

Variability of Nitric Oxide Signalling in Atrial Fibrillation: Potential Modulation

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through The University of Adelaide.

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Thesis Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Acknowledgments

“Space, the final frontier. These are the voyages of the starship Enterprise. Its continuing mission: to explore strange new worlds, to seek out new life and new civilizations, to boldly go where no one has gone before!” – Captain Jean-Luc Picard, USS Enterprise.

Thematically, this is much like how my PhD has been, starting out riding a wave of optimism and hope, fuelled with a desire to explore the realm of cardiovascular research and making discoveries that would revolutionise not only cardiovascular medicine, but the world as we know it, even reshaping the very foundations from which we understand the universe. Alas, my achievements are somewhat more humble than those of Jean-Luc Picard: no new civilizations were discovered, wars prevented or catastrophes averted as a result of this research.

Needless to say, there are a number of people I wish to thank because of their support over the course of this journey. My deepest gratitude goes to Professor John Horowitz who first gambled on the prospect that I have a mind at work and Dr Yuliy Chirkov for his invaluable advice throughout this project.

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P.S. Cheers to all the ‘crew’ who were always down for a bit of a chin-wag about all things non-sciencey, when we probably should have been discussing things sciencey. Ooroo.

P.P.S. *“For God hath not given us the spirit of fear; but of power, and of love, and of a sound mind.” 2 Timothy 1:7.*

List of Abbreviations

| Abbreviation | Term |
|---------------------------------------|---|
| ACE | Angiotensin-converting Enzyme |
| ACS | Acute Coronary Syndromes |
| ADMA | Asymmetric Dimethylarginine |
| ADP | Adenosine Diphosphate |
| AF | Atrial Fibrillation |
| Agxt2 | Amino-glyoxylate Aminotransferase 2 |
| ANCOVA | Analysis of Covariance |
| Ang II | Angiotensin II |
| ANOVA | Analysis of Variance |
| ATP | Adenosine Triphosphate |
| BH ₄ | Tetrahydrobiopterin |
| BNP | B-type Natriuretic Peptide |
| Ca ²⁺ | Calcium |
| cGMP | 3'5'-Cyclic Guanosine Monophosphate |
| CHADS ₂ | Congestive Heart Failure, Hypertension, Aged ≥ 75 years, Diabetes Mellitus, Prior Stroke/Transient Ischemic Attack |
| CHA ₂ DS ₂ VASc | Congestive Heart Failure, Hypertension, Aged ≥ 75 years, Diabetes Mellitus, Prior Stroke/Transient Ischemic Attack, Vascular Disease, Sex Category: Female |
| CRP | C-reactive Protein |
| DDAH | Dimethylarginine Dimethylaminohydrolase |
| ELISA | Enzyme-linked Immunosorbent Assay |
| FAD | Flavin Adenine Dinucleotide |
| FMN | Flavin Mononucleotide |

| | |
|----------|---|
| GTP | Guanosine Triphosphate |
| IQR | Interquartile Range |
| L-NMMA | N-monomethyl-L-arginine |
| MPO | Myeloperoxidase |
| mRNA | Messenger Ribonucleic Acid |
| NADPH | Nicotinamide Adenine Dinucleotide Phosphate |
| NLRP3 | Nod-like Receptor Protein 3 |
| NO | Nitric Oxide |
| NOS | Nitric Oxide Synthase |
| O_2^- | Superoxide |
| PBS | Phosphate Buffered Saline |
| PKG | 3'5'-Cyclic Guanosine Monophosphate-dependent Protein Kinase |
| PMN | Polymorphonuclear Neutrophil |
| PRMT | Protein Arginine Methyltransferases |
| RAAS | Renin-Angiotensin-Aldosterone System |
| ROS | Reactive Oxygen Species |
| SAFETY | Standard vs. Atrial Fibrillation spEcific managemenT studY |
| SDMA | Symmetric Dimethylarginine |
| SDS-PAGE | Sodium Dodceylsulfate-Polyacrylamide Gel Electrophoresis |
| S.E.M. | Standard Error of the Mean |
| sGC | Soluble Guanylate Cyclase |
| SNP | Sodium Nitroprusside |
| TIA | Transient Ischemic Attack |

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|--------------|----------------------------------|
| TNF α | Tumour Necrosis Factor- α |
| TSP-1 | Thrombospondin-1 |
| Txnip | Thioredoxin-interacting Protein |

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Abstract

Understanding of the biochemical bases of thromboembolic risk in atrial fibrillation (AF) is incomplete. In a cohort of AF patients admitted to hospital, integrity of platelet nitric oxide (NO) signalling, and its modulation by dimethylarginines, myeloperoxidase, thrombospondin-1 and thioredoxin-interacting protein, was investigated. This study identified that, (1) new onset AF is associated with impaired platelet NO response; (2) gender-specific platelet dysfunction exists in AF where females display increased platelet aggregability and impaired NO response compared to males; (3) plasma symmetric dimethylarginine correlated inversely with platelet aggregability in chronic AF patients. Abnormalities of NO signalling and its various determinants occur frequently in AF patients at risk of thromboembolism.

Keywords

Atrial fibrillation; platelet; aggregation; nitric oxide; asymmetric dimethylarginine; myeloperoxidase; thrombospondin-1; thioredoxin-interacting protein.