Delivery of customizable compressive patterns to human limbs to investigate vascular reactivity

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Running Head

A novel system for delivering customizable compression patterns

Keywords blood flow, hyperaemia, muscle compression, pneumatic compression. vascular reactivity

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ABSTRACT

Objective

Commercial devices for pneumatic compressive treatment of the limbs generally provide predefined stereotyped compressive profiles. The possibility to deliver compressive stimuli with a customizable pressure profile would be useful to differently probe the vascular reactivity to muscle compression (MC) and improve the understanding of MC-induced hyperemia. Aim of this study was the realization of a novel pneumatic system capable of generating adjustable and stable compressive conditions, preceding and following a "standard" MC stimulus

Approach

A custom-made pneumatic system specifically built to this purpose is tested and characterized in 10 subjects. Three different compressive patterns were delivered to the leg: 1) a constant level: 50 mmHg for 50 s; 2) MC: 200 mmHg for 1 s; 3) a complex profile: 20 mmHg for 50 s, 200 mmHg for 1 s, 50 mmHg for 50 s.

Main results

The implemented system allowed to deliver graded compressions to the limb characterized by fast transitions (0 to 200 mmHg in 0.5 ± 0.07 s) and stable plateau levels (50.4 ± 0.5 mmHg).

Significance

A new, low-cost, pneumatic prototype has been presented and tested in the present study allowing to deliver compressive stimuli with pre-and post-compressions of adjustable level. This device has been conceived for research purposes and may find application in therapeutic compressive treatments.

INTRODUCTION

Vascular reactivity to mechanical compression takes the form of a rapid dilatation and results in a prompt and short lasting hyperemia. This phenomenon has been originally observed in the isolated muscle (Mohrman and Sparks, 1974) and has also been documented in isolated feed arteries (Clifford *et al.*, 2006), in intact animals (Turturici *et al.*, 2012; Turturici and Roatta, 2013a) and in humans, in both upper (Kirby *et al.*; Messere *et al.*, 2017b) and lower limbs (Messere *et al.*, 2017a; Credeur *et al.*, 2015). This mechano sensitivity of the muscle vasculature is likely to contribute also to the hyperemia that develops with passive movements (Wray *et al.*, 2005) as well as with muscle contraction (Kirby *et al.*, 2007; Messere *et al.*, 2017a) and is considered to have a role in the hyperemia at the beginning of exercise (Clifford, 2007).

In humans, the muscle compression (MC) is generally obtained by a pneumatic cuff wrapped around a limb, typically the forearm or the calf, rapidly inflated to a "high" pressure level of 100 - 250 mmHg for a duration of 1-2 s, then rapidly deflated. Blood flow to the compressed limb rapidly increases, peaking in 3-4 s from pressure release and returns to control within 10-20 s (Tschakovsky *et al.*, 1996; Kirby *et al.*, 2007; Messere *et al.*, 2017b) however the mechanisms underlying this rapid hyperemia have not yet been univocally identified. The two major hypotheses concern: 1) the transient increase in perfusion pressure, due to the drop in venous blood volume and pressure produced by the muscle compression, which result in increased perfusion pressure (the muscle pump) (Laughlin, 1987); and 2) an active vasodilation of resistance vessels provoked by vessel deformation (Hamann *et al.*, 2004; Clifford *et al.*, 2006; Turturici *et al.*, 2012). In particular, the first mechanism is related to the decrease in vascular filling produced by the compression while the second is related to the changes in transmural pressure exerted by the external compression on the relevant vasculature (Jasperse *et al.*, 2015).

On this basis, and to the aim of improving the understanding of MC-induced hyperemia we considered that it would be helpful to alter perfusion pressure and transmural pressure gradients by modulating the cuff pressure levels in the time intervals that precede (pre-compression) and follow (post-compression) a "standard" MC stimulus.

Although several commercial devices exist to deliver pneumatic limb compression for different treatments (Comerota, 2011; Morris and Woodcock, 2004; Sheldon *et al.*, 2013), to our knowledge there is no available device capable of generating customizable complex pressure profiles. In fact, commercially available systems typical deliver compressive stimuli with predefined simple profiles, e.g., with trapezoidal or triangular time course.

Thus, aim of the present study was to develop and characterize a novel pneumatic system allowing to establish and maintain adjustable cuff pressure levels (in the range of 0-50 mmHg) preceding and/or following a sharp MC stimulus, i.e., capable of generating a pressure profile such as the one shown in Fig 1.

METHODS

Experimental pneumatic system

The basic idea of the device is a pneumatic circuit connected to a control system that allows to inflate a blood pressure cuff (Gima, Gessate, IT) wrapped around the limb to stimulate. It has been designed in order to control the pressure applied by the cuff with a step reference between 0 and 250 mmHg, with a good compromise between static performances in terms of accuracy (≤ 5 mmHg), and dynamic performances in terms of time responses (≤1 s).

