Πανεπιστήμιο Ιωαννίνων

Σχολή Επιστημών Υγείας

Τμήμα Ιατρικής

Παθολογικός Τομέας

Α' Καρδιολογική Κλινική

Η λειτουργικότητα της κερκιδικής αρτηρίας σε συνδυασμό με επιπρόσθετες αγγειακές παραμέτρους στον καθορισμό της βατότητάς της καθώς και η τροποποίηση των παραμέτρων αυτών μετά από διακερκιδικές προσπελάσεις

Radial artery function and additional vascular parameters as predictors of loss of radial patency and their modification after transradial catheterization

Ξενοφών Μ Σακελλαρίου

ΔΙΔΑΚΤΟΡΙΚΗ ΔΙΑΤΡΙΒΗ

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Ιωάννινα

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Η έγκριση της διδακτορικής διατριβής από το Τμήμα Ιατρικής του Πανεπιστημίου Ιωαννίνων δεν υποδηλώνει αποδοχή των γνωμών του συγγραφέα.

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"Radial artery function and additional vascular parameters as predictors of loss of radial patency and their modification after transradial catheterization"

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Sakellariou XM, Nikas DN, Papanagiotou P, Liberopoulos E, Florentin M, Bechlioulis A, Mastoridou EM, Kolettis TM. Structural radial artery modifications following transradial access: Mechanisms, clinical implications, and preventive strategies. World J Cardiol. 2025 Jul 26;17(7):107772. doi: 10.4330/wjc.v17.i7.107772. PMID: 40741015; PMCID: PMC12304872.

Sakellariou XM, Nikas DN, Papanagiotou P, Liberopoulos E, Mastoridou EM, Halapas A, Kolettis TM. Pre-Procedural Vascular Phenotyping Is Associated with Radial Artery Functional Impairment After Transradial Catheterization. J Clin Med. 2026 May 27;15(11):4135. doi: 10.3390/jcm15114135. PMID: 42278993; PMCID: PMC13258591.

Σε διεθνή συνέδρια:

Ultrasound-guided evaluation of diameter, flow characteristics and function of radial artery following transradial coronary procedures.
Xenofon Sakellariou, Dimitrios Nikas, Theofilos M. Kolettis, University Hospital of Ioannina, Ioannina, Greece
ACC Middle East & Eastern Mediterranean 2023

Αφιερωμένη με αγάπη στη μνήμη του πατέρα μου

Περίληψη Διατριβής στα Ελληνικά

Ανασκόπηση και στόχοι

Η διακερκιδική προσπέλαση έχει καθιερωθεί ως η προεπιλεγμένη οδός για τον καρδιακό καθετηριασμό, καθώς μειώνει τη θνητότητα, την αιμορραγία και τις αγγειακές επιπλοκές, βελτιώνοντας παράλληλα την άνεση του ασθενούς. Ωστόσο, η εισαγωγή του θηκαριού και ο χειρισμός των καθετήρων προκαλούν βλάβη και στους τρεις χιτώνες του τοιχώματος της κερκιδικής αρτηρίας· εντούτοις, οι λειτουργικές συνέπειες —σε αντίθεση με τις καλά μελετημένες δομικές— παραμένουν ελλιπώς χαρακτηρισμένες, ιδίως ως προς τη χρονική τους εξέλιξη και τους παράγοντες που προβλέπουν τη βαρύτητά τους. Η παρούσα διατριβή αξιολόγησε προοπτικά τον τρόπο με τον οποίο μεταβάλλονται η ενδοθηλιακή λειτουργία, η λειτουργία του λείου μυϊκού χιτώνα, η διάμετρος του αυλού και οι αιμοδυναμικές παράμετροι Doppler της κερκιδικής αρτηρίας μετά από προγραμματισμένο διακερκιδικό καθετηριασμό. Οι τρεις στόχοι της ήταν: (1) να περιγράψει τη χρονική εξέλιξη των παραμέτρων αυτών στην αρχική μέτρηση, στις 24 ώρες και στον έναν μήνα· (2) να προσδιορίσει τα χαρακτηριστικά των ασθενών που σχετίζονται με το μέγεθος της λειτουργικής βλάβης· και (3) να διερευνήσει εάν οι αρχικές αγγειακές παράμετροι μπορούν να προβλέψουν τη μετεπεμβατική βλάβη και, ως εκ τούτου, να υποστηρίξουν την προ-επεμβατική διαστρωμάτωση κινδύνου.

Μέθοδοι

Σε μια προοπτική, μονοκεντρική μελέτη παρατήρησης στο Πανεπιστημιακό Γενικό Νοσοκομείο Ιωαννίνων, 94 διαδοχικοί ασθενείς που υποβλήθηκαν σε προγραμματισμένο διακερκιδικό καρδιακό καθετηριασμό αξιολογήθηκαν σε τρία προκαθορισμένα χρονικά σημεία: στην αρχική μέτρηση (αμέσως πριν από την επέμβαση), στις 24 ώρες μετά τον καθετηριασμό και στην επανεξέταση του ενός μηνός. Σε όλες τις επεμβάσεις χρησιμοποιήθηκαν η δεξιά κερκιδική αρτηρία και θηκάρι 6 Fr, με ενδαρτηριακό σπασμολυτικό μείγμα, ηπαρίνη προσαρμοσμένη στο σωματικό βάρος και αιμόσταση με διατήρηση της βατότητας (patent hemostasis). Ένας μόνο εξεταστής διενήργησε υπερηχογράφημα Doppler υψηλής ευκρίνειας σε κάθε επίσκεψη, μετρώντας την ενδοθηλιο-εξαρτώμενη αγγειοδιαστολή (FMD), την ενδοθηλιο-ανεξάρτητη αγγειοδιαστολή (NMD, μετά από 400 μg υπογλώσσιας νιτρογλυκερίνης), τη διάμετρο του αυλού, καθώς και τους δείκτες ροής σε ηρεμία και κατά την υπεραιμία (PSV, EDV, RI, PI, VTI και τον όγκο ροής ανά παλμό). Η βατότητα της κερκιδικής αρτηρίας επιβεβαιώθηκε με φασματικό και έγχρωμο Doppler. Καθώς όλες οι μεταβλητές

απέκλιναν από την κανονικότητα, χρησιμοποιήθηκαν μη παραμετρικές μέθοδοι σε όλη την ανάλυση —δοκιμασία Friedman με post-hoc δοκιμασίες Wilcoxon για τις μεταβολές ατόμου, Mann–Whitney U και Kruskal–Wallis για τις υποομάδες, συσχέτιση Spearman και ανάλυση ROC για την πρόβλεψη— με το λογισμικό SPSS v27.

Αποτελέσματα

Η ομάδα μελέτης περιελάμβανε 69 άνδρες (73%) και 25 γυναίκες (27%), με μέση ηλικία 65.8 ± 10.6 ετών και υψηλό φορτίο παραγόντων κινδύνου (αρτηριακή υπέρταση 65%, δυσλιπιδαιμία 78%, σακχαρώδης διαβήτης 30%). Η μέση αρχική διάμετρος της κερκιδικής αρτηρίας ήταν 2.43 mm και ήταν σημαντικά μικρότερη στις γυναίκες (2.20 έναντι 2.48 mm, $p < 0.01$), προσδίδοντας στις γυναίκες υψηλότερο λόγο θηκαριού προς αρτηρία (≈1.15 έναντι ≈1.02). Απόφραξη της κερκιδικής αρτηρίας εμφανίστηκε σε τέσσερις ασθενείς (4.3%) στις 24 ώρες, όλοι άνδρες, και σε όλους αποκαταστάθηκε αυτόματα η ροή εντός ενός μηνός.

Στόχος 1 — Χρονικές μεταβολές. Και οι δύο δείκτες αγγειοδραστικότητας μειώθηκαν απότομα στις 24 ώρες και ανέκαμψαν διαφορετικά, ενώ οι αιμοδυναμικοί δείκτες συμπεριφέρθηκαν με διακριτό τρόπο (μέσες τιμές παρακάτω).

Παράμετρος	Αρχική	24 ώρες	1 μήνας	Πρότυπο αποκατάστασης
FMD (%)	11.58	7.97***	8.25	Χωρίς αποκατάσταση ($p = 0.08$)· επιμένει
NMD (%)	18.04	11.44***	13.51	Μερική αποκατάσταση· παραμένει < αρχικής
PSV ηρεμίας (cm/s)	78.62	66.60***	84.50	Επιστροφή στην αρχική ($p = 0.13$)
RI ηρεμίας	0.94	0.96**	0.84	Κάτω από την αρχική στον 1 μήνα
PI ηρεμίας	3.49	3.01***	2.83	Προοδευτική μείωση (όλα $p < 0.001$)
Διάμετρος αυλού (mm)	2.43	2.24**	2.32	Μερική, ατελής αποκατάσταση

*Μέσες τιμές· n = 94 στην αρχική μέτρηση και στον 1 μήνα, n = 90 στις 24 ώρες (τέσσερις περιπτώσεις RAO). ** p < 0.01, *** p < 0.001 έναντι της αρχικής τιμής. Η μείωση της NMD (−36.6%) υπερέβη τη μείωση της FMD (−31.2%), και μόνο η λειτουργία του λείου μυϊκού ιστού ανέκαμψε μερικώς — η ενδοθηλιακή λειτουργία όχι.*

Στόχος 2 — Καθοριστικοί παράγοντες της βλάβης. Ο σακχαρώδης διαβήτης, η αρτηριακή υπέρταση, η νεφρική λειτουργία και η χρόνια αγγειοπροστατευτική αγωγή δεν επηρέασαν τον βαθμό της οξείας βλάβης· η χρήση αναστολέων RAAS εμφάνισε μόνο οριακό προστατευτικό σήμα για την FMD ($p = 0.06$). Δύο παράγοντες των ασθενών έδρασαν επιλεκτικά, σχηματίζοντας μια διπλή διάσταση: το γυναικείο φύλο σχετίστηκε με σημαντικά μεγαλύτερη βλάβη του λείου μυϊκού χιτώνα (διάμεση ΔNMD −8.3% έναντι −5.8%, $p = 0.005$) χωρίς όμως επιπλέον ενδοθηλιακή βλάβη, ενώ η μεγαλύτερη

ηλικία (≥ 65 ετών) σχετίστηκε με μεγαλύτερη οξεία απώλεια FMD και, κυρίως, με πτωχότερη ενδοθηλιακή αποκατάσταση στον έναν μήνα (ηλικία έναντι ΔFMD στον έναν μήνα ρ = −0.62), χωρίς να επηρεάζει τη βλάβη του λείου μυϊκού χιτώνα.

Στόχος 3 — Πρόβλεψη. Η υψηλότερη PSV ηρεμίας, η μικρότερη διάμετρος αυλού, ο υψηλότερος RI και η μεγαλύτερη ηλικία προέβλεπαν το μέγεθος και τη μονιμότητα της βλάβης. Στην ανάλυση ROC, η αρχική PSV ηρεμίας έδωσε την καλύτερη —και τη μόνη αποδεκτή— διαχωριστική ικανότητα για απώλεια FMD άνω της διαμέσου τιμής (AUC 0.73)· οι FMD και NMD έδωσαν η καθεμία 0.67, η διάμετρος 0.64 και ο RI 0.56, χωρίς καμία να φτάνει το όριο της άριστης διαχωριστικής ικανότητας (AUC > 0.80). Καθώς η αρχική PSV ήταν ισχυρά αρνητικά συσχετισμένη με τη διάμετρο της αρτηρίας (ρ = −0.68), η υψηλότερη PSV ταυτοποιεί κατά κύριο λόγο ασθενείς με μικρές κερκιδικές αρτηρίες. Μελλοντικά μπορεί να προταθεί ένα πολυπαραγοντικό σκορ που να συμπεριλαμβάνει PSV, διάμετρο, ηλικία και RI.

Συμπεράσματα

Ο διακερκιδικός καθετηριασμός προκαλεί μια μετρήσιμη, πολυεπίπεδη λειτουργική βλάβη της κερκιδικής αρτηρίας, η οποία αφορά τόσο το ενδοθήλιο όσο και τον λείο μυϊκό χιτώνα και παραμένει στον έναν μήνα, με μια χαρακτηριστική διάσταση στην αποκατάσταση: η λειτουργία του λείου μυϊκού χιτώνα ανακάμπτει μερικώς, ενώ η ενδοθηλιακή λειτουργία όχι, παράλληλα με ατελή αποκατάσταση της διαμέτρου του αυλού και μια αντισταθμιστική πτώση της άπω αντίστασης. Η βαρύτητα και η παραμονή αυτής της βλάβης διαφέρουν συστηματικά μεταξύ των ασθενών και μπορούν εν μέρει να προβλεφθούν από έναν απλό προ-επεμβατικό αγγειακό φαινότυπο —διάμετρος κερκιδικής, PSV και RI ηρεμίας, και ηλικία— γεγονός που υποστηρίζει την ενσωμάτωση μιας σύντομης προ-επεμβατικής εκτίμησης με Doppler στην καθημερινή πρακτική. Οι γυναίκες (μεγαλύτερη ευπάθεια του λείου μυϊκού χιτώνα) και οι ηλικιωμένοι ασθενείς (διαταραγμένη ενδοθηλιακή αποκατάσταση) χρήζουν ιδιαίτερης προσοχής και ενδέχεται να ωφεληθούν περισσότερο από στρατηγικές περιορισμού της βλάβης, όπως μικρότερα ή χωρίς θηκάρι (sheathless) συστήματα και άπω κερκιδική προσπέλαση· η παραμονή της βλάβης στον έναν μήνα είναι επίσης σημαντική στις περιπτώσεις όπου η κερκιδική αρτηρία ενδέχεται αργότερα να χρειαστεί ως μόσχευμα. Συνολικά, η κερκιδική αρτηρία δεν συμπεριφέρεται ως παθητικός αγωγός, αλλά ως ζωντανό αγγείο που αποκρίνεται στην επεμβατική βλάβη με μια βιολογική διεργασία που εκτυλίσσεται επί εβδομάδες — μια διεργασία μετρήσιμη, εν μέρει προβλέψιμη και κλινικά αξιοποιήσιμη.

Thesis summary in English

Background and aims

Transradial access has become the default route for cardiac catheterization because it reduces mortality, bleeding, and vascular complications while improving patient comfort. Sheath insertion and catheter manipulation nonetheless injure all three layers of the radial artery wall, yet the functional consequences — as opposed to the well-studied structural ones — remain poorly characterized, particularly their time course and the factors that predict their severity. This thesis prospectively assessed how endothelial function, smooth-muscle function, lumen diameter, and Doppler hemodynamics of the radial artery change after elective transradial catheterization. Its three aims were to (1) describe the temporal evolution of these parameters at baseline, 24 hours, and one month; (2) identify patient characteristics associated with the magnitude of functional impairment; and (3) determine whether baseline vascular parameters can predict post-procedural damage and thereby support pre-procedural risk stratification.

Methods

In a prospective, single-center, observational study at the University Hospital of Ioannina, 94 consecutive patients undergoing elective transradial coronary catheterization were evaluated at three predefined time points: at baseline (immediately before the procedure), 24 hours after catheterization, and at one-month follow-up. All procedures used the right radial artery and a 6 Fr sheath, with an intra-arterial antispastic cocktail, weight-adjusted heparin, and patent hemostasis. A single operator performed high-resolution Doppler ultrasound at each visit, measuring endothelium-dependent vasodilation (FMD), endothelium-independent vasodilation (NMD, after 400 μg sublingual nitroglycerin), lumen diameter, and resting and hyperemic flow indices (PSV, EDV, RI, PI, VTI, and per-beat flow volume). Radial patency was confirmed by spectral and colour Doppler. As all variables devited from normality, non-parametric methods were used throughout - Friedman with Wilcoxon post-hoc tests for within-patient change, Mann–Whitney U and Kruskal–Wallis for subgroups, Spearman correlation, and ROC analysis for prediction - in SPSS v27.

Results

The cohort comprised 69 men (73%) and 25 women (27%), with a mean age of 65.8 ± 10.6 years, with a high-risk-factor burden (hypertension 65%, dyslipidaemia 78%, diabetes 30%). Mean baseline radial diameter was 2.43 mm and was significantly smaller

in women (2.20 vs 2.48 mm, $p < 0.01$), giving women a higher sheath-to-artery ratio (≈1.15 vs ≈1.02). Radial artery occlusion occurred in four patients (4.3%) at 24 hours, all male, and all recanalized spontaneously within one month.

Objective 1 — Temporal changes. Both vasoreactivity measures fell sharply at 24 hours and recovered differentially, while hemodynamic indices behaved distinctly (mean values below).

Parameter	Baseline	24 h	1 month	Recovery pattern
FMD (%)	11.58	7.97***	8.25	No recovery (p = 0.08); persists
NMD (%)	18.04	11.44***	13.51	Partial recovery; still < baseline
Resting PSV (cm/s)	78.62	66.60***	84.50	Returns to baseline (p = 0.13)
Resting RI	0.94	0.96**	0.84	Falls below baseline at 1 month
Resting PI	3.49	3.01***	2.83	Progressive decline (all p < 0.001)
Lumen diameter (mm)	2.43	2.24**	2.32	Partial, incomplete recovery

*Mean values; n = 94 at baseline and 1 month, n = 90 at 24 h (four RAO cases). ** p < 0.01, *** p < 0.001 vs baseline. The NMD decline (−36.6%) exceeded the FMD decline (−31.2%), and only smooth-muscle function recovered partially — endothelial function did not.*

Objective 2 — Determinants of injury. Diabetes, hypertension, renal function, and chronic vasoprotective medication did not influence the degree of acute injury; RAAS-inhibitor use showed only a borderline protective signal for FMD (p = 0.06). Two patient factors acted selectively, forming a double dissociation: female sex was associated with significantly greater smooth-muscle injury (median ΔNMD −8.3% vs −5.8%, p = 0.005) but no excess endothelial injury, whereas older age (≥ 65 years) was associated with greater acute FMD loss and, especially, poorer endothelial recovery at one month (age vs ΔFMD at one month ρ = −0.62) without affecting smooth-muscle injury.

Objective 3 — Prediction. Higher resting PSV, smaller lumen diameter, higher RI, and older age predicted the magnitude and persistence of impairment. On ROC analysis, baseline resting PSV gave the best — though only acceptable — discrimination for above-median FMD loss (AUC 0.73); FMD and NMD each gave 0.67, diameter 0.64, and RI 0.56, none reaching the threshold for excellent discrimination (AUC > 0.80). Because baseline PSV was strongly inversely correlated with diameter in this cohort (ρ = −0.68),

higher PSV largely identifies patients with small radial arteries. A multivariable score combining PSV, diameter, age, and RI is proposed as a stronger future tool.

Conclusions

Transradial catheterization produces a measurable, multi-domain functional impairment of the radial artery that involves both the endothelium and the vascular smooth muscle and persists at one month, with a distinctive recovery dissociation: smooth-muscle function recovers partially while endothelial function does not, alongside incomplete restoration of lumen diameter and a compensatory fall in distal resistance. The severity and persistence of this injury vary systematically between patients and can be partly predicted from a simple pre-procedural vascular phenotype — radial diameter, resting PSV and RI, and age — supporting the integration of a brief pre-procedural Doppler assessment into routine practice. Women (greater smooth-muscle vulnerability) and older patients (impaired endothelial recovery) warrant particular attention and may benefit most from injury-sparing strategies such as smaller or sheathless systems and distal radial access; the persistence of impairment at one month is also relevant where the radial artery may later be needed as a bypass conduit. In sum, the radial artery behaves not as a passive conduit but as a living vessel that responds to procedural injury with a biological process unfolding over weeks — one that is measurable, partly predictable, and clinically actionable.

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GENERAL SECTION

Chapter 1: Introduction

Coronary artery disease (CAD) remains the leading cause of mortality worldwide (1) and one of the major contributors to global morbidity, affecting millions of individuals each year (2). The development of interventional cardiology over the past few decades has transformed the treatment of this disease, making coronary catheterization and stent implantation the preferred option for millions of patients worldwide. The success of these procedures, however, relies not only on the operator's skill and proper equipment selection but also on selecting the optimal vascular access site.

Traditionally, the femoral artery was the preferred choice for diagnostic and interventional cardiovascular procedures, mainly because of its large diameter and easy accessibility. Despite these advantages, transfemoral access (TFA) is associated with a well-characterized spectrum of vascular complications, including access-site bleeding, hematoma formation, pseudoaneurysm, arteriovenous fistula, and retroperitoneal hemorrhage. Importantly, access-site bleeding has been consistently associated with adverse clinical outcomes, including increased mortality, highlighting its central role in determining the overall safety profile of transfemoral coronary procedures. Additionally, the need for prolonged bed rest after the procedure adds to the patient’s recovery burden and increases hospital costs (3-5).

In the 1990s radial artery started gaining interest as an alternative access. In the present day, transradial access (TRA) has become the preferred choice among many centers worldwide, and the rates of its use have increased tremendously in the last ten years (6-8).

This widespread adoption reflects the many advantages of TRA over the traditional transfemoral approach, especially in percutaneous coronary interventions (PCI). TRA is associated with lower mortality, significantly less bleeding, and fewer vascular complications. Meta-analyses strongly endorse its safety profile. Maqsood et al (9)

demonstrated a significant reduction in major bleeding and access-site hematoma (OR: 0.34; 95% CI: 0.24–0.48). Gargiulo et al (10) further emphasized a mortality benefit (hazard ratio (HR): 0.77; 95% CI: 0.63–0.95; P = 0.012), indicating that TRA's benefits go beyond bleeding prevention. In chronic total occlusion PCI, Nguyen et al (11) reported fewer access-site complications (OR: 0.33) and major bleeding (OR: 0.34), with similar procedural success. Likewise, Senguttuvan (12) et al observed a mortality benefit in acute coronary syndrome, particularly in ST-elevation myocardial infarction (STEMI), with relative risk (RR): 0.71; 95% CI: 0.56–0.90, along with fewer major adverse cardiac events and vascular complications. In this regard, the European Society of Cardiology (ESC) (13, 14) and the American College of Cardiology / American Heart Association (AHA) / Society for Cardiovascular Angiography and Interventions (15) recommend radial access as the primary option for coronary catheterization in both acute and chronic coronary syndromes due to its superior safety profile and clinical outcomes.

In addition to its well-established role in interventional cardiology, TRA has increasingly been adopted in neuroendovascular procedures. First described for cerebral angiography in 1997, early experience demonstrated that conversion from transfemoral to transradial access can be achieved without significant differences in procedural success rates. A retrospective analysis of 148 cerebral angiograms performed via the radial artery showed no major complications and a favorable learning curve for operators (16). The list of neurointerventional procedures now performed via the transradial approach has expanded significantly to include coil embolization and flow diverter placement for intracranial aneurysms, carotid artery stenting, mechanical thrombectomy for acute ischemic stroke, and embolization of arteriovenous malformations and dural arteriovenous fistulas (17).

In diagnostic cerebral angiography, a recent comprehensive meta-analysis demonstrated that TRA is associated with a significantly lower complication rate (OR: 0.5, $P = 0.02$) compared to TFA, supporting TRA as a safe and practical option following careful patients selection and procedural planning (18). In therapeutic procedures, TRA has shown comparable efficacy with added safety in several domains. In stroke thrombectomy, TRA achieves recanalization success similar to TFA, with shorter hospital stays (19). In peripheral vascular interventions, TRA reduces access-site complications

(OR: 0.64; 95% CI: 0.45–0.91) and minor bleeding (OR: 0.52; 95% CI: 0.31–0.86) but is associated with higher procedural failure rates (20). For posterior circulation neuro interventions, TRA reduces total complications (OR: 0.29; 95% CI: 0.12–0.73) and access-site complications (OR: 0.19; 95% CI: 0.06‑0.62), though it requires longer catheter retention times (21). In carotid artery stenting and intracranial aneurysm interventions, TRA achieves comparable outcomes to TFA, though higher crossover rates and technical challenges have been noted (22, 23). Lastly, in neuroendovascular procedures, TRA reduces access-site (1.62% *vs* 3.31%) and neurological complications (1.64% *vs* 3.82%) compared to TFA, despite higher rates of vascular spasm and wound infections (24). Taken together, these facts suggest that the benefits of the transradial technique—such as fewer access-site complications, improved patient comfort, and earlier mobilization—can extend well beyond interventional cardiology and become increasingly relevant for the planning and execution of neurointerventional procedures.

Despite these major benefits, TRA is associated with structural and functional changes in the radial artery. Optical coherence tomography (OCT) and high-resolution ultrasonography studies have shown a spectrum of vascular injury, ranging from acute to chronic alterations in arterial wall layers (25-27). Radial artery occlusion (RAO) remains the most clinically significant complication that, although often goes unnoticed due to hand perfusion through the ulnar artery, can still prevent further use of the vessel for repeat procedures or as a graft in coronary artery bypass (28-31).

The issue of identifying the factors influencing radial artery function and patency after catheterization is a critical focus of recent research. Although few studies have examined the structural changes in the artery, limited information exists on its functional parameters. Additionally, while several preventive measures have been proposed, their effectiveness has not been thoroughly tested in relation to specific features of the vessel. This research aims to fill this gap by exploring the connection between functional and structural vascular parameters and the changes induced by catheterization.

Chapter 2: Anatomy and Physiology of the Radial Artery

2.1 Anatomical and Histological Characteristics

The radial artery is a smaller terminal branch of the brachial artery that originates at the level of the radial neck. It runs along the lateral side of the forearm, passing deep to the brachioradialis muscle in its proximal part and becoming more superficial distally near the wrist. It crosses the floor of the anatomical snuffbox at the wrist and continues toward the palm, where it forms the deep palmar arch along with the deep branch of the ulnar artery. This dual arterial supply to the hand, through the superficial and deep palmar arches, provides a significant safety mechanism, so that occlusion of the radial artery alone usually does not affect hand perfusion (Figure 1.1) (32-34).

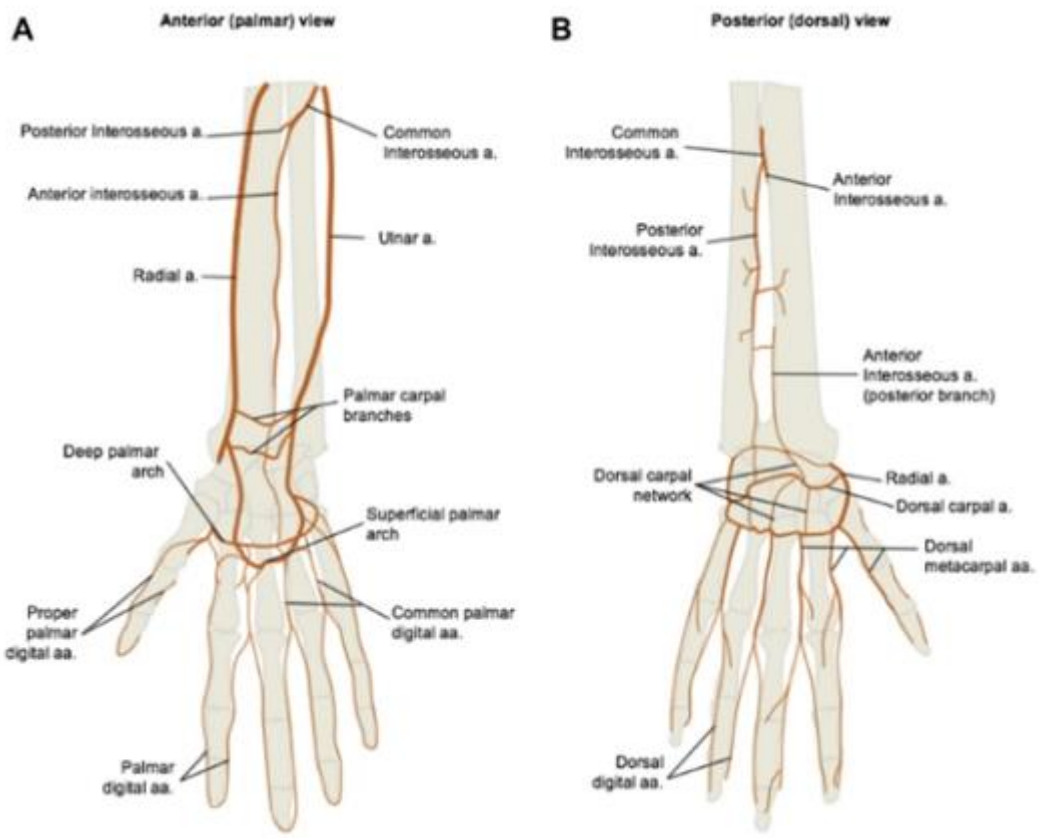

Figure 1.1. *Arterial circulation of the forearm and hand. Schematic illustration of the arterial blood supply to the upper limb in anterior (A) and posterior (B) views. The course of the radial and ulnar arteries along the forearm is shown, along with their contributions to the superficial and deep palmar arches. The*

interosseous arteries and terminal digital branches are also visible, demonstrating the collateral circulation of the hand [adapted from Sgueglia et al., (34)].

The diameter of the radial artery varies significantly between individuals and is affected by factors such as sex, age, and body size. Current evidence indicates that the average radial artery diameter in adults is about 2.7 mm, with women generally having smaller values than men. This anatomical difference is important clinically because a smaller arterial size has been linked to a higher risk of complications during transradial procedures, especially radial artery spasm (RAS) and occlusion (35). Additionally, the course and branching pattern of the radial artery exhibit anatomical variations, with abnormalities observed in 10-20% of individuals (36, 37).

Histologically, the radial artery, like any other medium-sized artery, is made up of three distinct layers that work together to maintain its structural integrity and proper function. The tunica intima consists of a single layer of endothelial cells that rests on a basement membrane and a thin layer of loose connective tissue. The endothelium is more than just a passive barrier between blood and the vessel wall; it is a dynamic endocrine organ that regulates vasodilation, vasoconstriction, hemostasis, and inflammatory responses. The thickest layer of the arterial wall is the tunica media, primarily composed of circular smooth muscle cells interspersed with elastic fibers and other components of the extracellular matrix. The outermost layer, the tunica adventitia, is a fibrous connective tissue containing collagen, elastin, fibroblasts, and the vasa vasorum (Figure 1.2, Figure 1.3) (38, 39).

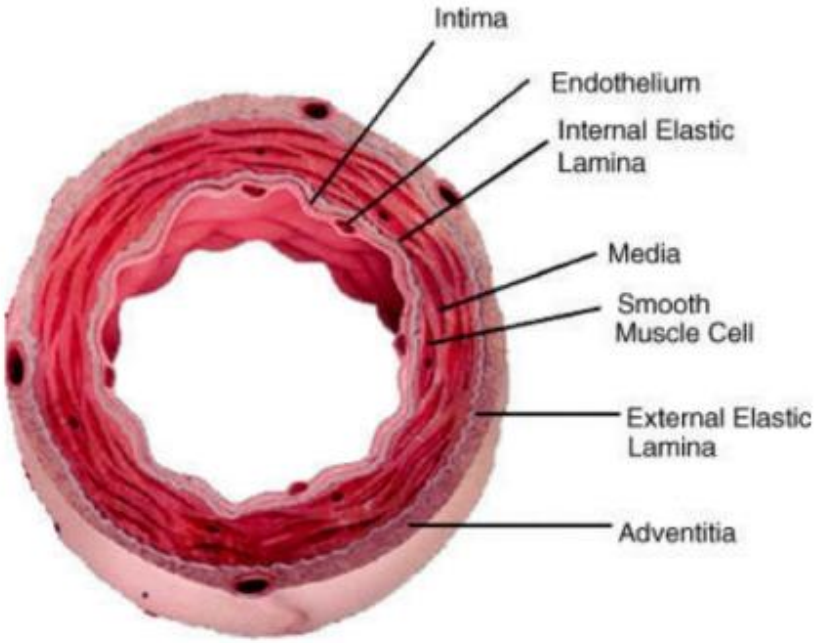

Figure 1.2. *Schematic illustration of the arterial wall structure. The three principal tunics are shown: the tunica intima with its monolayer endothelium and internal elastic lamina, the tunica media composed mainly of smooth muscle cells, and the tunica adventitia with its connective tissue and vascular supply [adapted from Sassi et al., (38)].*

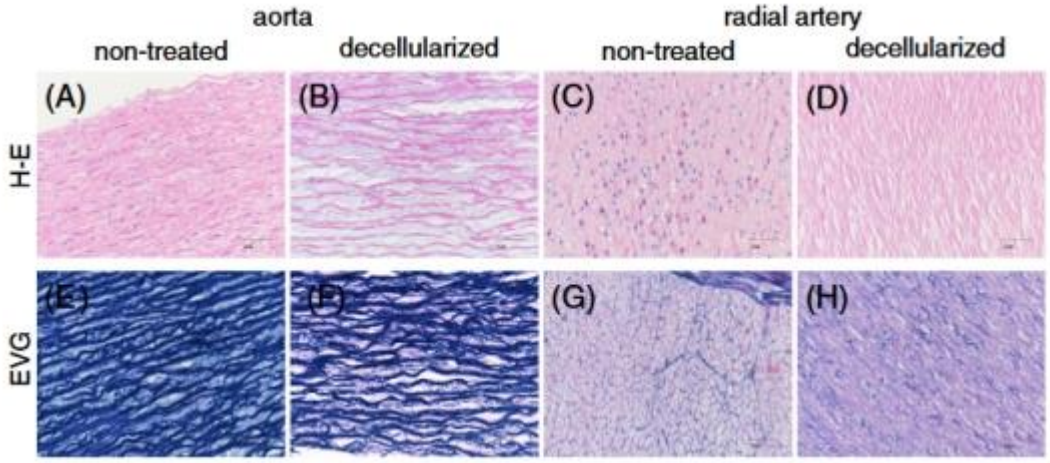

Figure 1.3. *Histological structure of the aorta and radial artery. Comparison of histological architecture between the aorta and the radial artery following hematoxylin-eosin (H-E) staining to evaluate cell removal and Elastica van Gieson (EVG) staining, which highlights elastic fibers (dark blue) and collagen (pink). (A–B) Aorta: multiple concentric elastic lamellae within the media, characteristic of elastic-type arteries. (C–D) Radial artery: fewer elastic fibers and a greater proportion of collagen, consistent with a muscular-type artery [adapted from Negishi et al., (39)].*

The relationship between the outer diameter of the sheath and the inner diameter of the radial artery is a key factor in vascular injury. A higher sheath-to-artery ratio has been associated with reduced radial flow and an increased risk of complications, including spasm and RAO. Current evidence indicates that these issues are primarily due to endothelial injury and flow reduction during transradial procedures (40, 41). Therefore, ultrasound evaluation of the radial artery before the procedure is recommended to select the right patients and sheath size.

2.2 Endothelial Function

Endothelial dysfunction refers to the disruption of the normal balance between vasodilatory and vasoconstrictive, antithrombotic and prothrombotic, as well as anti-inflammatory and pro-inflammatory functions of the endothelium. This condition is characterized by decreased bioavailability of nitric oxide, excessive production of reactive oxygen species, increased expression of adhesion molecules, and increased endothelial permeability. Endothelial dysfunction is a well-established early stage of atherogenesis and is linked to a higher risk of cardiovascular events (42-44).

Endothelial injury during TRA results from mechanical forces applied during artery puncture, guidewire and sheath insertion, and catheter movements within the vessel. Even localized endothelial denudation can trigger platelet adhesion, activate the coagulation cascade, and release pro-inflammatory cytokines. Additionally, the mechanical deformation of the arterial wall caused by the sheath changes the pattern of wall shear stress exerted by blood flow on the endothelium, which may impair endothelial function. Immunohistochemical analysis has shown widespread endothelial damage after transradial catheterization, and endothelial healing has not been fully completed 30 days after the procedure (25).

It is now recognized that endothelial dysfunction is a systemic condition that occurs before the development of overt atherosclerosis and is closely associated with known cardiovascular risk factors. Loss of nitric oxide bioavailability, linked to oxidative stress, chronic inflammation, and abnormal shear stress, is the primary mechanism behind endothelial dysfunction. This results in impaired vasodilation, a pro-inflammatory endothelial phenotype, and the activation of prothrombotic pathways. Biomarkers of

endothelial activation—such as asymmetric dimethylarginine, von Willebrand factor, E-selectin, and endothelial microparticles—are proposed as indicators of subclinical endothelial injury and have been shown to be strongly connected with the occurrence of cardiovascular events. Pre-existing endothelial dysfunction in a patient undergoing transradial catheterization—whether due to normal conditions or risk factors like diabetes mellitus, arterial hypertension, or dyslipidemia—may render the vessel wall more vulnerable to the immediate mechanical trauma of the procedure and less capable of mounting an effective vasodilatory and anti-thrombotic response, thereby increasing the risk of complications such as radial artery occlusion. Clinically, endothelial dysfunction is reversible and serves as a valuable therapeutic target. Angiotensin-converting enzyme (ACE) inhibitors, statins, and phosphodiesterase inhibitors are also pharmacological treatments that have been proven to improve endothelial function, along with lifestyle modifications such as smoking cessation, increased physical activity, and dietary changes (42-46).

