

Original Research

Reduced Pressure Wave Reflections in Patients with Active Clinical Status of Adamantiades-Behcet Disease

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Key words:

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Introduction: Acute and chronic inflammation has a deleterious effect on arterial structure and function. Increased arterial stiffness and pressure wave reflections may provide a pathophysiological link between inflammation and increased cardiovascular risk. Adamantiades-Behcet disease (ABD), a relapsing inflammatory vasculitis, is associated with impaired arterial properties modulated by corticosteroids. The effect of inflammation on arterial properties during the active state of ABD is not well known.

Methods: In 47 subjects with ABD, under no corticosteroid treatment, we examined pressure wave reflections (augmentation index, AIx) and central pressures by pulse wave analysis, as well as local aortic stiffness and left ventricular function by high resolution ultrasound. Thirty subjects with similar cardiovascular risk factors served as a control group.

Results: Subjects with active ABD (n=11) had lower AIx and central systolic blood pressure (CSBP), but similar peripheral blood pressure, stroke volume, and slightly higher local aortic stiffness in comparison to patients with inactive ABD (n=36) (AIx: 12.6 ± 11.4 vs. $23.2 \pm 19.1\%$, $p=0.009$; CSBP 104.2 ± 12.4 vs. 115.4 ± 15.7 mmHg, $p=0.028$). The arrival of the reflected pressure wave within the cardiac cycle was significantly delayed in subjects with active ABD. Low values of AIx (<10.5%) predicted with 73% sensitivity the presence of active ABD.

Conclusions: Patients with ABD, not treated with corticosteroids, have decreased pressure wave reflections and CSBP in the presence of active disease, possibly due to peripheral arterial vasodilation, but not due to altered left ventricular or aortic function. The underlying pathophysiological mechanisms and the role of low AIx in the presence of systemic inflammation need to be investigated further.

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The gradual increase of arterial stiffness as well as the decrease in diameter from the central to the peripheral arteries leads to the generation of pressure wave reflections. Ample data exist to show that increased systemic inflammation has a deleterious effect on both the structure and function of the arterial wall^{1,2} and may enhance the atherosclerotic and/or ar-

teriosclerotic process.³ Both acute and chronic inflammation, under various conditions, have been associated with endothelial dysfunction,⁴⁻⁶ increased arterial stiffness, and altered pressure wave reflections,⁷⁻¹³ the latter being a major hemodynamic consequence of stiffness gradient. These deleterious effects of systemic inflammation on the aforementioned surrogate markers of car-

diovascular risk¹⁴ may lead to increased central blood pressures in the absence of increased peripheral blood pressure and provide a pathophysiological link between inflammation and increased cardiovascular risk.¹⁴⁻¹⁷

Adamantiades-Behcet disease (ABD) is a relapsing multisystemic inflammatory vasculitis affecting both the small and large arteries.^{18,19} It has been shown previously that endothelial function is impaired in subjects with ABD.²⁰⁻²² We and others have also demonstrated that arterial stiffness is increased^{12,23,24} in ABD and that pressure wave reflections are modulated by corticosteroid treatment,²⁵ implying a role of inflammatory or autoimmune mechanisms in their generation. To the best of our knowledge, no data exist regarding the effect of the acute inflammation during a relapse of ABD on pressure wave reflections.

In a cohort of 82 consecutive subjects with ABD (excluding those patients who were under treatment with corticosteroids, either chronic or given upon relapse) we examined the relation between the activity of ABD, pressure wave reflections and local large artery stiffness. We also assessed left ventricular function in an attempt to interpret the different pathophysiological mechanisms involved in the potential alteration of pressure wave reflections.

