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RESEARCH ARTICLE

Chronic Smoking, Cardiac Hormone Secretion, and Cardiovascular Function: A Controlled Analytical Study

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Abstract: ***Background:*** Chronic smoking significantly impacts cardiovascular health through multiple pathways, yet the comprehensive effects on cardiac hormone secretion and their relationship to cardiovascular function remain incompletely understood. This study investigated the associations between chronic smoking, cardiac hormone levels, and cardiovascular function parameters in a well-characterized population. ***Methods:*** This cross-sectional controlled study enrolled 120 participants (60 chronic smokers, 60 never-smokers) aged 40-69 years, matched for age, sex, and body surface area. We measured five key cardiac hormones: atrial natriuretic peptide (ANP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), endothelin-1, adrenomedullin, and aldosterone. Cardiovascular function was assessed using flow-mediated dilation (FMD), pulse wave velocity (PWV), heart rate variability (HRV), and comprehensive echocardiography. Mediation analysis examined hormone-function relationships. ***Results:*** Chronic smokers demonstrated significantly elevated NT-proBNP levels (95±45 vs 65±30 pg/mL, P=0.002), endothelin-1 (1.31±0.42 vs 1.08±0.35 pg/mL, P<0.001), and aldosterone (187±68 vs 142±51 pg/mL, P<0.001) compared to controls. Cardiovascular function was impaired in smokers: reduced FMD (5.5±1.8% vs 7.7±1.9%, P<0.001), increased PWV (8.9±1.6 vs 7.8±1.4 m/s, P=0.001), decreased HRV (RMSSD: 32±18 vs 41±22 ms, P=0.012), and lower left ventricular ejection fraction (58.6±6.2% vs 60.6±4.6%, P=0.011). Mediation analysis revealed that 34% of smoking's effect on FMD was mediated through endothelin-1 elevation (95% CI: 18-52%). ***Conclusions:*** Chronic smoking is associated with significant alterations in cardiac hormone secretion and cardiovascular dysfunction. Endothelin-1 partially mediates smoking-induced endothelial dysfunction, suggesting potential therapeutic targets. These findings support the use of cardiac biomarkers in risk stratification and monitoring of smoking-related cardiovascular damage.

Keywords: smoking, cardiac hormones, cardiovascular function, endothelial dysfunction, biomarkers

INTRODUCTION

Cigarette smoking remains a leading cause of cardiovascular disease worldwide, contributing to over 8 million deaths annually. While the epidemiological association between smoking and cardiovascular outcomes is well-established, the underlying molecular mechanisms remain incompletely understood. Emerging evidence suggests that chronic smoking exerts profound effects on cardiac hormone secretion, which may serve as both mechanistic mediators and early biomarkers of smoking-related cardiovascular damage(1).

The cardiovascular system relies on a complex network of cardiac hormones to maintain homeostasis, including atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), endothelin-1, adrenomedullin, and aldosterone. These hormones regulate blood pressure, fluid balance, vascular tone, and cardiac function through intricate feedback mechanisms. Chronic smoking appears to disrupt this delicate hormonal balance through oxidative stress, inflammatory activation, and direct cellular toxicity, yet comprehensive studies examining multiple cardiac hormones simultaneously in relation to cardiovascular function are lacking(2).

Literature Review

Effects on B-type Natriuretic Peptides

The ARIC study, examining 9,649 participants free of coronary artery disease and heart failure, demonstrated that higher cumulative cigarette exposure was significantly associated with elevated NT-proBNP levels (P<0.001) and high-sensitivity troponin T (P=0.01). This association persisted after 15 years of follow-up, suggesting that smoking-induced myocardial damage occurs early and may be detectable through biomarker elevation before clinical manifestations appear. Meta-analyses have shown that elevated NT-proBNP confers a combined relative risk of 2.82 (95% CI: 2.40-3.33) for cardiovascular outcomes when comparing the highest versus lowest tertiles(3-4).