Additionally, non-invasive assessments of endothelial activity—using techniques like flow-mediated dilation and carotid intima-media thickness (IMT) —and measurements of arterial stiffness can help identify individuals at high risk before clinical events happen. Pre-procedural evaluation of endothelial function during transradial procedures may serve as a prognostic indicator of vascular injury and a tool for recognizing patients in whom modifying risk factors—especially before elective procedures—could lower the chances of procedural complications.

2.3 Smooth Muscle Function

In transradial procedures, the radial artery's smooth muscle layer can be affected by various mechanisms. Arterial spasm is one of the most common complications, characterized by transient vasoconstriction resulting from direct mechanical stimulation of the vessel wall. Spasm can impede catheter movement, prolong the procedure, and cause patient discomfort. Furthermore, frequent or severe vasospasm may cause mechanical damage to the vessel wall, leading to permanent structural changes. Therefore, vasodilatory agents—primarily verapamil and nitroglycerin—are routinely administered intra-arterially to prevent and treat spasm during the procedure (47, 48).

Dysfunction of smooth muscle following catheterization may manifest as a decreased vasodilatory response to physiological stimuli. The ability of external pharmacological agents to induce vasodilation has been shown to be impaired weeks after the procedure, likely due to structural changes, including hyperplasia of smooth muscle cells and changes in the extracellular matrix composition, both of which are discussed in the next chapter.

2.4 Hemodynamic Parameters and Doppler Ultrasound

The primary non-invasive method for evaluating hemodynamics in the radial artery is Doppler ultrasound. The volumetric flow rate can be estimated by measuring blood flow velocities along the vessel and determining the cross-sectional area from the arterial diameter. The accuracy of these measurements depends heavily on proper positioning of the Doppler sample volume and the insonation angle, as technique variations directly affect the measured velocities and the flow estimations derived from them.

The resistive index (RI) and pulsatility index (PI) are two Doppler-derived indices commonly used to evaluate the hemodynamic properties of peripheral arteries. RI was first defined by Pourcelot in 1974 and is calculated as the ratio of peak systolic velocity (PSV) minus end-diastolic velocity (EDV) to PSV: RI = (PSV - EDV) / PSV. The RI is relatively independent of the operator and the Doppler insonation angle, making it a reproducible parameter that reflects downstream vascular resistance. It ranges from 0 to 1, with lower values indicating a low-resistance vascular bed with persistent diastolic flow, and higher values indicating higher resistance and reduced diastolic flow velocity. The PI is calculated as the ratio of the difference between the highest systolic and lowest end-diastolic velocities to the mean velocity over the cardiac cycle: PI = (PSV - EDV) / Vmean. PI offers a more detailed description of waveforms by using the mean velocity instead of the peak systolic velocity in the denominator, making it more sensitive to changes in waveform shape, especially when the waveform morphology changes but peak velocities remain proportionally unaffected. Both indices reflect not only local vascular resistance but also systemic hemodynamic factors, including arterial stiffness, vascular compliance, and pulse pressure (49-51).

The physiological determinants of RI and PI extend well beyond elevated local vascular resistance. Hemodynamic analyses have demonstrated that RI reflects the relationship between pulse pressure and vascular properties in the downstream arterial bed and is sensitive to arterial wall compliance as well as resistance per se. Particularly, as compliance of the arterial walls reduces, e.g., due to medial calcification, fibrosis, or ageing, elastic recoil of the vessel wall decreases, end-diastolic velocity decreases, and both RI and PI increase even in the absence of any rise in true downstream vascular resistance. The implications of this observation for the interpretation of Doppler indices are far-reaching: a high RI is not necessarily indicative of obstructive arterial disease but may reflect diffuse arterial wall stiffness, an increase in systemic pulse pressure, or disrupted microvascular activity at the tissue level. Low RI, on the other hand, is an indicator of a compliant, vasodilated vascular bed with well-preserved diastolic perfusion, which in the case of the radial artery, is a sign of intact smooth muscle relaxation and a sufficient microvascular reserve (49, 50, 52).

The most well-studied Doppler index concerning its systemic cardiovascular importance is the renal RI. The experience gained with this index can be directly applied to interpreting peripheral arterial Doppler indices, such as those of the radial artery. It has been shown that the renal RI not only reflects intrarenal hemodynamics but also indicates systemic circulatory variables like aortic stiffness, central pulse pressure, and left ventricular filling pressures. Additionally, it is associated with target organ damage in arterial hypertension, such as left ventricular hypertrophy and carotid IMT (52, 53).

The diagnostic data given by the morphological pattern of the arterial Doppler waveform enhances the numerical values of RI and PI. In healthy peripheral arteries with normal vessel wall compliance and low arterial resistance, the waveform is typically triphasic. It consists of a sharp systolic increase, a low-resistance flow reversal in early diastole caused by the elastic recoil of the arterial wall, and a small forward flow component in late diastole. As arterial disease progresses and walls become stiffer, this triphasic pattern shifts to a biphasic waveform, and eventually to a monophasic waveform, in which forward diastolic flow is severely restricted or absent, indicating very high RI and PI values. Morphology analysis of waveforms can be performed visually by examining the

spectral Doppler trace without additional calculations, and when combined with quantitative velocity measurements and derived indices, it provides a comprehensive hemodynamic assessment in a single noninvasive test. Ultrasound, along with indirect physiological measurements such as waveform analysis, segmental pressure measurement, and flow volume estimation, is the standard approach for noninvasive evaluation of peripheral arterial disease at any level of the arterial tree (54, 55).

Doppler-derived indices for detecting arterial disease are especially useful in clinical practice, where traditional pressure-based measurements can become unreliable. The most common non-invasive screening tool for lower-extremity peripheral arterial disease, the ankle-brachial index, loses diagnostic accuracy when arterial walls become calcified and vessels become non-compressible. This is a common issue in patients with diabetes mellitus or chronic kidney disease, where non-compressible arteries can falsely elevate ankle pressures (56). Doppler-derived RI and PI can still serve their diagnostic purpose in these cases, as they rely on flow-velocity measurements rather than vessel compressibility. Ciuti et al. (57) demonstrated a significant correlation between the RI of the dorsal metatarsal artery and the ankle-brachial index in patients with peripheral arterial disease, and this correlation was not lost in the subgroup of diabetic patients, where the ankle-brachial index was unreliable due to arterial calcification. These findings suggest that Doppler waveform analysis at distal arterial sites can provide valuable hemodynamic insights into the condition of the arterial network, even without precise pressure data. Furthermore, Doppler flow indices can serve as additional tools for evaluating patients with complex vascular disease profiles.

Pre-procedural RI and PI values have prognostic implications in specific settings of radial artery and transradial catheterization, extending beyond their ability to simply describe baseline hemodynamics. A higher baseline RI, which reflects reduced diastolic flow, may indicate increased vascular stiffness, impaired microvascular function, or reduced vasodilatory capacity. Such vessels might be less efficient at accommodating mechanical stress during sheath insertion and catheter manipulation, more prone to vasospasm during catheter handling, and less capable of maintaining adequate wall shear stress during the procedure—all of which could theoretically promote endothelial damage and thrombotic

occlusion. Conversely, a well-dilated, compliant artery with a low RI and preserved diastolic flow is better equipped to handle the hemodynamic changes caused by arterial puncture and intravascular device passage. Although the relationship between pre-procedural radial artery Doppler indices and the risk of radial artery occlusion has not been extensively studied, the physiological basis for this association is well supported by the broader literature on RI and PI determinants and their connection to microvascular health. This research aims to provide direct evidence of this relationship by comparing pre-procedural RI and PI values in patients who experience radial artery occlusion after transradial catheterization with those who do not.

Chapter 3: Complications and Vascular Changes

3.1 Acute Injuries

The initial vascular damage after transradial catheterization is intimal injury, mainly caused by mechanical friction among the guidewire, sheath, catheter, and the radial artery wall. This leads to endothelial denudation and intimal tears. Immunohistochemical studies have shown that TRA causes widespread endothelial damage, which tends to heal over time but may leave incomplete endothelial recovery beyond 30 days, possibly affecting the artery's long-term usability (58). Intimal tears, a common form of acute injury following transradial intervention, indicate more extensive damage than just endothelial denudation. OCT studies report a wide range in the incidence of intimal tears (37.3%-67.1) (59, 60), though lower rates (2.2%-11.5%) are seen after distal TRA (61, 62). Repeat transradial procedures have been linked to higher rates of intimal tears, with some studies reporting up to 44.1% compared to 23.0% in first-time procedures ($P = 0.002$) (60), though other research finds no significant difference (46.2% vs 28%; $P = 0.18$) (59). Moreover, Zhang et al (63) found an even higher tear rate in repeat procedures (48.3% vs 29.4%; $P < 0.001$), suggesting repeated procedures increase intimal trauma.

Yonetsu et al. (60) observed that intimal tears were notably more common in the distal (43.8%) and mid-radial artery segments (34.2%) compared to the proximal radial artery (17.8%; $P = 0.001$ and $P = 0.038$, respectively). This highlights the impact of radial artery-sheath diameter mismatch in causing acute injury. Although these tears were more frequent in the distal and mid segments, they were also identified near the radial artery ostium, suggesting that other factors, such as mechanical stretching during sheath manipulation and radial spasm, may play a role regardless of vessel size. Conversely, Di Vito et al. (59) found a different pattern, with a tendency toward a higher incidence in the proximal segment (31.4% vs 15.7%; $P = 0.09$). They suggested that the use of a long hydrophilic-coated sheath might influence this distribution but didn't provide definitive evidence of a protective effect. Unlike earlier studies indicating that intimal tears mainly occur in either the proximal or distal segments, Niu et al. (61) reported a lower overall incidence and no significant difference across the proximal, mid-, and distal segments (2.5% vs 6.0% vs 5.0%; $P = 0.183$). They speculated that factors like the distal transradial approach and combined vasodilator therapy with nitroglycerin and verapamil might

contribute to these results, though further research is needed to establish any protective benefits.

Medial dissections, although less frequently reported than intimal tears, are an important type of vascular injury after transradial procedures and have been linked to increased intimal thickness. Among them, Costa et al (64) observed a much higher occurrence, with 89.8% of patients showing medial dissections three hours after the procedure. However, their study focused on a small area (4 mm before and after the puncture site), and these dissections were not associated with postprocedural RAO or pulse loss. Additionally, repeated manipulation of catheters and sheaths may influence the rate of medial dissections. Consistent with this, research indicates that in patients undergoing their first transradial coronary intervention, the incidence varies from 9.5% to 11.8%, whereas rates up to 30.2% have been reported in those undergoing multiple procedures (60, 63). Beyond localized injuries such as medial dissections, transradial procedures also cause widespread early arterial wall remodeling, as evidenced by increased IMT. Yan et al observed a significant increase in IMT from 0.25 ± 0.12 mm before the procedure to 0.69 ± 0.31 mm one day after the procedure (65).

Procedural and anatomical factors have been examined to understand their influence on the risk of medial dissection, given the variable incidence reports. Recent evidence indicates that distal TRA can reduce the occurrence of medial dissections, especially in patients with prior radial procedures. Niu et al (61) found a 16.5% incidence of medial dissection after distal TRA in patients undergoing their first transradial procedure, while Poletti et al (66) reported a slightly lower rate of 12%, including both first-time and repeat procedures. These results imply that distal TRA changes the entry point and may reduce catheter-related trauma, potentially providing a protective effect against medial injury, even in arteries previously catheterized.

The distribution of medial dissections along the radial artery appears to be influenced by mechanical factors and sheath coverage. Yonetsu et al (60) observed that medial dissections mainly occur in the proximal and distal parts of the artery, suggesting different causes depending on the segment. Dissections in the distal segment may result from stretching during sheath insertion, while those in the proximal part, which lacks sheath protection, are probably due to catheter movement near the radial ostium. Similarly, Niu et al (61) found a higher rate of medial dissections in the proximal radial artery compared

to the distal (11.0% vs 4.5%; $P < 0.05$), indicating that sheath presence might guard against trauma during distal transradial procedures. Conversely, Di Vito et al (59), using a long 25-cm hydrophilic-coated sheath covering the entire radial artery, found no difference in medial dissection rates between segments. This suggests that full-length sheath coverage provides consistent protection and may reduce site-specific medial injuries.

3.2 Radial Artery Occlusion

Besides histological changes in the arterial wall, TRA can cause direct clinical effects by reducing the lumen diameter of the radial artery. The acute phase is characterized by a significant decrease in lumen size in patients undergoing their first transradial procedure. It has been reported that the average radial artery diameter decreased from 2.37 ± 0.57 mm before the procedure to 1.95 ± 0.50 mm on the first day after the procedure ($p < 0.01$). Shen et al. similarly reported that the mean radial artery diameter was 2.32 ± 0.53 mm before the procedure and 1.93 ± 0.57 mm one day after the procedure ($P < 0.05$). This sudden narrowing of the lumen results from a combination of factors, including the inflammatory response to arterial puncture, mechanical friction between the sheath and the endothelium, early increased IMT, and functional vasospasm (65, 67).

Repeat transradial procedures have a greater impact on radial artery lumen narrowing compared with first-time interventions. In a high-resolution ultrasound biomicroscopy study, patients undergoing a repeat procedure had smaller arterial diameters in the early post-procedural period than first-time patients (1.79 mm vs 1.93 mm, respectively) (67). However, not all studies have demonstrated an immediate reduction in radial artery diameter. In a study by Yoo et al., no significant difference in mean radial artery diameter was observed between pre-procedural measurements and those obtained 1 day after the procedure, in both first-time and repeated TRA groups. These discrepancies likely reflect differences in study design, measurement techniques, and procedural characteristics. Nevertheless, repeated TRA has consistently been associated with a higher incidence of vascular injury, underscoring the importance of careful pre-procedural assessment of the radial artery (68).

The most significant complication of TRA is RAO. The incidence of RAO has been reported differently across studies due to variations in detection methods, assessment timing, and population characteristics. A recent meta-analysis of 41 studies comprising 30020 patients reported an overall RAO incidence of 13% (28). Notably, some occlusions spontaneously recanalize, with 32.6% recanalizing within 3 months, indicating that a portion of occlusions are dynamic and can be reversed (69).

The development of RAO is influenced by a combination of patient-related and procedural-related risk factors, many of which are potentially modifiable with proper technique and planning. Female sex is an independent predictor among patient-related factors, as women will be more prone to RAO, which is probably due to their smaller vessel diameter (28, 41, 70, 71). Another risk factor, also associated with an increased rate of occlusion, is older age, likely due to progressive age-related vascular and functional alterations (28, 30). Additionally, cardiovascular instability during the procedure has been identified as an independent predictor of RAO (69, 70). Traditional cardiovascular risk factors have also been associated with an increased risk of RAO. Dyslipidemia, with elevated levels of low-density lipoprotein cholesterol, is associated with higher rates of occlusion in patients undergoing repeat procedures (70, 72); chronic kidney disease (estimated Glomerular Filtration Rate (eGFR) less than 60 mL/min/1.73 m2) significantly elevated RAO risk (73); and diabetes mellitus is another significant contributor to RAO, with diabetic patients exhibiting nearly double the risk of occlusion as compared to non-diabetic patients (72). An overall cardiovascular risk assessment using comprehensive risk scores that combine multiple risk factors, including the CHA2DS2-VASc score, has been suggested, and these scores are independent predictors of RAO (74).

A key procedural-related factor affecting RAO is the mismatch between sheath size and radial artery diameter. Larger sheath sizes are independently linked to a higher risk of RAO, showing a stepwise increase in incidence from smaller to larger French sizes. At the same time, a smaller radial artery diameter—especially less than 2.5 mm—has consistently been identified as an independent predictor of occlusion. These findings emphasize the importance of pre-procedural vessel assessment, including ultrasound-

based sizing, and careful sheath selection to reduce vascular trauma and preserve long-term radial access (30, 69, 73, 75). Multiple attempts at puncturing the radial artery during cannulation are linked to a higher risk of RAO, probably due to cumulative endothelial damage and vasospasm. These findings highlight the significance of using ultrasound guidance, practicing meticulous technique, and relying on operator experience (73). Access site selection may further influence RAO risk. Although randomized data have shown no significant difference between distal and conventional transradial access when optimal hemostasis is applied, multiple studies and meta-analyses suggest that distal transradial access is linked to lower RAO rates and better arterial patency. When feasible, distal access might therefore serve as a vascular-protective strategy (76-79).

The loss of radial artery patency after transradial procedures has significant clinical implications beyond the immediate peri-procedural period, mainly by limiting future vascular access options. Additionally, the radial artery is commonly used as a graft in coronary artery bypass grafting, with excellent long-term patency and a lower risk of composite cardiovascular outcomes compared with saphenous veins. Previous transradial catheterization may impact the radial artery's suitability as a bypass graft due to structural and functional changes, including endothelial injury and neointimal hyperplasia. While some studies suggest avoiding or delaying its use in the preoperative period, others have not demonstrated a negative effect on graft patency or clinical outcomes. Overall, the influence of prior transradial access remains controversial, and thorough preoperative evaluation is crucial (80-83).

3.3 Pathophysiology of Vascular Injury

Mechanical injury caused by transradial catheterization triggers vascular repair responses that can also lead to pathological remodeling. OCT, intravascular ultrasound, and histopathological studies have shown endothelial and intimal injury, thrombus formation, medial inflammation, and subsequent intimal hyperplasia in the radial artery after transradial procedures. These findings support the idea that arterial wall trauma starts inflammatory and proliferative pathways, resulting in smooth muscle cell–driven neointimal remodeling (60, 80, 84, 85).

Mechanical damage to the arterial wall triggers a series of biological responses aimed at repair; however, these same mechanisms can also cause pathological vascular remodeling. Denudation of the endothelium exposes the underlying extracellular matrix to circulating blood, promoting platelet adhesion and activation. Activated platelets release various biologically active mediators, including platelet-derived growth factor, transforming growth factor-β, and tumor necrosis factor-α, which initiate both inflammatory and vascular remodeling pathways. These mediators stimulate the migration of vascular smooth muscle cells from the tunica media to the tunica intima, where they proliferate and contribute to neointimal hyperplasia (86-90).

Mechanical injury also triggers an inflammatory response with a dual role in vascular remodeling. On one hand, inflammation is vital for tissue repair and restoring arterial wall integrity. Inflammatory cells, including monocytes and macrophages, are recruited to the injury site, where they help clear necrotic debris and promote vascular healing. On the other hand, a prolonged or excessive inflammatory response can lead to pathological changes, such as neointimal hyperplasia, fibrosis, and endothelial dysfunction. Additionally, oxidative stress caused by inflammatory and activated endothelial cells further worsens endothelial dysfunction by lowering nitric oxide bioavailability. Nitric oxide plays important anti-inflammatory and anti-proliferative roles along with its vasodilatory effects; therefore, its reduction sustains both inflammation and neointimal growth (87, 91-94). In transradial catheterization, these biological mechanisms are directly triggered by mechanical trauma caused by arterial puncture, sheath insertion, and catheter manipulation. The radial artery undergoes repeated mechanical stress, including endothelial denudation, local overstretching, and altered shear forces, which start the same chain of platelet activation, inflammation, and smooth muscle cell migration described above.

Another key pathophysiological component is the adipose tissue surrounding the radial artery. Instead of just providing structural support, the perivascular adipose tissue is a metabolically active organ that produces various biologically active compounds, such as adipokines and vasodilatory factors, which regulate vascular tone and maintain the homeostasis of the underlying vessel (95, 96). Recent meta-analyses demonstrated that the no-touch saphenous vein harvesting technique is associated with significantly improved long-term graft patency compared with conventional harvesting. A plausible

mechanistic explanation is that the no-touch approach better preserves the vessel's structural integrity, including the surrounding perivascular adipose tissue, thereby minimizing surgical trauma (97, 98).

Perivascular adipose tissue exerts significant vasoprotective effects by releasing nitric oxide, prostacyclin, and other relaxing factors that influence vascular tone and cellular homeostasis. These bioactive mediators act in a paracrine manner on the underlying vessel wall, improving endothelial function and limiting the proliferation of vascular smooth muscle cells. Additionally, adipokines contribute to anti-inflammatory and anti-remodeling signaling pathways within the vascular wall. Experimental evidence shows that intact perivascular adipose tissue is vital for maintaining normal vascular function, while its removal or dysfunction promotes neointimal formation and vascular remodeling. Overall, these findings support the idea that it functions as a local regulator of vascular integrity and that preserving its structure and secretory activity is crucial for preventing maladaptive vascular remodeling (99, 100). Disruption of this tissue in arteries during puncture and sheath insertion could impair its functions, reduce the production of local vasoprotective factors, and result in vascular dysfunction.

Another significant way TRA affects the arterial wall is through vasospasm. Vascular spasm is a temporary increase in vascular smooth muscle tone in response to mechanical and local vascular stimuli and is closely linked to endothelial dysfunction and impaired vasomotor regulation (86, 93). In the context of transradial access, these mechanisms are directly triggered by arterial puncture, sheath insertion, and catheter manipulation, resulting in RAS. RAS is a well-known complication of transradial procedures, characterized by sudden vessel narrowing, patient discomfort, and technical challenges, with its reported incidence varying widely based on definition and methodology (47, 101). Recent angiographic data further emphasize its clinical significance, showing that RAS may occur in a considerable number of patients and is strongly associated with anatomical factors, especially smaller radial artery diameter and lower body weight, which independently predict its occurrence (102). Its pathophysiology is multifaceted, involving mechanical irritation and local vascular responses to endothelial injury. Although usually transient and responsive to vasodilator therapy, RAS remains an important factor affecting procedural complexity and access-site performance during transradial interventions (47, 101).

RAO is a process influenced by multiple factors, including mechanical, thrombotic, and hemodynamic mechanisms. Mechanical injury to the endothelium during arterial puncture and sheath insertion damages vascular integrity and creates a surface that encourages platelet adhesion and activates the coagulation process. Endothelial denudation also worsens thrombosis by decreasing the local production of nitric oxide and prostacyclin, which normally inhibit platelet aggregation and promote vasodilation. Additionally, the presence of an arterial sheath—particularly when maintained for a prolonged period—may impair antegrade blood flow, leading to reduced shear stress and relative flow stagnation, conditions that favor thrombus formation (40). Lastly, post-procedural hemostasis is crucial, as excessive or prolonged compression can block forward blood flow; the length and strength of compression are recognized as independent factors predicting RAO (30, 41, 73, 103).

Chapter 4: Functional Assessment of the Radial Artery

4.1 Endothelium-Dependent Vasodilation

Flow-mediated dilation (FMD) is an endothelium-dependent vasodilatory response that reflects the ability of conduit arteries to adapt to an acute increase in blood flow and the associated rise in shear stress (104, 105). Following transient distal ischemia - typically induced by a 5-minute period of supra-systolic cuff occlusion on the forearm - reactive hyperemia generates a rapid and transient increase in blood flow through the upstream conduit artery, producing a shear stimulus that serves as the primary physiological trigger for the response (105, 106).

The detection of shear stress by the vascular endothelium involves a complex network of mechanosensors located at or near the endothelial cell surface. Several molecular structures are involved in this process, including the mechanosensitive ion channel Piezo1, the endothelial glycocalyx and its heparan sulfate proteoglycan components, junctional protein complexes such as platelet endothelial cell adhesion molecule-1 and vascular endothelial cadherin, G-protein coupled receptors, caveolae, and integrins. Among these, Piezo1 has attracted particular attention as a true mechanosensor: when activated by shear stress, Piezo1 allows calcium influx across the endothelial membrane, initiating downstream phosphorylation of Akt and endothelial nitric oxide synthase, thus linking mechanical force detection directly to nitric oxide production (107-109). Meanwhile, the endothelial glycocalyx—a carbohydrate-rich layer projecting from the luminal surface—serves as a mechanical transducer by transmitting fluid shear forces to the underlying cortical cytoskeleton and intracellular signaling pathways. These mechanosensors do not act alone; instead, they function as an integrated signaling network where the detection and transduction of shear stress result from collaborative interactions among multiple molecular components (107, 110).

Once shear stress is transduced, the central effector pathway involves the activation of endothelial nitric oxide synthase and the subsequent production of nitric oxide. Nitric oxide diffuses into adjacent vascular smooth muscle cells, where it activates soluble guanylate cyclase, elevates intracellular cyclic guanosine monophosphate levels, and promotes vascular smooth muscle relaxation and consequent vasodilation (94). Although

flow-mediated dilation is predominantly nitric oxide-mediated under physiological conditions, a meta-analysis of crossover studies employing nitric oxide synthase blockade estimated that nitric oxide accounts for approximately half of the total dilatory response. This finding suggests that additional endothelium-derived mediators — including prostacyclin, generated via cyclooxygenase, and endothelium-derived hyperpolarizing factors acting through calcium-sensitive potassium channels — contribute meaningfully to the overall response, particularly during sustained or prolonged shear stimuli. The relative contribution of these pathways may vary depending on the vascular bed examined, the duration and pattern of the shear stimulus, and the presence of underlying vascular pathology (111, 112).

Moreover, the magnitude of FMD depends not only on endothelial function per se, but also on the characteristics of the shear stimulus driving the response, including its peak magnitude, rate of onset, and duration (106). Differences in cuff placement (proximal versus distal to the measurement site), occlusion duration, and the method of diameter analysis can substantially influence the measured response, underscoring the importance of rigorous methodological standardization when flow-mediated dilation is used as a research or clinical tool (113).

FMD has emerged as a widely accepted, non-invasive method for evaluating endothelial function and vascular health. A substantial body of evidence supports its role as a clinically relevant biomarker, with meta-analyses demonstrating that impaired brachial artery flow-mediated dilation is independently associated with an increased risk of future cardiovascular events across diverse patient populations, including those with established coronary artery disease, hypertension, diabetes mellitus, and chronic kidney disease (114-116). Each 1% decrease in FMD has been estimated to confer a 12% increase in the relative risk of cardiovascular events (117), reinforcing its potential utility as a prognostic tool for risk stratification and as a surrogate endpoint for interventions targeting endothelial function.

Although FMD is most commonly assessed in the brachial artery, it can also be measured in the radial artery, where it is particularly relevant to transradial catheterization. Radial artery FMD has been shown to be highly concordant with brachial artery measurements in hypertensive patients, supporting its validity as an alternative site for assessing

endothelial function (118). Transradial catheterization itself has been shown to impair radial artery FMD. Dawson et al. demonstrated that sheath insertion significantly reduced FMD at both the sheath placement site and the catheter passage segment, with values declining from approximately 9% pre-procedure to approximately 4.5% the day after catheterization—a reduction of about 50% (119). Nakata et al. further showed that the endothelial dysfunction induced by a 6 Fr sheath, particularly with longer procedure times, persisted for at least 6 months, whereas smaller sheaths (4–5 Fr) caused no significant change (120). Buturak et al confirmed that six months after transradial catheterization, both radial artery luminal diameter and FMD remained significantly lower than pre-procedural values, indicating chronic vascular remodeling at the access site (121). Importantly, exercise training may reverse this catheterization-induced endothelial dysfunction: Dawson et al demonstrated in a randomized study that a six-week handgrip exercise program preserved FMD in the radial artery following transradial catheterization (122). These findings collectively show that transradial catheterization causes measurable and potentially lasting endothelial dysfunction in the radial artery, with the extent of injury affected by sheath size and procedure duration. Radial artery FMD may therefore serve not only as a way to assess baseline vascular health before catheterization but also as a sensitive marker of vascular injury and recovery related to the procedure, with possible implications for predicting RAO risk and guiding strategies to preserve vascular health.

4.2 Endothelium-Independent Vasodilation

Endothelium-independent vasodilation is most commonly assessed as nitroglycerin-mediated dilation (NMD), which indicates the ability of vascular smooth muscle cells to relax in response to an external nitric oxide donor. This process largely bypasses endothelial signaling. In human vascular studies, this response serves as a functional marker of vascular smooth muscle function, complementary to flow-mediated dilation. Recent clinical research has even proposed diagnostic thresholds for normal nitroglycerin-induced vasodilation of the brachial artery. Mechanistically, nitroglycerin is bioactivated within the vascular wall, increasing the availability of nitric oxide at the level of the smooth muscle cell. The nitric oxide then activates soluble guanylate cyclase, elevates intracellular cyclic guanosine monophosphate, reduces intracellular calcium, and promotes smooth muscle relaxation and arterial dilation. Importantly, vasodilation caused

by nitroglycerin in human forearm resistance vessels seems to be largely independent of the vascular endothelium, supporting its use as an endothelium-independent test rather than an endothelial one (123-125).

A diminished NMD response thus indicates dysfunction outside the endothelium, at the level of vascular smooth muscle cells and/or the arterial wall's mechanical properties. This impairment has been linked to structural changes in the vasculature, alterations in smooth muscle biology, and increased atherosclerotic burden, suggesting that NMD is not just a control test for FMD but an informative marker of vascular wall pathology on its own (125, 126).

Endothelium-independent vasodilation testing can detect vascular smooth muscle dysfunction that may not be identified by endothelial function assessment alone (104, 105). Impaired nitrate-mediated dilation has been observed in the radial artery after transradial catheterization, suggesting that the procedure can affect not only endothelial responses but also overall radial vasoreactivity. Vascular injury related to the catheter may therefore have effects beyond the endothelium, possibly influencing smooth muscle responsiveness to external nitric oxide donors (127-129). Dawson et al (119) demonstrated that glyceryl trinitrate-mediated dilation of the radial artery decreased from 14.8% to 7.9% following sheath insertion, indicating that catheterization impairs not only endothelium-dependent responses but also smooth muscle reactivity to exogenous nitric oxide donors . Nakata et (120) al further showed that this vascular dysfunction persisted for at least six months when a 6 Fr sheath was used, particularly with longer procedure times. A reduced vasodilator response may, in turn, indicate structural remodeling of the arterial wall.

4.3 Haemodynamic Response and Assessment Method Limitations

RAS, which often occurs during transradial catheterization, is an exaggerated vasoconstrictive response of vascular smooth muscle to mechanical stimulation of the arterial wall. This phenomenon is caused by catheter manipulation, endothelial irritation, and the local release of vasoconstrictive mediators, and is recognized as a common procedural complication that can impact both patient comfort and procedural success (47, 101). Notably, pre-procedural radial artery FMD has been shown to predict the

occurrence of spasm during transradial coronary intervention, indicating a connection between baseline endothelial function and the likelihood of vasospasm (130).
Although RAS is usually transient and responds to pharmacological vasodilators, repeated or intense vasoconstrictive episodes may lead to changes in local vascular reactivity. While direct evidence of long-term changes in smooth muscle sensitivity after radial artery spasm is limited, vascular injury and repeated mechanical stress are known to affect smooth muscle behavior and regulation of vascular tone (47, 90). Whether recurrent spasm contributes independently to the risk of radial artery occlusion or to chronic impairment of vasomotor function remains an area requiring further investigation.

It is important to understand the limitations of different techniques used to measure radial artery function. Although it is non-invasive and accessible to nearly anyone, Doppler ultrasound depends heavily on the operator and the angle; any probe movement can cause significant errors in velocity measurements and, consequently, flow calculations. To ensure consistent FMD assessments, cuff inflation and deflation times, as well as image acquisition, must be strictly standardized. Measurements of endothelium-independent vasodilation are affected by the method and dose of drug administration. These methodological factors should be taken into account when interpreting functional data from various studies and when comparing results across different institutions.

Chapter 5: Structural Modifications

5.1 Intimal Hyperplasia

Intimal tears are often seen after transradial procedures, but usually disappear within 90 days (131). Despite the resolution of acute intimal disruptions, many patients develop intimal hyperplasia—a chronic vascular response triggered by inflammation and proliferation due to injury from sheath insertion and catheter manipulation. This represents the initial reaction to endothelial damage, involving smooth muscle cell proliferation, migration into the intima, and extracellular matrix buildup (26). Notably, Staniloae et al (84) reported that intimal hyperplasia was visible within 2-3 days after catheterization, indicating an immediate vascular response. Kamiya et al (80) documented an average of 46 days between preoperative transradial catheterization and radial artery harvesting for coronary artery bypass grafting, indicating that these structural changes persist over time. Kala et al (132) revealed a significant increase in radial artery intimal volume even 9 months after PCI. Additionally, Costa et al (64) found that intimal thickening appeared within 3 hours post-catheterization and remained at 30 days using high-resolution ultrasound. Overall, these studies suggest that intimal hyperplasia develops quickly after transradial interventions and persists over time, potentially affecting the artery's suitability as a bypass conduit.

The distribution of intimal hyperplasia in the radial artery varies; some studies do not identify a specific pattern along its length (80). Conversely, Staniloae et al (84) found that hyperplasia is more prominent in the distal radial artery, likely due to a mismatch between sheath and artery sizes. They also noted a statistical trend toward greater hyperplasia in the proximal artery. Additionally, multivariate linear regression showed that when the external sheath diameter exceeds the vessel diameter (ratio > 1), it is an independent predictor of increased intimal thickness (63). These results imply that although sheath insertion and catheter manipulation impact the entire vessel, injuries in the proximal segment may be less severe and more prone to partial recovery over time.

The distribution and severity of intimal hyperplasia after transradial intervention seem to be affected by procedural factors and the number of previous catheterizations. Di Vito et al (59) found no significant difference in intimal hyperplasia between first-time and repeat procedures. However, they used long hydrophilic-coated sheaths, which may have

lessened vessel trauma, though the extent of the protective effect remains unclear. They also noted that intimal hyperplasia was more prominent in the distal radial artery segment, suggesting this area may be naturally more prone to atherosclerosis and wall changes. Conversely, Yonetsu et al (60) reported significantly greater intimal thickening in repeat interventions at all radial artery sites, suggesting that repeated access causes cumulative vascular remodeling in both proximal and distal segments. Supporting this, Zhang et al (63) used very-high-frequency ultrasound, which showed significantly increased intimal thickness in patients undergoing multiple procedures ($P < 0.001$). Multivariate analysis confirmed repeated TRA as an independent predictor of post-procedural thickening, emphasizing that repeated trauma can accelerate structural vessel changes. These differing results underscore the influence of sheath choice on artery health and reinforce that while the distal radial artery is particularly at risk, repeated procedures worsen hyperplasia throughout the vessel.

The pathophysiological effects of neointimal hyperplasia extend beyond arterial wall thickening. Progressive neointimal hyperplasia can cause lumen narrowing, leading to reduced vessel diameter and increased resistance to blood flow. Additionally, neointimal hyperplasia can change the mechanical properties of the arterial wall, making it stiffer and less able to adapt to shifting haemodynamic conditions. Consequently, these structural alterations may impair the artery's adaptive capacity to changing hemodynamic conditions and adversely affect its suitability for repeated vascular access or use as a bypass graft.

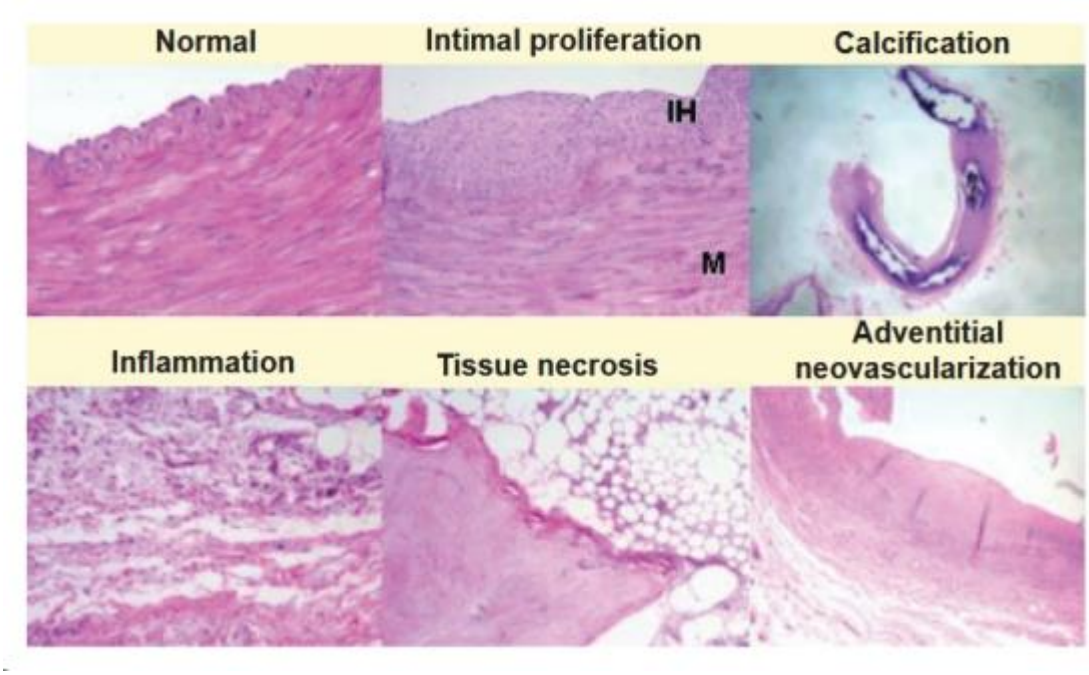

Figure 5.1. *Histopathological patterns of vascular injury and arterial wall remodelling. Characteristic histological changes observed in the arterial wall following mechanical trauma and chronic vascular remodelling. Normal vessel morphology is shown in the first panel. The second panel depicts intimal hyperplasia (IH), with thickening of the tunica intima and involvement of the media (M), consistent with smooth muscle cell migration and proliferation. Focal calcification, dense inflammatory infiltration, tissue necrosis, and adventitial neovascularisation are shown in subsequent panels (adapted from Staniloae et al., (84)).*

5.2 Medial and Adventitial Changes

In addition to intimal hyperplasia, the structural remodelling of the tunica media and tunica adventitia significantly contributes to the overall changes in the arterial wall after TRA (Figure 5.1). Transradial procedures cause widespread arterial wall remodeling, as evidenced by increased IMT. Tehrani et al (131) observed an average IMT increase of 0.07 mm at 90 days post-procedure, indicating persistent arterial wall thickening. IMT rise is a common response to transradial interventions; Zhang et al (63) found post-procedure thickening in 80.2% of first-time cases and 89.4% of repeat procedures ($P < 0.001$). These results are corroborated by Shen et al (67) and Yonetsu et al (60), who also reported significant medial thickening after repeat TRA, indicating that procedural repetition independently predicts arterial wall remodeling.

