

# SJR Journal of International Journal of Environmental Research and Public Health

H-Index 138

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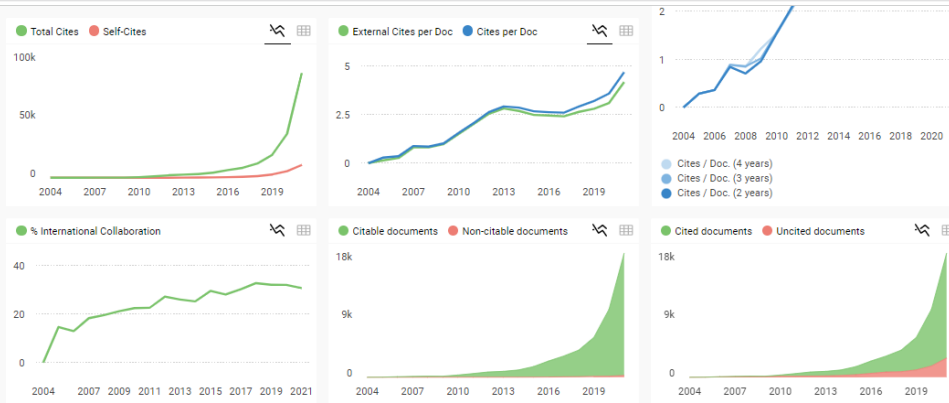
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## International Journal of Environmental Research and Public Health

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<b>PUBLICATION TYPE</b> Journals	<b>ISSN</b> 16604601, 16617827	<b>COVERAGE</b> 2004-2021	<b>INFORMATION</b> <a href="#">Homepage</a> <a href="#">How to publish in this journal</a> <a href="mailto:paul.b.tchounwou@jsums.edu">paul.b.tchounwou@jsums.edu</a>

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## Systemic Lactate Elevation Induced by Tobacco Smoking during Rest and Exercise Is Not Associated with Nicotine

by Sri Sumartaningih<sup>1,2,\*</sup>, Setya Rahayu<sup>1,2</sup>, Eko Handoyo<sup>2,3</sup>, Jung-Chang Lin<sup>4</sup>, Chin Leong Lim<sup>5</sup>, Michal Starczewski<sup>6</sup>, Philip X. Fuchs<sup>7</sup> and Chia-Hua Kuo<sup>8,\*</sup>

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*Int. J. Environ. Res. Public Health* **2022**, *19*(5), 2902; <https://doi.org/10.3390/ijerph19052902>

Received: 31 January 2022 / Revised: 21 February 2022 / Accepted: 26 February 2022 / Published: 2 March 2022

(This article belongs to the Special Issue Health-Related Physical Activity)

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## Riwayat Publikasi

No	Aktivitas Kegiatan	Tanggal
1.	Submit manuscript	31 January 2022
2	Revised	21 February 2022
3	Accepted	26 February 2022
4	Published	2 March 2022

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Editor Decision

Decision Accept in current form

Decision Date 25 February 2022

Review Report

Reviewer 1 [Review Report \(Round 1\)](#)

Reviewer 2 [Review Report \(Round 1\)](#)

APC information

Journal APC: 2,500.00 CHF

IOAP Participant: National Taiwan Normal University

IOAP Payment: Non-central: Invoiced to author

Author Eligible Central: No

IOAP Discount: 10%

Total Payment Amount: 2,250.00 CHF

Funding

Funding Information Indonesian Ministry of Education, Culture, Research, and Technology and LPDP:  
2817/E4.1/KK.04.05/2021

Manuscript Information

Received Date	31 January 2022
Revised Date	21 February 2022
Accepted Date	26 February 2022
Published Date	2 March 2022
Submission to First Decision (Days)	17
Submission to Publication (Days)	29
Round of Revision	1
Size of PDF	484 KiB
Word Count	2646
Page Count	8
Figure Count	3
Table Count	0
Reference Count	37
Citations	1

Editor Decision

Decision	Accept in current form
Decision Date	25 February 2022

Review Report

APC information

Journal APC:	2,500.00 CHF
IOAP Participant:	National Taiwan Normal University
IOAP Payment:	Non-central: Invoiced to author
Author Eligible Central:	No
IOAP Discount:	10%
Total Payment Amount:	2,250.00 CHF

Funding

Funding information	Indonesian Ministry of Education, Culture, Research, and Technology and LPDP: 2817/E4.1/KK.04.05/2021
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Previously Published Papers

Sumartiningih, S.; Lin, H.-F.; Lin, J.-C. Cigarette Smoking Blunts Exercise-Induced Heart Rate Response among Young Adult Male Smokers. *Int. J. Environ. Res. Public Health* **2019**, *16*, 1032. doi: [10.3390/ijerph16061032](https://doi.org/10.3390/ijerph16061032)

Related Papers Published in MDPI Journals

Neuberger, M. Tobacco, Nicotine and Health. *Medicina* **2021**, *57*, 740. doi: [10.3390/medicina57080740](https://doi.org/10.3390/medicina57080740)

Brose, L.S.; McDermott, M.S.; McNeill, A. Heated Tobacco Products and Nicotine Pouches: A Survey of People with Experience of Smoking and/or Vaping in the UK. *Int. J. Environ. Res. Public Health* **2021**, *18*, 8852. doi: [10.3390/ijerph18168852](https://doi.org/10.3390/ijerph18168852)

Ahmed, L.A.; Verlinden, M.; Alobeidli, M.A.; Alahbabli, R.H.; Alkathheeri, R.; Saddik, B.; Oulhaj, A.; Al-Rifai, R.H. Patterns of Tobacco Smoking and Nicotine Vaping

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Levy, D.T.; Sánchez-Romero, L.M.; Travis, N.; Yuan, Z.; Li, Y.; Skolnick, S.; Jeon, J.; Tam, J.; Meza, R. US Nicotine Vaping Product SimSmoke Simulation Model: The Effect of Vaping and Tobacco Control Policies on Smoking Prevalence and Smoking-Attributable Deaths. *Int. J. Environ. Res. Public Health* **2021**, *18*, 4876. doi: 10.3390/ijerph18094876

Felicione, N.J.; Cummings, K.M.; Gravely, S.; Hammond, D.; McNeill, A.; Borland, R.; Fong, G.T.; O'Connor, R.J. "Don't Know" Responses for Nicotine Vaping Product Features among Adult Vapers: Findings from the 2018 and 2020 ITC Four Country Smoking and Vaping Surveys. *Int. J. Environ. Res. Public Health* **2021**, *18*, 7928. doi: 10.3390/ijerph18157928

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Journal: IJERPH (ISSN 1660-4601)

Manuscript ID: ijerph-1599412

Type: Article

Title: Systemic lactate elevation induced by tobacco smoking during rest and exercise is not associated with nicotine

Authors: Sri Sumartiningih\*, Setya Rahayu, Eko Handoyo, Jung-Chang Lin, Chin Leong Lim, Michal Starczewski, Philip X. Fuchs, Chia-Hua Kuo\*

