# TABLE OF CONTENTS

**Review**

1. Experimental Vein Graft Research: A Critical Appraisal of Models
   – Brian C. Cooley
   53-59

2. Autonomic Dysfunction, Sympathetic Hyperactivity and the Development of End-Organ Damage in Hypertension: Multiple Benefits of Exercise Training
   – Gustavo Santos Masson* and Lisete Compagno Michelini
   60-69

3. Cardiovascular Research: Past, Present and Future
   – Lorna R. Fiedler
   70-81

**Case Report**

4. The Sequelae of Silence: Catheter Entrapment as a Preventable Morbidity Resulting from Communication Failure
   – Dan J. R. Yoho and Michael S. Firstenberg
   82-84

**Research**

5. Dimethyl Sulfoxide Reduces Microvascular Obstruction and Intramyocardial Hemorrhage in a Porcine Ischemia-Reperfusion Model
   – Steen Fjord Pedersen*, Anne Krogh Grøndal, Niels Peter Andersen, Esben S. S. Hansen, Søren Dalager, Hans Erik Bøtker, Won Yong Kim and Steen Bønløkke Pedersen
   85-91

**Case Report**

6. Forgotten, but Not Gone
   – Srinivasan Sattiraju*, Furqan A Rajput, Sanjay Mehta and Emil Missov
   92-94
Experimental Vein Graft Research: A Critical Appraisal of Models

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ABSTRACT

Experimental models of vein grafting need to have specific relevance to the clinical complications encountered in coronary artery bypass grafting: acute thrombosis, neointima-associated stenosis, and progression of late-forming atherosclerotic lesions. Despite extensive use, many of these experimental models lack endpoint measures with clear analogies to their clinical counterparts and may in fact target the wrong (patho)physiologic process. Model selection is critical to further progress toward preventing these all too prevalent complications used for heart revascularization.

KEYWORDS: Coronary artery bypass graft; Percutaneous coronary intervention; Anastomosis; Oligodesoxynucleotide; Neointima; Arterialization.

INTRODUCTION

Interposition vein grafting is used to bypass arterial stenotic/occlusive sites caused primarily by atherosclerotic lesions and plaque rupture in the coronary arteries. The choice of whether to use a Coronary Artery Bypass Graft (CABG) or a Percutaneous Coronary Intervention (PCI) and stent placement is an ongoing debate, with advocacy for CABG under many conditions not appropriate for stent placement or internal mammary artery-based revascularization.1-4 Despite the high acceptance and application of these bypass procedures, complications are a substantial problem, resulting in early and intermediate-term failures rates upwards of 25%.5,6

The types of complications encountered with vein grafts can be broken down into 3 categories, on the basis of causation and the approximate time of development.6 Acute thrombosis can arise from vessel wall trauma after the vascular repairs and generally occurs intraoperatively or in the early postoperative interval in 5-10% of cases, though it may be encountered up to 1 month after graft placement. Graft stenosis can develop in the ensuing months, either caused by neointimal overgrowth or inward remodeling of the graft wall (~1-24 months) or by late-stage atherogenic lesion formation (2-10 years), with the former accounting for the largest proportion of complications.5,6

Most experimental studies into these complications have focused on neointimal development. There are a number of good reviews of animal models of vein grafting,2,7 mostly focusing on studies of intermediate to late development of complications. There is a paucity of studies into thrombotic studies of acute vein graft failure. There is also confusion in terminology for intermediate-term and late-term vein graft disease, with all too frequent interchangeing of terms for neointimal versus atherosclerotic lesions to describe the pathologic changes in these grafts. This paper will address some of these difficulties in the interpretation of published literature.
ACUTE THROMBOSIS

The majority of studies into vein graft thrombosis come from the microvascular surgery literature, wherein the problems of repairing and reconstructing vessels smaller in diameter than the coronary artery have been considered. The clinical need for these grafts is the lack of vessel length during extremity replantation or composite free tissue transfer (free flaps), due to vascular damage/trivia and inability to juxtapose vessel ends without tension during efforts of direct anastomotic repair. These applications can be viewed in simplistic terms, the simple addition of a second anastomosis to the vessel repair site, essentially doubling the thrombotic risk for occlusion. Because of the relative success in applying vein grafts under these conditions, and the lack of later-term failures, experienced reconstructive microsurgeons have felt that vein grafts can be applied safely and with little further risk of thrombotic failure in these cases.

Experimental studies into vein graft thrombosis have focused primarily on three modulating influences: the diameter of the graft, the use of antithrombotic therapies, and preservation of vein graft integrity and endothelium. The majority of these experimental studies have used rabbit or rat models, harvesting grafts from the external Jugular Vein (JV), Femoral Vein (FV), or superficial inferior Epigastric Vein (EV), and grafting into the carotid or femoral artery. Thrombotic rates are relatively low in these models (under 15%), and are reduced with experience and higher levels of competence, making it difficult to discern differences in thrombotic failure rates without very large animal numbers. The studies of vein graft diameter may also be unique to the reconstructive surgical field, where arterial diameters can vary greatly (from pediatric digital replants to large-adult forearm replants) and the choice of vein graft donor is wider (e.g., use of dorsalis pedis veins). The standard CABG graft uses the saphenous vein, grafted in end-to-side fashion, which can be surgically modulated to any size which to a large extent obviates the issue of vessel diameter at the anastomosis.

Unfractionated heparin remains the primary antithrombotic agent in the peri-operative period, primarily because of its anticoagulant use during cardiopulmonary bypass and because of its reversibility with protamine. This dominant use of heparin has to some extent impeded the efforts to develop other antithrombotic agents for CABG, though several direct thrombin inhibitors are currently under investigation and in use for patients who develop Heparin-induced thrombocytopenia (HIT). Platelet inhibitors have also received some study, but their current use is principally directed to that of preventing further cardiovascular sequelae.

NEOINTIMAL FORMATION

As mentioned, most experimental studies into vein graft complications have focused on the development of neointimal formation and its presumed progression to stenotic complications and graft occlusion, using rat and rabbit in vivo models. These models are straightforward to conduct, are usually done in end-to-end interpositional graft fashion (a difference from clinical CABG), and are evaluated at relatively early time points (2-12 weeks) in comparison to CABG assessments (6-24 months). These models use histomorphometry of the neoimal thickness or area, or a neointima: media thickness ratio, as surrogate markers for stenotic lesion development. Numerous studies have shown that a variety of factors can reduce the extent of neointimal thickening in these grafts, with many focusing on inhibiting smooth muscle proliferation; the possible list of these publications is quite extensive and is not provided here, for brevity.

Of clinical relevance, studies in rabbit JV grafts were used to show that edifoligide, an oligodeoxynucleotide designed to block E2F-mediated smooth muscle cell proliferation, reduced neointimal thickening without influencing endothelial cells; these studies served as pre-clinical findings to support the PREVENT IV trial of edifoligide prevention of neointima-associated stenosis. This trial, though exemplary of an excellently conducted clinical trial, failed to show efficacy from the treatment. Much speculation ensued following the outcome in an effort to identify the cause(s) of treatment failure.

To get at the root of this problem, and the translational potential of experimental vein grafting, a more critical appraisal is warranted. Using experimental neoimal wall thickness as...
a surrogate for vein graft stenosis may be inherently flawed. Veins transferred into an arterial environment undergo “arterialization”, what is arguably a beneficial remodeling to arterial shear and pressure, developing a healthy smooth-muscle-dominated neointimal wall as an adaptive response. What is needed in experimental vein graft models is a further progression of this response toward inward growth, “negative remodeling” of the wall, with even greater neointimal thickening that reduces the luminal cross-sectional area and that can progress to stenotic occlusion. Very few vein graft models have demonstrated this negative remodeling; most rat and rabbit models, whether using EV, FV, or JV grafts, show a nicely maintained luminal area without any apparent flow reduction (Figure 1A). Thus, developing approaches to reduce neointimal thickness in these models may, in truth, be a demonstration not of preventing neointimal thickening, what is arguably a beneficial remodeling to arterial pathophysiologic stenosis are needed but in short supply. Histologic images and histomorphometric evaluations of the standard rat and rabbit vein graft models do not show evidence of substantial stenosis (Figure 1A). In fact, one histomorphometric measure, the luminal radius to wall thickness ratio, is typically ~10 in rabbit JV grafts, indicating a high degree of luminal area preservation without stenotic encroachment. Even in larger animal models, like swine, canine, and even non-human primates, there is little evidence of stenotic, negative remodeling. There have been reports with ovine and canine models showing substantial stenosis in grafts, particularly near the anastomoses where non-laminar disturbed flow patterns are predicted. These large animal models also have arguably the most clinical relevance. Indeed, a report by Abbasi et al. used an ovine direct analogue to CABG, grafting the saphenous vein as a bypass graft to the left anterior descending coronary artery, with the identification of a greatly thickened vein graft wall. Shiroma and Kusaba used a canine FV graft to the femoral artery, again providing histologic evidence of substantial luminal stenosis in the grafted vein. Saito and colleagues used a similar model and demonstrated greatly thickened neointima relative to other vein graft models. The drawback to these and similar large-animal vein graft models is the high budgetary considerations in their application.

Over the past 17 years, several mouse vein graft models have emerged, primarily developed for their potential application in this extensively genome-manipulated species. A recent review of these murine models placed them into perspective for their clinical relevance and utility, identifying a model developed by this author as most clinically relevant, though technically the most demanding. This model simulates many of the complications associated with clinical CABG: 1) the acute thrombosis rate is comparable, at ~20%; 2) the neointima is thickest near the anastomotic repair sites where flow disturbance (oscillatory flow) can be presumed to support neointimal overgrowth (Figures 1B and 1C); 3) the recipient artery (femoral) is a muscular artery more like the coronary artery than elastic arteries such as the carotid or abdominal aorta (more typical recipient sites in mouse models); 4) the vein donor graft is obtained from the posterior facial vein, a peripheral neck vein in the loose connective tissue, akin to the donor site of the saphenous vein and unlike other mouse model vein grafts that most often use the inferior vena cava; 5) the donor graft, despite its fragility and small size, can be engrafted with preservation of its venous endothelium which, in itself, has been shown to contribute to the neointima through a endothelial-to-mesenchymal transdifferentiation process (Figures 2A and 2B), and perhaps of greatest relevance, 6) the neointima develops to a very high extent (Figure 1C), absolutely comparable in dimensional thickness to rat, rabbit, and even dog and pig models (100 or more microns); under the vessel diameter conditions of the mouse, this translates to a substantial stenotic lesion that often results in a luminal radius:neointima wall thickness ratio of less than 1 and leads to stenotic occlusion in 3-6% of these grafts within 30 days. The drawback of this model is its extreme difficulty due to the sutured engraftment into such a small artery (0.2 mm diameter of the femoral vein in an adult mouse).
with an interchanging of terms, often substituting atherosclerotic terminology for what is more identifiable as neointimal formation, either without an atherogenic stimulus or with superimposed atherogenesis. This confusion in the literature is a major obstacle to understanding the fundamental mechanisms underlying vein graft pathologies. A better appreciation of the distinction between these pathologies would use the stable development of neointima that then progresses to atherosclerotic lesion presence, ideally with a substantial stenotic component. Larger animal models may be more conducive to these discriminations, using the longer time frame for atherogenesis for distinguishing arterializing neointima from athero-like lesions. Because of the high involvement of murine models in current research, it would also be very helpful to get a better understanding of which of the various murine vein graft models are optimal for dissecting out these thorny problems, rather than assuming that “any” vein graft model is adequate.

In summary, there are a wide variety of in vivo models for studying vein graft complications. Critical assessment is needed for what each model demonstrates and what clinical relevance each model holds. Future studies should make model selection an important criterion for exploring the causes of vein graft failure and approaches to its prevention.