Besides repeated TRA, various patient and procedural factors are linked to IMT progression after transradial procedures. Shen et al (67) showed that a smaller baseline radial artery diameter and PCI were associated with higher post-procedural IMT. Likewise, Tehrani et al found that older age and diabetes independently predicted increased IMT in the forearm radial artery at 90 days. These results emphasize the complex, multifactorial process of arterial remodeling and the need for pre-procedural risk assessment to maintain radial artery health, especially in patients needing multiple interventions. They also observed no significant difference in the average change of forearm radial artery IMT between distal and conventional TRA, but suggested that distal TRA might limit future access options. This is because it increases IMT in both the distal and forearm segments, whereas conventional access primarily affects the forearm segment (131).

Although less commonly emphasized than intimal or medial damage, adventitial injury has also been observed following transradial catheterization, especially near the access site. Histopathological studies by Staniloae et al (84) showed that the distal ends of previously catheterized radial arteries had significantly higher adventitial inflammation (33.3% vs 0%; P = 0.01) and periarterial necrosis (26.7% vs 0%; P = 0.02) compared to arteries that were not catheterized. Additionally, within the same artery, the distal segment exhibited more inflammation than the proximal segment (33.3% vs 0%; P = 0.011), likely due to localized trauma from sheath-vessel diameter mismatch and repeated manipulation during puncture. This adventitial inflammation may influence the structural stability of the intima and media and could facilitate radial artery shrinkage via ongoing inflammatory signaling and vessel wall remodeling. The persistent thickening observed at the puncture site underscores the prolonged inflammatory and remodeling response of the adventitial layer and underscores the importance of including adventitial changes when considering radial artery remodeling after TRA.

5.3 Lumen Diameter Changes and Remodeling

Radial artery lumen changes in response to TRA involve both early and late adaptive processes. In contrast to acute and subacute changes, which are primarily related to functional mechanisms, chronic changes are accompanied by arterial structural

remodeling and carry significant clinical implications for vessel patency and long-term suitability for future access or grafting.

Aykan et al (133) found a statistically significant decrease in radial artery diameter at 1 month post-procedure, dropping from 2.97 ± 0.46 mm to 2.82 ± 0.51 mm ($P < 0.001$). This indicates that the radial artery remains impaired in the short term. Shen et al (67) observed a partial recovery, with the mean inner diameter increasing to 2.23 ± 0.41 mm. Nonetheless, it remained significantly smaller than at baseline ($P < 0.05$), suggesting that complete luminal restoration does not occur within the first month. Additionally, IMT remained elevated, suggesting that the partial lumen recovery may result from improved endothelial function and reduced local vasoconstriction rather than from structural normalization.

Building on this, Buturak et al (121) found that the reduction in radial artery diameter continues for at least 6 months, decreasing from 2.85 ± 0.44 mm before the procedure to 2.74 ± 0.42 mm ($P = 0.0001$). While the clinical significance of this ongoing narrowing is still unclear, these results suggest that the radial artery can undergo long-term changes after TRA. Supporting this, Fan et al (134) observed that the radial artery diameter remained notably smaller even one year post-TRA, dropping from 2.44 ± 0.38 mm to 2.30 ± 0.41 mm ($P = 0.002$), indicating persistent narrowing beyond the typical recovery period. In addition to these localized findings, Kala et al (132) performed serial volumetric analysis using OCT and reported a significant decrease in arterial lumen volume from 356.3 mm^3 at baseline to 304.7 mm^3 at 9 months ($P < 0.001$). Lumen volume decreased in 79.2% of patients, whereas 20.8% experienced no change or an increase, showing variability between individuals. These studies show that radial artery narrowing after TRA is not limited to a single measurement point; it persists over time, supporting the idea of lasting arterial changes. Importantly, even simple, short transradial procedures can impact the radial artery as part of a broader vascular response. The authors noted that unmeasured factors like genetics, catheter handling differences, or antiplatelet therapy variations could explain the differences seen in lumen response.

Although narrowing of the radial artery is often reported after transradial procedures, data from structured access protocols indicate that a careful pre-procedural assessment of vascular anatomy and appropriate sheath selection can help maintain vessel diameter and lessen long-term remodeling risk. In two studies using Doppler ultrasound for planning,

Yoon et al (135) and Koziński et al (136) found no significant reduction in radial artery diameter at 7 and 60 days post-procedure, respectively. Both studies systematically excluded patients with unsuitable radial artery anatomy before treatment, ensuring an optimal sheath-to-artery size match. Combining this personalized access approach with the use of only 5 Fr or 6 Fr sheaths may reduce mechanical stress on the vessel wall and help preserve radial artery structure. These findings highlight the importance of individualized radial access planning for reducing vascular injury and maintaining vessel patency over time.

5.4 Preventive Interventions

Understanding the potential mechanisms by which TRA causes structural and functional changes in the radial artery has led to preventive measures to reduce injury and maintain long-term patency. These measures can be categorized into technical interventions, which relate to procedural technique, and pharmacological interventions, which may address vasospasm, thrombosis, and inflammation.

One of the most valuable technical interventions that reduces mechanical damage to the radial artery is choosing the right sheath size. As mentioned earlier, the sheath-to-artery area ratio is a key factor in determining the severity of injury and the risk of complications. The current trend toward smaller sheath sizes - especially 5-Fr or 6-Fr, rather than 7-Fr or 8-Fr - has led to significant reductions in RAO rates (28, 29, 40). Smaller sheath sizes limit arterial overdistension, thereby reducing endothelial disruption and medial injury, which are key triggers of vascular changes. Ultrasound assessment of arterial diameter beforehand helps identify the optimal sheath size for each patient to keep the sheath-to-artery ratio at or below 1.0, when possible.

Distal TRA via the anatomical snuffbox has emerged as an alternative approach that may reduce injury to the proximal radial artery by moving the puncture site farther distally, thereby protecting the forearm arterial segment. As summarized in the recent review by Rivera et al., distal TRA is consistently linked with lower rates of RAO, shorter hemostasis times, and improved patient comfort, although it also has a higher crossover rate and increased technical complexity (137). These findings are supported by recent randomized controlled trials, including the CONDITION trial, which showed a

significant reduction in both early and long-term RAO with distal TRA compared to conventional TRA (0.8% vs 3.3% at 3 months), and the RAPID III trial, which confirmed lower early RAO rates and shorter hemostasis time in STEMI patients undergoing primary PCI (138, 139).

Furthermore, recent meta-analyses have consistently demonstrated that distal TRA is associated with reduced RAO, while also highlighting important trade-offs, including longer access times, greater puncture difficulty, and higher rates of access failure or crossover. Overall, these data suggest that although distal TRA provides meaningful vascular protection, its overall clinical benefit depends on the context and is influenced by operator experience, procedural complexity, and patient selection (140-142).

Pharmacological prevention of vascular injury during TRA mainly targets RAS, endothelial dysfunction, and thrombosis using vasodilatory and antithrombotic agents. The use of vasodilators has become a standard part of TRA, with calcium channel blockers and nitrates being the most commonly used agents.

Evidence from clinical studies and meta-analyses supports the effectiveness of these agents in reducing RAS. Oral pre-treatment with verapamil has been shown to significantly decrease radial artery spasm and vasoconstriction (143). Intra-arterial administration of verapamil, especially at a dose of 5 mg, or in combination with nitroglycerin, has been identified as one of the most effective pharmacological strategies to minimize RAS (144). These findings are supported by pooled data from randomized trials showing a significant reduction in vasospasm with verapamil across different dosing regimens, as well as with nitroglycerin administration (145). Alternative vasodilators have also been studied, with nicardipine demonstrating comparable efficacy to verapamil in preventing RAS, while causing significantly less procedural discomfort during intra-arterial administration (146). Furthermore, emerging evidence suggests that subcutaneous nitroglycerin may reduce both RAS and radial artery occlusion, although intra-arterial or topical methods have not consistently shown similar benefits (147). Overall, these data indicate that pharmacological vasodilation - particularly with calcium channel blockers alone or in combination with nitrates - plays a key role in reducing radial artery spasm, although the optimal agent, route of administration, and dosing approach remain under study.

In addition to vasodilators, proper anticoagulation during the procedure, such as using intravenous unfractionated heparin at doses exceeding 50 IU/kg, is a key preventive measure against thrombosis and the increased risk of radial artery occlusion. Another important technique is post-procedural hemostasis (41). Patent hemostasis - maintaining antegrade flow of the radial artery at the compression site - and the use of controlled-pressure devices are considered some of the best practices to minimize the risk of occlusion (30, 41, 148).

Beyond intraprocedural anticoagulation and vasodilators, pre-existing pharmacological therapy with statins or renin–angiotensin–aldosterone system (RAAS) inhibitors may confer additional vascular protection during transradial procedures, although direct evidence remains limited. A systematic review and dose-response meta-analysis of randomized controlled trials confirmed that statin therapy significantly improves brachial artery FMD (149). In the specific context of transradial catheterization, Honda et al (150) demonstrated in a study of 500 consecutive patients that the absence of statin pretreatment was an independent predictor of RAO on multivariate analysis (odds ratio 0.50, $p < 0.05$). This remains the only published clinical study directly linking statin use to a reduced risk of RAO, and no study has yet evaluated whether statin therapy preserves radial artery FMD or NMD after catheterization. Similarly, no clinical study has directly evaluated whether pre-existing RAAS inhibitor therapy attenuates radial artery functional impairment or reduces the risk of RAO after transradial procedures. The potential vasoprotective role of these commonly prescribed medications in the context of catheterization-induced radial artery injury represents an important evidence gap warranting prospective investigation with serial functional vascular assessments.

Compared to other regions, there is limited evidence supporting the long-term use of pharmacological treatments specifically aimed at protecting the radial artery after TRA. Currently, there is insufficient data to guide management strategies focused solely on maintaining arterial patency after the procedure. Therefore, preventing structural changes mainly depends on careful technique during procedures, appropriate peri-procedural anticoagulation, and effective haemostasis protocols.

Operator training and procedural technique are critical determinants of vascular complication rates during TRA. Increasing operator experience has been consistently associated with lower rates of RAO and access-site complications, reflecting the well-

described learning curve of the radial approach (151, 152). Procedural factors such as limiting the number of puncture attempts, performing atraumatic catheter manipulation, and minimizing sheath dwell time help reduce endothelial injury and mechanical trauma to the arterial wall. Furthermore, structured training and dedicated educational programs in radial techniques may improve procedural success and safety across operators with varying levels of experience.

Chapter 6: Pre-procedural Risk Stratification for Radial Artery Occlusion

6.1 The Rationale for Risk Assessment Before the Procedure

RAO is the most common significant complication of transradial catheterization. Although many cases are clinically silent and a proportion of occluded vessels undergo spontaneous recanalization during follow-up, a substantial number remain persistently occluded. This is clinically relevant because loss of radial artery patency may preclude future ipsilateral TRA and limit the use of the vessel as a conduit for coronary artery bypass grafting or arteriovenous fistula creation. These consequences are particularly important in patients with CAD, who frequently require repeat invasive procedures or subsequent surgical revascularization. For this reason, pre-procedural identification of patients at increased risk for RAO has considerable practical value. Recognition of established predictors of RAO may help operators tailor access-site strategies, optimize anticoagulation and hemostatic techniques, and implement preventive measures for patients at higher risk. It may also support more informed pre-procedural counselling regarding preservation of radial artery patency (29, 30, 75, 153, 154).

RAO is not equally distributed among patients undergoing TRA. In a recent systematic review and meta-analysis, Khalid et al. included 41 studies with 30,020 patients and reported an overall RAO incidence of 13%, with early RAO occurring in 14% of cases and late RAO in 10%. These findings highlight significant variation in RAO incidence across different studies and clinical settings and show that losing radial artery patency is not a rare event after an otherwise routine procedure. Therefore, identifying patients at higher risk is a crucial step toward improving preventive strategies and understanding the mechanisms behind post-procedural radial artery occlusion (28).

The risk factors for RAO can be broadly divided into patient-related and procedure-related elements. From a practical standpoint, patient-related factors may be seen as either non-modifiable baseline traits or potentially modifiable pre-procedural features, while procedure-related factors are primarily associated with the technical and pharmacological aspects of the intervention. This structure is helpful because RAO is a multifactorial event that results from the interaction between the patient's vascular profile and the specifics of

the procedure. Therefore, a thorough risk assessment should consider both categories to enable personalized preventive strategies.

6.2 Patient-Related Risk Factors

6.2.1 Female Sex

Female sex is among the most consistently reported non-modifiable predictors of RAO after TRA. This association is generally attributed to anatomical rather than sex-specific pathological differences since women tend to have smaller radial artery diameters and lower body surface area, leading to a less favorable artery-to-sheath ratio (155). Practically, a sheath size well tolerated in a larger vessel may cause greater endothelial injury, flow reduction, and thrombogenicity when used in a smaller radial artery. The proRadial study, a prospective registry from Germany that included 2,004 patients undergoing transradial coronary angiography, supports this concept. It reported a post-procedural RAO rate of 4.6%. In that study, female sex was the strongest independent predictor of RAO. In the subgroup undergoing PCI, female sex remained a major predictor (156). These findings are consistent with broader published evidence (41, 70, 71). In the recent meta-analysis by Khalid et al (28), female sex was identified as a predictor of overall RAO, with an estimated effect size of 0.22.

A plausible mechanistic explanation for the higher risk of RAO in women is the relationship between radial artery diameter, sheath outer diameter, and the sheath-to-artery ratio, rather than an inherently different vascular response. When the sheath-to-artery ratio approaches or exceeds 1, the artery experiences greater mechanical stretch and wall injury, which may lead to endothelial dysfunction, blood flow disturbances, vasospasm, and thrombus formation, thereby increasing the risk of subsequent occlusion (40, 153). This mechanism is especially relevant in women, who generally have smaller proximal and distal radial artery diameters, resulting in a less favorable artery-to-sheath ratio for any given sheath size. In a prospective multicenter study of 868 distal radial access procedures, Rivera et al. demonstrated that women had significantly smaller distal and proximal radial arteries than men and experienced arterial spasm more frequently, although overall procedural success remained high and did not differ significantly

between sexes (157). These findings support the idea that the increased risk observed in women is mostly due to true anatomical differences in vessel size.

6.2.2 Age and Radial Artery Diameter

Another patient-related predictor of RAO is age. In the recent meta-analysis by Khalid et al (28), meta-regression showed that increasing age was linked to a higher likelihood of early RAO after transradial procedures. These findings are consistent with an earlier meta-analysis by Rashid et al (30), which also identified older age as a predictor of RAO following TRA. A plausible explanation is that vascular aging involves structural and functional changes in the arterial wall, such as intimal thickening, increased stiffness, impaired endothelial repair, and reduced vasomotor adaptability. Additionally, older patients more often have coexisting cardiovascular risk factors and a higher burden of systemic vascular disease, both of which can further weaken vascular integrity and promote thrombotic occlusion after catheter-related injury. Therefore, the relationship between older age and RAO likely reflects both age-related vascular remodeling and the cumulative impact of related comorbidities (158).

One of the most important anatomical predictors of radial artery occlusion is the pre-procedural internal diameter of the radial artery (30, 69, 75). In a prospective ultrasound-based study involving 1,023 patients undergoing transradial coronary catheterization, Ullah et al (159) demonstrated that a larger radial artery diameter was independently protective against occlusion, with an odds ratio of 0.24. The same study also proposed practical diameter thresholds below which the risk of occlusion increased significantly: 2.42 mm for diagnostic coronary angiography performed with a 6 Fr sheath, 2.38 mm for percutaneous coronary intervention with a 6 Fr sheath, and 2.85 mm for procedures requiring a 7 Fr sheath. These findings offer quantitative support for the idea that pre-procedural ultrasound assessment of radial artery size can be useful when selecting sheath size and planning access strategies. Similar results have been reported by Xu et al (160), who found that smaller proximal and distal radial artery diameters, as well as a smaller cross-sectional area, were significantly associated with post-procedural radial artery occlusion, with radial artery diameter remaining an independent predictor in multivariable analysis. Overall, these data reinforce the view that vessel caliber is a key factor in determining radial artery patency after transradial procedures.

6.2.3 Body Mass Index and Body Surface Area

Several studies have linked lower body mass index and smaller body surface area with an increased incidence of RAO, indicating that patients with a smaller body habitus tend to have narrower-diameter radial arteries (154, 156, 161). Xu et al (160) demonstrated that decreased body weight and lower body mass index were significantly more prevalent among patients who developed proximal RAO following transradial catheterization. In a retrospective study by Xie et al (162) that developed nomogram-based prediction models for radial artery occlusion among 781 patients undergoing coronary angiography and PCI, a body mass index of 25 kg/m^2 or higher was identified as a protective factor against occlusion in both the overall population and the angiography subgroup. The apparent protection conferred by a higher body mass index is likely attributable to the positive correlation between body size and radial artery diameter, rather than any intrinsic vascular benefit. These findings further underscore the importance of pre-procedural vascular assessment, particularly in smaller-framed patients, to guide appropriate sheath size selection and optimize procedural outcomes.

6.2.4 Prior Transradial Catheterization

Previous catheterization through the ipsilateral radial artery is a non-modifiable risk factor for RAO, reflecting cumulative histological damage to the vessel wall from prior instrumentation (29, 154). Repeated sheath insertion and catheter manipulation can cause endothelial denudation, injury to vascular smooth muscle cells, and a local inflammatory response, ultimately promoting neointimal hyperplasia and progressive luminal narrowing (84, 132, 163). This arterial remodeling complicates subsequent procedures by reducing the effective arterial lumen and elevating the sheath-to-artery ratio to levels that may impair blood flow and favor thrombosis. In the RIVARAD trial, previous TRA was identified as one of three factors independently associated with 30-day radial artery occlusion, along with female sex and current smoking (164). These findings suggest that patients undergoing repeat transradial procedures through the same access site carry a significantly higher baseline risk of occlusion and warrant closer pre-procedural evaluation, including ultrasonographic assessment of radial artery patency and diameter.

6.2.5 Smoking

Strong evidence shows that smoking is an independent predictor of RAO and one of the few modifiable risk factors related to the patient. In the proRadial trial, active smoking was one of the top two independent predictors of RAO, alongside female sex. Active smokers had more than three times the risk compared to non-smokers in the diagnostic angiography subgroup (156, 164). The exact way smoking causes RAO in this context isn't fully understood, but it likely involves the known vascular effects of tobacco, such as endothelial dysfunction, increased platelet adhesiveness and aggregation, higher fibrinogen levels, and reduced natural fibrinolysis (165, 166). These changes create a prothrombotic environment that can lead to clot formation at the catheterization site, especially with endothelial damage from sheath insertion. Recognizing smoking as a modifiable risk factor has important clinical implications, emphasizing the need for aggressive preventive measures like proper periprocedural anticoagulation, patent hemostasis techniques, and smoking cessation counseling.

6.2.6 Diabetes Mellitus and Metabolic Factors

Diabetes mellitus is recognized as one of the non-modifiable, pre-procedural risk factors for RAO (167). Diabetic vasculopathy involves widespread endothelial dysfunction, decreased vasodilation, and accelerated intimal thickening, all of which can reduce the radial artery's tolerance to mechanical injury from sheath insertion and catheter movement (168, 169). Other traditional cardiovascular risk factors have also been linked to a higher risk of RAO after TRA. Munir et al (70) identified dyslipidemia as an independent predictor of RAO, emphasizing its role in post-procedural vascular outcomes. Supporting this, Wang et al (72) reported that patients with elevated low-density lipoprotein cholesterol had a significantly higher incidence of RAO, with multivariate analysis confirming it as an independent risk factor (OR: 3.799; 95%CI: 1.292–11.166; P = 0.015), highlighting the importance of lipid management in patients undergoing repeated TRA. Dwivedi et al (73) showed that chronic kidney disease, defined as an eGFR below 60 mL/minute/1.73 m^2, significantly increased RAO risk (OR: 1.504; 95%CI: 1.085–2.083; P = 0.014). Ay et al (103) reported hypertension as an independent risk factor for radial artery thrombosis, a key precursor to RAO. Whether optimal pre-procedural control of diabetes, hyperlipidaemia, and other metabolic disorders can

significantly reduce the risk of short-term RAO has not been evaluated in randomized trials. Nevertheless, these comorbidities should be considered when assessing individual patient risk and planning procedural strategy.

6.2.7 Peripheral Artery Disease

Peripheral arterial disease (PAD) is acknowledged as a non-modifiable, pre-procedural risk factor for RAO, although direct evidence of an independent association remains scarce (40, 41). PAD may also increase the risk of RAO through systemic vascular mechanisms. Because PAD is associated with widespread atherosclerosis, endothelial dysfunction, arterial stiffness, and a prothrombotic inflammatory state, affected patients may have reduced vascular resilience and a lower threshold for thrombotic occlusion following catheter-related endothelial injury. However, the evidence supporting PAD as a direct and independent predictor of RAO is less extensive than that for established anatomical and procedural factors (170, 171). Importantly, peripheral arterial disease also increases the clinical significance of RAO, as it may compromise collateral hand perfusion through the palmar arches and raise the risk of symptomatic hand ischaemia — a rare but serious complication (172). Therefore, although the independent contribution of peripheral arterial disease to occlusion risk has not yet been definitively measured, its presence should lead clinicians to conduct a thorough pre-procedural vascular assessment, including evaluation of collateral circulation, and to use all available preventive measures during and after the procedure.

6.2.8 Palmar Arch

A less commonly recognized but physiologically important predictor of RAO is the extent of collateral blood supply from the palmar arterial arch to the distal radial artery. Bigler et al examined the haemodynamic significance of collateral circulation from the palmar arch in 630 patients undergoing transradial catheterization. Using invasive haemodynamic measurements, they calculated a collateral flow index, defined as the ratio of mean radial artery pressure during manual proximal occlusion to the pressure measured when the artery was not occluded, with both values corrected for central venous pressure. After a mean follow-up of 301 days, 200 patients underwent Doppler ultrasound assessment; 8 (4%) showed signs of RAO, with 4 (2%) having complete occlusion. Patients with RAO had a significantly higher collateral flow index compared to those with

radial artery patency (0.900 ± 0.074 versus 0.801 ± 0.154, p = 0.006). These results suggest that well-developed collateral circulation can paradoxically act as a risk factor for persistent RAO rather than serve as a protective mechanism. Mechanistically, strong collateral flow from the palmar arch may generate enough retrograde pressure to maintain distal perfusion even without antegrade radial flow, thus reducing the hemodynamic drive for spontaneous thrombus recanalization during the early post-procedural period (173).

In the same study, women exhibited a significantly higher collateral flow index than men (0.849 versus 0.797, p < 0.001), providing a possible additional mechanistic explanation for the higher rate of RAO observed in women beyond the well-established influence of smaller vessel diameter. This observation also offers a physiological rationale for the efficacy of prophylactic ipsilateral ulnar artery compression during hemostasis: by temporarily reducing collateral inflow from the ulnar artery through the palmar arch, this maneuver diminishes retrograde pressure in the distal radial artery, thereby promoting antegrade flow through the access site and facilitating thrombus clearance - a mechanism that aligns with the significant reduction in RAO demonstrated in the PROPHET-II trial (174).

6.3 Procedure-Related Risk Factors

6.3.1 Sheath Size and Sheath-to-Artery Ratio

Sheath size and the sheath-to-artery ratio are among the most extensively studied procedural variables in predicting RAO. A sheath-to-artery ratio nearing or exceeding one—indicating that the external diameter of the sheath matches or exceeds the internal diameter of the radial artery—is consistently recognized as a significant risk factor, as it causes near-complete interruption of antegrade blood flow and maximum endothelial contact with the sheath surface (30, 40, 167, 175). However, the relationship between sheath size and occlusion is more complex than a simple linear association. In a recent study by Ullah et al. involving 2,073 patients, a 7 French sheath was identified as an independent predictor of radial artery occlusion on multivariate analysis, compared with a 6 Fr sheath, with an odds ratio of 4.61 (95% CI 2.16–9.94, p < 0.001) (159). Conversely,

a meta-analysis comparing 5 Fr and 6 Fr systems found no statistically significant difference in occlusion rates between the two sizes, and a separate study reported no long-term increase in occlusion with 7 French compared to 6 French sheaths (134, 176). These seemingly conflicting findings suggest that the absolute sheath size may be less important than its ratio to the individual patient's radial artery diameter. The practical takeaway is that operators should use the smallest sheath size that allows the safe completion of the planned procedure, with pre-procedural ultrasound measurement of the radial artery guiding this choice, especially in patients with borderline vessel diameter. The sheathless technique offers an additional way to reduce the external profile of the access system: in a randomized trial of 600 patients, a 6.5 Fr sheathless guide catheter showed a lower combined rate of occlusion and spasm compared to a 6 Fr thin-walled sheath, although the crude rates of occlusion alone did not differ significantly (177).

6.3.2 Number of Puncture Attempts

Multiple puncture attempts during radial artery cannulation increase the risk of RAO through repeated endothelial trauma, arterial spasm, and the development of local prothrombotic conditions at the access site (29, 167). This association has been demonstrated across various clinical settings. In a predictive model developed from 248 elderly patients with cerebrovascular accident undergoing transradial cerebral angiography, Wang et al identified the number of radial artery punctures as one of seven independent risk factors for vascular complications in a multivariate logistic regression analysis (178). In a similar study, Xie et al confirmed that multiple punctures were among the most consistent predictors of RAO across both coronary angiography and PCI subgroups (162). Additionally, Dwivedi et al (73) found that repeated punctures were significantly associated with an increased incidence of RAO, likely due to compounded vascular trauma and increased arterial spasm. From a practical perspective, the use of real-time ultrasound guidance during radial artery cannulation has been shown to improve first-attempt success rates and reduce the number of puncture attempts needed for access (179). Adopting ultrasound-guided puncture as a standard practice, especially in patients with non-palpable or small-diameter radial arteries, is a logical and evidence-based strategy to minimize procedural vascular trauma.

6.3.3 Intraoperative Anticoagulation

Adequate intraprocedural anticoagulation represents one of the most important modifiable procedural risk factors for RAO, supported by high-quality evidence. In the multicenter randomized SPIRIT OF ARTEMIS trial, high-dose heparin (100 IU/kg) reduced the rate of RAO to 3.0% compared with 8.1% in the standard-dose group (50 IU/kg), corresponding to an odds ratio of 0.35 (95% CI 0.22–0.55, $p < 0.001$), without a significant increase in bleeding complications (180). The ARTEMIS meta-analysis, encompassing 112 studies with over 46,000 patients, further corroborated the finding that low-dose heparin was associated with significantly higher occlusion rates than high-dose regimens (181). In a separate clinical context, Wang and colleagues identified intraoperative heparin dosage as an independent predictor of vascular complications in 248 elderly patients undergoing transradial cerebral angiography, reinforcing the generalizability of this association beyond coronary procedures (178).

Recently, direct oral anticoagulants have been studied as a pharmacological strategy to prevent RAO. A meta-analysis by Alsubaiei et al, synthesizing data from four randomized controlled trials with 970 patients, showed that short-term post-procedure use of direct oral anticoagulants significantly lowered 30-day occlusion rates compared to no treatment (relative risk 0.49, 95% CI 0.31–0.79, $p < 0.001$) (182). The evidence mainly comes from the RIVARAD and RESTORE trials, both of which used rivaroxaban 10 mg daily for seven days (164, 183). Importantly, the same meta-analysis found that direct oral anticoagulants (DOACs) were not effective in resolving already existing occlusions. These findings suggest that short-term direct oral anticoagulants could be a promising additional pharmacological approach for preventing radial artery occlusion in high-risk patients, although more well-powered trials are needed before this method can be widely implemented in clinical practice.

6.3.4 Hemostasis Technique and Duration

The method and duration of post-procedural hemostasis significantly influence the risk of RAO. Occlusive hemostasis, in which the compression device completely arrests antegrade blood flow in the radial artery, promotes thrombus formation by creating a state of arterial stasis at the access site. Patent hemostasis - defined as compression adjusted to maintain hemostasis while preserving measurable antegrade radial flow - has been shown

to significantly reduce the incidence of occlusion. In the landmark PROPHET trial, patients randomized to a patent hemostasis protocol demonstrated a 59% reduction in RAO at 24 hours and a 75% reduction at 30 days compared with conventional occlusive compression (148). The addition of prophylactic ipsilateral ulnar artery compression during patent hemostasis further reduced 30-day occlusion from 3.0% to 0.9% in the PROPHET-II trial (174). The choice of compression device also appears to matter: Wang et al identified the mode of pressure hemostasis as one of the strongest independent predictors of vascular complications in elderly patients undergoing transradial cerebral angiography, with non-pneumatic compression methods associated with significantly higher complication rates (178). The Transradial Band Device, when used with optimized air volume/pressure, maintains an essential balance between hemostasis and patient comfort without increasing the risk of radial artery complications (184). Compression duration is equally important. A mixed-treatment-comparison meta-analysis of 10 randomized trials involving 4,911 patients evaluated four hemostasis duration categories and concluded that a compression duration of approximately 2 hours offers the best balance between efficacy in preventing radial artery occlusion and safety with respect to access-site hematoma and rebleeding. Durations shorter than 90 minutes ranked highest for occlusion prevention alone, but were associated with a significantly higher risk of access-site hematoma, whereas durations of 2 to 4 hours increased the risk of occlusion without additional hemostatic benefit (185). These findings support the use of dedicated pneumatic compression devices with patent hemostasis protocols as a standard, aiming for about 2 hours of compression to balance effectiveness and safety.

6.3.5 Procedure Type and Urgency

The type and urgency of catheterization are additional procedural risk factors for RAO. Patients undergoing diagnostic coronary angiography usually have shorter procedures but generally receive lower doses of anticoagulation than those undergoing PCI. Paradoxically, this leads to consistently higher rates of RAO in the diagnostic angiography group. In a large meta-analysis by Rashid et al, the occlusion rate was 8.8% following diagnostic angiography compared with 4.5% after PCI, a difference attributed to the more intensive anticoagulation and antiplatelet regimens used during interventional procedures (30). This finding was also supported by Ullah et al., who reported occlusion rates of 14.3% in the diagnostic angiography group versus 6.6% in the PCI group, despite

using the same sheath size (159). Procedural urgency also appears to influence complication rates. In the elderly cerebral angiography cohort studied by Wang et al, the timing of surgery was identified as an independent predictor of vascular complications, with emergency procedures carrying a significantly higher risk than elective interventions, possibly because of reduced procedural control and limited patient preparation in the acute setting. In the same cohort, longer procedure duration was independently associated with an increased risk of complications, a finding consistent with studies in coronary catheterization where prolonged sheath dwell time has been identified as an independent predictor of occlusion (41, 167, 178). These observations highlight the importance of ensuring adequate anticoagulation in all transradial procedures - including purely diagnostic ones - and of minimizing procedural duration where possible.

6.4 Prediction Models and Clinical Implications

Recognition that multiple patient- and procedure-related factors independently contribute to RAO risk has led to the development of multivariate prediction models that integrate these variables into clinically applicable risk estimates. Xie et al developed prediction models for patients undergoing coronary angiography, PCI, and the combined cohort, demonstrating discriminatory performance with areas under the receiver operating characteristic curve of 0.979, 0.921, and 0.951, respectively. The independent predictors varied by procedure type: in the coronary angiography subgroup, female sex, elevated creatine kinase, multiple puncture attempts, RAS, and puncture-site pain were identified as risk factors, with Body Mass Index (BMI) ≥25 kg/m² emerging as protective; in the PCI subgroup, heart failure, multiple punctures, and puncture-site pain were the main predictors; and in the overall population, smoking, heart failure, high CHA_2DS_2VASc score, multiple punctures, RAS, and puncture site pain, with BMI ≥25 kg/m² and elevated creatinine as protective factors. (162). A comparable prediction tool was developed by Wang et al. for elderly patients undergoing cerebral angiography via transradial access, incorporating intraoperative heparin dose, number of punctures, timing and duration of the procedure, method of hemostasis, compression time, and postoperative HAS-BLED score. This model achieved an area under the curve of 0.868 in the training set and 0.822 in the validation set (178). Although these nomograms represent a promising step towards individualized risk stratification, both were derived from single-center retrospective

cohorts and require prospective, multicenter external validation before clinical implementation can be recommended.

Another score studied in this context is the CHA_2DS_2-VASc score, originally developed to estimate stroke risk in patients with atrial fibrillation. In a prospective study of 500 patients undergoing transradial coronary catheterization, Nadir and colleagues demonstrated that higher CHA_2DS_2-VASc scores were significantly associated with increased rates of RAO, with a score of ≥3 identified as a predictive threshold (74). Similarly, a higher CHA_2DS_2-VASc score remained an independent predictor in the overall population prediction model developed by Xie et al (162). The HAS-BLED score has also been integrated into recommended management algorithms for patients with established RAO, as proposed by Didagelos et al, to help determine the intensity and safety of anticoagulation therapy (186). Conceptually, pre-procedural assessment of the HAS-BLED score can also help identify patients who might benefit from more aggressive preventive anticoagulation without facing unacceptable bleeding risks, although this use has not been directly tested in prospective studies. Compared to complex multivariate nomograms, these simple clinical scores offer the advantage of being easier to use in routine clinical practice, providing a practical way to translate evidence-based risk assessment into everyday procedural decisions.

The evidence examined in this chapter provides the basis for a structured pre-procedural risk assessment that can meaningfully reduce the incidence of RAO. Before any transradial procedure, the operator should consider the patient's sex, age, body habitus, smoking status, previous ipsilateral catheterization history, and relevant comorbidities. Pre-procedural ultrasound measurement of the radial artery diameter is a rapid assessment - requiring only a few minutes - that provides immediate, objective information to guide sheath selection and procedural planning. Ullah et al (159) identified procedure-specific diameter cutoff values for predicting radial artery occlusion: 2.42 mm for 6 Fr diagnostic coronary angiography, 2.38 mm for 6 Fr PCI, and 2.85 mm for 7 Fr PCI. Patients with a radial artery diameter below these thresholds - indicating a sheath-to-artery ratio likely exceeding 1 - should be considered for a smaller sheath size, a sheathless guiding catheter technique, or an alternative access strategy such as the contralateral radial artery or a distal radial approach via the anatomical snuffbox, which may preserve forearm radial artery patency even if local occlusion occurs at the access site.

The distal transradial technique has been validated as an evidence-based alternative to conventional proximal TRA, primarily by reducing the risk of forearm RAO. In the CONDITION trial, a prospective randomized study of 726 patients, the incidence of long-term RAO at three months was significantly lower with the distal approach compared with conventional TRA (0.8% versus 3.3%; risk ratio 0.25, 95% CI 0.07–0.88, $p = 0.02$), with the 24-hour occlusion rate also significantly reduced (2.5% versus 6.7%, $p < 0.01$) (138). Additionally, a prospective observational study by Xu et al (160) demonstrated a significantly lower early occlusion rate with the distal approach (3.8% versus 12.7% with the conventional route). However, the evidence is not entirely consistent: in the RAPID trial (187), distal TRA did not reduce RAO compared with conventional access when analyzed independently from anticoagulation strategy, suggesting that the benefit of the distal approach may be modulated by the use of intraprocedural anticoagulation.

Additional preventive measures should be systematically applied to patients identified as at elevated risk of RAO. These include administration of high-dose intraprocedural heparin (no less than 5,000 IU or 50–100 IU/kg), intra-arterial prophylaxis with vasodilators, maintenance of patent hemostasis using a dedicated pneumatic compression device for an optimal duration of approximately two hours to balance efficacy and safety, and prophylactic ipsilateral ulnar artery compression during the post-procedural hemostasis period. In patients with specific high-risk features - such as female sex, small radial artery diameter, active smoking, or previous ipsilateral access - a seven-day course of low-dose oral anticoagulation (e.g., rivaroxaban 10 mg daily) represents an additional pharmacological strategy supported by randomized evidence (164, 183). The rationale for early post-procedural anticoagulation is further strengthened by evidence from the treatment setting: a recent meta-analysis of six studies encompassing 398 patients with confirmed RAO demonstrated that anticoagulation therapy increased the likelihood of arterial recanalization sevenfold compared with no treatment (pooled odds ratio 7.36, 95% CI 3.82–14.17, $p < 0.001$), without any reported major bleeding events (188). These findings underscore the importance of both detecting established radial artery occlusion through routine post-procedural assessment and considering preventive pharmacological intervention in patients with an unfavourable risk profile.