Section: Exercise and Health

Special Issue: Health-Related Physical Activity

Abstract: Lactate is a metabolite produced during anaerobic glycolysis for ATP resynthesis, which accumulates during hypoxia and muscle contraction. Tobacco smoking significantly increases blood lactate. Here we conducted a counter-balanced crossover study to examine whether this effect is associated with nicotine or burned carbon particles. Fifteen male smokers (aged 23 to 26 y) were randomized into 3 inhalation conditions: tobacco smoking, nicotine vaping, and nicotine-free vaping, conducted two days apart. An electronic thermal evaporator (e-cigarette) was used for vaping. We have observed an increased blood lactate (+62%, main effect,  $p < 0.01$ ) and a decreased blood glucose (-12%, main effect,  $p < 0.05$ ) during thermal air inhalations regardless the content delivered. Exercise-induced lactate accumulation and shuttle run performance were similar for the 3 inhalation conditions. Tobacco smoking slightly increased the resting heart rate above the two vaping conditions ( $p < 0.05$ ), implicating the role of burned carbon particles on sympathetic stimulation, independent of nicotine and thermal air. The exercise response in heart rate was similar for the 3 conditions. The results of the study suggest an acute hypoxia induced by breathing thermal air, which explained the reciprocal increases in lactate and decreases in glucose. The impaired lung function in oxygen delivery of tobacco smoking is unrelated with nicotine.

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Authors' Responses to Reviewer's Comments (Reviewer 1)

**Author's Notes** Thanks for reviewer's time and effort. We agree with the reviewer that nicotine has clear adverse effects, and we confirm that the current findings of this manuscript deserve consideration in the context of public health. The second aspect of the reviewer's comment refers to the significance and practical application of the findings, linking specifically with nicotine in the context of health and physical activity. As per reviewer's suggestion, we strengthened the discussion (adaptation in the third paragraph and a new fourth paragraph) and conclusion sections by elaborating on both aspects outlined by the reviewer. We also added references to support the additions.

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**Comments and Suggestions for Authors**

I am grateful for the opportunity to review the interesting topic „Systemic lactate elevation induced by tobacco smoking during rest and exercise is not associated with nicotine“.

I read the author's article with pleasure and great interest. The manuscript is very interesting and well-prepared, even though it announces controversial results. However, I have minor observations regarding the further applicability of the results obtained.

As we know nicotine is a dangerous and highly addictive chemical. It can cause an increase in blood pressure, heart rate, flow of blood to the heart and a narrowing of the arteries. Nicotine may also contribute to the hardening of the arterial walls, which in turn, may lead to a heart attack.

Comments and Suggestions for Authors

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As we know nicotine is a dangerous and highly addictive chemical. It can cause an increase in blood pressure, heart rate, flow of blood to the heart and a narrowing of the arteries. Nicotine may also contribute to the hardening of the arterial walls, which in turn, may lead to a heart attack.

Despite this, the study demonstrated that the effect of heart rate increase after smoking is unrelated with nicotine. There may be a need for a more detailed interpretation of the results obtained depending on the context of public health.

In summary, I would recommend that authors anticipate the significance and practical application of the findings identified. It might be helpful to link findings not with smoking but specifically with nicotine use, physical activity levels and health-friendly and health-unfriendly determinants. Additional discussion may potentially increase the completeness of the content of the article.

My observations are minor. It is recommended to accept the manuscript.

Best Regards

Submission Date 31 January 2022  
Date of this review 02 Feb 2022 17:10:58

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## Author's Notes

*Thank you for the very precise suggestions. We addressed all of them and implemented changes accordingly.*

### Abstract

Line 29: Consider "...regardless **of** the content delivered."

A: Corrected after suggestion. Highlighted in red.

Lines 34-35: This sentence is worded strangely, consider revising for clarity

A: Corrected after suggestion. Highlighted in red.

Line 36: Consider "...is unrelated **to** nicotine."

A: Corrected after suggestion. Highlighted in red.

### Introduction

Line 42: Do we need to include the word "leaves?" It might be implied simply by saying "...the main stimulant component of tobacco during smoking."

A: Corrected after suggestion. Highlighted in red.

Line 45: Consider "...tobacco **leaf**."

A: Corrected after suggestion. Highlighted in red.

Lines 47-48: This sentence is worded strangely, consider revising for clarity.

A: Corrected after suggestion. Highlighted in red.



## Materials and Methods

Line 74: Consider "All participants **presented as free from** cardiovascular disease..."

A: Corrected after suggestion. Highlighted in red.

Line 84: Unclear what is meant by "a 12-hour fast...a 10-min rest."

A: Corrected after suggestion. Highlighted in red.

Line 86: Consider "...inhalation of the heated smoke" (instead of "smokes")

A: Corrected after suggestion. Highlighted in red.

Line 88: Consider "Participants were blind to..."

A: Corrected after suggestion. Highlighted in red.

## Results

Line 112-113: Consider "...and **after** exercise (B)."

A: Corrected after suggestion *as well as in the similar sentences in 3.2 and 3.3.*

Results section 3.2 is very well-worded and concise, consider revising results section 3.1 for parallel construction and to aid in clarity.

A: Corrected after suggestion. Highlighted in red.

## Figure 2

Consider revising the phrase "...elevated resting heart rate above both nicotine..." Maybe something like "...elevated resting heart rate **for** both nicotine..."

A: Corrected after accordingly. Highlighted in red.

## Discussion

Line 162: Consider "...whether this influenced..."

A: Corrected after suggestion. Highlighted in red.

Line 165: Consider "...tobacco cigarette smoking (nicotine: 3mg)."

A: Corrected after suggestion. Highlighted in red.

Line 166: Same as above, consider revising "increased heart rate **above**" to something more colloquial, maybe "increased heart rate **more than**..."

A: Corrected after suggestion. Highlighted in red.

Line 174-176: These sentences are worded strangely, consider revising for clarity.

A: Reworded after suggestion. Highlighted in red.

Line 183: Consider "...free e-cigarettes is..."

A: Corrected after suggestion. Highlighted in red.

Line 183: Consider "...smoking is unlikely **to be**..."

A: Corrected after suggestion. Highlighted in red. *In addition, we changed "contributed by" to "caused by ... alone" to be correct because, strictly speaking, the finding does not allow to assess the contribution.*

Lines 185-186: This sentence is worded strangely, consider revising for clarity  
A: Revised after suggestion. Highlighted in red.

Line 196-197: Consider "...is unrelated **to** nicotine."  
A: Corrected after suggestion. Highlighted in red.

Line 197: Consider "...higher doses of nicotine..."  
A: Corrected after suggestion. Highlighted in red.

Line 198: Consider "...**may** produce more pronounced effects in heart rate...."  
A: Corrected after suggestion. Highlighted in red.

Line 206: Consider "...chronic smoking or **smoking higher nicotine doses.**"  
A: Corrected after suggestion. Highlighted in red.

Line 208: Consider "...the study design **did not have a** non-vaping control..."  
A: Corrected after suggestion. Highlighted in red.

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Are the conclusions supported by the results?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Comments and Suggestions for Authors**

Very interesting article regarding the pre- and post-workout levels of lactate and glucose for three types of smoking (vaping with nicotine, vaping without nicotine, and smoking cigarettes). Very minor suggestions below:

Abstract

Line 29: Consider "...regardless of the content delivered."