The design of the experimental system had to meet several contrasting requirements. In order to minimize the static error, it would be preferable to use a pressure proportional valves with a regulation range comparable to that of the application. Those types of valves are normally of small size, and have therefore low maximum flow rate (typically 5-10 dm^3/min), which implies long cuff inflation time. Vice versa, pressure proportional valves able to regulate higher pressure ranges are of greater size, and therefore suitable in terms of flow performances, but with very low accuracy. Moreover, they often are unable to regulate the relative pressure at low values (close to 0).

Therefore, it is not possible to obtain a good trade-off between static and dynamic performance by using only one of the commercial low-cost pressure proportional valves.

In order to overcome this issue, the pneumatic circuit of Fig 2 has been designed. An air compressor (A), provided with a first pressure regulator, supplies two further precision pressure regulators. The first pressure regulator (B1) set to 1.8 bar, supplies a proportional pressure valve of small size (D) for the accurate regulation of the cuff pressure in stationary condition. The second pressure regulator (B2) set to 1.3 bar is connected to a 2/2 digital solenoid valve (C1), and supplies the cuff during dynamic conditions, in order to minimize the inflation time of the device. Another 2/2 digital solenoid valve (C2) is employed to quickly discharge the cuff during dynamic conditions and minimize the deflate response time. A pressure transducer (E) located at the cuff outlet and connected to a pressure monitor (Pressure monitor BP-1,WPI, Sarasota, FL, USA), measures the cuff pressure.

In detail, the valve D is a proportional pressure valve (ITV0010, SMC, Tokyo, Japan), with good static characteristics (linearity ≤ 1% full scale F.S.; hysteresis ≤ 0.5% F.S; repeatability ≤ 0.5% F.S), a pressure range from 0.001 to 0.1 MPa (7.5-750 mmHg), and proper dynamic characteristics (response time without load 0.1 s). The valves C1 and C2 are direct-operated solenoid normally-closed valves, two ports two positions 2/2 (VXE2330-02F-6D01, SMC, Tokyo, Japan) with an orifice diameter of 4.5 mm, and a sonic conductance of 2.3 dm^3/(s bar).

Control system

The control system is constituted by a personal computer connected to a data acquisition system (CED Micro 1041; Cambridge Electronic Design, Cambridge, UK). and is operated by a Spike2 routine (software version 6.10; Cambridge Electronic Design).

The actual pressure at the cuff is measured directly at the cuff outlet (BP-1, WPI, Sarasota, USA), sampled at 100 Hz by the acquisition system, used as a feedback control signal and stored on the computer for subsequent analysis.

The control system generates the driving signals for the three valves: an analog signal, corresponding to the target pressure profile is fed to the proportional valve (D), and two digital signals (0 V = valve closed; 5 V = valve open) control the digital valves, C1 and C2, through two relays.

Given the limited flow rate of the proportional valve, inflation of the cuff is performed with the additional contribution of the C1, allowing to achieve shorter inflation times. Along the same line, passive deflation of the cuff is accelerated thanks to the additional contribution of the C2 valve. Closing time of the C1 and C2 valves is regulated according to the feedback provided by the cuff pressure signal: the valves are closed upon attaining the desired pressure level.

Fig 3 shows the driving signals of the valves used to generate a pressure profile reproducing the intended (target) profile, as presented in Fig.1. Please note: 1) the very short-lasting opening time of the C1 valve during inflation phases; 2) constant pressure levels maintained by the proportional valve D alone; and 3) the involvement of C2 valve during deflation phases. The last closing time for C2 is not feedback-controlled: the valve is maintained open for a long (5 s) in order to ensure complete cuff deflation.

Experimental protocol

After being informed about the procedures and having signed the informed consent 10 healthy volunteers (9 males and 1 female; age: 29.6 ± 8.3 years; weight: 71.5 ± 7.9 kg; height: 169.9 ± 16.2 cm) with no history of cardiovascular diseases and without taking any medications that could alter the vascular response were enrolled in the study, approved by the Ethics Committee of the University of Torino.

Subjects sat on a comfortable chair with backrest, in a quiet room with temperature 21-23 °C. The left leg was fully extended with the foot resting on a pillow. To prevent any discomfort an additional pillow was placed under the knee, supporting the extended leg. The pressure cuff was wrapped around the same extended leg, just distally to the knee. The protocol started after 10 min of rest.

