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The Interplay between Cardiovascular Health and Parkinson's Disease: Implications for Incidence, Severity, and Mortality

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Review Article

The Interplay between Cardiovascular Health and Parkinson's Disease: Implications for Incidence, Severity, and Mortality | 1

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The Interplay between Cardiovascular Health and Parkinson's Disease: Implications for Incidence, Severity, and Mortality

© Christopher George¹, © Gurneer Sidhu², © Hridini Dave³, © Smira Sonthalia⁴, © Giuliana Ramirez², © Leah Rupp², © Rian Wasniewski², © Ashley Burnidge³, © Myka Punzalan⁵, © Aquib Ahmed⁶, © Peyton Warren⁶, © Manasa Maskey², © Diya Patel¹, © Paul Nguyen⁷

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Abstract

Parkinson's disease (PD) is a common neurodegenerative disorder that is becoming increasingly prevalent in the United States. Current research suggests a possible bidirectional relationship between cardiovascular disease (CVD) and PD. This review aims to synthesize relevant evidence to analyze the interplay between CVD and PD. Researchers utilized academic databases to find current and relevant studies that met the defined inclusion and exclusion criteria. After reviewing various articles, a majority of evidence suggests a correlation between CVD and worsening prognosis for PD patients regarding mortality, cardiac dysfunction, and blood pressure. Conflicting and inconclusive studies are acknowledged within this



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Abstract

review, showing the complexity of this subject and the need for continuing research to determine causality. Future research should adopt a prospective study design with stricter diagnostic methods and detailed sample demographics to identify confounding variables. The underlying biological and physiological background within these diseases should also be studied to help better understand the interplay between CVD and PD.

Keywords: Cardiology, cardiovascular medicine, heart, medicine

Introduction

Behind Alzheimer's, Parkinson's disease (PD) is the second-most common neurodegenerative disorder in the United States (US)⁽¹⁾. It is estimated that approximately one million Americans currently live with PD, with numerous others undiagnosed. Due to the progressive degeneration that accompanies PD, it further impacts thousands of spouses, children, and other caregivers.

The disruption of movement and emotion regulation in PD patients is often credited to the loss of dopamine-producing neurons. However, the actual cause of this phenomenon remains unknown. Approximately 80% of those diagnosed have an idiopathic form with no identifiable cause, while the remaining 20% are presumed to be genetically inherited. In the absence of genetic causes, environmental factors such as pesticide exposure, increasing age, and gender, among others, are thought to play a role⁽²⁾.

In recent years, researchers have also started to explore how cardiovascular disease (CVD) may be related to PD. However, these studies have yielded conflicting results. In a 2022 study published in the *Journal of the American Heart Association*, evidence showed that myocardial infarctions (MIs) were associated with a 20% decreased risk of PD and a 28% reduced risk of secondary Parkinsonism, which reflects an inverse relationship between cardiovascular risk factors and PD⁽³⁾. In contrast, a 2024 cohort-based study suggests that a history of CVD or MI may be a significant risk factor for the development of PD⁽⁴⁾. An additional cohort study utilizing data from

the National Health and Nutrition Examination Survey (NHANES) found that individuals with PD had a higher risk of CVD mortality compared to those without PD⁽⁵⁾.

Conflicting findings in current research reveal a crucial gap in understanding the connection between CVD and PD. These inconsistencies motivated a comprehensive literature review. The discrepancies highlight a critical gap in understanding the interplay between these two conditions. They force the question: What is the association between cardiovascular comorbidities and incidence rates, severity, and mortality of individuals diagnosed with PD compared to the general population?

This review aims to synthesize existing evidence, identify current gaps, and propose avenues for future research to better understand the complex interplay between CVD and PD.

Search Strategy

The objective of this analysis is to discuss the relationship between PD and CVD regarding incidence, severity, and mortality risk. In this review, databases such as PubMed and Google Scholar were used. A search was done to ensure a broad coverage of relevant literature. The search utilized a combination of various keywords in association with PD and cardiovascular health: "PD and cardiovascular health," "CVD and neurology," "Parkinson's Disease Associations," "cardiovascular and Parkinson's," "cardiovascular and motor impairment," "vascular disease and Parkinson's," "Parkinson's and heart," and "Parkinson's links."

Inclusion and Exclusion Criteria

Inclusion Criteria:

Studies were included if they:

1. Examined CVD in the context of PD.
2. Were published in high-quality, peer-reviewed journals to ensure credibility.
3. Utilized validated and reliable instruments to assess cardiovascular and neurological outcomes.
4. Followed established clinical guidelines or standards in the field.
5. Were initially published in English to facilitate the review process.

Exclusion Criteria:

Studies were excluded if they:

6. Were written in languages other than English.
7. Were inaccessible due to paywalls or a lack of open access
8. Did not explicitly discuss PD and/or cardiovascular health.
9. Were dissertations or non-peer-reviewed sources, which may not meet rigorous scientific standards.
10. Contained methodological flaws.
11. Provided insufficient data or poorly described outcomes.

Data Extraction and Synthesis

Data were systematically extracted from selected studies, focusing heavily on study design, population characteristics, outcomes, and key findings. Thirty-two studies were chosen to be reviewed based on the predefined inclusion criteria. The studies that were included provided diverse perspectives on the interplay between CVD and PD by utilizing the data included within the studies.

To maintain consistency, qualitative and quantitative data related to cardiovascular risk factors, incidence rates, mortality rates, and associated symptoms of PD were analyzed. Conflicting reports were also noted. Studies focusing on the interrelation of CVD, cardiovascular

autonomic dysfunction, non-motor symptoms, and cognitive impairments were given priority because they present an interaction between PD and CVD.

It is worth noting that the typical forest plot seen in many meta-analyses and literature reviews was excluded. This was because many of the studies used were not combinable due to significant design differences.

Quality Assessment

To ensure reliability, the studies were reviewed based on author credibility, study design, and compliance with standard reporting guidelines. A quality checklist was used to evaluate methodological soundness, including sample size and control for confounding variables. The review aimed to balance studies supporting and contradicting the association between PD and cardiovascular risks to offer an unbiased blend of available evidence. All studies included were categorized as either “for,” “inconclusive,” or “against” to determine which conclusion the data supports.

Assistive Technology

Artificial intelligence (AI) models were used to assist in this literature review. The AI model GPT-4o was utilized to efficiently filter the initial pool of articles based on the predefined inclusion and exclusion criteria and to generate concise summaries of key findings to aid in rapid relevance assessment. Crucially, all AI-assisted tasks were subject to rigorous human oversight; each filtered article and summary was manually reviewed and verified by the research team to ensure accuracy, relevance, and appropriate application of criteria. AI was not used to write any part of the actual manuscript.

The relationship between CVD and PD when measuring mortality rates is a vital link to explore, with strong evidence in support of a link between the comorbidities of these diseases and a higher risk of adverse outcomes, as seen in Table 1. Numerous studies have reported that patients with PD and symptoms of CVD, such as autonomic dysfunction or orthostatic hypotension (OH), face a higher risk of mortality in comparison to patients

who do not present with CVD-like symptoms. In a population-based prospective analysis study using data from the NHANES and linking it with the national death index, there was substantial evidence suggesting that patients with pre-existing CVD symptoms were at higher risk of death. The researchers used the hazard ratio (HR) to compare the frequency of an event occurring in one group versus another, and verified statistical significance of the results through the use of confidence intervals (CIs) and p-values. In the context of these clinical trials, HR refers to the survival rate of patients in one group compared

to the other. An HR of 1 indicates no difference in risk between the groups. A value greater than 1 indicates an increased risk of the event (e.g. mortality) in the study group, while a value less than 1 indicates a decreased risk⁽¹²⁾. Results showed that people with PD had a higher risk of CVD-related death than those without PD (HR: 1.82; 95% CI: 1.24-2.69; p=0.002) and a similar increase in the risk of death from any cause (HR: 1.84; 95% CI: 1.44-2.33; p<0.001), as seen in Figure 1⁽⁵⁾. These results can be attributed to autonomic dysfunction and other cardiovascular symptoms in PD patients.

Table 1. Summary of key studies on the interplay between cardiovascular disease and Parkinson's disease

Study (author, year) (reference)	Study design	Sample size	Key finding/outcome	Effect size/result
Mortality				
Ke, 2024 ⁽⁵⁾	Population-based prospective cohort (NHANES data)	28,242 participants (380 with PD; 27,862 without PD)	PD associated with a higher risk of both CVD-related and all-cause mortality	CVD death: HR: 1.82 (95% CI: 1.24-2.69; p=0.002) All-cause death: HR: 1.84 (95% CI: 1.44-2.33; p<0.001)
Bartl, 2022 ⁽⁶⁾	Analysis of plasma biomarkers (DeNoPa cohort)	109 drug-naïve PD patients 96 healthy controls	Biomarkers (e.g., IL-6, cystatin B) correlated with cognitive decline and motor progression	IL-6 vs. MMSE: Est. -0.33 (p<0.01) CSTB vs. MMSE: Est. -0.34 (p<0.01) IL-6 vs. MDS-UPDRS: Est. 0.28 (p=0.03)
Chen, 2024 ⁽⁷⁾	Two-sample mendelian randomization	GWAS data: PD (n=482,730) MI (n=462,933) AF (n=337,199) VTE (n=361,194)	Found a minimal, statistically significant protective association for PD on MI. No causal association found for PD on AF or VTE	PD on MI: OR: 0.9989 (95% CI: 0.9980-0.9998) PD on AF: OR: 1.0000 (95% CI: 0.9994-1.0007) PD on VTE: OR: 1.0000 (95% CI: 0.9994-1.0007)
CVD history & PD risk				
Acharya, 2024 ⁽⁴⁾	Cross-sectional observational study	676 idiopathic PD patients 874 non-PD controls	A history of CVD was associated with a higher risk of developing idiopathic PD, particularly in males	CVD history on idiopathic PD: OR 1.56 (95% CI: 1.09-2.08; p=0.013)
Sundbøll, 2022 ⁽³⁾	Nationwide population-based matched cohort (Danish registries)	181,994 MI patients 909,970 matched controls	Inverse relationship. MI survivors had a decreased risk of developing PD and secondary parkinsonism	PD risk (post-MI): aHR: 0.80 (95% CI: 0.73-0.87) Parkinsonism risk: aHR: 0.72 (95% CI: 0.54-0.94)

Table 1. Continued

Study (author, year) (reference)	Study design	Sample size	Key finding/outcome	Effect size/result
Cardiovascular risk factors & events				
Vikdahl, 2015 ⁽⁸⁾	Population-based nested case-control study (NSHDS)	84 PD cases 336 matched controls	Inverse relationship. Lower S-TG and lower SBP 2-8 years prior to diagnosis were associated with an increased risk of PD	S-TG: HR 0.61 (95% CI: 0.39-0.96) SBP: HR 0.98 (95% CI: 0.97-0.99)
Han, 2021 ⁽⁹⁾	Nationwide population-based matched cohort (Korean National Health Insurance Service)	57,585 PD patients 57,585 matched controls	PD was an independent risk factor for new-onset AF. The risk was notably higher in younger patients	Overall AF risk: aHR 1.27 (95% CI: 1.18-1.36) Age 40-49: HR 3.06 (95% CI: 1.20-7.77)
Lim, 2024 ⁽¹⁰⁾	Retrospective, propensity-score matched cohort (Electronic health record data)	1,194 PD patients 4,574 matched controls	MACE were significantly higher in patients with more severe PD (measured by H&Y scale)	MACE incidence: 12.7% (low-severity) vs. 27.6% (high-severity) (p<0.01)
Abugroun, 2020 ⁽¹¹⁾	Cross-sectional (National Inpatient Sample)	57,914 PD patients 231,646 matched controls	PD associated with reduced odds of most vascular risk factors, but increased odds of stroke	Hyperlipidemia: aOR 0.77 (95% CI: 0.71-0.75) Diabetes: aOR 0.73 (95% CI: 0.71-0.75) Hypertension: aOR 0.68 (95% CI: 0.67-0.70) Stroke: aOR 1.27 (95% CI: 1.24-1.31)

