

# Acute effect of heat-not-burn versus standard cigarette smoking on arterial stiffness and wave reflections in young smokers

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Tobacco cigarette smoking increases arterial stiffness and blood pressure (BP), which are independent predictors of cardiovascular risk.<sup>1,2</sup> Heat-not-burn cigarette (HNBC) products have been advocated as a less unfavourable smoking option.<sup>3</sup> However, whether HNBC smoking increases arterial stiffness acutely has not been investigated. We investigated the acute effect of HNBC smoking and standard tobacco cigarette on arterial stiffness and wave reflections, as assessed by carotid–femoral pulse wave velocity (*cf*PWV), brachial–ankle PWV (*ba*PWV) and augmentation index (AIx).

We studied 22 current smokers (age:  $33 \pm 5$  years, 55% females, no other risk factors, no medications) attending our hospital's Smoking Cessation Unit. All subjects smoked randomly: (a) HNBC (IQOS) heat stick for 5 min, (b) a standard tobacco cigarette for 5 min and (c) sham cigarette on three separate occasions. The mean nicotine content for both HNBC and tobacco cigarette was 0.5 mg. Every session took place in the morning, after a minimum 4-h fasting period, while the subjects had not smoked or consumed any caffeinated beverage. The order of smoking sessions was randomized. To eliminate possible carry-over effects, the sessions were conducted at least two days apart from each other.

Heart rate (HR), BP (both brachial and aortic), AIx corrected for HR (AIx@75), *cf*PWV and *ba*PWV were assessed immediately before and after smoking, and then at 5, 10, 20 and 30 min. The study protocol was approved by Research Ethics Committee and all subjects provided written informed consent. A non-inferiority trial design was conducted; we anticipated

that the largest difference would be at 5 min according to our study comparing the effect of e-cigarettes and tobacco cigarette on pulse wave velocity (PWV).<sup>4</sup> Based on a  $2 \times 2$  cross-over design with an equal number in each sequence, a total sample size of 22 subjects would achieve 80% power to detect non-inferiority using a one-sided *t*-test when the true mean difference between tobacco cigarette and HNBC at 5 min is 0.3, the margin of non-inferiority is 0.03, the significance level is 0.05 and the standard deviation of the paired differences is 0.6. The results at various time points were compared with the baseline measurements within each arm, and between the three arms using paired and unpaired *t*-tests, respectively. The composite effect of tobacco cigarette or HNBC versus sham over time was investigated with an analysis of variance for repeated measures. The areas under the curve (AUCs) of *cf*PWV, *ba*PWV and AIx@75 responses for each participant were calculated and compared between tobacco cigarette and HNBC by using paired *t*-test.

There were no differences in all baseline measurements between the three sessions. HR increased similarly in both the tobacco cigarette and HNBC sessions

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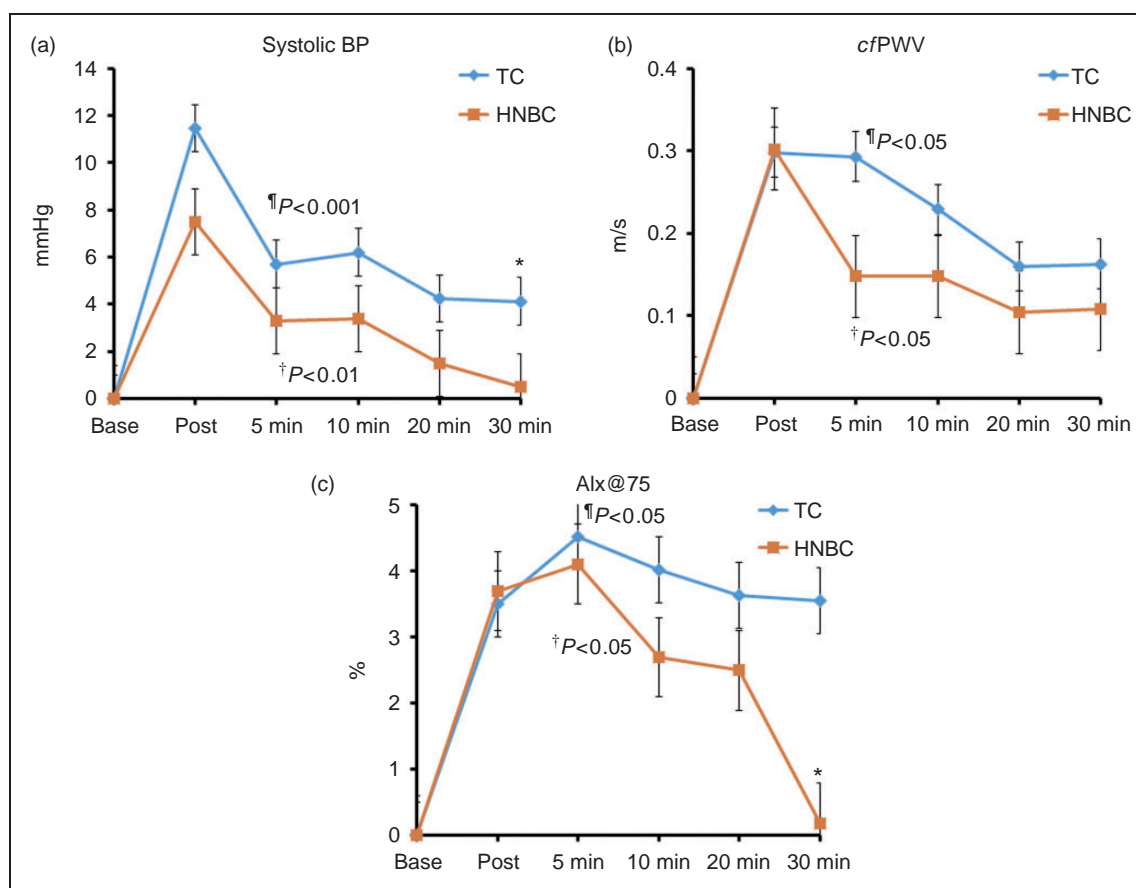
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(maximum increase by 10 beats/min). Both brachial (Figure 1(a)) and aortic systolic BP increased immediately after the end of smoking by tobacco cigarette (by 11.5 and 10.5 mmHg,  $p < 0.001$  and  $p < 0.01$ , respectively) and by HNBC (by 7.5 and 6 mmHg, all  $p < 0.01$ ). Responses from baseline between the two smoking forms were not statistically significant at any time point throughout the entire study period (all  $p > 0.05$ ).