Device characterization

The system has been tested on three different pressure profiles delivered in random order: 1) a constant pressure level of 50 mmHg lasting 50 s; 2) a MC pulse at 200 mmHg lasting 1 s; and 3) a MC pulse as in (2), following a pre-compression at 20 mmHg lasting 50 s and followed by a post-compression at 50 mmHg also lasting 50 s. A value of 50 mmHg was chosen for pre- and post compression since it is comparable to blood pressure in the venous compartment, with the adopted body posture and may thus produce changes in blood volume and transmural pressure that are relevant for these investigations. The duration of 50 s was judged adequate to reach a stable hemodynamic condition before MC and to allow for the completion of the hyperemia after MC, based on preliminary experiments

Different measures were collected from the recorded cuff pressure signal: the rise time (the time to reach the target pressure level), the descent time (the time to reach the pressure level of 5 mmHg, during deflation), the pressure level at the steady state (averaged over the last 30-s interval, in long-lasting compression, and over a 1-s interval in the MC pulse); the time required to reach a steady state (the time required to reach the target pressure level ± 5%, when inflating from the completely empty condition (0 mmHg) in profiles (1) and (3)).

Data are presented as means ± SD in the text and in figures. The coefficient of variation, CoV=SD/mean, is also computed to quantify the variability in the attained pressure levels across subjects.

As an example of possible application of this system, original recordings are presented from a representative healthy subject. The subject is sitting with one leg extended as described above, while leg compressions are delivered according to modified versions of the Fig.-4C profile, i.e. a MC preceded/followed by a pre/post-compression. The hemodynamic response is recorded from the femoral artery by means of Eco-Doppler Ultrasound (Esaote, MyLab 25 Gold, Italy) and displayed in a color-coded time-frequency representation (Doppler shift), which indicates the distribution of blood velocities in the artery, and is representative of femoral artery blood flow (since the artery cross-sectional area can be considered constant).

RESULTS

The average pressure curves, are reported in Fig 4, for the different tested profiles. For the 50-mmHg constant pressure profile (Fig. 4 A) the following parameters were calculated: rise time: 0.30 ± 0.06 s, time to plateau: 2.3 ± 1.2 s and pressure level at plateau: 50.4 ± 0.5 mmHg. (CoV = 1 %) For the MC pulse: rise time: 0.50 ± 0.07 s, pressure at plateau: 200.8 ± 2.7 mmHg (CoV = 1.3 %); descent time: 2.0 ± 0.2 s. For the more complex pattern of Fig. 4 C: pre-compression rise time: 0.23 ± 0.04 s, time to pre-compression plateau: 2.3 ± 2.3 s; pre-compression pressure: 20.9 ± 0.7 mmHg (CoV = 3.3 %); MC pulse rise time: 0.36 ± 0.06 s; MC pulse pressure: 200.7 ± 2.8 mmHg; post-compression descent time: 0.52 ± 0.05 s; pressure at post-compression plateau: 50.5 ± 0.9 mmHg. (CoV = 1.8 %)

The good reproducibility of the pressure profiles is evidenced by the small standard deviations (Fig. 4). In addition, all intended profiles are rather faithfully reproduced. The largest difference between intended and actual pressure curves occurred at initial transients, when attaining low pressure levels (Fig. 4 A and C).

Original recordings from a representative subjects are presented in Fig. 5 to show how the hyperemic response to the MC may be differently affected by different pre- and post-compression conditions.

DISCUSSION

A controlled pneumatic system has been developed that is capable of generating compressive stimuli with complex profiles, characterized by: 1) sharp pressure transients, as necessary to implement short-lasting compressive stimuli, precisely localized in time and thus adequate to induce a “standard” compression-induced hyperemia (Kirby *et al.*, 2007; Turturici *et al.*, 2012; Turturici and Roatta, 2013a, b), as well as 2) steady pressure levels maintained for long periods of time that can be used to alter the vascular conditions that precede and/or follow the MC. The pressure levels at plateaus were virtually identical in the different subjects (CoV =1-3 % of plateau pressure), thanks to the feedback-controlled proportional valve. This indicates that the apparatus is suited for reliable delivery of pre- and post- compressions of finely adjustable magnitude.

While commercial and custom-made devices exist for generating fast and short lasting compressive stimuli to our knowledge this is the first description of a system allowing to implement customizable pneumatic pressure profiles, consisting of a sequence of static pressure levels.

This feature was specifically developed for research purposes, in order to modulate the extent of vascular filling in venous compartments as well as pressure gradients across the wall of blood vessels, in the affected limb. In particular it will possibly help to identify the determinants of the mechano-sensitive rapid dilatation that have been discussed for decades and still fail to fit within a univocal interpretation (Mohrman and Sparks, 1974; Tschakovsky and Sheriff, 2004; Clifford and Tschakovsky, 2008; Turturici *et al.*, 2012; Turturici and Roatta, 2013b; Credeur *et al.*, 2015; Jasperse *et al.*, 2015). In particular, controlled changes in the pre-compression level can be used to modulate the extent of vascular filling prior to the delivery of the compressive stimulus while the post-compression level can be adjusted to modulate changes in perfusion pressure and in vascular transmural pressure at the release of the compressive stimulus. These effects are currently under investigation in an experimental series on healthy subjects.