Comments and Suggestions for Authors

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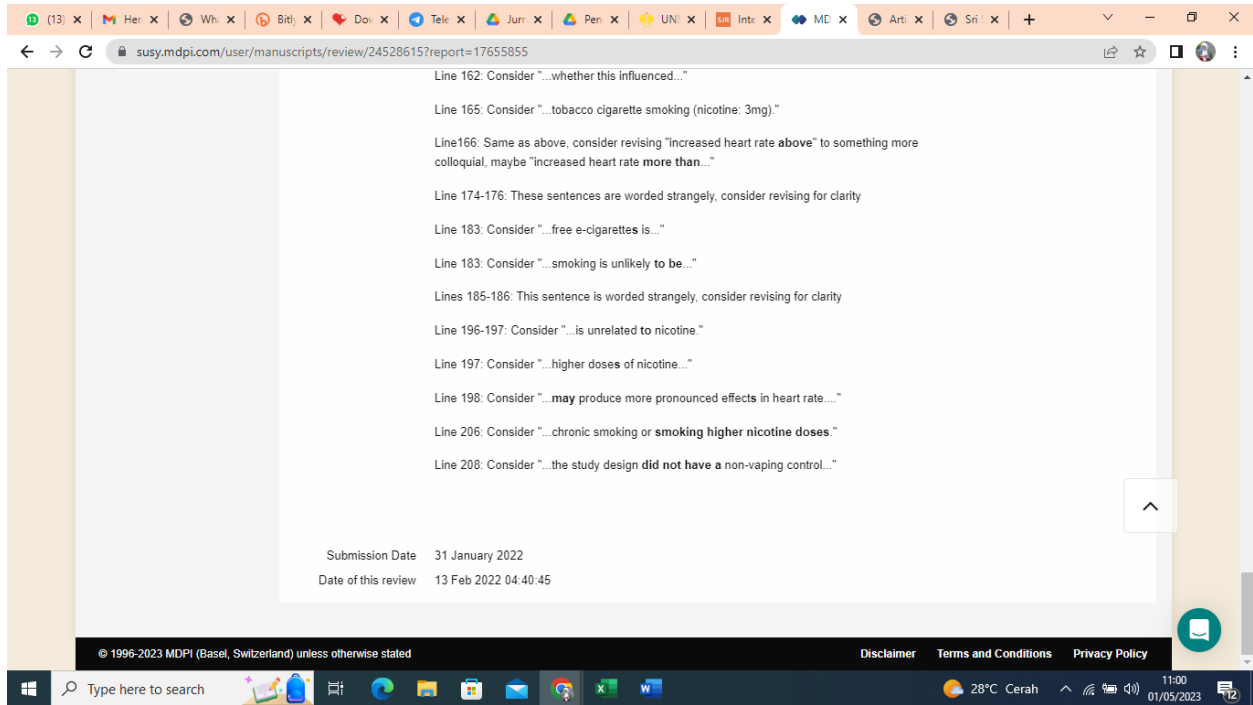
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Manuscript Information

Received Date

31 January 2022

Revised Date

21 February 2022

Accepted Date

26 February 2022

Published Date

2 March 2022

Submission to First Decision (Days)

17

Submission to Publication (Days)

29

Round of Revision

1

Size of PDF

484 KiB

Word Count

2646

Page Count

8

Figure Count

3

Table Count

0

Reference Count

37

Citations

1

Editor Decision

Decision

Accept in current form

Decision Date

25 February 2022

Review Report

Reviewer 1

[Review Report \(Round 1\)](#)

Reviewer 2

[Review Report \(Round 1\)](#)

APC information

Journal APC:

2,500.00 CHF

IOAP Participant:

National Taiwan Normal University

IOAP Payment:

Non-central: Invoiced to author

Author Eligible Central:

No

IOAP Discount:

10%

Total Payment Amount:

2,250.00 CHF

Funding

Funding information

**Indonesian Ministry of Education, Culture, Research, and Technology and LPDP:  
2817/E4.1/KK.04.05/2021**

Previously Published Papers

Sumartiningsih, S.; Lin, H.-F.; Lin, J.-C. Cigarette Smoking Blunts Exercise-Induced Heart Rate Response among Young Adult Male Smokers. *Int. J. Environ. Res. Public Health* **2019**, *16*, 1032. doi: [10.3390/ijerph16061032](https://doi.org/10.3390/ijerph16061032)

Related Papers Published in MDPI Journals

Neuberger, M. Tobacco, Nicotine and Health. *Medicina* **2021**, *57*, 740. doi: [10.3390/medicina57080740](https://doi.org/10.3390/medicina57080740)

Brose, L.S.; McDermott, M.S.; McNeill, A. Heated Tobacco Products and Nicotine Pouches: A Survey of People with Experience of Smoking and/or Vaping in the UK. *Int. J. Environ. Res. Public Health* **2021**, *18*, 8852. doi: [10.3390/ijerph18168852](https://doi.org/10.3390/ijerph18168852)

Ahmed, L.A.; Verlinden, M.; Alobeidli, M.A.; Alahbabi, R.H.; AlKatheeri, R.; Saddik, B.; Oulhaj, A.; Al-Rifai, R.H. Patterns of Tobacco Smoking and Nicotine Vaping among University Students in the United Arab Emirates: A Cross-Sectional Study. *Int. J. Environ. Res. Public Health* **2021**, *18*, 7652. doi: [10.3390/ijerph18147652](https://doi.org/10.3390/ijerph18147652)

Levy, D.T.; Sánchez-Romero, L.M.; Travis, N.; Yuan, Z.; Li, Y.; Skolnick, S.; Jeon, J.; Tam, J.; Meza, R. US Nicotine Vaping Product *SimSmoke* Simulation Model: The Effect of Vaping and Tobacco Control Policies on Smoking Prevalence and Smoking-Attributable Deaths. *Int. J. Environ. Res. Public Health* **2021**, *18*, 4876. doi: [10.3390/ijerph18094876](https://doi.org/10.3390/ijerph18094876)



Felicione, N.J.; Cummings, K.M.; Gravely, S.; Hammond, D.; McNeill, A.; Borland, R.; Fong, G.T.; O'Connor, R.J. "Don't Know" Responses for Nicotine Vaping Product Features among Adult Vapers: Findings from the 2018 and 2020 ITC Four Country Smoking and Vaping Surveys. *Int. J. Environ. Res. Public Health* **2021**, *18*, 7928. doi: [10.3390/ijerph18157928](https://doi.org/10.3390/ijerph18157928)

If you have any questions or concerns, please do not hesitate to contact [ijerph@mdpi.com](mailto:ijerph@mdpi.com).

