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Resolving the Smoking Paradox: No Evidence for Smoking-Induced Preconditioning in Large Vessel Occlusion Stroke

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Ischemic stroke · Large vessel occlusion · Collaterals · Smoking · Smoking paradox

Abstract

Introduction: Smoking is an established risk factor for stroke. However, several studies have reported a better outcome after stroke for patients who smoke. According to this "smoking paradox" hypothesis, smoking might promote less severe strokes, higher collateral scores, and smaller infarct cores. ***Methods:*** In this retrospective study, we screened data of 2,980 acute ischemic stroke patients with MCA-M1 occlusion treated with mechanical thrombectomy. Patients were categorized according to smoking status (current, former, or never). We assessed univariate associations between clinical characteristics and smoking status. Subsequently, we used adjusted regression analysis to evaluate associations of smoking with stroke severity on admission (National Institutes of Health Stroke Scale [NIHSS]; primary endpoint), infarct core volume, and collateral status (secondary endpoints). ***Results:*** Out of 320 patients, 19.7% (n = 63) were current smokers and 18.8% (n = 60) were former smokers. Admission NIHSS, reperfusion success, and modified Rankin Scale (mRS) after 3–6 months were similar in all groups. Current smokers were younger, more often male and less likely to have atrial fibrillation compared to former and never smokers. In regression analyses, smoking status was neither associated with admission NIHSS (estimate 0.54, 95% confidence interval [CI]: −1.27–2.35, p = 0.557) nor with collateral status (estimate 0.79, 95% CI: 0.44–1.44, p = 0.447) or infarct core volume (estimate −0.69, 95% CI: −15.15–13.77, p = 0.925 for current vs. never smokers). ***Conclusion:*** We could not confirm the smoking paradox. Our results support the fact that smoking causes stroke at a younger age, highlighting the role of smoking as a modifiable vascular risk factor.

Introduction

Tobacco smoking is one of the leading causes of stroke and preventable death globally, responsible for many years of life lost [1]. Despite its undisputed role as a risk

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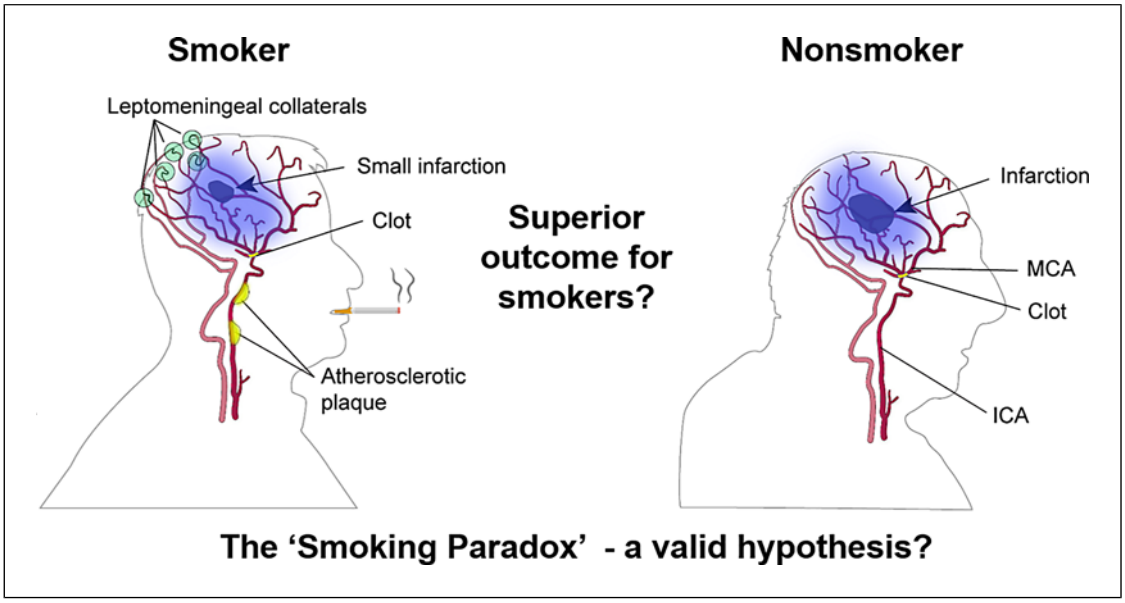