Integrating these measures into a logical, patient-centered pre-procedural protocol is a sensible use of the existing evidence. RAO is not accidental but a predictable result caused

by identifiable and often modifiable risk factors. The best way to maintain radial artery patency and preserve the long-term health of patients undergoing transradial catheterization is to identify these factors in advance and adjust the technical approach accordingly.

SPECIAL SECTION

Chapter 7: Aims and Research Hypotheses

7.1 Background, Rationale and Clinical Significance

TRA has increasingly replaced the transfemoral technique in most high-volume catheterization centers worldwide (6-8). It has been shown to be more effective in reducing mortality and major bleeding, preventing vascular complications, shortening hospital stays, and improving patient comfort (9, 10). As a result, the radial artery is being used more frequently as an access site in a broader and more diverse patient population, including those with acute coronary syndromes, chronic total occlusions, older adults, diabetics, and patients with pre-existing vascular disease (11, 12). This change in epidemiology has made understanding radial artery injury caused by the procedure not just an academic concern but also a clinically important issue.

The radial artery is a muscular conduit vessel with a small diameter, which in adult populations in Europe is approximately 2.3-2.5 mm in mean internal diameter. Its wall consists of an intima with a functional endothelium, a media with vascular smooth muscle cells, and an outer layer, the adventitia, containing the vasa vasorum and autonomic nerve fibers. These layers work together to regulate vascular tone, thromboresistance, and luminal homeostasis. Mechanical insertion of an arterial sheath, guidewire manipulation, and ongoing contact of intravascular devices with the endothelial surface during catheterization cause direct mechanical injuries to all three layers. However, this injury is not solely mechanical; it triggers a cascade of endothelial activation, inflammatory signaling, smooth muscle dysfunction, and hemodynamic changes that may persist long after the procedure.

FMD and NMD are widely accepted non-invasive measures of endothelium-dependent and endothelium-independent vasodilation, respectively. A decrease in FMD indicates endothelial dysfunction and reduced nitric oxide bioavailability, while a decrease in NMD suggests impaired smooth muscle responsiveness to exogenous nitric oxide, implying injury or phenotypic modulation in the tunica media. Both parameters can be measured serially using high-resolution Doppler ultrasound without additional risk to the patient,

making them ideal for evaluating catheterization-induced vascular injury. FMD and NMD can be assessed alongside Doppler flow indices—including PSV, RI, PI, velocity–time integral (VTI), and per-beat blood flow volume—to offer a comprehensive evaluation of the radial artery at three key time points: before the procedure, 24 hours after catheterization, and at one-month follow-up.

Although the literature on structural changes in the radial artery after transradial catheterization has expanded considerably, functional changes have received comparatively less attention. Although some published studies have assessed FMD or NMD after catheterization, few have evaluated both parameters across multiple post-procedural time points or integrated Doppler hemodynamic indices into the assessment. As a result, the temporal relationship between early vascular and hemodynamic impairment observed at 24 hours and the degree of recovery at one month remains poorly characterized. Moreover, the patient-specific, vascular and hemodynamic factors that predict the severity of functional impairment have not been systematically identified, despite their potential relevance to pre-procedural risk assessment and the development of targeted vascular protective strategies. Finally, it remains uncertain whether RAO, although frequently clinically silent and sometimes transient, is associated with distinct patterns of structural or functional vascular change when evaluated prospectively through systematic ultrasound follow-up.

The current research aimed to systematically address these gaps. Prospective enrollment of a consecutive group of 94 patients who underwent elective transradial cardiac catheterization at a single center was conducted. All patients received standardized Doppler ultrasound and vasoreactivity assessments at baseline, 24 hours after the procedure, and 1 month after, enabling within-patient comparisons across the spectrum of injury and recovery. The analysis was predefined around three main areas: describing the temporal changes in all measured vascular parameters; identifying patient subgroups that are differentially susceptible to functional damage; and evaluating baseline vascular parameters as predictors of post-procedural functional outcomes.

7.2 Aims of the Study

The primary aim of the research was to describe temporal changes in endothelial and vascular smooth muscle function of the radial artery, as well as in its structure and hemodynamic characteristics, after transradial cardiac catheterization at three predetermined time points, as assessed by non-invasive Doppler ultrasound and vasoreactivity. The secondary aim was to identify patient-specific variables that correlate with the degree of post-procedural functional impairment. The third aim was to determine whether baseline vasoreactivity and Doppler indices could predict the extent of functional damage at 24 hours and 1 month, with the aim of improving risk stratification during the pre-procedural phase.

These aims were operationalized through three distinct yet interconnected analytical objectives, all aimed at clarifying the functional, structural, and hemodynamic biology of the radial artery in the context of TRA. The first objective examines the temporal course of vascular injury, assessing whether functional, structural, and hemodynamic changes observed at 24 hours are statistically and clinically meaningful, their direction and magnitude, and the extent of recovery after one month. The second objective explores variability in the vascular response by assessing whether clinical factors - such as age, sex, diabetes mellitus, hypertension, renal function, and concurrent medication use - are associated with differences in post-procedural functional outcomes. The third objective focuses on predictability, evaluating whether baseline FMD, NMD, and Doppler-derived measures can help identify patients at higher risk of prolonged functional impairment.

The study also intended to provide a solid statistical basis for the conclusions. All continuous variables were first assessed for normality prior to statistical analysis, and the data distribution determined whether to use parametric or non-parametric tests. Within-individual temporal comparisons were performed using the Friedman test as a global test for each vascular parameter across the three measurement time points. Where a significant overall effect was identified, post-hoc pairwise comparisons were conducted using paired Wilcoxon signed-rank tests. The Mann-Whitney U test and the Kruskal-Wallis test were used to compare groups as appropriate. Associations between continuous variables were measured using Spearman rank correlation. In addition, receiver operating characteristic (ROC) curve analysis was used to evaluate the discriminative ability of baseline

parameters to predict a significant post-procedural decline in FMD. Statistical analyses were performed using IBM SPSS Statistics (version 27, IBM Corp., Armonk, NY, USA).

7.3 Research Hypotheses

7.3.1 Objective 1: Temporal Changes in Radial Artery Function and Hemodynamic Parameters

The first set of hypotheses concerned the direction and statistical significance of functional changes across the three measurement time points. It was hypothesized that both FMD and NMD would decrease significantly at 24 hours following transradial catheterization, reflecting acute vascular injury affecting both endothelial function and vascular smooth muscle responsiveness. Given the mechanical effects of sheath insertion and catheter manipulation on the arterial wall, it was further hypothesized that smooth muscle function would not be spared from injury; accordingly, the relative magnitude of change in NMD compared with FMD was explored to determine whether endothelial and smooth muscle dysfunction occur in parallel or to differing degrees. Partial but incomplete functional recovery was anticipated at one month, suggesting that a proportion of vascular impairment persists beyond the acute post-procedural phase.

Furthermore, these functional changes were expected to be accompanied by corresponding changes in Doppler hemodynamic parameters. Specifically, a decrease in baseline PSV and an increase in RI at 24 hours were hypothesized to reflect increased vascular resistance due to local edema, vasospasm, or temporary arterial wall stiffening. Hemodynamic flow parameters depend primarily on vessel geometry and tone, which may recover relatively quickly once edema and spasm resolve, whereas FMD and NMD depend on the biological integrity of the endothelium and smooth muscle, which require cellular regeneration and may take longer to restore. Therefore, at one month, Doppler hemodynamic parameters were expected to show greater reversibility than vasoreactivity indices, suggesting that hemodynamic recovery may precede the restoration of endothelial and smooth muscle function.

7.3.2 Objective 2: Subgroup Analysis and Predictors of Functional Damage at 24 hours

The second set of hypotheses examined differences in patients baseline characteristics associated with the extent of functional impairment after the procedure. It was hypothesized that patients with diabetes mellitus would show greater reductions in both FMD and NMD at 24 hours compared to non-diabetic patients, consistent with the well-documented endothelial dysfunction, increased oxidative stress, and impaired vascular repair mechanisms associated with diabetes. Similarly, greater post-procedural impairment of vasoreactivity was expected in patients with arterial hypertension, reflecting the structural and functional vascular changes with reduced nitric oxide bioavailability typical of hypertensive arteriopathy. Regarding sex differences, it was hypothesized that female patients would experience greater functional impairment than male patients, potentially due to a smaller radial artery diameter, a higher sheath-to-artery ratio often seen in women, and a higher collateral flow index, which may impede spontaneous restoration of antegrade flow following catheterization. Additionally, larger post-procedural reductions were expected to be associated with older age and lower eGFR, in line with age-related structural and functional changes in the arterial wall, including reduced vasomotor adaptability, as well as the vascular effects of chronic kidney disease. Finally, it was hypothesized that patients receiving statin therapy would demonstrate smaller reductions in FMD following the procedure, reflecting statin-mediated upregulation of endothelial nitric oxide synthase and anti-inflammatory effects on the vascular wall. A similar protective effect was anticipated in patients receiving RAAS inhibitors, through reduction of angiotensin II-mediated oxidative stress and enhancement of nitric oxide bioavailability.

7.3.3 Objective 3: Predictive Value of Baseline Parameters for Post-Procedural Functional Outcome

The third group of hypotheses focused on the predictive value of baseline vascular measurements for post-procedural functional outcomes. It was hypothesized that the magnitude of FMD and NMD reduction would vary according to patient-specific baseline vascular characteristics. In particular, baseline anatomical and hemodynamic parameters — including radial artery diameter, resting PSV, and RI) — were hypothesized to be

associated with the extent of post-procedural functional impairment. Regarding Doppler hemodynamic parameters, it was hypothesized that lower baseline PSV and lower RI, reflecting more favorable vascular conditions and lower peripheral vascular resistance, would be associated with smaller post-procedural functional declines. Finally, ROC analysis was expected to demonstrate that baseline vascular parameters obtainable from a single pre-procedural Doppler examination have clinically meaningful discriminative ability to identify patients at risk of significant post-procedural functional impairment. Establishing such predictive relationships would provide a mechanistic and empirical basis for integrating pre-procedural vascular assessment into clinical risk stratification prior to transradial catheterization.

These hypotheses collectively form a mechanistic model in which the pre-procedural parameters of the radial artery, together with patient-specific clinical characteristics, determine both the severity of acute catheterization-induced injury and the subsequent recovery trajectory. If confirmed, these findings would support incorporating baseline vascular assessment into pre-procedural risk stratification, enabling identification of high-risk patients who may benefit from targeted protective strategies such as smaller sheath selection, enhanced pharmacological prophylaxis, or alternative access approaches. Validating these hypotheses in a prospectively recruited, protocol-driven cohort using serial multimodal vascular assessments constitutes the principal scientific contribution of this thesis

Chapter 8: Materials and Methods

8.1 Study Design and Population

It was a prospective, single-center, observational study conducted at the Department of Cardiology at the University Hospital of Ioannina. The research participants were recruited sequentially throughout the study and were evaluated at three time points for radial artery structure, function, and hemodynamic parameters: pre-transradial catheterization, 24 hours post-procedure, and at one-month follow-up. The research was observational; it did not involve alterations to the standard protocol for the procedures due to enrolment, and the decision on treatment remained at the discretion of the interventional cardiologist treating the patient.

The research was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board of the University Hospital of Ioannina provided ethical approval before enrolment (1/6-4-2021, T. 284). Written informed consent was obtained from all participants before any study-specific assessment was performed. No personal information about patients was disclosed, and no identifiable personal details about participants are included in any part of this report. Participation in the study was entirely voluntary, and patients were assured that their involvement would not affect their standard clinical care in any way.

Inclusion Criteria

The inclusion criteria were as follows: patients had to be 18 years or older, be referred to elective coronary angiography or PCI by TRA, have a palpable radial pulse at the intended access site, be able to provide written informed consent, and attend the one-month follow-up visit.

Exclusion Criteria

Patients were excluded if any of the following conditions were present: a non-palpable radial pulse on physical examination; a history of previous transradial catheterization on the ipsilateral radial artery, as prior catheterization can cause persistent endothelial dysfunction and structural remodelling that may not fully resolve and would confound baseline vascular measurements; a known anatomical radial artery anomaly or documented prior RAO; hemodynamic instability requiring emergency intervention;

inability to cooperate with the ultrasound examination; or unwillingness to provide written consent. Patients presenting with acute coronary syndromes requiring urgent catheterization - including STEMI treated with primary PCI and non–ST-elevation myocardial infarction (NSTEMI) - were also excluded, as the time constraints of emergency management precluded the performance of pre-procedural vascular assessment according to the study protocol.

Study Cohort

Ninety-four patients completed all three assessment time points and formed the final study cohort. The cohort included patients undergoing both diagnostic coronary angiography and PCI, reflecting the spectrum of elective procedures routinely performed at the study center. Baseline clinical characteristics, including age, sex, comorbidities, current medications, hematological and biochemical parameters, and the indication and findings of the coronary procedure, were systematically documented for all participants.

8.2 Procedural Protocol and Ultrasound Assessment

Transradial procedures were performed by experienced interventional cardiologists in accordance with the center's standard protocol. The right radial artery was used in all cases. Arterial puncture was performed with a palpation-guided 20-gauge needle. After confirming arterial blood return, a 0.025-inch guidewire was inserted, and a hydrophilic-coated arterial sheath was positioned using the Seldinger technique. The sheath size was chosen based on the arterial diameter measured by pre-procedural ultrasound, aiming to keep the sheath outer diameter-to-artery inner diameter ratio at or below 1.0 whenever possible. In all patients, a 6 Fr introducer sheath (outer diameter 2.52 mm) was used.

An intra-arterial antispastic cocktail of verapamil and nitroglycerin was administered through the sheath immediately after sheath insertion to prevent arterial RAS and protect endothelial function during the procedure. Unfractionated heparin was given intravenously at a minimum dose of 50 units per kilogram of body weight, with additional boluses as needed to maintain an activated clotting time above 200 seconds throughout the interventional procedure. Patients on oral anticoagulation were exclusively treated with DOACs; vitamin K antagonists were not used. As per standard peri-procedural protocols, the final DOAC dose was given at least 24 hours prior to the procedure,

ensuring that the 24-hour post-procedure assessment occurred roughly 48 hours after the last dose.

After completing the procedure, the arterial sheath was removed, and hemostasis was achieved using a compression device placed over the puncture site. The targeted hemostasis technique was patent hemostasis, which involves maintaining antegrade flow in the radial artery during compression, verified by the reverse Barbeau test. The compression device was gradually deflated over 2 to 4 hours after sheath removal, and the patient was monitored for access-site complications before discharge the following day.

All ultrasound assessments were performed by a single experienced operator using a high-resolution linear vascular transducer (10–15 MHz). Patients were examined in the supine position with the right arm extended and comfortably supported on a padded surface, in a room maintained at a controlled ambient temperature of 22–24 °C. A resting baseline period of at least ten minutes was allowed before each assessment to ensure hemodynamic stability and normalization of peripheral vascular tone. Patients were instructed to abstain from caffeine, tobacco, and vigorous physical exertion for at least 4 hours prior to each assessment, given feasibility constraints in the clinical setting.

The radial artery was also visualized approximately three to four centimeters proximal to the styloid process of the radius and at the same site across all three time points. First, the vessel was checked in B-mode to measure the lumen diameter, followed by interrogation in pulsed-wave Doppler mode, with the sample volume centered in the arterial lumen and the insonation angle corrected to 60 degrees or less. Any measurements were averaged over at least three cardiac cycles.

Baseline Doppler Parameters

The parameters that were measured at rest, in the absence of a vasoreactivity stimulus, included arterial lumen diameter (cm); PSV (cm/s); EDV (cm/s); mean velocity (cm/s); RI; PI; VTI (cm) which was the area under the spectral Doppler waveform over one cardiac cycle; and estimated per-beat blood flow volume (mL/beat), calculated as the

product of VTI and the cross-sectional area of the artery derived from the measured diameter.

8.3 Vasoreactivity Tests and Outcome Measures

8.3.1 FMD — Endothelium-Dependent Vasodilation

FMD was assessed in accordance with the 2019 expert consensus recommendations on the assessment of flow-mediated dilation in humans (113). A pneumatic cuff was placed on the forearm proximal to the ultrasound imaging site. After all baseline Doppler parameters were recorded, the cuff was inflated to 200 mmHg for five minutes to induce distal limb ischemia. Reactive hyperemia was immediately induced in the forearm circulation after cuff deflation, causing a brief but significant increase in blood flow through the radial artery. This increase in shear stress on the arterial wall stimulates endothelial nitric oxide synthase activity, resulting in nitric oxide–mediated, endothelium-dependent dilation of the radial artery.

Ultrasound imaging of the radial artery was performed continuously throughout the hyperemic period. The peak shear stress stimulus was captured during the first 30 to 60 seconds following cuff deflation through pulsed-wave Doppler interrogation. The peak arterial diameter, which typically occurs later in the hyperemic response, was recorded at 60 to 90 seconds post-deflation. FMD was calculated as the percentage change in arterial diameter from baseline to peak hyperemic diameter, using the formula:

FMD (%) = (peak hyperemic diameter − baseline diameter) / baseline diameter × 100

During the hyperemic phase, the full set of Doppler hemodynamic parameters was also recorded, including PSV, EDV, mean velocity, RI, PI, VTI, and estimated per-beat blood flow volume.

8.3.2 NMD — Endothelium-Independent Vasodilation

Endothelium-independent vasodilation was assessed using sublingual administration of 400 μg glyceryl trinitrate (nitroglycerin). Glyceryl trinitrate acts as an exogenous nitric oxide donor that induces vascular smooth muscle relaxation independently of endothelial function, thereby allowing assessment of vascular smooth muscle responsiveness in

isolation from endothelial integrity. A resting period of at least 15 minutes was allowed following completion of the FMD test to permit arterial diameter to return to baseline and to avoid any residual influence of reactive hyperaemia on subsequent measurements. Baseline arterial diameter was then recorded prior to nitroglycerin administration.

Following sublingual administration of 400 μg glyceryl trinitrate, continuous ultrasound monitoring of the radial artery was performed for at least five minutes to capture the full dilatory response, as peak endothelium-independent dilation typically occurs between three and five minutes after nitroglycerin administration. The maximum arterial diameter observed during this monitoring period was recorded, and NMD was calculated as the percentage change in arterial diameter from pre-nitroglycerin baseline to peak post-nitroglycerin diameter, using the formula:

NMD (%) = (peak post-nitroglycerin diameter − baseline diameter) / baseline diameter × 100

The method for assessing radial artery patency involved using pulsed-wave Doppler ultrasound on the radial artery at the wrist and at the puncture site during both the 24-hour post-procedure visit and the one-month follow-up. Biphasic or triphasic Doppler waves were interpreted as normal antegrade flow and a patent artery. A monophasic waveform, indicating attenuated distal flow from collateral circulation around an obstructed segment, was considered a sign of RAO. When waveform interpretation was uncertain, colour-flow Doppler was used to verify the presence or absence of intraluminal flow. RAO was defined as the complete loss of forward flow in the radial artery based on Doppler images.

The same criteria were used to re-evaluate patency status at the one-month evaluation. Cases in which RAO was recorded at 24 hours but normal flow was observed at 1 month were considered spontaneous recanalisation.

The extent of CAD was evaluated during coronary angiography by the interventional cardiologist, who was blinded to the pre-procedural vascular function measurements. Findings were categorized as follows: normal coronary arteries or non-obstructive atherosclerosis; single-vessel disease, defined as significant stenosis (≥70%) of one major epicardial vessel; two-vessel disease; or three-vessel disease. Because baseline FMD

reflects systemic endothelial function, the relationship between pre-procedural FMD values and the extent of angiographically documented coronary atherosclerosis was also investigated to assess whether radial artery endothelial function could serve as a non-invasive surrogate for the severity of systemic atherosclerotic burden.

8.4 Data Collection

A standardized form was used to collect all clinical and demographic data at enrollment. Baseline laboratory parameters were obtained from routine pre-procedural blood tests performed within seven days prior to the procedure. These included a complete blood count, coagulation profile (prothrombin time expressed as international normalized ratio and activated partial thromboplastin time), renal function tests (urea and creatinine), serum electrolytes (sodium, potassium, and magnesium), glycated hemoglobin, and eGFR, calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

At enrollment, all current medications were recorded in detail, including ACE inhibitors, angiotensin II receptor blockers (ARBs), sodium–glucose cotransporter-2 inhibitors (SGLT2i), mineralocorticoid receptor antagonists (MRAs), beta-blockers, diuretics, calcium channel blockers (CCBs), statins, oral anticoagulants, and antiplatelet agents.

All ultrasound measurements and vasoreactivity test results were recorded numerically on the standardized case report form immediately after each assessment and then entered into a dedicated electronic database. All data entries were reviewed before any statistical analyses were conducted to ensure consistency and completeness.

Chapter 9: Results

9.1 Study Population and Baseline Characteristics

9.1.1 Demographics and Comorbidities

The study involved 94 consecutive patients undergoing elective transradial cardiac catheterization at a single center. The group consisted of 69 men (73%) and 25 women (27%), with a mean age of 65.8 ± 10.6 years. The age distribution was unimodal, peaking in the seventh decade with a notable tail extending into the eighth decade, which is typical for patients undergoing coronary angiography. The study population showed a high prevalence of cardiovascular risk factors and existing comorbidities. Hypertension was present in 61 patients (65%), dyslipidemia in 73 (78%), and diabetes mellitus in 28 (30%). A history of current or former smoking was reported by 39 patients (41%). Heart failure was diagnosed in 42 patients (45%), while atrial fibrillation was found in 21 (22%), with its status (paroxysmal versus persistent/permanent) remaining constant across all three within-subject timepoints. The mean eGFR was 75.88 ml/min/1.73m^2 (SD 15.70, median 73.50 ml/min/1.73m^2), corresponding to mildly reduced renal function. These prevalence rates align with those reported in modern transradial catheterization registries, indicating that the study cohort accurately reflects the clinical spectrum typically encountered in routine catheterization laboratory practice (41, 69, 156).

The cohort's high cardiovascular risk was also reflected in baseline medication use. Statins were prescribed in 69 patients (73%), RAAS inhibitors in 60 (64%), beta-blockers in 45 (48%), antiplatelet agents in 42 (45%), diuretics in 35 (37%), CCBs in 29 (31%), MRAs in 25 (27%), oral anticoagulants in 20 (21%), and SGLT2i in 13 (14%). The relatively frequent use of statins and RAAS inhibitors is particularly significant because of the well-documented pleiotropic vasoprotective effects of these medications. Their possible impact on vascular alterations following the procedure was therefore further examined as part of the second analytical objective in this study. A comprehensive overview of the baseline demographic characteristics, comorbidities, and medication profile of the study cohort is provided in Figure 9.1.

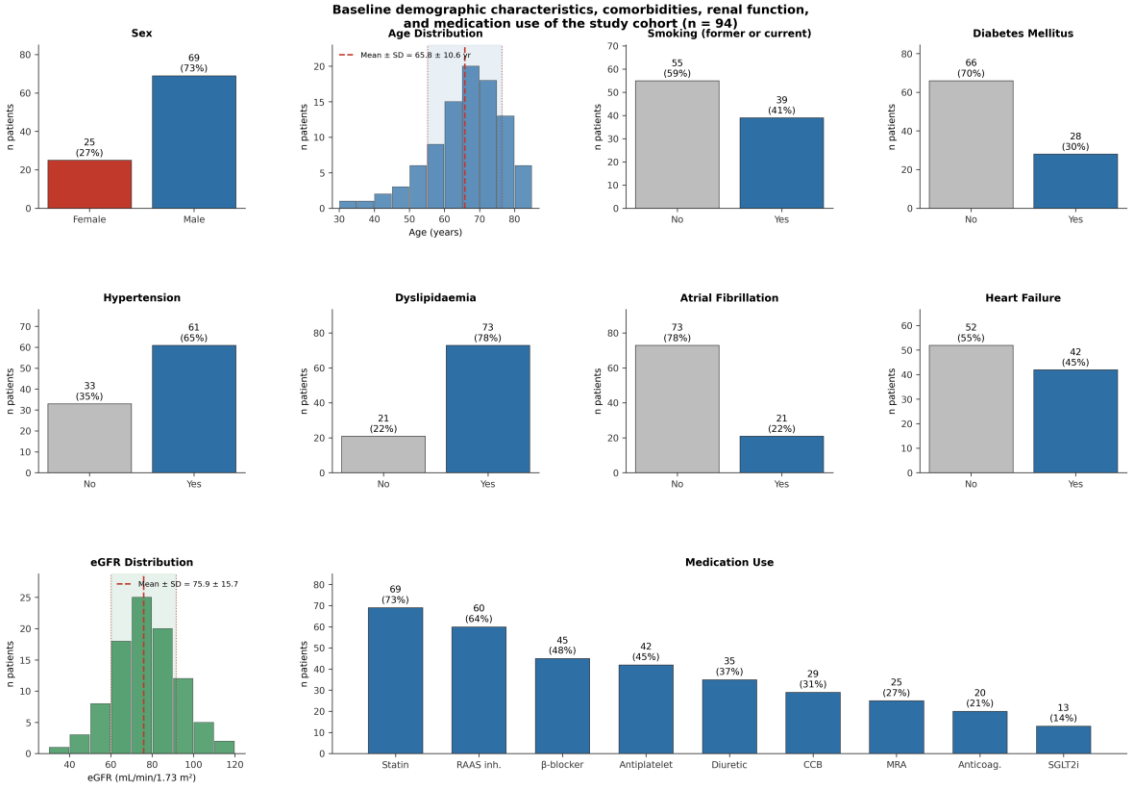

Figure 9.1. *Baseline demographic characteristics, comorbidities, and medication use of the study cohort (n = 94). Bar charts show absolute numbers and corresponding proportions for sex, key cardiovascular comorbidities, and smoking status. The age and eGFR histograms display the mean ± standard deviation (65.8 ± 10.6 years and 75.9 ± 15.7 mL/min/1.73 m², respectively), with shaded areas indicating the ±1 SD range. Baseline medication use is ordered from most to least frequently prescribed.*

9.1.2 Baseline Vascular Parameters — Descriptive Statistics and Distribution

Baseline vascular parameters were measured in all 94 patients prior to arterial sheath insertion. Mean FMD was 11.58% (SD 3.00; median 11.20%), and mean NMD was 18.04% (SD 4.01; median 16.70%). Doppler-derived hemodynamic parameters demonstrated the expected high-resistance pattern characteristic of the radial artery at rest. The mean resting PSV was 78.62 cm/s (SD 25.05; median 90.50 cm/s). The mean RI was 0.94 (SD 0.06; median 0.94) and the mean PI was 3.49 (SD 0.87; median 3.59), both consistent with the high peripheral vascular resistance of the hand arterial bed at rest. Resting VTI was 16.14 cm (SD 4.8 cm). Under hyperemic conditions, the mean hyperemic PSV was 118.13 cm/s (SD 26.85; median 129.00 cm/s). The mean VTI increased to 58.12 cm (SD 16.1; median 57.40 cm) and the mean per-beat blood flow volume to 2.68 mL/beat (SD 0.98; median 2.88 mL/beat), representing an approximate

3.6-fold increase in resting VTI and a 3.4-fold increase in resting blood flow volume following reactive hyperemia. The mean hyperemic RI decreased to 0.72 (SD 0.04; median 0.72) and the mean hyperemic PI to 1.44 (SD 0.20; median 1.39), representing a 23% reduction in RI and a 59% reduction in PI relative to resting values, consistent with the expected decrease in distal vascular resistance during reactive hyperemia. The mean baseline radial artery lumen diameter was 2.43 mm (SD 0.3 mm; median 2.5 mm). This value approaches the external diameter of a 6 Fr introducer sheath (2.52 mm), indicating that a substantial proportion of patients likely had a sheath-to-artery ratio approaching or exceeding unity — a previously established predictor of radial artery injury and occlusion (Figure 9.2). Baseline radial artery diameter was significantly smaller in women than in men (2.20 mm (SD 0.25 mm) vs 2.48 mm (SD 0.32 mm); $p < 0.01$). Since all patients received a 6 Fr sheath, this corresponded to a higher sheath-to-artery ratio in women (≈1.15) than in men (≈1.02).

The distributional properties of all study variables were formally assessed using the Shapiro–Wilk test of normality prior to any inferential analysis. Thirteen baseline vascular parameters were examined: radial artery lumen diameter, resting PSV, RI, PI, resting VTI, resting per-beat blood flow volume, FMD, NMD, hyperemic PSV, hyperemic VTI, hyperemic per-beat blood flow volume, hyperemic RI, and hyperemic PI.

All parameters showed statistically significant departure from normality (Shapiro–Wilk $p < 0.001$). Despite the statistical evidence of non-normality, several variables exhibited relatively symmetric distributions with low skewness values. Among the notably skewed variables, the RI demonstrated the most pronounced departure from symmetry (skewness −1.50), reflecting the narrow physiological range of the resistive index in a high-resistance peripheral arterial bed, where values approach unity. NMD showed a positive skewness of 1.21 and FMD a skewness of 0.94, both indicating a small number of patients with markedly elevated baseline vasoreactivity. The PI displayed a positive skewness of 0.84, consistent with a subset of patients exhibiting particularly pronounced pulsatile flow patterns. Under hyperemic conditions, the RI skewness reversed from −1.50 (resting) to +0.81 (hyperemic), reflecting a shift from values clustered near unity at rest to a concentration around 0.72 during hyperemia, with a small subgroup retaining higher resistance values. The hyperemic PI showed the strongest positive skewness of any

variable (1.51), indicating a minority of patients with persistently elevated pulsatility despite the hyperemic stimulus. The remaining parameters — including radial artery diameter, resting and hyperemic PSV, VTI, and per-beat blood flow volume — showed mild to moderate skewness (skewness < 0.7), and their non-normality was driven primarily by value clustering in the Doppler-derived measurements and by the sensitivity of the Shapiro–Wilk test at the present sample size (n = 94) (Figure 9.3).

Given the predominantly non-normal distributions, non-parametric methods were applied throughout for consistency and to ensure robustness against distributional violations. Where Friedman test identified a significant overall effect within-individual temporal comparisons, post-hoc pairwise comparisons were conducted using paired Wilcoxon signed-rank tests. Between-group comparisons were performed using the Mann–Whitney U test for dichotomous variables and the Kruskal–Wallis test for variables with three or more categories.

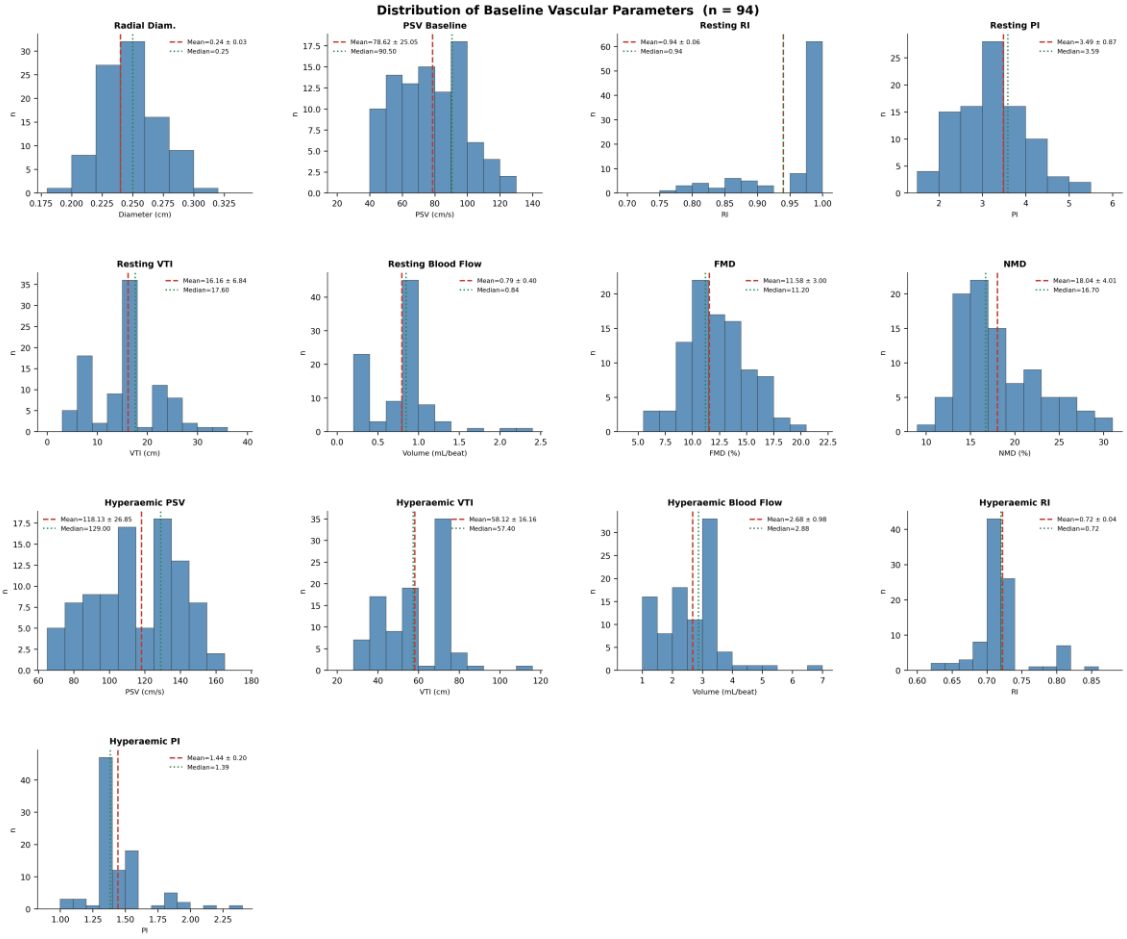

Figure 9.2. *Distribution of baseline vascular parameters in the study cohort (n = 94). Histograms display the frequency distribution of each parameter. The red dashed line indicates the mean (± standard deviation) and the green dotted line indicates the median. The distributional properties of all variables were formally assessed using the Shapiro–Wilk test. All thirteen parameters demonstrated significant departure from normality (p < 0.001).*

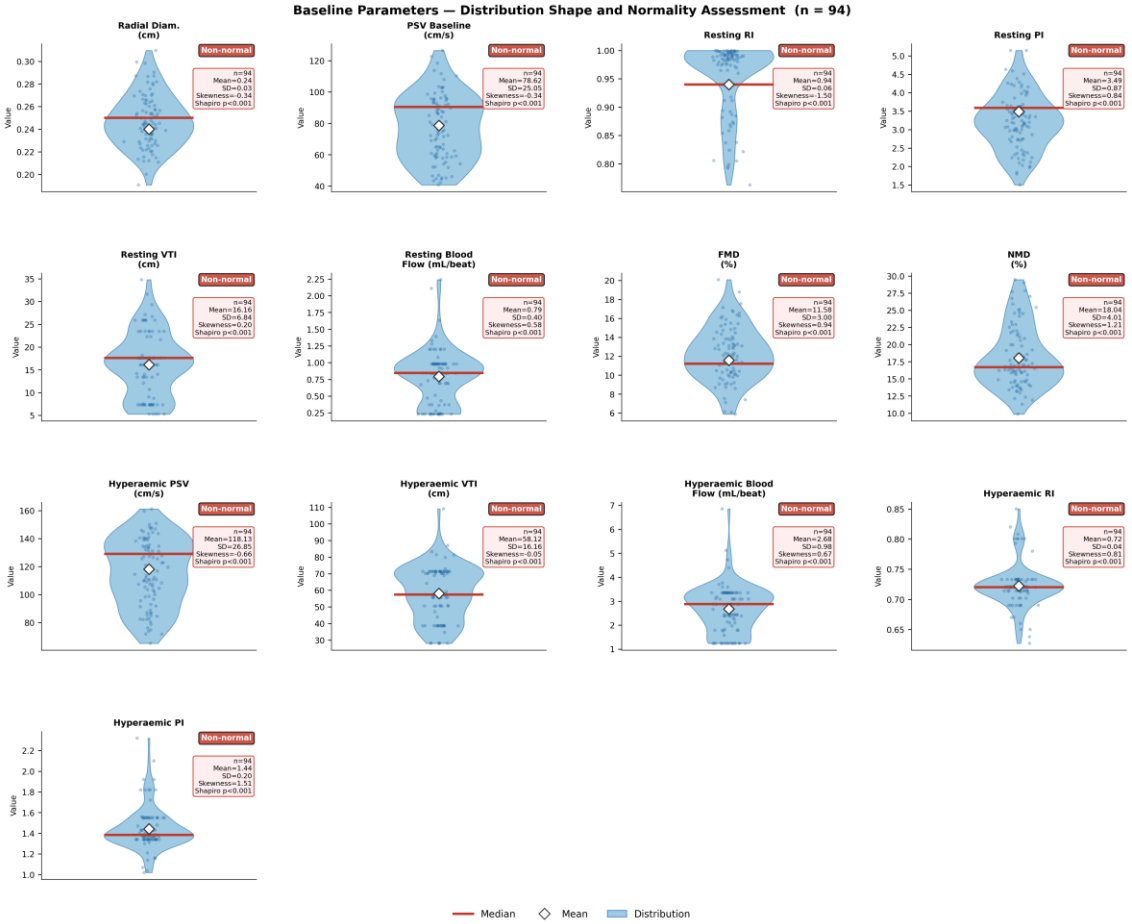

Figure 9.3. *Distribution shape and normality assessment of baseline vascular parameters (n = 94). Violin plots display the kernel density estimate of each variable's distribution, with individual data points (jittered), the median (red horizontal line), and the mean (white diamond). Each panel includes the sample size, mean, standard deviation, skewness, and Shapiro–Wilk test result.*

9.1.3 Baseline Correlations Among Vascular Parameters

Spearman rank correlation analysis was conducted to examine relationships among baseline vascular parameters. The results are shown in Figure 9.4. Several physiologically relevant relationships were identified. Age showed strong positive correlations with both hyperemic RI ($\rho = +0.71$) and hyperemic PI ($\rho = +0.54$), indicating that older patients tend to have higher microvascular resistance during hyperemia, consistent with age-related impairment in microvascular vasodilatory reserve. Age also exhibited a moderate negative correlation with radial artery diameter ($\rho = -0.58$), consistent with the age-related reduction in arterial size described in previous vascular studies. Interestingly, age correlated positively with baseline FMD ($\rho = +0.62$). This may reflect the well-known diameter dependence of percentage FMD measurements, where smaller baseline arterial diameters can produce proportionally larger percentage dilations for the same absolute change in vessel diameter. A strong inverse correlation was found between resting RI and resting VTI ($\rho = -0.83$). This relationship makes physiological sense because increased peripheral resistance decreases diastolic flow and reduces the forward flow. Additional moderate associations were identified. Baseline NMD showed a negative correlation with resting RI ($\rho = -0.60$), suggesting decreased vascular smooth muscle responsiveness in vessels with higher resting vascular resistance. Similarly, radial artery diameter was moderately negatively correlated with FMD ($\rho = -0.50$), reflecting the known diameter dependence of FMD measurements. FMD and NMD showed a moderate positive correlation ($\rho = +0.41$), suggesting that endothelium-dependent and endothelium-independent vasoreactivity share some common structural determinants — likely baseline arterial wall compliance and diameter — while remaining largely independent functional pathways. Finally, hyperemic Doppler parameters demonstrated strong internal consistency. Hyperemic PSV correlated strongly with hyperemic VTI ($\rho = +0.81$) and moderately with baseline VTI ($\rho = +0.57$), supporting the physiological coherence of flow reserve measurements across different Doppler-derived indices.

