IMPLICATIONS OF NATRIURETIC PEPTIDES AND ENDOTHELIN-1 RELEASE DURING MYOCARDIAL ISCHAEMIA.

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TABLE OF CONTENTS

CHAPTER 1 - INTRODUCTION

1.1. Myocardial ischaemia: Clinical forms, variations in severity and/or duration, and common treatments.

1.1.1. Tachycardia induced myocardial ischaemia with fixed stenoses in epicardial coronary arteries.

1.1.2. Tachycardia independent myocardial ischaemia with subtotal coronary flow reduction.

1.1.3. Incipient necrosis with occlusion of one of the epicardial coronary arteries.

1.1.4. Transient myocardial ischaemia with percutaneous transluminal coronary angioplasty (PTCA).

1.1.5. Sequelae of ischaemia/reperfusion: biochemical and haemodynamic.

1.2. Physiology and Pathophysiology of Natriuretic Peptides

1.2.1. Structure, synthesis, and release of natriuretic peptides

1.2.2. Natriuretic peptide receptors

1.2.3. Physiological actions of natriuretic peptides

1.2.4. Effect of myocardial ischaemia on release of natriuretic peptides

1.2.5. Available techniques for manipulating natriuretic peptides
1.3. Physiology and Pathophysiology of Endothelins

1.3.1. Structure, synthesis, and release of endothelins

1.3.2. Endothelin receptors

1.3.3. Physiological actions of Endothelins

1.3.4. Effect of myocardial ischaemia on release of endothelins

1.3.5. Available techniques for manipulating endothelins

1.4. Interactions between Natriuretic Peptides and Endothelins

1.4.1. Receptor based interactions

1.4.2. Physiological antagonism

1.5. Effects of anti-ischaemic therapy on release of Natriuretic Peptides and Endothelins

1.6. Plan of Research

CHAPTER 2 - MATERIALS AND METHODS

2.1. Animal Studies

2.1.1. Materials and Animals

2.1.2. The Isolated Perfused Rat Heart Preparation

2.1.3. Experimental Protocols

2.1.4. Cardiac Parameters

2.1.5. Radioimmunoassay of atrial natriuretic peptide
2.1.6. Radioimmunoassay of brain natriuretic peptide

2.1.7. Radioimmunoassay of endothelin-1

2.2. Human Studies

2.2.1. Patients undergoing percutaneous transluminal coronary angioplasty

2.2.2. Patients involved in investigation of glyceryl trinitrate-atrial natriuretic peptide-endothelin-1 interaction.

2.2.3. Blood collection

2.2.4. Plasma atrial natriuretic peptide radioimmunoassay

2.2.5. Plasma endothelin-1 radioimmunoassay

2.2.6. Plasma cyclic 3':5'-guanosine monophosphate radioimmunoassay

2.3. Data Analysis

CHAPTER 3 - DETERMINANTS OF ATRIAL NATRIURETIC PEPTIDE/ENDOTHELIN-1 RELEASE DURING ISCHAEMIA--

3.1. Introduction

3.2. Method

3.3. Results

3.3.1. Extent of Coronary Flow Reduction.

3.3.2. Determinants of atrial natriuretic peptide release
3.3.2.1. Perfusion flow reduction

3.3.2.2. Role of Bradycardia

3.3.3. Brain natriuretic peptide release

3.3.4. Endothelin-1 release

3.3.5. Correlation with cardiac function

3.4. Discussion

3.5. Summary

CHAPTER 4 - MECHANISMS OF ISCHAEMIA ASSOCIATED ATRIAL NATRIURETIC PEPTIDE RELEASE

4.1. Introduction

4.2. Method

4.3. Results

4.3.1. Role of Nitric Oxide on Ischaemia-induced Atrial Natriuretic Peptide Release

4.3.2. Role of Endothelins on Ischaemia-induced Atrial Natriuretic Peptide release

4.3.2.1. Effect of exogenous Endothelin-1 on ischaemia-induced Atrial Natriuretic Peptide release

4.3.2.1.1. Exogenous Endothelin-1 on Atrial Natriuretic Peptide release
4.3.2.1.2. Exogenous Endothelin-1 on perfusion flow rate