	Journal
<a href="#">IJERPH</a> (ISSN 1660-4601)	
	Manuscript ID
ijerph-1599412	
	Type
Article	
	Title
<a href="#">Systemic lactate elevation induced by tobacco smoking during rest and exercise is not associated with nicotine</a>	
	Authors

[Exercise and Health](#)

[Health-Related Physical Activity](#)

Lactate is a metabolite produced during anaerobic glycolysis for ATP resynthesis, which accumulates during hypoxia and muscle contraction. Tobacco smoking significantly increases blood lactate. Here we conducted a counter-balanced crossover study to examine whether this effect is associated with nicotine or burned carbon particles. Fifteen male smokers (aged 23 to 26 y) were randomized into 3 inhalation conditions: tobacco smoking, nicotine vaping, and nicotine-free vaping, conducted two days apart. An electronic thermal evaporator (e-cigarette) was used for vaping. We have observed an increased blood lactate (+62%, main effect:  $p < 0.01$ ) and a decreased blood glucose (-12%, main effect:  $p < 0.05$ ) during thermal air inhalations regardless the content delivered. Exercise-induced lactate accumulation and shuttle run performance were similar for the 3 inhalation conditions. Tobacco smoking slightly increased the resting heart rate above the two vaping conditions ( $p < 0.05$ ), implicating the role of burned carbon particles on sympathetic stimulation, independent of nicotine and thermal air. The exercise response in heart rate was similar for the 3 conditions. The results of the study suggest an acute hypoxia induced by breathing thermal air, which explained the reciprocal increases in lactate and decreases in glucose. The impaired lung function in oxygen delivery of tobacco smoking is unrelated with nicotine.

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Authors' Responses to Reviewer's Comments (Reviewer 1)

Author's Notes

Thanks for reviewer's time and effort. We agree with the reviewer that nicotine has clear adverse effects, and we confirm that the current findings of this manuscript deserve consideration in the context of public health. The second aspect of the reviewer's comment refers to the significance and practical application of the findings, linking specifically with nicotine in the context of health and physical activity. As per reviewer's suggestion, we strengthened the discussion (adaptation in the third paragraph and a new fourth paragraph) and conclusion sections by elaborating on both aspects outlined by the reviewer. We also added references to support the additions.

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- Moderate English changes required

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Does the introduction provide sufficient background and include all relevant references?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Is the research design appropriate?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Are the methods adequately described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Are the results clearly presented?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Are the conclusions supported by the results?	<input type="checkbox"/>	<input checked="" type="checkbox"/>

#### Comments and Suggestions for Authors

I am grateful for the opportunity to review the interesting topic „Systemic lactate elevation induced by tobacco smoking during rest and exercise is not associated with nicotine“.

I read the author's article with pleasure and great interest. The manuscript is very interesting and well-prepared, even though it announces controversial results. However, I have minor observations regarding the further applicability of the results obtained.

As we know nicotine is a dangerous and highly addictive chemical. It can cause an increase in blood pressure, heart rate, flow of blood to the heart and a narrowing of the arteries. Nicotine may also contribute to the hardening of the arterial walls, which in turn, may lead to a heart attack.

Despite this, the study demonstrated that the effect of heart rate increase after smoking is unrelated with nicotine. There may be a need for a more detailed interpretation of the results obtained depending on the context of public health.

In summary, I would recommend that authors anticipate the significance and practical application of the findings identified. It might be helpful to link findings not with smoking but specifically with nicotine use, physical activity levels and health-friendly and health-unfriendly determinants. Additional discussion may potentially increase the completeness of the content of the article.

My observations are minor. It is recommended to accept the manuscript.

Best Regards

31 January 2022

02 Feb 2022 17:10:58

Submission Date

Date of this review

Journal

Manuscript ID

ijerph-1599412

Type

Article

Title

[Systemic lactate elevation induced by tobacco smoking during rest and exercise is not associated with nicotine](#)

Authors

Sri Sumartiningsih \* , Setya Rahayu , Eko Handoyo , Jung-Charng Lin , Chin Leong Lim , Michal Starczewski , Philip X. Fuchs , Chia-Hua Kuo \*

Section

[Exercise and Health](#)

Special Issue

[Health-Related Physical Activity](#)

Abstract

Lactate is a metabolite produced during anaerobic glycolysis for ATP resynthesis, which accumulates during hypoxia and muscle contraction. Tobacco smoking significantly increases blood lactate. Here we conducted a counter-balanced crossover study to examine whether this effect is associated with nicotine or burned carbon particles. Fifteen male smokers (aged 23 to 26 y) were randomized into 3 inhalation conditions: tobacco smoking, nicotine vaping, and nicotine-free vaping, conducted two days apart. An electronic thermal evaporator (e-cigarette) was used for vaping. We have observed an increased blood lactate (+62%, main effect:  $p < 0.01$ ) and a decreased blood glucose (-12%, main effect:  $p < 0.05$ ) during thermal air inhalations regardless the content delivered. Exercise-induced lactate accumulation and shuttle run performance were similar for the 3 inhalation conditions. Tobacco smoking slightly increased the resting heart rate above the two vaping conditions ( $p < 0.05$ ), implicating the role of burned carbon particles on sympathetic stimulation, independent of nicotine and thermal air. The exercise response in heart rate was similar for the 3 conditions. The results of the study suggest an acute hypoxia induced by breathing thermal air, which explained the reciprocal increases in lactate and decreases in glucose. The impaired lung function in oxygen delivery of tobacco smoking is unrelated with nicotine.

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Authors' Responses to Reviewer's Comments (Reviewer 2)

Author's Notes

*Thank you for the very precise suggestions. We addressed all of them and implemented changes accordingly.*

Abstract

Line 29: Consider "...regardless **of** the content delivered."

A: Corrected after suggestion. Highlighted in red.

Lines 34-35: This sentence is worded strangely, consider revising for clarity

A: Corrected after suggestion. Highlighted in red.

Line 36: Consider "...is unrelated **to** nicotine."

A: Corrected after suggestion. Highlighted in red.

## Introduction

Line 42: Do we need to include the word "leaves?" It might be implied simply by saying "...the main stimulant component of tobacco during smoking."

A: Corrected after suggestion. Highlighted in red.

Line 45: Consider "...tobacco **leaf**."

A: Corrected after suggestion. Highlighted in red.

Lines 47-48: This sentence is worded strangely, consider revising for clarity.

A: Corrected after suggestion. Highlighted in red.

## Materials and Methods

Line 74: Consider "All participants **presented as** free **from** cardiovascular disease..."

A: Corrected after suggestion. Highlighted in red.

Line 84: Unclear what is meant by "a 12-hour fast...a 10-min rest."

A: Corrected after suggestion. Highlighted in red.

Line 86: Consider "...inhalation of the heated smoke" (instead of "smokes")

A: Corrected after suggestion. Highlighted in red.

Line 88: Consider "Participants were blind to..."

A: Corrected after suggestion. Highlighted in red.

## Results

Line 112-113: Consider "...and **after** exercise (B)."

A: Corrected after suggestion *as well as in the similar sentences in 3.2 and 3.3.*

Results section 3.2 is very well-worded and concise, consider revising results section 3.1 for parallel construction and to aid in clarity.

A: Corrected after suggestion. Highlighted in red.

## Figure 2

Consider revising the phrase "...elevated resting heart rate above both nicotine..." Maybe something like "...elevated resting heart rate **for** both nicotine..."

A: Corrected after accordingly. Highlighted in red.

## Discussion

Line 162: Consider "...whether this influenced..."

A: Corrected after suggestion. Highlighted in red.

Line 165: Consider "...tobacco cigarette smoking (nicotine: 3mg)."

A: Corrected after suggestion. Highlighted in red.

Line 166: Same as above, consider revising "increased heart rate **above**" to something more colloquial, maybe "increased heart rate **more than**..."

A: Corrected after suggestion. Highlighted in red.

