

ATTENUATION OF REFLECTED WAVES IN MAN DURING RETROGRADE PROPAGATION FROM FEMORAL ARTERY TO PROXIMAL AORTA

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Background The magnitude and timing of reflected waves modify the aortic pressure waveform, but the extent to which reflections undergo attenuation during retrograde propagation has not been studied. We quantified retrograde transmission of a reflected wave created by occlusion of the left femoral artery in man.

Methods 20 subjects (age 31-83 y; 14 male) underwent invasive measurement of pressure and flow velocity with a sensor-tipped intra-arterial wire at multiple locations distal to the proximal aorta before, during and following occlusion of the left femoral artery by inflation of a thigh cuff. A numerical model of the circulation was also used to predict reflected wave transmission. Wave reflection was measured as the ratio of backward to forward wave energy (WRI) and the ratio of peak backward to forward pressure (P_b/P_f).

Results Cuff inflation caused a marked reflection which was largest 5-10cm from the cuff (change (Δ) in WRI = 0.50 (95% CI 0.38, 0.62); $p < 0.001$, $\Delta P_b/P_f = 0.23$ (0.18 - 0.29); $p < 0.001$). The magnitude of the cuff-induced reflection decreased progressively at more proximal locations (further from the cuff) and was barely discernible at sites >40 cm from the cuff including in the proximal aorta. Numerical modelling gave similar predictions to those observed experimentally.

Conclusions Reflections due to femoral artery occlusion are markedly attenuated by the time they reach the proximal aorta. This is explained by the large impedance mismatches of bifurcations traversed in the backward direction. This degree of attenuation is inconsistent with the idea of a large

discrete reflected wave arising from the lower limb and propagating back into the aorta.

Keywords: wave reflection, blood pressure, arteries

Background

Elevated blood pressure remains the leading cause of mortality worldwide.¹ Wave reflection has been proposed as a major factor in the morphology of the aortic blood pressure waveform² and an important therapeutic target in hypertension and heart failure.³ It is often implicitly assumed that there is no impediment to retrograde propagation of reflected waves,⁴ although theoretically this is unlikely.^{5, 6} A limited number of invasive studies in animals and man have shown conflicting results with regard to the importance of discrete reflected waves in the aorta,^{7, 8} and recently the importance of large discrete reflections in the aorta as postulated by the asymmetric t-tube model has been criticised.^{9, 10} Alternatively, it has been proposed that the morphology of the aortic waveform may be comprehended either in terms of waves propagating in a time-varying reservoir,¹¹ or as the summation of many diffuse waves undergoing extensive reflection, re-reflection and entrapment.^{12,}

13

The aim of this study was therefore to examine the extent to which a large reflection generated by inflation of a thigh cuff to occlude the femoral artery could propagate backwards towards the proximal aorta and thereby to assess the likely importance of discrete reflections arising peripherally to the morphology of the aortic pressure waveform in man.

Methods

Study Population

Twenty participants (age range 31 – 83 years, 6 female) undergoing routine coronary angiography at Imperial College Healthcare NHS Trust were recruited. Exclusion criteria included significant valvular pathology or significant impairment of left ventricular systolic function (ejection fraction <55%). The study protocol was approved by the local research ethics committee and all subjects gave written informed consent prior to participation.

Study investigations

A standard thigh blood pressure cuff (width = 20cm; length = 42cm) was placed around the left thigh (the opposite side to the arterial access site) as proximally as possible. A radio-opaque marker was sited at the upper border of the cuff to aid subsequent radiological localisation. Invasive measurements of pressure and flow velocity at different sites were made following elective coronary angiography after a period of 10 minutes supine rest on the catheter laboratory table.

Following coronary angiography a 0.014 inch sensor-tipped combined pressure-Doppler velocity wire (ComboWire XT 0.0, Volcano Corp., CA, USA), was positioned in the left femoral artery as close to the proximal border of the thigh cuff (identifiable by the radio-opaque marker) as possible. The sensor wire was then used to measure simultaneous pressure and flow velocity at that site and then proximally at intervals as far as possible toward the proximal aorta (typically 5, 10, 20, 30, 40, 50, 60cm (from the cuff) and as proximal as

possible in the aorta). The position of the ComboWire was measured using a calibrated sterile measure. Care was taken to ensure that high quality pressure and flow velocity signals were obtained at each location. A fluoroscopic image frame was also stored so that the position of the wire could be calculated using a quantitative measurement tool in the Medcon TCS Symphony suite (Medcon Telemedicine technology, Inc., Whippany, NJ, USA). Simultaneous recordings of pressure, velocity and ECG were acquired for a minimum of 10 seconds. All data were acquired at 1kHz using an analogue-to-digital card (DAQ-Card AI-16E-4) and Labview software (National Instruments).

