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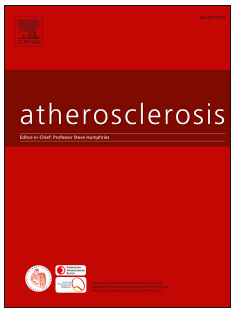

Reply to: “Endothelial progenitor cell release is usually considered a beneficial effect: Problems in interpreting the acute effects of e-cigarette use”

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Reply to: " Endothelial progenitor cell release is usually considered a beneficial effect: Problems in interpreting the acute effects of e-cigarette use"

To the Editor,

Vascular injury has long been known to be the main cause for mobilization of endothelial progenitor cells (EPCs) [1-3]. It has been proven that the strongest factor mobilizing EPCs is hypoxia in the vascular wall, causing the release of vascular endothelial growth factor 2 (VEGF-2) and stromal derived factor 1 (SDF-1) [1-3]. These two factors bind to receptors on EPCs, initiating mobilization and homing to the site of lesion. Therefore, it is not surprising that in cases of obvious vascular damage, such as in myocardial infarction or stroke, EPCs are highly elevated [1-3].

As previously suggested, chronic mobilization of EPCs may lead to depletion of EPCs, which is associated with an increased risk for cardiovascular disease [1-3]. Therefore, levels of circulating EPCs are lower in patients with cardiovascular risk factors such as daily smoking, diabetes, hypertension, dyslipidemia or stable coronary artery disease. Kondo *et al.* demonstrated that smoking cessation leads to an increase in EPCs in the following two weeks. Acute cigarette exposure, both actively and passively, leads to an immediate increase in EPCs and it is very likely that chronic exposure will lead to a depletion of these bone marrow derived cells [4, 5].

In contrast to the general consensus [1-3], Farsalinos and Polosa claim that a sudden elevation of EPCs is largely interpreted as beneficial. This interpretation is based on studies, which we believe are not applicable to our recent study. Firstly, Farsalinos and Polosa quote a review by Shantsila *et al*. regarding EPCs in cardiovascular disorders. The review clearly describes that chronic exposure to risk factors, such as hypertension, smoking, diabetes and dyslipidemia, damage the endothelial wall, which subsequently requires replacement, i.e. EPC mobilization. In addition, Shantsila *et al.* describe

how risk factors can also directly affect EPC mobilization as well as cause exhaustion of progenitor cells in the bone marrow; all of which are not considered to be a beneficial effect.

Moreover, Farsalinos and Polosa cite a review by Silva *et al*. on EPCs and physical activity. This review describes several studies that have demonstrated that levels of EPCs increase following physical activity. It also states that this increase is correlated with VEGF-2 levels in the blood of study participants. The authors of the review conclude that EPC mobilization observed after physical activity is most likely an effect of physiological ischemia of the vascular wall. Thus, they present a link between EPC mobilization and ischemia.

Lastly, Farsalinos and Polosa refer to several long-term studies were consumption of red wine, Mediterranean diet, and green tea cause increased levels of EPCs in healthy individuals over weeks. It is important to carefully read the study design to fully understand the results and discussion of the cited articles. Whilst our results demonstrate an acute EPC increase within the first 4 hours following exposure, the studies Farsalinos and Polosa refer to demonstrated EPC increase following 2-4 weeks of exposure. It is very important to highlight that these effects are more of *chronic* nature than *acute*. We strongly believe that the acute effects, following smoking and nicotine containing e-cigarette inhalation, where EPC levels are immediately increased over the course of hours and then later decrease to baseline levels, are an indication of a pathophysiological response [4, 6].

It is important to note that there are great economical interests in the emerging e-cigarette market. By the end of 2017, the sales margins of e-cigarettes are estimated to exceed those of the conventional cigarettes in the United States, and the tobacco companies have invested largely in e-cigarettes [7]. The e-cigarette industry has financed several studies and, not surprisingly, these studies have depicted the e-cigarette as harmless or almost harmless, especially when compared to conventional cigarettes [8]. Therefore, we are not surprised that scientists affiliated to the e-cigarette

industry would question our interpretation of data. Not long ago, second-hand combustible smoking was regarded as harmless by authors with associations with the tobacco industry [9]. In a review by Barnes *et al.*, the only factor that influenced the conclusion on whether second-hand smoking is harmful or not was the affiliation of the authors[9].

When discussing the potential dangers of e-cigarette use, one should not immediately compare e-cigarettes with conventional cigarettes. Today, much evidence points towards e-cigarettes being less toxic than cigarettes. However, the e-cigarette industry is not solely interested in targeting current smokers, but also smoking naïve young individuals like adolescents [10]. Therefore, it is important to further conduct e-cigarette industry independent research on electronic cigarettes, not only with the purpose of comparing with combustible tobacco products.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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