AF: Atrial fibrillation, aHR: Adjusted hazard ratio, aOR: Adjusted odds ratio, HR: Hazard ratio, OR: Odds ratio, a-OR: Adjusted odds ratio, CI: Confidence interval, SBP: Systolic blood pressure, S-TG: Serum triglycerides, H&Y: Hoehn and Yahr, MACE: Major adverse cardiovascular events, MI: Myocardial infarction, MMSE: Mini-mental state examination, MDS-UPDRS: Movement disorder society-unified Parkinson's disease rating scale, VTE: Venous thromboembolism, PD: Parkinson's disease, CVD: Cardiovascular disease, IL-6: Interleukin-6

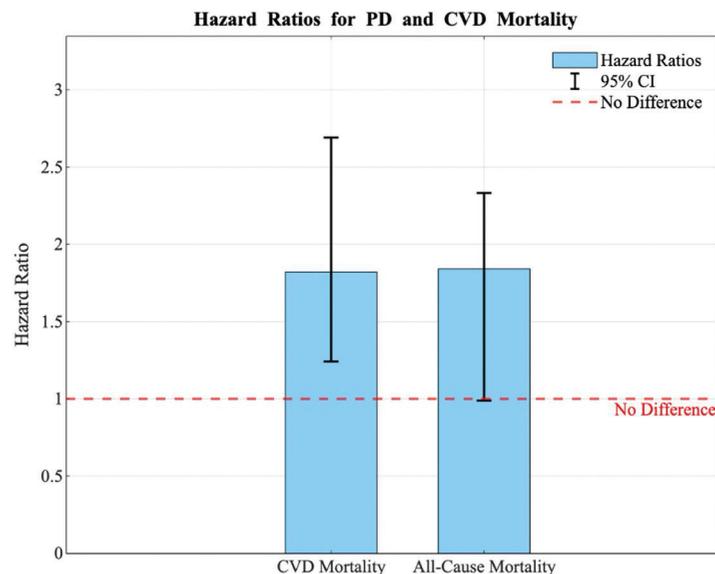


Figure 1. Hazard ratios for CVD and all-cause mortality in PD patients⁽⁵⁾
CVD: Cardiovascular disease, PD: Parkinson's disease, CI: Confidence interval



Figure 1. illustrates the HR values for cardiovascular and all-cause mortality in PD patients compared with non-PD individuals. The HR for CVD mortality significantly increases as its CI does not include 1. On the other hand, the HR for all-cause mortality shows a larger CI that narrowly contains 1. This suggests borderline statistical significance.

Another study researching blood markers of inflammation, neurodegeneration, and cardiovascular risk in early PD explores links to disease progression. The study identified inflammation and vascular pathology biomarkers in patients still in the early stages of PD. A proximity assay on 273 markers was applied to the plasma of 109 drug-naive at baseline PD patients and 96 healthy control patients⁽⁶⁾. At baseline, 35 plasma biomarkers showed downregulation of atherosclerosis risk factors such as E-selectin and B2-integrin, which both play key roles in stimulating endothelial contact and rolling with leukocytes⁽⁶⁾. Other contrasting results showed reduced markers in the plasminogen activation system, most notably the urokinase plasminogen activator⁽⁶⁾. Urokinase plasminogen activators and their reduction lead to decreased plasmin levels, the primary enzyme involved in dissolving blood clots. This study associated biomarker levels with disease progression, finding that higher plasma levels of parkers like interleukin-6 and cystatin B correlated with worse cognitive decline as measured by the Mini-Mental State Examination, and motor impairment, as measured by part III of the movement disorder society-unified PD rating scale⁽⁶⁾.

Additional studies examine the cardiac abnormalities associated with PD, emphasizing the role of autonomic dysfunction, which further supports the projected risk of adverse effects in PD patients. They report that PD patients experience a higher prevalence of arrhythmias, with one study cited indicating a 10-20% incidence of these cardiac issues in PD patients. Additionally, reduced heart rate variability (HRV) is common in PD patients, with a 25-30% decrease compared to healthy individuals, and is correlated with disease progression and motor

symptom severity⁽¹³⁾. The review also compares PD with other parkinsonisms, noting that while cardiac dysfunction is present in conditions like multiple system atrophy, PD patients exhibit more significant HRV reduction⁽¹³⁾. The authors advocate for routine monitoring of cardiac health, particularly HRV, as early intervention could improve cardiovascular outcomes.

PD patients also had prolonged electrocardiogram (ECG) parameters such as QTc, QRS, and QT. Having prolonged ECG parameters is associated with an increased risk of abnormal heart rhythms⁽¹⁴⁾. A study utilizing information from 28,242 patients, 380 of whom had PD, revealed that PD patients were, on average, older (mean 64.8 years vs. 60.1 years) and had a higher body mass index (BMI) (30.57 vs. 29.38 kg/m²) than their non-PD counterparts. The same patients were more likely to have diabetes (33.68% vs. 25.47%) and hypertension (68.16% vs. 56.49%) compared to others as well. Additionally, male PD patients exhibited higher CVD mortality rates, which may be related to the earlier onset of the disease and the lack of beneficial neuroprotective effects from the hormone estrogen⁽⁵⁾. This indicates that patients with PD face a higher risk of cardiovascular death and morbidity. Advanced age, greater BMI, diabetes, hypertension, abnormal heart rhythms, and earlier illness onset in male patients, together with the absence of estrogen's neuroprotective properties, are all associated with this higher risk⁽⁵⁾. These comorbidities not only raise the risk of CVD, but they may also exacerbate PD symptoms, resulting in a cyclical interplay that heightens the risk of serious cardiovascular events such as arrhythmias and sudden cardiac death. These findings underline the importance of an integrated clinical approach to addressing both PD and its accompanying comorbidities to reduce their combined impact on patient outcomes⁽⁵⁾.

Vascular comorbidities in PD also require more attention and may significantly contribute to the mortality of these patients. One study's results show that PD patients are more likely to experience major adverse cardiovascular events (MACEs), according to some research. In contrast,

other studies suggest that PD may be linked to a reduced cardiovascular risk profile⁽¹⁰⁾. Patients must be screened more often for CVD if they have PD. Other studies have shown that physicians can monitor disease progression in PD by utilizing biomarkers while managing cardiovascular complications. Biomarkers include urate, protein DJ-1, and coenzyme Q10, all associated with neuroprotective effects⁽²⁾. Additional studies further confirmed this view, finding that in patients with PD and previous symptoms of CVD, the risk of cardiovascular and overall mortality is significantly higher⁽¹⁵⁾. For instance, one report found that biomarkers of inflammation and neurodegeneration found in early-stage PD patients are associated with disease progression and cognitive decline, especially in vascular pathology⁽⁶⁾. Biomarkers are measurable and detectable biological changes that can track and predict disease development. Cholesterol and blood pressure are common biomarkers for heart disease.

While most studies support this link, one study using a two-sample Mendelian randomization approach presents a counter, finding a minimal but statistically significant protective association of PD with MI, with an odds ratio (OR) of 0.9989⁽⁷⁾. Another study suggests that PD may be associated with a lower cardiovascular risk profile, contradicting the hypothesis that PD worsens cardiovascular outcomes. It reveals that cardiovascular biomarkers may indicate a lower cardiovascular risk profile in PD patients. However, the findings reveal minimal to no significant causal links between PD and other factors, such as atrial fibrillation (AF) or venous thromboembolism, as they both had ORs of 1.0000⁽⁷⁾.

Further studies reveal a nuanced relationship between PD and CVD, presenting multivariate reports. Supporting studies suggest that patients with PD are at an increased risk for cardiovascular complications. They reveal that ECG abnormalities have prolonged ramifications in PD patients, such as QTc, QRS, and QT intervals, which may indicate a predisposition to arrhythmias. Additionally, investigations have documented an increased trend in BMI, with higher incidences of diabetes and hypertension,

which all seem to be cardiovascular risk factors in elderly PD patients⁽¹⁶⁾.

Cardiac Dysfunction/Heart Failure

Cardiac dysfunction and heart failure significantly contribute to the non-motor symptoms of PD, highlighting a critical connection between cardiovascular health and cognitive function⁽¹⁶⁾. One cross-sectional study provides evidence that mild cognitive impairment has been seen to worsen with cardiovascular autonomic dysfunction in PD patients, establishing a link between autonomic regulation and cognitive decline⁽¹⁷⁾. Alterations in cardiovascular autonomic control, including impaired HRV, are present in patients with PD and may lead to the development and worsening of cognitive deficits. A systematic review of cardiac changes in PD further supports this idea, demonstrating that PD accelerates both autonomic dysfunction and cardiac dysregulation, underscoring the role of cardiac dysfunction in the overall progression of the disease⁽¹⁸⁾. Further research suggests that increased physical fitness reduces the prevalence of cardiac dysfunction and heart failure, reducing PD diagnosis rates⁽¹⁹⁾.

Studies have also identified links between the cardiovascular sympathetic system and PD, showing concurrent degeneration in motor symptoms and autonomic functions in individuals with PD. This connection is valuable because identifying cardiovascular dysfunction may enable providers to identify PD earlier, even before traditional motor symptoms like tremors or stiffness appear. A study utilizing metaiodobenzilguanidin (MIBG) scintigraphy reports that PD patients often have reduced heart nerve activity (sympathetic denervation) on MIBG scans before experiencing motor symptoms. This diagnostic tool involves injecting a radioactive substance into the bloodstream to measure cardiac uptake and nerve function⁽²⁰⁾. These findings indicate that sympathetic denervation may precede motor issues, demonstrating the diagnostic value of MIBG scintigraphy for heart-related problems in PD patients and its role in revealing a link between PD and cardiovascular autonomic dysfunction.



As mentioned, impaired nerve activity is one of many cardiovascular ramifications caused by PD-induced neurodegeneration. PD is ascribed to progressive loss of motor function and coordination due to enduring degeneration of the substantia nigra, decreasing dopamine production, which impacts autonomic regulation⁽²¹⁾. White matter hyperintensity (WMH) is the pathological manifestation of damage and a radiological hallmark of cerebral small vessel disease, which involves endothelial dysfunction and compromises the integrity of the blood-brain barrier. This disruption leads to the formation of lacunes and microhemorrhages, which damage structural networks inside the brain. Neuropathological conditions like WMH adversely affect the autonomic nervous system (ANS), disrupting homeostasis and eliciting complications such as ischemia and arrhythmia, reflecting underlying vascular pathology. Specifically, sympathetic neuronal degeneration caused by PD can impair the cardiovascular system⁽²²⁾. The concept of a neurovascular unit highlights the tight, bidirectional relationship between the neurons, glia, and vascular cells, illustrating that vascular protection contributes to neuronal protection. Following this concept, interventions that protect vascular health may help preserve neuronal function and delay neurodegenerative consequences. These adverse cardio-related effects have been shown to impact the efficacy of therapeutic Levodopa treatment in PD patients by increasing the risk of OH. Presentation of OH can diminish brain dopamine levels, limiting Levodopa's use as a dopamine prodrug. Moreover, neurogenic OH results from ANS dysfunction; WMH can impair baroreceptor function, and neurodegeneration can affect vascular regulation and heart rate⁽²²⁾.

