EVALUATION OF ALTERATIONS IN CARDIOVASCULAR STRUCTURE AND FUNCTION IN END-STAGE RENAL FAILURE

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To Annabel, without whom

none of this would have been possible.

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ABSTRACT

Background:

Chronic renal dysfunction is associated with myriad alterations in cardiovascular structure and function, resulting in markedly elevated rates of cardiac and vascular morbidity and mortality. Utilising advances in cardiovascular magnetic resonance imaging (CMR), we evaluated the cardiovascular sequelae of arterio-venous fistula formation in advanced chronic kidney disease, and the impact of elective arterio-venous fistula ligation following successful renal transplantation. Furthermore, we undertook to evaluate the diagnostic accuracy of dobutamine-stress CMR in the detection of haemodynamically-significant coronary artery disease prior to renal transplantation. Finally, we invasively evaluated coronary endothelial function in the presence of advanced renal dysfunction, and compared this to subjects with preserved renal function.

Methods / Results:

Study 1: CMR was undertaken to evaluate cardiac structure and function, brachial artery endothelial function (as assessed by flow-mediated dilatation) and aortic distensibility in twenty-four subjects at baseline, and 6-months following, clinically indicated arterio-venous fistula creation in preparation for the commencement of haemodialysis for end-stage renal failure. Following arterio-venous fistula creation, mean cardiac output increased by 25.0% ($p<0.0001$), with substantial associated increases in left and right ventricular volumes, left and right atrial area and left ventricular mass (12.7% increase,

p<0.0001). Peripheral endothelial function was significantly impaired at follow-up (9.0±9% vs. 3.0±6%, p=0.01). No significant change in aortic distensibility was identified.

Study 2: Cardiac and vascular function were similarly assessed utilising CMR in eighteen subjects prior to, and 6-months following, clinically indicated arterio-venous fistula ligation in the context of successful, stable renal transplantation. Following AVF-ligation, mean cardiac output fell by 15.6% (p=0.004), with significant attendant decreases in atrial and ventricular chamber dimensions. Notably, left ventricular mass fell by 9.7% (p=0.0001) at follow-up. Aortic distensibility was unchanged following AVF-ligation, though endothelial function improved significantly (2.5±6.5% vs. 8.0±5.9%, p=0.043).

Study 3: Dobutamine-stress CMR was performed in twenty-one subjects prior to clinically-indicated invasive coronary angiography before potential renal transplantation. Dobutamine-stress CMR demonstrated 100% sensitivity and 93% specificity for the detection of angiographically significant coronary disease (≥70% stenosis severity). This compared favourably to results for the institutional-standard (SPECT: sensitivity 67%, specificity 38%; p<0.0001 compared to CMR).

Study 4: At invasive coronary angiography, endothelium-dependent and endothelium–independent coronary endothelial and microvascular function were evaluated amongst eight pre-renal transplant subjects with only minimal coronary artery disease (≤20% epicardial coronary stenoses). Utilising intra-coronary infusions of acetylcholine (10^{-7}M and 10^{-6}M), adenosine (48mcg) and glyceryl tri-nitrate (100mcg), results were compared to thirteen control subjects with minimal coronary artery disease but comparatively preserved renal function. There was no significant difference in endothelium-dependent or endothelium–independent coronary endothelial function between the cohorts. Microvascular function (as assessed by coronary flow reserve following adenosine administration) was markedly impaired in subjects with advanced renal impairment compared to controls (1.9±0.4 vs. 3.0±1.1, p=0.01).

Conclusions:

Chronic kidney disease is associated with substantial alterations in cardiovascular structure and function. Arterio-venous fistulae, though necessary for the performance of haemodialysis, appear to contribute significantly to the high burden of cardiovascular maladaptation present in this condition. Recent advances in CMR and stress-CMR may play a significant role in improving the detection of sub-clinical cardiovascular disease in these high-risk patients.

DECLARATION

This body of work contains no material which has been accepted for the award of any other degree or diploma in any university or 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.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

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It was with no small amount of trepidation that I initially committed to the commencement of this PhD. Having never been exposed to meaningful research during my under-graduate education or post-graduate clinical training, as an advanced trainee in Cardiology the idea of removing myself from clinical medicine for three years seemed a path both onerous and of little lasting professional value – merely a hoop to be jumped through in order to “tick the research box”. It is with great gratitude and humility that I commit this Thesis to the numerous colleagues who have mentored, aided and supported me through an experience that has proven to be of immense professional and personal value.