Fig. 1. Graphical depiction of the smoking paradox. Left: young smoking person with a clot in the middle cerebral artery (MCA), displaying a small stroke core (dark blue) with a large mismatch (light blue) and several leptomeningeal collaterals (light green), in accordance with the presumed underlying mechanisms of the smoking paradox. However, atherosclerotic plaques (yellow) in the internal carotid artery (ICA) are more common in these patients. Right: elderly nonsmoking person with a clot in the MCA, displaying a larger stroke core and a penumbra with a smaller mismatch. According to the smoking paradox, this person would be more severely affected by the same vascular lesion.

factor for cardiovascular disease, early studies on myocardial infarction reported better outcomes in patients with a history of smoking [2, 3]. This finding was corroborated in studies on thrombolysis in myocardial infarction [4, 5], and hence the term "smoking paradox" came into being. The smoking paradox was later discovered for stroke, when it was observed that smokers had better recanalization rates [6] and improved early outcomes in acute ischemic stroke when treated with intravenous thrombolysis [7–10].

One suggested mechanism for better outcome was a preconditioning-like protection (i.e., smoking-induced ischemia tolerance [11]) due to better collaterals and maintained perfusion (see Fig. 1). Alternatively, smoking might be associated with a particular subtype of stroke or indicate stroke patients with a more favorable outcome, such as younger patients [6, 12]. However, previous analyses included heterogenous patient cohorts with different types of vascular occlusion, so bias could have arisen due to different clot locations and varying degrees of stroke severity.

In our study, we aimed to resolve the smoking paradox by overcoming such bias and comparing only patients with middle cerebral artery M1 segment (MCA-M1) occlusions. In order to prevent potential treatment bias, we selected only patients who were submitted to treatment with mechanical thrombectomy (MT). We analyzed differences in stroke severity as well as patient clinical and imaging characteristics according to smoking status. To prove the concept of a smoking-induced vascular and tissue protection during stroke, we analyzed collateral status and brain perfusion on pre-MT imaging and further assessed recanalization rates on post-MT digital subtraction angiography (DSA) images. We aimed to assess whether 1) smoking was associated with less severe strokes and whether 2) collaterals were indeed more extensive or tissue perfusion was better maintained in smokers due to chronic tobacco exposure (preconditioning hypothesis).

Materials and Methods

Study Design and Cohort Description

The study was performed according to the ethical guidelines of the Canton of Zurich with approval from the Local Ethics Committee ("PREDICT" project; KEK-ZH-Nr. 2014-0304). Written consent was obtained from all subjects or legally authorized representatives as required. The protocol allowed use of data of deceased patients if no objection against use of data for research was documented (according to Article 34 of the Swiss Human Research Law [implemented in January 2014]).