Overall, neurodegeneration linked to PD is associated with various sources of damage to the ANS, manifesting as cardiovascular regulation malfunctions. Despite this association between cardiovascular dysautonomia and PD, contradictory findings also exist. A referenced Danish cohort addressed in the focal study found an inverse relationship between CVD and PD, reporting that patients with MI had a 20% decreased risk of

developing PD and a 28% reduced risk of developing secondary parkinsonism. The focal study suggests that these results may be influenced by confounding factors, such as demographic variability, comorbidities, and age, which impact the external validity of the data. Despite this counterclaim in the Danish study, a case-control study used univariate and multivariate logistic regression analysis to assess the association between CVD history and idiopathic PD development. The univariate analysis substantiates a direct correlation between CVD history and idiopathic PD, finding that PD and CVD associations remained statistically significant despite removing common confounds (i.e., Age, BMI, hypertension, diabetes, etc.) (OR: 1.56, 95% CI: 1.09-2.08, $p=0.013$)⁽⁴⁾. This analysis supports a direct relationship between PD and CVD, independent of comorbid conditions and additional risk factors such as those removed from the data set. Furthermore, PD and CVD exhibit bilateral effects, substantiating the intersectionality between neurologic and cardiovascular functions.

Together, these studies underline the significant relationship between cardiac dysfunction and heart failure with the incidence and progression of PD, reinforcing the need for expanded research targeting cardiovascular indicators of PD. This may improve the disease's prognosis through early diagnosis and intervention.

Blood Pressure/Cholesterol Increasing PD Rates

Cardiovascular risk factors, such as high blood pressure and high cholesterol, are associated with increasing PD rates. Researchers aimed to further investigate this and conducted a prospective study using data from the Northern Sweden Health and Disease Study, a population-based cohort study in Västerbotten County, Sweden. The study, led by researchers from Umeå University, had 101,790 subjects. Cases were identified through the Newly Diagnosed Parkinson in Umeå study from 2004 to 2009. The data sets were linked, and in doing so, researchers examined cardiovascular metrics 2-8 years before PD diagnosis to determine their association with PD risk. This nested case-control design minimized recall

and selection biases, improving the reliability of findings. One prospective study found an inverse relationship between systolic blood pressure, serum triglycerides (S-TG), and PD risk. Study participants with lower blood pressure had an HR of 0.98 (95% CI: 0.97-0.99). This shows a slightly lower risk of developing PD for those individuals. It was also found that lower S-TG values were associated with a greater risk of developing PD, and participants had an HR of 0.61 (95% CI: 0.39-0.96)⁽⁸⁾. These results highlight the idea that while lower systolic blood pressure and S-TG levels may be associated with better cardiovascular health in general, they paradoxically correlate with an increased risk of PD. This suggests a complex interplay between cardiovascular health and neurodegenerative processes. All of this evidence shows that specific cardiovascular health metrics substantiate a higher likelihood of PD development. However, further research is necessary to explore potential mechanisms and reconcile these findings with conflicting evidence from other studies.

Another study involving 57,585 patients with newly diagnosed PD who had matched controls showed that PD patients have a significantly higher risk of AF. Their adjusted HR was reported to be 1.27 (95% CI: 1.18-1.36).

The HR of 3.06 shows that patients aged 40-49 had a substantially greater risk than individuals in the control group⁽⁹⁾. This data supports a positive association between autonomic dysfunction onset in PD patients and AF. These findings highlight the role of autonomic dysfunction in PD and show its correlation to AF, which covaries with a patient’s cardiovascular and neurological morbidity.

An additional study using electronic health records from two tertiary hospitals examined the occurrence of MACEs among 1,194 PD patients. MACE occurrence was found to be much higher for patients with more severe cases of PD. Researchers used the Hoehn and Yahr (H&Y) scale to measure disease severity. Results showed that MACE incidence ranges from 12.7% in low-severity PD patients to 27.6% in high-severity PD patients (p-trend <0.01)⁽¹⁰⁾.

Figure 2 illustrates the MACE and CV risk across H&Y tertiles as outlined in a study by Lim et al.⁽¹⁰⁾ Data from the source was taken to formulate this figure, which illustrates the trend of increasing MACE occurrence and very high CV risk percentages across H&Y tertiles. This indicates worsening cardiovascular health alongside PD progression. The decrease in low-moderate CV risk

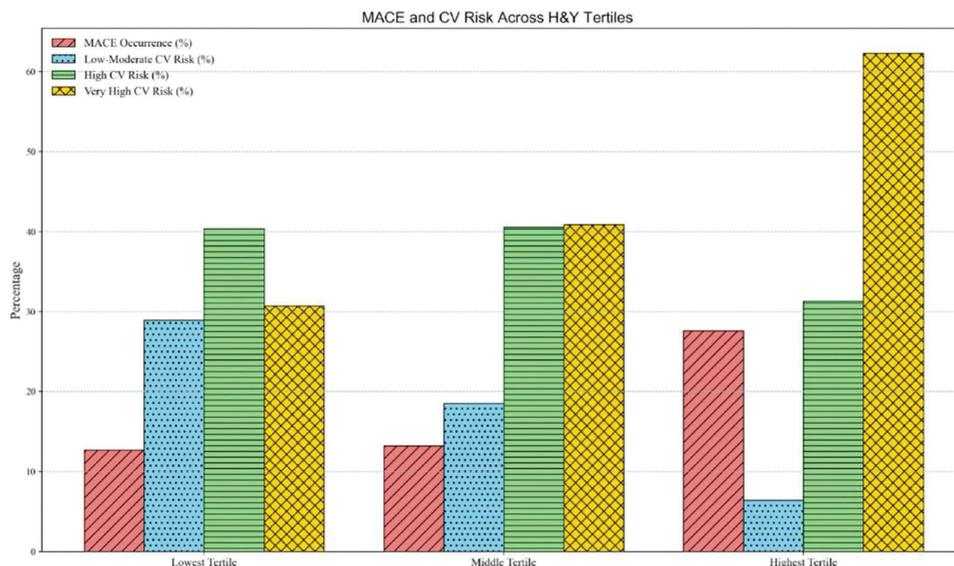


Figure 2. MACE and cardiovascular risk across H&Y tertiles⁽¹⁰⁾
H&Y: Hoehn and Yahr, MACE: Major adverse cardiovascular event, CV: Cardiovascular

highlights how cardiovascular complications can be more pronounced as PD severity increases. This data emphasizes the importance of cardiovascular risk management strategies for patients with PD that is advancing.

These findings highlight a significant correlation between the severity of PD and cardiovascular events, emphasizing the need to assess PD patients for cardiovascular risk factors such as hypertension and hyperlipidemia⁽²⁰⁾. While some studies have produced inconclusive or contradictory results, a growing body of evidence underscores the comorbidity of PD and CVD⁽²⁰⁾. However, limited research has explored the specific impact of CVD on PD progression. Recent advancements, such as those involving myocardial MIBG imaging, suggest that cardiac uptake decline often precedes motor symptoms and dopamine depletion in PD patients⁽²⁰⁾. These insights indicate that CVD plays a crucial role in influencing PD progression and overall prognosis, warranting further investigation into its potential as a therapeutic target⁽²⁰⁾.

PD patients were also found to have reduced rates of hyperlipidemia with an adjusted OR (a-OR): 0.77 (95% CI: 0.75-0.79), diabetes mellitus a-OR 0.73 (95% CI: 0.71-0.75), and hypertension a-OR 0.68 (95% CI: 0.67-0.70). This data compares PD patients with control individuals aged 65 or older. PD patients, however, had a significantly higher risk of a stroke, a-OR 1.27 (95% CI: 1.24-1.31), indicating a unique cardiovascular profile⁽¹¹⁾. Concerning vascular control and stroke prevention in particular, these findings raise significant concerns regarding the involvement of autonomic dysfunction in changing cardiovascular risk profiles in PD disease.

A previous systematic review investigated standard risk variables such as diabetes and inflammation, which are linked to both PD and CVD, further complicating the situation. Both of these factors contribute to an increase in cholesterol. While this complicates the picture, the study also found an inverse relationship between PD risk and other conventional cardiovascular risk factors, including smoking and high low-density lipoprotein cholesterol⁽²³⁾.

These results imply that although there is a strong correlation between cardiovascular health and PD outcomes, the underlying association remains unclear.

Findings from an additional cohort study focused on how people with PD had both an elevated risk of CVD and overall mortality⁽²⁴⁾. This supports the hypothesis that cardiovascular health is closely linked to PD outcomes, influencing disease severity, mortality rates, and overall quality of life.

Current research both supports and contradicts a link between blood pressure, cholesterol, and PD outcomes. Some research shows a protective effect, while other supports the idea that poor cardiovascular health accelerates the progression of PD. To address the impact of both neurological and cardiovascular disorders, the numerical evidence emphasizes the vital necessity for thorough cardiovascular examinations and individualized therapy options for patients with PD.

Hypothesis Confirmation

We hypothesized a bidirectional relationship between CVD and PD. The findings of this literature review revealed partial support for this hypothesis. Although substantial evidence supports the idea that PD worsens cardiovascular complications through mechanisms like autonomic dysfunction, reduced HRV, and neurovascular dysregulation, the reverse relationship we also hypothesized CVD acting as a causative factor for PD is less clear.

Multiple studies show that pre-existing cardiovascular conditions in patients may worsen PD outcomes and even contribute to PD progression. Even so, conflicting evidence from Mendelian randomization studies and analyses of MI risk suggests that CVD might not directly cause PD. These studies show how complex the relationship is and that more longitudinal research is needed to find potential causality.

Clinical Implications

An overwhelming portion of the literature examined suggests a correlation between CVD and worsening prognosis for PD patients. PD patients either concurrently have or are at an increased risk for developing cardiovascular conditions such as heart failure, hypertrophic cardiomyopathy, and ECG abnormalities, such as AF. Additionally, neurodegeneration linked to PD can worsen cardiac regulation, as damage to the ANS can disrupt electrical conduction within the heart, affecting cardiac rhythm. The mechanism described above hinders adequate perfusion to the brain, further exacerbating an individual's cognitive impairment. When either cardiovascular or neurological comorbidities remain unmanaged, patients face an increased risk of mortality.