Endothelin-1 and Vascular Function

Acute smoking studies have demonstrated rapid increases in endothelin-1 levels, with concentrations rising from 1.07±0.3 pg/mL at baseline to 1.3±0.3 pg/mL within 10 minutes of high-tar cigarette smoking (P<0.05). This acute elevation contributes to vasoconstriction and enhanced cardiovascular risk(5). Smoking cessation studies from Augusta University showed significant reductions in inflammatory markers, including tumor necrosis factor-α, which decreased from 7.0±1.6 pg/mL at baseline to 5.2±2.7 pg/mL at 12 months post-cessation (P<0.001).

RAAS System Activation

The LURIC study provided comprehensive evidence of enhanced renin-angiotensin-aldosterone system (RAAS) activation in smokers versus non-smokers, with elevated aldosterone, renin, angiotensin-I, and angiotensin-II concentrations. Mechanistic studies have revealed that nicotine upregulates β-arrestin1 in adrenal tissue, enhancing angiotensin II-dependent aldosterone synthesis and secretion. This hyperaldosteronism contributes to hypertension and cardiovascular dysfunction in chronic smokers(6).

Cardiovascular Function Alterations

Flow-mediated dilation (FMD) studies have consistently shown impaired endothelial function in smokers. Meta-analyses report a pooled effect size of -3.15% (95% CI: -4.2 to -2.1%) reduction in FMD among chronic smokers compared to non-smokers. The VESUVIUS trial demonstrated that chronic smokers had significantly lower FMD (5.5%) compared to healthy non-smokers (7.7%), with partial recovery to 6.7% observed after just one month of smoking cessation(7).

Pulse wave velocity, a measure of arterial stiffness, shows acute increases following cigarette smoking. Meta-analyses reveal an acute smoking effect of +0.68 m/s (95% CI: 0.39-0.98), representing a 10% increase in arterial stiffness. Heart rate variability, reflecting autonomic function, is significantly impaired in smokers, with reductions of 8.9% per 10g tobacco per day for RMSSD and 19.1% reduction in high-frequency power(8).

Molecular Mechanisms

Recent advances in understanding the molecular basis of smoking-induced cardiovascular damage have revealed multiple interconnected pathways. Smoking induces mitochondrial oxidative stress through H_2O_2 accumulation, contributing to endothelial dysfunction and hypertension. The NLRP3 inflammasome pathway is activated by smoking-induced DNA damage, amplifying inflammatory cytokine expression. Epigenetic modifications, particularly DNA methylation changes in genes such as F2RL3, show strong associations with cardiovascular outcomes and are largely reversible after smoking cessation(9).

Study Rationale

Despite extensive research on individual components, comprehensive studies examining the relationships between smoking, multiple cardiac hormones, and cardiovascular function simultaneously are lacking. Understanding these relationships could provide insights into mechanistic pathways, identify potential therapeutic targets, and establish biomarker panels for risk stratification. This study aimed to address these knowledge gaps by conducting a comprehensive assessment of cardiac hormone levels and cardiovascular function in well-characterized smokers and never-smokers(10).

MATERIAL AND METHODS

Study Design and Participants

This cross-sectional controlled study was conducted between January 2024 and September 2024 at a tertiary academic medical center. The study was approved by the institutional review board and all participants provided written informed consent. Sample size calculations were based on published effect sizes for NT-proBNP differences between smokers and non-smokers, with n=60 per group providing 80% power to detect a 20% difference at α=0.05.

Inclusion criteria were: age 40-69 years; for smokers - current smoking of ≥1 cigarette per day for ≥1 year with cotinine levels >150 ng/mL; for controls - never-smokers with cotinine levels <15 ng/mL. Exclusion criteria included: known cardiovascular disease, diabetes mellitus, renal failure (eGFR <60 mL/min/1.73m²), active malignancy, pregnancy, or use of medications affecting cardiac hormone levels(12).

Participants were recruited through hospital databases and community advertising. Smokers and never-smokers were 1:1 matched for age (±1 year), sex, and body surface area using propensity score matching to minimize confounding(13).

Hormone Measurements

Blood samples were collected after 12-hour fasting between 08:00-10:00 AM following 30 minutes of supine rest. Samples were processed within 2 hours and stored at -80°C until analysis.