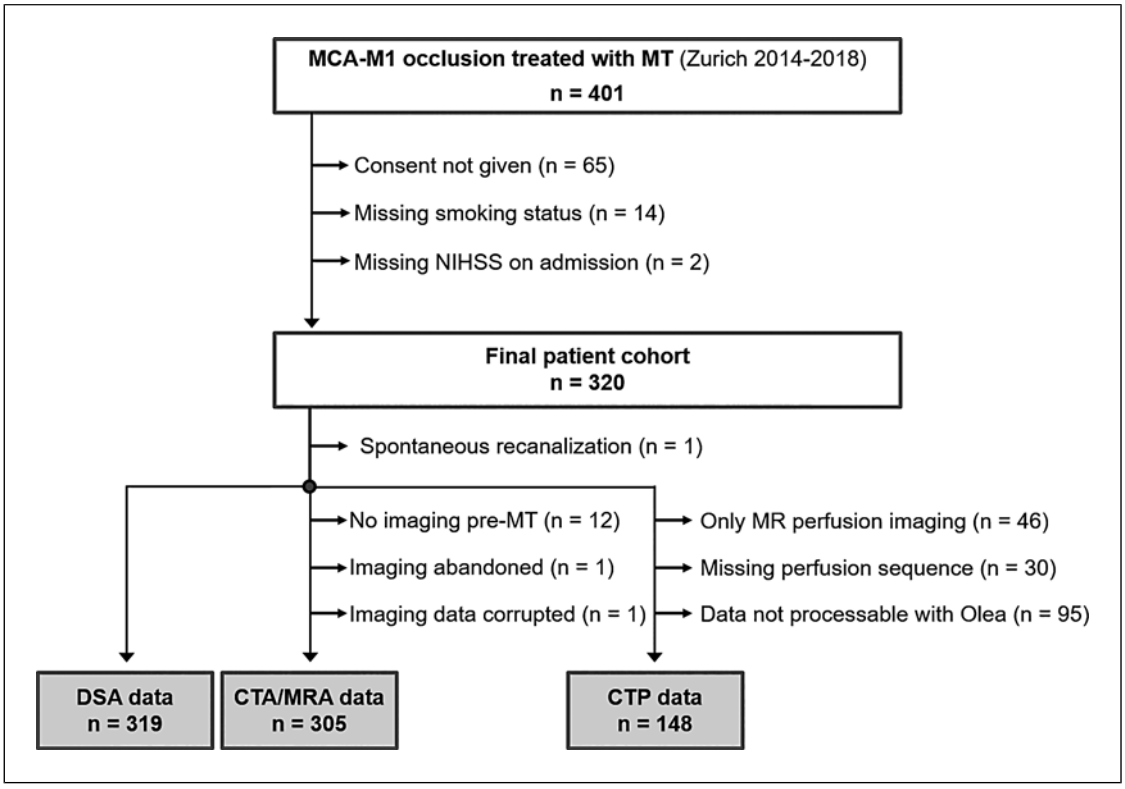

Fig. 2. Flowchart for patient selection: we screened 401 ischemic stroke patients with MCA-M1 occlusion sent to treat with mechanical thrombectomy (MT) and included 320 patients in our analysis. CTP, computed tomography perfusion; CTA, CT angiography; DSA, digital subtraction angiography; MR, magnetic resonance; MRA, magnetic resonance angiography; NIHSS, National Institutes of Health Stroke Scale.

We retrospectively collected data of patients with acute ischemic stroke due to MCA-M1 segment occlusion sent for MT at the University Hospital Zurich between 2014 and 2018. Exclusions were due to omitted consent to use data for research, missing NIHSS score on admission, or lack of information about smoking status. Details on inclusion/exclusion criteria are provided in Figure 2.

Thrombectomy decisions were made by treating stroke physicians according to current clinical guidelines. Standard demographic and clinical data were recorded (see Tables 1, 2). Patients were categorized according to smoking status (current, former, or never) using information available in medical records. Number of pack years and duration of abstinence could not be considered in our analysis.

Stroke imaging (computed tomography angiography (CTA), DSA, and CT perfusion [CTP]) was performed using routine stroke protocols – performed at the University Hospital Zurich or local referring hospitals. To avoid introducing inhomogeneity into core and mismatch imaging analysis (processed with Olea Sphere's Acute Stroke Care Plug-In [Olea Sphere Version 3.0.22, La Ciotat, France]), we excluded patients with initial magnetic resonance (MR) perfusion and analyzed CTP imaging only. Quantitative (cerebral blood flow [CBF], cerebral blood volume, and mean transit time) and qualitative/semi-quantitative (time-to-peak) maps were calculated from perfusion images. Automatic volume segmentation was used to define the core (rCBF <30%) and penumbral volumes (Tmax threshold at values > 6 s). An experienced neurologist and a neuroradiologist categorized CT or MR angiography data pre-MT according to the EXTEND-IA criteria [13] as good, moderate, and poor; and DSA data according to the modified treatment in cerebral infarction (mTICI) scale [14], including subcategory mTICI 2c [15].

Statistical Analyses

The primary clinical endpoint was the association of smoking with stroke severity on admission; i.e., the National Institutes of Health Stroke Scale (NIHSS) score on admission. Secondary endpoints were infarct core volume (CTP imaging) and collateral status (CTA, DSA).

For descriptive statistics, we calculated median and interquartile range (IQR) (see Table 2 and 4) for continuous variables and tested for group differences using a Kruskal-Wallis test. Categorical variables were expressed as frequencies and percentages; and χ^2 tests were used to test for differences between smoking groups.