Methods

Study population

The study was approved by the Institutional Scientific and Ethics Committee and all patients gave informed

consent. Eighty-two patients with ABD who fulfilled the International Study Group (ISG) inclusion criteria were examined as outpatients in the vascular laboratory of our department as previously described.¹² Of these, 35 were excluded from the present study on the basis of the following criteria: atrial fibrillation; severe aortic stenosis or aortic regurgitation (2/4); presence of diabetes mellitus; corticosteroid medication. Thus 47 patients (18 women) made up the study population, 11 of whom had active ABD, defined as having at least two symptoms according to the ISG criteria (Table 1). No sign of clinically active vascular disease was present in any patient at the time of the vascular tests. ABD-specific drug treatment is shown in Table 2. Since arterial stiffness and pressure wave reflections are highly related to age, cardiovascular risk factors and vasoactive medication, the patients with ABD were compared to 30 control subjects with similar age (age 41.9 ± 9.9 , 11 women), cardiovascular risk factors and drug treatment in order to have reference values (Tables 1 & 2). None of the subjects in the control group had any history or sign of cardiovascular disease on clinical examination and resting electrocardiogram.

A venous blood sample was obtained from each subject on the day of the vascular tests, after an overnight fast, for the determination of a routine biochemical profile including total cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol and glucose levels, all derived using standard methods. Low density lipoprotein (LDL) cholesterol was calculated by Friedewald's formula for patients with serum triglycerides <400 mg/dl.

Table 1. Anthropometric characteristics and cardiovascular risk factors in controls and patients with inactive and active Adamantiades-Behcet's disease (ABD).

	Controls	Inactive ABD	Active ABD	p
N	30	36	11	
Women/men	11/19	15/21	3/8	0.682
Age (years)	41.9 ± 9.9	42.3 ± 13.1	38.8 ± 8.9	0.664
Weight (kg)	81.8 ± 14.1	73.9 ± 15.4	80.45 ± 14.5	0.092
Height (cm)	171.5 ± 9.3	169.4 ± 8.1	$177.1 \pm 9.7^*$	0.047
BMI (kg/m^2)	27.7 ± 3.5	25.6 ± 4.8	25.6 ± 3.7	0.428
Total cholesterol (mg/dl)	202.8 ± 46.2	203.1 ± 47.3	201.0 ± 43.3	0.994
LDL-cholesterol (mg/dl)	130.3 ± 36.6	128.7 ± 25.3	116.6 ± 25.3	0.626
HDL-cholesterol (mg/dl)	46.9 ± 12.7	46.5 ± 10.7	44.9 ± 10.4	0.956
Triglycerides (mg/dl)	127.1 ± 85.3	127.3 ± 100.8	120.2 ± 72.7	0.987
Glucose (mg/dl)	81.1 ± 10.1	91.1 ± 14.2	96.1 ± 11.1	0.544
Smoking (pack years)	9.3 ± 13.8	14.4 ± 19.1	7.7 ± 10.4	0.455

Continuous variables are expressed as mean \pm standard deviation. BMI – body mass index; LDL – low density lipoprotein; HDL – high density lipoprotein. * $p < 0.05$ vs. inactive ABD.

Table 2. Vasoactive and disease-specific medication for Adamantiades-Behcet's disease (ABD). Values are given as n (%).

	Controls	Inactive ABD	Active ABD
Cardiovascular drugs:			
β-Blockers	1 (4.2)	2 (5.7)	0 (0)
ACE-inhibitors	1 (4.2)	1 (2.9)	0 (0)
Ca channel blockers	1 (4.2)	1 (2.9)	1 (9.1)
Diuretics	2 (8.4)	1 (2.9)	0 (0)
ABD drugs:			
Azathioprine	–	3 (8.7)	1 (9.1)
Colchicine	–	15 (41.7)	6 (54.5)
Cyclosporine	–	4 (11.4)	0 (0)

ACE – angiotensin converting enzyme.

