EXTENDED REPORT

Diffuse endothelial dysfunction is common to ANCA associated systemic vasculitis and polyarteritis nodosa

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The cardiovascular risk factors in the controls and patients with vasculitis are shown in web table W1, which can be found at www.annrheumdis.com

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Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) share an enhanced risk of cardiovascular morbidity and mortality.^{1,2} Recognition that acute vascular injury may be an initiating event in atherosclerosis³ has led to the proposal that increased cardiovascular mortality in RA might relate to earlier vasculitis, whether occult or overt.⁴ We have pursued this hypothesis by looking for evidence of endothelial dysfunction in primary systemic necrotising vasculitis (SNV).

Endothelial cell dysfunction (ECD) is now known to have a pivotal, possibly primary, role in atherogenesis, and is the earliest detectable physiological abnormality in atherosclerosis.⁵ Healthy vascular endothelium synthesises nitric oxide (NO) and a range of other substances responsible for aspects of vascular homeostasis, including smooth muscle tone, thrombosis, vascular permeability, and cellular adhesion.⁶ The functional integrity of vascular endothelium can be determined in vivo by flow mediated dilatation of the brachial artery.⁵ This technique uses high resolution ultrasound to measure arterial dilatation following transient occlusion, an effect mediated by NO.⁷ Measurement of this endothelium dependent vasodilatation (EDV) has shown that vascular risk factors, including smoking, hypertension, and hypercholesterolaemia, lead to endothelial dysfunction.⁸ In addition, brachial artery EDV correlates well with tests of coronary endothelial function and accurately reflects the extent of coronary vessel disease in studies of ischaemic heart disease.⁹ Functional integrity of dermal microvessels can be similarly assessed using laser Doppler flowmetry to measure changes in flow in response to vasodilator agonists. Agonists such as acetylcholine also elicit

Background: Excess cardiovascular mortality complicates systemic rheumatic disease, suggesting an accelerated atheromatous process, which it has been proposed relates to the vascular inflammation common in such diseases. Impaired endothelium dependent vasodilatation is an early marker of atheromatous disease. It has previously been shown that such endothelial cell dysfunction (ECD) occurring in the brachial artery can complicate primary systemic necrotising vasculitis (SNV).

Objective: To determine if ECD occurs in a wider spectrum of primary SNV, if it is restricted to the major arteries, and whether vasculitis subgroup, ANCA status, or renal involvement influenced the endothelial responses.

Methods: Fifty four patients attending the Birmingham vasculitis clinic, including patients with a range of ANCA and non-ANCA associated primary vasculitides, and a group of age matched controls were recruited. The length of patient follow up and disease activity was variable. Disease activity, damage scores, and cardiovascular risk factors were recorded before assessment of flow mediated brachial artery vasodilatation by high resolution ultrasound. Dermal microvascular responses to acetylcholine were also measured in 32 patients and 21 controls by laser Doppler flowmetry.

Results: ECD was demonstrated in all primary SNV subgroups of patients with ANCA associated vasculitis and in polyarteritis nodosa, compared with controls. Significant impairment occurred in both vascular beds, regardless of vessel size targeted in the inflammatory vasculitis, ANCA association and titre, or renal involvement.

Conclusions: Diffuse endothelial dysfunction, a predictor of atherosclerotic disease, is found extensively in primary systemic vasculitis. Involvement of different vascular beds is independent of target vessel size or ANCA association, and is unrelated to local disease expression. It is suggested that this results from a systemic response that may be a consequence of primary vasculitis, but is distinct from the local inflammatory vasculitic process.

NO mediated vasodilatation, and may be driven across the dermis by locally applying a low voltage to the skin, a process known as iontophoresis. This non-invasive, in vivo technique has again been used to demonstrate ECD in conditions associated with enhanced cardiovascular risk such as hyperlipidaemia and diabetes mellitus.^{10,11}

Using primary systemic vasculitis as a model for the effects of inflammatory vascular injury, we have previously shown in a small series that ECD is present at the brachial site in some cases of vasculitis.¹² The systemic vasculitides are a heterogeneous group of diseases, with different patterns of organ involvement, size and type of vascular target, and varying pathological mechanisms, such as ANCA associated damage. This current study aimed at determining if ECD could be found in vascular beds unaffected by the primary vasculitic process, and whether vasculitis subgroup or ANCA association influenced the observed degree of endothelium dependent responses. Multisystem disease such as systemic vasculitis is often complicated by secondary problems which are also associated with ECD, such as uraemia¹³ and hypertension.¹⁴ This