The association between smoking and NIHSS, stroke core volume, and collateral status was assessed using linear and ordinal logistic regression models. All regression models were adjusted for age, sex, admission parameters including systolic blood pressure

Table 1. Clinical characteristics of patients according to smoking status, pre-hospital phase

	All	Current smoker	Former smoker	Never smoker	*p* value
	n = 320	*n* = 63	*n* = 60	*n* = 197	
Demographic data					
Age, median years (range)	72.1 (19–97)	62.0 (25–89)	70.9 (46–90)	77.3 (19–97)	<**0.001***
Women, *n* (%)	163 (50.9)	24 (38.1)	21 (35.0)	118 (59.9)	<**0.001***
Risk factors, *n* (%)					
Hypertension	216 (67.5)	36 (57.1)	41 (68.3)	139 (70.6)	0.141
Diabetes	42 (13.1)	8 (12.7)	6 (10.0)	28 (14.2)	0.711
Dyslipidemia	160 (50.0)	32 (50.8)	32 (53.3)	96 (48.7)	0.833
Atrial fibrillation	124 (38.8)	11 (17.5)	24 (40.0)	89 (45.2)	<**0.001***
CHD	60 (18.8)	11 (17.5)	15 (25.0)	34 (17.3)	0.369
PAD	14 (4.4)	4 (6.3)	6 (10.0)	4 (2.0)	**0.019***
Past vascular events, *n* (%)					
Stroke	27 (8.4)	2 (3.2)	5 (8.3)	20 (10.2)	0.217
TIA	11 (3.4)	0 (0)	3 (5.0)	8 (4.1)	0.228
ICH	8 (2.5)	2 (3.2)	1 (1.7)	5 (2.5)	1.000
Pre-stroke medication, *n* (%)					
Antiplatelets	84 (26.3)	12 (19.1)	21 (35.0)	51 (25.9)	0.139
Dual antiplatelet therapy	9 (2.8)	1 (1.6)	4 (6.7)	4 (2.0)	0.132
OAC	59 (18.4)	4 (6.4)	14 (23.3)	41 (20.8)	**0.019***
OAC + antiplatelets	3 (0.9)	0 (0)	1 (1.7)	2 (1.0)	0.775
Antihypertensives	176 (55.0)	25 (39.7)	33 (55.0)	118 (59.9)	**0.019***
Lipid-lowering drugs	80 (25.1) *n* = 319	13 (21.0) *n* = 62	18 (30.0) *n* = 60	49 (24.9) *n* = 197	0.541

Clinical characteristics of all 320 patients according to smoking status (current, former, or never). Unadjusted data are expressed as median and range or number (*n*) and percentages (%). CHD, coronary heart disease; PAD, peripheral artery disease; TIA, transient ischemic attack; ICH, intracerebral hemorrhage; OAC, oral anticoagulation. *p values <0.05 in Pearson's χ^2 test and Kruskal-Wallis test.

and creatinine, pre-stroke medication with antihypertensives and antiplatelets, risk factors such as diabetes and peripheral artery disease, previous stroke, and presumed etiology (Trial of ORG 10172 in Acute Stroke Treatment [TOAST] criteria). These factors were selected according to expert knowledge and their potential association to the outcome measures observed in previous studies [16]. Estimates and corresponding 95% confidence intervals (CIs) are reported together with p values. p values <0.05 were considered statistically significant. Statistical analysis was performed in IBM SPSS Statistics (Version 27, 28) and R (Version 4.0.2).

To estimate the required sample size, we used the package pwr in R. We powered for the primary goal to show at least one difference in means across the three smoking groups for the normally distributed variable NIHSS by using an ANOVA. We assumed a power of 80%, a significance level of 0.05 and a medium effect size (0.25). This yielded a required sample size of 159 (53 per group).

Results

We screened 2,980 patients with acute ischemic stroke from 2014 to 2018 and identified 401 patients with MCA-M1 occlusion treated with MT. Ultimately, we were able to include 320 patients in our analysis. Exclusions were due to consent to use data for research not being given (n = 65), missing NIHSS score on admission (n = 2), or lack of information about smoking status (n = 14; see Fig. 2).

Median age for all patients was 72.1 years and 50.9% were female (see Table 1 for unadjusted results). Sixty-three patients (19.7%) were classified as current smokers, 60 (18.8%) as former smokers, and 197 (61.6%) as never smokers. Smokers were younger on average (median: 62 years, range: 25–89 years) compared to former smokers (median: 70.9 years, range: 46–90 years) and never smokers (median: 77.3 years, range: 19–97 years; $p < 0.001$). Current and former smokers were significantly more often male (61.9% and 65%) while never smokers were more often female (59.9%; $p < 0.01$, see Table 1).