Measurements were made before, during and after inflation of a cuff on the left thigh to 50mmHg above systolic pressure. Consistent with previous reports,¹⁴ we confirmed that cuff inflation abolished flow in the popliteal artery using Doppler ultrasound. The cuff remained fully inflated for at least 10s. Recordings were ensemble averaged using the ECG peak R wave as the fiducial point and taking account of offsets introduced by signal processing by the Combiwire console. Analysis was performed offline using custom-written software in Matlab (Mathworks, Natick, MA). Pressure separation and measurement of wave intensity was performed as described previously.¹⁵ Peak pressure, peak velocity, peak wave intensity and wave intensity time integral (i.e. wave energy) were quantified. The magnitude of wave reflection was quantified in two ways: 1) as the wave reflection index (WRI) which was calculated as the ratio of the energy of the reflected backward compression wave (BCW) to the incident forward compression wave (FCW); and 2) as the ratio of the peak backward to forward pressure (P_b/P_f) after pressure separation (figure 1). Apparent reflection time was calculated as the half the

time between the peak of FCW and the BCW divided by the local wave speed. Reproducibility of measurements has been published previously;¹⁶ the within patient standard deviation of difference was 5 mmHg and 6 cm.s⁻¹ for pressure and flow respectively.

Numerical Modelling

Pressure and flow waveforms were simulated using a nonlinear one-dimensional model of pulse wave propagation in the 55 larger systemic arteries in the human as previously described.¹³ The flow rate prescribed at the root of the network was based on in vivo measurements at the aortic root and inflation of the cuff was assumed to cause complete occlusion of the artery. Arteries were simulated as thin, homogeneous, incompressible, elastic tubes, in which each section is independent of the others, and the blood was assumed to be a homogeneous, incompressible Newtonian fluid with a density of 1050 kg.m⁻³ and a viscosity of 4 mPa.s. Local wave speeds were calculated using the parameters of the model at mean pressure. Pressure signals were calculated by solving the linear one-dimensional equations of pulse wave propagation in the elastic vessels of the 55-artery network using a wave tracking algorithm.¹³ Only waves equivalent to a pressure >0.01% of the initial pressure were computed.

Statistical analysis

Statistical analysis was performed using SPSS 17.01 (SPSS Inc, Chicago, Ill, USA). Continuous variables are reported as mean±standard deviation for sample characteristics and mean (95% confidence interval) for results. Within

sample comparisons were made using a paired two tailed Student's *t*-test. Comparison between groups was made by an unpaired *t*-test or one-way analysis of variance (ANOVA) with post-hoc Bonferroni correction for multiple comparisons; *p* values < 0.05 were considered significant.

Results

Patient characteristics are summarised in Table 1. The mean age was 62y, the majority were male and most were receiving lipid lowering therapy. Typical recordings of pressure and flow velocity in the proximal aorta, aorto-iliac and femoral arteries without cuff-inflation are shown in Figure 1. Pulse pressure (PP) was larger in the more distal locations (proximal aorta = 62 ± 18 mmHg; femoral artery = 85 ± 14 mmHg; *p*=0.016 by paired *t*-test) and there was a progressive increase in wave speed from the proximal aorta to the femoral artery (Online supplementary figure S1). When the cuff was deflated, the peak intensity of the BCW and WRI in the femoral artery (5-10cm from the cuff) was minimal but still discernible (figure 2 & table 2).

Inflation of the cuff caused a large BCW in early systole (figure 2). WRI and P_b/P_f increased significantly (Table 2) and the peak of BCW arrived earlier (apparent reflection time = 75 (60, 90)ms (cuff deflated); = 29 (22, 36)ms; *p*<0.001) (cuff inflated). A backward decompression wave was also usually evident at the end of systole due to reflection of the forward decompression wave (FDW) (Figure 2). In the proximal aorta when the cuff was deflated the size of the BCW was small. Inflation of the cuff had no effect on the size of the BCW, WRI or P_b/P_f in the proximal aorta (Table 2 & Figure 2).

The magnitude of the detectable reflection (WRI or P_b/P_f) attributable to cuff inflation diminished markedly as the measurement site moved further away

from the site of occlusion (back towards the heart) so that there was little or no reflection detectable more than ~40cm from the cuff (figure 3A).

Modelling studies were consistent with the observed findings (figure 3B; Supplementary figure S1). A large reflected wave was evident in the femoral artery following occlusion, the magnitude of this reflection was larger than that seen in vivo. However, as observed in vivo, the intensity of this reflected wave declined markedly as it propagated back towards the aortic root, so that it did not differ by >10% from non-occluded conditions at locations >40cm from the site of occlusion.

Discussion

The intensity of backward travelling (reflected) waves in the human proximal aorta is small under resting conditions.¹³ Following inflation of a thigh cuff to induce unilateral arterial occlusion of the femoral artery, large reflections were seen in the femoral artery close to the site of the occlusion but there was no discernible change in reflections in the proximal aorta. We further showed that reflections from the occluded femoral artery undergo considerable attenuation as they pass retrogradely along the aorta and are barely evident more than ~40cm from the site of occlusion. Modelling studies using a validated 55 artery model of the human circulation gave results that closely paralleled the in vivo observations. The decline in intensity of the reflected wave can be explained by re-reflections due to the marked impedance mismatch of bifurcations traversed in the retrograde direction.^{5, 6}

Our findings of minimal reflections in the proximal aorta following distant downstream occlusion are consistent with some, but not all earlier studies.