These findings suggest that a holistic approach to treatment may be beneficial for PD patients, addressing both the management of PD and associated comorbidities⁴. Managing risk factors such as diabetes and hypertension could be done earlier in a patient's treatment to potentially manage cardiovascular and neurological status better. Cardiac assessments, such as monitoring ECG abnormalities or using the Head-up tilt test, could be utilized to prevent further complications and consequences. Clinicians should prioritize recognizing potential adverse reactions such as ECG abnormalities, arrhythmias, and increased risk for cardiac events when prescribing PD medications⁽¹⁰⁾. Patients with both CVD and PD are likely to be on multiple medications. Therefore, side effects and drug interactions should be analyzed thoroughly. Outside the clinical setting, patients could be educated on lifestyle modification, such as getting adequate exercise and maintaining at-home blood pressure diaries to monitor their cardiovascular health, control PD progression, and maintain their independence in daily tasks⁽¹⁹⁾.

Conclusion

This study aimed to examine the bilateral relationship between CVD and PD. Our findings included results concerning the link between CVD and PD mortality,

cardiac dysfunction/heart failure, and blood pressure/cholesterol-increasing PD rates. Findings examining the link between CVD and PD mortality suggest that this relationship remains complex and multifaceted. Some studies support the conclusion that PD patients face an increased risk of cardiovascular mortality due to autonomic dysfunction and systemic inflammation; other studies suggest that PD serves as a protective factor against MI. Moreover, regarding cases of cardiac dysfunction and heart failure, symptoms of cognitive impairment, ANS malfunction, and motor symptoms were most commonly influenced. Cardiovascular issues were also observed to complicate the efficacy of PD treatment. Examination of the codependency between CVD risk factors such as blood pressure, cholesterol levels, and PD progression also occurred; the search strategy prompting these results employed databases such as PubMed and Google Scholar.

Additionally, stringent criteria were constituted to ascertain high-quality peer-reviewed studies. Our meta-analysis was limited to studies written in English, accessible within our departments, and ones that distinctly examined PD and CVD. Due to the inconclusive nature of our results, future research is necessary to refine clinical management and the use of biomarkers to predict disease progression and to find more evidence for conclusive CVD-PD comorbidity and risk factors. Ultimately, understanding the relationship between these two diseases will help clinicians improve early diagnosis, treatment strategies, and disease prognosis.

Ethics

Footnotes

Authorship Contributions

Surgical and Medical Practices: George C, Sidhu G, Dave H, Sonthalia S, Ramirez G, Rupp L, Wasniewski R, Burnidge A, Punzalan M, Ahmed A, Warren P, Maskey M, Patel D, Nguyen P, Concept: George C, Sidhu G, Dave H, Sonthalia S, Ramirez G, Rupp L, Wasniewski R, Burnidge A, Punzalan M, Ahmed A, Warren P, Maskey M,

Patel D, Nguyen P, Design: George C, Sidhu G, Dave H, Sonthalia S, Ramirez G, Rupp L, Wasniewski R, Burnidge A, Punzalan M, Ahmed A, Warren P, Maskey M, Patel D, Nguyen P, Data Collection and/or Processing: George C, Sidhu G, Dave H, Sonthalia S, Ramirez G, Rupp L, Wasniewski R, Burnidge A, Punzalan M, Ahmed A, Warren P, Maskey M, Patel D, Nguyen P, Analysis and/or Interpretation: George C, Sidhu G, Dave H, Sonthalia S, Ramirez G, Rupp L, Wasniewski R, Burnidge A, Punzalan M, Ahmed A, Warren P, Maskey M, Patel D, Nguyen P, Literature Search: George C, Sidhu G, Dave H, Sonthalia S, Ramirez G, Rupp L, Wasniewski R, Burnidge A, Punzalan M, Ahmed A, Warren P, Maskey M, Patel D, Nguyen P, Writing: George C, Sidhu G, Dave H, Sonthalia S, Ramirez G, Rupp L, Wasniewski R, Burnidge A, Punzalan M, Ahmed A, Warren P, Maskey M, Patel D, Nguyen P.

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Impact of On-pump Versus Off-pump Coronary Artery Bypass on Oxidative Stress and Postoperative Atrial Fibrillation

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Abstract

Objectives: Postoperative atrial fibrillation (POAF) is common after coronary artery bypass grafting (CABG). Gamma-glutamyl transferase (GGT), an index of oxidative injury, could provide predictive information regarding POAF.

Materials and Methods: Patients who underwent on-pump or off-pump CABG between January 2019 And December 2023 were included in this retrospective cohort study. Both pre- and post-CABG GGT concentrations were documented. POAF events were continuously monitored by means of telemetry. Tables provide information on demographics, biochemical measures, and POAF outcomes.

Results: A total of 183 patients were included in the analysis. POAF occurred more frequently in on-pump patients (35%) Than in off-pump patients (20%). Postoperative GGT levels were significantly higher in the POAF group. estimated p-values are included in all the tables below.

Conclusion: High levels of postoperative GGT are correlated with POAF after CABG.

Keywords: Coronary artery bypass grafting, gamma-glutamyl transferase, atrial fibrillation



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Introduction

Postoperative atrial fibrillation (POAF) remains one of the most frequent complications following coronary artery bypass grafting (CABG), with a reported incidence ranging from 20% to 40%⁽¹⁾. POAF is associated with prolonged hospitalization, increased risk of stroke, heart failure, and long-term mortality, underscoring its clinical importance⁽²⁾. Several clinical risk factors, including hypertension, obesity, metabolic syndrome, alcohol consumption, and advanced atherosclerosis, have been implicated in its development⁽³⁻⁵⁾.

Beyond traditional clinical predictors, increasing evidence suggests that oxidative stress plays a central role in the pathogenesis of atrial fibrillation (AF) by altering atrial electrophysiological properties and promoting structural remodeling⁽⁶⁻⁸⁾. Reactive oxygen species (ROS) contribute to atrial inflammation, calcium-handling abnormalities, and electrical instability, thereby facilitating the initiation and maintenance of POAF⁽⁹⁾.

Gamma-glutamyl transferase (GGT) is a key enzyme involved in glutathione metabolism and serves as an indirect marker of systemic oxidative stress and inflammation⁽¹⁰⁾. Elevated GGT levels have been associated with endothelial dysfunction, metabolic disturbances, increased cardiovascular morbidity, and the subsequent development of AF in various clinical settings⁽¹¹⁻¹³⁾. Moreover, higher GGT concentrations have been linked to adverse postoperative outcomes after cardiac surgery⁽¹⁴⁾.

The use of cardiopulmonary bypass (CPB) during on-pump CABG is known to amplify oxidative stress through ischemia-reperfusion injury, leukocyte activation, pro-inflammatory cytokine release, and excessive ROS production^(15,16). In contrast, off-pump CABG may attenuate this oxidative burden by avoiding extracorporeal circulation⁽¹⁷⁾. Given these mechanistic differences, perioperative GGT concentrations may provide biologically plausible predictive information on the risk of POAF in patients undergoing on-pump or off-pump CABG.

Therefore, this study aimed to evaluate the association between perioperative GGT levels and POAF occurrence and compare oxidative stress-related outcomes between patients undergoing on-pump and off-pump CABG.

Materials and Methods

All isolated CABG interventions performed between January 2019 and December 2023 were included in this retrospective cohort analysis. This study was approved by Ordu University Clinical Research Ethics Committee (approval no: 2403, date: 19.01.2021). The study was conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent was waived. Inclusion criteria: ≥ 18 years, isolated CABG, sinus rhythm, complete biochemical data available for analysis. Exclusion criteria: evidence of chronic liver disease [alanin aminotransferaz (ALT)/aspartat aminotransferaz (AST) concentrations >3 times upper limit of normal], preoperative AF, left atrium size >5.0 cm, emergency CABG, incomplete biochemical data^(2,12). Surgical assignments: it was decided whether on-pump or off-pump CABG could be done based on coronary anatomy, hemodynamic status, and GGT measurement:

- Preoperative GGT: within 24 hours before operation
- Postoperative early GGT: postoperative day 1-3
- Late postoperative GGT: 3-month follow-up visit

Definition and monitoring for POAF: POAF was defined as AF lasting ≥ 5 minutes⁽¹²⁾. Monitoring included continuous cardiac telemetry for the first 72 hours, with electrocardiograms at discharge and at 1- and 3-month clinic visits.

Statistical Analysis

Continuous variables were assessed for normality by visual inspection and were presented as mean \pm standard deviation, whereas categorical variables were expressed as frequencies and percentages. Comparisons between the on-pump and off-pump CABG groups were performed using independent-samples t-tests for continuous variables and chi-square tests for categorical variables,

as appropriate. All statistical tests were two-tailed, and p-values <0.05 were considered statistically significant. multivariable regression analysis was not performed because the complete individual-level covariate data required for comprehensive adjustment were unavailable. Statistical analyses were conducted using standard statistical software.

Results

Table 1 shows that there were no significant differences in baseline demographic and clinical characteristics between the groups. however, there was a significant difference in POAF between these groups, with a higher incidence in the on-pump CABG group. The postoperative biochemical changes showed an overall increase in levels of oxidation and inflammatory mediators in on-pump CABG. These, summarized in Table 2, show a higher incidence of POAF in on-pump CABG, consistent with the overall increase in oxidation caused by CPB^(8,16). More in-depth studies reported in Table 3 showed significantly increased postoperative levels of GGT, AST, ALT, lactate dehydrogenase, white blood cell, creatinine, and glucose in patients undergoing on-pump CABG. Of note, late postoperative GGT level was also significantly higher at 3 months, indicating its persistence due to ongoing oxidation caused by CPB.

Table 1. Demographic data

Variable	On-pump (n=96)	Off-pump (n=87)	p-value
Age (years)	56±2.3	54±2.3	0.12
Sex (F/M)	46/50	41/46	0.88
Family history	65%	60%	0.48
Smoking	68%	70%	0.79
Hypertension	48%	47%	0.91
Carotid disease	13%	12%	0.88
Peripheral artery disease	21%	19%	0.74
Angina	56%	49%	0.32
MI history	26%	25%	0.89
COPD	27%	26%	0.91

COPD: Chronic obstructive pulmonary disease, MI: Myocardial infarction, F/M: Female/male

Table 2. Operative and postoperative data

Variable	On-pump	Off-pump	p-value
Diseased arteries	2.3	2.1	0.21
Revascularized vessels	2.1	2.0	0.33
Pre-op EF (%)	46%	48%	0.18
Post-op EF (%)	43%	49%	0.01
Early POAF	35%	20%	0.03
POAF at 3 months	11%	8%	0.47
Late GGT	74	36	0.002

EF: Ejection fraction, POAF: Postoperative atrial fibrillation, GGT: Gamma-glutamyl transferase

Table 3. Postoperative biochemistry

Marker	On-pump	Off-pump	p-value
WBC	12,300	7,100	<0.001
Hemoglobin	8.7	9.8	0.04
Hematocrit	26	28	0.07
Platelets	143,000	227,000	<0.001
Creatinine	1.3	0.8	0.002
BUN	33	17	<0.001
Glucose	156	124	0.03
AST	53	18	<0.001
ALT	119	26	<0.001
LDH	1048	768	0.02
GGT	89	33	<0.001

WBC: White blood cell, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, GGT: Gamma-glutamyl transferase

Discussion

It shows that there is a marked relationship between postoperative GGT levels and af following CABG. There is reason to believe, based on significantly higher levels in those undergoing on-pump CABG, that postoperative levels of GGT are consistent with what is known about their substantial CPB Uoxs Burdens, which are attributable to predominant ischemia-reperfusion injury, leukocytosis, and excessive ROS production^(4,10,13,14). Whilst multiple pathophysiological mechanisms interact collectively to maintain uoxs-mediated POAF, they include individual cell-level hypotheses such as mitokinesis, neural

differences, mitochondria damage and channelopathies, as well as various cardiovascular mechanisms^(8,16). GGT, being one of its electron carriers, is proposed as its biomarker because this molecule directly represents its uoxs activity in these inflammatory disorders and has been suggested for monitoring postoperative arrhythmias; it is considered an optimal arrhythmia biomarker owing to its low cost and clinical relevance⁽¹³⁻¹⁷⁾.

