CARDIAC DYSFUNCTION IN RENAL TRANSPLANT RECIPIENTS

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ABSTRACT

Adrenomedullin has been shown to be increased in case of cardiac and renal impairments, in relation with the severity of the diseases. This work was performed to investigate whether an increase in circulating Adrenomedullin might be related to cardiac functions in RTRs.

Methods: thirty eight subjects, 28 RTRs and 10 healthy controls participated in the study. After 15 min rest in supine position, Heart rate, systemic blood pressure were measured together with cyclosporine trough levels, creatinine and ADM. Systolic and diastolic cardiac functions were assessed, using Doppler echocardiography.

Results: creatinine and Adrenomedullin (130.7 ± 51.6 pg/ml vs. 31.9 ± 14.4 pg/ml, p=0.0001) were significantly increased in RTR, (60 ± 24.8 months after renal transplantation). RTR was presented with increased LVMI (124.6 ± 51.7 g/m^2). Cardiac systolic function was normal in RTR, but reduced mitral E: A ratio was observed in RTR (0.92 ± 0.3 vs. 1.4 ± 0.07, p= < 0.0001) reflecting their impaired left ventricular relaxation. Such a ratio was negatively correlated with Adrenomedullin (r= −0.5, p= 0.006)

Conclusions: LVH is not uncommon after renal transplantation and cardiac diastolic dysfunction is a significant clinical concern and likely participates in increased ADM observed in RTR.

Keywords:

(Adrenomedullin – cardiac function – diastole – renal transplantation)

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List of appreviations

ACE…….……: Angiotensin converting enzyme.

AMP……....: Adenosin monophosphate.

AOD……..: Aortic root diameter.

ATP……..: Adenosine triphosphate.

AV……....: Arteriovenous.

AVFs……....: Arteriovenous fistulas.

BMI……..: Body mass index.

cAMP……....: Cyclic adenosine monophosphate

cGMP…….....: Cyclic guanosine monophosphate.

CGRP……...: Calcitonin gene- related peptide

CHF…….…..: Congestive heart failure.

CKD……...: Chronic Kidney disease.

CL…….: Calcitonin receptor like.

cm/sec. ……..: centimeter per seconde**.**

CRP…….……..: C-reactive protein.

CSA…….....: Cyclosporine A.

CVD……..: Cardiovascular disease.

DBP……..: Diastolic blood pressure.

DM……...: Diabetes mellitus.

DT……....: Decelration time.

EDV……..: End diastolic volume.

EF……....: Ejection fraction.

ESRD……: End stage renal disease.

ESV…….....: End systolic volume.

FKBP 12…….....: FK binding protein.

FS…….....: Fractional shortening.

GM-CSF……..: Granulocyte-macrocyte colony-stimulating factor.

GMP……:Guanosine monophsphate.

CREs……...: Corticosteroid response elements.

HD……...: Hemodialysis.

HGPRT……..: hypoxanthine-guanine-phosphoribosyl transferase.

HLA……....: Human leucocyte antigen.

HSPs……...: Heatshock proteins

iADM……..: Immature adrenomedullin.

IHD……..…..: Ischemic heart disease.

IL-1…….: Interleukin- 1.

IL-6…….: Interleukin- 6.

IMP…….…: Inosin monophosphate.

IRT…….....: Isovolumic relaxation time.

IVS……..: Inter ventricular septum.

LA……...: Left atrium.

LAD……....: Left atrium diameter.

LV……...: Left ventricle.

LVEF……..: Left ventricle ejection fraction.

LVH……....: Left ventricular hypertrophy.

LVIDD……....: Left ventricular diameter in diastole.

LVIDS…….: Left ventricular internal diameter in systole.

LVM……....: Left ventricular mass.

LVMI……..: Left ventricular mass index.

mADM……: Mature adrenomedullin.

MAP……: Mean arterial pressure.

MHz……: Milli hertz.

MMF……...: Mycophenolate mofitil.

MPA……....: Mycophenolic acid.

mTOR…….....: Mammalian target of rapamycin.

NEB……: Neutral endopeptidase.

