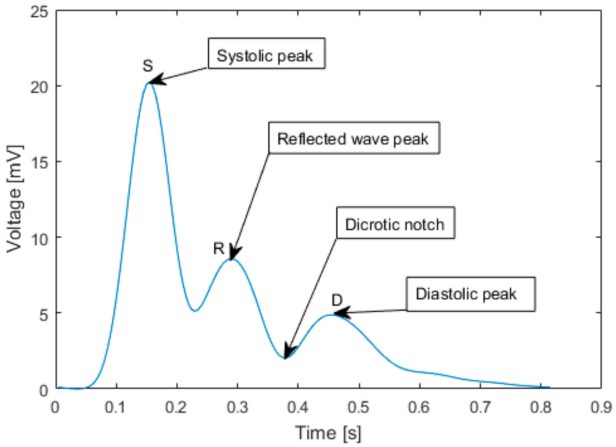

Figure 2. The typical pulse wave acquired from the left brachial artery by the arm cuff inflated to suprasystolic pressure. Systolic peak (S) corresponds to contraction of the left ventricle, Reflected wave peak (R) corresponds to reflected wave from iliac bifurcation and Diastolic peak (D) corresponds to the delayed reflected wave from the lower body.

2.2. Measurement Protocol

Measurements were performed in cooperation with 2nd Department of Internal Medicine—Cardiology and Angiology of General University Hospital and 1st Medical Faculty of Charles University (Prague, Czech Republic). All subjects signed the informed consent approved by the local ethical committee.

Before the beginning of the measurement, the physician measured the blood pressure of the subject in a sitting position. After that, the subject moved to the supine position and after 10 min of rest the first phase of the measurement started. The PWV of the subject was first measured with SphygmoCor VX according methodology [5], i.e., it was taken two measurements and if the difference between the two measurements was more than 0.5 m/s, it was performed a third measurement and the median value was used. That took approximately twenty minutes and after that, we continued with measurement using the prototype of the device. All SphygmoCor measurements were performed by the same physician.

The second phase of the measurement began with inflation of the arm cuff (standard OMRON CM2 cuff) in the pneumatic part of the measurement system to the suprasystolic pressure by an electrical pump. As was mentioned, the suprasystolic pressure is about (35–40) mm Hg above systolic pressure. The arm cuff was inflated about 5 mm Hg even more because of the stabilization the pressure in the pneumatic part and also because of the pressure drop, which was about 2 mm Hg per minute. After the stabilization of the pressure in the circuit, the mechanical valve was closed and the pressure pulsations from brachial arm cuff were sensed by the differential pressure sensor.

After twenty seconds of the suprasystolic pressure pulsations measurement the mechanical valve was turned back to open state and the valve was released the pressure out of the arm cuff and the whole pneumatic circuit by electromagnetic decompression. The pressure in the cuff was recorded, and values were continuously stored in the memory of the device (sampling frequency F_s = 200 Hz). Similarly, we took two measurements and if the difference between the two measurements was more than 0.5 m/s we performed a third measurement and used the median value. All measurements were instrumented by an identical qualified technician.

As a distance for PWV evaluation, we used a distance ref. equation defined by:

$$DIST_{PWV} = |JUG\text{-}UMB| + |UMB\text{-}SYM|/2 \quad (1)$$

where |JUG-UMB| is a distance between jugulum and umbilicus and |UMB-SYM| is a distance between umbilicus and symphysis.

2.3. Study Population

All participants were healthy volunteers from hospital staff. Each volunteer was familiar with the measurement and gave informed consent to participate in the research. A total of 25 participants were measured during the study (9 women). Table 1 displays demographics of the study participants. Exclusion criteria were: second level of obesity, defined by body mass index (BMI) > 35 kg·m^{-2}, systolic blood pressure (SBP) > 180 mm Hg or diastolic blood pressure (DBP) > 120 mm Hg, which means a hypertensive crisis, the history of any cardiovascular diseases, a taking of any regular medication or subjects with an arm circumference that was outside the range of (23–32) cm. After the measurements, participants with the reporting signs of any cardiac arrhythmias were also excluded from the study (one man, AF) and also participants, whose data was not possible to evaluate because of erroneous readings from the SphygmoCor VX (one subject), or from the experimental device (one subject). One woman was not included in the study because of her pregnancy, which was found afterwards. Nobody had diabetes and only two were smokers. All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of General University Hospital, Prague, Czech Republic (Project identification code: 89/16 Grant VES 2017 AZV VFN), 23 June 2016.

Table 1. Study participants.

Subject No.	Sex	Age (Years)	Height (cm)	Weight (kg)	BMI (kg·m^{-2})	BMI Classification	SBP (mm Hg)	DBP (mm Hg)
1	F	23	165	60	22.0	Normal weight	127	75
2	M	21	193	86	23.1	Normal weight	151	72
3	M	66	178	94	29.7	Overweight	167	86
4	M	36	188	86	24.3	Normal weight	151	87
5	F	50	170	69	23.9	Normal weight	127	82
6	F	54	173	64	21.4	Normal weight	117	65
7	F	53	167	63	22.6	Normal weight	151	94
8	M	34	190	80	22.2	Normal weight	127	80
9	M	32	180	92	28.4	Overweight	122	63
10	F	40	174	73	24.1	Normal weight	125	74
11	M	46	183	105	31.4	Obesity Class 1	122	67
12	M	25	180	75	23.1	Normal weight	126	66
13	F	23	173	67	22.4	Normal weight	122	74
14	F	42	172	62	21.0	Normal weight	118	70
15	F	39	165	62	22.8	Normal weight	116	72
16	M	35	174	71	23.5	Normal weight	112	68
17	M	21	184	108	31.9	Obesity Class 1	128	68
18	M	21	180	75	23.1	Normal weight	106	68
19	M	41	192	86	23.3	Normal weight	118	68
20	M	29	198	110	28.1	Overweight	126	72
21	M	53	176	75	24.2	Normal weight	118	72
Mean ± STD		37.3 ± 12.6	178.8 ± 9.2	79.2 ± 15.2	24.6 ± 3.2		127.5 ± 14.7	73.5 ± 7.9

2.4. Data Evaluation

PWV was determined using a custom GUI software in MATLAB Inc. In the first part of algorithm, we choose only an effective part of measured signals. The algorithm is applied only to the parts of the data, where suprasystolic pulse waves were measured. The data where the pneumatic leaks caused distortions were filtered by algorithm for baseline wander removing (polynomial fitting and designed high-pass FIR filter). High-pass FIR filter with cut-off frequency of 0.5 Hz designed by Hamming window was used to remove isoline by polynomial fitting for every suprasystolic pulsation. To remove high frequency noise, caused by breathing, moving artifacts, electromagnetic artifacts with higher frequencies, and the frequency 50 Hz, caused by line noise interference, we used a low-pass FIR filter with cut-off frequency 20 Hz.