Beside addressing basic questions in vascular physiology, this system may possibly find applications among clinical compressive treatments. For instance intermittent pneumatic compression is employed to improve perfusion in the treatment of peripheral arterial disease (Sheldon *et al.*, 2013). By using a custom-made pneumatic device it was recently shown that slow and long lasting compressions were more effective in raising tissue oxygenation in the affected limb, compared to standard short-lasting compressions (Manfredini *et al.*, 2014). However the efficacy of different compressive patterns has generally been little investigated, possibly because of lack of the necessary equipment.

Limitations and possible improvements

In its current form, the system presents a slow settling time at low pressure levels , with a relatively high variability in the different subjects (Fig. 4 a). As recently investigated by means of a mathematical model

(Ferraresi *et al*, in press) this is likely to be attributed to the compliance of limb tissues and to different cuff-tissue coupling in different subjects. In particular the initial fast pressure increase triggers the closure of the digital valve and stops the high-flow inflation, which then requires several seconds for the target pressure level to be attained through the slow-flow proportional valve. However, this initial transient is unlikely to influence the conditioning effects produced by the pre-compression condition which lasts 50 s.

Although better pneumatic performance may be achieved by employing more expensive equipment, e.g., a proportional valve allowing for larger flow rate and digital valves with faster response time, the presented low-cost prototype demonstrated a performance adequate to pursue the research objectives.

Finally, a safety valve to prevent excessive pressure in the cuff was not included in this prototype, as the connections between the pneumatic components were sufficiently loose to serve the purpose. However, it could easily be inserted at the cuff outlet in a commercial version of the device.

Conclusions

In the present study a new, low-cost, pneumatic device for the delivery of compressive stimuli with pre-and post-compressions of adjustable level has been presented and tested in human subjects. The device has been conceived for research applications but may possibly find applications among clinical and therapeutic treatments.

ACKNOWLEDGMENTS

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FIGURE CAPTIONS

Fig 1 Desired pressure profile

Example of the desired pressure profile for the pneumatic limb compressor. The short-lasting compressive stimulus (200 mmHg, 1-s duration) should be preceded by a pre-compression and followed by a post-compression of adjustable levels (0-50 mmHg, 50-s duration).

Fig 2 Schematic representation of the pneumatic compression system

The pneumatic system includes: an air compressor (A), two precision pressure regulators (B1 and B2), a proportional pressure valve (D), two 2/2 digital solenoid valves (C1 and C2), a control system, a blood pressure cuff and a pressure transducer (E).

Fig 3 Control signals and cuff pressure

From top to bottom: control signals fed to the proportional valve (D valve, with reference to Fig. 2) and to the two 2/2 digital solenoid valves controlling fast inflation (C1) and deflation (C2), and the pressure (Pressure) obtained at the cuff, in one subject. In this representative example a pressure profile replicating the one proposed in Fig. 1 is obtained. Note that the control signal to the proportional valve coincides with the target pressure profile while the digital valves are activated only during step pressure changes.

Fig 4 Average cuff pressure responses to different compressive profiles

A) a constant pressure at 50 mmHg, 50-s duration; B) a high-pressure compression at 200 mmHg, 1-s duration, and C) a high-pressure compression preceded by a pre-compression of 20 mmHg and a followed by post-compression of 50 mmHg, each lasting 50 s; The thick lines represent the average curve while thin lines (almost always overlapped to the average) represent ± standard deviation (n=10).

Fig 5 Hemodynamic response

The Doppler shift, indicating blood flow in the femoral artery, is shown in response to a compressive stimulus preceded by a pre-compression (A) or followed by a post-compression (B) at 50 mmHg and lasting 50 s, delivered to the leg of a healthy subject. Note that the pre- and post-compression differently affect the hemodynamic response.