Study Limitations

Limitations of the study include its retrospective design and the absence of raw biochemical data, which precluded analyses using multivariate models. nonetheless, the relationships described remain relevant clinically.

Conclusion

Postoperative GGT levels are significantly associated with POAF after CABG. GGT could be used in perioperative risk assessment to optimize postoperative rhythm management, serving as an accessible and informative biomarker for postoperative care. The use of GGT analysis in clinical practice could enable more individualized postoperative management for patients identified by the analysis.

Ethics

Ethics Committee Approval: This study was approved by Ordu University Clinical Research Ethics Committee (approval no: 2403, date: 19.01.2021). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Due to the retrospective nature of the study, the requirement for informed consent was waived.

Footnotes

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Effect of Preoperative Plant-based Versus Animal-based Diets on Myocardial Protection in a Rat Model of Cardiac Surgery

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Abstract

Objectives: Myocardial ischemia-reperfusion injury remains a major source of morbidity in cardiac surgery, and novel strategies for cardioprotection are needed. Preoperative dietary modulation has been proposed as a feasible approach to enhance myocardial resilience. This study investigated the effects of preoperative plant-based versus animal-based diets (ABD) on myocardial protection in a rat model of cardioplegic arrest, with emphasis on apoptosis, oxidative stress, and stress response markers.

Materials and Methods: Sixteen male Wistar albino rats were initially randomized to receive either a plant-based diet (PBD) (soy protein, palm oil) or an ABD (casein, milk fat) for 12 weeks. Due to peri-experimental losses, final analyses were performed on 6 rats in the PBD group and on 7 rats in the ABD group. At the end of the feeding period, rats underwent a standardized cardioplegic arrest induced by St. Thomas II crystalloid solution, resulting in 10 minutes of ischemia; blood cardioplegia was then administered prior to tissue harvesting. Left ventricular tissues were harvested for biochemical analysis. Bcl-2 and Bax, glutathione (GSH), protein carbonyls and malondialdehyde (MDA), and heat



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shock protein 70 (Hsp-70) were measured as markers of apoptosis, redox defense, oxidative damage, and stress response, respectively.

Results: Bcl-2 levels were significantly higher in the PBD group compared to the ABD group (11.28 ± 1.22 vs. 9.50 ± 1.25 , $p=0.025$), indicating enhanced antiapoptotic signaling. Among other markers, Bax, MDA, protein carbonyls, and GSH showed trends favoring the PBD group that were not statistically significant, whereas Hsp-70 levels were numerically higher in the ABD group but not statistically significant.

Conclusion: In this experimental rat model of cardioplegic arrest, preoperative plant-based nutrition enhanced antiapoptotic signaling through significant upregulation of Bcl-2, while other oxidative and apoptotic markers showed favorable but not statistically significant trends. These findings suggest that diet composition can influence myocardial resilience to surgical stress, supporting the potential role of plant-based preoperative regimens as an adjunct to established cardioprotective strategies. Further validation in larger studies is warranted.

Keywords: Plant-based diet, animal-based diet, myocardial protection, ischemia-reperfusion injury, apoptosis, cardiac surgery

Introduction

Cardiovascular diseases remain the leading cause of global mortality despite advances in medical and surgical therapy. Dietary habits are pivotal, modifiable determinants of cardiovascular risk⁽¹⁾. A growing body of evidence shows that diets emphasizing plant-derived proteins and lipids improve lipid metabolism, reduce oxidative stress and systemic inflammation, and are associated with lower cardiovascular risk and mortality⁽²⁻⁴⁾. By contrast, patterns rich in animal-derived proteins and fats have been linked to greater atherosclerotic burden and adverse coronary outcomes⁽⁵⁾.

In the perioperative setting of cardiac surgery, myocardial ischemia-reperfusion (I/R) injury remains a major driver of morbidity. Cardioplegic arrest and subsequent reperfusion trigger the generation of reactive oxygen species, calcium overload, mitochondrial dysfunction, and apoptosis in cardiomyocytes. However, translation of many experimental cardioprotective strategies to clinical benefit has been challenging⁽⁶⁾.

Given this background, preoperative dietary modulation represents a biologically plausible and clinically feasible approach to influence myocardial susceptibility to I/R. However, whether preoperative

intake of plant-versus animal-based protein and lipid sources alters myocardial protection during cardiac surgery remains unclear. Recent experimental reports continue to explore adjuncts for I/R mitigation in rat models, underscoring the relevance of this question⁽⁷⁾.

Accordingly, we compared the effects of preoperative plant-based and animal-based diet (ABD) on myocardial protection in a rat model of cardiac surgery with cardioplegic arrest. To elucidate these effects, we focused on biologically well-established markers. These included Bcl-2/Bax for apoptosis, glutathione (GSH) for redox defense, protein carbonyls as hallmarks of oxidative protein damage, and heat shock protein 70 (Hsp-70) as a key indicator of the cellular stress response⁽⁸⁻¹¹⁾.

Materials and Methods

This experimental study was approved by the Dokuz Eylül University Multidisciplinary Laboratory Animal Experiments Local Ethics Committee (protocol no: 07/2019, date: 30.01.2019) and was conducted in compliance with the Guide for the Care and Use of Laboratory Animals between June 2019 and March 2020.

A total of 16 male Wistar albino rats, weaned at 21 days of age, were randomly assigned to two equal groups:

the plant-based diet (PBD) and ABD (n=8 each). Rats were housed at a controlled temperature and on a 12-hour light/dark cycle, with free access to food and water. The PBD consisted of soy protein as the protein source and palm oil as the lipid source. The ABD contained casein as the protein source and milk fat as the lipid source. Both diets shared the same carbohydrate source and the same vitamin and mineral premixes, and their macronutrient composition was designed to be compatible with standard purified rat chow (based on the D12450J formulation). Rats were fed ad libitum for 12 weeks. During the feeding period, one rat per group died, and an additional rat the PBD group died under deep anesthesia, leaving 7 rats in the ABD group and 6 rats in the PBD group for final analyses.

Surgical Procedure

At the end of week 12, rats were anesthetized by intraperitoneal injection of ketamine (50 mg/kg) and xylazine (10 mg/kg). A midline laparotomy followed by a thoracotomy extending into the left hemithorax was performed to expose the heart. After visualization, a blood sample was obtained and transferred into a heparinized syringe in preparation for blood cardioplegia. Systemic anticoagulation was provided with heparin (300 IU/kg) administered directly into the left ventricle. Following systemic heparinization, the ascending aorta was cross-clamped, and St. Thomas II crystalloid cardioplegia was delivered via the aortic root to induce cardiac arrest. A 10-minute period of global ischemia was maintained. At the end of this ischemic interval, cardioplegia prepared with the rat's own blood was administered to initiate reperfusion. Immediately thereafter, the hearts were excised under direct vision. The left ventricle was separated, rinsed in phosphate-buffered saline (PBS), wrapped in Parafilm to prevent drying, and stored at -80 °C until biochemical analysis.

Tissue Homogenization and ELISA Procedure

Left ventricular myocardium was homogenized in PBS (100 µL per 0.01 g of tissue) using a bead tissue

lyser. Supernatants were obtained after vortexing and centrifugation. Protein quantification was performed using the bicinchoninic acid kit. Blood samples were centrifuged at 2000 rpm for 10 min to separate serum. The following markers were measured using ELISA kits (Bioassay Technology Laboratory, Shanghai, China), according to the manufacturer's instructions, and optical densities were read at 450 nm: Bcl-2, Bax, GSH, protein carbonyls, malondialdehyde (MDA), Hsp-70.

Statistical Analysis

Statistical analyses were performed using SAS software (version 9.4). The significance level for statistical analyses was set at 0.05. Descriptive statistics for each score were presented by study group: n, mean, median, standard deviation, minimum, maximum, 95% lower confidence limit, and 95% upper confidence limit.

Whether there was a statistically significant difference between the group means (arithmetic mean or median) was determined based on the distribution of the scores, using either the two-sample Student's t-test or the Wilcoxon (Mann-Whitney U). For scores that were normally distributed, the Student's t-test was used to compare group means. For scores not conforming to a normal distribution, the Wilcoxon rank-sum test (Mann-Whitney U test) was used to compare group medians. Normal distribution was evaluated by Shapiro-Wilk test prior to choosing parametric or non-parametric analyses.

Results

Analysis of myocardial tissue markers revealed a significant difference between the two dietary groups. Bcl-2 expression was significantly higher in the PBD group compared with the ABD group (11.28±1.22 vs. 9.50±1.25 ng/mg protein, p=0.025), indicating stronger antiapoptotic activity in rats fed a PBD (Table 1).

In contrast, Bax levels, representing pro-apoptotic signaling, were lower in the PBD group than in the ABD group [median 18.03 (14.07-24.62) vs. 22.18 (17.85-49.69)], but this difference was not statistically significant (p=0.100).

Table 1. Biochemical parameters

Parameter	PBD Mean \pm SD/median (min-max)	ABD Mean \pm SD/median (min-max)	p-value
Bcl-2	11.28 \pm 1.22	9.50 \pm 1.25	0.025
Bax	18.03 (14.07-24.62)	22.18 (17.85-49.69)	0.100
MDA	1.41 (1.23-1.72)	1.72 (1.24-3.23)	0.080
Protein carbonyl	57.93 \pm 9.76	62.17 \pm 13.44	0.536
GSH	116.19 \pm 26.01	99.08 \pm 25.02	0.253
Hsp-70	3.60 \pm 0.47	4.01 \pm 1.03	0.381

Data are presented as mean \pm SD or median (min-max), depending on the statistical test used. Bold values indicate statistical significance ($p < 0.05$). PBD: Plant-based diet group, ABD: Animal-based diet group, MDA: Malondialdehyde, GSH: Glutathione, SD: Standard deviation, Hsp-70: Heat shock protein 70

Regarding oxidative stress markers, MDA levels were lower in the PBD group [median 1.41 (1.23-1.72)] compared with the ABD group [median 1.72 (1.24-3.23)], representing a borderline trend that did not reach statistical significance ($p=0.080$). Protein carbonyl content was also lower in the PBD group (57.93 \pm 9.76 vs. 62.17 \pm 13.44), although the difference was not statistically significant ($p=0.536$).

GSH levels were higher in the PBD group (116.19 \pm 26.01) than in the ABD group (99.08 \pm 25.02), but this increase was not statistically significant ($p=0.253$).

Finally, Hsp-70 levels were slightly lower in the PBD group than in the ABD group (3.60 \pm 0.47 vs. 4.01 \pm 1.03), but the difference was not statistically significant ($p=0.381$).