The determination of PWV during suprasystolic pressure depends on the right detections of systolic peaks and reflected wave peaks (Figure 2), caused by reflection in aortic bifurcation, which is supposed to be the main source of wave reflection [19]. We based our detection algorithm on the first and second

order difference combined with thresholding. The identified potential, systolic as well as reflected peaks, was then compared with criteria, which was used for the determine a PWV. The time difference between two suprasystolic waves had to be in the interval of HR (30 < HR < 200) beats/min. As a secondary criterion, each value of PWV that exceeded a physiological interval (3 < PWV < 15) m/s was considered as an artefact and was excluded from the results [20]. The PWVs, which values were different than (MEAN ± 1.96·STD) were also excluded and the final PWV was to be determined at least from 5 suprasystolic pulse waves.

2.5. Statistical Analysis

The statistical analysis was performed in MATLAB Inc. software statistical toolboxes. The data were divided into quantitative and qualitative groups. The quantitative data were summarized by their MEAN ± STD values (Table 1) the qualitative by percentage representations in the dataset. The error analysis is in the detail described in the discussion. The comparative analysis included Bland-Altman plots, regression analysis, Pearson correlation analysis and Lin's concordance correlation coefficient. Bland-Altman plots shows a graphical representation of the comparison between two methods by analysis of their means and differences and show a potential sign of correlation [21], which was determined by Pearson's correlation coefficient. To confirm relationship between measurements, we also calculated Lin's concordance correlation coefficient [22]. To define linear association and its regression coefficients we calculated a linear regression analysis. All analyses were two-tailed and associated p values of less than 5% were taken as indication of statistical significance.

3. Results

Patients' demographics are described in Table 1. From a total number of 25 participants, 21 were included in the analysis. The reasons for exclusion of 4 participants are described in the study population section of the methods. The mean age of 21 subjects (8 women) was 37 ± 13 years (21 to 66 years). Regarding to one BP, there was only one hypertensive patient and according to BMI, only two of them had first class obesity and higher.

The multivariate linear regression ($p < 0.001$) confirmed the hypothesis about PWV as an age dependent parameter. Other characteristics did not have so strong correlation in this study sample.

The mean PWV measured by novel cuff-based method was (6.67 ± 0.96) m/s compared to SphygmoCor VX (6.15 ± 1.0) m/s. The mean difference between methods was (0.61 ± 0.35) m/s. According to Artery society guidelines [23] that describes the process of validating new device for PWV measurement, a new device is acceptable, if the mean difference with standard deviation of results between the validated device and the ground truth device is not more than (1.0 ± 1.5) m/s. Figure 3 graphically displays a non-significant difference ($p > 0.05$) between measurements of both devices.

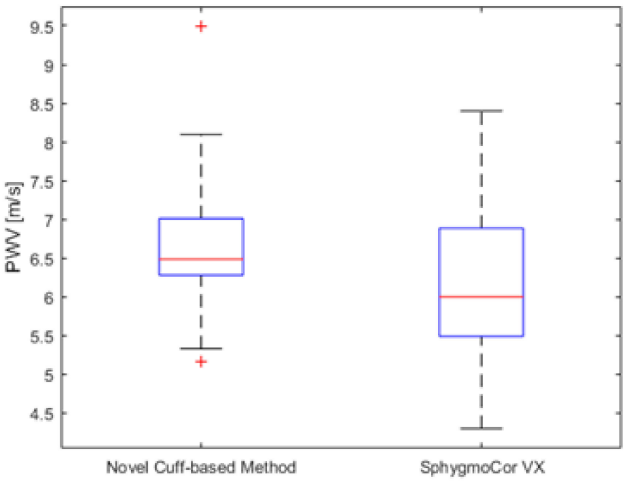

Figure 3. Device comparison of PWV measurements.

Pearson's correlation coefficient r = 0.88 ($p < 0.001$) and Lin's concordance correlation coefficient r = 0.77 confirmed a relationship between the novel cuff-based method and SphygmoCor VX, which determines cfPWV a gold standard (ground truth) in PWV measurement. Bland-Altman plot (Figure 4) graphically displays a comparison of methods in our dataset and shows the measurements that differ from the mean value more than ± 1.96·STD (95% confidence interval). In our case, there were only two values outside this confidence interval (10%).

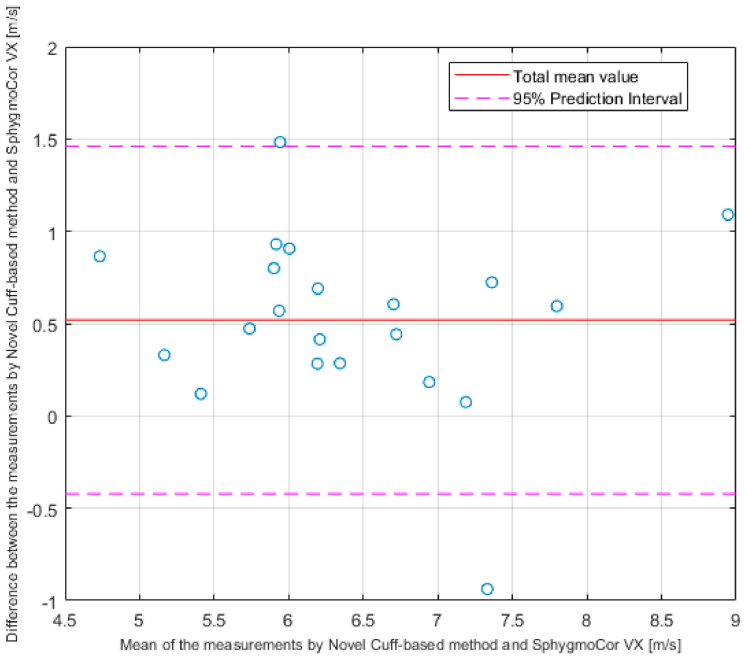

Figure 4. Bland-Altman plot.