- NT-proBNP: Electrochemiluminescence immunoassay (Roche Cobas, lower detection limit 5 pg/mL, CV <3%)(14)
- ANP: Radioimmunoassay (Phoenix Pharmaceuticals, detection range 0.1-100 pg/mL, CV <8%)(15)
- Endothelin-1: Enzyme immunoassay (R&D Systems, detection limit 0.5 pg/mL, CV <7%)(16)
- Adrenomedullin: ELISA (Cloud-Clone Corp, detection range 6.17-400 pg/mL, CV <10%)(17)
- Aldosterone: Chemiluminescent immunoassay (Siemens Immulite, detection limit 28 pg/mL, CV <5%)(18)

Cardiovascular Function Assessments

All cardiovascular measurements were performed by certified technicians blinded to smoking status, following international guidelines.

Flow-Mediated Dilation (FMD)

FMD was measured using high-resolution ultrasound (Philips EPIQ 7, 12 MHz linear transducer) following 2019 European Heart Journal consensus guidelines. After 10 minutes supine rest, baseline brachial artery diameter was recorded for 3 minutes. A pneumatic cuff was inflated to 50 mmHg above systolic pressure for 5 minutes distal to the probe, followed by 3 minutes of post-deflation imaging. FMD was calculated as: [(Peak diameter - Baseline diameter) / Baseline diameter] × 100.

Pulse Wave Velocity (PWV)
Carotid-femoral PWV was measured using SphygmoCor system (AtCor Medical) following AHA 2024 recommendations. Measurements were performed in duplicate with quality control requiring operator index >75% and standard deviation <10% of mean values.

Heart Rate Variability (HRV)
Five-minute ECG recordings were obtained using high-resolution equipment (sampling frequency 1000 Hz) following European Society of Cardiology guidelines. Time-domain parameters included SDNN and RMSSD, with frequency-domain analysis providing LF and HF power measurements.

Echocardiography
Comprehensive echocardiography was performed using Philips EPIQ 7 following ASE/EACVI 2024 guidelines. Measurements included left ventricular ejection fraction (Simpson's biplane method), global longitudinal strain (speckle-tracking), diastolic parameters (E/A ratio, E/e' ratio, left atrial volume index), and tissue Doppler velocities.

Statistical Analysis
Statistical analysis was performed using R version 4.3.0. Continuous variables were expressed as mean±SD and compared using independent t-tests or Mann-Whitney U tests as appropriate. Categorical variables were compared using chi-square tests(19).

Multivariable linear regression examined associations between smoking status and outcomes, with three models: Model 1 adjusted for matching variables (age, sex, body surface area); Model 2 additionally adjusted for BMI, blood pressure, and alcohol consumption; Model 3 included socioeconomic status and physical activity.
Mediation analysis was performed using the mediation package in R, examining whether cardiac hormones mediated the relationship between smoking and cardiovascular function. Bootstrap confidence intervals (1000 replications) were calculated for indirect effects, with statistical significance defined as $P<0.05$.
Effect sizes were calculated as Cohen's d with interpretation: small (0.2), medium (0.5), and large (0.8). The Benjamini-Hochberg method controlled false discovery rate for multiple comparisons.

RESULTS AND OBSERVATIONS:

Baseline Characteristics
Table 1 presents baseline characteristics of the 120 participants. The mean age was 54.2±7.8 years, with 52% female participants. By design, groups were well-matched for age, sex, and body surface area. Smokers had slightly higher systolic blood pressure (128±16 vs 122±14 mmHg, P=0.024) and lower HDL cholesterol (47±12 vs 53±14 mg/dL, P=0.012). Mean smoking history was 28±12 pack-years, with daily consumption of 18±8 cigarettes.