Estimation of pressure wave reflections and hemodynamic parameters

Radial artery tonometry and pulse wave analysis (PWA) technique, using a Sphygmocor apparatus (PWA, AtCor Medical, Sydney, Australia) and calibrated from brachial blood pressure recording, was performed for the estimation of pressure wave reflections. This method estimates the aortic pressure waveform noninvasively through a mathematical transformation of the radial pressure waveform.²⁶ The technique has been found to be accurate when compared to intra-arterial blood pressure measurements and reproducible under various hemodynamic states.^{27,28} The aortic augmentation index (Aix) expresses the increase in aortic systolic blood pressure caused by the arrival of reflected pressure waves. It is defined as the increment of aortic pressure from the first systolic shoulder, called the inflection point, to the peak systolic pressure, expressed as a percentage of pulse pressure; therefore, higher values of aortic Aix correspond to increased pressure wave reflections. Arterial structural properties, involving atherosclerosis, hypertrophy or remodeling of arterial and arteriolar vessels, as well as microvascular architecture, determine the site of reflections and the amplitude of the backward traveling reflected pressure waves. In the present study, pulse wave velocity (PWV) was indirectly assessed by calculating the time between the foot of the aortic pressure wave and the inflection point (reflected wave, time transit, RWTT), which corresponds to the round trip (forward and backward travel) of the pressure wave, as previously described,²⁹ and then the ratio RWTT/ED (ED: ejection duration, measured from the foot of the pressure wave to the diastolic notch) was calculated as an index of timing of wave reflections in the cardiac cycle.

Local aortic stiffness and left ventricular function were estimated as previously described.¹² In brief, all studies were performed using a Toshiba Sonolayer SSH 140A phased array ultrasound system with a 2.5 MHz-duplex transducer. Stroke volume was assessed from cross-sectional echocardiographic images of the left ventricle. The following parameters were measured from cross-sectional echocardiographic images of the aorta. Thoracic aorta (Ao) diameters (mm/m²) were measured 3 cm above the aortic valve by 2-dimensional guided M-mode transthoracic echocardiography of the aortic root using the left parasternal long axis view. Aortic systolic diameter (AoS) was measured at the time of full opening of the aortic valve and diastolic (AoD) diameter at the peak of the QRS complex on the simultaneous ECG recording. Maximal abdominal Ao diameter (mm/m²) was measured from the subcostal window. Aortic stiffness index was calculated as $\ln(\text{SBP}/\text{DBP})/[(\text{AoS}-\text{AoD})/\text{AoD}]$, where SBP and DPB are systolic and diastolic blood pressures. Note that, as previously reported,¹² there is no statistically significant difference in the aortic stiffness index regardless of whether central or peripheral blood pressure is used in the formula.

All the hemodynamic studies were conducted by physicians who were blinded to the ABD status (active or non active) and the related medication.

Statistical analysis

Analysis of variance (ANOVA) was used to compare continuous variables between the control group and patients with inactive and active ABD. When needed, analysis of covariance (ANCOVA) was performed in order to adjust for confounding factors (age, sex, height, heart rate) by introducing them as covariates. Bonferroni post hoc analysis was performed for pair-

wise multiple comparisons when needed. The chi square test was used for assessing differences regarding qualitative variables. Receiver operator curve analysis was used in order to define the ability of low AIx to predict the clinical status of the disease and to determine the best available cutoff level for both sensitivity and specificity. Analysis was performed using SPSS statistical software (v.13.0, Chicago IL, USA). A p-value <0.05 was considered as the level of statistical significance.

Results

There were no significant differences between the control group and patients with active and inactive ABD regarding age, sex and classical cardiovascular risk factors (Table 1). Subjects with inactive disease were significantly shorter. No differences among the 3 groups were observed regarding the use of vasoactive drugs or ABD-specific drugs (Table 2).

Peripheral blood pressures were similar in the 3 groups (Table 3). Central SBP, but not DBP, was significantly lower in patients with active ABD compared to those with inactive ABD. Similarly, lower AIx was found in patients with active ABD compared to those with inactive disease; we also found that AIx in patients with inactive ABD had a trend to be higher compared to the control group. The differences in central SBP and AIx were not affected after adjustment for age, sex,

height and heart rate (Figure 1). Subjects with active ABD tended to have a higher heart rate and had a significantly smaller ED, when compared to those with inactive ABD. Although the absolute value of arrival of the reflected pressure wave (RWTT) differed only slightly among the groups, the final relative timing (RWTT/ED) of this parameter in the systolic phase was significantly delayed in patients with active ABD compared to those with inactive ABD. No significant differences between the 3 groups were observed concerning left ventricular systolic function. The aortic stiffness index and the abdominal aorta diameter increased gradually, and significantly, from the controls to subjects with inactive ABD, and even more to those with active ABD.

Receiver operator curve analysis showed that low AIx may adequately predict the clinical activity of ABD (area under the curve: 0.730; p=0.015, 95% CI: 594-866). A value of AIx <10.5% had 73% sensitivity and 80% specificity in the prediction of the active state of ABD (Figure 2).