NFAT-1……...: Nuclear factor of activated T cells- 1.

NKF……..…..: National Kidney Foundation

NO……...: Nitric oxide.

NODAT……..: New onset diabetes after transplant.

NYHA…….: New York Heart Association.

PAL…….: Peptidylhydroxyglycine α-amidating lyase.

PAM……: Peptidoglycine α-monooxygenase.

PANP……...: Proadrenomedullin N-terminal 20-peptide.

PHM……: Peptidoglycine hydroxylating monooxygenase.

PWT……: Posterior wall thickness.

Rpm…….: Round per minute

SA-HRP…….: Streptavidin-horseradish peroxidase.

SBP……..: Systolic blood npressure.

SD……: Standard deviation.

SPSS……: Statstical Package for social science.

TAC…….....: Tacrolimus.

TNF-α……..: Tumour necrosis factor alpha

TPMT……..: thiopurine methyltransferase**.**

USRDS……: United States Renal Data System

XO…….....: Xanthine oxidase.

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INTRODUCTION

Nowadays, with growing experience and the development of more effective immunosuppressive therapy, the quality of life for most kidney transplant recipients is excellent (***Humar et al., 2003***).

For the vast majority of patients with end-stage renal disease, kidney transplantation is the best therapeutic alternative (***Wolfe et al., 1999***). Kidney transplantation provides a superior prognosis (***Kanawar et al., 2006***) compared with any form of dialysis. Many centers report a one-year patient and graft survival rate of >95% following living donor kidney transplantation. (***Oien et al., 2007***)

Kidney transplantation may decrease cardiovascular mortality and the risk for CHF specifically compared with long-term dialysis therapy (***Meier-Kriesche el al., 2004***). Furthermore, renal transplantation exerts a beneficial impact on cardiomyopathy manifested by LVH and systolic dysfunction (***Dudziak et al., 2005***). However, CHF remains a significant clinical concern after kidney transplantation for reasons that are not fully defined (***Lentine et al., 2005***).

As renal transplantation is often a state of chronic renal insufficiency, Claudio and his colleagues hypothesized that CHF would occur frequently, would be associated with potentially reversible risk factors, and would be a prognostically important event among RTR (***Claudio et al., 2002).***

Mortality after transplantation is just as likely to be due to underlying cardiovascular disease as to infectious and neoplastic complications of immunosuppression (***Hill et al., 1991***)

Adrenomedullin (ADM) is a 52-amino-acid peptide involved in many functions, including electrolyte balance, neurotransmission, growth and hormone secretion regulation (***Lopez & Martinez, 2002***)

This powerful vasorelaxing, natriuretic and antimitotic peptide, mainly produced by vascular smooth muscle cells and endothelial cells, is particularly involved in cardiovascular homeostasis through its cardiorenal protective role. Thus, ADM increases local blood flow in kidneys and the heart and attenuates renal dysfunction and transition from left ventricular hypertrophy to heart failure (***Tsuruda & Burnett, 2002***).

Such beneficial effects might also be observed in other territories as ADM is considered as a protective factor for blood vessels, reducing intimal thickening, fatty streak formation and perivascular hyperplasia, and thus allowing to reduce the progression of vascular damage and remodeling (***Kato et al., 2005***). Furthermore, ADM has been shown to reduce glomerular injuries (***Vesely, 2003***).

ADM is present in the plasma of normal humans and has been shown to be increased in case of cardiac and renal impairments, in relation with the severity of the diseases (***Chao & Chao, 2002***).

ADM appears nevertheless particularly interesting to study. Indeed, relatively few data are available concerning ADM and transplantation, despite the fact that ADM is importantly involved in protective cardiorenal and vascular mechanisms (***Tsuruda & Burnett, 2002***).

AIM OF THE WORK

Prove or disprove the hypothesis that increased plasma level of adrenomedullin (ADM) in renal transplant recipients might be linked with cardiac systolic and/or diastolic dysfunction to prevent further deterioration of their cardiac affection.