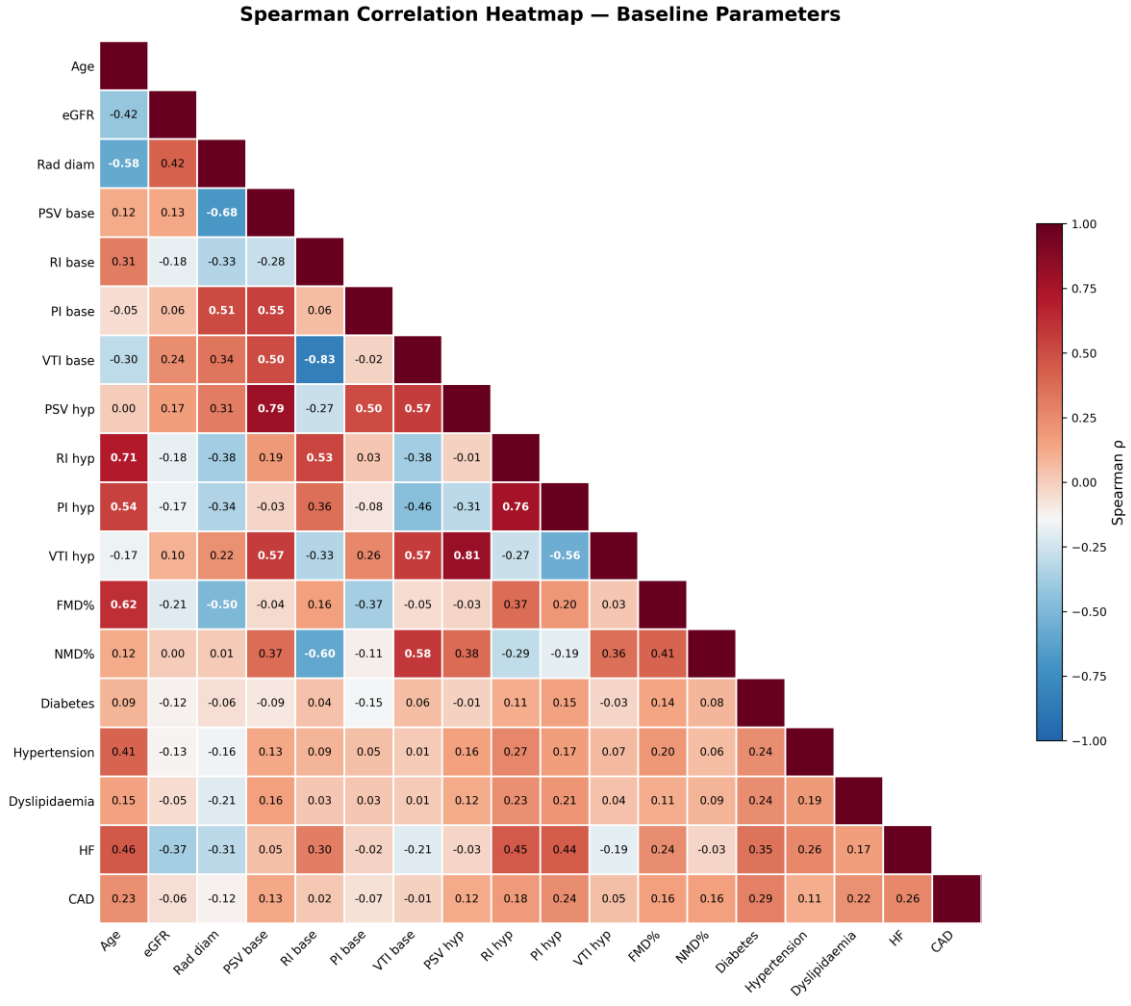

Figure 9.4. *Spearman rank correlation heatmap of baseline vascular parameters and clinical covariates (n = 94). Colour intensity reflects the magnitude and direction of the correlation coefficient (ρ), with red indicating positive and blue indicating negative correlations.*

9.1.4 Radial artery patency and temporal evolution during follow-up

Four patients (4.3%) developed RAO at the 24-hour follow-up assessment. This incidence is consistent with contemporary transradial catheterization series; the proRadial trial reported RAO in 4.6% of patients following diagnostic coronary angiography (156), and a recent meta-analysis of 31,345 patients reported pooled RAO rates of 7.7% within 24 hours, decreasing to 5.5% at longer follow-up (30).

All four affected patients were male, aged 51, 57, 69, and 74 years (mean 62.8 ± 10.6 years). Their mean radial artery diameter was 2.5 mm (range 2.1–3.1 mm), mean baseline

FMD was 10.2% (range 6.4–15.5%), and mean baseline NMD was 15.5% (range 11.1–23.0%). Notably, the four patients appeared to segregate into two distinct profiles. Two younger patients (aged 51 and 57 years) had adequate arterial diameter (3.1 and 2.6 mm; sheath-to-artery ratio < 1) but markedly impaired baseline vasoreactivity (FMD 6.4% and 6.9%; NMD 11.1% and 12.2%), both substantially below the cohort means of 11.58% and 18.04%, respectively. In contrast, the two older patients (aged 69 and 74 years) had small radial arteries (both 2.1 mm; sheath-to-artery ratio 1.20) with preserved or above-average vasoreactivity (FMD 11.9% and 15.5%; NMD 15.8% and 23.0%). The small number of events precludes formal statistical inference, but this observation warrants further investigation in larger cohorts.

An available-case analytical strategy was applied, in which each timepoint comparison included all patients with technically valid measurements at the relevant timepoints. Vascular measurements at 24 hours were unavailable for these four patients because the occluded radial artery precluded assessment of FMD or NMD. They were therefore excluded from all paired analyses involving the baseline-to-24-hour comparison, reducing the effective sample size to 90 patients. Exclusion at 24 hours was thus determined solely by the technical feasibility of measurement and not by any outcome value. At the one-month follow-up, duplex ultrasonography confirmed restoration of antegrade flow and complete radial artery patency in all four cases, consistent with spontaneous recanalization. No specific pharmacological treatment for RAO was administered; the recanalization occurred spontaneously without targeted anticoagulation or other intervention. The occurrence of spontaneous recanalization in all four patients is consistent with published data suggesting that early RAO frequently resolves within weeks, with recanalization rates of 35–69% at 30 days reported in the literature (154). These four patients were reincorporated into the paired analyses involving the baseline-to-one-month comparison, restoring the full sample size of 94 for the one-month time point.

9.2 Temporal Changes in Radial Artery Function and Hemodynamic Parameters (Objective 1)

9.2.1 Endothelial and Smooth Muscle Function: FMD and NMD

The Friedman test revealed a significant overall temporal effect for both FMD and NMD ($p < 0.001$) across the three time points. Post-hoc pairwise comparisons were therefore conducted using Wilcoxon signed-rank tests. The temporal evolution of FMD and NMD is shown in Figure 9.5.

In the 90 patients with paired baseline and 24-hour measurements, FMD decreased significantly from 11.58 ± 3.00% at baseline to 7.97 ± 2.04% at 24 hours ($p < 0.001$), representing an absolute reduction of 3.61 percentage points (31.2% relative decrease). NMD showed a more pronounced decline, falling from 18.04 ± 4.01% to 11.44 ± 2.52% at 24 hours ($p < 0.001$), an absolute reduction of 6.60 percentage points (36.6% relative decrease). Both reductions are consistent with the study hypothesis that transradial catheterization impairs endothelial and smooth-muscle vasoreactivity in the early post-procedural period. Notably, the magnitude of NMD decline exceeded that of FMD in both absolute (6.60 vs 3.61 percentage points) and relative terms (36.6% vs 31.2%). This observation suggests that the mechanical effects of sheath insertion and catheter manipulation extend beyond the endothelial layer to affect the deeper arterial wall structures, including the tunica media with vascular smooth-muscle cells.

At the one-month follow-up, after examining all 94 patients (including the four cases with vascular recanalization after RAO), both parameters remained significantly lower than at baseline. FMD at one month was 8.25 ± 2.64%, which was significantly lower than baseline ($p < 0.001$) but did not differ significantly from the 24-hour value ($p = 0.08$). This lack of significant FMD recovery between 24 hours and one month suggests persistent endothelial dysfunction that has not substantially resolved within this time frame. NMD at one month was 13.51 ± 2.83%, which was significantly higher than at 24 hours ($p < 0.001$) but remained significantly lower than baseline ($p < 0.001$). The partial recovery of NMD — but not FMD — between 24 hours and one month suggests that smooth-muscle function may recover more readily than endothelial function following catheterization-induced injury, possibly reflecting the greater regenerative capacity of

smooth-muscle cells compared to the endothelium, or the resolution of medial edema that does not fully restore endothelial signalling.

The standard deviations of both parameters narrowed at 24 hours (FMD 2.04% vs 3.00% at baseline; NMD 2.52% vs 4.01% at baseline), suggesting that the acute injury produced a relatively uniform degree of functional impairment across patients regardless of their baseline values. By one month, however, the variability partially re-expanded (FMD SD 2.64%; NMD SD 2.83%), indicating heterogeneous recovery trajectories among individual patients. This widening of inter-individual variability during the recovery phase suggests that patient-specific factors, such as baseline vascular function, comorbidity burden, and vasoprotective medication use, may modulate the degree of functional restoration.

Figure 9.6 displays the individual patient trajectories of FMD and NMD across the three study time points, with the superimposed group mean trajectory shown as a bold black line in each panel. All 94 patients are represented; the four patients who developed RAO are shown as blue dashed lines connecting their baseline and one-month values, reflecting the absence of 24-hour measurements in this subgroup.

In both panels, the predominance of red lines — representing patients whose values decreased from baseline to 24 hours — confirms that the group-level reduction reflects a consistent individual-level response. A small minority of trajectories (shown in green) demonstrated stable or slightly increased values at 24 hours, representing patients in whom the procedure did not induce measurable functional impairment at the acute time point. The NMD trajectories appeared more parallel and consistent in direction, whereas the FMD trajectories crossed more frequently between 24 hours and one month, indicating heterogeneous individual recovery patterns despite a similar group-level variability (FMD 1-month SD 2.64%; NMD 1-month SD 2.83%). The four RAO patients showed a heterogeneous pattern consistent with their baseline characteristics (Section 9.1.4): two patients with low-baseline vasoreactivity remained at low values throughout, while two patients with preserved baseline vasoreactivity showed notable decline at one month, consistent with post-recanalization functional injury.

The superimposed group mean trajectories illustrate the differential recovery pattern: a larger absolute reduction in NMD than in FMD at 24 hours (−6.60 vs −3.61 percentage

points), followed by a partial but significant recovery of NMD between 24 hours and one month (+2.07 percentage points). In contrast, the FMD mean trajectory remained essentially flat between 24 hours and one month, consistent with the non-significant pairwise comparison reported above (p = 0.08). Together, these individual-level and group-level patterns reinforce the interpretation that endothelial and smooth-muscle vasoreactivity follow distinct recovery trajectories following transradial catheterization.

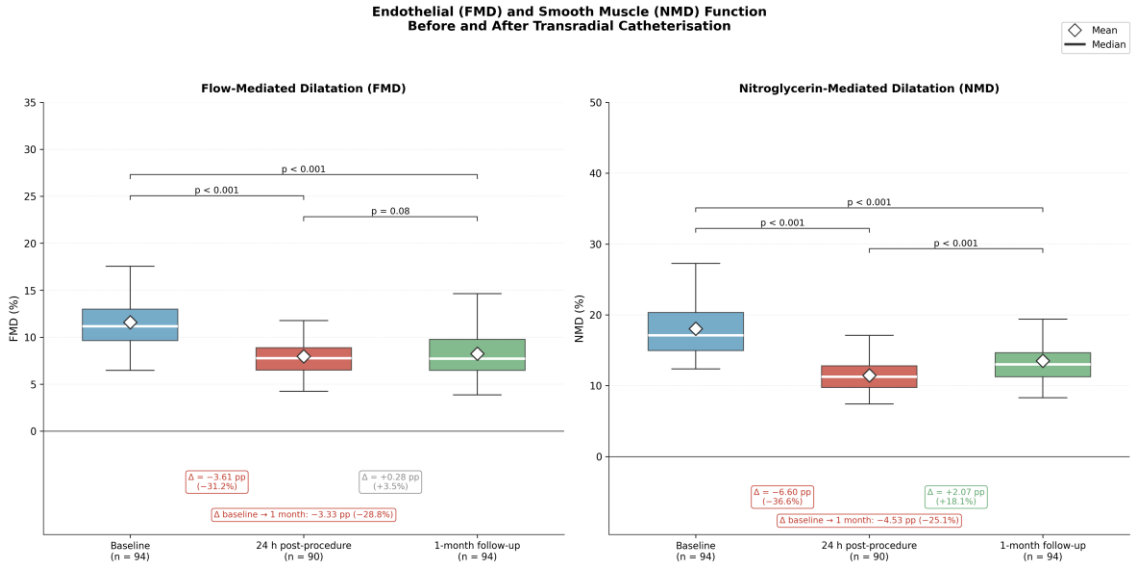

Figure 9.5. *Temporal evolution of FMD and NMD before and after transradial catheterisation. Box plots display the distribution of each parameter at baseline (n = 94), 24 hours post-procedure (n = 90; four patients excluded due to RAO) and one-month follow-up (n = 94; full sample restored following spontaneous recanalization). Each box represents the interquartile range (25th to 75th percentile), the horizontal white line indicates the median, and the white diamond indicates the mean. Whiskers extend to the most extreme values within 1.5 × IQR of the box edges. The coloured annotations below each panel summarise the absolute and relative changes between time points. Both FMD and NMD decreased significantly at 24 hours. NMD partially but significantly recovered at one month, whereas FMD showed no significant recovery (p = 0.08), suggesting differential recovery trajectories between endothelium-dependent and endothelium-independent vasoreactivity.*

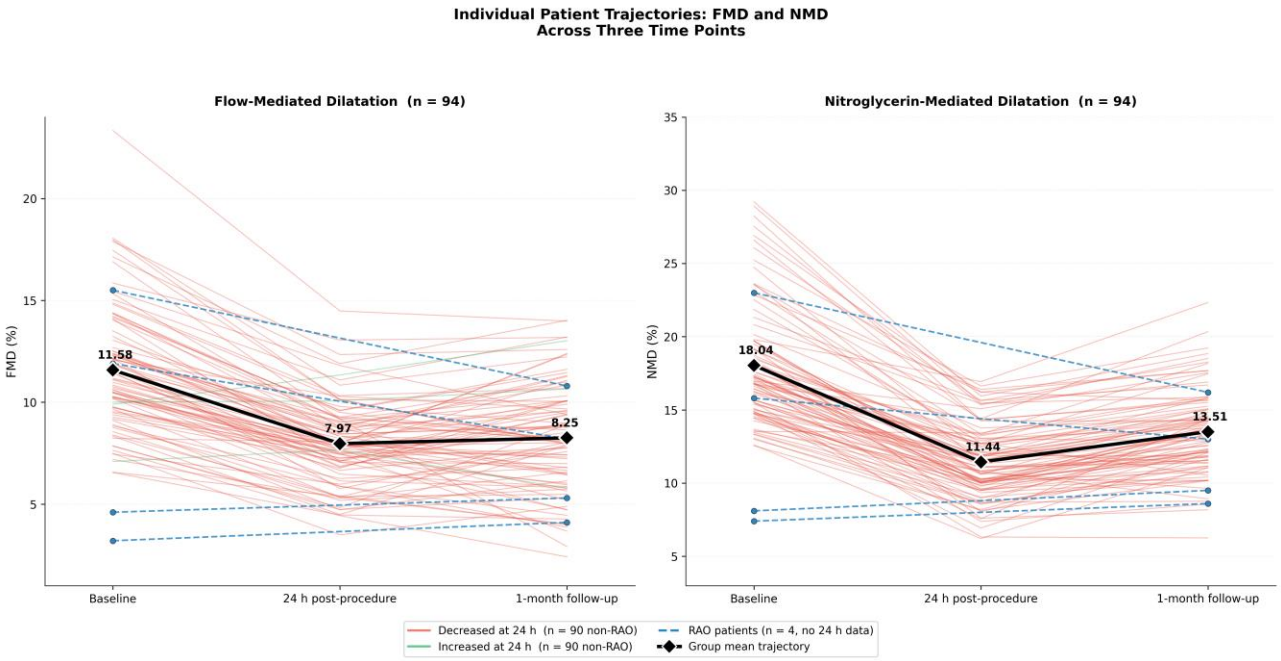

Figure 9.6. *Individual patient trajectories of FMD and NMD across baseline, 24 hours post-procedure, and one-month follow-up (n = 94). Each thin line represents one patient. Red lines indicate patients whose values decreased at 24 hours, and green lines indicate patients whose values increased at 24 hours. The four patients who developed RAO are shown as blue dashed lines connecting their baseline and one-month values. The bold black line overlaid with diamond markers represents the group mean trajectory, with annotated values at each time point. Both FMD and NMD showed a consistent decline at 24 hours across the majority of individual patients. NMD demonstrated a partial but visible recovery at one month, whereas FMD remained essentially unchanged between 24 hours and one month, indicating distinct recovery trajectories for endothelium-dependent and endothelium-independent vasoreactivity.*

9.2.2 Resting Doppler Flow Parameters: PSV, VTI, RI, and PI

Resting PSV decreased significantly from 78.62 ± 25.05 cm/s at baseline to 66.60 ± 22.10 cm/s at 24 hours ($p < 0.001$), possibly due to post-procedural vasospasm, local vessel wall edema and thickening, or a combination of both, resulting in vascular constriction. The redistribution of flow toward the ulnar artery may subsequently reduce forward flow velocity in the radial artery. At one month, mean PSV increased to 84.50 ± 18.90 cm/s, which was not significantly different from baseline ($p = 0.13$), indicating recovery of

hemodynamic parameters. Resting VTI followed a similar directional trend as PSV but did not reach statistical significance, decreasing numerically from 16.14 ± 4.80 cm at baseline to 14.00 ± 3.90 cm at 24 hours, then recovering to 18.00 ± 4.40 cm at one month (all comparisons non-significant). The parallel, non-significant decline in VTI at 24 hours is therefore most consistent with the same transient reduction in radial flow proposed above, and the lack of significance likely reflects the greater variability of the integrated measure. The modest recovery at one month may reflect improved radial flow, accompanied by a reduction in downstream resistance.

The temporal pattern of RI differed from that of PSV. The mean RI increased slightly at 24 hours, from 0.94 ± 0.06 to 0.96 ± 0.03 ($p = 0.001$), reflecting an increase in peripheral vascular resistance following the procedure. At one month, however, the mean RI decreased to 0.84 ± 0.06, significantly lower than both the baseline and 24-hour values (both $p < 0.001$). This finding reflects a reduction in distal vascular resistance one month after catheterization due to compensatory adaptive mechanisms within the distal vascular bed. Such compensatory responses may include microvascular vasodilation mediated by local release of endothelium-derived relaxing factors, reduced sympathetic vasoconstrictor tone in the healing arterial segment, or remodelling of the downstream microcirculation in response to the transient proximal injury.

The PI showed a progressive decline across all three time points, from 3.49 ± 0.87 at baseline to 3.01 ± 0.48 at 24 hours and 2.83 ± 0.54 at one month, with all pairwise comparisons statistically significant (all $p < 0.001$). This sustained reduction in PI is consistent with the one-month reduction in RI. Together, these concordant changes in two resistance-derived Doppler indices support the interpretation that compensatory mechanisms in the distal vascular bed gradually reduce peripheral resistance following transradial catheterization, warranting further investigation in larger cohorts. Temporal alterations of PSV, RI and PI are depicted in Figure 9.7.

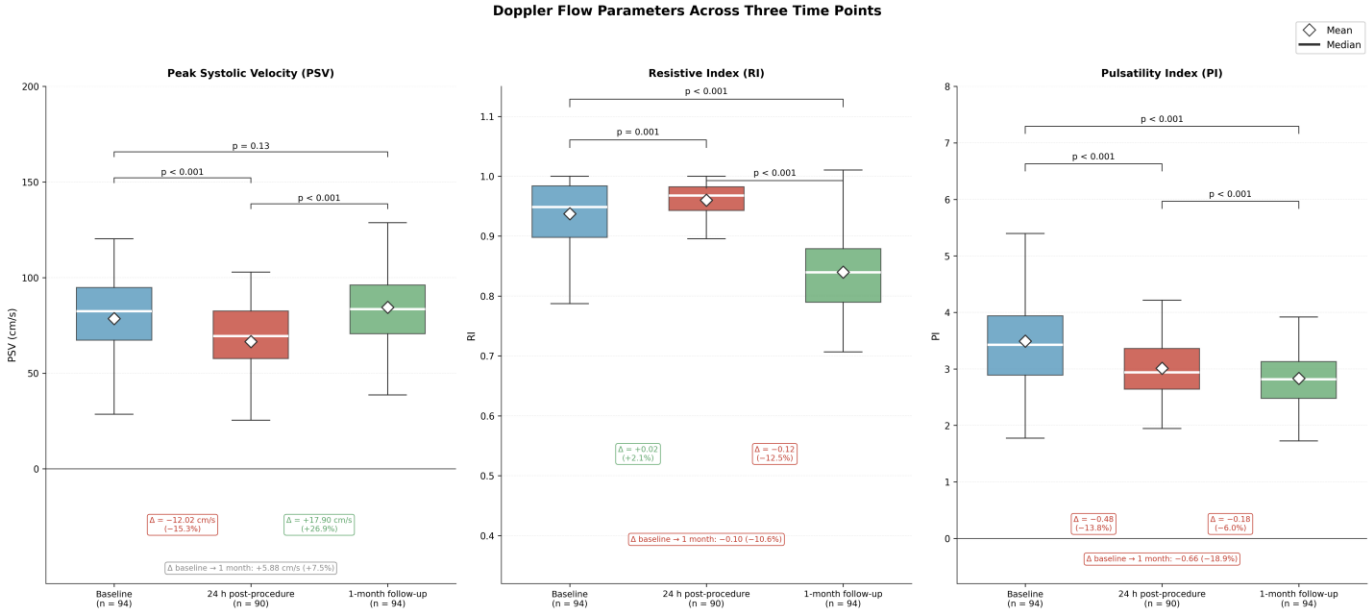

Figure 9.7. *Temporal changes in resting Doppler flow parameters: PSV, RI, PI across the three time points. Each box represents the interquartile range (25th to 75th percentile), the horizontal white line indicates the median, and the white diamond indicates the mean. Whiskers extend to the most extreme values within 1.5 × IQR of the box edges. PSV decreased significantly at 24 hours and recovered by one month to values not significantly different from baseline. RI increased modestly at 24 hours and decreased significantly below baseline at one month. PI declined progressively across all three time points, with all pairwise comparisons statistically significant.*

9.2.3 Radial Artery Diameter

The lumen diameter of the radial artery showed a significant reduction at 24 hours following catheterization, with partial but incomplete recovery at one month (Figure 9.8). The mean radial artery diameter decreased from 2.43 ± 0.30 mm at baseline to 2.24 ± 0.25 mm at 24 hours ($p = 0.003$), representing an absolute reduction of 0.19 mm (−7.8% relative to baseline). At the one-month follow-up, the mean diameter recovered partially to 2.32 ± 0.28 mm, which was significantly higher than the 24-hour value ($p < 0.01$) but remained significantly lower than baseline ($p < 0.01$).

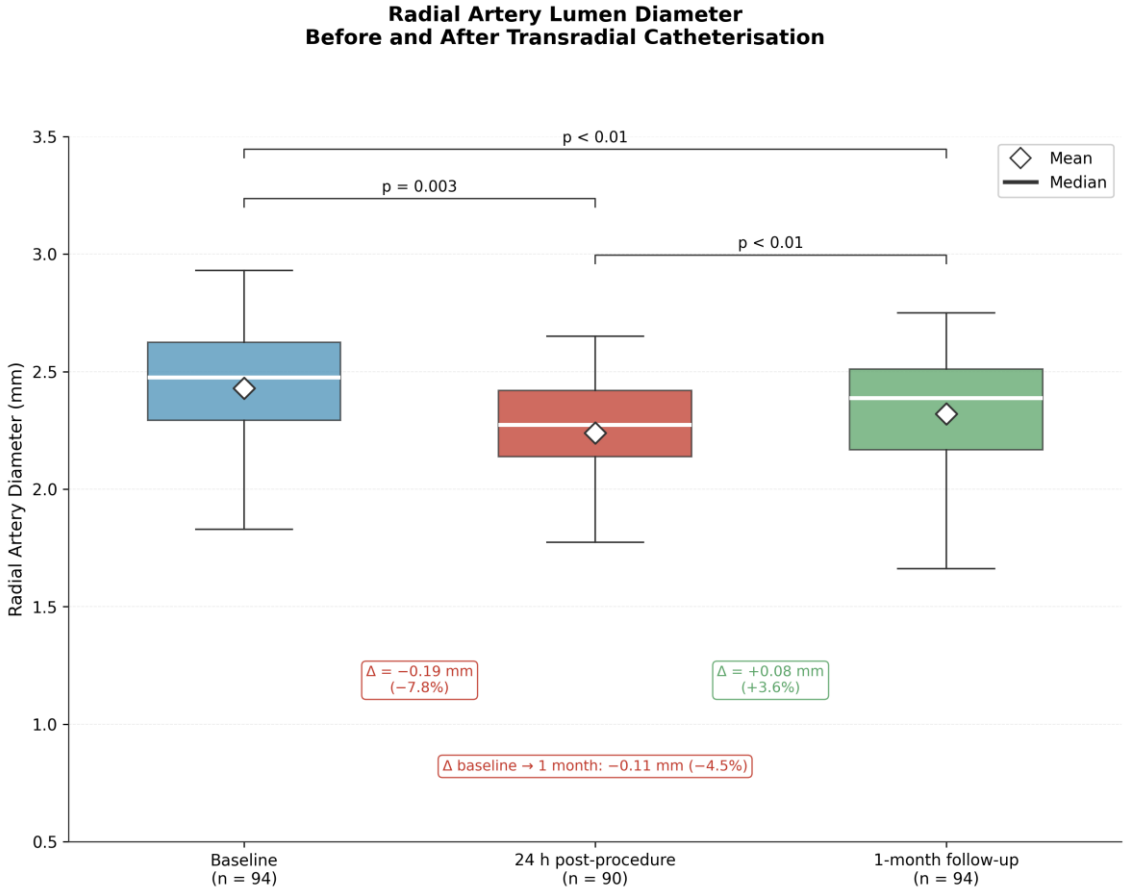

Figure 9.8. *Temporal evolution of radial artery lumen diameter before and after transradial catheterisation. Box plots display the distribution of the lumen diameter at baseline (n = 94), 24 hours post-procedure (n = 90; four patients excluded due to radial artery occlusion) and one-month follow-up (n = 94; full sample restored following spontaneous recanalization). Each box represents the interquartile range (25th to 75th percentile); the horizontal white line indicates the median and the white diamond indicates the mean. Whiskers extend to the most extreme values within 1.5 × IQR of the box edges. The radial artery lumen diameter decreased significantly at 24 hours and recovered partially but incompletely at one month, remaining significantly below baseline values.*

9.2.4 Hyperemic Flow Reserve: VTI and Blood Volume

Figure 9.9 displays the temporal evolution of hyperemic VTI and hyperemic blood flow volume per beat — two complementary indices of radial artery hyperemic flow reserve. The mean hyperemic VTI decreased from 58.12 ± 16.16 cm at baseline to 55.46 ± 18.45 cm at 24 hours ($p = 0.01$), indicating a transient reduction in hyperemic flow reserve during the early post-procedural period. At one month, hyperemic VTI had increased to 62.81 ± 9.66 cm, which was significantly higher than both the 24-hour value ($p = 0.008$) and baseline ($p = 0.01$). The increase in hyperemic VTI above baseline at one month is consistent with the concurrent reductions in RI and PI reported in Section 9.2.2, which suggest microvascular vasodilation in distal vascular bed during the recovery phase.

Mean hyperemic blood flow volume of 2.19 mL/beat at 24 hours, representing an 18.4% reduction compared with the baseline value of 2.68 ± 0.98 mL/beat. At one month, mean hyperemic blood flow volume was 2.66 mL/beat, essentially identical to baseline (−0.9% relative change). Since volumetric flow depends on both VTI and the square of the arterial diameter, this near-complete numerical recovery occurred because the increase in VTI above baseline was offset by the reduction in cross-sectional area resulting from the persistent diameter reduction at one month.

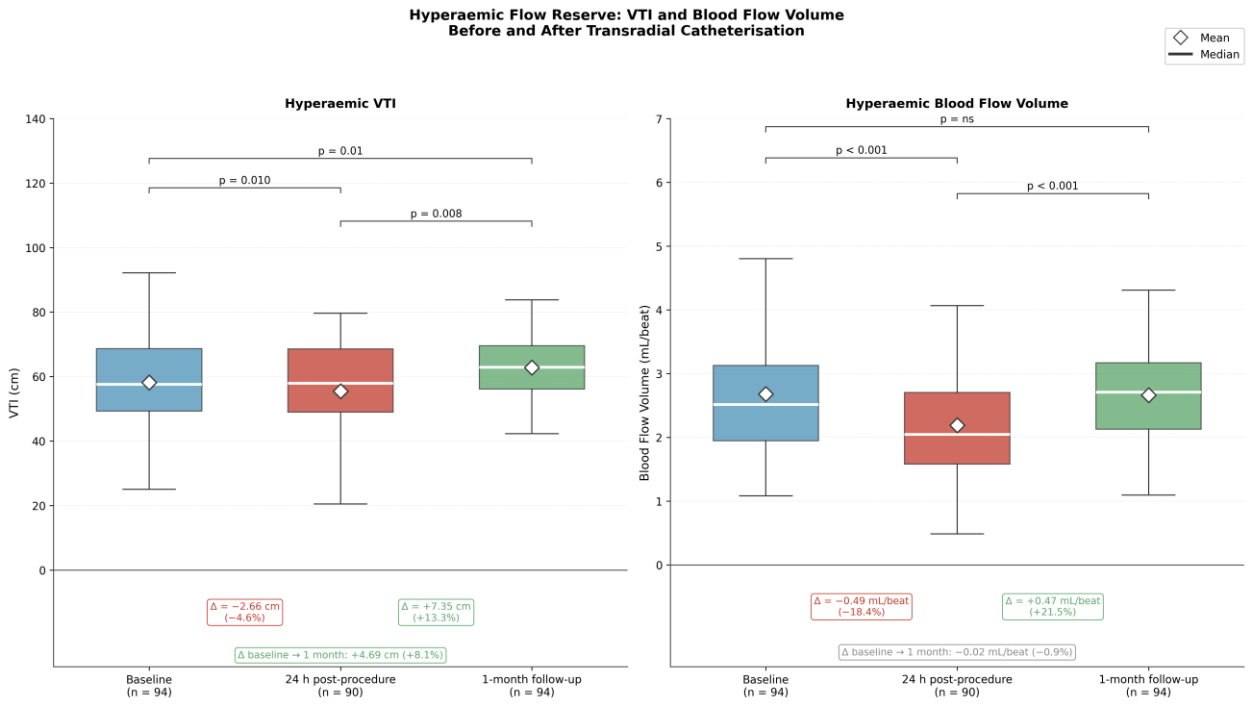

Figure 9.9. *Temporal evolution of hyperemic flow reserve parameters before and after transradial catheterization. The left panel displays hyperemic VTI and the right panel displays hyperemic blood flow volume per beat. Box plots display the distribution of each parameter at baseline (n = 94), 24 hours post-procedure (n = 90), and one-month follow-up (n = 94). Each box represents the interquartile range (25th to 75th percentile); the horizontal white line indicates the median and the white diamond indicates the mean. Whiskers extend to the most extreme values within 1.5 × IQR. Hyperemic VTI decreased significantly at 24 hours and increased significantly above baseline values at one month. In contrast, hyperemic blood flow volume decreased substantially at 24 hours and returned to baseline values at one month.*

9.3 Subgroup Analysis and Predictors of Functional Damage at 24 hours (Objective 2)

9.3.1 FMD Damage by Sex, Diabetes Mellitus, and Hypertension

Subgroup analyses assessed whether key clinical characteristics influenced the magnitude of FMD reduction at 24 hours post-procedure. Mann–Whitney U tests compared the change in FMD from baseline to 24 hours (ΔFMD) between subgroups defined by sex, diabetes mellitus, and hypertension status. All analyses were performed on the 90 patients with paired baseline and 24-hour measurements.

None of the three clinical variables tested was significantly associated with the magnitude of FMD reduction at 24 hours (Figure 9.10). Female patients (n = 25) showed a numerically greater reduction in FMD than male patients (n = 65), with median ΔFMD of approximately −4.3% and −3.3%, respectively (p = 0.40). Patients with diabetes mellitus (n = 26) had a median ΔFMD of approximately −3.7%, compared with approximately −3.2% in those without diabetes (n = 64; p = 0.81). Hypertensive patients (n = 58) and normotensive patients (n = 32) had nearly identical reductions, with median ΔFMD of approximately −3.5% in both groups (p = 0.40).

These findings do not support the hypotheses formulated in Section 7.3.2, that female sex, diabetes mellitus, and hypertension would be associated with greater post-procedural FMD reduction. However, the relatively small subgroup sizes limit statistical power to detect modest between-group differences. The 1.0 percentage-point greater FMD reduction observed in female patients, although not statistically significant, is consistent with the direction predicted by mechanisms previously proposed in the literature,

including a smaller radial artery diameter, a higher sheath-to-artery ratio, and more robust collateral flow. Endothelial injury also carries a substantial size-independent component, mediated by alterations in luminal shear stress and direct endothelial contact with the sheath surface. This shared component may contribute to the observation that post-procedural FMD reduction was not significantly greater in female patients, despite their smaller radial arteries and consequently higher sheath-to-artery ratios.