Most common risk factors were hypertension (67.5%), dyslipidemia (50%), and atrial fibrillation (38.8%). Atrial fibrillation occurred more often in never smokers (45.2%) and former smokers (40%) compared to current smokers (17.5%; $p < 0.01$). Peripheral artery disease was more

Table 2. Clinical characteristics of patients according to smoking status, in-hospital phase/follow-up

	All	Current smoker	Former smoker	Never smoker	*p* value
	n = 320	*n* = 63	*n* = 60	*n* = 197	
Vital parameters on admission, median [IQR]					
BP systolic, mmHg	151 [33] *n* = 319	147 [30] *n* = 62	148 [35] *n* = 60	154 [32] *n* = 197	0.122
BP diastolic, mmHg	85 [23] *n* = 319	83 [23] *n* = 62	81 [24] *n* = 60	85 [24] *n* = 197	0.588
Glucose, mmol/L	6.4 [1.7] *n* = 313	6.3 [1.8] *n* = 63	6.5 [1.3] *n* = 59	6.4 [1.9] *n* = 191	0.680
LDL, mmol/L	2.6 [1.4] *n* = 251	2.6 [1.4] *n* = 51	2.3 [1.5] *n* = 46	2.7 [1.3] *n* = 154	0.115
Creatinine, µmol/L	77 [27] *n* = 319	75 [24] *n* = 63	78 [27] *n* = 59	77 [27] *n* = 197	0.779
BMI, kg/m^2	25.2 [4.8] *n* = 309	24.5 [4.9] *n* = 61	25.6 [5.6] *n* = 58	25.4 [5.1] *n* = 190	0.577
Acute stroke treatment					
i.v. thrombolysis with rtPA, *n* (%)	186 (58.1)	41 (65.1)	38 (63.3)	107 (54.3)	0.218
Onset-treatment time, median min [IQR]	130 [89] *n* = 186	145 [130] *n* = 41	110 [53] *n* = 38	128 [89] *n* = 107	0.166
Symptomatic in-hospital complications, *n* (%)					
ICH	10 (3.1)	2 (3.2)	3 (5.0)	5 (2.5)	0.668
Stroke	4 (1.3)	0 (0)	1 (1.7)	3 (1.5)	0.645
Death	34 (10.6)	1 (1.6)	8 (13.3)	25 (12.7)	**0.036***
Duration hospital stay, median days [IQR]	8.4 [10.2]	11.1 [12]	8.5 [10.7]	8.0 [10]	**0.008***
Presumed etiology, *n* (%)					
TOAST I (large vessel)	47 (14.7)	17 (27.0)	11 (18.3)	19 (9.6)	
TOAST II (cardioembolic)	137 (42.8)	18 (28.6)	24 (40.0)	95 (48.2)	
TOAST III (small vessel)	0 (0)	0 (0)	0 (0)	0 (0)	
TOAST IV (other)	22 (6.9)	5 (7.9)	3 (5.0)	14 (7.1)	
TOAST V (undetermined)	114 (35.6)	23 (36.5)	22 (36.7)	69 (35.0)	**0.017***
Clinical scores, median [IQR]					
mRS pre-stroke	0 [0] *n* = 309	0 [0] *n* = 61	0 [0] *n* = 60	0 [1] *n* = 188	**0.002***
NIHSS on admission	14 [8]	11 [8]	15 [9]	14 [7]	0.090
NIHSS at 24 h	9 [10] *n* = 279	10 [11] *n* = 57	7 [12] *n* = 51	9 [10] *n* = 171	0.711
mRS at 90–180 days	3 [3] *n* = 305	3 [3] *n* = 61	2.5 [5] *n* = 60	3 [4] *n* = 184	0.185

Clinical characteristics of all 320 patients according to smoking status (current, former, or never). Unadjusted data are expressed as median and interquartile range [IQR] or number (*n*) and percentages (%). BP, blood pressure; LDL, low-density lipoprotein; BMI, body mass index; rtPA, recombinant tissue plasminogen activator; ICH, intracerebral hemorrhage; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale. **p* values <0.05 in Pearson's χ^2 test or Kruskal-Wallis test.

common in former smokers (10%) and current smokers (6.3%) compared to never smokers (2%; $p = 0.019$). Regarding history of cerebrovascular events (previous stroke, transient ischemic attack, or intracerebral hemorrhage); no significant differences between smoking groups were found.