Abbreviations: BVAS, Birmingham Vasculitis Activity Score; CRP, C reactive protein; CSS, Churg-Strauss syndrome; ECD, endothelial cell dysfunction; EDV, endothelium dependent vasodilatation; EIV, endothelium independent vasodilatation; GTN, glyceryl trinitrate; NO, nitric oxide; PAN, polyarteritis nodosa; RA, rheumatoid arthritis; RBC, red blood cells; SLE, systemic lupus erythematosus; SNV, systemic necrotising vasculitis; TAK, Takayasu's arteritis; TNF α , tumour necrosis factor α ; WG, Wegener's granulomatosis

Table 1 Demographic and disease data. Values are expressed as median (range) or No (%)

	Controls	Vasculitis				
		All vasculitis	WG	CSS	PAN	TAK
Number	41	54	32	6	11	5
Age	45 (26–78)	52 (23–79)	59 (23–79)	51.5 (27–54)	38 (25–75)	41 (33–53)
Female:male	21:20	23:31	15:17	2:4	3:8	3:2
Disease duration (years)		5.1 (0.08–34)	5.9 (0.2–20)	4.1 (2–12)	0.5 (0.08–13)	19 (2.3–34)
Active at scan (%)		16 (30)	8 (25)	1 (17)	7 (64)	0
Remission at scan (%)		38 (70)	24 (75)	5 (83)	4 (36)	5 (100)

WG, Wegener's granulomatosis; CSS, Churg-Strauss Syndrome; PAN, polyarteritis nodosa; TAK, Takayasu's arteritis.

study further aimed at identifying the influence of these factors on the responses seen.

PATIENTS AND METHODS

Patients

Ethical approval was obtained and subjects gave informed consent. Fifty four new and follow up patients with primary SNV fulfilling Chapel Hill criteria¹⁵ were studied: 32 with Wegener's granulomatosis (WG), (13 systemic, 19 limited), 6 with Churg-Strauss syndrome (CSS), 11 with polyarteritis nodosa (PAN), and 5 with Takayasu's arteritis (TAK). Vasculitis disease activity was measured using the Birmingham Vasculitis Activity Score (BVAS)¹⁶ and organ damage was assessed with the vasculitis damage index.¹⁷ Clinical remission was defined as the absence of significant disease activity for at least one month (BVAS=0–1), active disease was defined as BVAS>1. Forty one age matched controls were studied. For all subjects cardiovascular risk factors, blood pressure, serum cholesterol, biochemical profile, and immunological markers were recorded. Risk factors were defined as follows: hypertension, systolic blood pressure >145 mm Hg or diastolic blood pressure >85 mm Hg; hypercholesterolaemia, serum cholesterol >5.0 mmol/l; smoking, history of current smoking or giving up smoking within 10 years (web extra table W1). Subjects had avoided caffeine, alcohol, smoking, and vaso-active drugs for 12 hours, and a heavy meal for three hours before the study. Subjects with current serum creatinine >150 µmol/l or taking angiotensin converting enzyme inhibitors were excluded. Brachial artery scans were performed on all subjects. Microvascular responses of 32 patients (19 WG, 4 CSS, 6 PAN, 3 TAK) and 21 controls were also assessed by laser Doppler flowmetry.

Brachial artery ultrasonography

Brachial artery ultrasonography was performed by standard techniques.¹⁸ EDV was measured after release of distal arterial occlusion. Endothelium independent vasodilatation (EIV), reflecting vascular smooth muscle function and therefore a positive control, was assessed by the response to glyceryl trinitrate (GTN). A B mode scan of the right brachial artery in longitudinal section, 2–12 cm proximal to the antecubital fossa, was obtained in supine subjects using a 7.5 MHz phased array transducer on a Sigma 44 HVD system. The anterior and posterior media-intima interfaces were used to demarcate artery diameter, calculated as the average of measurements during four cardiac cycles at end diastole. Each study comprised the following artery diameter measurements: (a) baseline, recorded after a 10 minute rest period; (b) EDV, 60–90 seconds after the sudden release of a pneumatic cuff inflated to suprasystolic pressure for five minutes on the ipsilateral forearm; (c) second baseline, after 10 minute rest period; (d) EIV, four minutes after sublingual GTN. The average baseline diameter was calculated from the two baseline recordings. EDV and EIV were expressed as the percentage change in artery diameter from baseline. Sonography was performed by

one of two investigators (JT, LL) who was unaware of the subjects' clinical details. Intraobserver variability, based on six and 17 subjects, showed coefficients of variation for baseline diameter, EDV, and EIV of 1.2%, 1.6%, 2.4% and 2.1%, 3.7%, 2.9% for investigators 1 and 2, respectively.