Fig. 1

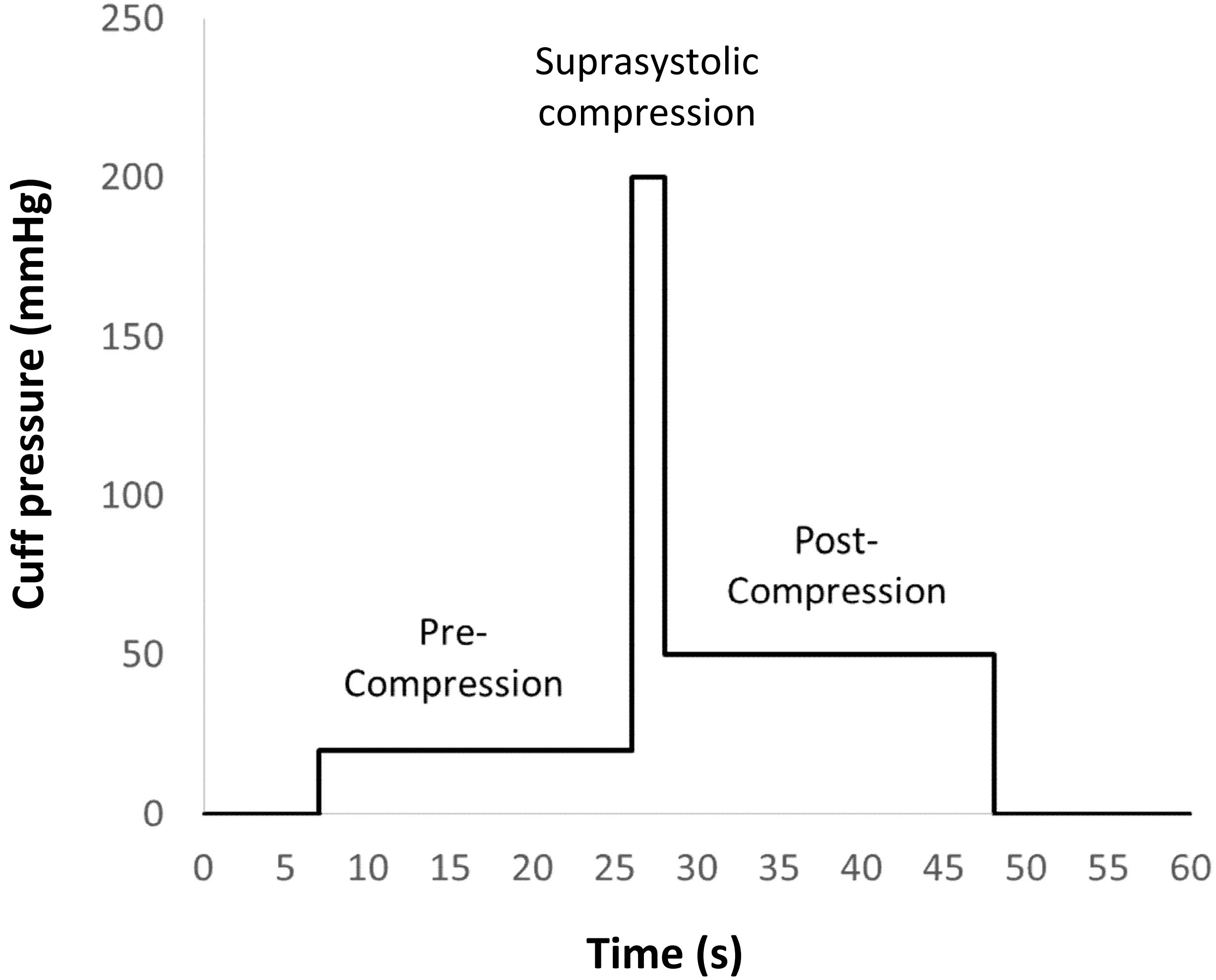

Suprasystolic
compression
Pre-
Compression
Post-
Compression
Cuff pressure (mmHg)
250
200
150
100
50
0
0 5 10 15 20 25 30 35 40 45 50 55 60
Time (s)