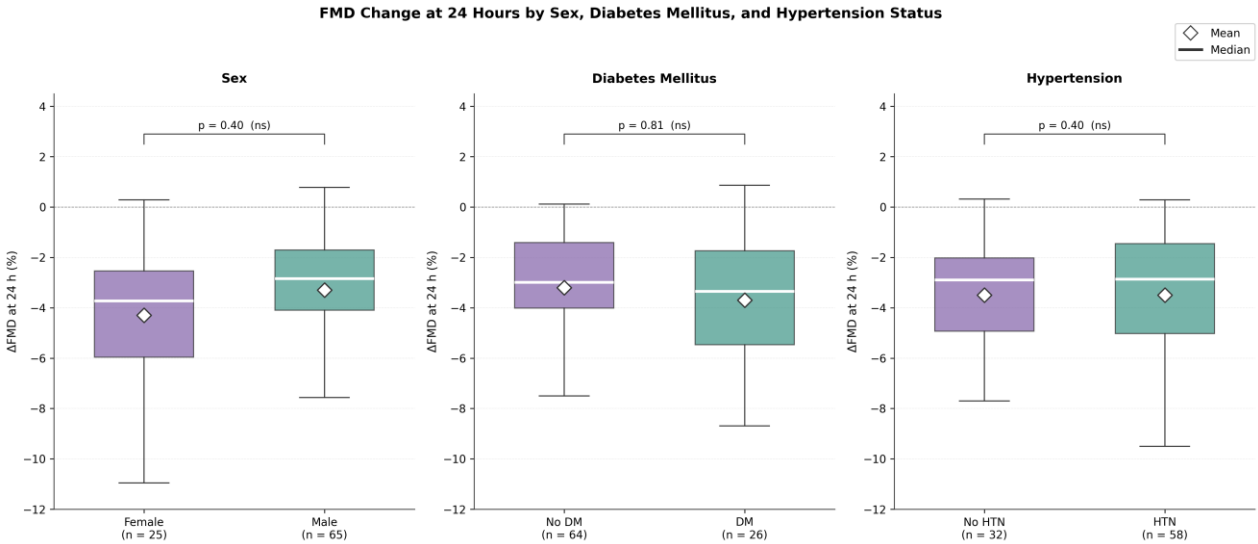

Figure 9.10. *Change in FMD at 24 hours stratified by sex (left), diabetes mellitus (centre), and hypertension (right). Boxes show median and IQR; diamonds indicate group means. Mann-Whitney U test p-values are shown for each comparison.*

9.3.2 FMD Damage by Age Group and Renal Function

Mann–Whitney U tests and Kruskal–Wallis tests were used to examine whether age and renal function influenced the magnitude of FMD reduction at 24 hours post-procedure. Figure 9.11 illustrates these subgroup comparisons.

Older patients (≥ 65 years, n = 55) showed a significantly greater reduction in FMD compared with younger patients (< 65 years, n = 35), with median ΔFMD values of approximately −3.8% and −3.0%, respectively ($p < 0.05$). This finding supports the hypothesis formulated in Section 7.3.2 that older patients appear to be more susceptible to acute endothelial injury, possibly reflecting both a diminished capacity of the aging endothelium to maintain vasodilatory function due to structural and functional alterations and an age-related reduction in the availability of circulating endothelial progenitor cells involved in early vascular repair.

When patients were stratified into tertiles based on eGFR, no significant differences in ΔFMD at 24 hours were detected among the three groups (Kruskal–Wallis test, p = 0.202). The lowest eGFR tertile (n = 37), middle tertile (n = 25), and highest tertile (n = 28) showed similar median ΔFMD values around −3.5%, −3.5%, and −2.5%, respectively. This null finding does not support the hypothesis that reduced renal function would be associated with greater post-procedural endothelial dysfunction. However, this interpretation must be considered in the context of the limited renal function range within the cohort.

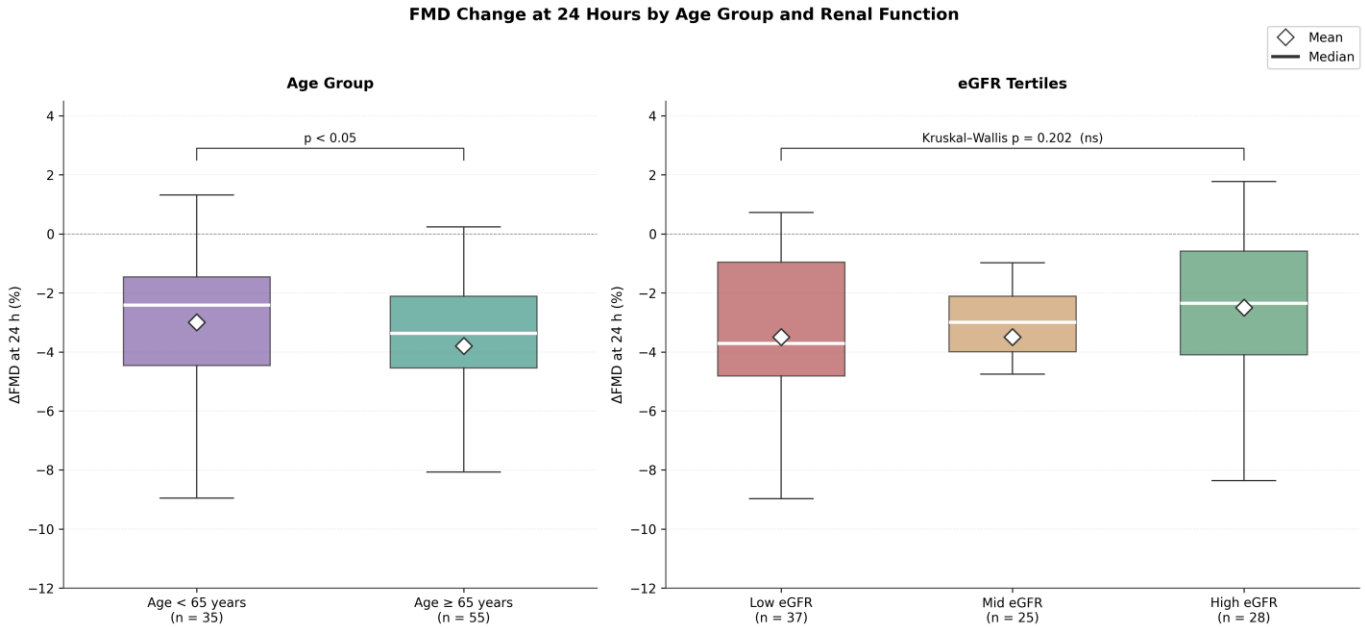

Figure 9.11. Change in FMD at 24 hours stratified by age group (left: under 65 versus 65 or older) and eGFR tertile (right: low, mid, high). Boxes display median and IQR; diamonds represent group means. Mann-Whitney U test p-values are shown for age groups; Kruskal-Wallis p-values are shown for eGFR tertiles.

9.3.3 NMD Damage by Sex, Diabetes Mellitus, Hypertension, Age Group and Renal Function

Mann–Whitney U tests and Kruskal–Wallis tests were used to compare the change in NMD from baseline to 24 hours (ΔNMD) between subgroups defined by sex, diabetes mellitus, hypertension, age, and renal function. Figure 9.12 illustrates the comparisons by sex, diabetes, and hypertension.

In contrast to the findings for FMD, a significant sex-related difference was observed in the magnitude of NMD reduction at 24 hours. Female patients (n = 25) experienced a

substantially greater reduction in NMD than male patients (n = 65), with median ΔNMD values of approximately −8.3% versus −5.8%, respectively (p = 0.005). This finding suggests that the smooth muscle of the radial artery wall may be more susceptible to procedural injury in women, most plausibly through direct circumferential compression of smooth muscle cells by the introducer sheath, a pattern plausibly mediated by the smaller radial artery diameter and the consequently higher sheath-to-artery ratio typically observed in women during transradial catheterization.

No significant differences in ΔNMD were observed by diabetes mellitus status (n = 26 with DM vs n = 64 without; p = 0.20) or hypertension status (n = 58 with increased arterial pressure vs n = 32 without; p = 0.34). Median ΔNMD values were similar across these groups, ranging from approximately −5.8% to −6.3%, suggesting that these risk factors were not significantly associated with the magnitude of smooth-muscle dysfunction after transradial catheterization in this cohort.

Subgroup analyses by age and renal function similarly showed no significant association with ΔNMD at 24 hours. Older patients (≥ 65 years, n = 55) and younger patients (< 65 years, n = 35) showed comparable reductions in NMD. Stratification into eGFR tertiles likewise revealed no significant difference in ΔNMD among the lowest (n = 37), middle (n = 25), and highest (n = 28) tertiles. This contrasts with the FMD findings reported in Section 9.3.2, where older age was significantly associated with greater endothelial impairment. The dissociation may suggest that, while aging appears to decrease endothelium-dependent vasoreactivity after catheterization, NMD, in contrast, is relatively spared from age-related biological decline and is instead modulated primarily by mechanical factors.

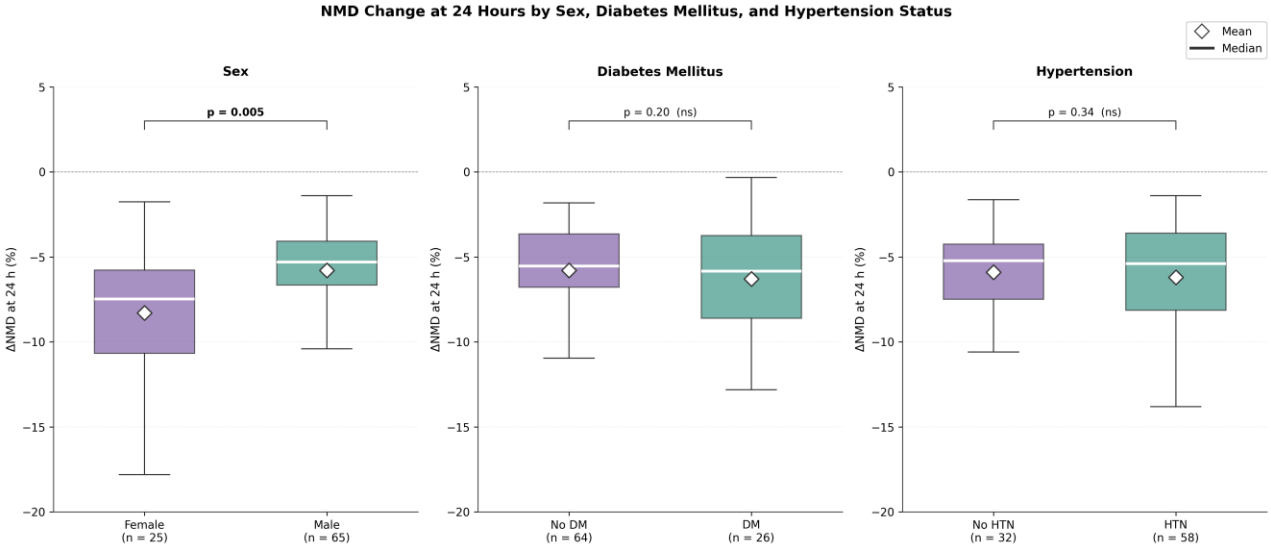

Figure 9.12. *Change in NMD at 24 hours stratified by sex (left), diabetes mellitus (center), and hypertension (right). Boxes show median and IQR; diamonds indicate group means. Mann-Whitney U test p-values are shown for each comparison.*

9.3.4 Effect of Baseline Medication Use on FMD and NMD Damage

The potential impact of vasoprotective medications on post-procedural changes in FMD and NMD at 24 hours was studied for four common drug classes: statins, RAAS inhibitors, beta-blockers, and CCBs, as shown in Figure 9.13. No statistically significant differences in ΔFMD at 24 hours were found between patients taking these medications and those not receiving any of them. Specifically, statin therapy did not significantly alter FMD ($p = 0.58$) or NMD ($p = 0.38$) responses. Likewise, beta-blockers and CCBs showed no significant effects on post-procedural changes in either FMD ($p = 0.62$ and $p = 0.55$, respectively) or NMD ($p = 0.85$ and $p = 0.74$, respectively). Among the drug classes studied, RAAS inhibitors were closest to reaching statistical significance for ΔFMD at 24 hours ($p = 0.06$), hinting at a possible but modest protective effect. However, use of RAAS inhibitors was not linked to a significant difference in ΔNMD ($p = 0.39$). The lack of a clear medication-related effect across these drug classes may partly be due to the high prevalence of these therapies within the cohort, which limits the ability to detect differences between treated and untreated patients—especially for statins (73% of patients) and RAAS inhibitors (64%). Additionally, chronic pre-procedural exposure to these medications might have already reached their maximum vasoprotective effects on

baseline vascular function, reducing their capacity to influence the extent of acute vascular injury after catheterization.

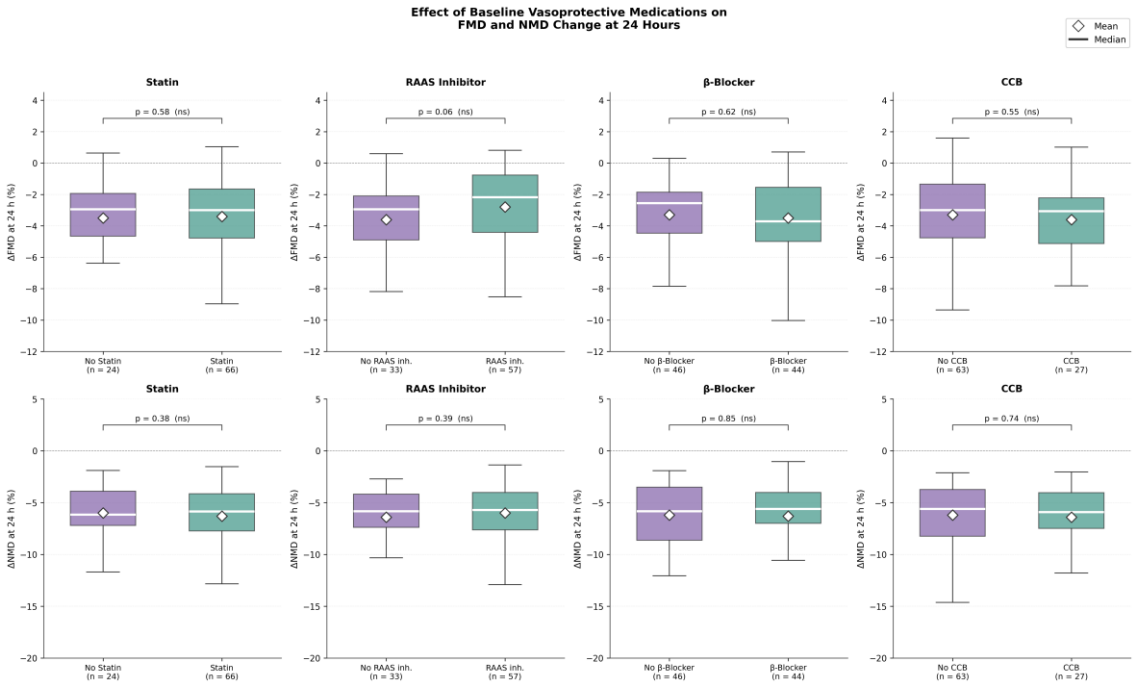

Figure 9.13. *Effect of baseline medication use on ΔFMD% (upper row) and ΔNMD% (lower row) at 24 hours, stratified by statin, RAAS inhibitor, beta-blocker, and CCBs use. Boxes show median and IQR; diamonds indicate group means. Mann-Whitney U test p-values are shown for each comparison.*

9.4 Predictive Value of Baseline Parameters for Post-Procedural Functional Outcome (Objective 3)

9.4.1 Cross-Parameter Spearman Correlations

Spearman correlations were calculated between baseline vascular parameters and the four outcome measures (ΔFMD at 24 hours, ΔNMD at 24 hours, ΔFMD at one month, and ΔNMD at one month). The full correlation matrix is presented in Figure 9.14.

Baseline RI and ΔNMD. A moderate inverse correlation was observed between baseline RI and ΔNMD at 24 hours ($\rho = -0.51$, $p < 0.001$) and at one month ($\rho = -0.46$, $p < 0.001$), indicating that patients with higher baseline peripheral vascular resistance experienced greater post-procedural reductions in smooth-muscle-dependent vasoreactivity.

Age and ΔFMD at one month. Age was strongly inversely correlated with ΔFMD at one month ($\rho = -0.62$, $p < 0.001$), indicating that older patients experienced substantially greater residual FMD reductions at the one-month follow-up. In contrast, the correlation between age and ΔFMD at 24 hours was weak ($\rho = -0.21$, $p = 0.050$), despite the significant dichotomized comparison reported in Section 9.3.2. No corresponding age effect was observed for ΔNMD. Age preferentially affects endothelium-dependent function — not smooth-muscle function — and does so predominantly during the recovery phase rather than the acute injury phase.

Baseline radial artery diameter and ΔFMD at one month. A moderate positive correlation was observed between baseline radial artery diameter and ΔFMD at one month ($\rho = +0.50$, $p < 0.001$). Patients with larger baseline arteries experienced smaller residual FMD deficits at one month, consistent with the mechanical-protection hypothesis that a larger-diameter artery is less vulnerable to catheter-induced endothelial injury due to a lower sheath-to-artery ratio, reduced intimal contact pressure, and less mechanical stress on the vessel wall.

Male sex and ΔNMD. Male sex showed a positive correlation with ΔNMD at both 24 hours ($\rho = +0.30$, $p < 0.01$) and one month ($\rho = +0.41$, $p < 0.001$). Because male patients tend to have smaller post-procedural reductions in NMD than female patients, this correlation reinforces the significant sex effect identified in the subgroup analysis, where female patients experienced substantially greater smooth-muscle injury (median ΔNMD approximately −8.3% versus −5.8%, $p = 0.005$). The consistency between the correlation matrix and the subgroup analysis strengthens the robustness of the sex-specific smooth-muscle vulnerability finding, which most plausibly reflects the smaller baseline radial artery diameter in women and the resulting higher sheath-to-artery ratio during catheterization.

PSV and ΔFMD, ΔNMD. Baseline PSV showed modest but statistically significant inverse correlations with multiple outcome measures: ΔFMD at 24 hours ($\rho = -0.24$, $p = 0.012$), ΔFMD at one month ($\rho = -0.22$, $p = 0.04$), and ΔNMD at one month ($\rho = -0.42$, $p = 0.001$). The consistent direction of these correlations indicates that patients with higher baseline resting PSV experienced greater post-procedural reductions in both endothelium-dependent and endothelium-independent vasoreactivity.

Other associations either did not reach statistical significance or showed associations whose interpretation required consideration of confounding by the variables discussed above, and are not further analyzed here.

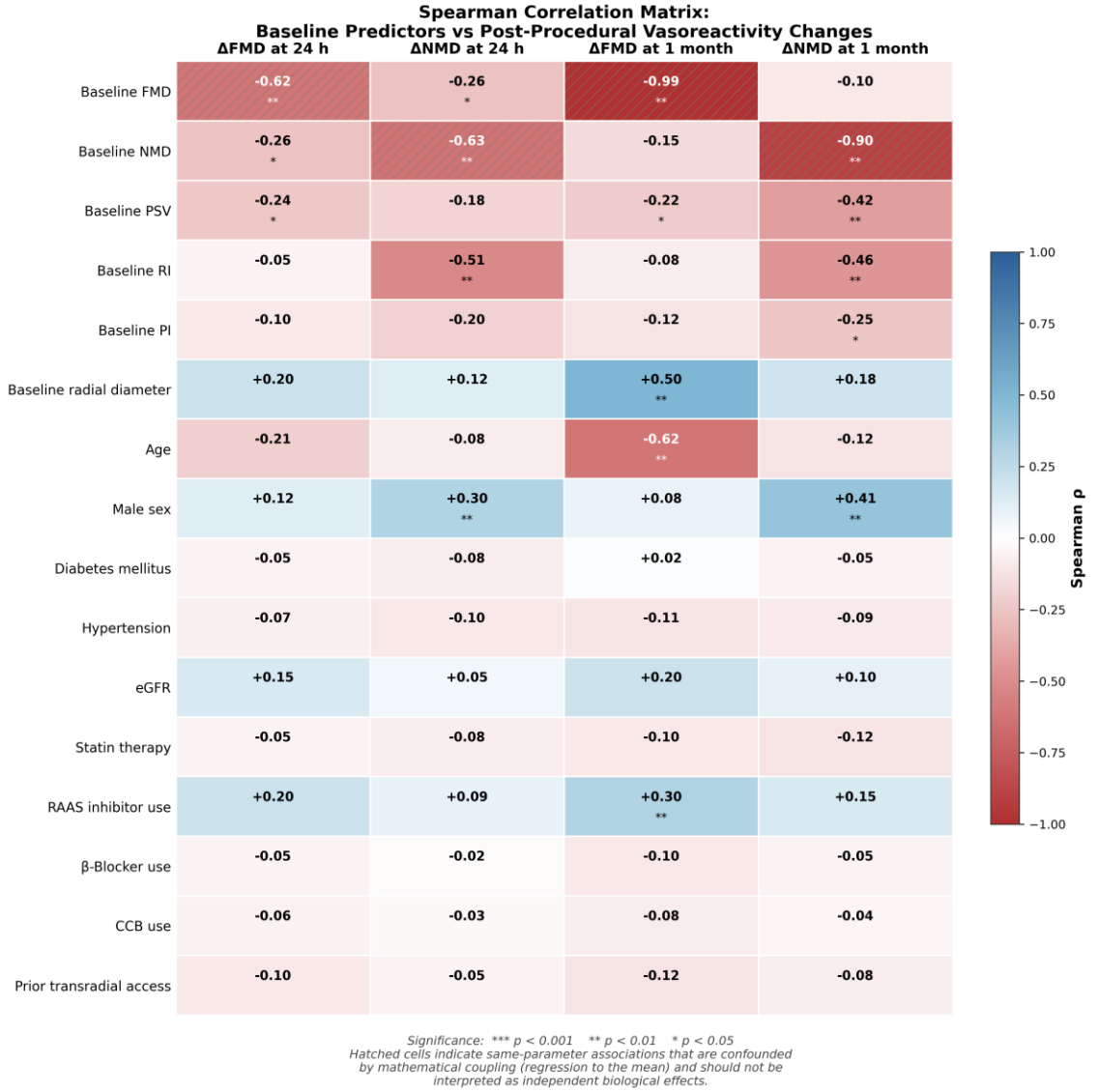

Figure 9.14. *Spearman correlation matrix of baseline clinical, anatomical, and hemodynamic predictors against the four outcome measures: ΔFMD at 24 hours, ΔNMD at 24 hours, ΔFMD at one month, and ΔNMD at one month. Cell values indicate Spearman rho; significance is indicated by stars (*** p < 0.001, ** p < 0.01, * p < 0.05). Colour intensity reflects the magnitude of the correlation (red = negative, blue = positive).*

9.4.2 Discriminatory Performance of Baseline Parameters (ROC Analysis)

The discriminatory ability of baseline Doppler-derived vascular parameters to identify patients at higher risk of acute post-procedural endothelial injury was evaluated using ROC analysis. The analysis included five continuous parameters available from a single pre-procedural vascular ultrasound examination — PSV, FMD, NMD, radial artery diameter, and RI — because these are practical parameters for a clinically deployable pre-procedural risk stratification tool. A "large" reduction in FMD was defined as a ΔFMD at 24 hours more negative than the cohort median (−3.8%). The ROC curves are presented in Figure 9.15.

Among the five baseline parameters tested, baseline PSV showed the highest discriminatory performance (AUC = 0.73; 95% CI 0.64–0.82), indicating acceptable discrimination between patients with larger versus smaller acute FMD reductions. Baseline FMD and baseline NMD each yielded an AUC of 0.67 (95% CI: 0.56–0.78 and 0.58–0.76, respectively), indicating fair discrimination. Baseline radial artery diameter yielded AUC = 0.64 (95% CI 0.54–0.74), also in the fair-discrimination range. Baseline RI had minimal discriminatory ability (AUC = 0.56; 95% CI 0.44–0.68). None of the parameters reached the conventional threshold for excellent discrimination (AUC > 0.80)

The direction of the association — higher baseline PSV predicting larger post-procedural FMD reductions — must be interpreted in the context of the continuity equation, which renders velocity inversely proportional to the square of arterial diameter. In this cohort, baseline PSV was strongly negatively correlated with baseline radial artery diameter ($\rho = -0.68$, Section 9.1.2), meaning that higher baseline PSV primarily identifies patients with smaller radial arteries. Such patients are more vulnerable to catheter-induced injury and show reduced recovery capacity, which manifests as greater post-procedural FMD reduction.

The AUC values for baseline FMD and baseline NMD (both 0.67) should be interpreted with caution, as the outcome definition—based on the cohort median ΔFMD—introduces a degree of mathematical coupling with baseline FMD. The AUC values for baseline PSV, diameter, and RI, by contrast, are not subject to this methodological concern and therefore reflect genuine predictive associations.

Overall, while none of the individual baseline parameters reached the threshold for strong clinical discrimination, baseline resting PSV showed acceptable and methodologically robust discriminatory ability. The combination of PSV and other baseline parameters — including diameter, age, and RI — in a multivariable risk score may yield stronger discriminatory performance than any single parameter alone, and represents a useful direction for future investigation.

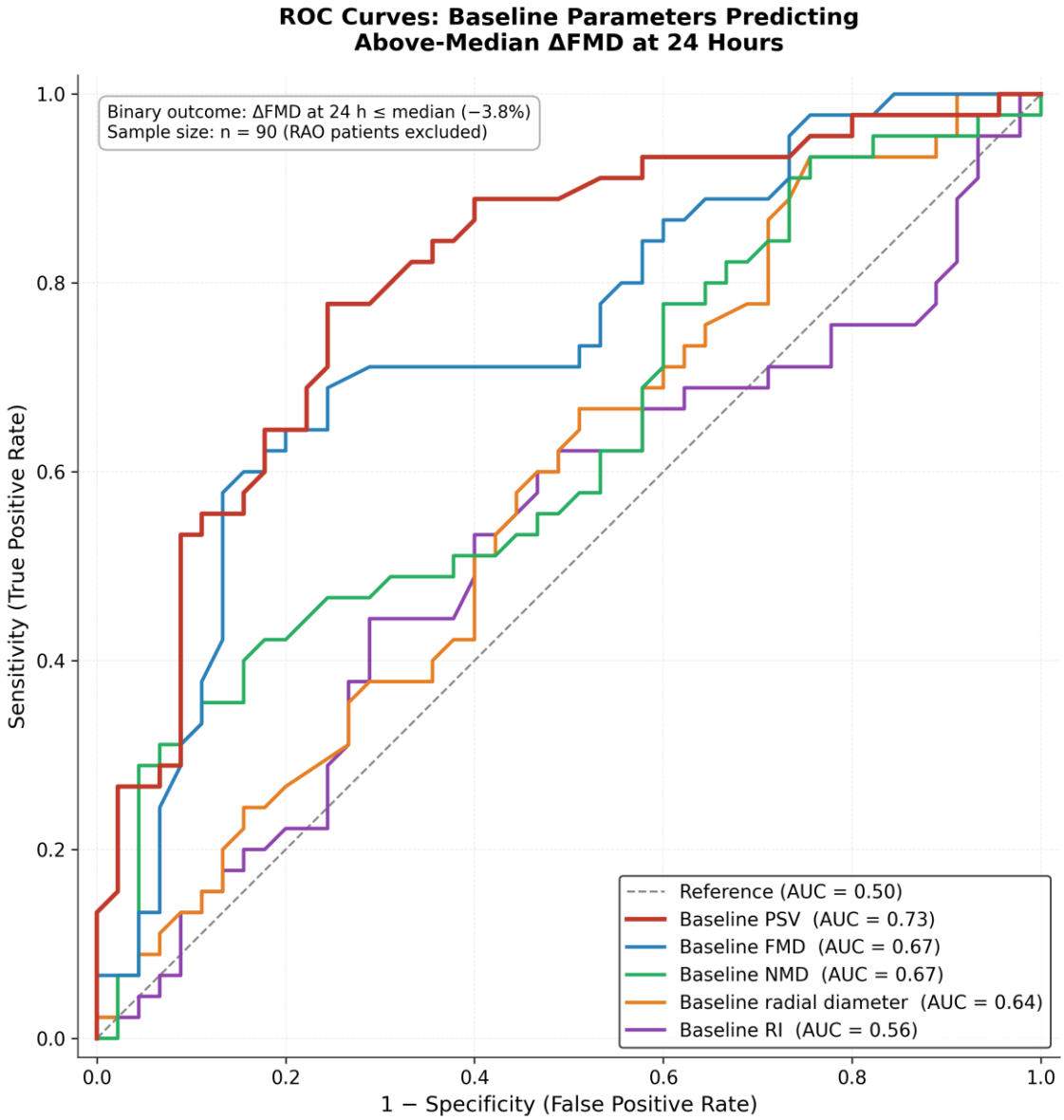

Figure 9.15. *ROC curves for five baseline vascular parameters predicting above-median ΔFMD at 24 hours. The binary outcome was defined as a change in FMD at 24 hours more negative than the cohort median (ΔFMD ≤ −3.8%). Analyses were performed in the 90 patients with paired baseline and 24-hour*

measurements. Area under the curve (AUC) values are shown in the legend. None of the parameters reached the threshold for excellent discrimination (AUC > 0.80).

Chapter 10: Discussion

10.1 Principal Findings and Contextual Overview

10.1.1 Summary of the Three Analytical Objectives

This section provides a summary of the three analytical objectives.

The current research investigated the functional and structural effects of transradial cardiac catheterization on the radial artery using three complementary analytical objectives, each addressing a distinct but complementary research question. The first objective described changes in endothelial vasoreactivity, smooth-muscle responsiveness, resting and hyperemic Doppler hemodynamics, and arterial diameter at three predefined time points — baseline, 24 hours, and one month — thereby characterising the temporal evolution of radial artery function, structure, and hemodynamic behaviour. The second objective examined the extent to which clinical patient characteristics, cardiovascular comorbidities, and baseline pharmacological therapy were associated with the magnitude of post-procedural vascular dysfunction. The third objective evaluated the predictive value of pre-procedural vascular measurements for outcomes at both time points, with the aim of identifying parameters that could be used to stratify the risk of procedural vascular injury across different patients.

Across all three objectives, several internally consistent findings emerged with potential clinical relevance. FMD and NMD decreased significantly at 24 hours and remained significantly below baseline at one month, indicating that functional vascular impairment from transradial catheterization is not fully reversible within this follow-up period. The magnitude of smooth-muscle injury, as reflected by the reduction in NMD, exceeded the endothelial injury reflected by the reduction in FMD at 24 hours, suggesting that the two vascular wall compartments have differing vulnerabilities to the combined mechanical, inflammatory, and ischaemic insult of the procedure. Female sex was significantly associated with greater smooth-muscle injury, indicating a sex-related vulnerability between the two compartments of the radial artery wall, whereas traditional cardiovascular comorbidities such as diabetes mellitus, hypertension, and renal function were not. Baseline vascular phenotype also emerged as an important determinant of post-

procedural functional change: baseline PSV was the strongest discriminator among Doppler-derived baseline parameters evaluated by ROC analysis, while age and baseline radial artery diameter showed the strongest continuous correlations with residual FMD reduction at one month. Overall, these findings support a biological framework in which the procedural insult causes acute vascular dysfunction, followed by differential recovery — partial in smooth-muscle function but limited in endothelial function at one month — alongside evidence of compensatory microvascular adaptation reflected in reduced peripheral vascular resistance indices.

10.1.2 Positioning the Study Within the TRA Literature

The introduction of TRA for coronary procedures began in the early 1990s and has since become the preferred artery approach in most modern catheterization laboratories worldwide (6-8). This adoption was driven not only by lower rates of major access site bleeding complications compared to transfemoral access, but also by consistent data from meta-analyses showing reduced mortality, shorter hospital stays, and improved patient comfort (9, 10, 12). Beyond serving as an access route for interventional procedures, the radial artery also plays important clinical roles, including its use as a graft for coronary artery bypass and for hemodynamic monitoring. Additionally, the vessel's functional integrity affects hand perfusion and long-term vascular health.

Previous studies examining the functional effects of transradial catheterization on the radial artery have generally been limited by small sample sizes and a narrow range of vascular parameters evaluated. Several prospective observational studies have documented impairment of radial artery vasodilation following catheter insertion (119-121), but few have simultaneously assessed both endothelium-dependent and endothelium-independent vasoreactivity across multiple post-procedural time points. Two prior studies are directly comparable to the present work in their use of both FMD and NMD: Yan et al examined 65 patients undergoing transradial coronary procedures and documented significant post-procedural impairment of both FMD and NMD (189), while Mitchell et al examined 30 patients undergoing diagnostic transradial catheterization and demonstrated impairment of both parameters at 24 hours, with partial recovery of FMD by three months (190). Together, these studies established that procedural vascular injury of the radial artery can be detected non-invasively and may

persist beyond the immediate post-procedural period. The present study builds on these findings by including a larger study population, a wider assessment of Doppler-derived hemodynamic parameters, a quantitative analysis of radial artery lumen diameter, and systematic evaluation of clinical and physiological factors that predict post-procedural vascular dysfunction — areas not thoroughly explored in previous research.

The current research has unique methodological features that set it apart from previous studies, increasing its robustness and the reliability of its findings. Standardized measurement procedures help minimize operator-related variability in FMD and NMD testing, a common issue in studies of vascular reactivity. The internal validity is further reinforced by having all ultrasound measurements performed by the same investigator at each time point. Additionally, nonparametric statistical tests were used throughout because the distribution of the main variables deviated from normality. This is shown by the inclusion of a formal outlier analysis and a strong Shapiro-Wilk test for normality before all inferential tests, demonstrating a commitment to methodological transparency often missing in similar research. Together, these measures support confidence in the data interpretation and lay a solid methodological foundation for the discussion.

10.1.3 The Multidimensional Assessment Approach as a Methodological Contribution

A key feature of this research, which should be clearly discussed, is the extent of the vascular examination at each time point. Past studies on the effects of transradial access on radial artery function have mostly focused on one or two measures, usually FMD and NMD. In this study, nine vascular parameters were assessed simultaneously, including endothelial and vascular smooth muscle function, resting flow velocity, resistance indices, pulsatility indices, hyperemic flow reserve, and arterial diameter. This multidimensional assessment strategy enables the simultaneous evaluation of multiple aspects of radial artery vascular physiology, thereby identifying divergent responses across different vascular parameters that would not be detectable with a more limited measurement framework.

The value of this multidimensional methodological approach goes beyond measuring individual vascular parameters by offering a more comprehensive biological

understanding of how the radial artery responds to the immediate mechanical trauma of arterial access. Instead of showing a single change in one marker, the present study offers a temporally detailed view of the vascular response. Specifically, the radial artery seems to undergo acute functional impairment, followed by selective hemodynamic recovery, partial restoration of smooth muscle function, persistent endothelial dysfunction, and structural remodeling indicated by changes in arterial lumen diameter. These different response patterns suggest that various vascular parameters are involved in separate yet interconnected pathways of injury, repair, and adaptation after catheter-induced trauma.

10.2 Temporal Changes in Radial Artery Function and Haemodynamic Parameters (Objective 1)

10.2.1 Acute Endothelial Impairment: FMD Reduction at 24 Hours and Its Mechanistic Basis

The impairment of endothelial function during transradial catheterization—shown by the decrease in FMD from 11.58% to 7.97%—is both statistically significant and clinically meaningful. The 3.6-percentage-point reduction is enough to move a large part of the normal or mildly impaired endothelial function range into the zone associated with endothelial dysfunction, based on standard FMD thresholds used in cardiovascular risk groups. The endothelial layer of the arterial intima is highly sensitive to mechanical and hemodynamic forces, and inserting an introducer sheath into the radial artery causes direct trauma, changes in local shear stress patterns, and sustained circumferential stretching of the vessel wall during catheter manipulation. These mechanical forces can activate endothelial responses, cause nitric oxide synthase uncoupling, and produce reactive oxygen species, all of which decrease nitric oxide availability and impair the shear-mediated vasodilatory response measured by FMD.

The pathophysiology of the acute endothelial dysfunction observed after transradial catheterization appears to be primarily mechanical rather than metabolic or ischemic, although ischemic effects from post-procedural hemostatic compression cannot be ruled out. After removing the sheath, hemostasis is usually achieved by applying external pressure to the radial artery puncture site, often for up to two hours. This process may cause a transient period of distal arterial ischemia, which can lead to endothelial activation via hypoxia–reoxygenation mechanisms and the release of vasoactive substances such as

endothelin-1. However, the design of this study does not allow us to distinguish between the relative roles of intra-procedural mechanical injury from sheath insertion and catheter manipulation and the possible ischemic effects of post-procedural compressive hemostasis in explaining the reduction in FMD seen at 24 hours. Because no intermediate vascular assessment was performed between the end of the procedure and the 24-hour follow-up, the sequence of these mechanisms cannot be fully determined.

These results showing an acute reduction in FMD after transradial catheterization align with those of Mitchell et al in their series of 30 patients undergoing diagnostic transradial catheterization, in which radial artery FMD was significantly impaired at 24 hours and showed only partial recovery at three months (190). The present findings confirm and expand on these observations in a much larger group and with better timing details. Similar findings have been reported by Bi et al, who studied patients undergoing transradial catheterization with nifedipine pre-treatment and demonstrated significant post-procedural reductions in both flow- and nitroglycerin-mediated dilations of both proximal and distal segments of the radial artery (127). The consistent FMD reductions across these independent studies, despite different methods and patient populations, support the conclusion that acute endothelial damage is predictable and common after transradial arterial access, rather than unique to those studies.