Discussion

The novel finding reported in this study was that subjects with increased acute systemic inflammation during a clinical relapse of ABD have lower pressure wave reflections (AIx) and central SBP, but similar periph-

Table 3. Comparison of hemodynamic parameters between subjects with active and inactive Adamantiades-Behcet's disease (ABD). Values are expressed as mean \pm standard deviation.

Cardiovascular parameters	Controls	Inactive ABD	Active ABD	p
P-SBP (mmHg) ¹	123.2 \pm 15.4	124.0 \pm 16.2	124.0 \pm 16.2	0.981
P-DBP (mmHg) ¹	77.2 \pm 2.0	82.1 \pm 2.8	77.5 \pm 3.3	0.178
C-SBP (mmHg) ²	109.6 \pm 15.4	115.4 \pm 15.7	104.2 \pm 12.4*	0.030
C-DBP (mmHg) ²	82.5 \pm 11.5	83.3 \pm 10.8	79.2 \pm 11.6	0.114
AIx (%) ¹	18.0 \pm 14.1	23.8 \pm 19.3	13.4 \pm 12.4*	0.028
AIx (%) ²	14.9 \pm 13.4	23.2 \pm 19.1 [†]	12.6 \pm 11.4*	0.009
AIx (%) ³	18.8 \pm 14.6	21.8 \pm 18.3	17.8 \pm 13.9	0.463
RWTT (ms)	104.9 \pm 13.9	105.8 \pm 11.6	111.7 \pm 8.3	0.388
Heart rate (beats/min)	79.1 \pm 15.5	74.0 \pm 11.1	81.1 \pm 12.4	0.156
ED (ms)	278.9 \pm 30.4	297.2 \pm 24.5 [†]	281.0 \pm 24.8*	0.020
RWTT/ED (%)	37.8 \pm 4.4	35.7 \pm 4.8	39.9 \pm 3.2*	0.019
Stroke volume (ml)	54.8 \pm 18.1	54.2 \pm 12.9	52.9 \pm 13.9	0.967
Aortic stiffness index	4.5 \pm 2.2	14.5 \pm 8.9 [†]	18.3 \pm 9.7 [†]	<0.001
Abdominal aorta D (mm/m ²)	17.1 \pm 2.6	18.6 \pm 2.8	20.8 \pm 2.4 [†]	0.009
Thoracic aorta D (mm/m ²)	28.6 \pm 3.2	30.2 \pm 3.1	32.1 \pm 3.1	0.147

¹p values are adjusted for age and sex; ²p values are adjusted for age, sex, height and heart rate; ³p values are adjusted for: age, sex, height and RWTT/ED. *p<0.05 vs. inactive ABD; [†]p<0.05 vs. control.

AIx – augmentation index; C – central (aortic); D – diameter; ED – ejection duration; P – peripheral; RWTT – reflected wave time transit; SBP/DBP – systolic/diastolic blood pressure.

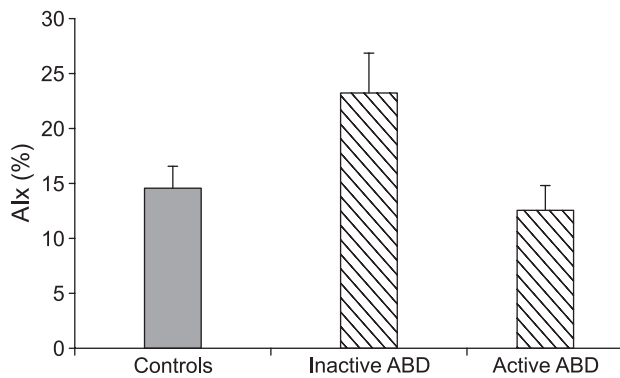


Figure 1. Difference in augmentation index (AIx) (mean \pm SEM) between the control group and patients with inactive and active Adamantiades-Behcet's disease (ABD). Values are adjusted for age, sex, height and heart rate by ANCOVA, $p=0.009$. Pairwise comparison by Bonferroni post hoc analysis: $p=0.030$ for inactive vs. active, $p=0.038$ for inactive ABD vs. controls.

eral blood pressure in comparison to patients with inactive ABD. This finding was independent of age, sex, heart rate and height. It could be explained by the presence of altered pressure wave reflections, potentially due to peripheral vasodilation, but not due to changes in left ventricular systolic function or aortic elastic properties. Low values of AIx ($<10.5\%$) were able to predict the presence of active ABD with 73% sensitivity.