Fig. 2

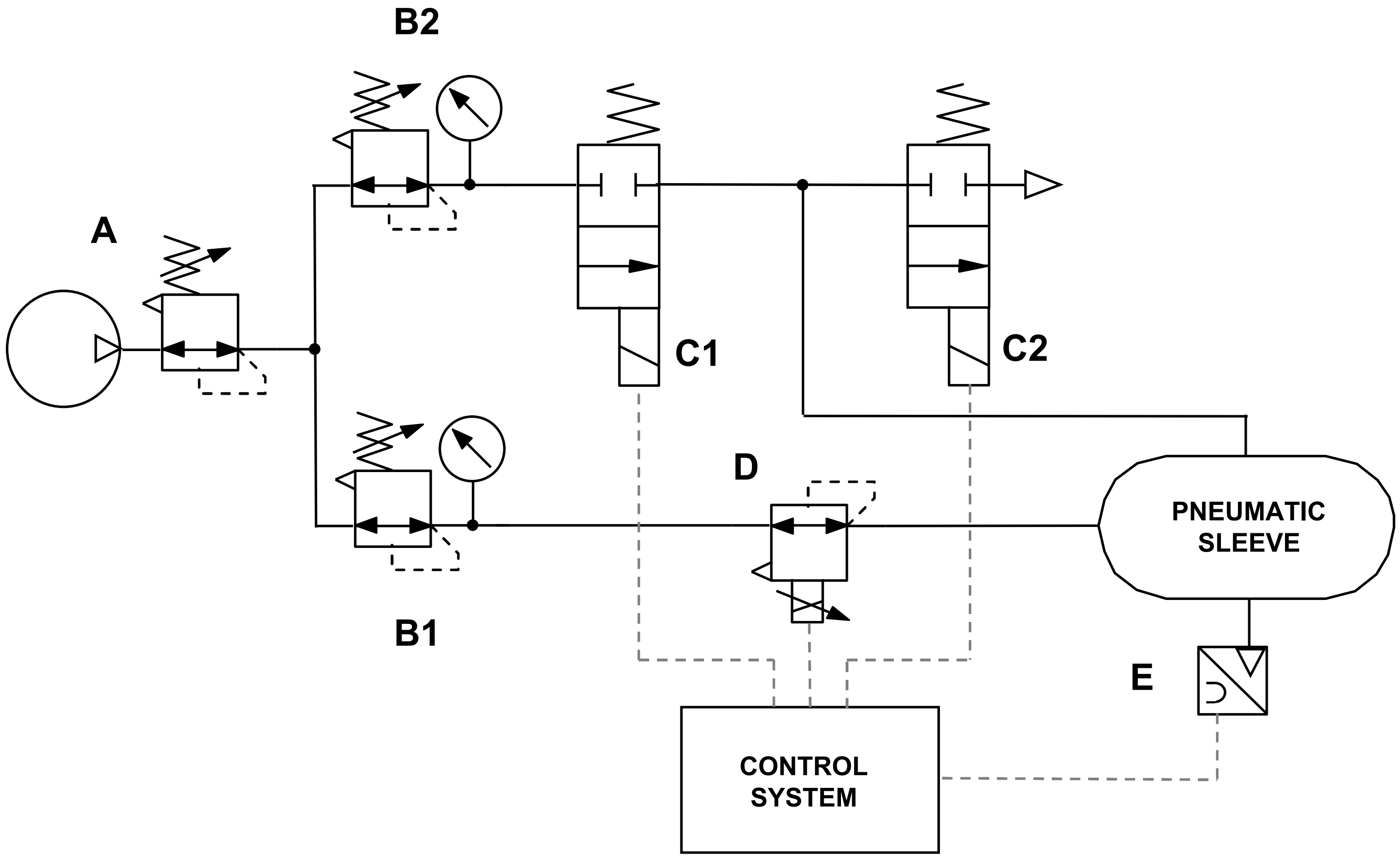


Fig. 3

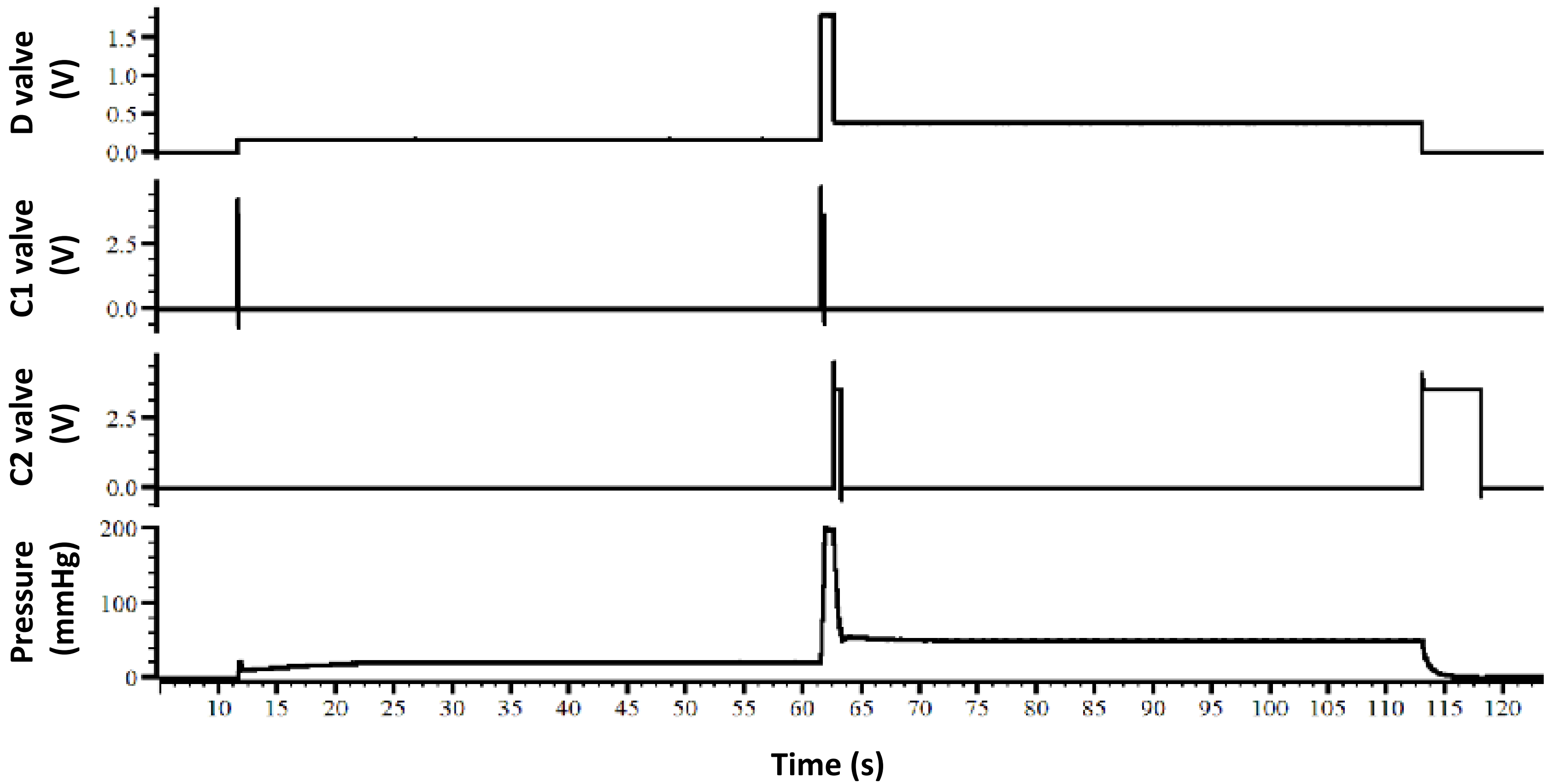

D valve (V)
1.5
1.0
0.5
0.0
C1 valve (V)
2.5
0.0
C2 valve (V)
2.5
0.0
Pressure (mmHg)
200
100
0
10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120
Time (s)