IMMUNOSUPPRESIVE DRUGS

There are three "regimens" of immunosuppressive therapy: induction, maintenance, and anti-rejection. Induction therapy describes the combination of drugs given immediately after the transplant with the aim of preventing acute rejection. Maintenance immunosuppression consists of immunosuppression drugs used to prevent acute and chronic rejection. Anti-rejection therapy is a drug or combination of drugs given to treat an ongoing episode of acute rejection (***Barshes et al., 2004***).

Here, we only discuss mode of action and side effects of those common immunosuppresion drugs used in the maintenance regimen.

1- Antimetabolites

(a) AZATHIOPRINE

Mode of action

Azathioprine is an imidazole derivative of 6- mercaptopurine. After ingestion and absorption of the drug by the gastrointestinal tract, Azathioprine is converted to 6- mercaptopurine by the glutathione-S-transferase in erythrocytes. 6-mercaptopurine is then metabolized via one of three pathways: to 6-thioinosinic acid and 6-thioguanine acid via hypoxanthine-guanine-phophoribosyl transferase (HGPRT); to thiouric acid via xanthine oxidase (XO); and to 6-methyl-mercaptopurine via thiopurine methyltransferase (TPMT). 6-thioinosinic acid and 6-thioguanine acid are active metabolites which interfere with metabolism of inosine monophosphate (IMP) to adenosine-monophosphate (AMP) and adenosine triphosphate (ATP) in RNA and DNA synthesis in the salvage pathway.

Thus, it interferes with purine sythesis and inhibits *de novo* purine synthesis. This results in a suppression of proliferating B- and T lymphocytes. It also has some anti-inflammatory action (***Pirsch & Neto, 2001***).

Adverse effects

The most common adverse effect of azathioprine is bone marrow depression mainly leukopenia, but also macrocytic anemia and thrombocytopenia. Dose reduction should be considered when leukocyte counts fall below 4000 cells/mL. Gastrointestinal toxicity (specifically, nausea, vomiting and diarrhea) occurs often. Hepatotoxicity occurs by an unknown mechanism, though it is now thought that some of the hepatotoxicity attributed to azathioprine in past studies may have in fact been undiagnosed viral hepatitis. The hepatotoxicity is often manifest as an increase in liver enzymes, but toxicity occurs even at azathioprine doses too low to cause an elevation in these enzymes. Other common adverse effects include skin rashes and fever ***(Pirsch & Neto, 2001)***.

(b) MYCOPHENOLATE MOFITIL (MMF)

Mode of action

MPA acts as a highly selective and reversible inhibitor of IMPDH, thus inhibiting the conversion of IMP to GMP. Because MMF inhibits only this *de novo* pathway, is relatively selective for actively replicating lymphocytes. Of the two isoforms of IMPDH, MPA has a four to five times higher affinity for isoform II, the predominant isoform in the lymphocyte, further enhancing selectivity for lymphocytes. Unlike azathioprine, MMF is not a nucleotide analogue and thus will not produce the possible mutagenic

effects such as inhibition of DNA repair enzymes (**Rayhill & Sollinger, *1999***)

Advers effects

The most common adverse effect of mycophenolate mofetil is gastrointestinal toxicity, producing nausea, vomiting, diarrhea and abdominal pain. Diarrhea is especially common with the combination of cyclosporine and MMF. Bone marrow suppression also occurs. MMF is a potential teratogen and therefore should not be used in pregnant women , it also decreases effectiveness of oral contraceptives (***Stuart, 2000***).

2- Corticosteroids

Mode of action

Corticosteroids have two main immunosuppressive effects on the immune system: the sequestration of CD4+ T-lymphocytes in the reticuloendothelial system (RES); and inhibition of both proliferation and function of lymphocytes via inhibition of lymphokines and cytokines. Upon administration, the hydrophilic corticosteroid molecule diffuses into the cytoplasm. In the cytoplasm corticosteroids displace heatshock proteins (HSPs) and forming a complex with heat shock protein–receptor. Corticosteroids bind the HSP receptor then, in the nucleus, bind to DNA sites called corticosteroid response elements (GREs). The result is an inhibition in transcription of lymphokine and cytokine genes, especially IL-1 and IL-6 (***Goldfien, 1998***).