Laser Doppler flowmetry

Iontophoresis studies were performed by two investigators (JMG, LL) who were unaware of both diagnosis and disease activity, in a vascular laboratory maintained at constant temperature of 25°C (± 0.5°C). Thirty two subjects matched with 21 controls were examined. Subjects rested semirecumbent in light clothing for 20 minutes before study. Blood flow in the skin microcirculation was recorded at clinically unaffected sites by laser Doppler flowmetry (DTR4, Moor Instruments, Devon, UK) and recorded as red blood cell (RBC) flux. The vasodilators acetylcholine, an endothelium dependent vasodilator (Miochol, CIBAvision Ophthalmics), and sodium nitroprusside, an endothelium-independent vasodilator (Bull laboratories), were freshly prepared as 1% solutions in 0.5 M saline (vehicle). The iontophoresis chamber (Medical Physics Department, University of Birmingham) was attached, in a randomised order, to the dorsum of the fingers or volar aspect of the forearm of the non-dominant hand. The laser Doppler probe was incorporated in the centre of the chamber and recorded RBC flux continuously from the area to which iontophoresis was applied (MIC 1, Moore Instruments, Axminster, Devon, UK). Vehicle alone (anode and cathode), acetylcholine, and sodium nitroprusside were administered by iontophoresis, in a random order, to the different sites, as determined from previous studies.¹⁹ Currents of increasing intensity and duration were delivered to give a charge of 1–16 mC, and the peak response was recorded. Baseline RBC flux was recorded for one minute before, and two minutes after, iontophoresis. Baseline and maximum RBC flow were calculated for each period of iontophoresis for all three substances. Microvascular flow at control finger and forearm sites, which did not receive iontophoresis, was recorded to determine any environmental changes in RBC flux. There was no significant change in RBC flux from iontophoresis of vehicle alone, or at control sites not receiving iontophoresis in any subjects (data not shown). The change in flux was calculated as proportional change from baseline (maximum flux – baseline flux/baseline flux). A mean of two repeated finger measurements and two forearm measurements was used in the final calculation. There was no difference between the magnitude of forearm and finger responses.

Statistical analysis

Results are presented as the median and either interquartile range (IQR) or range as shown. Control and patient groups were compared with the Mann-Whitney test. Stepwise regression analysis was used to determine the independent impact of selected demographic, clinical, and laboratory findings on vascular responses. All results are presented as two tailed values and considered significant at $p < 0.05$.

Table 2 Brachial artery and microvascular endothelium dependent vasodilatation compared with controls. Data given represent median (range) for flow mediated brachial artery or for acetylcholine mediated dermal microvascular vasodilatation

	Controls	Vasculitis				
		All vasculitis	WG	CSS	PAN	TAK
Number	41	54	32	6	11	5
Brachial artery EDV (%)	7.2 (2.5–14.1)	3.8 (–12.9–10.8)	3.4 (–12.9–10.8)	3.3 (–2.4–6.8)	2.0 (–2.4–7.7)	5.8 (4.5–7.6)
p versus controls		<0.0001	<0.0001	0.008	<0.0001	0.26
Number	21	32	19	4	6	3
Microvascular EDV (%)	3.9 (1.9–6.1)	2.3 (0.8–4.2)	2.2 (1.3–4.2)	2.4 (0.9–4.2)	2.3 (0.8–3)	3.3 (2.1–3.3)
p versus controls		0.0002	0.0015	0.09	0.008	0.16

WG, Wegener's granulomatosis; CSS, Churg-Strauss Syndrome; PAN, polyarteritis nodosa; TAK, Takayasu's arteritis.