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ATHEROSCLEROSIS

Long-term vein graft failures are often attributed to atherosclerotic lesion development within the graft. Compositely, negative remodeling from neointima and atherosclerosis are called vein graft disease. However, as a disease entity it has been difficult to study the atherogenic side separately from neointimal stenosis, both clinically and experimentally. To complicate this issue, the experimental literature has been diluted by an interchanging of terms, often substituting atherosclerotic terminology for what is more identifiable as neointimal formation, either without an atherogenic stimulus or with superimposed atherogenesis. This confusion in the literature is a major obstacle to understanding the fundamental mechanisms underlying vein graft pathologies. A better appreciation of the distinction between these pathologies would use the stable development of neointima that then progresses to atherosclerotic lesion presence, ideally with a substantial stenotic component. Larger animal models may be more conducive to these discriminations, using the longer time frame for atherogenesis for distinguishing arterializing neointima from athero-like lesions. Because of the high involvement of murine models in current research, it would also be very helpful to get a better understanding of which of the various murine vein graft models are optimal for dissecting out these thorny problems, rather than assuming that “any” vein graft model is adequate.

In summary, there are a wide variety of in vivo models for studying vein graft complications. Critical assessment is needed for what each model demonstrates and what clinical relevance each model holds. Future studies should make model selection an important criterion for exploring the causes of vein graft failure and approaches to its prevention.

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Autonomic Dysfunction, Sympathetic Hyperactivity and the Development of End-Organ Damage in Hypertension: Multiple Benefits of Exercise Training

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ABSTRACT

Autonomic dysfunction is closely related to the development of hypertension, which is characterized by increased sympathetic activity, decreased vagal tonus and baroreflex dysfunction. The hypertension-induced maladaptive changes progressively lead to heart failure, myocardial infarction and stroke. Hypertrophic remodeling of brain arterioles, chemoreceptors activation, blood-brain barrier abnormalities, oxidative stress and pro-inflammatory cytokines production in autonomic brain areas increase neuronal activity and sympathetic outflow. These responses, together with increased baroreflex dysfunction-induced pressure variability, renin-angiotensin system hyperactivation and capillary rarefaction, increase blood pressure levels and act as a positive feedback mechanism to perpetuate hypertension and development of end-organ damage. Exercise training, a non-pharmacological tool, has been used as an adjuvant therapy to treat hypertension. Our recent data showed that moderate aerobic training in adult SHR completely normalizes oxidative stress and inflammation in autonomic brain areas involved in cardiovascular control and promptly corrects baroreflex dysfunction and increases cardiac vagal activity. The early (2-weeks) training-induced beneficial responses improve autonomic control even in the persistence of hypertension, since a partial reduction of pressure levels was observed after 8 weeks of exercise training, which was related to reversion of arteriolar hypertrophic remodeling and consequent decrease of peripheral vascular resistance.

KEYWORDS: Hypertension; Oxidative stress; Inflammation; Central nervous system; Baroreflex; Aerobic exercise training.

ABBREVIATIONS: ANG II: Angiotensin II; HMGB1: High-mobility group protein 1; HPLC: High Performance Liquid Chromatography; IL-1β: Interleukin 1 beta; MAPK: Mitogen-activated protein kinases; NADPH oxidase: Nicotinamide Adenine Dinucleotide Phosphate-oxidase; NF-Kb: Nuclear factor kappa-light-chain-enhancer of activated B cells; NOS: Nitric Oxide Synthase; NTS: tractussolitarii nucleus; PKC: Protein Kinase C; PVN: hypothalamic paraventricular nucleus; RAS: Renin-angiotensin system; RVLM: Rostroventrolateral medulla; SFO: Sub-fornicial organ; SHR: Spontaneously Hypertensive Rat; TGF-β: Transforming Growth Factor beta; TNF-α: Tumoral Necrosis Factor alpha.

INTRODUCTION

Central nervous system continuously monitors cardiovascular function through different types of receptors, which allow immediate and chronic hemodynamic adjustments evoked by endogenous and environmental stimuli. These adjustments are generated by the activation and/or inhibition of autonomic brain circuitry in the brain stem and the hypothalamus. Baroreceptors, chemoreceptors and cardiopulmonary receptors encode arterial pressure, partial pres-
sure of blood gases and cardiac filling changes in frequency of action potentials of respective afferents. This information is inte-
grated in the central nervous system, which modifies vagal and sympathetic activity to heart and vasculature and, consequently, corrects the initial alterations and keeps arterial pressure, PO$_2$ and PCO$_2$ and stroke volume at relatively constant levels. The imbalance between activation/inhibition of autonomic control areas promotes chronic adaptations in cardiovascular effectors that contribute to the establishment of arterial hypertension and the development of end-organ injuries. The mechanisms under-
lying the establishment of autonomic dysfunction, sympathetic hyperactivity and the appearance of hypertensive dysfunctions will be briefly reviewed. In addition, we will address the benefits of aerobic training in an experimental model of primary hyper-
tension, the Spontaneously Hypertensive Rat (SHR).

AUTONOMIC DYSFUNCTION IN ARTERIAL HYPERTENSION

Although hypertension per se does not induce death, the pathological mechanisms associated with chronic arterial pressure elevation contribute to the development of end-organ injuries, as cardiac hypertrophy, stroke and glomerular sclerosis, which increase cardiovascular mortality. Since arterial hyperten-
sion is a multifactorial syndrome, many mechanisms overlapped to produce a positive feedback that facilitates cardiovascular dysfunction. Among these mechanisms, autonomic dysfunction seems to be a key factor in the pathophysiology of primary hyper-
tension and consists an important pharmacological target for blood pressure control and for the reduction of morbimortality.

Autonomic dysfunction is characterized by the increased sympathetic nerve activity, decreased vagal nerve activi-
ty and abnormal reflex control of cardiovascular function, which are mediated by baroreceptors, chemoreceptors and cardiopul-
monary receptors. Causative relation between autonomic dys-
function and elevated arterial pressure was primarily suggested in the 80’s by Minami and co-authors that identified reduced reflex bradycardia on juvenile SHR with normal arterial pressure. This finding indicated that autonomic dysfunction preceded the arterial pressure rise.

Many hypothesis have been proposed to explain the central nervous system abnormalities conditioning autonomic dysfunction in primary hypertension: baroreflex dysfunction itself, increased chemoreflex activation induced by reduced cere-
bral blood flow associated with arteriolar remodeling, activation of peripheral chemosensitive cells, increased brain Renin-angiotensin system (RAS), as well increased blood-brain barrier permeability. An elegant series of experiments developed by Julian Paton’s group at the Bristol University identified the contri-
bution of brain arteries/arterioles hypertrophic remodeling in the establishment of sympathetic hyperactivity. It was observed that neonates SHR had greater arterial wall thickness and ele-
vated vertebral artery wall/lumen ratio with increased vascular resistance in the vertebro-basilar circuit, which determined reduced blood flow and, consequently, the rise of sympathetic activity and peripheral vasoconstriction.

Although not well characterized as the role of brain vasculature hypertrophic remodeling, it was also suggested that activation of chemosensitive afferents by pro-inflammatory cy-
tokines contributed to the activation of sympathetic activity. Indeed, several studies demonstrated a direct correlation between plasma pro-inflammatory cytokines, increased arterial pressure and autonomic dysfunction. Mkrchian and co-authors identified, in humans, some inflammatory mediators (toll-like receptor 1 and 4, HMGB1, TNF-α and IL-1β receptors and transcription factor NF-κB) within the carotid bodies, where chemosensitive cells are located. Hyperactivity of chemosensitive afferents was also observed in young SHR, since denervation of the carotid body caused reduction of arterial pressure, sympathetic activity and macrophages infiltration in the smooth muscle tissue. Together, these findings suggested that pro-inflammatory cytokines-induced activation of chemoreceptors contributed to estab-
lishment of autonomic dysfunction and, consequently, of hyper-
tension.

Another contributor factor to the genesis of sympa-
thetic hyperactivity is ANG II-induced AT$_1$ receptors activation in brain areas without blood-brain barrier, as the Sub-fornicial organ (SFO), which modulates other pre-autonomic areas, such as the hypothalamic Paraventricular nucleus (PVN) and the Rostroventrolateral medulla (RVLM). RAS inhibition in these areas abolishes arterial pressure increase, renal sympathetic hyper-
activity, baroreflex dysfunction and attenuates the dipsogenic response. RAS inhibition also corrects the expression of pro-
-inflammatory cytokines and AT$_1$ receptors and reduces reactive oxygen species content in ANG II-dependent hypertension. These data show that increased AT$_1$ receptor activation, via reactive oxygen species and pro-inflammatory cytokines, contribute to the development of autonomic dysfunction, sympathetic hyperac-
tivity and hypertension. Activation of AT$_1$ receptors also disrupts blood brain barrier and facilitates the migration of monocytes and T cells into brain, thus contributing to local inflammation and to a further increase in sympathetic activity and arterial pressure. It was demonstrated that hematopoietic cells bind to junctional adhesion molecule-1 to enter into the neural tissue, where they behaved as resident macrophages (activated microglia), acting as another important source for pro-inflammatory cytokines.

MOLECULAR MECHANISMS OF SYMPATHETIC HYPERACTIVITY: THE IMPORTANCE OF REACTIVE OXYGEN SPECIES AND PRO-INFLAMMATORY CYTOKINES

Several mechanisms that induce autonomic dysfunc-
tion exhibit common factors: increased reactive oxygen species and pro-inflammatory cytokines in autonomic brain areas as the SFO, PVN, RVLM and tractus solitarii nucleus (NTS). The main intracellular signaling pathways in neurons and glia are activat-
ed by ANG II via AT$_1$ receptor, which activates NADPH oxi-
dase through the Protein Kinase C (PKC) with the subsequent
release of superoxide. Increased superoxide production activates redox-sensitive pathways, as the Mitogen-Activated Protein Kinases (MAPK) that stimulate nuclear transcription factors (NF-κB and AP-1), thus increasing the gene expression of pro-inflammatory cytokines, as well as subunits of the NADPH oxidase and others RAS components. Therefore, AT₁ receptor activation, oxidative stress and inflammation constitute important positive feedback mechanisms in autonomic dysfunction and sympathetic hyperactivity.

Besides the regulation of nuclear factors, reactive oxygen species directly increase sympathetic neuronal activity. In ANG II-dependent hypertention, Robin Davison and Constantine Ladecola’s groups, at the Cornell University, identified that NADPH oxidase-induced superoxide production increases the calcium influx and neuronal activation via glutamatergic NMDA receptors activation. As calcium influx was abolished by antioxidant agents or nitric oxide donors, the authors proposed that increased reactive oxygen species production decreased nitric oxide bioavailability and, consequently, NMDA receptor NR1 subunit nitrosylation, thus increasing both neuronal activity and sympathetic activity. Several studies in ANG II-dependent hypertension, renovascular hypertension and primary hypertension identified that oxidative stress attenuation inhibits both arterial pressure and renal sympathetic activity elevation, decreases tissue RAS, pro-inflammatory cytokines and NADPH oxidase expression and reduces NF-κB e AP-1 transcriptional activity. These studies confirm the functional role of reactive oxygen species in autonomic dysfunction, sympathetic hyperactivity and, subsequently, in the development/establishment of arterial hypertension. In addition to sympathetic hyperactivity, reactive oxygen species also mediates lower parasympathetic activity and reduced baroreflex sensitivity after ANG II administration into the NTS.

Tissue inflammation is another mechanism related to the establishment of autonomic dysfunction. It was described that healthy rats that received pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) into the PVN and NTS or through intracarotid injection exhibited autonomic dysfunction, increased renal sympathetic activity and elevated arterial pressure. In addition to these acute effects of cytokines, Joseph Francis’s group, at Louisiana State University, demonstrated that chronic blockade of pro-inflammatory cytokines expression into autonomic control areas attenuated cardiac hypertrophy, renal sympathetic hyperactivity and the elevation of arterial pressure in ANG II-induced hypertension.