4.3.2.1.3. Exogenous Endothelin-1 on cardiac function

4.3.2.2. Effect of ET receptor antagonists on ischaemia-induced Atrial Natriuretic Peptide release

4.4. Discussion

4.5. Summary

CHAPTER 5 - EFFECTS OF ENDOTHELIN ANTAGONISTS ON CORONARY FLOW, ENDOTHELIN-1 RELEASE AND SYSTOLIC FUNCTION-----------------------------------130

5.1. Introduction

5.2. Methods

5.3. Results

5.3.1. Effects of BQ-123 and bosentan on coronary perfusion flow rate

5.3.2. Effects of BQ-123 and bosentan on endothelin-1 release

5.3.3. Effects of BQ-123 and bosentan on cardiac function

5.4. Discussion

5.5. Summary
CHAPTER 6 - EFFECTS OF ENDOTHELIN ANTAGONISTS ON HYPOXIA-INDUCED ATRIAL NATRIURETIC PEPTIDE RELEASE FROM ISOLATED PERFUSED RAT HEARTS——155

6.1. Introduction

6.2. Method

6.3. Results

6.3.1. Effects of hypoxia on Atrial Natriuretic Peptide, Brain Natriuretic Peptide and Endothelin-1 release.

6.3.1.1. Effect of hypoxia on Atrial Natriuretic Peptide release.

6.3.1.2. Effect of hypoxia on Brain Natriuretic Peptide release.

6.3.1.3. Effect of hypoxia on Endothelin-1 release.

6.3.2. Changes in cardiac performance and coronary flow.

6.3.3. Effect of BQ-123 and bosentan on Atrial Natriuretic Peptide and Endothelin-1 release during hypoxia/re-oxygenation.

6.3.3.1. Effect of BQ-123 and bosentan on Atrial Natriuretic Peptide release.

6.3.3.2. Effect of BQ-123 and bosentan on Endothelin-1 release.

6.3.4. Effect of BQ-123 and bosentan on hypoxia-induced changes in coronary flow and heart performance.

6.4. Discussion

6.5. Summary
CHAPTER 7 - TRANSIENT MYOCARDIAL ISCHAEMIA IN MAN: EFFECT ON ENDOTHELIN-1 AND ATRIAL NATRIURETIC PEPTIDE RELEASE

7.1. Introduction

7.2. Method

7.3. Results

7.3.1. Patient characteristics and haemodynamic parameters

7.3.2. Effects of percutaneous transluminal coronary angioplasty on plasma Atrial Natriuretic Peptide concentrations

7.3.3. Effects of percutaneous transluminal coronary angioplasty on plasma Endothelin-1 concentrations

7.4. Discussion

7.5. Summary

CHAPTER 8 - INTERACTIONS BETWEEN ANTI-ISCHAEMIC THERAPY WITH ORGANIC NITRATES, HAEMODYNAMIC EFFECTS AND RELEASE OF ENDOTHELIN-1/ATRIAL NATRIURETIC PEPTIDE

8.1. Introduction

8.2. Method

8.3. Results
8.3.1. Effect of acute glyceryl trinitrate infusion on plasma Atrial Natriuretic Peptide and Endothelin-1 concentrations.

8.3.1.1. Patient characteristics

8.3.1.2. Haemodynamic responses to 10 min iv glyceryl trinitrate

8.3.1.3. Effects of glyceryl trinitrate on plasma Atrial Natriuretic Peptide and cyclic 3':5'-guanosine monophosphate levels

8.3.1.4. Effects of glyceryl trinitrate on plasma Endothelin-1 levels

8.3.2. Effects of chronic nitrate therapy on plasma Atrial Natriuretic Peptide and Endothelin-1 concentrations

8.3.2.1. Patient characteristics

8.3.2.2. Comparisons of haemodynamic parameters between acute and chronic nitrate administration.

8.3.2.3. Comparisons of plasma Atrial Natriuretic Peptide concentrations between acute and chronic nitrate administration.