Figure 1 Brachial artery endothelium dependent vasodilatation split by disease group versus healthy controls. Bars represent median values. * $p < 0.01$ versus controls. **Figure 2** Microvascular endothelium dependent vasodilatation split by disease group versus healthy controls. Bars represent median values. * $p < 0.01$ versus controls.

RESULTS

Patient characteristics

Table 1 shows demographic variables and baseline disease characteristics. Cardiovascular risk factors were similarly distributed in patients and controls, with at least one risk factor present in 29 (71%) of the controls and 39 (72%) of the patients with vasculitis. There was no significant difference in age or total cholesterol between patient and control groups. All patients had at some time received steroids and immunosuppressant drugs, including cyclophosphamide, azathioprine, or methotrexate. Neither previous nor current drug use had any clear relationship to endothelial reactivity. Only one patient was receiving treatment with a statin.

Brachial artery responses

In this study EDV was significantly impaired at the brachial artery in all patients with primary SNV ($p < 0.0001$) compared with controls (table 2, fig 1). ANCA associated disease subgroups and patients with PAN both demonstrated significantly impaired brachial artery reactivity (table 2, fig 1). By contrast, there was no significant difference in brachial artery EIV positive control responses to GTN in any group (patients v controls, median 16.9% (IQR 11.7–20.6) v 18.8% (12.1–23.3)) or in baseline diameter (patients v controls, 0.43 cm (0.36–0.47) v 0.40 cm (0.34–0.49)).

Dermal microvascular responses

Dermal microvascular responses were studied to assess whether ECD in primary SNV was a generalised response or was restricted to larger muscular arteries. Significant impairment of microvascular EDV was seen in patients with primary SNV (all patients with SNV v controls, 2.3 (0.8–4.2) v 3.9 (1.9–

6.1), $p = 0.0002$), (table 2, fig 2). In individual patient subgroups, microvascular reactivity was significantly impaired in WG and PAN, $p = 0.0015$ and $p = 0.008$, respectively (table 2, fig 2). A similar figure was seen for the non-significantly impaired responses in the smaller CSS group. As with the brachial responses, there was no significant difference between patient groups and controls in the positive control EIV studies (patients v controls, 3.20 (2.2–4.1) v 3.35 (2.7–4.4)). There was consistency between impairment of brachial artery and microvascular EDV measured by the two methods in individual patients (rank correlation analysis, $p = 0.023$).

Relationship of ECD to cardiovascular and inflammatory risk factors

The relations between flow mediated brachial artery dilatation or agonist mediated microvascular flow with vessel size, cardiovascular risk factors, age, and vasculitic disease were explored by use of stepwise regression analyses for each technique (table 3). The presence of vasculitis was confirmed as an important determinant using both techniques. Baseline diameter emerged as an independent predictor of brachial artery EDV as in previous studies.²⁰ EDV was inversely correlated with age using both techniques, but not with total cholesterol, or the incidence of other cardiovascular risk factors. In regression models for patients alone, there was similar correlation between brachial artery EDV and baseline diameter. Analysis confirmed the relationship previously shown¹⁶ between disease activity measured by BVAS and C reactive protein (CRP; $p = 0.001$), but showed no correlation between brachial artery EDV or microvascular EDV and CRP, von-Willebrand factor, BVAS, or vasculitis damage index. No significant difference was detected in brachial artery EDV between the 16 patients with active primary SNV and the 38 in remission according to the BVAS. Changing the threshold

Table 3 Regression analysis of determinants of flow mediated (brachial artery) and agonist mediated (microvascular) dilatation in all subjects

	Brachial artery EDV		Microvascular EDV	
	Regression coefficient	p	Regression coefficient	p
Age	-0.30	0.02	-0.54	<0.001
Hypercholesterolaemia	-0.11	0.40	-0.19	0.20
Hypertension	-0.02	0.88	0.06	0.68
Smoking	-0.15	0.27	0.12	0.44
Diabetes	0.06	0.98	0.04	0.79
Baseline diameter	-0.30	0.02	—	—
Vasculitis	-0.47	<0.001	-0.46	<0.001

for disease remission did not alter this result. Duration of disease was not correlated with endothelial reactivity.

Relationship of ANCA to ECD

Data for brachial artery EDV were split by ANCA association of disease subgroup and by positive ANCA serology (table 4). Impairment occurred irrespective of ANCA association of the disease subgroup. In the same way, positive ANCA serology at the time of the scan did not relate to the presence or absence of ECD.