Line 174-176: These sentences are worded strangely, consider revising for clarity.

A: Reworded after suggestion. Highlighted in red.

Line 183: Consider "...free e-cigarettes is..."

A: Corrected after suggestion. Highlighted in red.

Line 183: Consider "...smoking is unlikely **to be**..."

A: Corrected after suggestion. Highlighted in red. *In addition, we changed "contributed by" to "caused by ... alone" to be correct because, strictly speaking, the finding does not allow to assess the contribution.*

Lines 185-186: This sentence is worded strangely, consider revising for clarity

A: Revised after suggestion. Highlighted in red.

Line 196-197: Consider "...is unrelated **to** nicotine."

A: Corrected after suggestion. Highlighted in red.

Line 197: Consider "...higher doses of nicotine..."

A: Corrected after suggestion. Highlighted in red.

Line 198: Consider "...**may** produce more pronounced effects in heart rate..."

A: Corrected after suggestion. Highlighted in red.

Line 206: Consider "...chronic smoking or **smoking higher nicotine doses**."

A: Corrected after suggestion. Highlighted in red.

Line 208: Consider "...the study design **did not have a** non-vaping control..."

A: Corrected after suggestion. Highlighted in red.

## Review Report Form

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Quality of English Language

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- I am not qualified to assess the quality of English in this paper

	Yes	Can be improved
Does the introduction provide sufficient background and include all relevant references?	(x)	( )
Is the research design appropriate?	(x)	( )
Are the methods adequately described?	(x)	( )
Are the results clearly presented?	(x)	( )
Are the conclusions supported by the results?	(x)	( )

#### Comments and Suggestions for Authors

Very interesting article regarding the pre- and post-workout levels of lactate and glucose for three types of smoking (vaping with nicotine, vaping without nicotine, and smoking cigarettes). Very minor suggestions below:

#### Abstract

Line 29: Consider "...regardless **of** the content delivered."

Lines 34-35: This sentence is worded strangely, consider revising for clarity

Line 36: Consider "...is unrelated **to** nicotine."

#### Introduction

Line 42: Do we need to include the word "leaves?" It might be implied simply by saying "...the main stimulant component of tobacco during smoking."

Line 45: Consider "...tobacco **leaf**."

Lines 47-48: This sentence is worded strangely, consider revising for clarity

#### Materials and Methods

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Line 84: Unclear what is meant by "a 12-hour fast...a 10-min rest."

Line 86: Consider "...inhalation of the heated smoke" (instead of "smokes")

Line 88: Consider "Participants were blind to..."

## Results

Line 112-113: Consider "...and **after** exercise (B)."

Results section 3.2 is very well-worded and concise, consider revising results section 3.1 for parallel construction and to aid in clarity.

## Figure 2

Consider revising the phrase "...elevated resting heart rate above both nicotine..." Maybe something like "...elevated resting heart rate **for** both nicotine..."

## Discussion

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Line 183: Consider "...smoking is unlikely **to be**..."

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Line 197: Consider "...higher doses of nicotine..."

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Line 206: Consider "...chronic smoking or **smoking higher nicotine doses**."

Line 208: Consider "...the study design **did not have a** non-vaping control..."

31 January 2022

13 Feb 2022 04:40:45

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**Gorana Belegisanin** <belegisanin@mdpi.com>

Wed, Mar 2, 2022,  
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On 2.3.2022. 09:55, [ijerph@mdpi.com](mailto:ijerph@mdpi.com) wrote:

> Dear Authors,

>

> We are pleased to inform you that your article "Systemic Lactate Elevation Induced by Tobacco Smoking during Rest and Exercise Is Not Associated with Nicotine" has been published in IJERPH as part of the Special Issue Health-Related Physical Activity and is available online:

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11:37 PM

to Gorana, Setya, Eko, Jung-Charng, Lim, Michał, Philip, Chia-Hua, IJERPH

Yes, everything is correct.

--

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Article

# Systemic Lactate Elevation Induced by Tobacco Smoking during Rest and Exercise Is Not Associated with Nicotine

**Citation:** Sumartiningih, S.; Rahayu, S.; Handoyo, E.; Lin, J.-C.; Lim, C.L.; Starczewski, M.; Fuchs, P.X.; Kuo, C.-H. Systemic Lactate Elevation Induced by Tobacco Smoking during Rest and Exercise Is Not Associated with Nicotine. *Int. J. Environ. Res. Public Health* **2022**, *19*, x. <https://doi.org/10.3390/xxxxx>

Academic Editor(s): José Carmelo Adsuar Sala, Ben D. Kern, Lawrence W. Judge and David M. Bellar

Received: date

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**Abstract:** Lactate is a metabolite produced during anaerobic glycolysis for ATP resynthesis, which accumulates during hypoxia and muscle contraction. Tobacco smoking significantly increases blood lactate. Here we conducted a counter-balanced crossover study to examine whether this effect is associated with inhaling nicotine or burned carbon particles. Fifteen male smokers (aged 23 to 26 years) were randomized into 3 inhalation conditions: tobacco smoking, nicotine vaping, and nicotine-free vaping, conducted two days apart. An electronic thermal evaporator (e-cigarette) was used for vaping. We have observed an increased blood lactate (+62%, main effect:  $p < 0.01$ ) and a decreased blood glucose (-12%, main effect:  $p < 0.05$ ) during thermal air inhalations regardless of the content delivered. Exercise-induced lactate accumulation and shuttle run performance were similar for the 3 inhalation conditions. Tobacco smoking slightly increased the resting heart rate above the two vaping conditions ( $p < 0.05$ ), implicating the role of burned carbon particles on sympathetic stimulation, independent of nicotine and thermal air. The exercise response in the heart rate was similar for the 3 conditions. The results of the study suggest that acute hypoxia was induced by breathing thermal air. This may explain the reciprocal increases in lactate and decreases in glucose. The impaired lung function in oxygen delivery of tobacco smoking is unrelated to nicotine.

**Keywords:** e-cigarette; nicotine; vaping; tobacco; heart rate; glucose

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## 1. Introduction

Tobacco smoking is a risk factor for all-cause mortality and impaired pulmonary function [1–4]. Nicotine is widely regarded as the main addictive component of tobacco during smoking [5]. Breathing smoke from nicotine-

containing tobacco cigarettes (1–14 mg) [6] or electronic (E) cigarettes (3–19 mg/mL) increased heart rate and blood pressure [7–9]. In addition to nicotine, a variety of carbon particles is generated during the burning process of tobacco leaves. Burned carbon particles and various chemicals in combination of thermal stress can also cause edema and injury to the lower airway and alveoli [10]. It is unclear whether nicotine stimulation or burned carbon particles are responsible for compromised oxygen delivery in the respiration system.

Lactate is a glycolic metabolite produced at hypoxia when oxygen is insufficiently supplied for aerobic ATP production. An acute episode of tobacco smoking increases the rate of lactate appearance in the blood [11]. These results implicate a potential hypoxia effect associated with a metabolic shift from aerobic to anaerobic substrates.