4. Discussion

The aim of the study was to present a novel, proprietary method for ad non-invasive measurement of PWV based on the cuff occlusion and to test how the method compares to ground truth using a gold standard measurement device SphygmoCor VX. The vision of this novel method is to provide a non-invasive, fast, easy, and yet precise determination of hemodynamic parameters without a need of having trained personnel performing the measurement. SphygmoCor allows to measure hemodynamic parameters that are used to assess static and dynamic variables of the cardiovascular system. One of a few hemodynamic parameters, which could be determined by SphygmoCor VX is carotid-femoral PWV (cfPWV) [24]. The cfPWV is traditionally used as a gold standard for PWV measurements and is considered as one of the most important predictors of arterial stiffening, an important feature of cardiovascular system. Arterial stiffness is recognized as a significant factor of cardiovascular health and potentially as an important index of prediction of hypertension and high pulse pressure. SphygmoCor VX was chosen as a reference for comparison with our method because its widely use in the Europe, where cfPWV is considered as a key parameter for arterial stiffness prediction, unlike in Asia regions, where is more common to predict arterial stiffness by brachial-ankle PWV (baPWV).

SphygmoCor VX is based on the applanation tonometry principle with simultaneous measurement of synchronous ECG. It works as a time reference for determination of cfPWV and results in sequential-based measurement, which, amongst others, results in longer estimation time. The measurement should be provided by trained physician or technician and has to follow strict protocol to obtain reliable results. Our method removes these limitations of having ECG, trained specialist, and strict protocol. This new method is standardized, cuff-based measurement with a fully automatic control of the pressure in the brachial cuff. The measurement is very short, repeatable and

can be carried easy in clinic or even in the home environment, and thus suits well for screening and disease prevention

The results have shown a high correlation between both methods (r = 0.88, $p < 0.001$). All the readings, except one, lay in the ± 1.96·STD of the mean value. The analysis of the differences between values (0.61 ± 0.35) m/s described by B-A plot shown the trend of the shift. According to the artery society, this result can be taken as an acceptable and close to an excellent result [23]. Based on these results we can say that the method systematically measures slightly higher PWV values than the ground truth SphygmoCor VX device. This systematic error is given by methodologically imperfect measurement of the distance described above. As was previously described in the study [25], it is possible to use umbilicus as a mark for the AB. Our method used a distance that was taken closer to symphysis (Equation (1)) to try to be in the middle of the 80% population interval for the generation of the main reflected wave. This 'higher' landmark resulted in systematic estimation of distance shorter than actually is and it caused a difference of means (0.52 m/s). This conclusion was also confirmed by the linear regression analysis (Figure 5), where the shift was also observed.

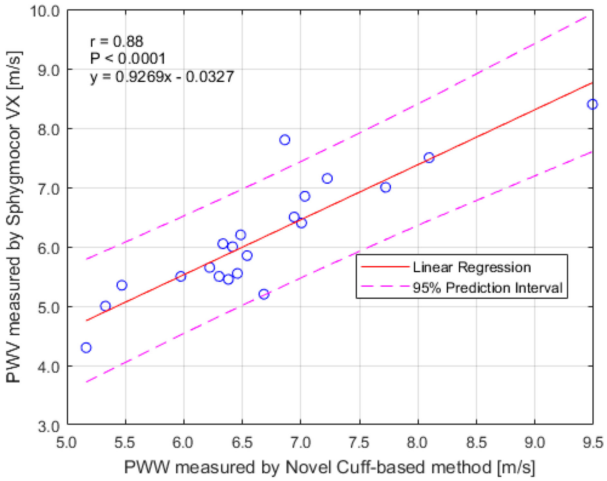

Figure 5. Linear regression.

Despite of the pros of the method, there are several limitations that needs to be considered. Most of them are caused by random and systematic errors during the measurement itself. First limitation is the precision of a manual measurement that determines the aortic bifurcation (AB), which is considered as a main source of the forward wave reflection. The precision of AB determination and its distance from the jugulum is one of the most important parameters in the computation of the PWV. According to the study [25], it is possible to get close to the real position of the AB, but only in 80% of the population is AB and close surroundings taken as the main source of the reflection [19]. In the rest of them, the source of the reflection is moved closer to the femoral sites, which makes the distance longer. This also depends on the shape of the aorta. There are few factors that change the shape and subsequently the distance of traveling of the pulse wave. However, our study population had wide range of height (from 165 cm to 198 cm), and the results show that the correlation of results from both devices is still good across all subjects of the group. This is a clear limitation of our method in face of methods with ECG synchronization and sequential measurements that get the distance precise because of the known positions of the pulse wave acquisition sensors. The other important systematic error during the data recording is caused by a resolution of tape measure, sampling frequency, and leakages in the pneumatic circuit and comes with the data evaluation by developed algorithms. These algorithms do filtering, averaging, and peak detection to find maximums of the forward and the reflected wave in the signal to estimate the times of propagation. Sometimes a various shapes and amplitudes of every reflected waves lead in a total dampening of the reflected wave so there is no maximum but only

an inflection point in the forward primary wave and seemed to be a very challenging and difficult to detect automatically. To deliver a high-quality automated monitor, further studies need to be focused on the optimization of the pneumatic system, precise determination of aortic bifurcation distance, and development of the algorithms for the accurate recognition of the primary and reflected waves in situation of contra-phase coupling.

5. Conclusions

Our results confirmed that the novel design of single brachial-cuff technique generating high fidelity signal compares very closely with the current gold standard method SphygmoCor VX for PVW assessment. Results have also shown that PWV is an age-dependent parameter, where the PWV is increasing with the age because of the loss of the elasticity of aortic walls and their calcification. Since the clinical need is to recognize the alterations of cardiovascular system prior developing organ complications, the presented technique can be used in the home monitoring and primary care setting.

A proprietary hardware solution allows for building the presented design in a standard non-invasive brachial cuff blood pressure monitor. The simplicity of use, yet ability to provide consistent results strongly supports feasibility of the proposed solution in preventive care and can be translated into clinical practice.

Author Contributions: Conceptualization, V.F. and D.Z.; methodology, D.Z. and P.S.; software, L.M. and V.K.; validation, L.M. and J.H.; formal analysis, V.K.; investigation, L.M., K.B. and J.P.; resources, D.Z.; data curation, L.M.; writing—original draft preparation, V.F.; writing—review and editing, D.Z., P.S. and V.K.; visualization, L.M.; supervision, D.Z.; project administration, V.F.; funding acquisition, V.F. and D.Z.

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Conflicts of Interest: The authors declare no conflict of interest.

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APPENDIX A6

SAJGALIK, P., KREMEN, V., CARLSON, A., R., FABIAN, V., KIM, C., WHEATLEY, C., GERLA, V., SCHIRGER, J., A., OLSON, T., P., JOHNSON B., D. Noninvasive assessment of cardiac output by brachial occlusion-cuff technique: comparison with the open-circuit acetylene washin method. *Journal of Applied Physiology*, 2016, 121.6: 1319-1325. ISSN 8750-7587.
DOI 10.1152/japplphysiol.00981.2015.