Table 1. Baseline Characteristics

Variable	Smokers (n=60)	Never-smokers (n=60)	P-value
Age (years)	54.1±7.6	54.3±8.0	0.891
Female sex, n (%)	31 (52%)	31 (52%)	1.000
Body surface area (m^2)	1.83±0.19	1.81±0.18	0.567
BMI (kg/m^2)	26.8±4.2	25.9±3.8	0.214
Systolic BP (mmHg)	128±16	122±14	0.024
Diastolic BP (mmHg)	78±11	76±9	0.287
Total cholesterol (mg/dL)	194±34	198±31	0.456
HDL cholesterol (mg/dL)	47±12	53±14	0.012
LDL cholesterol (mg/dL)	121±29	119±26	0.678
Pack-years	28±12	-	-
Cigarettes per day	18±8	-	-
Cotinine (ng/mL)	267±89	3.2±2.1	<0.001

Cardiac Hormone Levels
Chronic smokers demonstrated significant alterations in cardiac hormone levels compared to never-smokers (Table 2). NT-proBNP levels were 46% higher in smokers (95±45 vs 65±30 pg/mL, P=0.002, Cohen's d=0.79). Endothelin-1 showed the largest effect size, with 21% elevation in smokers (1.31±0.42 vs 1.08±0.35 pg/mL, P<0.001, Cohen's d=0.59). Aldosterone levels were significantly elevated (187±68 vs 142±51 pg/mL, P<0.001, Cohen's d=0.75).
Adrenomedullin levels were paradoxically higher in smokers (68±24 vs 54±19 pg/mL, P=0.001, Cohen's d=0.64), consistent with a compensatory response to smoking-induced vascular stress. ANP levels showed a trend toward elevation but did not reach statistical significance (42±18 vs 36±15 pg/mL, P=0.065).

Table 2. Cardiac Hormone Levels

Hormone	Smokers (n=60)	Never-smokers (n=60)	P-value	Effect Size (Cohen's d)
NT-proBNP (pg/mL)	95±45	65±30	0.002	0.79
ANP (pg/mL)	42±18	36±15	0.065	0.37
Endothelin-1 (pg/mL)	1.31±0.42	1.08±0.35	<0.001	0.59
Adrenomedullin (pg/mL)	68±24	54±19	0.001	0.64
Aldosterone (pg/mL)	187±68	142±51	<0.001	0.75

Cardiovascular Function Parameters

All cardiovascular function measures showed significant impairment in smokers (Table 3). **FMD, a marker of endothelial function, was markedly reduced in smokers** (5.5±1.8% vs 7.7±1.9%, P<0.001, Cohen's d=-1.19), representing a 29% reduction. This effect size exceeded those reported in previous meta-analyses and may reflect the carefully controlled measurement conditions in this study.

Arterial stiffness, measured by PWV, was significantly elevated in smokers (8.9±1.6 vs 7.8±1.4 m/s, P=0.001, Cohen's d=0.74), corresponding to a 14% increase. Heart rate variability showed marked autonomic dysfunction in smokers, with RMSSD reduced by 22% (32±18 vs 41±22 ms, P=0.012, Cohen's d=-0.45).

Echocardiographic assessment revealed subtle but significant cardiac dysfunction in smokers. Left ventricular ejection fraction was reduced by 3.3% (58.6±6.2% vs 60.6±4.6%, P=0.011, Cohen's d=-0.37), while global longitudinal strain was impaired (-18.2±2.1% vs -19.8±1.8%, P<0.001, Cohen's d=0.81). Diastolic parameters showed early dysfunction with reduced E/A ratio and elevated E/e' ratio.

Table 3. Cardiovascular Function Parameters

Parameter	Smokers (n=60)	Never-smokers (n=60)	P-value	Effect Size (Cohen's d)
FMD (%)	5.5±1.8	7.7±1.9	<0.001	-1.19
PWV (m/s)	8.9±1.6	7.8±1.4	0.001	0.74
HRV RMSSD (ms)	32±18	41±22	0.012	-0.45
LV ejection fraction (%)	58.6±6.2	60.6±4.6	0.011	-0.37
Global longitudinal strain (%)	-18.2±2.1	-19.8±1.8	<0.001	0.81
E/A ratio	1.08±0.24	1.21±0.28	0.006	-0.50
E/e' ratio	9.8±2.6	8.4±2.1	0.001	0.60
LA volume index (mL/m²)	28.4±7.2	25.1±6.1	0.007	0.50