In this study, we hypothesized that an increased lactate accumulation in the blood after tobacco smoking at rest and following exercise is associated with the heated air from tobacco leaves, independent of nicotine. To address this question, a nicotine-containing aerosol and nicotine-free aerosol were also inhaled into the lungs of smokers via an e-cigarette thermal evaporator. The rate of glucose appearance increases during exercise [12]. Thus, blood levels of lactate and glucose were also assessed following tobacco smoking, nicotine vaping, and nicotine-free vaping conditions at rest and post-exercise compared with a non-smoking baseline.

## **2. Materials and Methods**

### *2.1. Participants*

A total of 20 eligible participants initially joined this study with five dropouts due to time constraints to comply with the testing schedule. Fifteen male smokers (averaged 9 cigarettes per day, 3.5 years, estimated 19 mg of nicotine per day) aged  $23.9 \pm 1.1$  years (height  $1.7 \pm 0.1$  m and weight  $65 \pm 8.8$  kg) voluntarily participated in this study. All participants completed a medical history and an informed consent form before testing. The Faculty of Medicine Diponegoro University, Semarang, Indonesia, approved the study (Project no. 580/EC/FK-RSDK/IX/2017). All experimental procedures were conducted in accordance with the Declaration of Helsinki. Participants were given a full explanation of the purpose, testing procedure, and the potential risks of participation. All participants presented as free from cardiovascular diseases and diabetes mellitus according to their routine physical examination.

### *2.2. Study Design*

This study was conducted using a randomized counter-balanced crossover design of three smoking conditions: nicotine free vaping (e-cigarette without nicotine), nicotine vaping (e-cigarette smoking with nicotine, 3 mg), and tobacco cigarette smoking (nicotine, 3 mg).

### *2.3. Testing Protocol*

All participants arrived at the laboratory in the morning from 09: 00 am to 12: 00 pm after a 12-h fast (free of smoking and alcohol). After arrival, participants rested for 10 min. Lactate, glucose, and heart rate responses were

then assessed at baseline (designated as Pre) under a sedentary condition. For each smoking trial, inhalation of the heated smoke lasted for 45 min. Blood samples were then collected immediately following the smoking session (designated as Post). Participants were blinded to the nicotine ingredients during the electronic cigarette smoking. Lactate, glucose, and heart rate responses to exercise (shuttle runs) were assessed 10 min after the smoking session. Each participant conducted three sessions of a Maximal Multistage 20 m Shuttle Run Test (MMST) at their best effort. Blood samples were collected again for assessment of exercise response (designated as Post).

#### 2.4. MMST (Maximal Multistage 20 m Shuttle Run Test)

The MMST was designed to evaluate the exercise performance. The participants were required to run back and forth on a 20 m course and touch the 20 m line. A sound signal was emitted from a prerecorded tape at the same time. For the MMST, the participants were required to run until exhaustion, and the levels and shuttles were then calculated [13].

#### 2.5. Lactate, Glucose, and Heart Rate

Lactate and glucose concentrations were assessed immediately following blood collection using Accutrend® Plus (Roche Diagnostics, Rotkreuz, Switzerland). Heart rate (HR) was measured by a Polar RS800X Heart Rate Monitor Polar Electro (Kempele, Finland).

#### 2.6. Statistics

All results were presented as mean  $\pm$  standard error (SE). Type 1 error equal or less than 5% for comparing mean difference was considered significant. Two-way ANOVA with repeated measures was used to determine the main effect and interactive effects of intervention. The percentage (%) change after smoking and after exercise from baseline for lactate, glucose and HR were analyzed using paired t-test. Effect size was indicated by Cohen's  $d$ , interpreted as small ( $d = 0.2$ ), medium ( $d = 0.5$ ), and large ( $d = 0.8$ ) [14].

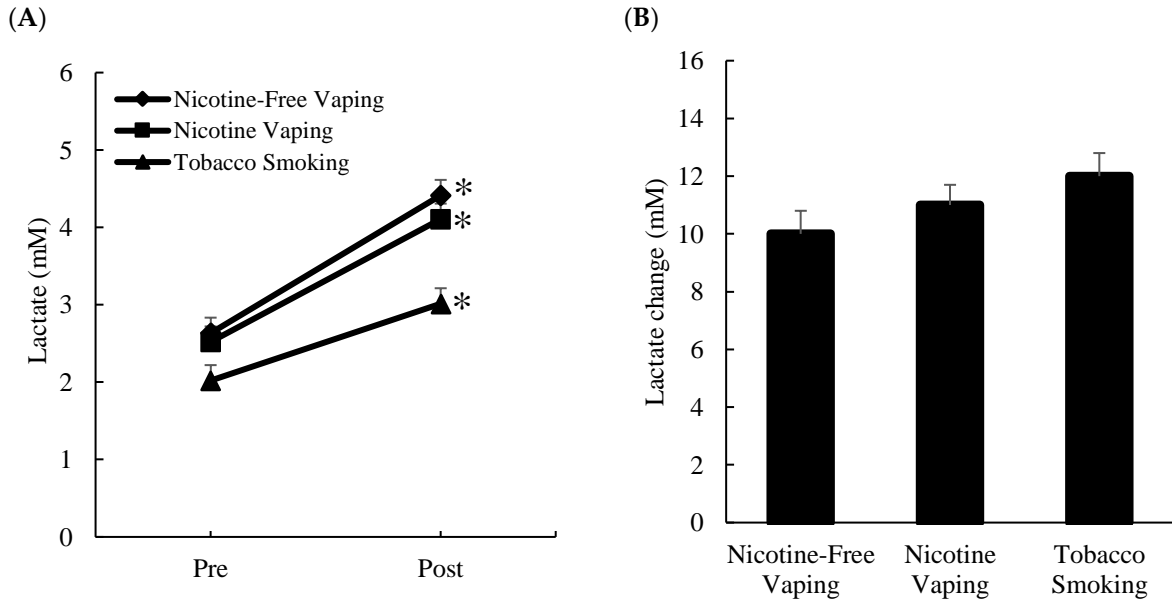
### 3. Results

#### 3.1. Blood Lactate Response

Figure 1 shows the blood lactate response to three inhalation conditions at rest (Figure 1A) and exercise (Figure 1B). At rest, blood lactate increased after tobacco smoking, nicotine-free vaping, and nicotine vaping to a similar extent ( $d = 1.1$ , main effect of time:  $p < 0.001$ ).

Following a standard shuttle run protocol, the performance times for the three post-inhalation conditions were comparable (nicotine free vaping,  $347 \pm 33$  s; nicotine vaping,  $349 \pm 33$  s; tobacco smoking,  $325 \pm 30$  s). Blood lactate increased above the non-smoking baseline (Pre). Lactate accumulation after exercise was similar for all three conditions (nicotine free vaping,  $10.0 \pm 0.6$  mM; nicotine vaping,  $11.0 \pm 0.5$  mM; tobacco smoking,  $12.0 \pm 0.4$  mM) ( $d = 0.96$ , main effect of time,  $p < 0.001$ ).





**Figure 1.** Blood lactate increases after smoking at rest and exercise. Blood lactate levels elevated for the three inhalation conditions were similar at rest (A). Exercise-induced increases in blood lactate levels from non-inhalation baseline were also similar among the three inhalation conditions (B). Intervention: Nicotine-free vaping (0 mg); nicotine vaping (nicotine: 3 mg); tobacco cigarette (nicotine: 3 mg). Main effect of intervention:  $p < 0.01$  (two-way ANOVA). Main effect of exercise:  $p < 0.001$  (two-way ANOVA). \* Significant difference versus nicotine-free vaping condition.