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Noninvasive assessment of cardiac output by brachial occlusion-cuff technique: comparison with the open-circuit acetylene washin method

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[1]*Department of Internal Medicine; Division of Cardiovascular Diseases, Mayo Clinic & Foundation, Rochester, Minnesota;* [2]*1st Department of Internal Medicine, Cardio Angiology-International Clinical Research Center, Masaryk University; Brno, Czech Republic;* [3]*Czech Institute of Informatics, Robotics, and Cybernetics, Czech Technical University in Prague, Prague, Czech Republic; and* [4]*Department of Physics, Czech Technical University in Prague, Prague, Czech Republic*

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Sajgalik P, Kremen V, Carlson AR, Fabian V, Kim C, Wheatley C, Gerla V, Schirger JA, Olson TP, Johnson BD. Noninvasive assessment of cardiac output by brachial occlusion-cuff technique: comparison with the open-circuit acetylene washin method. *J Appl Physiol* 121: 1319–1325, 2016. First published October 20, 2016; doi:10.1152/japplphysiol.00981.2015.—Cardiac output (CO) assessment as a basic hemodynamic parameter has been of interest in exercise physiology, cardiology, and anesthesiology. Noninvasive techniques available are technically challenging, and thus difficult to use outside of a clinical or laboratory setting. We propose a novel method of noninvasive CO assessment using a single, upper-arm cuff. The method uses the arterial pressure pulse wave signal acquired from the brachial artery during 20-s intervals of suprasystolic occlusion. This method was evaluated in a cohort of 12 healthy individuals (age, 27.7 ± 5.4 yr, 50% men) and compared with an established method for noninvasive CO assessment, the open-circuit acetylene method (OpCirc) at rest, and during low- to moderate-intensity exercise. CO increased from rest to exercise (rest, 7.4 ± 0.8 vs. 7.2 ± 0.8; low, 9.8 ± 1.8 vs. 9.9 ± 2.0; moderate, 14.1 ± 2.8 vs. 14.8 ± 3.2 l/min) as assessed by the cuff-occlusion and OpCirc techniques, respectively. The average error of experimental technique compared with OpCirc was −0.25 ± 1.02 l/min, Pearson's correlation coefficient of 0.96 (rest + exercise), and 0.21 ± 0.42 l/min with Pearson's correlation coefficient of 0.87 (rest only). Bland-Altman analysis demonstrated good agreement between methods (within 95% boundaries); the reproducibility coefficient (RPC) = 0.84 l/min with $R^2 = 0.75$ at rest and RPC = 2 l/min with $R^2 = 0.92$ at rest and during exercise, respectively. In comparison with an established method to quantify CO, the cuff-occlusion method provides similar measures at rest and with light to moderate exercise. Thus, we believe this method has the potential to be used as a new, noninvasive method for assessing CO during exercise.

noninvasive; cardiac output; occlusion; brachial cuff

NEW & NOTEWORTHY

This study provides an initial assessment of a new non-invasive technique for estimating cardiac output. We compared cardiac output derived from a novel formula adapted for the brachial occlusion method to the previously validated open circuit acetylene method. Both techniques provided similar estimates of cardiac output at rest and during exercise. Accordingly, this technique may provide an alternative method to non-invasively assess cardiac output in a wide range of environmental conditions.

SUFFICIENT CARDIAC OUTPUT (CO) is an essential component in maintaining the metabolic homeostasis of peripheral organs. Maximal CO determines the amount of blood available for delivery to working muscles, it directly influences performance, and therefore is of interest in exercise physiology (2). In addition, peak exercise CO serves as a powerful prognostic marker in heart failure (HF), and repeated invasive measurement of CO is currently a part of diagnostic testing in advanced HF (28, 37). Since the Fick (17) principle was introduced in 1870, a method to estimate CO that avoids blood sampling has been sought, yet the invasive thermodilution method developed by Fegler (16) in 1954 has been broadly accepted in clinical practice. An indirect Fick method of analyzing expired gases instead of blood samples was the first noninvasive method of an effective CO estimate (12). Although the gold standard for the most accurate CO assessment remains the direct Fick method (15, 40), several rebreathing techniques have been evaluated and used to measure noninvasive CO at rest and during exercise (24, 26). These methods require nonportable, sophisticated equipment, technical expertise, and subject cooperation. Advances in ultrasound imaging with Doppler allow noninvasive CO estimates with moderate precision compared with thermodilution at rest and during light exercise (correlation 0.85 and 0.84, respectively) (13, 36). Advantages include portability, broad use in emergency situations in hospitals, and minimal subject cooperation; however, the equipment necessary for echocardiographic CO estimates is expensive and requires a trained ultrasound technician to acquire quality images. High image quality during the exercise at higher workloads remains a challenge.

Verdouw et al. (47) in 1975 tested limitations of most known mathematical algorithms developed for CO estimates from intra-arterial blood pressure (BP) waveforms. Despite the fact that many of these pulse contour methods (PCMs) have shown adequate relationships to traditional methods, other studies have suggested wide variation over a broad range of hemodynamic changes (3, 26, 32, 34, 43–45, 49).

To overcome limitations of invasive PCMs based on intra-arterial BP curve and to allow continuous monitoring, a finger cuff method has been used to measure CO. In this method, CO is derived from the volume clamp principle of continuous BP monitoring as first described by Czech physiologist Penáz (41, 45). However, the accuracy of the method relies significantly on the quality of finger BP recording, which can be limited due

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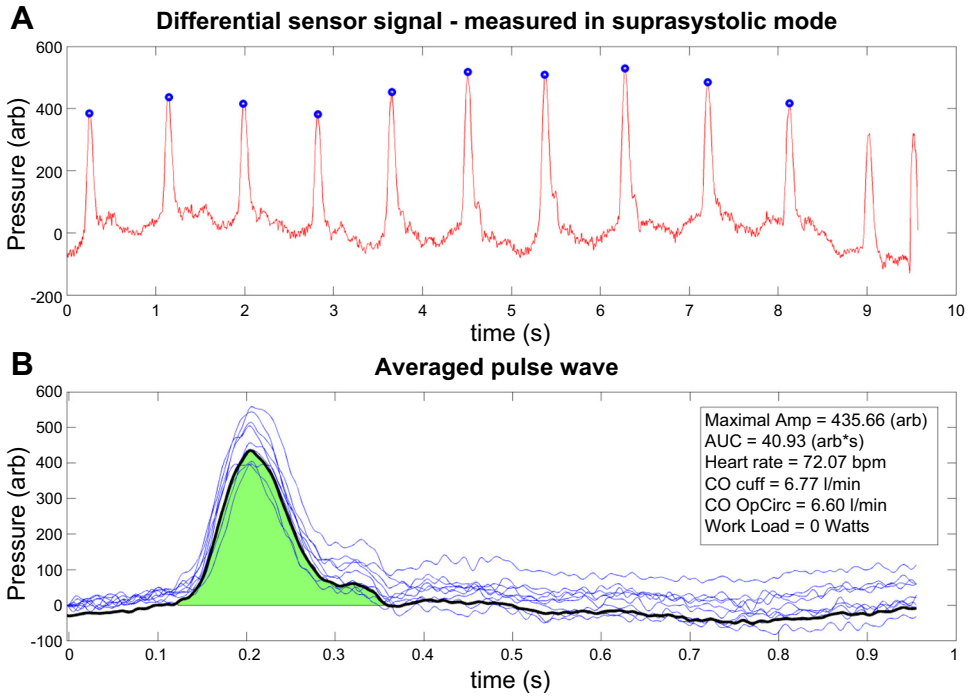