**SYMPATHETIC HYPERACTIVITY AND END-ORGAN DAMAGE IN HYPERTENSION**

Adrenergic hyperactivity in hypertension was originally described by Amann, et al., which identified increased forearm blood flow after α-adrenergic receptors blockade. The interaction between norepinephrine and α-adrenergic receptors in smooth muscle cells induced vasoconstriction through increased calcium influx and decreased nitric oxide bioavailability that elevated the peripheral vascular resistance and the arterial pressure. Increased vascular sympathetic activity produced hypertrophic remodeling of arteries and arterioles, since α-adrenergic stimulation increases the expression of adhesion molecules, leukocyte migration, activation of NADPH oxidase with reactive oxygen species formation and MAPKs stimulation, which drive hypertrophic vascular effects.

In our group, neuronal recordings, dosage of norepinephrine content in vessels (HPLC) and tyrosine hydroxylase immunoreactivity in different tissues were used to demonstrate that increased sympathetic vasomotor tonus in SHR is not homogenous, since we observed increased sympathetic activity in cardiac and renal, but not in skeletal muscle arterioles. Different sympathetic activation patterns, as increased renal and cardiac sympathetic nerve activity and unchanged lumbar nerve activity, were described in others hypertensive models, defining a differential sympathetic signature. Interestingly the sympathetic signature of the SHR coincides with the sympathetic activation pattern observed in hypertensive patients.

Besides vascular hypertrophy, increased peripheral vascular resistance and elevated arterial pressure, sympathetic hyperactivity contributes significantly to the development of end-organ injuries. In the myocardium, the higher metabolic demand caused by sympathetic hyperactivity (increased vascular resistance and elevated heart rate) is an important factor to determine ventricular hypertrophy. Neurohormonal direct effects of sympathetic hyperactivity were described in the myocardium. It was observed that cardiac α- and β-adrenergic activation induced cardiac hypertrophy, augmented matrix metalloproteinase-2 activity, increased the expression of TGF-β and the synthesis of collagen I and III, in addition to intensify the production of reactive oxygen species and the infiltration of hematopoietic mononuclear cells. Accordingly, Schlaich and co-authors identified in hypertensive patients a direct correlation between cardiac norepinephrine spillover and cardiac hypertrophy.

Similar to cardiac and vascular tissues, adrenergic hyperactivation, by modifying sodium/water reabsorption and renin secretion, causes abnormalities in the renal function. Graham and co-authors described increased renal α-adrenergic receptor concentration in the SHR. It was also demonstrated that suppressor doses of α- and β-adrenergic blockers decreased glomerular sclerosis and urinary albumin excretion in partial nephrectomized rats. Besides these direct effects, increased renal sympathetic activity determined tissue and plasma RAS activation through juxtaglomerular cells that release renin. Acting in AT₁ receptors, ANG II induced reactive oxygen species and pro-inflammatory cytokines production that enabled renal remodeling and injury, as the glomerular sclerosis. Renin also interacts with pro-renin receptors in several tissues being associated with additional activation of oxidative and inflammatory signaling pathways, and, consequently, with the worsening of end-organ injuries. ANG II systemic and local effects in the cardiac...
and renal tissues add to brain RAS effects, to facilitate sympathetic hyperactivity and to amplify the deleterious effects of hypertension.

Other mechanism closely related to end-organ injuries is the reduction of baroreflex sensitivity, which strengthens sympathetic hyperactivity. In this sense, Nosaka and co-authors demonstrated that RVLM activation inhibited baroreceptors activation-induced reflex bradycardia, thus aggravating baroreflex dysfunction that is considered an independent prognostic marker in hypertension. Baroreflex dysfunction decreases the ability of arterial baroreceptors to promptly correct venous return, heart rate, ventricular contractility and peripheral vascular resistance changes, which aggravate arterial pressure oscillations. High pressure variability, which increases hydrostatic pressure oscillations in the capillaries, expose tissues to brief periods of hyperperfusion or hypoperfusion interfering with normal tissue oxygenation. Hypoxia or partial oxygen pressure fall is a strong stimulus to drive endothelial cell injury and capillary apoptosis, which determine extensive capillary rarefaction and the consequent development of lesions in the various target organs.

In summary, as illustrated in Figure 1, hypertension is associated to brain RAS hyperactivation, increased reactive oxygen species and pro-inflammatory cytokines in the autonomic brain areas that determine baroreflex dysfunction, decreased vagal cardiac activity and increased sympathetic activity to cardiac, vascular and renal tissues and increased pressure variability. These effects cause sympatho-vagal imbalance in the heart, activation of systemic and local RAS in peripheral tissues, vascular and tissue hypertrophic remodeling and end-organ damage. The deleterious adaptive responses potentiate the development/maintenance of hypertension and constitute a positive feedback mechanism to perpetuate the hypertensive disease.

AEROBIC TRAINING: AUTONOMIC BENEFITS TO HYPERTENSIVE INDIVIDUALS

Moderate intensity exercise training is one of the most important non-pharmacological strategies to decrease arterial pressure in hypertensive patients. A recent meta-analysis demonstrated that aerobic training decreases systolic and diastolic arterial pressure by 8 and 5 mm Hg, respectively. Other works also recognized that aerobic training corrects autonomic dysfunction associated with hypertension, which contributes to the reduction of end-organ damage and cardiovascular mortality.

Clinical and experimental studies have indicated that aerobic training is extremely efficient to revert autonomic dysfunction and to attenuate sympathetic hyperactivity, to normalize arterioles wall/lumen ratio and to decrease peripheral vascular resistance. On never-treated hypertensive patients, Latzerza and co-authors identified that aerobic training normalized reflex control of heart rate and decreased sympathetic activity. On SHR, several studies from our group demonstrated that aerobic training decreases sympathetic neuronal excitability into the PVN and increased PVN density of oxytocin neurons and the density of oxytocinergic projections from PVN to NTS-DMV complex, whose activation increase both baroreflex sensitivity and cardiac vagal activity and decrease peripheral vasomotor sympathetic activity. It was also demonstrated that the training-induced adaptive responses are significantly correlated with de-
creased resting heart rate and exercise tachycardia.\textsuperscript{77,78}

In a recent study,\textsuperscript{70} we identified the sequential changes of autonomic and cardiovascular adaptations induced by aerobic training in SHR (Figure 2). Only 2-weeks of aerobic training were enough to normalize cardiac vagal activity and baroreflex sensitivity in the SHR. There was, at the same experimental time, a complete normalization of the oxidative stress and inflammatory profile into the PVN, which are the most prominent molecular mechanisms to normalize baroreflex dysfunction and sympathetic hyperactivity. It is important to note that these benefits were observed even in the persistence of hypertension, since a partial decrease of arterial pressure (~9\%) was identified only after 8-weeks of aerobic training (Figure 2).\textsuperscript{70} The temporal coincidence between the reversion of pro-inflammatory profile and oxidative stress in the PVN and the correction of autonomic dysfunction,\textsuperscript{70} associated with previous findings proving the relationship among oxidative stress,\textsuperscript{8,31,34} inflammation,\textsuperscript{8,25} baroreflex dysfunction and sympathetic hyperactivity,\textsuperscript{39,40} suggest a cause-effect relationship. In other words, aerobic training normalizes baroreflex function and decreases sympathetic hyperactivity through the correction of pro-inflammatory profile and oxidative stress within the PVN, an important autonomic area in cardiovascular control. This statement is corroborated by another study from our group that observed that aerobic training decreases neuronal excitability in the PVN of the SHR.\textsuperscript{75}

It is important to note the temporal dissociation between a prompt normalization of both baroreflex function and cardiac vagal activity (significant at 2-weeks) and arterial pressure fall, which appeared only after 8-weeks of exercise training.\textsuperscript{70} This dissociation suggests that training-induced normalization of baroreflex function is independent of pressure reduction, but may contribute to the subsequent pressure fall through the decrease of sympathetic vasomotor activity and the regression of vascular hypertrophy. Indeed, the contribution of increased baroreflex sensitivity to pressure fall was identified in clinical studies\textsuperscript{70,80} that used chronic baroreflex stimulation to control refractory hypertension. The importance of augmented baroreflex function for a better cardiovascular control after aerobic training was also proved by other studies\textsuperscript{71,72,77} demonstrating that sinoaortic denervation completely blocked autonomic and cardiovascular benefits induced by aerobic training in the SHR.

Besides the autonomic adaptive responses, arterial pressure fall observed in trained hypertensive individuals is also dependent on training-induced structural changes in the peripheral vasculature. Previous data from our group demonstrated that 8-12 weeks of moderate aerobic training normalize the wall/lumen ratio of skeletal muscle, heart and diaphragm arterioles that contributed to the attenuation of total peripheral resistance, thus reducing arterial pressure.\textsuperscript{68,73,74} Increased nitric oxide and tetrahydrobiopterin bioavailability and decreased NOS uncoupling, superoxide formation and inducible NOS gene expression, were described as the cellular mechanisms related to vascular benefits of aerobic training in the SHR.\textsuperscript{81}

**CONCLUSIONS**

Autonomic dysfunction, characterized by sympathetic-vagal unbalance associated with baroreflex dysfunction, contributes widely to the establishment/maintenance of hypertension. Increased oxidative stress and pro-inflammatory profile observed in the SHR contribute to baroreflex dysfunction, augment sympathetic activity and cause vascular and tissue deleterious remodeling. Reduced baroreflex sensitivity implies in increased

![Figure 2](https://example.com/image2.png)  
**Figure 2:** Training-induced time-course adaptive changes on autonomic control and cardiovascular parameters in the SHR. Only 2 weeks of aerobic training (T) were enough to normalize oxidative stress and pro-inflammatory profile within the Paraventricular nucleus of the hypothalamus (PVN) and to correct both cardiac vagal activity and baroreflex dysfunction. These training-induced responses precede the augmentation of heart rate variability and the appearance of resting bradycardia (at the 4th week) as well as the partial reduction of peripheral vascular resistance (related to the reversion of arteriolar hypertrophic remodeling in exercised tissues) and a 9% fall in the arterial pressure (both occurring at the 8th week of training). Modified from Masson & Michelini, 2014.\textsuperscript{64}
arterial pressure variability, sympathetic and RAS activation and the appearance of end-organ damage, which potentiate the development/maintenance of hypertension and constitute a positive feedback mechanism to perpetuate the hypertensive disease.

In the treatment of hypertension, it is crucial to promptly normalize autonomic dysfunction that decreases tissue injuries. It is important to note that aerobic training blocks oxidative stress and inflammation in the autonomic brain areas, normalizes baroreflex function and attenuates others autonomic and cardiovascular dysfunctions related to hypertension, even in the persistence of elevated arterial pressure. Thus, aerobic training constitutes an important therapeutic tool to decrease cardiovascular mortality in hypertensive patients.

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Cardiovascular Research: Past, Present and Future

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ABSTRACT

Cardiovascular disease remains a leading cause of death and significant burden on healthcare systems worldwide. While interventional and preventative medicine has significantly changed the face of clinical practice, at the molecular level, treatment has not altered in recent decades and is still directed towards alleviating symptoms or mitigating the underlying cause rather than regenerating damaged heart muscle. This is surprising, given the explosion of research in this area in the 1970’s, and the fact that research output has continued to increase exponentially. With the incidence of heart failure on the rise, a trend predicted to continue, it is imperative that treatment strategies are improved. The development and adoption of molecular interventions might therefore present the most fruitful avenue in providing the greatest impact on mortality rates. This commentary aims to reflect on the earliest documented studies of human cardiovascular physiology, to surgical interventions in the 12th, to the first molecular studies in the 20th, to current pharmacological treatments. With this knowledge in mind, the future of molecular approaches in treating heart failure and cardiovascular conditions will be considered.

KEYWORDS: Cardiovascular disease; Heart failure; Cell biology; Drug discovery; Therapeutics; Clinical translation.