From a pathophysiological point of view, the sharp decrease in FMD can be seen as a localized macrovascular sign of endothelial activation in the accessed radial artery segment. During transradial catheterization, endothelial cells face continuous mechanical stretching, disruption of normal laminar shear stress during catheter manipulation, and direct contact between the introducer sheath and the endothelium. The resulting endothelial dysfunction is marked by lower nitric oxide availability, compromised vasodilation ability, and a prothrombotic endothelial phenotype. Since FMD measures nitric oxide–dependent vasodilation in response to reactive hyperemia, it is especially sensitive to disruptions in endothelial function. Therefore, FMD is a widely accepted marker for evaluating endothelial injury and dysfunction related to transradial arterial access.

10.2.2 Smooth Muscle Dysfunction: Dissociation Between NMD and FMD and Its Pathophysiological Implications

One of the most notable findings of this study is that the overall reduction in NMD at 24 hours exceeded that of FMD, both in percentage points and relative to their baseline values. The decrease in NMD was 6.60 percentage points, or 37 percent of its baseline, compared to a 3.61 percentage-point drop in FMD, or 31 percent of its baseline. NMD reflects endothelium-independent vasodilation, mediated by direct relaxation of vascular smooth muscle cells after administering exogenous nitroglycerin, primarily through activation of the cyclic guanosine monophosphate signaling pathway. A greater reduction in NMD than in FMD suggests that smooth muscle dysfunction contributes to the overall decrease in vasoreactivity at 24 hours, rather than changes solely due to endothelial nitric oxide deficiency. This dissociation, which has not been consistently observed in earlier studies of TRA, offers new insights into the mechanisms of arterial injury during procedures.

The most plausible explanation for the smooth muscle dysfunction observed after transradial catheterization is direct medial injury caused by mechanical compression of the arterial wall by the introducer sheath. The outer profile of the sheath applies radial pressure against the tunica media, where vascular smooth muscle cells responsible for vasomotor regulation are located, especially when the sheath-to-artery diameter ratio nears one. This mechanical stress may temporarily disrupt smooth muscle cell integrity and impair intracellular signaling pathways involved in nitric oxide–mediated relaxation, thus reducing the vasodilatory response to exogenous nitroglycerin. These effects are probably more noticeable in smaller radial arteries, where the sheath takes up a larger proportion of the luminal diameter. Histopathological studies of radial arteries after TRA have shown medial smooth muscle disruption, vacuolization, and focal necrosis in segments that were in contact with the sheath, supporting the mechanistic explanation suggested in this study.

The idea that FMD and NMD are separate but related measures of vascular reactivity is well recognized in the non-invasive vascular function literature. FMD measures the response triggered by shear stress–induced endothelial nitric oxide production, which then diffuses to the underlying vascular smooth muscle causing it to relax. In contrast, NMD does not involve the endothelium and depends entirely on smooth muscle cells

reacting to externally supplied nitric oxide. The finding that NMD decreased more than FMD in this study suggests that smooth muscle dysfunction could be a key factor in the vascular damage caused by transradial catheterization. Additionally, the decrease in FMD might underestimate the overall impairment in vasoreactivity, as FMD responses could be affected by nonuniform endothelial injury along the artery rather than by consistent endothelial dysfunction throughout the vessel wall.

A redox-mediated component of vascular injury may also play a role in the reduction of NMD observed in this context. Mechanical trauma from sheath insertion can cause a temporary rise in reactive oxygen species within the vessel wall by activating NADPH oxidase in both endothelial and smooth muscle cells. These reactive species decrease nitric oxide bioavailability by quickly scavenging nitric oxide and disrupting downstream smooth muscle signaling pathways involved in cyclic GMP–mediated relaxation. Consequently, vasodilatory responses may be diminished regardless of whether nitric oxide is produced by endothelial cells (as in FMD) or provided externally through nitroglycerin (as in NMD). This mechanism may partly account for the reduction in both endothelium-dependent and endothelium-independent vasoreactivity following transradial catheterization. Evidence from models of vascular mechanical injury and exercise-induced endothelial stress supports the role of oxidative pathways in affecting FMD responses, with antioxidant treatments shown to lessen redox-mediated endothelial dysfunction.

10.2.3 Resting Doppler Haemodynamics: Temporal Trajectories of PSV, RI, and PI

PSV decreased significantly at 24 hours, consistent with the expected decline in resting forward flow due to post-procedural arterial spasm, wall edema, and increased resistance within the immediately catheterized segment. At one month, PSV returned to a value not significantly different from baseline, indicating that the hemodynamic disturbance of resting forward flow is fully reversible within one month, even when longer-term impairment of vasoreactivity persists. The observation that hemodynamic recovery occurs before functional recovery is physiologically meaningful, as it indicates that adequate resting blood flow to the hand resumes well before the endothelial and smooth-muscle components return to their pre-procedural state.

The behaviour of the RI followed a biphasic pattern. At 24 hours, RI increased slightly, consistent with the expected acute rise in peripheral vascular resistance caused by local vasoconstriction and edema. At one month, however, RI decreased significantly below baseline (mean 0.84 compared with 0.94 at baseline). Because RI reflects the resistance of the vascular bed distal to the measurement point, this decrease indicates a compensatory reduction in downstream peripheral vascular resistance — that is, a vasodilatory adaptation of the hand microvascular bed. Such compensatory microvascular vasodilation is a recognized response to upstream conduit artery dysfunction, serving to preserve distal tissue perfusion when proximal vasodilatory capacity is impaired. In this context, the reduction in RI below baseline is not paradoxical but biologically coherent: it represents a microvascular adaptation that partially compensates for the persistent impairment of conduit artery vasoreactivity observed at the same time point.

The PI showed a steadily declining trajectory across the three time points, with statistically significant pairwise comparisons. Because PI is affected by both upstream cardiac output and downstream vascular resistance, the progressive decline from baseline to 24 hours and to one month reflects a sustained shift of the radial vascular bed towards a lower-resistance, lower-pulsatility profile. This pattern aligns directly with the RI trajectory and supports the same interpretation of compensatory microvascular adaptation. Whether the sustained reduction in peripheral resistance observed at one month represents a stable compensatory adaptation or a transitional state that resolves with longer-term follow-up cannot be determined from the present dataset; the increase in hyperaemic flow reserve observed at one month (Section 10.2.5) is consistent with the former interpretation.

10.2.4 Radial Artery Diameter: Biphasic Response and the Evidence for Compensatory Remodelling

The temporal course of lumen diameter of the radial artery in the current study showed a biphasic pattern, which makes sense biologically and aligns with how arteries typically react to acute trauma. After 24 hours, the diameter decreased significantly from a baseline mean of 0.243 cm to 0.234 cm, a difference of about 0.009 cm, indicating the expected acute vasoconstrictive and edematous response to sheath-related wall injury. The main processes behind this early diameter constriction are likely a combination of reactive

smooth muscle spasm in the peri-sheath area, wall thickening due to mural edema and inflammatory infiltration pressing against the lumen, and possibly hematoma formation at the puncture site, which compresses the nearby vessel wall. The relatively small size of the diameter reduction, along with the limited variability between individuals at this time point—as shown by the lower standard deviation—suggests that the constrictive response is modest and unlikely to significantly restrict resting blood flow in most patients.

At the one-month follow-up, radial artery diameter showed partial recovery compared to the 24-hour measurement but remained below the baseline value. This suggests that the early post-procedural luminal narrowing was only partly reversible within the one-month observation period. The improvement relative to the 24-hour mark indicates resolution of transient factors contributing to early diameter reduction, such as vasospasm, mural edema, and local inflammatory response. However, the continued presence of a smaller lumen compared to baseline suggests that structural changes within the arterial wall may still be present. Previous structural studies of radial arteries after transradial access have shown histological changes including intimal hyperplasia, medial smooth muscle cell injury, and adventitial remodeling. As summarized in the structural review by Sakellariou et al, these processes can lead to complex geometric responses in the vessel wall, with both inward and outward remodeling mechanisms potentially occurring after arterial injury (25). The current findings imply that at the one-month mark, the radial artery has not yet returned to its pre-procedural size, indicating that structural recovery may be incomplete or that inward remodeling processes remain partially active during this phase of vascular healing.

The study by Kala et al, which used serial OCT to examine structural changes after transradial PCI, demonstrated a significant increase in radial artery intimal volume and a corresponding decrease in lumen volume at nine-month follow-up (132). The PRESERVE RADIAL trial similarly documented intimal-medial thickening of the forearm radial artery at 90 days following transradial access for coronary angiography, with no significant difference in the magnitude of thickening between distal and proximal access approaches (131). The persistent reduction in radial artery diameter observed at one month in the present study is consistent with the early stages of this structural remodelling process, occurring before the longer-term intimal changes documented in

those studies become fully apparent. The continued presence of a smaller lumen compared to baseline suggests that, while transient factors responsible for the acute narrowing — such as vasospasm, mural edema, and local inflammation — may have largely resolved, early structural changes in the arterial wall are likely already underway. The structural literature thus offers a plausible biological framework for understanding the diameter patterns observed, indicating that healing and remodelling of the radial artery remain active during the first months after TRA. Longer follow-up with serial measurements would be necessary to determine whether complete lumen recovery or more persistent inward remodelling ultimately prevails.

10.2.5 Hyperemic Flow Reserve: Reactive Hyperaemia at 24 Hours and Volumetric Augmentation at One Month

The parameters of hyperemic flow, such as hyperemic VTI and hyperemic blood volume per beat, showed temporal variations that were mechanistically different from the resting Doppler parameters and required a new interpretive approach. Over 24 hours, hyperemic VTI also exhibited a small but statistically significant decrease from a baseline mean of 58.12 cm to 55.46 cm. This early decline indicates a mild impairment in the radial artery's ability to increase blood flow during reactive hyperemia. Such findings align with the functional impairment reflected by decreases in FMD and NMD at the same time point. When endothelial function and vascular smooth muscle responsiveness are impaired, the vessel’s capacity to dilate in response to vasodilatory stimuli—such as shear stress, exogenous nitric oxide donors, or post-ischemic reactive hyperemia—may be diminished. Notably, the reduction in hyperemic VTI was smaller than the declines observed in FMD and NMD. This difference suggests that hyperemic flow reserve may still be partly maintained despite reduced conduit artery vasoreactivity. From a physiological perspective, this makes sense because flow increase during reactive hyperemia depends not only on radial artery diameter but also on vasodilatory responses within the distal microvascular bed. These additional regulatory mechanisms could buffer the overall decrease in hyperemic flow, even if there is localized vascular injury at the site of arterial access.

The decrease in hyperemic blood volume observed at 24 hours should be understood in relation to the concurrent reduction in radial artery diameter. Since the radial artery diameter was smaller at 24 hours, the calculated hyperemic blood volume was also lower

compared to baseline, despite only a slight decrease in hyperemic VTI. This suggests that early post-procedural geometric changes in the vessel wall may affect the artery's volumetric flow.

At one month, hyperemic VTI rose above baseline, reaching 62.81 cm compared with a baseline of 58.12 cm, reflecting decreased resistance of the peripheral vascular bed. Both the baseline-versus-one-month and the 24-hour-versus-one-month comparisons were statistically significant. However, the radial artery diameter remained slightly smaller than baseline at that time point. As a result, the derived hyperemic blood volume per beat did not differ significantly from baseline values. The increase in hyperemic VTI therefore indicates recovery of flow dynamics rather than a structural enlargement of the vessel lumen.

Overall, the hyperemic flow reserve data emphasize a key difference between hemodynamic and functional measurements of the radial artery after TRA. Adequate or normalized flow volumes do not necessarily mean full recovery of vascular function, as endothelial and smooth muscle vasoreactivity might still be significantly impaired. Without additional vasoreactivity testing, such functional issues could go unnoticed when only using Doppler flow measurements.

10.2.6 Persistence of Functional Impairment at One Month: Clinical Significance and Comparison with Prior Data

The observation that FMD and NMD remained significantly impaired one month after transradial catheterization carries important clinical implications. The mean FMD at one month (8.25%) was not significantly different from the 24-hour value ($p = 0.08$, Section 9.2.1), indicating that endothelial vasoreactivity showed no meaningful recovery between the acute time point and one month. NMD, by contrast, showed a partial but statistically significant recovery from 24 hours to one month ($p < 0.001$), though the one-month value (13.51%) remained substantially below baseline (18.04%). The more rapid partial recovery of NMD compared with the persistent FMD trajectory is consistent with the greater regenerative capacity of vascular smooth muscle cells relative to the slower, progenitor-cell-dependent process of endothelial repair. Together, these data indicate that at one month after transradial catheterization, the radial artery exhibits a vasoreactivity

profile that differs significantly from the pre-procedural state and does not follow a clear trajectory towards complete functional restoration over this interval.

These findings are particularly relevant when placed in the context of previous research on the timeline of radial artery functional recovery after transradial procedures, supporting the broader conclusion that endothelial function of the accessed radial artery does not return to pre-procedural levels within the first few months following catheterization. Whether full recovery of vasoreactivity eventually occurs at later time points — for example, at six or twelve months — or whether a lasting decline in endothelial function becomes part of the long-term remodelling process of the artery cannot be determined from the present dataset. Longer-term follow-up studies are necessary to characterize the ultimate course of vascular functional recovery following transradial access.

The clinical significance of ongoing radial artery functional impairment depends on patient-specific circumstances. In terms of hand perfusion, the radial artery is one of two principal sources supplying the palmar arch, with the ulnar artery providing the majority of flow in most individuals. Persistent radial vasoreactivity impairment is therefore unlikely to compromise resting hand perfusion in patients with healthy ulnar circulation, particularly given that resting PSV returns to near pre-procedural values within one month. The picture may differ in patients with ulnar artery disease or anatomical variations in the palmar arch, where the radial artery could play a more important role in digital blood flow during increased demand. The more pressing clinical concern arises in patients who may require the radial artery as a surgical graft for coronary artery bypass grafting after transradial catheterization, where combined endothelial and smooth-muscle impairment — together with early intimal hyperplasia and altered resistance to vasospasm — could adversely affect long-term graft patency. The implications for radial artery conduit use are discussed in detail in Section 10.5.4.

10.3 Subgroup Analysis and Predictors of Functional Damage at 24 hours (Objective 2)

10.3.1 The Null Effect of Classical Cardiovascular Risk Factors

The lack of a strong link between traditional cardiovascular risk factors such as diabetes mellitus, hypertension, and dyslipidaemia and the extent of post-procedural FMD or NMD decline is a finding that warrants careful interpretation. These conditions are known as major contributors to endothelial dysfunction in the general population. Each has been linked to impaired FMD and decreased NMD in observational studies and meta-analyses of non-invasive vascular function.

10.3.2 The Sex-Specific Effect on Smooth Muscle Damage: Mechanisms and Implications

One of the most interesting findings of this study, both clinically and scientifically, is the significantly greater NMD decrease observed in female versus male patients, with mean values of approximately -8.3% and -5.8%, respectively, and a p-value of 0.005. The fact that this sex effect was specific to NMD and not FMD—since the sex-specific difference in FMD was not significant at p=0.40—suggests that the smooth muscle component is uniquely vulnerable to the procedure in women. This is not easily explained by the usual pathways of sex-related endothelial dysfunction, which would typically be more evident in FMD than in NMD. Therefore, the differential effect indicates the presence of a mechanism that disproportionately impairs smooth muscle responsiveness in the female radial artery following catheter-mediated injury.

The strongest anatomical link is related to arterial diameter. The smaller diameter of female radial arteries, compared to males, is a well-known anatomical factor confirmed by multiple large-scale cohort studies and has direct implications for the outcomes of transradial catheterization (35, 155). With a smaller-caliber diameter, the ratio of the outer to the inner diameter of the introducer sheath increases, meaning the sheath occupies a larger percentage of the luminal space and exerts a greater radial compressive force against the inner medial smooth muscle layer during the procedure. This increased sheath-to-artery ratio has been repeatedly associated with poorer post-TRA outcomes, such as higher risks of RAO (30, 167), greater intimal injury observed on OCT (60), and provides a mechanistically sound explanation for the increased smooth muscle damage seen in women.

The evidence about sex differences in TRA outcomes comes from large randomized trials and registries. These studies suggest that female sex is an independent factor affecting the level of vascular injury. Large randomized trials and individual-patient meta-analyses comparing transradial with transfemoral access have consistently shown that female patients have smaller radial arteries and experience more access-site complications, and that the bleeding-reduction benefit of transradial access is partly attenuated in women by higher access-site failure rates attributed to anatomical limitations (10, 157).

Sex-related differences in vascular smooth muscle function may also contribute to the observed findings and are not limited to the mechanical explanation related to arterial diameter. Experimental and clinical studies have shown that the functional responses of female radial arteries to pharmacological and mechanical stimuli may differ from those of male vessels. In particular, male sex has been identified as an independent predictor of nitroglycerin-induced vasodilation (126). Although the biological mechanism for this sex difference is incompletely characterized, possible contributors include differences in smooth-muscle receptor density, hormonal modulation of vascular tone, or efficiency of the nitric oxide–cyclic GMP signalling pathway. Such inherent biological differences in smooth muscle physiology may increase the susceptibility of the female radial artery to oxidative stress and mechanical injury, which can impair nitric oxide–mediated relaxation independently of the sheath-to-artery diameter ratio. While the smaller arterial diameter often seen in women contributes to a higher sheath-to-artery ratio and thus greater mechanical stress during catheterization, biological differences in smooth muscle signaling pathways may further enhance the vulnerability of the vessel wall. Consistent with this, female sex has been linked to higher rates of TRA failure, particularly in emergency settings such as STEMI (157). This increased procedural challenge has been attributed to smaller arterial diameters and increased vasoreactivity to mechanical stimulation, which predispose to radial artery spasm and haemostatic complications (47).

The lack of a sex difference in FMD reduction in the context of a large sex difference in NMD reduction also has other implications on the relative vulnerability of the two vascular compartments to procedural injury in women. One of such is that it is not the smaller arterial diameter that makes the endothelium of female radial arteries more susceptible to the acute shear and contact trauma of sheath insertion than that of males. This may indicate that due to the fact that the endothelial layer is a monolayer of cells on

the luminal surface that are exposed to comparable changes in shear stress in both sexes with the insertion of a sheath of the identical outer diameter, as the changes in shear perturbation at the luminal surface are dictated by the flow velocity field and not by the absolute size of the arteries. The smooth muscle layer, however, is more directly influenced by the transmural compressive stress produced by the sheath, which is inversely related to arterial diameter and thus is systematically larger in female patients.

The lack of a significant sex difference in FMD reduction, despite the notable sex difference in NMD reduction, provides additional insight into how different layers of the vascular wall are vulnerable to procedural injury in women. This suggests that the smaller arterial diameter in female patients does not necessarily make the endothelial layer more prone to shear stress and surface contact trauma from sheath insertion. One possible explanation relates to the structural organization of the arterial wall. The endothelium, made up of a single cell layer lining the luminal surface, is mainly exposed to changes in local shear stress caused by the flow within the lumen. Since the sheath used during the procedure has the same external diameter in both sexes, the immediate disturbance to luminal flow patterns may be fairly similar regardless of vessel size. In contrast, the vascular smooth muscle layer is more directly impacted by the mechanical compression and transmural stress generated by the sheath inside the artery. Because this compressive stress is inversely related to arterial diameter, it tends to be greater in smaller vessels, which are more common in female patients. This mechanism might explain why smooth muscle dysfunction, indicated by the greater reduction in NMD, seems to be more significant in women even though there is no corresponding sex difference in endothelial damage.

10.3.3 Age as a Modulator of Recovery Rather Than of Acute Susceptibility

The subgroup analysis of FMD reduction at 24 hours by age group (< 65 vs ≥ 65 years) demonstrated a significantly greater reduction in older patients ($p < 0.05$, Section 9.3.2). The Spearman correlation between age and ΔFMD at 24 hours, evaluated as a continuous variable, was weaker ($\rho = -0.21$, $p = 0.050$, Section 9.4.1), indicating that the age effect at the acute time point is modest and becomes statistically apparent primarily when the cohort is dichotomised. By contrast, at one-month follow-up, age was strongly inversely correlated with ΔFMD ($\rho = -0.62$, $p < 0.001$), reflecting a substantial age-dependent

residual endothelial deficit at this later time point. Notably, age did not correlate significantly with ΔNMD at either time point, indicating that the age effect is selective for endothelium-dependent vasoreactivity rather than smooth-muscle function.

This pattern suggests a temporal dissociation in how age influences the post-procedural vascular response: increasing age has a modest effect on the acute magnitude of endothelial injury at 24 hours but a much stronger effect on the completeness of endothelial recovery at one month. There is a robust biological basis for this differential effect. Ageing is associated with decreased endothelial nitric oxide bioavailability, impaired mobilization of circulating endothelial progenitor cells, and reduced endothelial regenerative capacity, all of which tend to slow recovery and limit functional restoration after vascular injury without necessarily affecting the initial injury response (158, 191).

Clinically, these findings suggest that older patients undergoing transradial catheterization face an increased risk of persistent endothelial impairment at one month, primarily because they have reduced regenerative capacity to repair catheterization-induced vascular injury. Age should therefore be considered as a key component of the pre-procedural vascular phenotype discussed in Section 10.4.1 and as a practical factor in planning post-procedural monitoring. Older patients may benefit most from extended follow-up beyond the standard one-month check, and from future research into pre-procedural or peri-procedural vasoprotective strategies that could accelerate endothelial recovery.

10.3.4 The Borderline RAAS Signal: Endothelial Protection or Statistical Limitation?

The association between RAAS inhibitor use and a smaller reduction in FMD at 24 hours should be interpreted cautiously. In the subgroup comparison, the difference between treated and untreated patients did not reach conventional statistical significance ($p = 0.06$, Section 9.3.4), although the direction of the effect suggested a smaller decline in endothelial function among patients receiving RAAS inhibitors. In the cross-parameter Spearman analysis (Section 9.4.1), RAAS inhibitor use showed a positive correlation with ΔFMD at 24 hours ($\rho = +0.20$) and a stronger positive correlation with ΔFMD at one month ($\rho = +0.30$) — both consistent with a protective directional trend, and the one-

month correlation reaching statistical significance. The consistency of the directional signal across both the acute and the one-month time points supports the possibility of a modest protective effect, though the observational nature of the analysis and the high prevalence of RAAS inhibitor use in the cohort preclude definitive causal conclusions. This interpretation is biologically plausible, given the well-established vasoprotective effects of RAAS inhibitors.

It cannot be conclusively determined from the current study design whether the borderline RAAS signal in the data reflects a real biological protective effect or a statistical artefact. The principal methodological limitation is the high proportion of RAAS inhibitor use in the cohort (64%), which reduces the size of the untreated comparison group and limits the statistical power of the between-groups comparison. Additionally, RAAS inhibitor use in this observational cohort is not randomly allocated but driven by clinical indication — most often hypertension, heart failure, or diabetes. These conditions are themselves associated with altered baseline vascular function, creating potential confounding by indication whose direction is difficult to predict: patients with these comorbidities may have lower baseline FMD (and therefore less mathematical room for reduction), but they may also have greater intrinsic vulnerability to procedural injury. Determining whether a genuine pharmacological effect on preventing endothelial damage exists would require a randomized trial specifically designed to assess pre-procedural RAAS inhibition as a vascular protective strategy in patients undergoing transradial catheterization.

10.3.5 Medications in Aggregate: Why Vasoprotective Agents Did Not Reach Significance

The inability of statin therapy, beta-blockers, and calcium channel blockers to significantly protect against FMD or NMD damage at 24 hours aligns with the overall null results for these medications in the study. This can be explained by both the limited statistical power mentioned earlier and the mechanistic nature of these drug classes concerning acute procedural vascular injury. Statins primarily exert their vasoprotective effects through long-term upregulation of endothelial nitric oxide synthase, reduction of oxidative stress, and stabilization of the endothelial glycocalyx—all processes that occur over weeks to months of sustained therapy, not during acute events. The immediate sheath-mediated injury, which occurs within hours, may not be significantly mitigated by

these chronic adaptive mechanisms, especially when the extent of mechanical insult exceeds the protective capacity afforded by chronic statin use.

The vasomotor effects of beta-blockers and calcium channel blockers are mainly mediated through different mechanisms than those directly involving endothelial biology. Beta-blockers primarily affect the cardiovascular system by reducing heart rate and modulating sympathetic activity, while calcium channel blockers mainly work through inhibiting L-type calcium channels in vascular smooth muscle cells, causing direct vasodilation. These mechanisms do not directly target endothelial oxidative stress and inflammatory pathways that cause acute procedural endothelial dysfunction, unlike RAAS inhibitors or statins, which are well known for protecting the endothelium. From a pharmacodynamic standpoint, it is therefore not surprising that these drug classes did not influence vasoreactivity outcomes after the procedure in this analysis. This is consistent with the larger body of research, where beta-blockers and CCB have not been shown to significantly protect against endothelial injury from acute vascular procedures. The lack of a clear effect across most medication classes, along with only a modest signal for RAAS inhibition, indicates that pharmacological approaches to reducing procedural vascular injury may have limited impact in the short term. Instead, procedural and technical factors—such as choosing the right sheath size for the arterial diameter, using patent hemostasis protocols, and using hydrophilic sheath coatings—are likely to be more effective strategies for reducing radial artery injury after transradial access (167).

10.4 Predictive Value of Baseline Parameters for Post-Procedural Functional Outcome (Objective 3)

10.4.1 The Baseline Phenotype as a Predictor of Post-Procedural Outcome

The third analytical objective of the present study was to identify which pre-procedural vascular parameters carry predictive information about the magnitude and persistence of procedural vascular injury. Although Spearman correlations were calculated across all baseline parameters and outcome measures (Figure 9.14), the interpretation in Section 9.4 focused specifically on cross-parameter associations — that is, associations between one

baseline parameter and the change in a different vasoreactivity outcome — because same-parameter associations such as baseline FMD versus ΔFMD are confounded by mathematical coupling and regression to the mean, and therefore cannot be reliably interpreted.

Four baseline parameters emerged as meaningful cross-parameter predictors of post-procedural outcome in this cohort: baseline radial artery diameter, baseline PSV, baseline RI, and age. These four variables share a common interpretive thread: each reflects a different aspect of pre-procedural arterial health, and together they constitute a pre-procedural vascular phenotype that shapes both the magnitude of acute injury and the completeness of subsequent recovery.

Baseline radial artery diameter showed a moderate positive correlation with ΔFMD at one month ($\rho = +0.50$, $p < 0.001$), with no corresponding association at 24 hours or for ΔNMD at either time point. The temporal and parameter-specific nature of this association suggests that baseline diameter predicts arterial health relevant to endothelial recovery. Patients with larger baseline arteries experienced smaller residual FMD deficits; mechanical protection via lower sheath-to-artery ratio may support more effective endothelial repair following catheter-induced injury (30, 159, 167). The absence of a parallel diameter–ΔNMD correlation may argue against a purely mechanical injury interpretation, since a mechanical injury mechanism would be expected to affect smooth-muscle function as well.

Baseline PSV mirrors the diameter finding through the continuity equation, which renders flow velocity inversely proportional to the square of arterial diameter. In this cohort, baseline PSV was strongly negatively correlated with baseline radial artery diameter ($\rho = -0.68$), meaning that higher baseline PSV primarily identifies patients with smaller radial arteries. Consistent with the diameter findings, baseline PSV showed modest but statistically significant inverse correlations with ΔFMD at 24 hours ($\rho = -0.24$), ΔFMD at one month ($\rho = -0.22$), and ΔNMD at one month ($\rho = -0.42$). Higher baseline PSV — indicating smaller arteries — was associated with greater post-procedural reductions in vasoreactivity.

Baseline RI, a Doppler-derived index reflecting the resistance of the vascular bed distal to the measurement point, correlated inversely with ΔNMD at 24 hours ($\rho = -0.51$) and

at one month ($\rho = -0.46$). Patients with higher baseline peripheral vascular resistance experienced greater post-procedural reductions in smooth-muscle-dependent vasoreactivity. Elevated peripheral RI is associated with microvascular dysfunction, reduced vasodilator reserve, and cardiovascular risk factor burden — particularly ageing, hypertension, and diabetes (52, 158). The inverse association between baseline RI and post-procedural smooth-muscle vasoreactivity is therefore consistent with the interpretation that patients with more extensive systemic vascular dysfunction, as reflected in their distal microvascular resistance, are more vulnerable to the injury caused by transradial catheterization. Shared confounding with age and cardiovascular comorbidities, which independently raise baseline RI and may independently increase injury susceptibility, cannot be excluded in the present bivariate analyses.

Age emerged as a strong predictor of residual FMD impairment at one month ($\rho = -0.62$, $p < 0.001$), with only a weak association at 24 hours ($\rho = -0.21$). This temporal profile suggests that age acts predominantly on endothelial recovery rather than on the magnitude of acute injury, a pattern already discussed in Section 10.3.3. The absence of an age effect on ΔNMD at either time point supports the interpretation that age preferentially affects endothelium-dependent function through impaired repair capacity, mediated by reduced mobilization of circulating endothelial progenitor cells and accumulated oxidative stress in the ageing vascular endothelium (158, 191).

Taken together, these four predictors converge on a coherent interpretation: the pre-procedural state of arterial health — reflected in baseline diameter, resting hemodynamics, vascular resistance, and age — determines both how much injury the procedure inflicts and how well the artery recovers afterwards. Patients with larger diameter arteries, lower resting PSV, lower RI, and younger age represent a "healthier baseline phenotype" that experiences both less acute injury and more complete recovery. Patients with the opposite phenotype — smaller arteries, higher resting PSV, elevated RI, and advanced age — are more vulnerable to acute injury and recover less completely at one month.

Beyond these four baseline vascular parameters, male sex also showed significant predictive associations with ΔNMD at both 24 hours ($\rho = +0.30$) and one month ($\rho = +0.41$), reflecting the greater smooth-muscle injury sustained by female patients. Because this association is primarily a consequence of the smaller radial artery diameter in women

and the resulting higher sheath-to-artery ratio (30, 155, 167), the mechanistic interpretation of the sex effect is discussed in detail in Section 10.3.2 and is not reiterated here. From a predictive standpoint, however, patient sex complements the baseline vascular phenotype described above and should be considered alongside it in pre-procedural risk stratification.

A separate biological hypothesis should also be considered — that patients with higher baseline FMD or NMD may have greater functional reserve, and therefore show larger reductions after acute vascular injury. The present analyses cannot test this hypothesis directly. The correlation between baseline FMD and ΔFMD is affected by mathematical coupling, because the baseline value appears in the calculation of the change. This confounding makes it difficult to distinguish a true biological effect from regression to the mean. Testing the functional reserve hypothesis properly would require different analytical methods or larger studies. It therefore remains a biologically plausible idea that has not been tested in the present cohort, and represents an important question for future research. The convergent predictive value of these four parameters suggests that a combined pre-procedural vascular assessment — integrating diameter, Doppler flow velocities, RI, and patient age — may offer stronger risk stratification than any single parameter alone, a possibility formally examined by ROC analysis in the following section

10.4.2 ROC Analysis of Baseline Vascular Predictors

The ROC analysis evaluated how well baseline vascular parameters could predict the binary outcome of an above-median reduction in FMD at 24 hours (ΔFMD more negative than the cohort median of −3.8%). Five parameters available from a single pre-procedural ultrasound examination were tested: baseline PSV, baseline FMD, baseline NMD, baseline radial artery diameter, and baseline RI. Among these, baseline PSV had the highest area under the curve (AUC = 0.73; 95% CI 0.64–0.82), indicating acceptable discrimination. Baseline FMD and NMD each yielded an AUC of 0.67 (95% CI 0.56–0.78 and 0.58–0.76, respectively). Baseline radial artery diameter had an AUC of 0.64 (95% CI 0.54–0.74), and baseline RI had an AUC of 0.56 (95% CI 0.44–0.68). None of the parameters reached the conventional threshold for excellent discrimination (AUC > 0.80).

The comparative interpretation of these AUC values requires a methodological caveat. The binary outcome was defined relative to the cohort median ΔFMD at 24 hours, a definition that introduces mathematical coupling with baseline FMD — since ΔFMD is calculated as the follow-up value minus the baseline — and, to a lesser extent, with baseline NMD through the strong positive correlation between baseline FMD and baseline NMD (ρ = +0.41, Section 9.1.3). The AUC values for baseline FMD (0.67) and baseline NMD (0.67) may therefore partly reflect this statistical coupling rather than a purely biological predictive relationship. By contrast, baseline PSV, baseline diameter, and baseline RI are not subject to the same coupling and therefore provide methodologically robust predictive information. Within this methodologically unconfounded subset, baseline PSV is the strongest discriminator, with an AUC that is in the "acceptable" range for clinical discrimination.

The biological interpretation of these findings is consistent with the pre-procedural vascular phenotype framework developed in Section 10.4.1. Baseline PSV, baseline diameter, and baseline RI all reflect aspects of pre-procedural arterial health; the ROC hierarchy broadly confirms that smaller arteries and poorer hemodynamic conditions are associated with greater procedural injury. It is worth noting that baseline PSV slightly outperformed direct diameter measurement as a binary discriminator (AUC 0.73 versus 0.64). This likely reflects the composite nature of PSV — which captures both arterial diameter and resting flow state within a single measurement — and the fact that PSV can be obtained with high reproducibility from the Doppler waveform, whereas direct diameter measurement on B-mode imaging is more susceptible to measurement variability. From a clinical standpoint, no single parameter achieved sufficient discriminatory power for individual risk stratification; however, combining multiple baseline predictors in a multivariable risk score — as suggested by the convergent predictive associations of baseline diameter, PSV, RI, and age demonstrated in Section 10.4.1 — may yield stronger discriminatory performance than any single parameter alone and represents a useful direction for future investigation

10.5 Clinical Implications

10.5.1 Pre-Procedural Vascular Phenotyping as a Risk Stratification Tool

The findings of this study support the concept of pre-procedural vascular phenotyping as a risk stratification tool for patients undergoing transradial cardiac catheterization. As detailed in Section 10.4.1, four baseline parameters — radial artery diameter, PSV, RI, and patient age — emerged as methodologically robust predictors of post-procedural functional outcome, together constituting a pre-procedural vascular phenotype that modulates both the magnitude of acute injury and the completeness of subsequent recovery. Of these, age is a universally available clinical variable, while the three Doppler-based parameters can be obtained from a focused pre-procedural vascular ultrasound that requires only a few additional minutes beyond the routine radial artery diameter measurement already performed in many centres. The incremental cost and time of incorporating resting PSV and RI measurements into the baseline assessment would be minimal in any catheterization laboratory equipped with vascular ultrasound, while the resulting risk stratification data would be available before the procedure, allowing clinicians to tailor vascular access strategies and post-procedural monitoring to the individual patient's predicted risk profile.

While the present study was not designed to derive and validate specific clinical cut-off thresholds for these parameters, the continuous gradient of risk demonstrated in the Spearman and ROC analyses supports the concept that patients with the combined phenotype of smaller radial artery diameter, higher baseline PSV, higher baseline RI, and older age constitute a higher-risk group for substantial acute endothelial injury and persistent functional impairment at one month. In the current clinical setting, the immediate utility of this stratification is limited by the absence of pharmacological interventions demonstrated to reduce procedural endothelial injury. The primary role of such pre-procedural phenotyping may therefore lie in targeted post-procedural monitoring — identifying patients who would benefit from structured vascular reassessment at one month and potentially beyond — and in guiding procedural decisions such as sheath size selection, sheathless guide catheter use, or the choice of distal versus conventional radial access in patients with borderline vessel diameter. Future prospective validation of these predictive associations in larger multicentre cohorts, together with derivation of clinically applicable risk scores, will be necessary before pre-procedural vascular phenotyping can be translated into routine clinical practice.

10.5.2 Implications for High-Risk Subgroups: Women and Older Patients

The two patient subgroups identified as bearing a disproportionate burden of post-procedural vascular injury in the current study are women, who exhibited greater smooth-muscle damage, and older patients, who showed poorer endothelial recovery at one month. These groups warrant particular clinical attention during procedural planning and post-procedural care. For female patients, the larger reduction in NMD is most plausibly explained by smaller arterial diameter and higher sheath-to-artery ratio which produce greater mechanical and functional injury to the tunica media during procedures of similar technical nature. Clinically, this finding supports the use of strategies to reduce the sheath-to-artery ratio in women — including smaller-diameter sheaths, sheathless guide catheters, and distal radial access at the anatomical snuffbox — as access-specific measures to minimize procedural vascular injury in this subgroup.

The biological basis for sex-specific access strategies is supported by converging evidence from randomized trials, large registries, and the present dataset, all of which show that the female radial artery is more vulnerable to procedural injury, whether measured by RAO rates, vascular function impairment, or smooth-muscle damage. Implementing tailored access strategies in routine practice requires operator training in alternative access techniques and access to pre-procedural ultrasound-guided radial artery diameter measurement.

The main clinical implication of the age-related recovery impairment observed in older patients is that they may benefit from post-procedural follow-up extending beyond the standard one-month assessment used in the present study. If the delayed recovery in older patients reflects an underlying deficit in endothelial regenerative capacity rather than simply a slower recovery process, then follow-up at three and six months could identify chronic vasoreactivity dysfunction that might eventually become a target for specific therapeutic strategies. Practically, categorizing patients aged 65 years and older as a high-risk group for persistent functional impairment in post-procedural follow-up planning is straightforward, as age is a universally available clinical variable requiring no additional diagnostic testing. Logical clinical extensions of this observation include the development of age-stratified vascular monitoring protocols after transradial procedures, analogous to risk-based surveillance programmes used after other cardiovascular interventions.