Fig. 1. Supervised semiautomated analysis of cardiac output (CO) using the noninvasive, single cuff method at rest. *A*: raw signal is analyzed, and only beats with an optimal signal quality are selected (indicated by a blue marker). *B*: average beat curve is calculated from selected beats and heart rate, area under the curve (AUC), and maximal peak amplitude (Maximal Amp) are extracted. CO is then calculated based on *Eq. 1*. CO cuff, CO output assessed by the cuff method; CO OpCirc, CO assessed by the comparative Acetylene wash-in method.

to any cause of profound centralization of circulation. Restricted peripheral circulation in cold conditions and finger movements during exercise are common causes of reading error (23, 29).

The brachial cuff-occlusion method was originally developed as a noninvasive measurement of the aortic pulse wave velocity (PWVao), central BP, and augmentation index (Aix) by analysis of wave reflections superimposed on calculated central BP waveforms obtained during occluded conditions from the upper part of the brachial artery (22). Because this method yields a clean arterial pressure curve with a high correlation to the invasively measured arterial curve (22), we propose to use this approach to quantify CO at rest and during exercise. We introduce and test a formula that is not dependent on an often problematic experimentally set constant. We propose that the cuff-occlusion technique will compare closely with a validated method for determining CO, the open-circuit acetylene (OpCirc) method (26), at rest and during exercise. As such, some of the limitations of the finger volume-clamp method introduced by recording BP from the acral circulation could be overcome. In addition, the cuff-occlusion technique has advantages over the volume-clamp method in its technical simplicity and the ability to apply a less complex equation for stroke volume.

METHODS

Subjects. All aspects of the study were approved by the Mayo Clinic Institutional Review Board and conformed to the Declaration of Helsinki. Thirteen healthy adult subjects with no history of tobacco use were recruited from the surrounding community of Rochester, MN, and provided written informed consent. With one exception, all subjects maintained various levels of physical activity, mostly recreational, during the time of the study.

Exercise protocol. Subjects participated in one submaximal exercise study. CO measurements were performed simultaneously using an experimental brachial occlusion-cuff method and the OpCirc method as described previously (7, 8, 26). All measurements were carried out in an upright position. At baseline, participants were seated on an upright cycle ergometer (Corival, type 906902 V 1.01; Lode B.V. Medical Technology, Groningen, The Netherlands). For gas analysis, the Marquette 1100 (The Mass Spectrometer Experts, St. Louis, MO) integrated with Medical Graphics CPXD (Medical Graphics, St. Paul, MN) was used as described previously by Johnson et al. (26) Subjects breathed into a mouthpiece only during the time of CO measurement. A single inflatable arm cuff with size based on arm circumference with 5 cm of overlap (3 cm above the cubital fossa) was wrapped around the left arm over the brachial artery (the cuff was identical to a standard OMRON CM2 cuff) and connected to the prototype BP monitor developed initially by Fabian et al. (14, 19). After 3 min of rest, systemic arterial BP was measured by the auscultatory method before the experiment. CO and standard BP measurements (according to the British Hypertension Society evaluation protocol for oscillometric BP measurement devices) were then assessed twice within 2–4 min to allow a complete inert gas washout from the lungs. Consequently, on the basis of the estimated fitness of each participant, a submaximal protocol consisting of three levels of exercise intensity was performed for 4 min at each level. Measurements of CO were carried out using both methods simultaneously at *minutes 3* and *4* at each stage of exercise resulting in a total of eight CO measurements (including rest) for each participant, along with BP assessed at the end of the last stage. During the data acquisition periods, subjects were encouraged to remain still, breathe in a regular rhythm, avoid coughing or swallowing, take partial breaths, and fully relax the left arm to minimize any muscle activity, if possible.

Occlusion-cuff method for estimating CO. Each measurement with the experimental cuff method consisted of the following steps: the cuff was pressurized to 190 mmHg for 20 s, and the raw BP curve data were recorded on a prototype BP monitor (Figs. 1*A* and 2*A*). Measured values were continuously stored in the memory of the device at a sampling rate of Fs = 400 Hz. No other filtering was used during the hardware measurement phase. Semiautomatic signal postprocessing was performed as follows. Stored signals were filtered to reduce high-frequency noise (Butterworth filter of second order with a cutoff frequency 50 Hz). A trained operator selected uniform beats with a characteristic pattern that was not