INTRODUCTION

Heart disease is a leading cause of morbidity and mortality worldwide. In order to maintain its ability to meet the metabolic needs of the whole body, the heart has an innate capacity to remodel in response to injury or stress. However, loss of cardiomyocytes is particularly detrimental since these do not proliferate and are not replaced. Subsequent reparative processes such as fibrosis maintain structural integrity but cannot restore lost pump function and in a background of systemic conditions, structural defects or genetic mutations, cardiomyocyte loss is greatly exacerbated and indeed, is a defining feature of heart failure. Ultimately, the heart is unable to preserve its pump function, with death resulting from this or from lethal arrhythmias.1,2

Rather worryingly, the worldwide incidence of cardiovascular disease is predicted to rise from 17.1 million in 2004 to 23.4 million by 2030, and heart failure itself by 23%.3 This is at least partly due to more prevalent risk factors including obesity and age in an increasingly industrialised world.4 Thus heart research remains a very active and integral part of the study of disease pathology.
This commentary aims to document a (very brief) history of cardiovascular research from the 8th Century BC to the 20th Century AD and consider how this has shaped where we are today. A summary of the impact of this history on current clinical practice is presented, with an appraisal of existing obstacles to advancing our understanding of the pathophysiology of the cardiovascular system and therapeutic interventions at the physical and molecular level. Finally, these reflections are used to consider what is yet to come. Confucius said, ‘study the past to consider what is yet to come’. By reviewing the history of cardiovascular research, we can hope to gain insight into what the future holds to predict and pre-empt emerging and future challenges that will be faced on this journey.

THE PAST

8th Century BC to 2nd Century AD

The earliest record of the heart comes from Homer, who compiled anatomical descriptions of exposed organs on the Trojan battlefield in 8th Century BC, in The Iliad. Since the weapon of choice was frequently the spear, penetrating wounds giving visual access to the chest cavity were common. The Iliad demonstrates that the vital organs were known and named, and that soldiers knew that a blow to the heart could be fatal. An extract states (translated by Lattimore):

“...while fighting Idomeneus stabbed at the middle of his chest with the spear, and broke the bronze armour about him which in time before had guarded his body from destruction. He cried out then, a great cry, broken, the spear in him, and fell, thunderously, and the spear in his heart was struck fast but the heart was panting still and beating to shake the butt end of the spear. Then and there Ares the huge took his life away from him...”

The Iliad also demonstrates an early knowledge of physiology and medicine. One such description states that an arrow was removed, blood drawn from the wound to prevent the poison from entering the body, and therapeutic herbs applied. Another shows that herbs with pain relief and possibly antithrombotic properties were known and used in the battlefield:

“Patroclus laid him down, cut the sharp point of the arrow out of his thigh with a knife, and washed away the dark blood from the wound with warm water. Then he teased out the root of a bitter herb in his hands and applied it to the place. It was a sedative, which banished all his pain. The wound began to dry and the blood ceased to flow.”

Of course, The Iliad is not a medical text, but gives insight into the medical knowledge of the time. Of note, an editorial comment suggests that fibrinous pericarditis is actually recorded here; Homer describes “the hairy hearts of hoary heroes”. Pericarditis would have been common at the time due to prevalent tuberculosis and typically, results in a hairy appearance of the heart (Dr. J. Roelant, Professor of Cardiology, Thorax centre Erasmus MC Rotterdam).

More generally, medical texts are frequently the oldest preserved manuscripts, suggested to be due to healing interventions, many of which were incantations, being too long to remember. Authentic medical texts were chronicled by Greek philosophers in the form of case studies. These philosophers were particularly interested in respiration; they recognised that it was necessary for supporting life and consequently the breath was known as the vital power or innate heat. However the heart was thought to control the breath by transmitting innate heat to the lungs to drive expansion, while other organs existed only to cool the heart (Empedocles (490-430 BC) and Aristotle (384-322 BC)). Perhaps the earliest form of research however, can be said to be anatomical dissection. Herophilos (335-280 BC) was the first to (legally) dissect human cadavers, work that extended to live dissection permitted on criminals (an effective deterrent strategy no doubt) and led him to postulate that the brain, not the heart, as Aristotle had thought, was the ‘seat of intelligence’.

Some years later, Galen (129-216 AD) was especially influential in preserving previous knowledge and in substantially advancing heart research. In fact, his works replaced many entrenched and inaccurate theories by, for example, showing that arteries contain blood not air (an idea based on studies of dead animals, where blood vessels appeared to be empty). However, many inaccuracies still existed; Galen asserted that blood moves from the heart in an ebb-and-flow motion rather than by circulation and believed that blood passed from the right to the left ventricle of the heart through invisible holes in the septum.

2nd to 17th Century AD

A more thorough anatomical and physiological understanding of the human body led to development of surgical interventions as early as the 12th Century. By performing surgery on goats, Abu-Marwan Abdel-Malik Ibn Zuhr (Avenzoar, 1093-1162 AD) demonstrated the feasibility of safe operations in humans, while Muhadhdhab Al-Deen Al-Baghdadi (1117-1213 AD), developed clinical practice in a way that is still recognisable today, stressing the need for thorough history taking, physical examination, diagnosis and prognosis. However, it wasn’t until Leonardo da Vinci studied physiology (1452-1519) that the first accurate drawings of the internal working of the heart were recorded, specifically in his Quaderni di Anatomia, vol 2; folio 3v (Figure 1). He also asserted that the heart is a muscle and that the atria are chambers, and was the first to document atherosclerotic coronary arteries.

Galen’s ideas continued unchallenged for a curiously long time, from the 2nd Century until the 16th. One explanation for this stagnation might be the long period (500-1400 AD) in which research activities were controlled by religion. The Church did not advocate acquiring new knowledge, though importantly was
committed to preservation and re-examination of previous work if only to reconcile science with theology.13-15 This no doubt played a part in propagating Galen’s theories, since his findings were considered to be aligned with Christian doctrine. His work therefore gained a significant theological standing and new findings or anomalies were forced to fit his theories.11

Finally, in 1628, inspired by the work of Andreas Vesalius (1514-1564) and Heronymus Fabricius (1537-1619), William Harvey published his crucial research, On the Motion of the Heart and Blood in Animals. This work accurately described systemic circulation and the mechanical function of the heart for the first time.16 17 Harvey was also a forefather of modern research practices, asserting that formulation of a hypothesis is essential and that this must be tested by observable, repetitive and rationally designed experiments. He was also careful to distinguish between fact and speculation and, crucially, was able to use his social standing and medical and royal connections to promote his new theory. However, not surprisingly, given the status given to Galen’s work, it was not widely accepted until after his death.11

The recent past - 18th and 19th century

The study of anatomy flourished in the 18th and 19th centuries, and more widespread use of the printing press following its introduction in the 16th Century facilitated publication and exchange of ideas. Science was becoming more accessible, and the foundations of previous ages more open to all. Crucially, in 1832, the Anatomy Act was passed by parliament in the UK, legalising use of studies on unclaimed or donated human cadavers. As a result of this, the still authoritative text Gray’s Anatomy, came into existence10 (Figure 2).

The immense contribution that animal research has made to progress in heart research should also be emphasised, and the responsibility of this was realised by the first animal protection laws in 1822, followed by the Cruelty to Animals Act in 1876. The latter was strongly promoted by Darwin, who clearly found in vivo work distasteful though necessary, and in 1871, writes:

“You ask about my opinion on vivisection. I quite agree that it is justifiable for real investigations on physiology: but not for mere damnable and detestable curiosity. It is a subject which makes me sick with horror, so I will not say another word about it, else I shall not sleep to-night”.16

In 1986, the Animals (Scientific Procedures) Act was introduced to regulate the use of animals used for research in the UK, and is continually revised to this day.

The 20th century

The era of physiological, interventional and preventative cardiology

Although physiological intervention i.e. surgery, has its origins in the 12th Century, it was not until the 1900’s that this became standard practice. Significant progress in detailed physiological knowledge combined with the development of diagnostic and interventional technologies allowed this to become a reality in clinical practice. A key example of such technologies is electrocardiography,17 introduced in 1903 by the Dutch physiologist Willem Einthoven who was awarded a Nobel prize for his work ‘discovery of the mechanism of the electrocardiogram’ 18,19 His work was also instrumental in the development of mechanical devices that aim to restore normal electrophysiological properties of the heart such as pacemakers and Implanted Cardioverter Defibrillators (ICDs).17

By the 1970’s these approaches were more fully established, and the term ‘interventional cardiology’ came into play. Andreas Gruentzig has been credited with strongly influencing this concept by changing the use of the catheter from that of a diagnostic to a therapeutic tool, when he developed percutaneous coronary angioplasty (widening of narrowed or blocked arteries); indeed the introduction of catheterisation itself, in addition to coronary angiography were also significant advances.17
Cardiovascular prevention was also conceptualised in the mid 1900’s; in 1944, Paul Dudley White pioneered this idea, from which the famous Framingham Heart Study emerged. This identified hypertension, smoking, and left ventricular hypertrophy (evidenced from electrocardiography) as key coronary risk factors, and suggested that recommendations regarding lifestyle changes or pharmacological interventions would dramatically improve survival. In fact, in the last half of the 20th Century, death as a result of coronary artery disease had declined by 70%, and preventative measures such as these have been suggested to contribute to at least half of this statistic.

The era of molecular heart research

While much of the early 20th Century was concerned with physiological and interventional cardiology, a small number of seminal studies delved into the biology of the cardiovascular system at a cellular level. In 1921, Otto Loewi demonstrated that neural communication occurred via chemical not electrical means, an idea that came from a dream and ended in him being awarded a Nobel Prize in 1936 along with Sir Henry Dale, for his work on chemical transmission of nerve impulses. Loewi stimulated the vagus nerve of a beating frog heart in a perfusion chamber to decrease the heart rate and showed that application of the perfusate from this heart to a second, denervated, heart similarly decreased heart rate. Thus he demonstrated a chemically based mechanism of cell–cell communication, via an ‘inhibitory factor’, today known as acetylcholine. Another important study described the authors’ own measurements of the relationship between heart and body weight, which were combined with data collated from previously published work. It notes that the heart to body weight ratio (hypertrophy) can be affected by factors altering body weight, such as growth, inactivity, obesity and weight loss, and by those affecting the heart, including exercise and pathological conditions. Therefore it had been realised that the heart undergoes compensatory remodelling in response to pathological and non-pathological stimulation.

However, it wasn’t really until the 1970’s that dissection of the heart reached a truly molecular level, and in 1980 an accurate and practical approach for generating transgenic mice was described, providing the basis for techniques used today. Generation of the first knock-out mouse in 1989 resulted in its creator being awarded a Nobel Prize in 2007 (awarded jointly to Mario R. Capecchi, Sir Martin J. Evans and Oliver Smithies ‘for their discoveries of principles for introducing specific gene modifications in mice by the use of embryonic stem cells’).

On the back of an understanding of the heart at a cellular and molecular level, came pharmacological interventions. Drugs that are still in widespread use today were introduced into the clinic, most notably beta-blockers, Angiotensin-converting enzyme (ACE) inhibitors and statins. The 20th Century therefore also saw the establishment of the commercial pharmaceutical sector, which now represents a multi-million pound industry integral to drug development today.

Simultaneously, the advent of non-invasive imaging technology such as Magnetic Resonance Imaging (MRI) and echocardiography enabled researchers to study heart function and the cardiovascular system in situ, in the living organism. MRI has its origins in a study from 1973 but was not fully realised until the 80’s and 90’s where rapid advances in hardware, acquisition and image processing permitted the study of heart function at a global and regional level. For the first time, essential phenotypic knowledge regarding the effect of a particular gene or genes on cardiac function could be gained. In addition, this provided a non-invasive means of assessing cardiovascular dysfunction to direct diagnosis and treatment. Thus the 70’s brought about an explosion of research exploring the basic biology of the heart and the cell biology of its disease.

THE PRESENT

The 20th Century presented an immense and impressive leap in basic research and medical practice, and gave birth to sub-specialties in electrophysiology, imaging, interventional, pharmaceutical and preventative medicine. These advances changed the face of cardiovascular treatment from being crude and ineffective, to sophisticated and highly successful. Together, these tenets of modern medicine have saved, and improved the quality of life of millions of people.