The detrimental effect of systemic inflammation on arterial stiffness is now well established,^{4,13,21-23} but

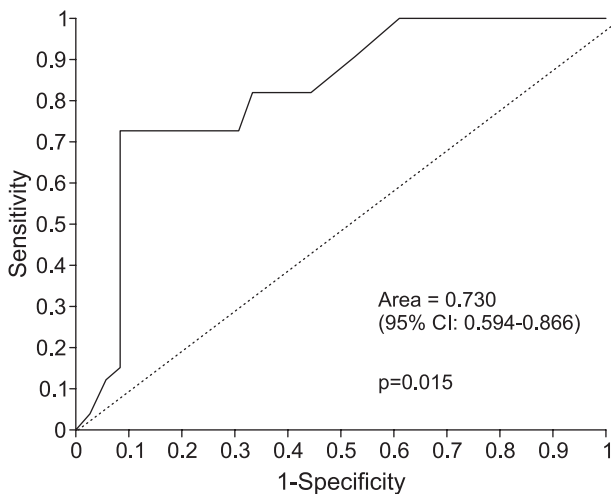


Figure 2. Receiver operator curve (ROC) for the prediction of the activity of Adamantiades-Behcet's disease (ABD): area under the curve: 0.730; $p=0.015$, 95% CI: 0.594-0.866. A value of augmentation index (AIx) $<10.5\%$ had 73% sensitivity and 80% specificity in the prediction of the active state of ABD.

differences regarding its effect on pressure wave reflections have been described. In patients with rheumatoid arthritis, a severe chronic inflammatory disease (subjects on high dose of corticosteroids were excluded), higher AIx and central blood pressures were found compared to the control group.⁷ The same study found a weak correlation between AIx and high-sensitivity C-reactive protein. In contrast, in apparently healthy individuals there are conflicting data regarding the correlation of the degree of systemic inflammation (C-reactive protein) and AIx,^{10,11} even though C-reactive protein was independently associated with PWV.¹⁰ Similarly, in a recent study we showed that in hypertensive subjects low grade chronic inflammation, assessed by high-sensitivity C-reactive protein, was independently correlated with a large degree of artery stiffness (carotid-femoral PWV) but not with pressure wave reflections (AIx).²⁹ Finally, in subjects with antibody-associated systemic vasculitis (AASV), a primary vasculitis affecting predominantly the small arteries, both PWV and AIx were significantly higher than in controls, but not in those subjects with disease remission.⁹ The aforementioned discrepancies may be related to: (i) the vascular bed (small, medium or large arteries) that is predominantly (directly or indirectly) affected in each disease; (ii) the degree of the inflammatory stimulus; as well as (iii) the model (acute, relapsing or chronic) of the inflammatory process.

In this study we aimed at assessing pressure wave reflections non-invasively at the level of the aorta via a widely used index, namely AIx, which has been shown previously to be an independent predictor of mortality in various diseases.¹⁴ AIx quantifies the pressure wave reflections, but it depends not only on the amplitude of the reflected pressure wave, but also on the timing of the arrival of the reflected wave within the cardiac cycle.³⁰ Therefore, AIx greatly depends also on height, sex (due to differences in height), heart rate/ejection duration, as well as on PWV.^{15,30} Although increased arterial stiffness, and hence increased PWV, tends to cause an earlier arrival of the pressure wave, leading to higher AIx, under certain conditions this effect may be counterbalanced by peripheral vasodilation, tachycardia, or other modulators of the timing of the arrival of the reflected pressure wave.³¹ Indeed, recently Vlachopoulos et al¹³ showed that, although arterial stiffness (pulse wave velocity) may increase abruptly in the presence of acute inflammation, pressure wave reflections (AIx) may decrease. In that study,¹³ low pressure wave reflection indices were considered to be the result of peripheral vasodilation induced by transient acute systemic inflammation, leading to an attenuation of the reflected