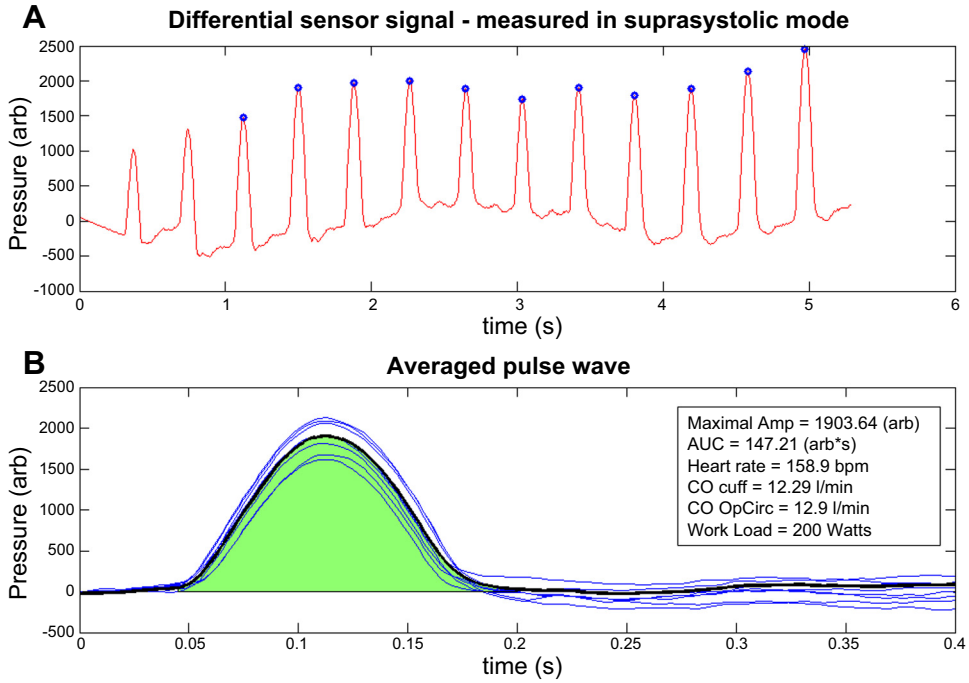

Fig. 2. Supervised semiautomated analysis of CO using the noninvasive, single cuff method during exercise. *A*: raw signal is analyzed, and only beats with an optimal signal quality are selected (indicated by a blue marker). *B*: average beat curve is calculated from selected beats and heart rate, AUC, and Maximal Amp are extracted. CO is then calculated based on *Eq. 1*.

influenced by artifacts (Figs. 1 and 2). Thus, beats that were partially dropped or had sudden changes in configuration (e.g., baseline shift) due to arm/muscle movement were excluded. Examples of typical beats are indicated by a marker (blue dot at pressure curve vertices), whereas beats omitted from the analysis are excluded (Figs. 1*A* and 2*A*). We also analyzed subjects with normal sinus rhythm only, and excluded aberrant beats, atrial fibrillation, premature ventricle contractions, and premature atrial contractions (approximately <20% of beats were considered artifacts). No automated or statistical process was used for beat selection in the current study. To estimate CO, on average, 12 but not less than 8 beats selected from a 20-s record were considered for further analysis. The average BP beat curve (Figs. 1*B* and 2*B*) was calculated automatically, and consequently, the heart rate (HR), systolic area under the curve (AUC) and amplitude of maximal peak (MaximalPeak_{amp}) were determined automatically. CO was calculated using *Eq. 1* based on calculated BP features and stroke volume quantification.

$$\text{CO}\left(\frac{\text{l}}{\text{min}}\right) = \text{HR}\left(\frac{\text{beat}}{\text{min}}\right) \times \frac{\text{AUC}}{\text{MaximalPeak}_{amp}}\left(\frac{\text{l}}{\text{beat}}\right) \qquad (1)$$

Data analysis and statistical approach. Data are reported as mean ± SD unless otherwise specified. Adapted OpCirc data analysis was performed as described by Johnson et al. (26). Measurement analysis of the BP cuff method are described above and in the APPENDIX. To test the agreement of both methods, a Bland-Altman (B-A) analysis was used. The results are presented as a mean difference with SD, supported by a 95% limit of agreement between the methods (1, 9). Pearson's product-moment correlation coefficients were calculated to evaluate covariation of methods.

RESULTS

Six men and seven women were tested. One woman was excluded due to low-quality signal burdened by movement artifacts of the arm, causing unreadable results. Data from a total of 12 healthy subjects (age, 27.6 ± 5.4 yr; 50% male; BMI, 24.5 ± 3.3) were therefore analyzed. Based on the estimated fitness level of the individuals, five men and two women followed an exercise protocol consisting of 100, 150, and 200 W power loads. One man and three women followed a protocol consisting of 50, 100, and 150 W. One woman with a history of a sedentary lifestyle and no sports activities underwent exercise at 50, 100, and 120 W.

The average error of experimental technique compared with that of OpCirc was −0.25 ± 1.02 l/min, with a Pearson's correlation coefficient of 0.96 (rest + exercise) (Fig. 3), and 0.21 ± 0.42 l/min with a Pearson's correlation coefficient of 0.87 (rest only). B-A analysis supports agreement of the methods within (95% boundaries) 1.7/−2.3 l/min [B-A coefficients of reproducibility (RPC) 2 l/min], $r^2 = 0.92$ at rest and exercise 1/−0.62 l/min (RPC 0.84 l/min) and $r^2 = 0.75$ at rest, respectively. B-A analysis for CO lower than 15 l/min improves agreement to 1.4/−1.5 l/min (RPC 1.4 l/min), $r^2 = 0.92$. Figure 4 represents a comparison of both methods using $\dot{V}O_2$ as an independent factor to illustrate the range of aerobic workload we performed during validation of the cuff technique. Table 1 shows estimates of CO using both methods during rest and particular steady-state exercise levels.

DISCUSSION

The present study focuses on comparing measurements of CO via a noninvasive, experimental cuff-occlusion method against those using the validated OpCirc wash-in technique at rest and during mild to moderate aerobic exercise. For the OpCirc method, the computational technique adapted by Johnson et al. (26) was used to quantify the uptake of acetylene and to account for changes in lung volume, dead space ventilation, and breath-by-breath variability. The cuff-occlusion method was analyzed via semiautomated beat-to-beat pulse pressure wave signal analysis. There was a tendency for the cuff-occlusion method to underestimate OpCirc at the higher work intensities by up to 4%; however, the cuff method demonstrated a lower variability during exercise.

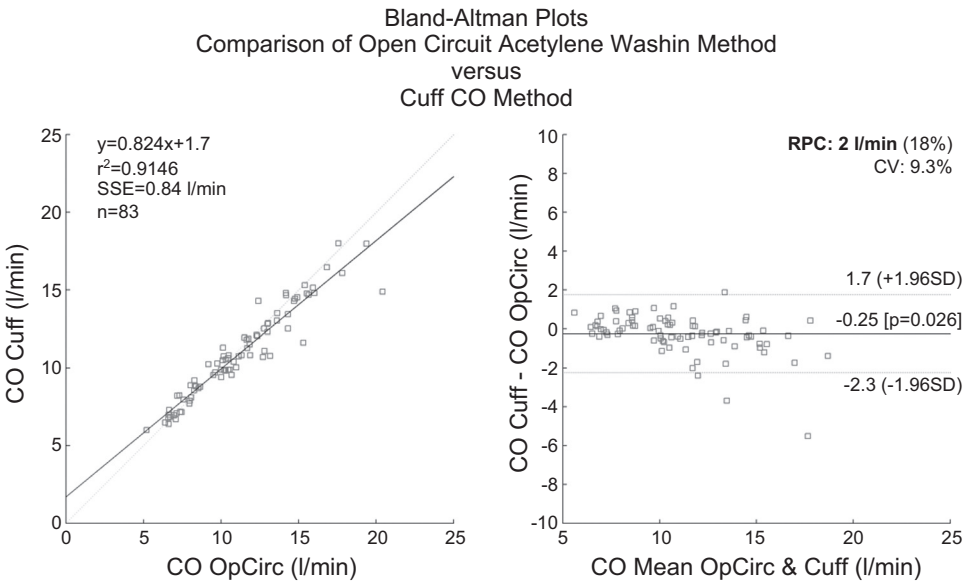

Fig. 3. Bland-Altman analysis of CO assessed by the experimental cuff method (CO Cuff) vs. the open-circuit acetylene wash-in method (CO OpCirc) in resting and during exercise. RPC, reproducibility coefficient, computed as the mean bias ±1.96 times its SD.