Stroke Severity and Outcome

Median NIHSS scores on admission did not differ significantly between groups (never smokers 14 [IQR 7], former smokers 15 [IQR 9], current smokers 11 [IQR 8]; $p = 0.09$, see Table 2 and online suppl. Figure S3; for all online suppl. material, see https://doi.org/10.1159/000533436). In accordance with their higher age at stroke, former smokers more often suffered from pre-stroke disability (modified Rankin Scale [mRS]; $p = 0.002$). However, disability after 3–6 months was similar in all groups (median mRS 3 for current and never smokers [IQR 3 and 4, respectively]; median mRS 2.5 for former smokers [IQR 5]; $p = 0.185$).

The most common presumed cause of stroke overall was cardioembolic (TOAST II; 42.8%), followed by undetermined origin (TOAST V; 35.6%) and large vessel disease (TOAST I; 14.7%). Current and former smokers more often showed large vessel disease (TOAST I; 27% and 18.3%) compared to never smokers (9.6%; $p = 0.017$).

Occurrence of in-hospital complications such as symptomatic stroke or intracerebral hemorrhage did not differ significantly between groups. However, more never

Table 3. Vascular imaging of patients according to smoking status

	All	Current smoker	Former smoker	Never smoker	*p* value
	n = 320	*n* = 63	*n* = 60	*n* = 197	
Collateral status (CTA data), *n* (%)					
Good	111 (36.4) *n* = 305	19 (31.1) *n* = 61	20 (34.5) *n* = 58	72 (38.7) *n* = 186	
Medium	125 (41.0) *n* = 305	28 (45.9) *n* = 61	21 (36.2) *n* = 58	76 (40.9) *n* = 186	
Poor	69 (22.6) *n* = 305	14 (23.0) *n* = 61	17 (29.3) *n* = 58	38 (20.4) *n* = 186	0.559
mTICI (DSA data), *n* (%)					
0	33 (10.3) *n* = 319	8 (12.7) *n* = 63	4 (6.7) *n* = 60	21 (10.7) *n* = 196	
1	4 (1.3) *n* = 319	0 (0) *n* = 63	3 (5.0) *n* = 60	1 (0.5) *n* = 196	
2a	10 (3.1) *n* = 319	0 (0) *n* = 63	3 (5.0) *n* = 60	7 (3.6) *n* = 196	
2b	124 (38.9) *n* = 319	38 (60.3) *n* = 63	22 (36.7) *n* = 60	64 (32.7) *n* = 196	
2c	1 (0.3) *n* = 319	0 (0) *n* = 63	0 (0) *n* = 60	1 (0.5) *n* = 196	
3	147 (46.7) *n* = 319	17 (27.0) *n* = 63	28 (46.7) *n* = 60	102 (52.0) *n* = 196	**0.001***
mTICI dichotomized, *n* (%)					
Unsuccessful recanalization (mTICI grades 0, 1, 2a)	47 (14.7) *n* = 319	8 (12.7) *n* = 63	10 (16.7) *n* = 60	29 (15.3) *n* = 196	
Successful recanalization (mTICI grades 2b, 2c, and 3)	272 (85.3) *n* = 319	55 (87.3) *n* = 63	50 (83.3) *n* = 60	167 (85.2) *n* = 196	0.856

CTA (computed tomography angiography) and DSA (digital subtraction angiography) data according to smoking status (current, former, or never). Unadjusted data are expressed as number (*n*) and percentages (%). mTICI, modified treatment in cerebral infarction. *p values <0.05 in Pearson's χ^2 test.

(12.7%) and former smokers (13.3%) passed away during their hospitalization than current smokers (1.6%; p = 0.036).

Vascular Imaging Data

There was no significant difference regarding collateral status between groups (see Table 3). Successful recanalization (mTICI scores 2b, 2c, and 3) was achieved in 85.3% of all patients (p = 0.856), with a similar distribution between groups. However, when looking at individual mTICI scores, never and former smokers more often gained complete reperfusion (mTICI 3; 52% of all never smokers and 46.7% of all former smokers) than current smokers (27%); while current smokers were more often classified with mTICI 2b (60.3%) than former (36.7%) and never smokers (32.7%; p = 0.001). Please note that mTICI 2c was achieved in 1 patient only. CTP imaging analysis showed no significant group difference regarding median volume of stroke core (current smokers 29.5 cm^3 [IQR 5.7], never smokers 33.9 cm^3 [IQR 4.2], former smokers 43.1 cm^3 [IQR 4.3]), median stroke penumbra (current smokers 89.7 cm^3 [IQR 5.2], never smokers 90.3 cm^3 [IQR 4.0], former smokers 102.6 cm^3 [IQR 4.5]), or any of the perfusion parameter maps (see Table 4).