10.5.3 Pharmacological Considerations: RAAS Inhibitors and the Case for Prospective Trials

The borderline protective signal associated with RAAS inhibitor use, evidenced by consistent directional effects in both the subgroup analysis ($p = 0.06$ for ΔFMD at 24 hours) and the Spearman correlation analysis ($\rho = +0.20$ at 24 hours and $\rho = +0.30$ at one month, Section 9.4.1), raises the hypothesis that pre-procedural RAAS inhibition might reduce endothelial injury during transradial catheterization. Potential mechanisms include attenuation of procedure-induced oxidative stress, preservation of bradykinin signalling, and increased endothelial nitric oxide synthase activity. While the present observational data cannot support a clinical recommendation for RAAS inhibitor pre-treatment as a vascular protective measure, the biological plausibility of the mechanism and the consistency of the directional signal across two independent analytical approaches justify conducting a prospective randomized trial to test this hypothesis. Such a trial could randomize RAAS-inhibitor-naïve patients scheduled for elective transradial catheterization to short-term pre-procedural treatment with an ACE inhibitor or ARB versus placebo. The primary endpoint could be the change in FMD at 24 hours, with secondary endpoints including changes in NMD, RI, and radial artery diameter at one month. Sample size estimation for such a trial would need to account for the observed directional signal and the inherent variability of FMD measurements at 24 hours in this population.

Beyond RAAS inhibition, other pharmacological classes merit prospective evaluation for their potential to modify procedural vascular injury. The null result for statins in the current study cannot be interpreted as definitive evidence against a protective effect, as the very high prevalence of baseline statin use (73%) and the consequent limited size of the untreated comparator group reduced the statistical power to detect between-group differences. A study specifically designed to evaluate high-dose statin pre-loading during the 24 to 48 hours before transradial catheterization — analogous to pre-procedural statin studies addressing procedural myocardial injury in PCI — would provide more informative data on whether this drug class can mitigate procedural damage to the radial artery endothelium. The anti-inflammatory and antioxidant rationale for vascular protection extends potentially to other agents, including phosphodiesterase inhibitors,

antioxidant vitamins, and exogenous nitric oxide donors administered immediately before the procedure, all of which represent a broader pharmacological research agenda. The mechanistic insights from the current study provide a foundation for prioritizing research into these candidate strategies.

10.5.4 Implications for Radial Artery Use as a Surgical Graft Post-Catheterization

The persistence of functional impairment of the radial artery at one month after transradial catheterization has direct implications for its subsequent use as a graft in coronary artery bypass grafting, particularly in patients who undergo diagnostic angiography and are subsequently found to require surgical revascularization. In contemporary coronary surgery, the radial artery is the second-choice graft after the left internal thoracic artery, and its long-term patency depends on resistance to vasospasm, integrity of the endothelium, and intact smooth-muscle responsiveness. A radial artery with persistent endothelial and smooth-muscle impairment at one month after catheterization may be of suboptimal quality for bypass grafting if surgery is performed within this interval.

The present findings demonstrate that impairment in both endothelial and smooth-muscle vasoreactivity persists at one month and does not fully resolve within the typical interval between diagnostic angiography and elective coronary artery bypass grafting. Clinically, pre-harvest functional assessment of the radial artery — using measures such as FMD and NMD — may therefore provide valuable complementary information alongside conventional anatomical evaluation in patients who have recently undergone transradial catheterization prior to bypass surgery.

10.5.5 Future Directions: Gaps in the Literature and Proposed Research Agenda

This study has identified several specific gaps in the literature on TRA vascular injury that represent priority areas for future research. The most immediate gap is the lack of follow-up data beyond one month, which prevents characterization of the long-term trajectory of radial artery function and structure after transradial catheterization. Serial evaluations at three, six, and twelve months would help determine whether the functional impairment observed at the one-month follow-up represents a persistent adverse effect, a stable compensatory state, or a temporary plateau preceding further recovery. Long-term

data would also clarify whether the compensatory microvascular adaptation inferred from the one-month RI and PI patterns (Section 10.2.3) persists, progresses, or resolves over longer follow-up.

The second major gap is the lack of a histological or structural-imaging counterpart to the functional measures used in the present study. Combining non-invasive functional assessment with optical coherence tomography or high-resolution intravascular ultrasound in the same radial arteries would allow direct correlation of FMD, NMD, and diameter changes with structural parameters such as intimal thickness, medial smooth-muscle cell disruption, and adventitial fibrosis. Such integrated functional–structural research would substantially enhance the mechanistic interpretation of the present findings and contribute to a comprehensive understanding of post-procedural radial artery remodelling, which neither functional nor structural assessment can provide alone.

A third priority is the prospective comparative evaluation of different procedural strategies — traditional proximal versus distal radial access, different sheath sizes, hydrophilic versus non-hydrophilic sheaths, and alternative hemostasis protocols — using the multidimensional assessment framework applied in the current study. Such comparative research would characterize procedural factors influencing vascular injury with the same rigor as the patient-level predictors evaluated here, and would generate the evidence needed to support an evidence-based approach to procedural optimization aimed at minimizing radial artery damage.

10.6 Limitations of the Study

10.6.1 Sample Size and Statistical Power Considerations

The sample size of 94 patients in the study was enough to meet the main goals of Objective 1, which focused on detecting significant paired changes in FMD, NMD, and Doppler parameters across the three time points. It was also sufficient for the correlation analysis in Objective 3, where strong effect sizes were observed with high significance despite the small sample. However, the secondary analyses in Objective 2, such as comparisons between subgroups based on comorbidity status and medication use, were

limited by smaller effective sample sizes within individual subgroups. With only 28 diabetic patients and 33 normotensive patients, the ability to detect moderate effect sizes similar to those seen in larger pharmacological studies was limited. Consequently, null findings in various clinical variables could be due to insufficient power rather than a true absence of effect. To properly power these subgroup analyses, it would be necessary to include at least 200 to 300 patients, ensuring proportional representation of all relevant comorbidities and medications in the subgroups, similar to those studied here.

10.6.2 Single-Centre Design and Generalisability

The single-center nature of the study, which ensures consistency in methodology and minimizes operator variation when measuring vascular parameters, limits the ability to generalize the results to the entire spectrum of patients, procedures, and measurement protocols at the enrollment center. The cohort characteristics, such as a high rate of dyslipidemia (78%), heart failure (45%), and statin use (73%), reflect the case mix of a tertiary cardiology referral center, and they may not represent populations in catheterization laboratories nationwide or internationally. The FMD and NMD values were also influenced by specific measurement protocols, including cuff position, occlusion duration, and imaging software, and therefore were obtained by a standardized approach from a single operator that may differ from protocols used at other centers. Reproducing the current findings in a multicenter setting using a harmonized measurement protocol would significantly enhance the external validity and provide the variability data necessary for designing adequately powered multicenter trials.

10.6.3 The 4.3% RAO Rate and Exclusion from 24-Hour Analysis

The four patients who developed RAO at 24 hours were excluded from the paired analyses at this time point because paired comparisons require detectable vascular parameters. Although necessary from a methodological standpoint, this exclusion introduces potential selection bias by omitting patients with the most severe procedural complications. All four RAO cases occurred in male patients aged 51 to 74 years. Their exclusion means that the 24-hour vasoreactivity and Doppler results shown in this study only reflect the subset of patients with patent radial arteries and may underestimate the

overall extent of functional impairment across the entire post-procedural population. Notably, all four occluded arteries recanalized by the one-month follow-up, indicating that this non-random exclusion does not affect the one-month analyses. However, it probably leads to a systematic underestimation of the severity of early post-procedural functional changes at 24 hours. Future studies with larger sample sizes and more RAO cases would be better suited to characterize the acute functional profile of patients with radial artery occlusion and to incorporate these cases into the analysis through methods such as sensitivity analyses or multiple imputation techniques.

10.6.4 Absence of a Control Group and the Regression-to-Mean Concern

The absence of a contemporary control group of patients who underwent non-invasive cardiac investigation without arterial access can be considered a methodological limitation that should be taken into account when interpreting the observed changes at 24 hours and one month. Each patient served as their own control, with all parameters compared to their individual baseline measurements taken before the procedure. This paired within-subject design helps mitigate the effect of inter-individual variability but does not eliminate the possibility that some of the changes observed at 24 hours or one month are due to natural variation in FMD and NMD measurements over time, even without any intervention, or regression-to-the-mean effects in the sample selected based on clinical referral to coronary angiography. The magnitude and consistency of the 24-hour variation across all patients, along with the statistical significance at $p=0.001$ in the paired comparisons, make a purely artefactual explanation unlikely. However, due to the absence of a control group, the exact contribution of the procedural insult to the observed changes cannot be precisely measured. Therefore, the results should be viewed as evidence of procedure-related vascular changes, rather than definitive proof of causation in the strictest causal sense.

10.6.5 Measurement Methodology: FMD Variability and Operator Dependence

Flow-mediated dilation has become one of the operator-sensitive and protocol-dependent non-invasive measures of vascular health in clinical studies. Its variability is an accepted limitation of any study that uses it as a key outcome. The coefficient of variation of FMD

in well-conducted research environments ranges between 15 to 30, affecting the interpretation of small between-group differences and the confidence limits of individual patient measurements. In this study, all measurements were taken in the same way, with the same trained operator, and non-normal data distribution was confirmed; consequently, non-parametric statistical tests were used to minimize, or at least address, the effects of FMD measurement variability on the results. The NMD measure, which involves administering a sublingual dose of nitroglycerin, is also subject to variability in absorption rate and the timing of peak vasodilation response, adding further protocol uncertainty that must be acknowledged. A critical review of the protocol and comparison with other published series is possible through standardized reporting of measurement conditions such as occlusion time, cuff position, and analysis software, as outlined in the Methods chapter of this thesis. However, these measures do not eliminate the fundamental variability inherent in such measurements.

10.6.6 One Month as the Final Follow-Up: What Lies Beyond?

One of the most significant limitations of this research regarding clinical relevance is the relatively short follow-up period of less than one month after the procedure. The observed operational dysfunction at one month—just under zero FMD recovery, partial NMD recovery, persistent below-baseline RI, and above-baseline arterial diameter—indicates ongoing vascular remodeling. However, the ultimate outcome of this remodeling remains unpredictable based on the current data. The long-term clinical significance of transradial access—whether it fully recovers to pre-procedural levels after three, six, or twelve months, reaches a stable endpoint, or continues with progressive intimal hyperplasia—is a fundamental question that cannot be answered with the current dataset. Additionally, the coincidence of the one-month increase in arterial diameter with the phase of maximum neointimal accumulation observed in OCT studies—where the highest neointima occurs between one and three months—suggests that structural changes in the radial artery are still evolving at the time of the last measurement. Furthermore, functional measures taken at one month may not reflect a stable post-remodeling state. To fully understand the long-term vascular effects of transradial cardiac catheterization, long-term longitudinal cohort studies with follow-ups at six and twelve months are necessary. These should include the

functional measurements used in the current study, as well as structural imaging with high-resolution ultrasound or OCT.

10.7 Originality and Novel Contributions of the Present Study

10.7.1 Novelty in Study Design

The present research occupies a methodologically distinctive position within the existing literature on radial artery function after transradial cardiac catheterization, based on three design features. First, the study provides a simultaneous multidimensional functional, structural, and hemodynamic profile of the radial artery, with concurrent measurement of nine vascular parameters at each of three predefined time points. These parameters span endothelial vasoreactivity (FMD), smooth-muscle responsiveness (NMD), resting and hyperemic Doppler hemodynamics (PSV, RI, PI, VTI, per-beat volume), and arterial structure (lumen diameter). No previously published prospective TRA study has incorporated this breadth of parameters within a single cohort. The trajectories of individual parameters can be interpreted only in relation to each other, and the framework of simultaneous multi-parameter measurement is itself a contribution to the discipline — not merely a larger data set.

The second design contribution is the use of a 24-hour post-procedural assessment as an intermediate time point between the procedure and the one-month follow-up. Earlier studies evaluated radial artery function at one day and at three months without an intermediate measurement, which prevented separation of the acute injury phase from subsequent recovery and remodelling. In the present study, the 24-hour time point was selected because it captures the vasoreactivity impairment at its greatest magnitude, while being sufficiently distant from the procedure to ensure that the injury profile is not substantially altered by transient hemostatic compression effects. The three-time-point design allowed quantitative separation of acute injury (baseline to 24 hours) from recovery (24 hours to one month), and revealed patterns — such as the differential recovery trajectories of FMD and NMD between 24 hours and one month, and the dissociation between hemodynamic and functional recovery — that would not have been detectable with only pre-procedural and late follow-up measurements.

The third design contribution is the predictor analysis used as the third analytical objective. The combination of cross-parameter Spearman correlation analysis with ROC analysis provides complementary perspectives on predictor–outcome relationships: correlations quantify monotonic associations across the continuous range of outcome, while ROC analysis evaluates discriminatory performance for a clinically relevant binary classification. The deliberate restriction of the correlation-based interpretation to cross-parameter associations — thereby avoiding the mathematical coupling that confounds same-parameter analyses such as baseline FMD versus ΔFMD — represents a methodological standard that has not been consistently applied in earlier studies of post-procedural vascular function. Together, these three design features constitute a methodological improvement over the existing literature that is independent of the specific numerical findings produced.

10.7.2 Novel Quantitative Findings

Beyond the methodological characteristics of the study design, the present research produced a set of quantitative findings that add substantively to the existing literature on transradial access.

First, the acute reduction in NMD at 24 hours exceeded that of FMD, both in absolute magnitude (6.60 versus 3.61 percentage points) and in relative terms (36.6% versus 31.2% of baseline). This indicates a relative vulnerability of the smooth-muscle compartment to the mechanical injury of sheath insertion, compared with the endothelial compartment, in this patient population. Although the selective vulnerability of smooth muscle to direct medial compressive injury is mechanistically plausible and supported by histological evidence from post-catheterization radial artery specimens, the observation that this compartmental dissociation manifests as a larger non-invasive NMD reduction than FMD reduction is a novel contribution that bridges the structural and functional assessment literatures.

Second, the differential recovery trajectories of FMD and NMD between 24 hours and one month — no significant recovery in FMD ($p = 0.08$) versus partial but statistically significant recovery in NMD ($p < 0.001$) — represent a novel temporal finding. This differential recovery pattern indicates that smooth-muscle function has a greater capacity

for early recovery than endothelial function after transradial catheterization, contrary to the intuitive expectation that the more mechanically vulnerable smooth-muscle compartment would also show slower recovery.

Third, the biphasic radial artery diameter response — acute luminal reduction at 24 hours followed by partial recovery at one month but incomplete return to baseline — provides a non-invasive hemodynamic record of the remodeling process previously described using only invasive intravascular imaging. This demonstrates that serial Doppler ultrasound can capture structural remodelling patterns that were previously documented only with optical coherence tomography or intravascular ultrasound.

Fourth, the present study identifies a double dissociation between patient characteristics and vascular injury compartments: sex preferentially affects smooth-muscle injury (with women experiencing greater NMD reduction, $p = 0.005$, despite no significant sex difference in FMD), while age preferentially affects endothelial recovery (with a strong age correlation with ΔFMD at one month, $\rho = -0.62$, and no corresponding age effect on ΔNMD). This elegant pattern — sex acting through mechanical factors (smaller diameter and higher sheath-to-artery ratio), age acting through biological recovery-capacity factors — has not been reported in previous TRA research and provides a mechanistically coherent framework for understanding patient-specific susceptibility.

Finally, the compensatory microvascular adaptation inferred from the one-month trajectories of RI (decrease below baseline) and PI (progressive decline) is a novel hemodynamic observation. It suggests that the hand microvascular bed responds to sustained upstream conduit artery dysfunction through a downstream vasodilatory adaptation that partially preserves tissue perfusion — a pattern that has not been previously documented in the transradial catheterization literature.

10.7.3 Methodological Contributions

Several methodological decisions made during this study represent independent contributions that do not rely on the specific substantive findings. The use of the Shapiro–Wilk test to formally assess normality of all vascular parameters before inferential analysis, combined with the systematic application of non-parametric statistical tools when normality assumptions were violated, constitutes a methodological standard that is

not consistently followed in the published literature on post-procedural radial artery function. Some earlier studies of vasoreactivity in cardiac surgical populations applied parametric tests to FMD and NMD data without formally testing for normality, which can produce biased significance testing given the characteristic right-tailed skewness of these parameters in populations with cardiovascular disease. The present data showed that all thirteen baseline vascular parameters deviated significantly from normality (Shapiro–Wilk $p < 0.001$), even in a cohort of 94 patients, underscoring the importance of formal normality testing before statistical method selection in this type of research. The transparent reporting of distributional properties and the decision to retain all observations based on biological rather than statistical criteria also demonstrate a commitment to methodological rigour that can serve as an example for the field.

A further methodological contribution is the deliberate restriction of the cross-parameter Spearman correlation interpretation to associations between one baseline parameter and the change in a different outcome variable, thereby avoiding the mathematical coupling and regression-to-the-mean artefacts that affect same-parameter correlations such as baseline FMD versus ΔFMD. This conservative interpretive stance — while reducing the apparent strength of some findings — provides a more rigorous foundation for identifying genuine predictor-outcome relationships and offers a methodological template for future research on post-procedural vascular function.

10.8 Comparison with the Existing Literature

10.8.1 Where the Present Findings Agree with Prior Work

The present findings are consistent with a growing body of literature indicating that transradial cardiac catheterization produces measurable and reproducible injury to the radial artery, extending beyond the immediate post-procedural period. Previous investigations employing FMD and NMD assessment have consistently documented an acute reduction in endothelium-dependent vasoreactivity within the first 24 hours following sheath insertion, with incomplete recovery over subsequent weeks to months. The magnitude and temporal pattern of FMD reduction observed in the present cohort align with this established body of evidence, supporting the conclusion that acute

endothelial injury is a predictable and generalisable consequence of transradial arterial access rather than a finding specific to particular cohorts, measurement techniques, or procedural protocols.

The structural findings of the present study are similarly concordant with existing evidence. The biphasic radial artery diameter response — acute reduction at 24 hours followed by partial recovery at one month — fits within the broader framework of vascular wall remodelling that has been characterised through complementary imaging modalities, including OCT, high-resolution ultrasound, and intravascular ultrasound. Prior structural studies have consistently documented intimal hyperplasia, medial smooth-muscle injury, and inflammatory changes in radial artery segments exposed to introducer sheaths, together with progressive neointimal development over subsequent weeks and months. The functional impairment of smooth-muscle vasoreactivity observed at 24 hours in the present cohort, together with the incomplete diameter recovery at one month, is mechanistically consistent with this structural evidence — providing a non-invasive functional correlate to tissue-level and intravascular imaging observations reported elsewhere. The convergence of findings across independent research groups, using different methodologies and follow-up intervals, strengthens the overall case that transradial catheterization produces a combined structural and functional injury to the accessed radial artery that is detectable acutely and that persists beyond the immediate post-procedural period.

10.8.2 Where the Present Findings Diverge or Extend Beyond Prior Work

Several findings of the present study cannot be directly compared with prior literature because the relevant questions have not been systematically addressed in previous TRA research. The absence of a significant effect of diabetes mellitus or hypertension on the extent of acute post-procedural FMD reduction contrasts with expectations derived from the general endothelial dysfunction literature, in which these conditions consistently reduce basal vasoreactivity and are typically assumed to increase susceptibility to further endothelial damage. Potential explanations for this null finding include the floor-effect of reduced baseline FMD in patients with these comorbidities (which limits the magnitude of detectable further reduction), limited statistical power in subgroup comparisons, and confounding by chronic vasoprotective medications commonly prescribed to these

patients. These null findings should therefore be interpreted cautiously rather than as evidence of a complete absence of a comorbidity effect. Because the specific influence of these comorbidities on procedural vasoreactivity injury has not been systematically studied in previous transradial access research, direct comparisons with prior literature are not possible, leaving this as an open empirical question for future investigation.

A second finding without a clear precedent in the transradial access literature is the sex-specific vulnerability of the smooth-muscle compartment. Women in the present cohort experienced a substantially greater reduction in NMD than men ($p = 0.005$), despite no significant sex difference in FMD reduction. Although sex differences in radial artery diameter and the resulting higher sheath-to-artery ratio in women are well documented as predictors of RAO and access site complications, the functional manifestation of this anatomical difference as a selective smooth-muscle vulnerability — rather than a non-specific endothelial susceptibility — introduces a novel mechanistic perspective. It suggests that sex effects on transradial injury are not solely mediated by hemodynamic and anatomical factors but also involve a specific compartmental vulnerability of the tunica media to the combined mechanical, inflammatory, and ischaemic insults of the procedure.

A third finding that extends beyond prior work is the double dissociation between patient characteristics and vascular injury compartments: sex preferentially affects smooth-muscle injury, while age preferentially affects endothelial recovery (with the strong correlation between age and ΔFMD at one month, $\rho = -0.62$, accompanied by no significant age effect on ΔNMD at either time point). This mechanistically coherent pattern — sex acting through mechanical factors (smaller diameter and higher sheath-to-artery ratio), age acting through biological factors (reduced endothelial repair capacity) — has not previously been reported in transradial access research and provides a framework for understanding patient-specific susceptibility that goes beyond conventional cardiovascular risk factors.

10.8.3 Gaps That Remain Unresolved by the Present Study

Despite the breadth of the assessment framework used, several fundamental questions about the vascular effects of transradial access remain unresolved by the present dataset

and represent priorities for future research. The most important unanswered question concerns the trajectory of functional parameters beyond one month — whether the persistent impairment observed at this time point is temporary or represents a lasting adverse change in radial artery function following catheterization. The relationship between non-invasive functional measurements and structural changes documented by optical coherence tomography in other cohorts has not been directly examined in the same subjects. As a result, the link between functional and structural alterations remains a critical unresolved question that can be addressed only through combined functional and structural imaging in the same patients. Additionally, the present study was conducted exclusively in patients undergoing standard proximal transradial access with a 6 Fr introducer sheath, leaving open the question of whether functional outcomes would differ with smaller sheaths, sheathless guide catheters, or distal radial (snuffbox) access. Resolving these questions has direct implications for the evidence-based optimization of procedural strategies aimed at minimizing radial artery injury.

10.9 Translational and Clinical Implications — Synthesis

10.9.1 What the Clinician Should Take Away from This Study

The clinical message of the present study can be summarised in three related points. First, transradial cardiac catheterization causes a multidomain functional impairment of the accessed radial artery, affecting both endothelial and smooth-muscle vasoreactivity, detectable at 24 hours and persisting at one month, and therefore representing lasting functional change rather than a purely transient phenomenon. Second, the magnitude of post-procedural functional impairment varies substantially between patients and can be partly predicted from pre-procedural baseline vascular characteristics — specifically radial artery diameter, resting Doppler flow parameters, and patient age — which together constitute a pre-procedural vascular phenotype that modulates both acute injury and subsequent recovery (Section 10.4.1). Third, two patient subgroups bear a disproportionate burden of injury: women, who experience greater smooth-muscle injury, and older patients, who show less complete endothelial recovery at one month. Together, these observations support the integration of pre-procedural vascular phenotyping into

routine clinical assessment before transradial catheterization, as detailed in Sections 10.5.1 and 10.5.2.

10.9.2 Implications for the Catheterization Laboratory

Within the catheterization laboratory, the findings support an expanded pre-procedural vascular assessment that combines the anatomical measurement already routine in modern practice with a brief focused Doppler evaluation of resting PSV and RI. This expanded assessment — taking only a few additional minutes in a laboratory equipped with vascular ultrasound — would enable identification of patients with the combined higher-risk phenotype of smaller arterial diameter, elevated baseline PSV, elevated baseline RI, and advanced age. For such patients, access-specific protective strategies including smaller-diameter sheaths, sheathless guide catheters, or distal radial access via the anatomical snuffbox should be considered to minimize mechanical injury. The pharmacological implications are more tentative: the borderline protective signal associated with pre-procedural RAAS inhibitor use requires confirmation in a dedicated prospective randomized trial before it can inform routine practice (Section 10.5.3). A separate but related question is whether patients identified as higher-risk should receive structured post-procedural vascular follow-up beyond the standard pulse check performed at discharge; the persistent functional impairment documented in the present study at one month provides an empirical basis for considering such follow-up in this population, though its optimal timing, content, and clinical thresholds remain to be defined.

10.9.3 Implications for Cardiac Surgery

The present findings have direct relevance for cardiac surgical practice when the radial artery is considered as a conduit for coronary artery bypass grafting in patients who have recently undergone transradial catheterization. The persistence of combined endothelial and smooth-muscle impairment at one month — together with the diameter reduction that does not fully recover by this time point — indicates that a radial artery harvested within this interval may exhibit less favourable functional characteristics than a pristine vessel, with potential implications for long-term graft patency. Pre-harvest functional assessment using FMD and NMD may therefore provide valuable complementary information

alongside conventional anatomical evaluation in such patients, particularly when the interval between catheterization and surgery is short. The mechanistic basis, supporting literature, and clinical recommendations for this application are discussed in detail in Section 10.5.4.

10.10 Proposed Research Agenda

10.10.1 Short-Term Priorities (1 to 3 Years)

The most immediate research priority identified by the present study is a randomized controlled trial assessing the effect of pre-procedural RAAS inhibition on post-procedural endothelial function of the radial artery in patients undergoing elective transradial cardiac catheterization. The consistent directional signal observed in the present observational data (subgroup comparison with $p = 0.06$ at 24 hours; Spearman correlations of +0.20 at 24 hours and +0.30 at one month), combined with the well-established mechanistic rationale for RAAS inhibition as an endothelial protective strategy, provides a strong *a priori* justification for such a trial. The proposed design would randomize RAAS-inhibitor-naïve patients scheduled for elective transradial catheterization to short-term pre-procedural treatment with an ACE inhibitor or ARB versus placebo, with the primary endpoint being ΔFMD at 24 hours and secondary endpoints including ΔNMD, changes in resting Doppler parameters, and radial artery diameter at one month. Sample size estimation would need to be based on prospective effect size assumptions that account for the inherent variability of FMD measurements in this patient population.

The second short-term priority is to extend the follow-up period — either for the current cohort or for a newly recruited cohort — to include assessments at three, six, and twelve months, using the same multidimensional measurement protocol as the present study. This extension would address the most significant question left unanswered by the one-month data: whether the functional impairment observed at one month represents a stable outcome, the beginning of a slow recovery towards the pre-procedural state, or progression towards further structural and functional deterioration. A parallel short-term priority is a prospective functional comparison between the conventional proximal transradial approach and the distal radial access at the anatomical snuffbox, using the

multidimensional assessment framework employed in the present study. This comparison would directly test the hypothesis that the distal approach is associated with less functional vascular injury and a more complete recovery trajectory, a hypothesis supported by the smaller vessel size, different flow dynamics, and altered hemostasis characteristics of the distal access site.

10.10.2 Medium-Term Priorities (3 to 5 Years)

The principal medium-term research priority is the multicentre prospective validation of the pre-procedural vascular phenotype framework identified in the present study (Section 10.4.1) — comprising baseline radial artery diameter, resting PSV, resting RI, and patient age — as a predictor of post-procedural functional outcome. Such a study would enroll patients undergoing elective transradial catheterization at five to ten centres across different healthcare systems, using a standardized measurement protocol, and would assess whether the predictive associations observed in the present single-centre cohort generalize to a geographically and demographically diverse population. A parallel analytic objective would be the derivation of a multivariable risk score that integrates these four baseline parameters, together with sex, into a single clinically applicable metric — something that the bivariate analyses of the present study cannot provide. External validation in an independent cohort would then be required before such a score could be recommended for routine clinical use.

A second medium-term priority is the establishment of functional–structural correlations at the individual-patient level, an aspect that the present non-invasive dataset cannot address alone. A combined-assessment protocol would pair the multidimensional Doppler and vasoreactivity panel used in the present study with optical coherence tomography or high-resolution intravascular ultrasound of the same radial arteries, ideally at the time of a repeat coronary procedure or immediately prior to elective radial artery harvesting for coronary artery bypass grafting. Such integrated functional–structural research would clarify whether the functional impairment detected non-invasively corresponds to specific structural changes — intimal hyperplasia, medial smooth-muscle disruption, or adventitial remodelling — and would substantially enhance the mechanistic interpretation of non-invasive findings in future studies.

10.10.3 Long-Term Vision

The long-term research vision inspired by the present findings is the integration of pre-procedural radial artery vascular phenotyping into routine clinical assessment before transradial catheterization, analogous to the standard pre-procedural assessment of renal function. This ultrasound-based vascular assessment would provide anatomical information (radial artery diameter and sheath-to-artery ratio estimation) alongside hemodynamic information (resting PSV and RI, as surrogates for arterial health), all obtained in a single focused pre-procedural examination. Combined with age as a universally available clinical variable, these data would enable identification of higher-risk patients before the procedure and allow tailoring of procedural and post-procedural strategies to the individual patient's predicted risk profile. Realizing this vision will require standardization of measurement protocols across catheterization laboratories, development of operator training programmes, establishment of population-specific reference values for each parameter, and, ultimately, the development and prospective validation of clinically applicable risk scores. This will occur progressively as evidence accumulates from the short-term and medium-term research agenda outlined above. The present study provides foundational data that support this vision as scientifically plausible and clinically motivated.

10.11 Contribution to the PhD Degree — Statement of Originality

The submitted doctoral dissertation contributes independently to the scientific understanding of radial artery vascular biology in the context of transradial cardiac catheterization. It involves the design, implementation, and analysis of a prospective, single-centre observational study conceived to test three pre-planned analytical objectives using a multidimensional assessment framework not previously applied to this clinical area. The research was planned, structured, and carried out solely under the academic supervision of the thesis supervisor. All aspects of patient recruitment, pre-procedural and follow-up vascular measurements, and data analysis were conducted by the doctoral candidate, following the predetermined study protocol. The statistical analysis plan — including the selection of non-parametric methods appropriate to the non-normal distribution of the study variables, the definition of the three analytical objectives, and the structure of the predictor analysis — was developed before data collection and applied

without post-hoc modifications, with methodological decisions made transparently where the interpretation of results required additional scrutiny (most notably the restriction of Spearman correlation interpretation to cross-parameter associations, thereby avoiding confounding by mathematical coupling).

The contribution of the thesis to the doctoral degree rests on the novelty of the research question, the methodological rigour of the study design, the breadth of the assessment framework, and the clinical relevance of the findings. The demonstration that transradial catheterization produces a multi-domain functional impairment of the accessed radial artery — detectable at 24 hours and persisting at one month, with differential recovery trajectories for endothelial and smooth-muscle vasoreactivity — advances the scientific understanding of procedural vascular injury in a clinically applicable direction. The identification of a pre-procedural vascular phenotype (comprising baseline radial artery diameter, resting PSV, resting RI, and patient age) that predicts the magnitude of procedural injury and the completeness of subsequent recovery provides a foundation for evidence-based pre-procedural risk stratification. The observed double dissociation between patient characteristics and vascular compartments — sex preferentially affecting smooth-muscle injury, age preferentially affecting endothelial recovery — introduces a mechanistic framework that has not previously been reported in the TRA literature. Together with the compensatory microvascular adaptation documented in the resting Doppler parameters at one month, these findings contribute new empirical and conceptual elements to the study of post-procedural radial artery biology. The thesis therefore fulfills the criteria of an original contribution to the body of knowledge in cardiology for a doctoral degree and provides a scientific foundation on which future research and clinical practice can build towards reducing procedural vascular injury and preserving radial artery health in the contemporary era of transradial catheterization.

10.12 Concluding Remarks of the Discussion

This chapter has discussed the results of the present study from mechanistic, comparative, methodological, and clinical perspectives, placing them within the existing literature on transradial access vascular injury and its implications for clinical practice and future

research. The three analytical objectives of the study align to form a coherent biological narrative: transradial cardiac catheterization produces an acute multi-domain functional impairment of the radial artery, arising from the combined mechanical, inflammatory, and ischaemic insults of sheath insertion and catheter manipulation on both the endothelial and smooth-muscle layers of the arterial wall. This impairment persists at one month — with partial recovery of smooth-muscle function but limited recovery of endothelial function — and is accompanied by incomplete restoration of radial artery lumen diameter and by evidence of compensatory microvascular adaptation in the downstream vascular bed. The magnitude of this injury and the extent of subsequent recovery vary systematically between patients and can be partly predicted from a pre-procedural vascular phenotype comprising baseline radial artery diameter, resting Doppler flow parameters, and patient age, enabling the foundations of a clinically applicable pre-procedural risk stratification strategy.

The novelty of these findings lies both in the quantitative observations themselves and in the methodological approach used to derive them. The multidimensional assessment framework — simultaneous measurement of nine vascular parameters at three predefined time points — provides higher temporal and parametric resolution than has been applied previously to this clinical area. The conservative interpretive approach, which restricted Spearman correlation analyses to methodologically robust cross-parameter associations and acknowledged regression-to-the-mean confounding of same-parameter analyses, offers a methodological template for future research on post-procedural vascular function. The limitations of the present study, outlined in Section 10.6 and contextualised against the existing literature in Section 10.8, define the scope of the conclusions that can be drawn and delineate a clear research agenda whose pursuit could substantively advance the field. Chapter 11 summarises the principal findings and their implications, providing a concise overview of what has been established, what remains unresolved, and how the present work contributes to the scientific understanding of the vascular effects of transradial cardiac catheterization.

Chapter 11: Conclusions

11.1 Principal Findings

The present study, a prospective single-center observational investigation of 94 patients undergoing elective transradial cardiac catheterization, yielded three principal findings. First, transradial catheterization produces a multi-domain functional impairment of the accessed radial artery, affecting both endothelial and smooth-muscle vasoreactivity, detectable at 24 hours and persisting at one month — with differential recovery trajectories in which smooth-muscle function partly recovers but endothelial function does not. This functional injury is accompanied by acute reduction of the radial artery lumen diameter with incomplete recovery at one month, and by a reduction of the resistive index below baseline at one month that is consistent with compensatory microvascular adaptation in the downstream vascular bed. Second, two patient characteristics were identified as selective determinants of post-procedural injury: female sex, associated with greater smooth-muscle injury but no corresponding difference in endothelial injury, and advanced age, associated with poorer endothelial recovery at one month but no comparable effect on smooth-muscle injury — together constituting a double dissociation between patient factors and vascular compartments. Third, a pre-procedural vascular phenotype comprising baseline radial artery diameter, resting PSV, resting RI, and patient age emerged as a cross-parameter predictor of the magnitude and persistence of post-procedural functional impairment, providing a foundation for pre-procedural risk stratification.

11.2 Clinical Implications

The findings support the integration of a focused pre-procedural vascular assessment into routine clinical practice before transradial catheterization. Such an assessment — combining radial artery diameter measurement already performed in many centers with brief additional Doppler evaluation of resting flow velocities and resistance indices, alongside the patient's age — would enable identification of higher-risk individuals

before the procedure. For patients identified as higher risk, strategies to reduce mechanical injury (smaller sheath sizes, sheathless guide catheters, or distal TRA) may be particularly valuable. Women and older patients represent subgroups warranting particular attention: women because of their greater smooth-muscle vulnerability, and older patients because of their reduced capacity for endothelial recovery at one month. The persistent functional impairment observed at one month also has implications for patients in whom the radial artery may later be required as a conduit for coronary artery bypass grafting, supporting consideration of pre-harvest functional assessment in this setting. The borderline protective signal associated with pre-procedural RAAS inhibitor use warrants prospective randomized evaluation before any pharmacological recommendation can be established.

11.3 Scientific Contribution

This thesis contributes four elements to the scientific understanding of post-procedural radial artery biology. It provides a prospective multidimensional characterization of radial artery function, structure, and hemodynamics before and after transradial catheterization, with concurrent measurement of nine vascular parameters at three predefined time points — a breadth of assessment not previously applied to this clinical area. It documents a novel dissociation between endothelial and smooth-muscle compartments, with smooth-muscle injury exceeding endothelial injury acutely and with differential recovery trajectories subsequently. It identifies a double dissociation between patient characteristics and vascular injury, with sex and age acting selectively on different compartments through distinct mechanistic pathways. Finally, it applies a deliberate methodological restriction of correlation interpretation to cross-parameter associations, thereby avoiding regression-to-the-mean confounding that has affected earlier analyses of baseline-to-change relationships — a methodological template for future research on post-procedural vascular function.

11.4 Final Statement

TRA is now the preferred approach for the majority of cardiac catheterization procedures worldwide, with well-established benefits in terms of bleeding reduction, patient comfort, and procedural efficiency. The present thesis demonstrates that the biological consequences of this access strategy extend beyond the immediate post-procedural period and involve a measurable, partly predictable, and clinically relevant disturbance of radial artery function and structure. The radial artery is not a passive conduit whose function resumes intact once procedural access is completed, but a living vessel that responds to catheter-induced injury with a multidimensional biological process unfolding over weeks. Characterizing this process, identifying its determinants, and developing pre-procedural risk stratification tools to predict its severity represent the core contribution of this thesis and provide a foundation from which future researchers and clinicians may develop targeted strategies to minimize procedural vascular injury and preserve radial artery integrity in the contemporary era of transradial catheterization.

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