Assessment of CO from the arterial pressure curve has been studied (33, 35, 44, 45). In theory, if the vascular system does not transmit any reflected pressure waves, the flow and pressure curve would be identical to the amplitude and phase shift difference, reflecting the total peripheral resistance if measured at the same place. In vivo, the estimate of ultimate measured flow is affected by the superimposed reflected pressure waves present as differences in the shape of the pressure and the flow curve, and thus might influence the accuracy of measurement (18). Presented experimental data suggest either a negligible effect of reflected waves on the stroke volume calculation in the ejection phase recorded during occluded conditions or that the energy of reflected waves is manifested in the ratio of AUC to the MaximalPeak_{amp} (27, 49).

The novel approach of using the occlusion-cuff method confirms superior accuracy of CO estimates at rest (0.21 ± 0.42 l/min within 95% limits of agreement) compared with the most accurate formula proposed by Liljestrand and Zander (32a) (−1.76/+1.41 l/min at rest within 95% limits of agreement) tested in the study by Sun et al. (44), providing retrospective comparative analysis of eight investigational CO measurements from arterial BP algorithms using the Multiparameter Intelligent Monitoring in Intensive Care database. Another method, known as triangulation, can also be used to calculate stroke volume. This approach presumes no flow at the beginning of the cardiac cycle, and maximal flow at the pressure amplitude peak with returns to no-flow in times of aortic closure (dicrotic notch) (18, 42). The arterial pressure curve is primarily obtained invasively during catheterization. Although

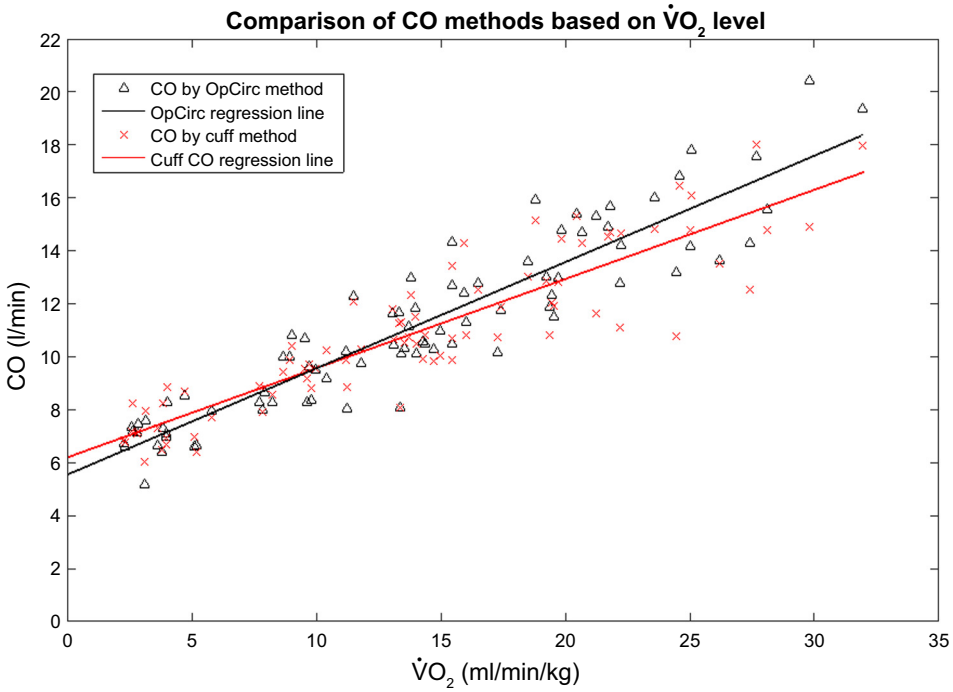

Fig. 4. Comparison of CO assessed by open circuit (OpCic), and cuff (Cuff CO) methods based on volume of oxygen consumption ($\dot{V}O_2$).

Table 1. *Experimental cuff method vs. open-circuit method*

Load Level	Power, W	SBP/DBP, mmHg	$\dot{V}O_2$, ml·min^{-1}·kg^{-1}	OpCirc CO, l/min	Cuff CO, l/min
Rest	0	125 ± 10/72 ± 11	4.2 ± 1.9	7.2 ± 0.77	7.41 ± 0.82
Level1	82 ± 29		11.5 ± 3.2	9.95 ± 2.03	9.80 ± 1.79
Level2	132 ± 35		17.6 ± 5.2	12.67 ± 3.01	12.26 ± 2.7
Level3	176 ± 47	164 ± 11/80 ± 17	22.4 ± 6.2	14.76 ± 3.24	14.08 ± 2.78

Values are means ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; $\dot{V}O_2$, volume of oxygen consumption; OpCirc CO, cardiac output assessed by the open-circuit acetylene wash-in method; Cuff CO, cardiac output assessed by the cuff method.

it is possible to estimate CO from this invasive peripheral arterial curve (4, 33), the central aortic pressure curve is typically used for the calculation (10, 18, 20, 33, 39). In our case, the peripheral arterial pressure curve was obtained through the arm cuff inflated to suprasystolic pressure (occlusion technique) using the differential pressure sensor showing high correlation with the invasively recorded pressure curve (6, 22). Our results demonstrate that CO calculated as an integral of the systolic part of the pressure wave measured noninvasively in occlusion at the level of the upper brachial artery divided by its maximal amplitude highly correlates with a blood flow measured by the comparative method.