Lack of effect of renal involvement

As neither factors related to primary SNV disease mechanisms nor those related to classical cardiovascular risk factors explained the observed ECD, we examined its relationship with renal involvement in systemic vasculitis. Among the patients with WG, renal involvement defined by characteristic renal histology was not associated with more frequent or severe dysfunction; ECD was clearly present in the substantial group of patients with non-renal WG.

DISCUSSION

This study confirms and extends previous work,¹² showing that patients with vasculitic disease commonly have impaired endothelial function. Impaired EDV was seen not only in the brachial artery but also in the dermal microvasculature, regardless of whether any given disease subgroup affected small or medium sized vessels. None of the subjects had any clinical evidence of disease affecting the sites used to assess ECD. Direct damage to a particular size or type of blood vessel, a characteristic of systemic vasculitides, is therefore unlikely to explain this finding. Furthermore, our studies show that impaired endothelial reactivity is not specific to particular vasculitis subgroups, because ECD was seen in all subgroups, apart from the small cohort with TAK. Therefore it is vasculitis itself, rather than epiphenomena of certain forms of disease, which appears to cause the observed impairment of endothelial function. This observation of a diffuse effect upon the endothelium raises interesting questions, not only about the cellular mechanism of impaired reactivity but also about

the systemic effects of vasculitis and their mechanisms. There are concerns that the observed ECD may have the effect of promoting the inflammation of vasculitis itself, and also that such ECD may be linked to subsequent increased cardiovascular risk.

Age was the only cardiovascular risk factor to emerge as an independent predictor in multivariate analysis of disease and control groups. This result may reflect the broad age range of our patient and control groups, and the status of age as the most powerful cardiovascular risk factor. The relationship of other risk factors to endothelial dysfunction is less clear. The striking endothelial functional abnormalities in our patients were not correlated with smoking, total cholesterol, diabetes, or hypertension, which are independently associated with endothelial dysfunction.^{14 21–23} We conclude that the ECD, which is common in primary SNV but occurs at sites distant to the local vessel wall inflammation, arises from a different mechanism.

One potential mechanism for endothelial dysfunction in vasculitis is renal disease, because many patients with vasculitis have some degree of renal involvement. Renal impairment itself has been shown to impair EDV,¹³ hence the exclusion of patients with overt uraemia in this study. We suggested that previous renal disease, with periods of endothelial exposure to oxidative and cytokine stress, might function as a risk factor specific to vasculitis. However, there was no difference in endothelial function between patients with WG with and without renal involvement. An alternative mechanism for endothelial dysfunction in systemic vasculitis is direct endothelial cell activation and damage by the disease process involved in the primary inflammatory vasculitis. The best defined of such mechanisms are antibodies to neutrophil granules. ANCA mediate polymorphonuclear leucocyte damage to the endothelium through proteinases, reactive oxygen species, and toxic levels of NO.²⁴ However, no difference in endothelial response was shown between ANCA associated and non-ANCA associated disease. Moreover, positive ANCA serology (or significantly raised proteinase 3 or myeloperoxidase titres) at the time of scan had no independent effect on the ECD observed. However, such ECD may still have a role in

Table 4 Influence of renal involvement, ANCA association, and positive ANCA serology upon brachial artery EDV. Values given for brachial artery EDV (%) are shown as median (interquartile range)

	Renal involvement		ANCA association		ANCA serology	
	Involved	Non-involved	ANCA associated	Non-ANCA associated	Positive	Negative
Number	13	19	38	16	28	26
Brachial artery EDV (%)	4.1 (1.9–5.3)	3.1 (0.05–4.9)	3.4 (0.25–5.1)	4.2 (1.7–5.6)	3.3 (0.65–5)	4.1 (1.8–5.5)
p Value		0.24		0.32		0.32

The effect of renal involvement was studied in patients with WG only.

potentiating inflammatory vasculitis, by priming the endothelium for ANCA mediated cell damage. This would be analogous to the endothelial activation by factors such as tumour necrosis factor α (TNF α), which is an important part of current in vitro models of ANCA mediated effects.²⁴ It will be important in future to establish whether subjects who show persistent ECD despite apparent clinical remission of vasculitis are more likely to have a relapse of their disease.

