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**Cutaneous vascular response to local warming - a response
to letter from Cracowski and Roustit**

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5 Roustit
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9 ¹Clough, GF, ^{1,2}Avery, MR, ²Voegeli D, ¹Byrne CD and ³Simpson DM
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12 ¹School of Medicine, ²School of Health Sciences and ³ISVR, University of Southampton,
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14 Southampton, UK.
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19 Thank you for allowing us a reply you the letter by Cracowski & Roustit (2) regarding
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21 our recently published manuscript (1). We also thank Cracowski and Roustit for their
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23 interest in our study in which we set out to investigate and quantitate the relative impacts
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25 of age and smoking habit on vasomotor control in the skin during local warming.
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28 As Cracowski and Roustit admirably review in their letter and papers, the cutaneous
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30 vascular response to local warming in healthy individuals is now well characterised and
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32 the mechanism contributing to both the early and later components of the local
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34 hyperaemic response extensively investigated (3)(4). It is for these reasons that we chose
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36 to use thermal provocation as our tool to investigate microvascular control in our study.
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38 We do agree with Cracowski and Roustit that our use of mean heated flux during the
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40 plateau phase of the response and area under the response curve (AUC) during 10 min of
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42 skin warming may disadvantage an interpretation of the physiological factors modulating
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44 the response. However our clearly stated aims were to explore associations between
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46 smoking habit, age and cutaneous blood flow and flow motion using the dynamic
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48 approach of power spectral density (PSD) analysis of the very low component
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50 frequencies of the laser Doppler flux trace to explore deficits in control rather than
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52 pharmacological intervention. PSD analysis was undertaken using the final 350 sec of
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54 the 600 second recording acquired during the plateau phase of the response; i.e.
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56 commencing 150 sec (2.5 min) after the start of warming and excluding the early phase
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58 of the thermally induced hyperaemia. In this was we were able to avoid biasing our
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60 spectral estimates though inclusion of the initial transient response – attributed to

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3 increased neurogenic axon-reflex mediated activity - and to focus on the sustained largely
4 endothelium-dependent response that we hypothesized would be influenced by age and
5 smoking history. To maintain consistency in our analyses in the spectral and time
6 domains, we used mean plateau flux (excluding the early response) as our flux measure.
7 We also report the AUC of the total response above baseline as this has previously been
8 shown to be a sensitive integrated indicator of the total response (6)(7).
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16 It should be noted, as illustrated in Fig 1 of our paper (1), discussed in our text, and
17 alluded to by Cracowski and Roustit, many of our cohort who were smokers, did
18 additionally show a much attenuated and often delayed early peak, that is indicative of a
19 non – NO dependent component. As this was extremely variable and difficult to quantify
20 we decided to exclude an analysis of this from our final report. We would argue that our
21 conclusions on endothelial function over the plateau phase of the response are ‘clear cut’
22 within the defined limitations of the protocol. These conclusions remain that the total
23 hyperaemic response is dominated by an increase in endothelial/metabolic activity and
24 that smoking results in up to a 100% reduction in activity in both the time and spectral
25 domains.
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35 Cracowski and Roustit also comment on the overlap of the values of mean plateau flux
36 and AUC in smokers and non smokers that we report of our paper. We agree that there is
37 overlap and used the box plots in Fig 2 as an honest representation of this. However, the
38 similarity in mean heated flux and AUC between both groups may be due to a differential
39 impact of smoking and aging to affect the local hyperaemic response. The box plots show
40 that the variance around the mean was considerable, particularly in the non smokers. In
41 an attempt to elucidate the contribution of aging and smoking to affect the mean heated
42 flux and AUC, we undertook linear regression modelling to ascertain what proportion of
43 the variance was accounted for by either factor. Our data show that both smoking and age
44 were *independently* associated with AUC, and that together they contribute
45 approximately one third of the variance in endothelium-associated microvascular
46 vasomotor activity in our study cohort. We further reported that age is having a slightly
47 more marked effect to influence the outcome than is smoking as it accounts for a greater
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3 proportion of the variance. Whether this is due to a diminished NO-dependent
4 mechanism as suggested by Minson et al (5) or to a reduction in nutritive vessels as
5 discussed and referenced in our paper, remains to be further elucidated. We concur with
6 Cracowski and Roustit that any change in tissue anatomy brought about through the
7 natural process of aging or as a consequence of vascular pathologies should be taken into
8 consideration when attempting to interpret the output from laser Doppler flowmetry.
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16 Finally, there are an increasing number of investigations that have been performed and
17 even more that could be undertaken to more fully explore the mechanisms underlying
18 altered vascular responsiveness and its impact on tissue health. We believe that our study
19 through its clearly stated aims, protocol design and outcomes contributes to this body of
20 knowledge and opens the way for further studies using approaches such as those
21 described in our paper and suggested by Cracowski and Roustit in their letter. Together
22 these should be directed at improving our understanding of the role played by
23 microvascular (dys)function in the disease burden placed upon us by both non-modifiable
24 risk factors such as age and modifiable risk factors, such as smoking and life style.
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