Compared with sham smoking,  $cfPWV$  (Figure 1(b)),  $baPWV$  and  $AIx@75$  (Figure 1(c)) increased immediately after the end of tobacco cigarette smoking (by 0.29 m/s, 93 cm/s and 3.3%, respectively) and remained increased after 5 min. Likewise, HNBC smoking induced a significant increase in  $cfPWV$ ,  $baPWV$  and  $AIx@75$  (by 0.30 m/s, 86 cm/s and 3.5%, respectively). Although HNBC compared with tobacco cigarette smoking resulted in less potent numerical increases in arterial stiffness indices after the end of smoking, the changes between types of smoking were

not different ( $p > 0.05$ , for interaction). The mean differences of  $cfPWV$ ,  $baPWV$  and  $AIx@75$  AUCs between HBNC and tobacco cigarette (by 0.06 m/s, 4.50 cm/s and 1.97%, respectively) were insignificant (all  $p > 0.05$ ).

In the present cross-over, randomized trial comparing the acute effects of HNBC and tobacco cigarette based on equivalent nicotine consumption in young smokers we found that use of any of these two products was associated with comparable acute detrimental effects on arterial stiffness. HNBC products largely avoid pyrolysis and thus the generation of several related harmful molecules is less; however, this aspect may warrant further study.<sup>3,5</sup> Of note, users changing from tobacco cigarette to HNBC usually increase their smoking sessions during the day and thus, the overall cumulative daily deleterious exposure could be increased. It is likely that the acute effect of HNBC on arterial stiffness is mediated, at least in part, by nicotine and its effect on BP. Our finding expands



**Figure 1.** (a) Systolic BP, (b)  $cfPWV$  and (c)  $AIx@75$  responses. Each line represents response defined as net tobacco cigarette/HNBC smoking effect minus sham procedure effect at each time point.  $p$  values refer to the composite effect of tobacco cigarette or HNBC versus sham over time. † = tobacco cigarette versus sham; ‡ = HNBC versus sham.

\* $p < 0.05$  for statistically significant pairwise comparisons between tobacco cigarette and HNBC at time points.

BP: blood pressure;  $cfPWV$ : carotid-femoral pulse wave velocity;  $AIx@75$ : augmentation index corrected for heart rate; TC: tobacco cigarette; HNBC: heat-not-burn cigarette.

knowledge on the acute comparative effects of HNBC and tobacco cigarette and builds upon the existing evidence from trials comparing the acute effect of e-cigarettes and tobacco cigarette on haemodynamic (HR, BP) and vascular function (PWV, flow-mediated dilation) parameters.<sup>4,6</sup> Given the predictive role of arterial stiffness, the finding that HNBC is similarly impactful to tobacco cigarette for aortic stiffness and central haemodynamics casts doubt on the advocating of smoking HNBC as a risk-reduction product among current smokers for the primary and secondary prevention of cardiovascular diseases, such as coronary artery disease,<sup>7</sup> heart failure<sup>8</sup> and atrial fibrillation,<sup>9</sup> at least in the short-term.

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