Regression Analyses

Linear regression analysis adjusted for potential covariables showed no statistically significant association of smoking with stroke severity on admission (see Table 5). Never and former smoking status were not associated with NIHSS scores on admission (estimate of 0.54, 95% CI: −1.27–2.35, p = 0.557 for never smokers and estimate of 0.56, 95% CI: −1.53–2.64, p = 0.598 for former smokers). Only previous stroke was significantly associated with higher NIHSS on admission (estimate of 2.47, 95% CI: 0.19–4.75, p = 0.034).

The ordinal logistic regression analysis showed no statistically significant association of smoking or any other variable with collateral status (see online suppl. Table S1). Furthermore, the linear regression analysis showed no statistically significant association between smoking status or any other variable with stroke core volume (see online suppl. Table S2).

Discussion

The results of our study do not support the existence of a "smoking paradox" in stroke, i.e., a better outcome after stroke for patients who smoke due to stroke-induced protection. Neither stroke severity nor collateral status or perfusion parameters were suggestive of a preconditioning effect provided by smoking (current or former smoking status). In this cohort of stroke patients with M1 occlusion, smokers were younger, male, and more often diagnosed with large vessel disease (TOAST I). Both younger age and atherosclerotic stroke cause are associated with a better prognosis after stroke [17, 18]. However, despite their

Table 4. Perfusion imaging of patients according to smoking status

	All	Current smoker	Former smoker	Never smoker	*p* value
	n = 148	*n* = 30	*n* = 29	*n* = 89	
Volume, median cm^3 [IQR]					
Core	34.5 [4.5]	29.5 [5.7]	43.1 [4.3]	33.9 [4.2]	0.497
Penumbra	91.6 [4.3]	89.7 [5.2]	102.6 [4.5]	90.3 [4.0]	0.577
Hypoperfused area	127.7 [8.8]	116.2 [10.9]	148.0 [8.8]	127.4 [8.2]	0.574
TTP, median s [IQR]					
Core	36.6 [7.4]	36.9 [8.2]	35.1 [7.9]	37.0 [7.0]	0.598
Penumbra	34.1 [6.8]	34.6 [7.7]	32.9 [7.1]	34.3 [6.3]	0.594
Hypoperfused area	70.7 [14.2]	71.5 [15.9]	68.0 [15.0]	71.3 [13.4]	0.585
CBF, median mL/100 g/min [IQR]					
Core	5.5 [3.1]	6.0 [3.5]	4.7 [2.6]	5.5 [3.1]	0.595
Penumbra	11.2 [10.6]	12.4 [12.8]	10.0 [9.2]	11.2 [10.4]	0.749
Hypoperfused area	16.7 [13.7]	18.4 [16.3]	14.6 [11.8]	16.7 [13.5]	0.800
CBV, median mL/100 g [IQR]					
Core	0.85 [0.68]	0.99 [0.88]	0.84 [0.63]	0.80 [0.63]	0.931
Penumbra	1.68 [1.63]	2.11 [2.14]	1.61 [1.72]	1.56 [1.43]	0.858
Hypoperfused area	2.53 [2.31]	3.10 [3.02]	2.45 [2.35]	2.36 [2.07]	0.901

CTP (computed tomography perfusion) data of 148 patients according to smoking status (current, former, or never), processed with Olea Sphere's Acute Stroke Care Plug-In. Unadjusted data are expressed as median and interquartile range [IQR]. TTP, time-to-peak; CBF, cerebral blood flow; CBV, cerebral blood volume. *p* values in Kruskal-Wallis test.

Table 5. Linear regression for NIHSS on admission

	Estimate	95% CI	*p* value
Former versus current smoker	0.56	−1.53 to 2.64	0.598
Never versus current smoker	0.54	−1.27 to 2.35	0.557
Age, years	0.04	−0.02 to 0.10	0.173
Male versus female sex	0.74	−0.64 to 2.13	0.290
BP systolic, mmHg	−0.01	−0.04 to 0.02	0.428
Creatinine, µmol/L	0.01	−0.01 to 0.03	0.330
Antiplatelets	0.27	−1.32 to 1.87	0.736
Antihypertensives	0.50	−1.01 to 2.01	0.516
Diabetes	−1.41	−3.32 to 0.50	0.147
PAD	−0.30	−3.49 to 2.88	0.851
History of previous stroke	2.47	0.19 to 4.75	**0.034***
TOAST II versus I	0.11	−1.90 to 2.12	0.913
TOAST III versus I	2.77	−3.15 to 8.68	0.358
TOAST IV versus I	−0.92	−3.96 to 2.13	0.553
TOAST V versus I	−0.39	−2.43 to 1.65	0.707