Discussion

In this experimental model of cardioplegic arrest, PBD was associated with significantly higher myocardial Bcl-2 levels compared with ABD, indicating a stronger antiapoptotic profile. Other markers, including Bax, MDA, protein carbonyls, GSH, and Hsp-70, showed no significant differences between groups. Nevertheless, the overall trend favored PBD, with lower Bax expression, reduced oxidative stress indices, and higher GSH levels. These data suggest that preoperative dietary modulation can shift myocardial signaling toward cell survival, even when oxidative stress readouts do not reach statistical significance.

The Bcl-2 family is a critical regulator of apoptosis in cardiomyocytes exposed to I/R. Increased Bcl-2 stabilizes mitochondrial membranes, while Bax promotes permeabilization and release of cytochrome c, triggering apoptosis^(8,12,13). Our finding of significantly higher Bcl-2 levels in the PBD group highlights a potential mechanism for diet-induced cardioprotection. Although Bax reduction was not statistically significant, its directionality suggests attenuation of proapoptotic signaling. The balance between Bcl-2 and Bax is widely regarded as a determinant of myocardial survival after I/R injury.

I/R injury generates reactive oxygen species that induce lipid peroxidation and protein oxidation. In our study, MDA and protein carbonyls were lower in the PBD group, although the differences were not statistically significant. Protein carbonylation is a robust marker of oxidative protein damage and has been linked to adverse cardiovascular outcomes^(14,15). At the same time, higher GSH levels in the PBD group suggest enhanced antioxidant reserves. GSH is crucial for detoxifying ROS, and impaired GSH metabolism exacerbates myocardial I/R injury^(16,17). Although not statistically significant, the favorable GSH trend supports the biological plausibility that plant-based nutrients augment endogenous redox defenses.

Hsp, particularly Hsp-70, are protective mediators during I/R stress. They stabilize proteins, regulate calcium handling, and reduce apoptosis^(11,18). In our study, Hsp-70 levels were numerically higher in the ABD group compared to the PBD group, although the difference was

not statistically significant. This pattern may suggest that animal-based feeding induced a modest stress response, potentially reflecting an early or compensatory activation of Hsp-70. In contrast, the lower, though not significantly different, values in the PBD group could indicate a reduced cellular stress burden, consistent with the favorable trends observed in apoptotic and oxidative markers. Nonetheless, given the short ischemic duration and immediate tissue sampling, Hsp-70 expression may not have fully manifested, and these findings should be interpreted with caution. Future studies with longer reperfusion times are required to clarify whether diet type meaningfully modulates Hsp-70 dynamics. Epidemiological and clinical studies consistently associate PBDs with reduced cardiovascular morbidity^(19,20). Beyond systemic benefits, our findings indicate potential direct myocardial effects during surgical I/R. The significant increase in Bcl-2 suggests that antiapoptotic signaling may be a robust contributor to perioperative cardioprotection. By contrast, oxidative stress and antioxidant markers did not differ significantly; nevertheless, their consistent trends in favor of PBD suggest additional biological contributions that may require larger or differently timed studies to confirm. Importantly, these observations indicate that the protective impact of plant-based nutrition is unlikely to be mediated by a single pathway. Rather, it may reflect the convergence of multiple mechanisms, including modulation of apoptosis, redox homeostasis, inflammatory responses, and mitochondrial function. Recognizing this multifactorial nature is critical for translating nutritional interventions into perioperative strategies and long-term cardiovascular prevention.

Beyond apoptosis and oxidative stress, ischemia-reperfusion injury is strongly mediated by inflammatory cascades. PBDs are rich in bioactive compounds such as polyphenols, which have been shown to modulate inflammatory pathways and reduce the production of proinflammatory cytokines in cardiovascular and inflammatory models⁽²¹⁾. Although we did not directly

assess inflammatory mediators in this study, the favorable trends in oxidative and apoptotic indices within the PBD group may indirectly reflect lower inflammatory activation. Future studies should incorporate inflammatory biomarkers to clarify whether dietary modulation exerts additive protective effects through suppression of inflammatory signaling pathways.

From a translational standpoint, these findings may have particular relevance for patients undergoing heart surgery, especially those at high risk of perioperative myocardial injury. Short-term preoperative nutritional optimization with plant-based regimens could augment myocardial protection when combined with conventional strategies such as cardioplegia and pharmacologic conditioning. While current evidence is preliminary, it suggests that perioperative dietary interventions may represent a simple, low-cost, and non-invasive adjunct for improving surgical outcomes and merit further evaluation in clinical trials.

Study Limitations

This study has several limitations that should be acknowledged. First, the relatively small sample size reduces statistical power and increases the likelihood of a type II error, particularly for oxidative stress parameters. Second, the ischemic protocol consisted of only a 10-minute cardioplegic arrest followed by immediate tissue sampling, which may have led to underestimation of the full extent of reperfusion-related oxidative injury and stress protein induction. In addition, the absence of a sham or standard chow control group limits the ability to distinguish the effects of dietary composition from baseline physiology. Furthermore, histopathological assessment was not performed, which could have provided additional validation of the biochemical findings. Finally, although the 12-week dietary period was sufficient to induce measurable tissue changes, it may not fully reflect the long-term effects of plant- and ABD. These limitations should be considered when interpreting our results, as they highlight the need for larger, more comprehensive studies.

Conclusion

Our findings demonstrate that preoperative plant-based nutrition can modulate myocardial responses to surgical I/R, most notably by enhancing antiapoptotic signaling through significant upregulation of Bcl-2. While other biochemical markers showed only favorable but non-significant trends, the overall profile supports the concept that diet composition may influence myocardial tolerance to perioperative stress. These results provide a biological rationale for exploring plant-based strategies as adjuncts to established cardioprotective approaches in cardiac surgery. Validation in larger experimental models and clinical trials will be essential to determine whether such dietary interventions can translate into meaningful perioperative and long-term benefits.

Ethics

Ethics Committee Approval: This experimental study was approved by the Dokuz Eylül University Multidisciplinary Laboratory Animal Experiments Local Ethics Committee (protocol no: 07/2019, date: 30.01.2019) and was conducted in compliance with the Guide for the Care and Use of Laboratory Animals.

Informed Consent: Experimental research.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Kemahlı MB., Gençpınar T., Concept: Koçtürk S., Metin K., Design: Koçtürk S., Metin K., Data Collection and/or Processing: Kemahlı MB., Erkmén T., Sert Serdar B., Analysis and/or Interpretation: Erkmén T., Sert Serdar B., Yüksel K., Literature Search: Kemahlı MB., Writing: Kemahlı MB.

Conflict of Interest: The authors declare no conflicts of interest concerning the authorship or publication of this article.

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Prevalence and Clinical Relevance of Extracardiac Findings on Preprocedural Computed Tomography Angiography for Catheter Ablation of Atrial Fibrillation

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Abstract

Objectives: Atrial fibrillation (AF), a common cardiac arrhythmia with significant stroke risk, is expected to increase in prevalence with an ageing population. Cardiac computed tomography angiography (CCTA) is a non-invasive imaging modality that provides detailed cardiac and extracardiac anatomical information, particularly relevant for preprocedural assessment of AF catheter ablation. This study aimed to determine the prevalence of extracardiac findings (ECFs) during CCTA performed prior to AF catheter ablation.

Materials and Methods: This retrospective single-center study reviewed data from 163 patients with AF who underwent catheter ablation between January 2021 and January 2022. Among the 163 patients, 140 (85.88%) underwent preprocedural CCTA. ECFs were defined as newly detected findings necessitating follow-up, diagnostic workup, or therapeutic measures, excluding known abnormalities and clinically nonsignificant findings.

Results: Out of the 140 patients who underwent CCTA, 50 patients (35.7%) had 52 incidental ECF. Pulmonary findings were the most common, including pulmonary nodules (>6 mm) in 20 patients (14.2%), pulmonary infiltrates in 8 patients (5.71%), and a pulmonary mass in 1 patient (0.71%). Other significant findings included aortic aneurysms in 3 patients (2.13%), enlarged mediastinal lymph nodes in 8 patients (5.71%), abdominal mass in 1 patient (0.71%), and unclear liver lesions in 5 patients (3.55%). Two incidental findings led to the postponement of the AF catheter ablation procedure.



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Conclusion: Pre-procedural CCTA serves as a valuable opportunistic screening tool, identifying significant ECF in over one-third of patients. These findings underscore the importance of multidisciplinary collaboration between cardiology and radiology to optimize comprehensive patient management in these workflows.

Keywords: Extracardiac findings, incidental, computed tomography, atrial fibrillation

Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias with serious consequences, including stroke⁽¹⁾. The incidence is expected to increase in parallel with population ageing⁽²⁾.

Cardiac computed tomography angiography (CCTA) is a rapidly advancing non-invasive imaging modality that facilitates preprocedural imaging for AF ablation⁽³⁾. It can visualize any thrombus in the heart chambers and produce a highly detailed 3-dimensional (3D) image of the heart, providing an in-depth view of the cardiac chambers and vessels⁽⁴⁾. Early studies suggested that integrating computed tomography (CT) images into 3D mapping systems could reduce ablation time and radiation exposure^(5,6). Recent studies, following advancements in electro-anatomical mapping (EAM)⁽⁷⁾ and the emergence of “zero-fluoroscopy” techniques⁽⁸⁾, have led to a re-evaluation of the necessity of routine pre-procedural CT for this purpose. However, recent studies show that cardiac CT remains widely used. In a Europe-wide survey, 44% of electrophysiologists reported routinely performing preprocedural CT, and one-third of these reported integrating it with EAM⁽⁹⁾.

Pre-procedural CCTA can also provide diagnostic information about non-cardiac organs and contribute to the procedure, depending on the field of view (FOV) used. CCTA has been reported to reveal incidental ECFs in 23.8-72% of cases⁽¹⁰⁻¹⁷⁾. Although most extracardiac findings (ECFs) are benign, reports have highlighted pathologically significant findings in 4.2%-38% of cases^(13-16,18).

This study aimed to determine, based on one year of experience at our institute, the clinical characteristics and prevalence of ECFs identified on CCTA performed before atrial fibrillation catheter ablation (AFCA).

Materials and Methods

The study employed a retrospective, single-center design. All data were collected, managed, and analyzed at the Heart Rhythm Center and the Radiology Department of Dokuz Eylul University. This study reviewed 163 patients who underwent AFCA between January 2021 and January 2022 and who were referred for preprocedural CT.

The study protocol was approved by the Institutional Ethics Committee and conformed to the tenets of the Declaration of Helsinki. This study included data from the identified medical records. All patients who underwent AFCA were included in this study. Exclusion criteria included patients with previous AFCA and previously known abnormalities on computed tomography angiography (CTA); CTA data were analyzed for all cardiac CTAs performed, and all incidental findings were identified. The CCTA images were independently reviewed at Dokuz Eylul University by an experienced radiologist (M.M.B., 10 years of experience in cardiac imaging) and an experienced cardiologist (R.Y.Y., 4 years of experience in preprocedural imaging of AF). The interpreters were blinded to the patients' clinical outcomes and procedural details of the AFCA to minimize bias.

A total of 163 patients who underwent catheter ablation for AF were retrospectively reviewed. CTA was performed in 140 patients (85.88%). The two main reasons for not performing CTA were glomerular filtration rate <50 and patient refusal; these affected 23 patients.