The pressure curve indeed carries information regarding several parameters of the cardiovascular system (BP, blood flow, and peripheral arterial resistance) (11, 18, 21, 22, 37, 40a, 42, 47). PCMs established for CO estimate based on the parameters of the peripheral or aortic BP curve have been extensively studied as a means of estimating stroke volume from analysis of the continuous arterial BP signal (4, 28, 30, 31, 34, 46). Traditionally, a two-parametrical Windkessel model involving aortic compliance (C_a) and total peripheral resistance has been used. CO and stroke volume can be estimated from the measurement of mean arterial pressure, C, Windkessel time constant (τ), and pulse pressure measured in central aorta. However, these methods have limitations if arterial BP waveforms are measured invasively from peripheral circulation because arterial BP waveforms in the peripheral arteries do not display exponential decay during the diastolic phase and are exposed to distortion as they propagate through the elastic, tapered arterial network. Therefore, it is difficult to obtain (τ) (39), and the PCMs have achieved limited accuracy to be adopted broadly clinically (32). To overcome this limitation, more sophisticated approach for CO calculation has been handled by applying three parametric Windkessel models (4, 48). Arai et al. (4) refers overall estimation errors in CO and stroke volume derived from radial arterial BP were 10.1% and 14.5%, respectively, and 12.7% and 16.5% from femoral arterial BP compared with values obtained through a surgically implanted aortic flow probe. In our work, the proposed method carries an overall error of approximately 4%; specifically, the error ~3 ± 6% at rest (using 6.5 l/min as resting CO average) and an error of ~1.4 ± 6% at rest and during exercise (using 17.5 l/min as CO average) tested against another noninvasive method for CO estimate validated with direct Fick, which also has an inherited error compared with precise aortic flow probe measures.

The difference between the occlusion-cuff technique and other methods such as a hybrid of three Windkessel models (4, 48), including those based on the quantification of wave reflection (28), is that these methods were tested and applied on BP curves obtained during a free blood flow (mainly invasively) from the radial or femoral artery, whereas the BP signal of the occlusion-cuff method is obtained noninvasively from a fully occluded brachial artery. Recorded arterial pressure curve represents changes from the upper edge of the cuff, which is near the axillary artery, and as such, is much closer to the central circulation and aortic pressure. Previous studies have confirmed high correlation between invasively obtained BP curves from the brachial artery (~1 cm above the upper edge of the inflated cuff) and the noninvasive signal from the cuff (22). It is possible that recording a BP waveform from a fully occluded brachial artery generates a BP waveform that is morphologically closer to central aortic waveforms relative to that obtained from a brachial artery in free flow conditions, and thus is less affected by peripheral arterial capacitance and (τ). Further studies need to confirm this hypothesis.

The occlusion-cuff method for quantifying CO has not been previously described. Preliminary data have shown that this technique has a good potential for use in perhaps more difficult clinical conditions such as heart failure, in intensive care units, and in monitoring of patients on hemodialysis due to the robustness of the signal. Simplicity and mobility create the potential for utilization in other, more remote settings, and in exercise physiology. This technique was well tolerated by participants, and because the occlusion-cuff technique differs little from the standard noninvasive BP measurement, risks of occlusion-cuff technique should not differ from risks associated with noninvasive BP measurement using the arm cuff.

Study limitations. Data were collected on a sample of healthy subjects at rest and during light to moderate steady-state aerobic exercise. Further studies need to be conducted to improve accuracy assessment at maximal aerobic capacity of subjects and higher peak $\dot{V}O_2$ values. Currently, the occlusion-cuff technique is somewhat motion sensitive. Arm motion during 20 s of data acquisition may result in a distorted BP signal. At this stage, a trained operator is required to select clean beats free of artifacts (see METHODS). Using a sufficiently tightened arm cuff and motionless arm conditions with relaxed muscles are required to obtain accurate BP signals, otherwise signal quality becomes affected. A longer time of cuff occlusion (30 s) during vigorous exercise can be considered to increase the likelihood of quality BP recording. Studies of a different mode of exercise, specifically during isometric exercise with a highly increased total peripheral resistance, are needed to specify potential limitations of the cuff-occlusion technique. Similarly, further studies using animal experiments with precise aortic flow probes are required to test the proposed method on changes in stroke volume during large shifts of intravascular volume.

Conclusion. Preliminary data confirm the feasibility of this novel, noninvasive principle for CO measurement. Unlike the most similar technique, the volume clamp method, the occlu-

sion technique eliminates the need for technically challenging servo-regulated cuff pressure to record the BP curve. Furthermore, the pressure signal obtained from the brachial artery might be less likely affected by peripheral vasoconstriction. Thus, the occlusion principle has the potential to be developed into an easy-to-perform, accurate, and relatively mobile method for the noninvasive assessment of CO at rest and during exercise.

APPENDIX

Occlusion Method

The basic principle of the occlusion method lies in using an inflatable arm cuff as a pressure sensor in special conditions. When the arm cuff is pressurized above the systolic BP, it occludes the brachial artery and disables the blood flow distally from the cuff. By creating this no-flow condition, a small diaphragm develops in the brachial artery at the level of the upper edge of the overpressurized cuff. As the central pressure changes, pressure waves reach the virtual diaphragm and cause a beat on the membrane, like a drumstick. This causes small volume/pressure changes in the cuff because the upper arm tissues are practically incompressible. The pressure changes are recorded by the sensor of the device. In this setup the local influence of the characteristics of the brachial artery wall is practically eliminated because the arterial wall does not move beneath the cuff, and so the received curves are pure pressure waves; importantly, identical to those measured invasively. This method was first developed for the oscillometric device Arteriograph (TensionMed, Budapest, Hungary), validated against invasive BP measurement and published by Horávth et al. (22) in 2010, showing strong correlation ($r = 0.95$, $P < 0.001$) between the invasively measured and noninvasively calculated central systolic BP. The occlusion method was validated with the gold standard method for PWVao and Aix using the Sphygmocor (AtCor Medical, Sydney, Australia) device (3). Comparison of the Arteriograph to Sphygmocor devices by Rezai (43) showed close correlation of measured values ($r = 0.9$) with no statistical significance in systolic BP 0.9 (−1.1 to +2.9) mmHg using an accurately calibrated Sphygmocor. A similarly strong correlation ($r = 0.89$, $P < 0.001$) in PVWao and Aix between the Sphygmocor and Arteriograph was presented by Jatoi et al. (25) in 2009 from a sample of 254 patients with hypertension. Another large clinical study published in December 2012 (21) included 3,374 healthy individuals between ages 3 to 18 yr that focused on arterial stiffness and used an Artheriograph device to measure mean arterial pressure, PVWao, and other characteristics.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

P.S., V.K., A.R.C. and B.D.J. conceived and designed research; P.S., V.K., A.R.C, C.M.W. performed experiments; P.S., V.K., A.R.C., V.F., V.G. analyzed data; V.K. prepared figures; P.S., V.K. drafted manuscript; the whole collective interpreted results of experiments; the whole collective edited and revised manuscript; the whole collective approved final version of the manuscript.

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