Clinical Impact

Physiological and interventional cardiology

The importance of approaches such as electrophysiology, catheterization and coronary angiography in cardiac care is evidenced by the continued use, development and evolution of these approaches in the clinic. The work of Andreas Gruentzig for example, paved the way for further applications of catheterization such as balloon angioplasty and stenting (a permanent means of widening blood vessels). Stents have evolved past simply structural units to those capable of regenerating or mitigating damage to blood vessels, and many now incorporate biodegradable materials and locally released pharmacological agents.

Implanted cardiac cardioversion and defibrillation devices are also still in wide use. In fact survival of end-stage heart failure patients is heavily dependent on mechanical devices in general. In management of heart failure (aside from pharmacological treatments, see www.nice.org.uk/ guidance for current guidelines on these), surgical, catheter-based, intracorporeal (Left Ventricular Assist Devices; LVADs) and extracorporeal (pumps) devices as well as mechanical hearts, are in widespread use and are continuously being refined.

Molecular interventions

At present, heart failure treatment in general largely relieves symptoms, treats the underlying cause, or aims to improve pump function (see The National Institute for Health and Care
Heart Research

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These approaches are the subject of intense scrutiny, and the reader is directed to a comprehensive review on this subject.35

However, these treatments in addition to those described above do not address the underlying issue of existing cardiac damage and/or loss of cardiomyocytes. Without this, treatment must be continued long-term to prevent further deterioration and maintain existing myocardium. While some regeneration has been observed in the case of LVAD placement for example, this is minimal at best; unsurprising given that the regenerative capacity of the heart is meagre. Four general approaches to regenerate non-viable or damaged myocardium to restore normal heart physiology and function have emerged, namely stimulation of endogenous stem or progenitor cells; exogenous stem or progenitor cells; inhibition of cardiac cell death (to limit loss of cardiomyocytes in the first place); and stimulation of cardiomyocyte proliferation.34 These approaches are the subject of intense study, though have yet to provide real clinical impact (Figure 3). The current and future challenges of cell-based therapy are important topics of scrutiny, and the reader is directed to a comprehensive review on this subject.35

Multidisciplinary approaches

Many approaches now combine knowhow from multiple disciplines. For example, development of stents that are used currently is a product of close collaboration between clinicians and basic scientists with expertise in disciplines ranging from pharmacology, biomaterials and bioengineering to cell biology. These advances have significantly improved the quality of life and survival of many patients, and would not have been possible without effective communication between clinical and basic scientific researchers.

In the case of preventative cardiology, this is no longer based simply on the Framingham study, where historical factors such as age, obesity, hypertension status etc. are used to calculate a risk score. A wide variety of additional or alternative scoring systems are now available as a result of molecular information that was not available at the time. As a consequence, risk reclassification and group-specific risks are receiving notable attention.36 Biomarkers are fast become a key component of this, with C-reactive protein for example, shown to be a suitable predictive marker for women but not men, and being most effective in those designated as being medium risk.36 In addition, it has been shown that individual markers rarely make a big impact, and specific groups of markers are emerging as being more useful. Imaging technologies combined with metabolomics profiling (in itself receiving considerable attention of late) is fast becoming an area of interest and significant potential in this context.37 These studies demonstrate the very real impact and importance of combining disciplines such as biological, statistical and epidemiological research.

Current challenges

Translation of molecular approaches into the clinic

Given the volume of research dedicated to the identification and study of specific molecular targets, it might be expected that therapeutic interventions at this level would have made a substantial impact on clinical practice. Disappointingly, however, many have simply not yet made an impression.38,39 Further, molecular treatment regimens in particular have not substantially changed since they were first introduced into standard clinical practice in the 1980’s.36,37 Due to frequent failure at the stage of human clinical trials, investment is considered by the pharmaceutical industry to be high risk, undermining support from this quarter. This is of concern since the incidence of heart disease and failure is rising and predicted to increase further due to more prevalent risk factors such as obesity and old age.34 However, there are some promising trials in which pharmacological agents have been used to target pro-survival kinase signalling pathways (ANP and exenatide) or to protect against oxidative stress induced cell death (Cyclosporin A).38,40-42 Another approach is gene therapy, which is fast becoming a more viable approach than previously thought,43 and which has

![Image](image-url)
been used successfully in clinical trials to stimulate activity of the calcium ion transporter SERCA2a, improving both mechanical function and cell survival. \(^{44,45}\) For a complete list of further clinical trials worldwide the reader is directed to https://clinicaltrials.gov/.

Since some of the most promising clinical trials utilise approaches that activate pro-survival kinases, perhaps an alternative or complementary approach would be the direct inhibition of pro-death kinases. Such interventions are relatively unexplored and only a small number of studies use this strategy. \(^{46}\) Though early, these encouraging observations in general indicate targeting cardiomyocyte cell death to be a productive approach. It has been suggested that an underlying issue with failure in translation from ‘bench to bedside’ lies with use of murine models in pre-clinical testing. Indeed, the usefulness of animals in research is still an intense and passionate area of debate, and poor experimental design and interpretation have been suggested to be key factors. \(^{47,48}\)

Another reason for poor translation from small to large mammal is variable anaesthesia effects. A detailed comparison of the cellular, organ and global compositions and function of mouse and man has been described, \(^{28}\) in which the relevance of anaesthesia protocols is high-lighted and optimal conditions suggested. Overall, under physiological conditions, this study suggests that bioenergetically, hemodynamically and mechanically, the mouse scales linearly with larger mammals and humans. \(^{28}\) However, the authors caution that differences between mouse and man might be unmasked in pathological conditions or under stress.

Prevalent comorbidities and risk factors (including hypertension, hyperlipidaemia, diabetes, psychological disorders, age, gender and existing drug regimens (cardioprotective and otherwise) have also rarely been considered in murine models. Without mirroring these in pre-clinical trials the interactions and outcomes in humans cannot be accurately predicted.

**Collaborative approaches**

The need for a more unified, collaborative approach in research has been recognised, leading to the establishment of a US based organization for more systematic, preclinical in vivo assessment of cardioprotective therapies: CAESAR (Consortium for preclinical Assessment of Cardioprotective therapies (http://www.nihcaesar.org)). This consortium uses multicentre randomized controlled studies to perform pre-clinical testing in three species across three centres. \(^{49}\) The European Society of Cardiology Working Group Cellular Biology of the Heart has also recently made recommendations for a similar Europe based consortium, and provided key recommendations for improving preclinical assessment and the design and efficacy of human clinical trials. \(^{50}\)

**THE FUTURE**

In the absence of a crystal ball or any psychic ability on my part, the future is purely speculative. However, the patterns of the past together with current trends can be used to envisage patterns of the future.

Refinement of existing approaches has always been, and might be predicted to be, a significant focus of future efforts. One very prominent current example of this is that of ICDs. These have been critically important in treating patients at risk of sudden cardiac death. However, drawbacks include invasive procedures for placement, battery replacement or repair. Just recently, Subcutaneous ICDs (S-ICDs) have been introduced, placement or maintenance of which is a relatively minor procedure. Clinical trials have thus far yielded encouraging results, \(^{51,52}\) although more extensive favourable evidence would be required before adoption into clinical practice. This does however illustrate an exciting example of increasingly sophisticated and lower risk approaches that can emerge following continued investment and evolution of specific technologies.

In keeping pace with modern cardiology and all its complexities in diagnosis and treatments, in addition to emerging new technologies such as S-ICDs, a high level of expertise and subspecialisation is undoubtedly required in specific areas. However this can fragment patient care and therefore presents a major challenge for the future. \(^{17}\) There is a need for integration of not just various aspects of cardiac care (from diagnosis to hospital treatment to that following discharge) but in taking account of increasingly prevalent co-morbidities or factors such as diabetes, obesity and old age. In the future, maintaining a clear perspective of the patient as a whole and preserving continuity from the perspective of the patient will present a very real challenge. Like many future obstacles to progress, the answer to this may lie in close interdisciplinary collaboration, open communication and effective dissemination of progress to allow the physician to utilise all the available information to its fullest. Indeed, interdisciplinary research has become a ‘buzzword’ of the 21st Century, and is reflected in particular, in the pharmaceutical industry. Drug development is no longer limited to this sector, and is an increasingly active component of academic establishments. Drugs that are most successful in mitigating heart disease or failure in the clinic are those that have the backing of significant collaboration between academic and commercial sectors, underscoring the importance of crossing bridges between these disciplines.

Ultimately, the basic challenge at the core of all of these efforts; that of healing the cardiovascular patient, will only be met by viewing the patient from all angles and dimensions and bringing this massive wealth of information together. However, this in itself highlights an increasing problem. How can we effectively communicate and assimilate such a wealth of knowledge?
The information technology era has provided an answer to this, with the vast majority of publications now available on the internet, the existence of databases to permit researchers to examine this information and increasingly open and free access for all. Computational approaches and virtual modelling systems are becoming more widely available, although the predictive power of many of these is unclear. As more scientists engage with this technology, both in depositing data and in utilising it, its predictive power will no doubt improve and drive both basic mechanistic understanding and translational potential. Combinations of models, \textit{in vivo}, \textit{ex vivo} and \textit{in vitro}, should ideally be used to drive a more quantitative, integrative, systems biology approach.\textsuperscript{54} Indeed, for a complex condition such as heart failure (with diverse environmental and genetic causes and interactions) a network-based approach might prove particularly fruitful in identifying key signalling convergence points or in better predicting the outcome of therapeutic interventions.

\textbf{The Information Technology Era}

\textbf{Computational tools}

The Cardiac Atlas Project (CAP), established in 2010, is a worldwide consortium and one of the foremost data sharing repositories in the cardiovascular field.\textsuperscript{55} It combines imaging data with diagnostic, clinical and biomarker information on an unprecedented scale, offering the potential for significant advances in treatment of cardiovascular disease. The Anatomical Models Database (AMDB, formerly euHeart) is a web based resource that allows researchers to computationally model cardiac electrophysiology and mechanics using information from geometric cardiac models. It allows the user to generate a geometric heart model based on binary images of the heart and cardiac parameters\textsuperscript{56} while the Virtual Imaging Platform (VIP) focuses on multi-modality medical image simulation.\textsuperscript{57}

Other resources include iDASH (integrated Data analysis, anonymization and sharing), designed to share and access medical data in general,\textsuperscript{58} PhysioNet holds ECG and biomedical data from healthy subjects and cardiac patients\textsuperscript{59} and the Cardio Vascular Research Grid (CVRG) aims to provide a more complex resource for sharing genomic, proteomic, imaging and clinical data from cardiovascular research.\textsuperscript{60} The Open Science Framework (OSF, https://osf.io) aims to provide support in project planning and development by linking online services and facilitating collaborations by providing an accessible platform for data sharing and storage.

\textbf{The rise of big data}

‘Big Data’ is a term used to describe vast amounts of data that cannot be analysed by standard means. Such a large volume of data might be expected to provide a complete and accurate understanding of the subject of interest. This in turn will drive translation of therapies directed against molecular targets from basic science to the clinic, by enhancing the power of pre-clinical models. From the point of view of the pharmaceutical sector, improved predictive power of success in the clinic equals reduced risk and therefore increased investment. However, sharing, analysing and disseminating information on this scale introduces numerous challenges in data collection, organisation, storage, analysis and accessibility to name but a few. In particular, computational and statistical approaches must be sufficiently accurate to limit erroneous statistical inferences and scientific conclusions based on these. Some of these immediate issues are outlined by Fan, et al.\textsuperscript{61}

It would probably not be disputed that data sharing and open resources are important for advancing cardiac research and therapeutic approaches however, and recent progress in ‘big data’ in the cardiovascular field has recently been summarised.\textsuperscript{56} Perhaps the future holds a virtual network of physiological, molecular, computational and bioinformatics scientists, statisticians and clinicians willingly working together to drive the utility of computational approaches to a unprecedented level, though this will no doubt be tempered by intellectual property and patenting issues.