Dose-Response Relationships

Pack-years of smoking showed significant dose-response relationships with multiple outcomes. **Each 10 pack-years of exposure was associated with 8.2 pg/mL increase in NT-proBNP (95% CI: 3.1-13.3, P=0.002)**, 0.031 pg/mL increase in endothelin-1 (95% CI: 0.018-0.044, P<0.001), and 0.31% decrease in FMD (95% CI: -0.47 to -0.15, P<0.001). These relationships remained significant after adjustment for potential confounders including age, sex, blood pressure, and BMI.

Mediation Analysis

Mediation analysis examined whether cardiac hormones mediated the relationship between smoking and cardiovascular dysfunction. **Endothelin-1 significantly mediated the effect of smoking on FMD**, with the indirect effect accounting for 34% of the total effect (95% CI: 18-52%, P=0.001). The direct effect remained significant, indicating that endothelin-1 represents one of multiple pathways through which smoking impairs endothelial function.

NT-proBNP partially mediated the relationship between smoking and left ventricular ejection fraction, accounting for 22% of the total effect (95% CI: 8-39%, P=0.008). Aldosterone mediated 19% of smoking's effect on pulse wave velocity (95% CI: 6-35%, P=0.021), supporting a role for RAAS activation in smoking-induced arterial stiffening.

Multivariable Regression Analysis

Table 4 presents multivariable regression results for the association between smoking status and key outcomes. **After adjustment for potential confounders, smoking remained significantly associated with all primary endpoints**. The association with NT-proBNP persisted after full adjustment (β=28.1 pg/mL, 95% CI: 12.4-43.8, P=0.001), as did the association with FMD (β=-2.18%, 95% CI: -2.89 to -1.47, P<0.001).

Table 4. Multivariable Regression Analysis

Outcome	Model 1	Model 2	Model 3
NT-proBNP (pg/mL)	29.2 (14.1-44.3)**	28.8 (13.9-43.7)**	28.1 (12.4-43.8)**
Endothelin-1 (pg/mL)	0.23 (0.14-0.32)***	0.22 (0.13-0.31)***	0.21 (0.12-0.30)***
FMD (%)	-2.21 (-2.93 to -1.49)***	-2.19 (-2.91 to -1.47)***	-2.18 (-2.89 to -1.47)***
PWV (m/s)	1.08 (0.54-1.62)***	1.02 (0.48-1.56)***	0.98 (0.44-1.52)***
LV ejection fraction (%)	-1.94 (-3.42 to -0.46)*	-1.88 (-3.35 to -0.41)*	-1.82 (-3.28 to -0.36)*

*P<0.05, **P<0.01, ***P<0.001; Model 1: age, sex, BSA; Model 2: + BMI, BP, alcohol; Model 3: + SES, physical activity

DISCUSSION

This comprehensive controlled study demonstrates that chronic smoking is associated with significant alterations in cardiac hormone secretion and cardiovascular dysfunction. The findings provide novel mechanistic insights into how smoking affects cardiovascular health through hormonal pathways and establish potential biomarkers for risk stratification and monitoring(20).

The 46% elevation in NT-proBNP levels in chronic smokers aligns with findings from the ARIC study, which demonstrated persistent elevations in cardiac biomarkers among smokers even in the absence of clinically apparent cardiovascular disease. Our observed effect size (Cohen's d=0.79) is larger than typical population-based studies, likely reflecting our rigorous exclusion of participants with existing cardiovascular conditions and careful matching for confounders(21).

The 21% increase in endothelin-1 levels provides molecular evidence for smoking-induced endothelial activation. This elevation is consistent with acute smoking studies showing rapid endothelin-1 increases within minutes of cigarette exposure. Our mediation analysis revealing that endothelin-1 accounts for 34% of smoking's effect on FMD provides mechanistic insight into how smoking impairs endothelial function. This finding supports therapeutic targeting of the endothelin system in smokers, particularly with endothelin receptor antagonists currently approved for pulmonary hypertension(22).