pressure wave. A similar effect of acute inflammation in patients with active ABD might represent the most probable explanation of our results. Increased sympathetic nervous system activity leading to the acceleration of heart rate, and especially alterations in the ejection time duration in subjects with active ABD, have in part modulated the final pattern of the timing, as assessed by RWTT/ED. However, this difference in timing, as well as the fact that patients with active disease were taller, could not explain the differences observed in AIx, as shown after additional adjustment, suggesting the presence of an attenuation of the pressure wave reflection. On the other hand, the fact that in patients with active ABD pressure wave reflections arrived later (higher RWTT) than in those with inactive ABD – although aortic stiffness (and thus possibly PWV, too) tended to be higher – strongly implies a distal shift of the effective reflecting distance. Finally, there were no changes in left ventricular function that could potentially account for our findings.

On the other hand, the fact that in patients with active ABD pressure wave reflections arrived later (higher RWTT) than in those with inactive ABD – although aortic stiffness (and thus possibly PWV, too) tended to be higher – strongly implies a distal shift of the effective reflecting distance.

In ABD, C-reactive protein does not reflect the degree of clinical activity of the disease and thus the degree of systemic inflammation, which was therefore assessed only via the disease status.^{12,16} On the contrary, interleukin-8 has been suggested as a more adequate marker of ABD activity.³² Increased production of interleukins, which are known to evoke vasodilation,³³ has been observed during the acute decrease of AIx.¹³ Similarly, increased production of interleukins at the level of the microcirculation has been observed in patients with active ABD³⁴ and may therefore represent the common pathophysiological link.

In this analysis we excluded patients under corticosteroid treatment because we have previously shown that corticosteroids have a potent and beneficial effect on AIx independently of the ABD status.²⁵ Nevertheless, we have shown, in agreement with previous findings,^{12,21,25} that inactive ABD is associated with increased arterial stiffness and that pressure wave reflections are higher compared to the control group. Unfortunately, the “gold standard” parameter of segmental aortic stiffness (PWV) was not available in this study, and this may in part limit our interpretation.

Taking the above results together, as well as the results of previous studies that evaluated arterial stiffness

in ABD, we suggest that this relapsing syndrome may provide useful information regarding the effect of the inflammatory process on arterial mechanics. It seems that even the relapsing episodes of inflammation may have a chronically stable detrimental effect on both large and small arteries, due to structural changes (e.g. arterial remodeling) at the level of the macro- and microcirculation.^{12,21,23-25} On the other hand, during the acute phase of the inflammatory process, particular patterns of central blood pressures may develop due to functional changes (peripheral vasodilation) leading to alterations in pressure wave reflections. The differences observed between acute ABD and other acute phases of primary vasculitis, such as in AASV (increased AIx),⁹ may therefore be attributed to the underlying differences at the histological level, since AASV is a necrotizing vasculitis with a preference for small arteries, whereas ABD is characterized by perivascular mononuclear cell infiltration involving large, medium and small arteries. We speculate that in necrotizing small vessel vasculitis, the structural changes at the level of the arterioles lead to a “fixed” increase in reflection coefficient predominating over any functional-vasodilatory effect, thus increasing the magnitude of the pressure wave reflected. Whether the reduction of AIx in the presence of increased aortic stiffness represents a compensatory mechanism in order to protect the heart from increased central blood pressures remains to be further investigated.

Another finding of this study was that low AIx (<10.5%) had a very good sensitivity and specificity in detecting ABD activity. Since disease activity of ABD is based solely on clinical grounds, due to the lack of available circulating plasma markers, the potential ability of AIx to detect the relapse of the disease, as well as its correlation with disease specific manifestations, should be further evaluated in prospective studies.

In conclusion, we have shown for the first time that patients with ABD who are not under corticosteroid treatment have decreased pressure wave reflections and central SBP in the presence of active disease, possibly due to functional peripheral vasodilation. The pathophysiological role of low AIx in the presence of systemic acute inflammation, as well as the responsible mechanisms underlying this phenomenon, need to be studied further.

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