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ABBREVIATIONS

Ach	Acetylcholine
ACS	Acute Coronary Syndrome
ADMA	Asymmetrical dimethylarginine
AF	Atrial Fibrillation
AGE	Advanced Glycosylation End-products
AIx	Augmentation Index
ANP	Atrial Natriuretic Peptide
ANZDATA	Australian and New Zealand Dialysis and Transplant Registry
APV	Average Peak Velocity
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
AVF	Arterio-Venous Fistula
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CAFÉ	Conduit Artery Function Evaluation
CBF	Coronary Blood Flow
CCF	Congestive Cardiac Failure
CFR	Coronary Flow Reserve
CKD	Chronic Kidney Disease
CMR	Cardiovascular Magnetic Resonance Imaging
CO	Cardiac Output

CrCL	Creatinine Clearance
CT	Computed Tomography
CV	Cardiovascular
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
eGFR	Estimated Glomerular Filtration Rate
eNOS	Endothelial Nitric Oxide Synthase
EPO	Erythropoietin
ESKD	End Stage Kidney Disease
ESRF	End-stage Renal Failure
ET-1	Endothelin-1
FAME	Fractional Flow Reserve versus Angiography for Multivessel Evaluation
FFR	Fractional Flow Reserve
FISP	Fast-imaging with Steady State Free Precession
FMD	Flow-mediated Dilatation
FOV	Field of View
GFR	Glomerular Filtration Rate
GTN	Glyceryl Tri-nitrate
Hb	Haemoglobin
HDx	Haemodialysis
HMG-CoA	Hydroxyl-methylglutaryl coenzyme-A
HR	Heart Rate
ICA	Invasive Coronary Angiography
IHD	Ischaemic Heart Disease

IMR	Index of Microvascular Resistance
IQR	Inter-quartile Range
IVUS	Intravascular Ultrasound
K/DOQI	National Kidney Foundation Kidney Disease Outcome Quality Initiative
LA	Left Atrial
LAD	Left Anterior Descending Artery
LDL	Low Density Lipoprotein
LIFE	Losartan Intervention for Endpoint Reduction in Hypertension
LV	Left Ventricular
LVEDP	Left Ventricular End-Diastolic Pressure
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
LVM	Left Ventricular Mass
LVSV	Left Ventricular Stroke Volume
MDRD	Modification of Diet in Renal Disease Study Group
MI	Myocardial Infarction
MOD	Method of Discs
MPI	Myocardial Perfusion Imaging
NO	Nitric Oxide
NPV	Negative Predictive Value
NSF	Nephrogenic Systemic Fibrosis
NSTEMI	Non-ST-segment Elevation Myocardial Infarction
NYHA	New York Heart Association
oxLDL	Oxidised Low Density Lipoprotein

PAP	Pulmonary Artery Pressure
PCI	Percutaneous Coronary Intervention
PGI_2	Prostacyclin (Prostaglandin I_2)
PHT	Pulmonary Hypertension
PP	Pulse Pressure
PPV	Positive Predictive value
PTCA	Percutaneous Trans-luminal Coronary Angioplasty
PTH	Parathyroid Hormone
PWV	Pulse-wave Velocity
QALY's	Quality-Adjusted Life Years
QCA	Quantitative Coronary Angiography
RA	Right Atrial
RAAS	Renin-Angiotensin-Aldosterone System
RRT	Renal Replacement Therapy
RTx	Renal Transplantation
RV	Right Ventricular
SBP	Systolic Blood Pressure
SPECT	Single Photon Emission Computed Tomography
SSFP	Steady-State Free Precession
STEMI	ST-segment Elevation Myocardial Infarction
TIIDM	Type II Diabetes mellitus
TE	Echo Time
TR	Repetition Time
TTE	Trans-thoracic Echocardiography
TXA_2	Thromboxane

UVB	Ultraviolet B
25(OH)VitD3	25-hydroxyvitamin D_3