Computed Tomography Angiography Protocol

Cardiac CT scans were performed on a 64-slice scanner with prospective electrocardiogram-triggered axial acquisition mode, with current adjusted according to patient characteristics. To control heart rate, metoprolol

was administered orally (100 mg) and, if necessary, intravenously (5-10 mg). Iomeprol contrast was used, with a maximum volume of 100 mL at a flow rate of 4.5-5.5 mL via antecubital venous access using an 18-gauge catheter. Bolus tracking in the left atrial (LA) was used to ensure accurate scan timing.

Definition of Extracardiac Findings

ECF was defined as any newly detected ECF necessitating follow-up, diagnostic workup and/or therapeutic measures. Known extracardiac abnormalities were not considered ECFs. The official clinical CCTA report was reviewed for any described abnormal extracardiac structures, excluding cardiac-related findings, clinically nonsignificant nodules (<5 mm), atelectasis, and degenerative bone abnormalities. These findings were divided into three anatomical sections based on their localization (thorax, upper abdomen, vascular).

ECFs are defined as pulmonary parenchymal abnormalities, pleural effusion, mediastinal lymph node enlargement, and aortic dilatation. Aortic dilatation is defined as an inner-edge-to-outer-edge diameter of the ascending aorta exceeding 40 mm. Mediastinal lymph node enlargement is defined as a lymph node diameter greater than 10 mm or as lymph nodes requiring follow-up. If an abdominal finding requires follow-up or treatment, it is defined as an ECF (Figure 1). This classification is based on Sohns et al.⁽¹⁴⁾.

Statistical Analysis

Data are presented as counts and percentages for categorical variables and as medians (interquartile ranges) or means \pm standard deviations for continuous variables. Chi-square and Fisher's exact tests were used to compare the categorical variables. As appropriate, continuous variables between groups were analyzed using the student's t-test or the Mann-Whitney U test. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using the SPSS 26.0 software package (SPSS Inc., Chicago, IL).

Results

A total of 140 consecutive patients (mean age 62 ± 10 years; 59% male) were included in the CTA (+) group. The mean CHA₂DS₂-VASc score was 2.3 ± 1.4 . The prevalence of tobacco use was 37%. A total of 52 ECFs were observed. Demographic and clinical characteristics were summarized (Table 1).

A total of 52 ECFs in the chest and upper abdomen were identified in 50 patients. Two patients each had two incidental findings identified simultaneously. Pulmonary findings were the most common, observed in 31 patients (22.1% of the cohort), and included pulmonary nodules (>6 mm) in 20 patients (14.9%), pleural effusion in 2 patients, pulmonary infiltrates in 8 patients (5.7%), and a pulmonary mass in 1 patient (0.7%). Other significant findings included aortic aneurysms in 3 patients (2.1%), enlarged mediastinal lymph nodes in 8 patients (5.7%), abdominal masses in 1 patient (0.7%), and unclear liver lesions in 5 patients (3.6%). Detailed incidental findings are summarized in Table 2.

Two of these incidental findings led to the procedure being postponed. One patient was diagnosed early with asymptomatic lung cancer, and another patient had pneumonia requiring antibiotic therapy. Patients with pulmonary nodules >6 mm and enlarged mediastinal lymph nodes (10 mm) were recommended for follow-up. One patient with a 40-mm ascending aortic aneurysm was recommended for echocardiographic follow-up. Some of these patients are summarized in Figure 2.

Discussion

In this retrospective study, the prevalence of incidental ECFs during pre-procedural CCTA was 35.7% (50 patients). While the primary clinical objective of CCTA is to delineate LA geometry and pulmonary vein (PV) anatomy, our results show that over one-third of patients have ECFs that may necessitate follow-up or clinical management. Notably, in 1.4% of our cohort, these findings led to the postponement of the AFCA (Figure 3).

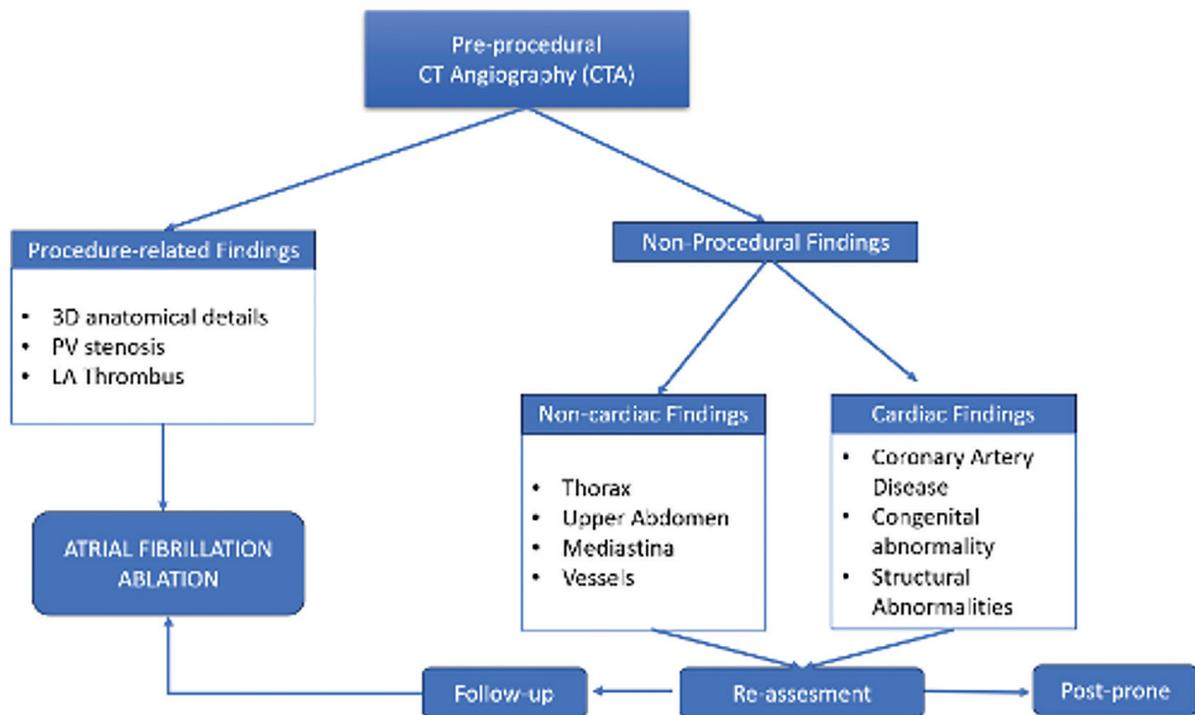


Figure 1. Schematic visualization of the management of preprocedural computed tomography angiography findings undergoing atrial fibrillation ablation

CT: Computed tomography, CTA: Computed tomography angiography, 3D: 3-dimensional, PV: Pulmonary vein, LA: Left atrium

Several studies have shown that cardiac imaging performed before AFCA frequently identifies incidental cardiac or ECFs. The prevalence of incidental findings on CT scans reported in previous studies varies widely due to differences in FOV and definitions. Schietinger et al.⁽¹²⁾ identified ECFs in 69% of the 149 patients undergoing pre-procedural multidetector CT, with pulmonary nodules being the most frequent abnormality detected. Wissner et al.⁽¹⁰⁾ observed unexpected findings in 53% of the 95 patients. Sohns et al.⁽¹⁴⁾ studied 158 patients and screened only for extracardiac incidental findings, finding that 72% had such findings. At least one clinically or potentially significant finding was present in 31% of patients. The most common significant abnormalities included mediastinal lymph node enlargement and degenerative spinal disease; lung cancer was histologically confirmed in two patients. Martins et al.⁽¹⁶⁾ reported an incidental finding prevalence of 23.2% in their cohort of 250 patients,

noting that patients with findings were significantly older than those without. Pulmonary abnormalities accounted for 50% of the findings, and the identification of two lung cancers directly altered patient management, leading to cancellation of the ablation procedure⁽¹⁶⁾. Hamed et al.⁽¹³⁾ also reported only incidental findings, including cardiovascular diseases such as coronary artery disease (CAD), incomplete cor triatriatum, and pericardial effusion. They found incidental findings in 23.8% of 218 patients undergoing CTA for AF ablation. Casella et al.⁽¹⁷⁾ reported that among 173 patients undergoing AF ablation, 56% had collateral findings on chest CT scans, of which 28% were clinically significant. Simon et al.⁽¹⁵⁾ conducted the largest study to date, involving 1,952 patients, and identified incidental ECFs in 42.0% of the cohort, of which 21.3% were categorized as clinically significant.

Lung masses and nodules were the most common ECFs in our study and in other studies. Our study included only

Table 1. Demographical and clinical characteristics of groups

	All patient (+) n=140	ECF (+) n=50	ECF (-) n=90	p-value
Age	56.5±10.6	56.6±10.3	56.5±9.5	0.7
Gender (male)	77 (55%)	25 (50%)	52 (57.8%)	0.2
HT	56 (40%)	18 (36%)	38 (42.2%)	0.47
DM	22 (15.7%)	9 (18%)	13 (14.4%)	0.58
CAD	7 (5%)	5 (10%)	2 (2.2%)	0.04
Stroke	5 (3.6)	4 (8%)	1 (1.1%)	0.03
Prior pulmonary disease	16 (11.4%)	7 (14%)	9 (10%)	0.4
Smoking history	70 (50%)	31 (62%)	39 (43%)	<0.01
LVEF (%)	56.06±8.5	53.7±10.1	57.3±8.3	<0.01
LA diameter (mm)	41.86±5.8	44±5.0	40±5.4	0.79
CHADS2VASc	1.6±1.2	1.8±1.2	1.5±1.2	0.58
RF ablation	87 (62.1%)	37 (74%)	50 (55.6%)	0.04
Type of AF (paroxysmal AF)	110 (78.6%)	39 (78%)	71 (78.9%)	0.5

All patients, extracardiac finding (ECF) positive group, ECF negative groups

AF: Atrial fibrillation, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, CT: Computed tomography, LVEF: Left ventricular ejection fraction, RF: Radiofrequency, LA: Left atrium

one patient newly diagnosed with lung cancer, consistent with previous research. The etiologies of lung nodules are wide-ranging and include both benign and malignant causes. In our study, 37% of patients were smokers, and lung parenchymal changes, such as consolidation and interstitial lung diseases, were the second most frequent findings. Notably, the prevalence of ECFs was more pronounced in patients with a high atherosclerotic burden, specifically those with a history of smoking, stroke, CAD, or a reduced left ventricular ejection fraction. This clinical profile is of particular importance as these comorbidities significantly impact both procedural success and long-term clinical outcomes following AF ablation. Specifically, Duğral et al.⁽¹⁹⁾ demonstrated that smoking is a significant and independent predictor of arrhythmia recurrence after ablation therapy.

Incidental ECFs have several clinical implications. In our study, all clinical findings were clinically significant. In addition, 1.4% of the patient cohort requires postponement due to a clinical condition. Casella et al.⁽¹⁷⁾ reported that

Table 2. The regional distribution and prevalence of incidental extracardiac (clinically significant or potentially significant) computed tomography findings in computed tomography angiography.