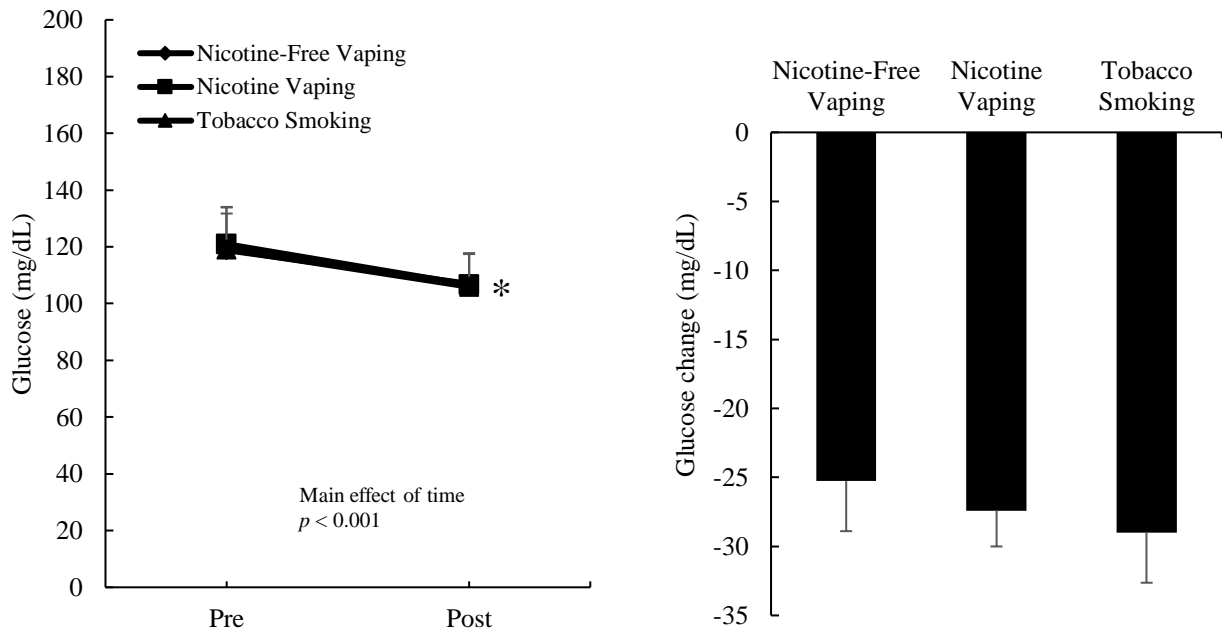
### 3.2. Blood Glucose Response

Figure 2 shows blood glucose response to three inhalation conditions at rest (Figure 2A) and exercise (Figure 2B). At rest, blood glucose decreased after smoking, and was similar for the tobacco smoking ( $d = 0.8$ ,  $p < 0.01$ ), nicotine-free vaping ( $d = 1.6$ ,  $p < 0.01$ ), and nicotine vaping ( $d = 1.2$ ,  $p < 0.01$ ) conditions.

Following a standard shuttle run protocol, blood glucose decreased below the non-inhalation baseline (Pre). This decrease was similar for the three inhalation conditions (nicotine free vaping,  $25.3 \pm 11.9$  mg/dL, nicotine vaping,  $27.4 \pm 11.4$  mg/dL, tobacco smoking,  $29.0 \pm 11.6$  mg/dL,  $d = 0.9$ , main effect of time:  $p < 0.01$ ).

(A)

(B)

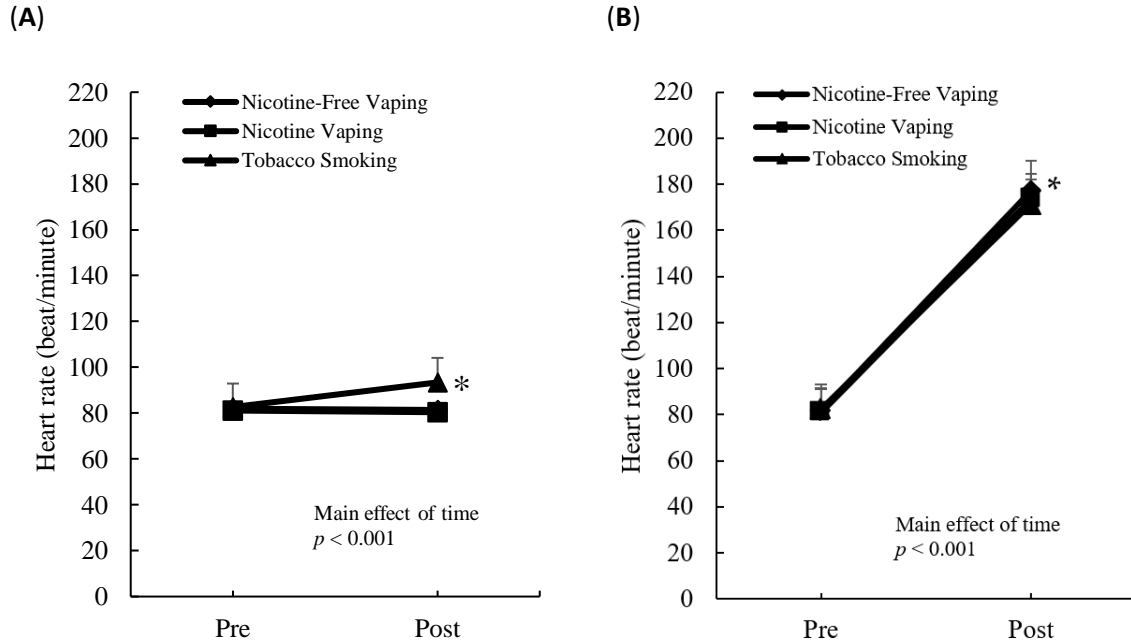


**Figure 2.** Blood glucose responses to smoking at rest and exercise. Blood glucose levels at rest decreased to a similar level for all inhalation conditions (A). Exercise-induced decreases in blood glucose from non-smoking baseline were similar after all inhalation conditions (B). Intervention: Nicotine-free vaping (0 mg); nicotine vaping (nicotine: 3 mg); tobacco cigarette (nicotine: 3 mg). Main effect of smoking:  $p < 0.01$  (two-way ANOVA). Main effect of exercise:  $p < 0.001$  (two-way ANOVA). \* Significant difference versus nicotine-free vaping.

### 3.3. Heart Rate Response

Figure 3 shows the heart rate response to the three inhalation conditions at rest (Figure 3A) and exercise (Figure 3B). Resting heart rate significantly increased (+ 12%) after tobacco smoking ( $d = 0.8$ ,  $p = 0.041$ ). Both nicotine vaping and non-nicotine vaping had no significant effect (- 3%) on resting heart rate.

Following the standard shuttle run protocol, heart rate increased significantly for the tobacco smoking ( $89 \pm 2.8$  beat/min), nicotine vaping ( $93 \pm 2.8$  beat/min), and non-nicotine ( $95 \pm 2.8$  beat/min) conditions. No difference in the post-exercise heart rate was found among the three conditions.