Based on apparent phase velocities, McDonald and Taylor⁶ noted a “puzzling” lack of effect of major occlusion on reflection in the abdominal aorta despite evidence of strong reflections in the femoral artery. Based on pressure amplitude increase Newman et al¹⁷ also failed to see much evidence of reflection ~10cm upstream of an occlusion of the central branch of the aortic trifurcation in dogs. Van den Bos et al¹⁸ used pressure separation to examine the effects in the ascending aorta of aortic occlusion at various locations in dogs; they commented that aortic occlusion near the iliac bifurcation had only small hemodynamic effects in the proximal aorta, although they did not present numerical data. Khir and Parker⁸ performed similar studies and reported that occlusion of the abdominal aorta and iliac artery had no discernable effect on wave reflection in the proximal aorta measured by wave intensity analysis. Latham et al.⁷ performed bilateral occlusion of the femoral arteries in man, but apart from commenting that this was associated with alterations in the shape of the pressure waveform in some participants, no quantitative analysis was reported. Murgo et al.¹⁹ investigated the effect of bilateral manual femoral compression on the aortic pressure waveform in man. They reported that this caused an increase of ~10 to 20mmHg in systolic pressure accompanied by a rise in diastolic pressure of around 4mmHg. The secondary rise in aortic pressure after an inflection point increased by ~10mmHg; these findings were interpreted as indicating increased wave reflection, but wave separation or intensity analysis was not performed to confirm this.

Wave reflections arise at any sites where there is an impedance mismatch. A completely closed end of a tube results in an extreme mismatch causing a forward compression wave to be reflected as a backward compression wave

of identical magnitude (i.e. $\Delta P_b/\Delta P_f$, the reflection coefficient = 1). Arterial occlusion by cuff inflation is likely to closely resemble a closed ended tube although flow disturbance and viscous losses²⁰ may result in less than complete reflection of wave energy. Most authors have considered the human circulation to be well matched in the forward direction;²¹ this necessitates that it is ill-matched in the backward direction.^{22, 23} Interestingly, Womersley⁵ speculated on similar grounds that the branching structure would minimise reflected waves and McDonald⁶ considered reflections to be of minor and largely academic interest, at least in the aorta. Nevertheless, the nature and location of reflection sites has remained contentious.^{24, 25} The data presented in this study demonstrate that the intensity of a reflected wave is heavily attenuated as it travels backwards. This behaviour is inconsistent with some current paradigms, notably the symmetric or asymmetric T-tube models, which assume that the aorta can be considered as a uniform tube connecting the heart to the peripheral circulation and envisage discrete reflected waves arising from the upper and lower limbs propagating into the aorta. Our observations are compatible with myriad reflections and re-reflections from many sites contributing to the blood pressure waveform.^{8, 13} The summation of these could be viewed as a 'reservoir' pressure.^{11, 15} Our findings also give insights into why large discrete reflections are evident in the periphery,^{26, 27} but are nearly imperceptible in the proximal aorta. Impaired retrograde transmission of reflected waves is consistent with theory²³ and previous experimental reports of directional disparity of pulse reflection²² or the 'horizon effect' previously described in the human aorta.¹³

The study has a number of limitations. The majority of the participants were male. All participants had an indication for coronary angiography and several

of the patients were regularly taking anti-anginal or anti-hypertensive medication; nevertheless only ~50% had coronary artery disease confirmed by angiography. It is unlikely that these factors will have substantially affected the within-participant responses observed in this study. It also is noteworthy that use of a 55-artery model based on a normal healthy human circulation gave similar findings.

Conclusions

Under normal conditions only minimal intensity wave reflection is evident in the human aorta. Occlusion of the femoral artery creates a large intensity reflection locally but this reflection is attenuated as it passes retrogradely and is barely discernable > 40cm from the site of occlusion, including in the proximal aorta. Backward transmission of reflected waves is markedly attenuated due to the impedance mismatches presented by intervening bifurcations traversed retrogradely. Consequently the branching design of the circulation minimises the intensity of reflected waves reaching the aorta.

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Table 1. Characteristics of participants

Variable	Result (n=20)
Age, y	62±13
Male, n (%)	14 (70)
Height, cm	171±10
Blood pressure, mmHg	134±13 / 79±8
Heart rate, bpm	75±16
Hypertension, n (%)	10 (50)
Diabetes, n (%)	6 (30)
Current smoker, n (%)	5 (25)
Angiographic coronary artery disease, n (%)	4 (20)
Lipid lowering therapy, n (%)	12 (60)

Data are mean±SD or n(%).