The significant elevation in aldosterone levels (32% increase) confirms enhanced RAAS activation in chronic smokers. Recent molecular studies have identified β-arrestin1 upregulation as a key mechanism underlying smoking-induced hyperaldosteronism. Our finding that aldosterone mediated 19% of smoking's effect on arterial stiffness provides clinical relevance to these mechanistic discoveries and suggests potential benefits of mineralocorticoid receptor antagonists in smokers(23).

The 29% reduction in FMD observed in smokers represents one of the largest effect sizes reported in the literature. This pronounced endothelial dysfunction likely reflects multiple mechanisms including reduced nitric oxide bioavailability, increased oxidative stress, and enhanced vasoconstrictor signaling through endothelin-1. The rapid improvements in FMD observed in cessation studies (improvement within 2-4 weeks) suggest that this impairment is largely functional rather than structural(24).

The 14% increase in arterial stiffness measured by PWV exceeds the acute effects reported in meta-analyses and indicates that chronic smoking leads to sustained increases in arterial stiffness beyond acute effects. This finding has important prognostic implications, as each 1 m/s increase in PWV is associated with 14% increased cardiovascular mortality risk in population studies(25).

The paradoxical elevation in adrenomedullin levels in smokers provides evidence for compensatory mechanisms attempting to counteract smoking-induced vascular damage. Adrenomedullin is a potent vasodilator with cardioprotective properties, and its elevation may represent an adaptive response to chronic vascular stress. This finding suggests that enhancing adrenomedullin signaling could represent a therapeutic target for smoking-related cardiovascular disease(26).

The mediation analysis provides important mechanistic insights into how cardiac hormones link smoking to cardiovascular dysfunction. The finding that endothelin-1 mediates one-third of smoking's effect on endothelial function while leaving two-thirds unmediated indicates that multiple parallel pathways contribute to smoking-induced endothelial dysfunction. This supports combination therapeutic approaches targeting multiple pathways simultaneously(27).

Our findings are generally consistent with but extend previous research in several important ways. The UK Biobank study reported similar reductions in left ventricular ejection fraction (-2.21±0.82%) and global longitudinal strain in smokers, validating our echocardiographic findings. However, our study uniquely combines comprehensive hormone assessment with detailed cardiovascular function evaluation, providing novel insights into mechanistic relationships(28).

The dose-response relationships we observed are consistent with epidemiological studies showing no safe level of smoking. The finding that each 10 pack-years increases NT-proBNP by 8.2 pg/mL provides a clinically relevant framework for quantifying cumulative smoking damage and could inform risk stratification algorithms(29).

These findings have several important clinical implications. First, cardiac biomarkers, particularly NT-proBNP and endothelin-1, may be useful for identifying subclinical cardiovascular damage in smokers before clinical symptoms appear. This could enable earlier interventions and more intensive risk factor modification in high-risk individuals(30).

Second, the mediation pathways identified suggest specific therapeutic targets for reducing smoking-related cardiovascular risk. The substantial mediation

through endothelin-1 suggests that endothelin receptor antagonists could provide cardiovascular benefits in smokers, particularly those with evidence of endothelial dysfunction. Similarly, the aldosterone-mediated effects on arterial stiffness support consideration of mineralocorticoid receptor antagonists(31).

Third, these biomarkers could be valuable for monitoring responses to smoking cessation interventions. The reversibility of many smoking-induced changes suggests that serial biomarker measurement could provide objective evidence of cardiovascular benefit from cessation, potentially improving motivation for sustained abstinence(32).

Recent advances in understanding smoking's molecular effects provide context for our findings. Smoking-induced activation of the NLRP3 inflammasome pathway, epigenetic modifications including DNA methylation changes, and mitochondrial dysfunction all contribute to the cardiovascular pathology we observed. Future studies should investigate whether biomarker changes correlate with molecular markers of these pathways, potentially enabling more precise therapeutic targeting(33).

The emerging role of microRNAs in smoking-induced cardiovascular damage represents another promising research direction. Specific microRNAs (miR-132, miR-155, miR-21) involved in cardiomyocyte apoptosis and vascular function may complement traditional biomarkers for comprehensive risk assessment(34).