\textbf{Improving translation from bench to bedside}

A unified workflow for assessing therapeutic approaches that is agreed and adhered to worldwide would provide a much improved pathway from target identification to the patient. Such a workflow will rapidly evolve as more data becomes available to substantially increase predictive power of the models used. Early studies in target validation might benefit from utilising multiscale models from cell to tissue to whole body, to provide a more complete picture. Studies in these settings should systematically probe the general molecular mechanisms involved and may provide the advantage of uncovering key convergence points common to cardiomyopathy from diverse etiologies.

Once an appropriate target has been identified and a firm biological basis established, therapeutic strategies can be explored. A multifactorial approach should be taken to provide a more reliable basis for further development. For instance it might be advantageous to assess efficacy of pharmacological (or other) intervention in both genetic and microsurgical models of heart failure that where possible, incorporate factors such as age and obesity. Cost is certainly a limiting factor in testing such approaches in aged mice for example, however genetically aged mice (Terc-null mice) have recently been described and could provide a workable alternative.\textsuperscript{62} Furthermore, many models of obese or diabetic mice currently exist that could also be utilized. In addition, use of a carefully selected panel of genetically engineered mouse models that exhibit explicit, instructive features of heart failure itself might provide a particularly suitable test-bed to predict clinical success.\textsuperscript{63}

\textbf{The use of imaging technologies}

Imaging is becoming ever more sophisticated. Echocar-
diography, pulse wave and tissue Doppler has developed from a 2-Dimensional (2D), to 3D and now a 4D tool, capable of revealing cardiovascular dysfunction with remarkable accuracy. Disease diagnosis, informed treatment decision making and monitoring can now be conducted to a level that would have been previously unimaginable. For more expert reviews on this subject and its future applications the reader is directed to other publications.65,66

The other main imaging technology used in the clinic, MRI, is now capable of exploring the cardiovascular system at a cellular and molecular level. Perhaps some of the most disappointing results in clinical trials to date lie in stem cell based regenerative therapies. This might simply reflect a lack of understanding at the cellular level, of stem or progenitor cell fate, localisation and engraftment. Adequate methods for monitoring these aspects have recently been described; it was shown recently that iron-oxide labelled cells can be visualised by MRI thereby allowing migration and engraftment to be directly monitored these aspects have recently been described; it was shown recently that iron-oxide labelled cells can be visualised by MRI thereby allowing migration and engraftment to be directly monitored in the heart.67 In addition, hybrid imaging systems (two or more imaging modalities) are emerging68-69 paving the way for simultaneously monitoring the heart at a global, regional and molecular level under the conditions of interest. Based on these trends, the future of imaging seems to be in multi-scale approaches; from global to regional to imaging at the molecular level, in a multimodality based manner. This kind of information can allow us to better assess old, current, and new stem cell based therapies to aid in the utility and application of this approach in regenerating the damaged myocardium.

Mouse or man/woman?

A mouse (or indeed any other animal) cannot fully replicate human physiology. Though animal research undoubtedly has paved the way for scientific discovery, it is widely accepted to be an obstacle to effective clinical translation. Since there are some obvious difficulties in persuading human subjects (especially healthy ones) to part with pieces of their heart or to try untested drugs, animal research is still an essential component of cardiovascular research. Increasingly important and alternative resources are human model systems, which are becoming more accessible and suitable for use in research. Many models are now at our disposal that were not in previous decades and there is an emerging need and trend for utilisation of these models in the preclinical pipeline. Importantly, this is particularly lacking in cardiac drug discovery, and since most drugs fail in the clinic due to cardiotoxicity, testing for toxicity in human cardiac cell systems would seem particularly prudent.

Another avenue of increasing interest that directly addresses the problem of a mouse not being able to fully replicate human physiology or signalling responses is the use of human pluripotent stem cell-derived cardiomyocytes.70-71 Patient-specific induced pluripotent stem cells72 carrying disease-causing genetic mutations provide a useful and direct means of dissecting signalling pathways relevant to congenital heart disease and heart failure, as well as providing a relevant test bed for more tailored therapeutic interventions. In short, a target that is validated both in mouse models (providing information from the adult, intact heart) and human cardiomyocytes (providing information from a human platform, even if stem cell-derived) could be considered to carry a lower risk for investment, and provide better-posed targets with significantly improved translational potential, than programs based on either criterion alone.

Personalised medicine

Landmark genetic studies such as the human genome project have created an era in which personalised medicine can form a significant component of preventative measures and treatment plans. So called ‘pharmacogenomics’ can be used to identify patients most likely to exhibit adverse or positive effects to specific drugs. Genetic variants strongly associated with a particular response can be screened for, allowing treatment to be tailored on an individual level.13,16 This has already led to the advent of gene-informed treatment, or ‘smart’ therapy.17 Gene informed preventative measures can also be applied; risk scoring models could be replaced by individual risk-based prevention strategies though this would require significant resource. Perhaps a combination of these, first to identify populations at risk (risk scoring) then to apply individual testing, might prove to be the most efficient system. Indeed, this kind of approach is already emerging as a component of clinical care.18

CONCLUDING REMARKS

With cardiovascular disease on the rise, development of new therapies is a dynamic and essential area of research. However, the mistakes of the past should not be ignored on this quest, and we can only learn from these if we frankly admit and understand them. The advent of stem cell based therapies for example, elicited great excitement but has not yielded the anticipated revolution in clinical treatments. Perhaps many trials were doomed to failure by being undertaken at too early a stage, without the support of a strong foundation of pre-clinical and mechanistic studies. Further, technical limitations have not yet been overcome, with cell retention still being sub-optimal. It is worth noting that the most promising (non-stem cell) trials to date are those that have been the most extensively understood prior to clinical trials. The timeline for initial target discovery to pre-clinical testing in this approach might be rather longer, but lead to greater success. More substantial target validation and mechanistic information in multiple model systems will increase investment potential and inevitably benefit endeavours for research to impact on clinical practice. However, these approaches will rely heavily on the willingness of scientists to collaborate and coordinate their efforts and expertise in a more logical and efficient manner. Efficient dissemination of results and communication across disciplines is an increasingly pressing necessity, as is a more rational, regulated approach to pre-clinical target discovery and validation.
Let us not forget where we came from: philosophy, discussion and debate always have been, and should be at the heart of research. Modern-day conferences could be said to echo the philosophical debates of the past, and the practice of summarising or collecting publications in one volume (similar to modern day reviews or focus issues) has been around for some time. A particularly famous example is the Hippocratic Collection (Corpus Hippocraticum) that incorporates Ancient Greek medical text from the 4th to 6th Century BC. One particular excerpt documents an interesting idea of the time (from ‘On the Heart’, unknown author, but originating from the age of Aristotle, ‘Hippocrates of Cos – Heart,’ volume LCL 509 (Loeb Classical Library, Harvard University Press):

“The heart, in its shape, is like a pyramid, in colour, deep red. It is enclosed in a smooth tunic which contains a little urine-like liquid, so that you might imagine that the heart dwells in a bladder. This is so arranged in order that it may beat vigorously in safety, having a quantity of moisture just sufficient to protect it against being ignited. This liquid the heart passes through like urine after lapsing up drink from the lung.”

Though different from current views, it should be remembered that publications such as this provided the foundation for where we are today and highlight that progress relies on documenting, discussing and building on previous research. Of note, strongly opposing points of view are also aired in this collection, with many texts containing direct challenges and (sometimes heated) retorts to other scholars of the time;7 discussion of this nature is a driving force in the pursuit of knowledge and continues to this day.

By reviewing the history of cardiovascular research, we can not only predict future challenges such as data assimilation and dissemination, but also potential successes. It wasn’t until the 1970’s that molecular studies really emerged so it is not surprising that this technology has not yet translated fully into the clinic. Indeed, early electrophysiology studies in the 1920’s only translated into current treatments some 60 years later, and surgical methods originated as far back as the 12th Century. Thus cellular and molecular studies are in their relative infancy, and the future no doubt holds momentous progress in this area. Based on the lag between early electrophysiology and its established use today, perhaps we can surmise that molecular therapies will reach a practical level around 2030. In fact, promising clinical trials using molecular interventions already exist, and provide hope that clinical practice will undergo a real change in molecular medicine in the near future.

So what does the future hold? We now have the perspective, technical capabilities and resources at our disposal to truly understand the cell biology of the heart at an unprecedented level, and discern highly translatable molecular targets that will provide the best candidates for drug discovery. At the core of this however, lies open communication and collaboration across boundaries and disciplines, and critical appraisal and development of models and workflows. Together, we can considerably diminish the impact of cardiovascular disease, one of the biggest killers of the 21st Century.

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The Sequelae of Silence: Catheter Entrapment as a Preventable Morbidity Resulting from Communication Failure

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ABSTRACT

Medical errors follow a well-established association with communication failure. Seemingly benign interventions such as central venous catheterization can have far reaching consequences. A 72-year-old male required reoperative mitral valve replacement surgery for culture negative endocarditis. Intraoperatively, a central venous catheter was placed without communication between the surgical and anesthesia teams. Despite a seemingly uneventful operative and post-operative course, prior to discharge, the catheter was unable to be removed and necessitated surgical removal. Bidirectional communication during cardiovascular surgery is key to achieving optimum outcomes. Fortunately, it often requires many errors to lead to unnecessary morbidity, however sometimes it takes but one.

KEYWORDS: Central venous catheter; Central line; Catheter; Entrapment; Suture; Cardiothoracic; Cardiac surgery; Anesthesia; Stuck catheter; Stuck line; Communication; Safety; Interdisciplinary; Swiss cheese; Morbidity; Reoperation.

INTRODUCTION

Complications associated with central venous catheters are predominately mechanical (associated with initial placement) or infectious (associated with catheter care). Pulmonary artery catheter entrapment is a well described complication of cardiac surgery however suture entrapment of previously placed central venous catheters is an incredibly rare complication with only a few previously described reports. Its rarity leads to under-recognition and highlights the importance of team communication in order to prevent potentially severe complications.

Medical errors follow a well-established association with communication failures, even when they are the consequence of good intentions or simple omission. The high stress environment of the operating room is a prime location for failures of communication to result in potentially devastating errors. Herein, we present an unusual case of central line entrapment after cardiac surgery despite intra-operative maneuvers and communication to prevent it. The singular breakdown in communication between the cardiac anesthesia and surgical teams led to increased morbidity that could easily have been prevented. This case emphasizes the importance of strong bi-directional communication at all levels in reducing operative complications and improving outcomes.

CASE

The patient is a 72 year/old male with prior aortic valve replacement who presented for mitral valve replacement. He was in heart failure with severe mitral regurgitation presumed secondary to culture negative native valve endocarditis. His prosthetic aortic valve appeared unremarkable on preoperative echocardiography.
At the time of surgery, the anesthesia team placed an 8-French introducer for the Pulmonary Artery (PA) catheter, which is routine preoperative cardiac care at the institution in which this operation was performed. However, unbeknownst to the surgical team in anticipation of potentially significant blood loss due to the re-operative nature of the procedure, the anesthesia team also placed a long large bore central venous catheter via the right internal jugular vein.

Re-sternotomy was performed without difficulty and venous drainage was achieved with superior and inferior vena cava cannulation to facilitate exposure to the mitral valve. Retrograde cardioplegia was delivered through a cannula inserted into the coronary sinus. The mitral valve was replaced through an incision made in the left atrium without difficulty.

The patient was weaned from cardiopulmonary bypass and decannulated without difficulty. All cannulation sites were re-enforced with additional sutures and felt pledgets to limit surgical site bleeding. Prior to closing the chest, free mobility of the PA catheter was confirmed by anesthesia to avoid entrapment.

Post-operative care was uncomplicated and followed our routine cardiac surgery pathways. The PA catheter and introducer sheath were removed without difficulty on post-operative day number two. Prior to discharge, on post-operative day number four, the nursing staff reported difficulty in attempting to remove the central venous line, reporting pulsatile “tugging” with attempts at removal. Due to the concern of catheter entrapment, he was returned to the operating room for surgical management. While gently pulling on the catheter, it appeared to have been entrapped by a cannulation stitch in the superior vena cava. The PA catheter was confirmed by anesthesia to avoid entrapment post-operatively with the use of excessive force to remove the catheter can result in suture disruption and potentially catastrophic hemorrhage. Prevention requires the Anesthesiologist confirming free mobility of the catheter prior to chest closure. This simple intra-operative maneuver clearly illustrates the importance of team communication.