Thorax	n	Prevalance
Nodule (>6 mm)	20	14.2%
Mass-malignity	1	0.7%
Parenchymal disease (bronchiectasis, infiltration)	8	5.7%
Pleural effusion	2	1.4%
Lymphatic node enlargement (>10 mm)	8	5.7%
Mammarial mass	1	0.7%
Upper abdomen		
Liver nodules or mass	4	3.5%
Gallbladder stone	3	2.1%
Adrenal mass-incidentoma	1	0.7%
Kidney stone	1	0.7%
Vascular		
Ascendant aorta aneurism (40 mm<)	1	0.7%
Mural thrombus	1	0.7%
Median arcuate ligament syndrome	1	0.7%

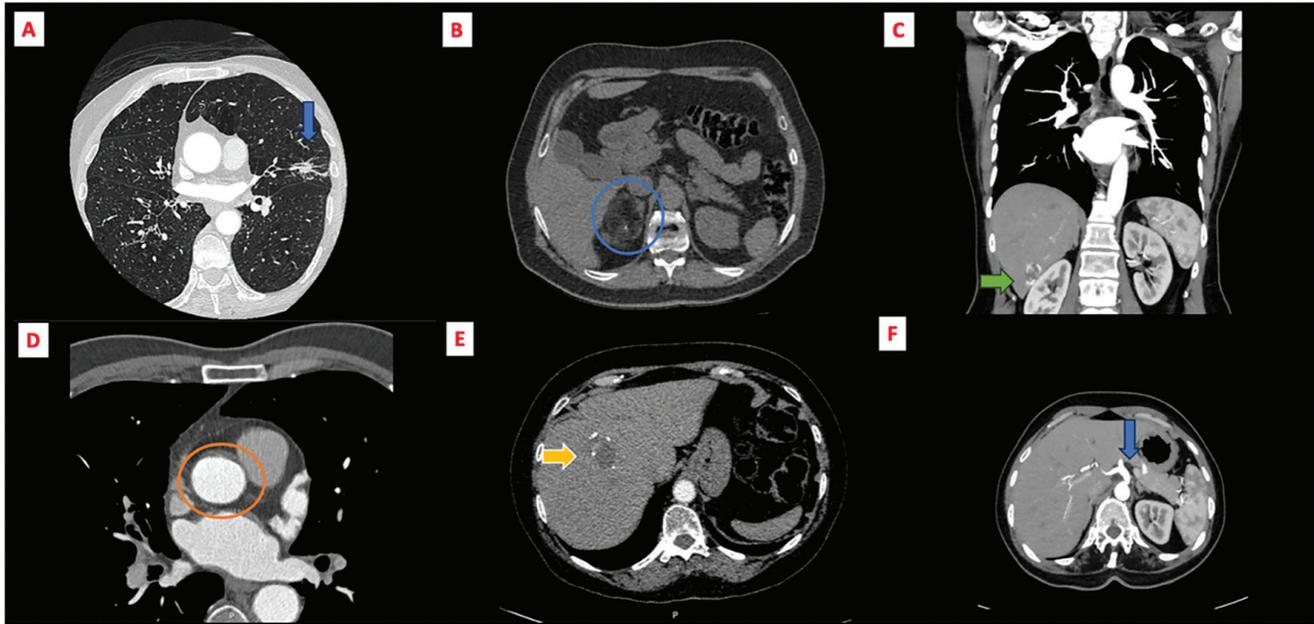


Figure 2. Examples of extracardiac findings detected during computed tomography angiography before atrial fibrillation ablation. A) Lung cancer (blue arrow) B) Surrenal adrenal myolipoma (blue circle) C) Hepatic cyst (green arrow) D) Mural thrombus in ascending aorta (orange circle) E) Hepatic cystic hydatid (yellow arrow) F) Coeliac arcuate ligament (blue arrow)

Prevalence and impact of extracardiac findings (ECFs) on the atrial fibrillation ablation workflow.

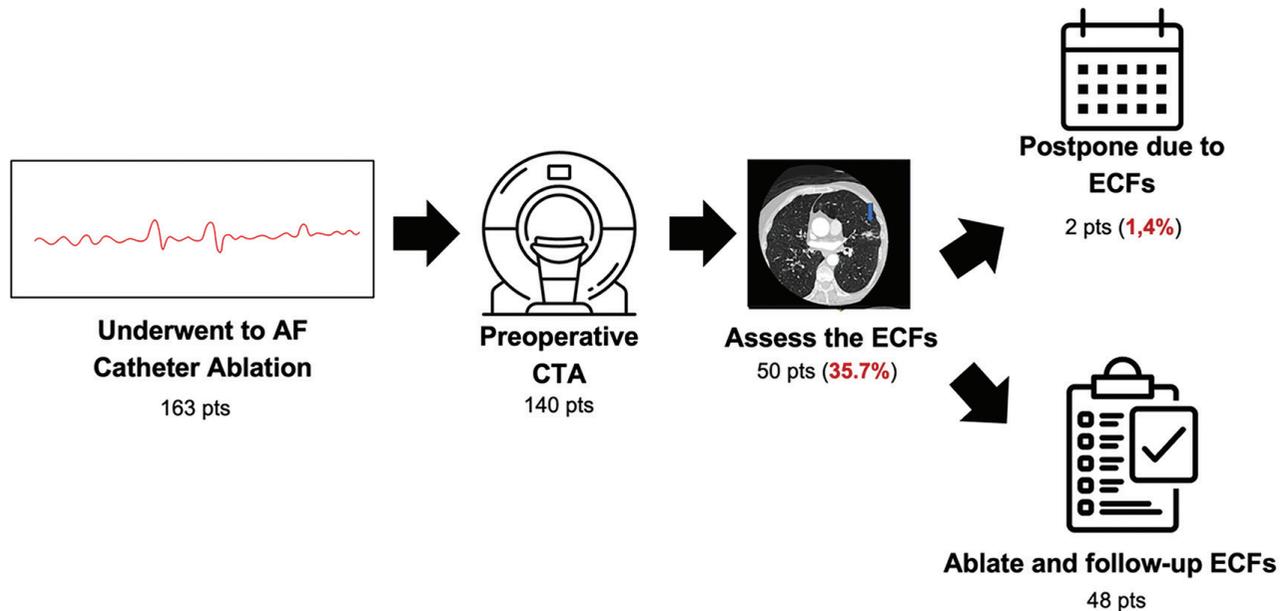


Figure 3. Prevalence and impact of extracardiac findings (ECFs) on the Atrial fibrillation ablation workflow. The diagram illustrates the screening of 140 patients via preoperative CTA. Although the majority of patients with ECFs (n=50) underwent the planned ablation and subsequent follow-up, 1.4% of the total cohort required postponement of the procedure because of clinically significant findings CTA: Computed tomography angiography

Table 3. Previous studies about incidental findings or extracardiac findings detected cardiac computer tomography

Study	Year	Sample size	IF/ECF	Malignancy rate	CT	Ref
Schietinger et al. ⁽¹²⁾	2008	149	69% (ECF)	0%	16-slice	12
Wissner et al. ⁽¹⁰⁾	2009	95	53% (IF)	1.1%	16-slice	10
Martins et al. ⁽¹⁶⁾	2011	250	23% (IF)	0.8%	64-slice	16
Sohns et al. ⁽¹⁴⁾	2011	158	72% (ECF)	1.3%	64-slice	14
Casella et al. ⁽¹⁷⁾	2012	173	56% (IF)	1.7%	64-slice	17
Hamed et al. ⁽¹³⁾	2022	218	28.8% (ECF)	0.45%	NR	13
Simon et al. ⁽¹⁵⁾	2022	1.952	42.0% (ECF)	NR	256-slice	15
Present study	2026	140	35.7% (ECF)	0.7%	64-slice	*

*: Refers to the present study
 Incidental finding, an incidentally discovered mass or lesion, detected by imaging modalities (such as CT or MRI), which is not related to the primary objectives of the examination. These are also referred to as “collateral findings” or “incidentalomas.”
 Any unsuspected abnormality detected outside of the pericardium within the field of view (e.g., lungs, mediastinum, spine, or upper abdomen) during a cardiac imaging study
 FOV: Field of view, IF: Incidental findings, ECF: Extracardiac finding, NR: Nothing reported, Ref: Reference, MRI: Magnetic resonance imaging, CT: Computed tomography

10% of patients required treatment. In Simon et al.⁽¹⁵⁾ multivariate logistic regression analysis, after adjusting for potential confounders such as hypertension, gender, and CAD, age (odds ratio: 1.04; 95% confidence interval: 1.02-1.06) emerged as the independent predictor of clinically significant ECFs. Wissner et al.⁽¹⁰⁾ report that ECFs led to additional diagnostic testing in 16% of the cohort and to a direct change in clinical management in 7%. Notably, their findings resulted in life-saving diagnoses, such as pulmonary embolism and lung cancer, and led to the postponement of ablation therapy in four patients. CTA may be a useful opportunistic screening technique for detecting previously unknown, clinically relevant diseases, especially lung cancer. AF cancer often coexist due to shared pathophysiological mechanisms, indicating comorbidity^(20,21). Previous literature on the prevalence of malignancies is summarized in Table 3. Beyond the cost-effectiveness of screening, radiation exposure is

another primary concern of CCTA. Lee et al.⁽²²⁾ revealed incidental ECFs in 43% of patients, of which 52% were potentially clinically significant. Only 4% receive follow-up, with average additional costs of \$17.42 per patient screened and \$438.39 per patient with imaging follow-up. However, it remains uncertain whether the increased cost, radiation exposure, and invasive procedures associated with CTA will result in lower mortality rates or improved quality of life for patients^(23,24). Pre-procedural atrial imaging can define a patient’s atrial anatomy, and studies suggest that integrating CT images with EAM may be beneficial. The development of the EAM system and the emergence of the zero-fluoro concept in the EP lab led to the avoidance of CT imaging before AFib ablation procedures. Di Cori et al.⁽⁷⁾ found that preprocedural CT did not improve procedural duration or fluoroscopy time, but was associated with increased radiation exposure.

While electrophysiologists primarily utilize these images for anatomical road-mapping of the left atrium and PV, or to exclude LAA thrombus, the CT-irradiated FOV contains vital extracardiac information that falls within the expertise of radiologists.

Study Limitations

This study has several limitations. First, it was a retrospective, single-centre study with a small sample size, which may have affected the generalizability of the results. In addition, the reported results are based on retrospective analyses, which may have affected the accuracy of the data collected. This observational study determined the prevalence of these incidental findings and did not include long-term follow-up. Further studies with larger cohorts are needed to perform robust multivariate analyses to identify independent predictors of significant ECFs in the AF population. Despite these limitations, this study provides valuable real-world data that can inform future research.

Conclusion

Pre-procedural CCTA imaging in clinical workflows may extend beyond procedural guidance for ablation. Our findings indicate that CCTA is an effective opportunistic screening tool; significant ECFs were observed in more than one-third of patients. This underscores the importance of multidisciplinary collaboration between cardiologists and radiologists to optimize patient management.

Ethics

Ethics Committee Approval: Approval was obtained from the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval no: 2023/37-21 date: 22.11.2023).

Informed Consent: The records of the patients were retrospectively examined through the hospital information system and archival records.

Acknowledgment: The study was presented as an abstract at the EHRA 2025 Congress.

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Footnotes

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Authorship Contributions

Surgical and Medical Practices: Yılcıoğlu RY, Özcan EE, Barış MM, Concept: Yılcıoğlu RY, Özcan EE, Barış MM, Data Collection and/or Processing: Yılcıoğlu RY, Barış MM, Analysis and/or Interpretation: Yılcıoğlu RY, Writing: Yılcıoğlu RY,

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