Results of linear regression analysis for the association of different variables with National Institutes of Health Stroke Scale (NIHSS) on admission. The influence of smoking status when adjusting for age, sex, systolic blood pressure (BP), creatinine, antiplatelets, antihypertensives, diabetes, peripheral artery disease (PAD), history of previous stroke, and Trial of ORG 10172 in Acute Stroke Treatment (TOAST) on NIHSS on admission was investigated. Estimates and corresponding 95% confidence intervals (CI) are displayed. *p values <0.05 in Kruskal-Wallis and Wilcoxon test.

younger age and less common cardiac stroke etiology, smokers did not have a better outcome or more favorable reperfusion success, arguing once more against the preconditioning hypothesis. Our study indicates that, in unadjusted descriptive analysis, smoking is associated with certain patient and stroke characteristics (younger age, male sex, and atherosclerotic stroke); favoring less severe strokes.

These findings are in line with previous work [6, 10, 12, 19] investigating the smoking paradox in stroke. Similar to our results, the association between smoking and good outcome lost significance [6, 20] when adjusting for confounders such as age and sex. While previous studies had indicated that collateral supply did not differ between smokers and nonsmokers [10, 19], we added the analysis of infarct core and mismatch volume as potential correlates of smoking-induced preconditioning (see Fig. 1). However, volume of the infarct core and mismatch were similar in all patient groups. While the results of our study corroborate previous reports doubting the existence of a truly beneficial (preconditioning) effect of smoking on the cerebrovascular system, we aimed to further dissect a potential adaptation of the vascular network in response to tobacco exposure: a more favorable perfusion profile (small core, large mismatch), better collaterals, or more successful recanalization. None of this was found in our selected patient cohort with similar vascular occlusions (MCA-M1 occlusions; all deemed good candidates for MT).

Strengths and Limitations

Assignment of patients to different groups according to smoking status was difficult as information about number of cigarettes per day/pack years or years of abstinence was usually not available in medical records. The classification of a patient as a current, former, or never smoker depended on the individual doctor responsible for the patient's medical management at the time of administration and thus his/her recordings. Investigating a dose-response relationship between smoking and stroke severity on admission was not possible.

Furthermore, our study was a single-center retrospective analysis. Thus, without a randomized controlled study design, we could not derive unequivocal conclusions about causality with respect to smoking. Selecting a group of patients with similar vascular occlusions and treatment limited our sample size, and may reduce generalizability of our results, but it was crucial for overcoming bias regarding stroke type.

The availability of DSA data for patients sent for treatment with MT allowed a thorough assessment of recanalization success. Only 1 patient within our cohort was classified with an mTICI score of 2c. We attributed this to the fact that this subcategory was rather new and not widely used in the years of the data collection. Image quality in the earlier years of our study might also have been insufficient for a confident visual classification of a near-perfect result. Lastly, this single case might have been a coincidence.

Conclusion

We demonstrate no advantage of tobacco smoking that would support the existence of a smoking paradox in stroke. On the contrary; smoking puts patients at risk for stroke at a younger age, thus increasing suffering and disability across the life span. Thus, with respect to the paramount importance of stroke prevention and implementation of preventive strategies including campaigns against smoking, we suggest closing the chapter of the enigmatic "smoking paradox" in stroke.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of the Canton of Zurich, Switzerland ("PREDICT" project; approval number KEK-ZH-Nr. 2014-0304). Written consent was obtained from all subjects or legally authorized representatives as required. The protocol allowed use of data of deceased patients if no objection against use of data for research was documented (according to Article 34 of the Swiss Human Research Law [implemented in January 2014]).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

R.E.W. and S.W. conceived and designed the study. R.E.W. wrote the first draft of the manuscript and was responsible for patient recruitment, image analysis, and statistical data analysis. A.B. and J.H. were involved in concept development and image

analysis. L.H. performed statistical data analysis. M.E.A., H.S., Z.K., and A.R.L. contributed to data acquisition. S.W. was involved in patient recruitment, image analysis, interpretation of study data, and was responsible for the overall supervision of the project. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants, but are available from S.W. upon reasonable request.

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