8.3.2.4. Comparisons of plasma Endothelin-1 concentrations between acute and chronic nitrate administration.

8.4. Discussion

8.5. Summary
CHAPTER 9 - CONCLUSIONS AND FUTURE DIRECTIONS---
-----------------------------------------------215

9.1. Conclusions

9.2. Future directions

BIBLIOGRAPHY-----------------------------------------------222

APPENDIX-----------------------------------------------280
Abstract

The majority of (in vitro) studies were performed in the Langendorff-perfused, isolated rat heart, utilizing a paradigm in which atrial distension was prevented. The release of natriuretic peptides (ANP, BNP) and endothelin-1 (ET-1), along with cardiac function was monitored during periods of transient ischaemia or hypoxia. Additional studies were performed in patients undergoing cardiac catheterization.

A. In vitro studies (the Langendorff-perfused rat hearts)

1). Ischaemia-induced ANP release: determinants.

Coronary flow reduction greater than 50% increased ANP, but not BNP or ET-1 release. Right atrial pacing at a rate of 10% over spontaneous heart rate did not affect basal or ischaemia-induced ANP release. Ischaemia-induced bradycardia had no effect on ANP release.


The nitric oxide synthase inhibitor L-NAME (10^{-4} M), and the endothelin receptor antagonists BQ-123 (10^{-6} M) and bosentan (10^{-5} M) did not affect basal or ischaemia-induced ANP release. Exogenous ET-1 (5x10^{-10} M) perfusion induced a delayed increase in ANP release. L-NAME perfusion did not alter ET-1 release rate. Hypoxia (5% O_2) induced an 8-fold increase in ANP release rate, but did not affect BNP or ET-1 release. Bosentan attenuated hypoxia-induced ANP release. Thus, ET mediates, in part, hypoxia but not low flow ischaemia-induced ANP release.

3). ET-1 regulation of local vasomotion and myocardial contraction during ischaemia or hypoxia.

Exogenous ET-1 caused significant perfusion flow reduction, but did not significantly affect cardiac force of contraction. BQ-123 decreased coronary flow rate in the non-ischaemic heart. In ischaemic heart, BQ-123 abolished the post-ischaemic increase in
perfusion flow rate. Neither BQ-123 nor bosentan induced significant variation in force of contraction in non-ischaemic hearts. Bosentan significantly accentuated and BQ-123 tended to (P=0.06) accentuate the ischaemia-induced impairment in force of contraction. Bosentan also impaired the recovery of systolic function during reperfusion. Both BQ-123 and bosentan perfusion significantly increased ET-1 efflux rate. This effect was abolished during ischaemia for BQ-123, but not for bosentan. During hypoxia, heart rate and force of contraction were reduced, while coronary flow rate increased. Bosentan tended to increase ET-1 release (P=0.051) and decrease cardiac force of contraction (P=0.059) during hypoxic periods. BQ-123 abolished the hypoxia-induced increase in perfusion flow rate.

**B. In vivo studies (human)**

1). **Effects of percutaneous transluminal coronary angioplasty (PTCA)-induced ischaemia on ET-1 release into systemic circulation in man.**

Plasma ANP and ET-1 concentrations, measured prior and subsequent to the initial intra-coronary balloon inflation in patients undergoing elective PTCA, did not change in femoral and pulmonary arteries (FA, PA).

2). **Interactions between anti-ischaemic therapy with Glyceryl trinitrate (GTN), haemodynamic effects and ET-1/ANP release.**

Intravenous GTN infusion (10 μg/min) significantly decreased pulmonary capillary wedge and systolic arterial pressure. Plasma ANP concentrations in FA, FV and PA and ANP gradient across the femoral vascular bed (FA-FV) decreased following GTN infusion. ET-1 concentrations in FA and PA plasma did not change significantly in the presence of GTN. However, plasma ET-1 concentration gradient across the femoral vascular bed (FV-FA) increased.