Another potential risk factor specific to vasculitis is inflammatory disease activity and its correlate CRP, which might be expected to vary inversely with EDV, as suggested by our previous small longitudinal study.¹² Raised basal CRP levels have a well described relationship with coronary risk,²⁵ and raised CRP levels correlate with risk of coronary events in angina.²⁶ However, the increased CRP levels seen in these studies were minor in comparison with those seen in inflammatory vasculitis, and no such relationship emerged in this study. We speculate that in our heterogeneous group of patients, endothelial dysfunction may be seen both early in disease, when intensive treatment may normalise function,¹² and late in disease in association with established vascular end organ damage. As a result only those peaks of activity seen early in disease will correlate with loss of endothelial reactivity. Such peaks will only infrequently be included in a cross sectional study such as this. A calculation of the area under the curve for CRP in a future serial study should provide a better estimate of the effects of prolonged exposure to acute phase proteins on the endothelium. The relationship of endothelial responses to treatment requires further investigation, which can only be achieved by prospective, serial studies.

The nature of the relationship between the acute phase response and atherosclerosis is controversial. The former may simply be an indicator of events that induce the endothelial injury which is seen as the first step in atherogenesis. Thus systemic inflammation may promote a cytokine response that not only induces CRP release from hepatocytes but also results in direct endothelial injury.⁸ TNF α has been shown to cause prolonged local endothelial dysfunction in vivo in human models.²⁷ Serum levels may also correlate with endothelial dysfunction in diabetes,²⁸ and are correlated with atherosclerosis in the elderly.²⁹ Vasculitic disease is characterised by inflammatory cytokine release, although there is little correlation of plasma concentrations of these cytokines with disease activity.³⁰⁻³¹ However, preliminary experience with the use of TNF blockade in primary SNV suggests real clinical benefit, supporting the concept that TNF α may be a key mediator in vasculitic inflammation, and potentially also in induction of ECD.

A related mechanism of endothelial damage may be low density lipoprotein oxidation, promoted by the inflammatory microenvironment.³ Local oxidative stress due to inflammation, cytokines, and thrombotic occlusion might result in the generation of superoxide and peroxide radicals, oxidation of low density lipoprotein, and subsequent uptake by monocytes, resulting in perpetuation of the cycle of endothelial injury. Anti-endothelial cell antibodies found in vasculitis, SLE, and the antiphospholipid syndrome have also been shown both to activate and to directly damage the endothelium.³²⁻³³

Weyand *et al* have described expanded clones of CD4⁺ CD28^{null} T cells which are common to the peripheral blood of both patients with unstable coronary plaques and patients with RA at high risk of vasculitic complications. These clones appear to have escaped regulatory apoptotic mechanisms in the plaque environment, possibly owing to persistence of immunogenic infectious or self antigens.³⁴⁻³⁵ Similar cells have been documented in WG.³⁶ Such changes in the immune cell repertoire may also have a role in the diffuse endothelial dysfunction seen in this study. However, their presence in late established atheroma, at the time of clinical presentation, suggests they are more likely to relate to persistence than to initial induction of ECD.

Our results lead to the prediction that systemic vasculitis will exhibit an enhanced cardiovascular morbidity comparable with that seen in SLE and RA. This might have been obscured in the past by the continuing morbidity and mortality of primary SNV. Our findings inform and encourage further clinical studies to confirm this prediction, given the improved prognosis now seen in these diseases. Our finding that a diagnosis of vasculitis can carry an independent possibility of cardiovascular risk has potential implications for the treatment and surveillance of patients with vasculitis, particularly in the use of antiplatelet treatment, with screening and treatment of other risk factors becoming an important management strategy. As a model of direct vascular inflammation and damage, the study of endothelial function in systemic vasculitis may prove useful in assessing the impact of therapeutic interventions on the endothelium. Finally, the identification of a vasculitis related endothelial dysfunction provides a mechanism to substantiate our previous hypothesis that vasculitis underlies the accelerated cardiovascular risk associated with SLE and RA, both diseases where similar vascular inflammation is well established. In our current model, ECD induced by vasculitis is thus seen as the initiating event for ischaemic heart disease in RA.³⁷ This ECD in itself can promote atheroma, but in RA will prime the endothelium to induce enhanced susceptibility to other factors related to rheumatoid inflammation, which together produce the accelerated atherosclerosis of RA.

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