Fig. 4

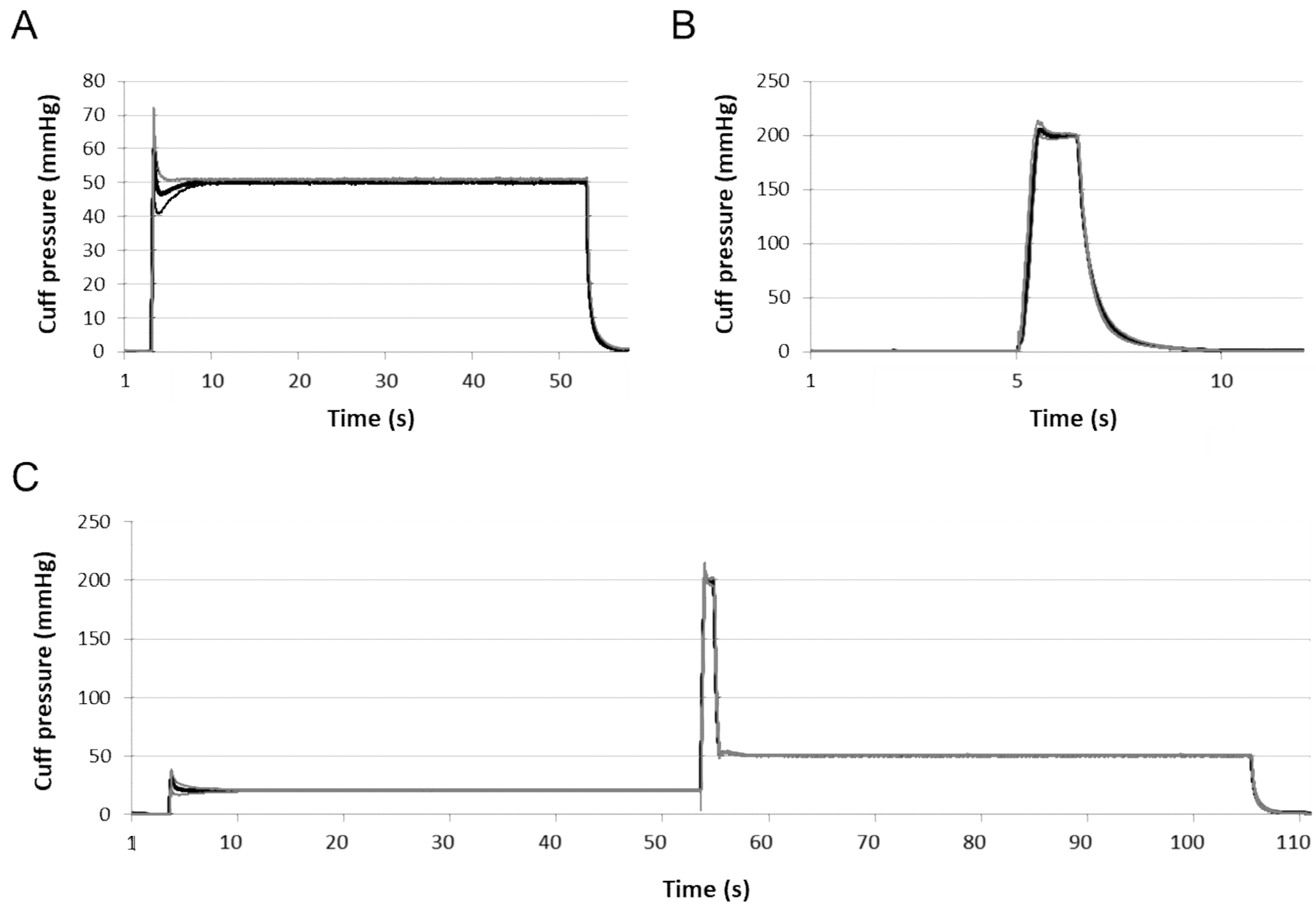
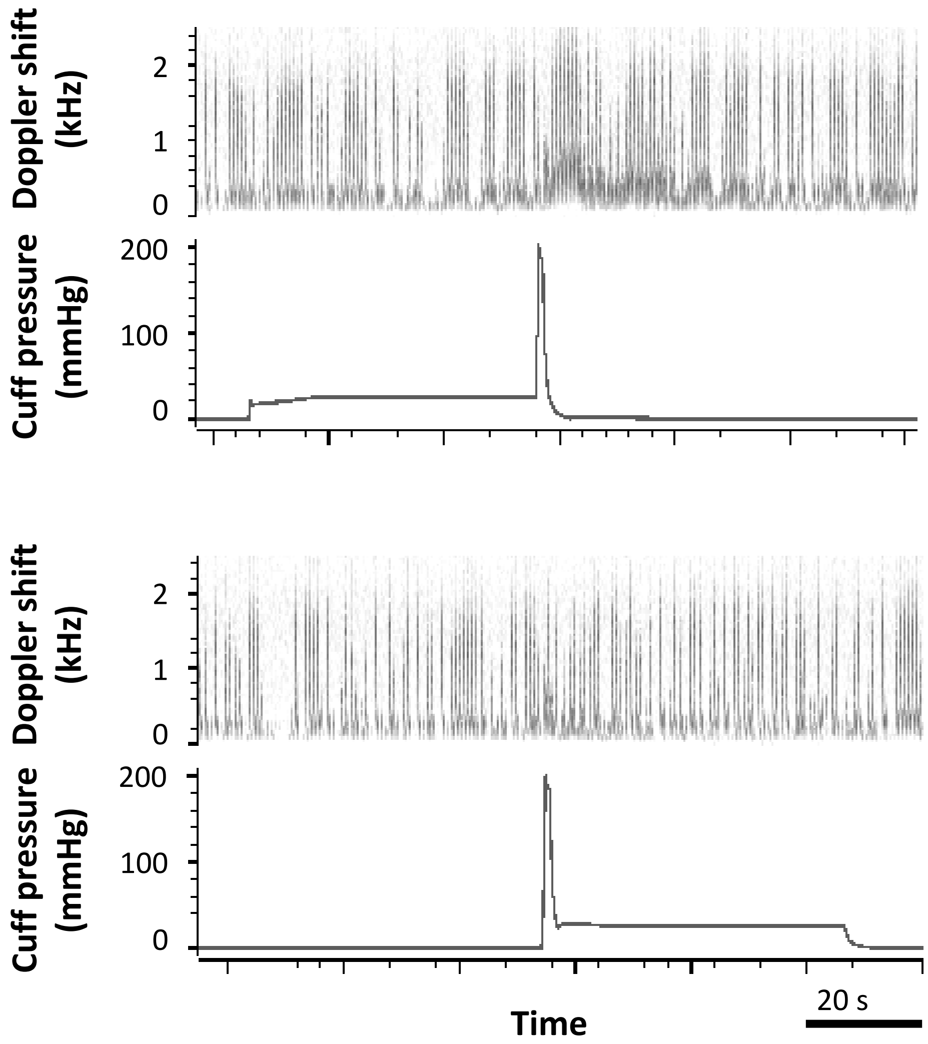

A
B
C
Cuff pressure (mmHg)
Time (s)
0
10
20
30
40
50
60
70
80
100
150
200
250
1
5
90
110

Fig. 5


Doppler shift (kHz)
2
1
0
Cuff pressure (mmHg)
200
100
0
Doppler shift (kHz)
2
1
0
Cuff pressure (mmHg)
200
100
0
20 s
Time