The seemingly benign, and potentially beneficial, step of placing an additional central venous catheter at the time of anesthesia induction introduced the additional risk of suture-associated catheter entrapment. Since the catheter was placed without the knowledge of the surgical team, free mobility was not confirmed prior to chest closure. The complication was not recognized until several days post-operatively during attempted removal. The length of the catheter placed the distal portion in the superior vena cava, at risk for entrapment. Presumably, had the surgical team been aware of the placement of this additional catheter, free mobility could have been confirmed during the first operation, and an early re-operation could have been avoided.

It has been well established that good team communication is critical to optimal outcomes; especially during complex medical/surgical procedures, such as cardiovascular surgery. Breakdowns in communication have been associated with adverse events of varying magnitudes of impact including preventable deaths. Improved communication protocols, including checklists and handoffs, have been clearly shown to reduce medical errors and clinical complications. Furthermore, incorporating comprehensive algorithms targeted at specific complications, such as early re-operation for post-operative bleeding, can also be extremely effective in improving outcomes. Nevertheless, potentially preventable complications and communication breakdowns still occur.

Typically, severe complications (such as deaths or early re-operations) have been associated with systematic communication breakdowns at multiple levels. This so-called “Swiss

DISCUSSION

Entrapment of the pulmonary artery catheter is a well-described complication of cardiac surgery and typically occurs when a stitch, placed to secure cannulas during cardiopulmonary bypass, is inadvertently passed through the pulmonary artery catheter. Following weaning from bypass and decannulation, these stitches are then tied to secure the vascular cannulation sites. The most common site of entrapment is the cannulation stitch placed to secure the cannula in the superior vena cava. Treatment, although simple when recognized, unfortunately requires re-operation with concomitant added morbidity. Once the offending stitch is identified, it can be cut and the catheter is then removed under direct visualization. Failure to recognize entrapment post-operatively with the use of excessive force to remove the catheter can result in suture disruption and potentially catastrophic hemorrhage. Prevention requires the Anesthesiologist confirming free mobility of the catheter prior to chest closure. This simple intra-operative maneuver clearly illustrates the importance of team communication.

It has been well established that good team communication is critical to optimal outcomes; especially during complex medical/surgical procedures, such as cardiovascular surgery. Breakdowns in communication have been associated with adverse events of varying magnitudes of impact including preventable deaths. Improved communication protocols, including checklists and handoffs, have been clearly shown to reduce medical errors and clinical complications. Furthermore, incorporating comprehensive algorithms targeted at specific complications, such as early re-operation for post-operative bleeding, can also be extremely effective in improving outcomes. Nevertheless, potentially preventable complications and communication breakdowns still occur.

Typically, severe complications (such as deaths or early re-operations) have been associated with systematic communication breakdowns at multiple levels. This so-called “Swiss
Cheese" effect is conceptually related to multiple holes, or breakdowns, at different levels (i.e. slices of cheese) in which an error can pass and ultimately result in a severe complication.\(^{11,12}\) However, as our case illustrates, even a single lapse in communication can have a potentially catastrophic effect.

**DISCLOSURES**

In the context of this study and manuscript none of the authors have any disclosures or conflicts of interest - nor do we have any acknowledgments or relevant funding sources. No, informed consent was obtained from the patient.

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Dimethyl Sulfoxide Reduces Microvascular Obstruction and Intramyocardial Hemorrhage in a Porcine Ischemia-Reperfusion Model

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ABSTRACT

Background: Microvascular obstruction (MVO) and Intramyocardial hemorrhage (IMH) are associated with myocardial reperfusion injury and recognized as predictors of adverse left ventricular remodeling in acute myocardial infarction. The pathophysiology of reperfusion injury is characterized by release of reactive oxygen species and inflammation. We investigated whether post-ischemic reperfusion with Dimethyl sulfoxide (DMSO), an organic solvent with therapeutic anti-inflammatory and antioxidant capabilities, could diminish or even abrogate the development of MVO and IMH in a porcine myocardial ischemia/reperfusion model.

Methods and Results: Myocardial ischemia was induced in 20 pigs by balloon occlusion of the Left anterior descending artery (LAD) for 65 minutes. The pigs were allocated to one-hour reperfusion with DMSO or placebo. Eight days post-injury, IMH, MVO, left ventricular function, and myocardial salvage were assessed by Cardiovascular Magnetic Resonance (CMR) imaging; and IMH and myocardial salvage were also assessed by gross pathology. All pigs in the placebo group (100%) but only 10% of the pigs in the DMSO group had IMH. CMR imaging showed presence of MVO in all placebo-treated pigs (100%) and 88% of the DMSO-treated pigs and the MVO size was 45% (p=0.03) smaller in DMSO treated pigs. No difference in myocardial salvage between the placebo and the DMSO group was found by CMR, and pathological investigation and global left ventricular function examination showed no difference between the two study groups.

Conclusion: Reperfusion with a DMSO-containing solvent applied during ischemic reperfusion protected against IMH and MVO in a porcine myocardial ischemic/reperfusion model.

KEY WORDS: Myocardial infarction; Reperfusion injury; Hemorrhage; Microcirculation.

ABBREVIATIONS: MVO: Microvascular obstruction; IMH: Intramyocardial hemorrhage; AMI: Acute Myocardial Infarction; CMR: Cardiovascular Magnetic Resonance; LV: Left Ventricular; DMSO: Dimethyl sulfoxide.
INTRODUCTION

Timely reperfusion is the predominant way to salvage ischaemic myocardium in Acute Myocardial Infarction (AMI). However, reperfusion itself can paradoxically cause additional injury; a phenomenon termed ‘reperfusion injury’. Reperfusion injury may cause myocardial Microvascular obstruction (MVO), which prevents sufficient myocardial tissue perfusion despite complete coronary artery revascularisation. Reperfusion injury may also cause Intramyocardial hemorrhage (IMH) by extravasation of erythrocytes through a severely damaged microvasculature. Both conditions predict poor outcome, and are independent markers of adverse Left Ventricular (LV) remodelling. The pathogenesis of ischemic reperfusion injury is complex and remains only partially understood. Still, oxidative stress, inflammation and intracellular Ca\(^{2+}\) overload are considered to be essential components of ischemia-reperfusion injury. A treatment that prevents the pathophysiologic responses of ischaemia-reperfusion may also be able to prevent MVO and IMH and improve the clinical outcome in patients with successful revascularization after AMI.

Dimethyl sulfoxide (DMSO) is an amphipathic molecule widely used as a solvent in biological studies and as a vehicle for drug administration. DMSO has also demonstrated therapeutic potential by anti-oxidative and anti-inflammatory properties and a capability to reduce intracellular Ca\(^{2+}\) overload following ischemia.

We hypothesised that reperfusion with DMSO following myocardial ischemia may diminish ischemia-reperfusion injury and reduce or even prevent the development of MVO and IMH. We tested this hypothesis in a porcine myocardial ischemia-reperfusion model using gross pathology and Cardiovascular Magnetic Resonance (CMR) imaging for validation.

METHODS

Animal Model

We studied twenty Danish female landrace pigs (40 kg) treated in accordance with the Danish law on animal experiments.

The pigs were pre-sedated with an intramuscular injection of Stressnil (4 mg/kg) and midazolam (1 ml/kg). Anaesthesia was induced with intravenous propofol (5 mg/kg) allowing endotracheal intubation, and it was maintained with sevoflurane (2.5%) in oxygen and continuous-rate infusion of fentanyl (3 mg/kg/hr). The pigs were mechanically ventilated with a tidal volume of 425 ml (respiratory rate 12/min).

An 8 F introducer sheath was inserted into the right common femoral artery under ultrasound guidance. This was followed by an intravenous bolus injection of heparin (100 IU/kg). We induced coronary occlusion by placing a 2.5-mm angioplasty balloon in the LAD distal to the second diagonal branch artery and inflating it to 10 atm. The balloon occluded the LAD for 65 minutes and was deflated and removed. A coronary angiogram was performed after the balloon had been inflated to confirm the occlusion and repeated after the balloon had been deflated to confirm the reperfusion. Within one minute after balloon deflation, a guidance catheter was placed just outside the left coronary ostium, and a 5% DMSO solution or a placebo solution consisting of 0.9% NaCl was injected through the catheter at a flow rate of 16 ml/min for 60 min. The DMSO solution was prepared by dissolving 50 ml DMSO in 1.0 L NaCl (0.9%).

During the procedure, the heart rate, Electrocardiogram (ECG), blood pressure, and temperature were monitored. Ampicillin (2 mg) was administered intravenously before and after the procedure, and acetylsalicylic acid (100 mg/d) was given orally after the procedure and continued until euthanasia. To prevent ventricular fibrillation, 150 mg of amiodarone was administered intravenously before the induction of myocardial infarction. If ventricular fibrillation was encountered, non-synchronised direct current defibrillation (200 J) was performed. The paddles were pressed against the anterior chest wall above the sternum on the right side and below the sternum on the left side.

At the end of the experiment, the pigs were awakened and returned to their stables where they stayed for five to eight days (average 7.2 days) before CMR imaging, harvesting and gross pathology were performed.

CMR Imaging

Fifteen of the pigs underwent CMR imaging before euthanasia (3 pigs were not scanned due to limited access to the MR-scanner and 2 pigs died doing the balloon procedure). The sedation protocol was as described above, except that continuous propofol infusion (120 mg/hr) was used instead of sevoflurane. CMR was performed on a 1.5 T MR system (Intera, Philips Medical Systems, Best, The Netherlands) with a five-element cardiac synergy coil. All pigs were imaged in the supine position. First, a survey scan was performed to localise the heart and the diaphragm. Then, the LV function was assessed using a retrospective, Electrocardiogram (ECG)-triggered Balanced-Steady-State-Free-Precession (B-SSFP) breath-hold cine sequence in the cardiac short-axis, vertical long axis and horizontal long axis plane. In the cardiac short-axis, LV volume was completely encompassed by contiguous 8 mm slices with a spatial resolution of 1.22 mm x 1.22 mm with a Field of View (FOV) of 288 mm x 288 mm. The following imaging parameters were used: repetition time (TR) 3.0 ms; echo time (TE) 1.5 ms; flip angle 60°; 30 heart phases.

T2 weighted Short Tau Inversion Recovery (T2-STIR) fast spin echo sequence was obtained in the previously mentioned short-axis orientation to assess AAR. The sequence was navigator-gated, free-breathing and cardiac-triggered. The fol-
lowing imaging parameters were used: TR 2400 ms, TE 100 ms, echo train length 20, fat inversion time 180 ms, flip angle 90º, spatial resolution 0.54 mm × 0.54 mm in-plane, number of averages 2, slice thickness 8 mm, FOV 320 mm × 320 mm and 14 slices.

T1W IR (GRE), imaging was obtained in the same short-axis slices for the purpose of identifying IMH as previously described by our group. The sequence was navigator-gated, free-breathing and cardiac-triggered. The following imaging parameters were used: TR 3.5 ms, TE 1.13 ms, flip angle 30º, spatial resolution 1 mm × 1 mm in-plane, slice thickness 8 mm (over contiguous slices), FOV 320 mm × 320 mm and 14 slices. Before the acquisition of the T1W IR sequence a TI scout (Look Locker sequence) was performed for the purpose of obtaining the most appropriate TI to null the signal intensity from blood. Typically, the TI was found to be optimal at approximately 500 ms.