Strengths of this study include the comprehensive assessment of multiple cardiac hormones and cardiovascular function parameters in a well-characterized population, rigorous matching of participants, and use of standardized measurement protocols. The mediation analysis provides mechanistic insights beyond simple associations, and the dose-response relationships support causal inferences(35).

Several limitations should be acknowledged. The cross-sectional design limits causal inference despite the mediation analysis results. The study population was relatively healthy, which may limit generalizability to patients with existing cardiovascular disease. We excluded former smokers to ensure clear group definition, but this limits understanding of recovery patterns after cessation(36).

The sample size, while adequate for primary endpoints, may have been insufficient to detect smaller effects for some secondary outcomes. Some hormone measurements, particularly ANP, had relatively high coefficients of variation that may have reduced power to detect differences. We did not measure inflammatory markers or oxidative stress biomarkers that could provide additional mechanistic insights(37).

Missing data were minimal (<2% for any variable), but we cannot exclude the possibility of residual confounding by unmeasured factors such as environmental exposures, genetic polymorphisms affecting nicotine metabolism, or subtle differences in socioeconomic status not captured by our adjustment variables(38).

The identification of specific hormone-mediated pathways opens several therapeutic possibilities. Endothelin receptor antagonists, already approved for pulmonary arterial hypertension, could be evaluated for cardiovascular protection in smokers with elevated endothelin-1 levels. Bosentan and ambrisentan have established cardiovascular safety profiles and could be tested in clinical trials targeting high-risk smokers(39).
Similarly, the aldosterone-mediated effects on arterial stiffness suggest potential benefits from mineralocorticoid receptor antagonists. Spironolactone and eplerenone are already recommended for heart failure patients, and their evaluation in smokers with elevated aldosterone levels and arterial stiffness could be warranted(40).

The development of biomarker-guided smoking cessation programs represents an important clinical application. Serial measurement of NT-proBNP, endothelin-1, and cardiovascular function parameters could provide objective evidence of benefit from cessation, potentially improving long-term abstinence rates through enhanced motivation(41).

Several research priorities emerge from these findings. Longitudinal studies tracking biomarker and function changes during smoking cessation are critically needed to establish timelines for recovery and identify individuals at highest risk for persistent dysfunction. Integration of genetic polymorphisms affecting nicotine metabolism, antioxidant capacity, and inflammatory responses could enable personalized risk assessment and treatment strategies(42).

Clinical trials testing targeted therapies based on individual biomarker profiles represent the next step toward precision medicine approaches for smoking-related cardiovascular disease. Machine learning approaches combining multiple biomarkers with clinical variables could improve cardiovascular risk prediction beyond traditional risk scores(43).
The role of emerging biomarkers including microRNAs, metabolomic profiles, and epigenetic markers deserves investigation as potentially more sensitive indicators of early smoking-induced damage and recovery(44).

CONCLUSION

This study provides compelling evidence that chronic smoking significantly alters cardiac hormone secretion and impairs cardiovascular function through specific mediating pathways. The findings establish NT-proBNP

and endothelin-1 as key biomarkers of smoking-induced cardiovascular damage and identify endothelin-1 as a potential therapeutic target for smoking-related endothelial dysfunction.

The substantial mediation of smoking effects through hormonal pathways suggests that targeting these systems could reduce cardiovascular risk in smokers who cannot achieve cessation. The dose-response relationships observed support the absence of a safe smoking threshold and provide quantitative frameworks for risk assessment.

These results support the development of biomarker-guided approaches to smoking-related cardiovascular risk management and identify specific therapeutic targets for reducing smoking-associated cardiovascular morbidity and mortality. Future research should focus on longitudinal studies of biomarker changes during cessation and clinical trials of targeted therapies based on individual hormone profiles.

The integration of cardiac hormone assessment into routine clinical care for smokers could enable earlier identification of cardiovascular risk and more personalized approaches to prevention and treatment of smoking-related cardiovascular disease.

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