**Figure 3.** Heart rate responses to smoking at rest and exercise. Tobacco smoking significantly elevated resting heart rate in comparison with both nicotine and nicotine-free vaping conditions (A). Exercise-induced increases in heart rate from non-smoking baseline were similar for tobacco smoking, nicotine vaping, and nicotine-free vaping conditions (B). Intervention: Nicotine-free vaping (0 mg); nicotine vaping (nicotine: 3 mg); tobacco cigarette (nicotine: 3 mg). Main effect of exercise:  $p < 0.001$  (two-way ANOVA). \* Significant difference from the e-cigarette vaping (nicotine or nicotine-free) conditions,  $p < 0.05$ .

#### 4. Discussion

The present study was designed to examine whether the tobacco smoking-induced blood lactate increases are mediated by nicotine [11,15], and whether this influenced blood glucose and exercise performance. In this study, we found an increased blood lactate accumulation together with decreased blood glucose after nicotine-free vaping (0 mg), nicotine vaping (nicotine: 3 mg), and tobacco cigarette smoking (nicotine: 3 mg). Furthermore, tobacco smoking significantly increased heart rate in comparison with e-cigarette smoking containing nicotine. Hypoxia is known to increase glucose transport in skeletal muscle [16] and cardiac muscle [17]. Therefore, the findings of the study suggest that (1) tobacco smoking induces an acute systemic hypoxia associated with impaired lung function in oxygen delivery, independent of nicotine; (2) autonomic modulation, reflected by an increased resting heart rate, is associated with the inhalation of burned carbon particles during tobacco smoking; (3) nicotine is not associated with the heart rate increase during tobacco smoking; (4) exercise performance seems to be unaffected by an acute session of tobacco smoking among the young smokers.

As a consequence of tobacco smoking, carbon monoxide has been widely assumed to cause hypoxia. This assumption is based on increased carbon monoxide observed in tobacco cigarette smokers than in non-smokers [18–21]. This is also strengthened by the fact that chronic tobacco smokers

show a greater carboxyhemoglobin concentration level than acute tobacco smokers [22]. However, in this study, the magnitude of the blood lactate increase was similar regardless of ingredients, suggesting that the thermal air inhalation is the main cause of impaired oxygen delivery in the lungs, not nicotine or burned carbon particles. Lactate is an anaerobic metabolite produced during glycolysis, which is a good metabolic marker of tissue hypoxia [23,24]. Hypoxia is known to increase glucose uptake by skeletal muscle [25]. Since the amount of carbon monoxide produced by nicotine-free e-cigarettes is neglectable [19], the hypoxia effect of tobacco smoking is unlikely to be caused by carbon monoxide alone.

Burned carbon particles during tobacco smoking may contribute to the observed increased heart rate. Heart rate is directly associated with the magnitude of sympathetic activation or parasympathetic inhibition to alter oxygen delivery in circulation [26]. The finding of an increased heart rate on tobacco smoking indicates a modulation in the autonomic nervous system. Both e-cigarettes with and without nicotine have no effect on heart rate. Taken together, the influence of tobacco smoking on increased heart rate is likely associated with carbon particles from burned tobacco leaves, independent of thermal air and nicotine. This is supported by a previous report that the inhalation of fine carbon particles alters heart rate and heart rate variability in diabetes patients [27]. Furthermore, the present study also demonstrated that the increase in heart rate after smoking is not due to nicotine alone. In this study, we could not preclude the possibility that higher doses of nicotine may produce more pronounced effects in the heart rate response at rest and exercise [28]. Furthermore, an increase in heart rate after intravenous nicotine infusion was reported previously [29]. Therefore, the isolated effect of nicotine should be noted. The difference on heart rate between tobacco smoking and e-cigarette smoking (with and without nicotine) diminished after exercise at maximal effort, suggesting that exercise at such an intensity has to activate the sympathetic nervous system towards a maximal level. Despite a significant elevation in the resting heart rate after tobacco smoking, the shuttle run performance was not negatively influenced. This result is consistent with several previous reports in athletes [30,31].

The current data suggest that nicotine as an addictive component of cigarette is not the only determinant for changes in lactate, glucose, and heart rate. Other contributing factors are likely to be the burned carbon particles and thermal air inhalation. Nevertheless, adverse effects of nicotine itself must be recognized (e.g., on heart rate, blood pressure, and perceived smoking urge) [29]. The specific effects of nicotine itself as well as effects of smoking in general are highly important in the context of public health. Tobacco smoking is associated with increased levels of toxic metals [32] and chemicals [33], and the significance for public health and health care systems is well-known [34]. E-cigarettes also include numerous harmful components besides nicotine (e.g., formaldehyde, acetaldehyde, and acrolein) that we have not investigated in the study. E-smoking also has a harmful impact on human health (e.g., increase in impotence, peripheral airway flow resistance, and oxidative stress) [35] that is relevant for public health.

One limitation of the study is that the knowledge generated in the acute study cannot be generalized to chronic smoking or smoking higher nicotine doses. The harmful effect of chronic tobacco cigarette smoking on mortality

has been well-documented in the past [36,37]. In addition, the study did not include a non-vaping control and, therefore, cannot preclude a possibility that thermal vaping (free of nicotine) may negatively impact exercise performance.

## 5. Conclusions

Inhalation of heated air into human lungs significantly increased blood lactate and decreased blood glucose, suggesting a transient hypoxia associated with a declined lung function for oxygen delivery. This metabolic response was not fully explained by nicotine and burned carbon particles alone. Nevertheless, adverse effects of nicotine on human health should not be underestimated. Moreover, smoking involves many other toxic components and is well-known for its significance for public health and health care policies.

**Author Contributions:** Conceptualization, S.S. and J.-C.L.; Methodology, S.S. and J.-C.L.; Software, S.S., M.S., P.X.F., S.R. and E.H.; Validation, C.-H.K., C.L.L. and J.-C.L.; Formal analysis, S.S.; Resources, S.S.; Data Curation, S.S., M.S. and P.X.F.; Manuscript preparation, S.S., M.S. and C.-H.K.; Review and Editing, C.-H.K., C.L.L., J.-C.L., S.S. and P.X.F.; Visualization, S.S. and C.-H.K.; Supervision, C.-H.K., J.-C.L. and C.L.L.; Project administration, S.S.; Funding acquisition, S.S., S.R. and E.H. Manuscript submission and final revision, C.-H.K. All authors have read and agreed to the published version of the manuscript.

**Funding:** This study was supported by a grant from The Graduate & Postgraduate School, Universitas Negeri Semarang; The Indonesian Ministry of Education, Culture, Research, and Technology and LPDP (2817/E4.1/KK.04.05/2021).

**Institutional Review Board Statement:** This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the UNIVERSITY OF DIPONEGORO (protocol no. 580/EC/FK-RSDK/IX/2017).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

**Data Availability Statement:** Available upon request.

**Acknowledgments:** Sri Sumartiningsih thanks the World Class Professor program managed by the Indonesian Ministry of Education, Culture, Research, and Technology and LPDP (2817/E4.1/KK.04.05/2021).

**Conflicts of Interest:** The authors declare no conflict of interest.

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