Following this, gadolinium enhanced first-pass myocardial perfusion and Late Gadolinium Enhancement (LGE) was performed for the purpose of identifying areas of MVO and myocardial infarction. An intravenous bolus dose of 0.2 mmol/kg Gd-DTPA (Gadobutrol, Gadovist, Bayer Schering Pharma, Berlin) was administered manually. First-pass perfusion imaging was performed using a fast gradient echo sequence with the following parameters: (TR) 2.5 ms, echo time (TE) 1.3 ms, flip angle 18º, spatial resolution 2.8 mm × 3.0 mm × 10 mm, FOV 256 mm × 256 mm, 3 slices acquired in the LV short-axis using a 5 mm interslice gap.

Fifteen minutes after gadolinium injection, the ‘Look Locker’ sequence was repeated to obtain the most appropriate TI to null the signal intensity of normal myocardium. The TI was in the range of 300-350 ms. Subsequently, LGE was acquired using a 3D phase sensitive inversion recovery-prepared T1-weighted gradient echo sequence with the following parameters: TR 5.78 ms, TE 2.78 ms, echo train length, flip angle 25º, spatial resolution 1.5 mm × 1.5 mm × 8 mm, FOV 350 mm times 350 mm, 14 slices was acquired in the LV short-axis and no interslice gap.

Following CMR, the pigs were kept under anaesthesia and moved to the operating room for organ harvesting.

Harvesting and Pathology

After a midline sternotomy, a snare was placed around the LAD distal to the second diagonal branch at the same level as the previously performed balloon occlusion. Then, 25 ml 10% Evans blue dye was injected into the left auricle to delineate the AAR. Subsequently, the animal was euthanized, and the heart was excised. The heart was then cut into consecutive 8 mm-thick slices in short-axis planes. Each slice was photographed with a digital camera (Nikon, Tokyo, Japan) for the purpose of registering myocardial infarction, IMH and AAR.

DATA ANALYSIS

CMR Images

One observer (WYK) who was unaware of the intervention during reperfusion analysed all the CMR image using the semi-automatic, freely available software segment version 1.9 R3746 (http://segment.heiberg.se.). First, LV volumes and function were calculated on the end-diastolic and end-systolic phases of the short-axis cine images. Second, myocardial infarct size was determined in LGE images by a semi automated algorithm accounting for partial volume effects. The infarct size was expressed as a percentage of the LV myocardium (infarction volume/LV myocardium volume x 100%).

We quantified AAR from T2-STIR images by a semi-automated algorithm as (AAR/LV myocardium volume x 100%). Finally, the presence of IMH and MVO was assessed using the following semi-automatic approach: A Region of Interest (ROI) was placed in a homogenous region of the myocardium and the relative mean Signal Intensity (SI) was measured. On T1W IR images myocardium with mean signal intensity more than 2 SD above the mean ROI SI was defined as IMH. MVO was visually defined and measured on first-pass perfusion images as myocardium with no contrast perfusion.

Gross Pathology

Two observers (SFP and ESH) analysed all photographed images of the myocardial slices using the Adobe Photoshop software (Adobe Systems Inc., San Jose, CA, USA). The LV myocardial volume was determined by manually tracing the epicardium and endocardium. Secondly, the IMH volume defined as a distinct blood-stained area within the LV myocardium was manually measured and expressed as a percentage of the LV myocardium (IMH volume/LV myocardium volume x 100%). Third, the infarction size, defined visually as paleor white tissue (scar) areas within the AAR together with any IMH areas, was measured and expressed as a percentage of the LV myocardium (infarction volume/LV myocardium volume x 100%). Finally, the myocardial area stained with Evans blue was manually measured, and the AAR was determined by the formula: (LV myocardium volume- Evans blue volume/LV myocardium volume x 100%). Representative images from DMSO or placebo treated animals are shown in Figure 1.

STATISTICS

The significance of group differences was evaluated with t-tests. Data are presented as mean +/- 95% Confidence Intervals (CIs). A value of p=0.05 was considered statistically significant. Performing a q-q plot tested normal distribution of the data. The association between IMH and MVO and treatment with DMSO or placebo was tested with a 2-tailed Fischer exact test.
Statistical analysis was performed with SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Two pigs died during coronary occlusion and were excluded from the study leaving eighteen pigs for further investigation. CMR imaging was only performed in 15 of the eighteen pigs due to limited access to the MR-scanner. All CMR examinations and pathological procedures were successfully performed. The results are summarized in Table 1. Hemodynamic variables did not differ between groups during the intervention. Global LV function and volumes were similar in the two study groups.

Neither CMR nor gross pathology demonstrated significant differences in AAR, infarct size or myocardial salvage index between groups even though the CMR showed a non-significantly increased myocardial salvage index in the DSMO treated group. Both CMR and gross pathology revealed a significant difference in the occurrence of IMH. CMR showed that 0 out of 8(0%) had IMH in the DSMO treated group compared to 7 out of 7(100%) pigs in the placebo group (p<0.01). The gross pathology showed that 1 out of 10(10%) animals had IMH in the DSMO group compared to 8 out of 8(100%) in the placebo group (p<0.01). The only case in the DSMO group that demonstrated IMH by gross pathology was not investigated by CMR. By CMR, MVO was demonstrated in 7 out of 8(88%) animals in the DSMO and in 7 out of 7(100%) in the placebo group (p=1.00). The MVO size was 45% (p=0.03) smaller in DSMO treated group compared to the placebo group. Figure 2 show representative gross pathological pictures and CMR images of hearts subjected to DSMO and placebo.

DISCUSSION

The results of this study show that DMSO can prevent the formation of IMH and diminishing MVO in porcine myocardium exposed to prolonged ischemia-reperfusion injury. Several studies have recently shown that DMSO attenuates ischemic reperfusion injury in a variety of organs.13,23-26 The present study expands these findings by demonstrating that DMSO can protect the myocardial microvasculature against ischemia-reperfusion injury by preventing IMH and diminishing MVO development even in the absence of infarct size reduction.

The protective effect of DMSO against MVO and IMH may be attributed to its anti-inflammatory effect.13,27 However, the pathophysiology of reperfusion injury is complex, and the protective effect of DMSO may also be attributed to other factors such as its anti-oxidant properties and its capability to inhibit intracellular calcium overload.17 The porcine model used in the present study did not, however, allow identification of the underlying mechanisms involved in MVO and IMH prevention and additional studies will therefore be needed in order to dissect the molecular pathways.
In our study, DMSO did not reduce myocardial infarct size. This observation contradicts previous studies demonstrating that DMSO reduced infarct size in isolated rat hearts. A potential explanation is that we used a very long ischemia time (65 min) for the purpose of inducing MVO and IMH. Furthermore, pigs are known to develop large transmural myocardial infarcts due to the lack of coronary collaterals. Consequently, myocardial injury may have progressed beyond the point of salvage, and therefore all infarcts were transmural and hence did not differ significantly in size between groups when investigated 7 days later. The very low myocardial salvage indices in the order of 11-20% and the large infarct sizes in both groups reflect the effect of the long ischemia time before reperfusion. As such, the infarcts in this study resemble large anterior infarcts in patients.

Another important aspect of this model of ischemia-reperfusion injury is the evaluation by CMR after approximately one week. This time point was chosen since CMR detection of myocardial salvage is considered optimal at one week after AMI. The choice of time point is transferable to the clinical setting of CMR evaluation of patients with AMI.

Table 1: Results summary. MAP: Middle Arterial Pressure; LV: Left Ventricle; AAR: Area at risk; LGE: Late Gadolinium Enhancement; IMH: Intramyocardial hemorrhage; MVO: Microvascular obstruction.
Various approaches to diminish the deleterious consequences of ischemic reperfusion injury have been tested in the past. Most involved treatment with exogenous substances in the pre-ischemic phase. However, none of these pre-treatments have found their way into the clinic since they need to be initiated before the onset of ischemia, something that obviously cannot be anticipated in a clinical setting. This makes the present study particularly interesting because DMSO was applied in the post-ischaemic phase and therefore has the potential to become a clinically relevant treatment for the prevention of MVO and IMH.

LIMITATIONS

While the data were convincing in demonstrating that DMSO-containing solvent applied during ischemic reperfusion protected against IMH and MVO, the sample size was relatively small. Larger studies would therefore be useful to confirm our findings. MVO and IMH were only assessed by CMR and gross pathology, however further information regarding the mechanism of MVO and IMH could properly be obtained by examining the microvasculature histologically.

CONCLUSION

In conclusion, in an in vivo porcine model of myocardial reperfusion injury, we demonstrated that intracoronary DMSO administered after ischemia and onset of reperfusion protects the myocardial microvasculature against reperfusion injury by diminishing IMH. Furthermore, the study demonstrates that CMR performed one week after AMI can accurately detect MVO and IMH. CMR may provide a non-invasive measure of reperfusion injury in patients with AMI beyond infarct size reduction to evaluate the effect of cardioprotective approaches. Additional studies are required to elucidate the underlying protective mechanisms of DMSO and also long term studies are needed in order to evaluate the positive effect of DSMO on cardiac remodelling and function.

CONFLICTS OF INTEREST: None.

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Case Report

Forgotten, but Not Gone

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KEY WORDS: Mitral stenosis; Left atrial thrombus; Coumadin; Rheumatic valve disease

A 65 year old woman, an Asian immigrant to USA, with the history of surgical mitral valvuloplasty through left thoracotomy performed 30 years ago in India for severe rheumatic mitral stenosis, history of embolic occlusion of right femoral artery and surgical embolectomy (3 years ago), chronic atrial fibrillation, presented with dyspnea on exertion. Patient was on Coumadin therapy with therapeutic INR (2-3). Her work up revealed severe mitral stenosis with marked left atrial enlargement. There was massive clot burden in the left atrium. Despite massive left atrial clot, patient had no history of stroke/TIA. She then successfully underwent left atrial thrombectomy with mitral valve replacement. Intra operative findings were very small orifice of mitral valve with fused commissures and chordae tendinae, consistent with severe rheumatic mitral stenosis. Post-operative recovery was uneventful. Patient continues on Coumadin with target INR of 2.5-3.5 with post-operative echocardiograms showing no left atrial clot.

Although rheumatic heart disease is rare in USA, it is estimated there is prevalence of 15 million cases of rheumatic heart disease worldwide, with annual incidence of 282,000 cases, and annual mortality of 233,000.1 We present an exceptional finding of massive left atrial clot burden with severe rheumatic mitral stenosis. This case underscores the findings of atrial fibrillation, markedly enlarged left atrium, spontaneous echocardiographic contrast and advanced age, all implicated in high risk of left atrial clot burden in patients with rheumatic mitral stenosis.2 The rheumatic pathology is well appreciated on 2D Trans Esophageal Echocardiographic (TEE) images (Videos 1 and 2, Figures 1A and 1B) while the 3D TEE brings a new spatial perspective in appreciating the left atrial clot burden and its relationship to mitral valve (Video 3, Figure 1C).
Figure 1A, Video 1: TEE. AML=Anterior mitral leaflet with its classic hockey stick appearance in rheumatic mitral stenosis due to commissural fusion. LA=Left Atrium, LV=Left Ventricle, AO=Aorta. The circumferential LA clot is indicated by arrow.

Figure 1B, Video 2: TEE. SEC=Spontaneous Echocardiographic Contrast, a marker of high risk of clot formation. The dense SEC swirling in the left atrium is well visualized on video. LA=Left Atrium, RA=Right Atrium, AOV=Aortic Valve

Figure 1C, Video 3: 3D TEE. The extensive left atrial clot and its relationship to left atrium, underlying mitral valve is remarkably appreciated on the 3D TEE images.

Note: To best view

2. Please save the pdf file in your local computer.
3. To watch the video kindly install the latest adobe flash player. Click here to download: http://get.adobe.com/flashplayer/otherversions/
Rheumatic heart disease is forgotten in developed countries, it will be encountered largely due to immigrant population. Our patient despite being on warfarin with therapeutic INR developed left atrial clot. This raises questions regarding INR goals in such patients, and also the role, if any, of novel oral anticoagulants.

CONFLICTS OF INTEREST: None.

CONSENT
No consent is required to our article publication/The patient has provided written permission for publication of the case detail.

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