Cardiac inotropes in management of decompensated heart failure : current agents and future directions

Essay

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List of abbreviations

TN: Troponin

THs: Thyroid hormones

SR: Sarcoplasmic reticulum

ATPase: Adenosine triphosphatase

ATP: Adenosine triphosphate

ADP: Adenosine diphosphate

cAMP: Cyclic adenosine monophosphate

LV: Left ventricle

PGE2: Prostaglandin E2

PGEI2: Prostaglandin EI2

ACE: Angiotensin converting enzymes

TNF: Tumour necrosis factor

CHF: Congestive heart failure

LVEDP: Left ventricular end-diastolic pressure

LVP: Left ventricular pressure

EDV: End diastolic volume

ESV: End systolic volume

EF: Ejection fraction

Vmax: Maximum velocity

HF: Heart failure

PDE: Phosphodieesterase

ACCF: American College of Cardiology Federation

ESC: European Society of Cardiology

AHFS: Acute haeert failure syndromes

NYHA: New York Heart Association

SVR: Systemic vascular resistance

PDI: Phosphodiesterase inhibitors

D1, D2: Dopaminrergic receptors 1, 2

Gs-GTP: Gamma-s guanosine triphosphate

DAG: 1,2- Diacyl glycerol

PiP2: Phosphatidyl-inositol-4,5-biphosphate

CO: cardiac output

MAP: Mean arterial pressure

GPCR: G protein- coupled receptors

AC: Adenyl cyclase

CAD: Coronary artery disease

DOB: Dobutamine

COMT: Catechol-Omethyl transferase

AMI: Acute myocardial infarction

ISO: Isoproterenol

cGMP: 3,5 cyclic Guanosine monophosphate

PKA: Protein kinase A

CICR: Calcium induced calcium release

PVR: Peripheral vascular resistance

IV: Intravenous

SA: Sinoatrial node

AV: Atrioventricular

RMP: Resting membrane potential

ERP: Effective refractory period

AF: Atrial fibrillstion

VF: Ventricular fibrillation

VT: Ventricular tachycardia

KATP: ATP dependant K

TnC: N-terminal domain of troponin C

LTCC: L- type Ca 2+ channels

RYR: Ryanodine receptors

NCX: Na-Ca exchanger

SERCA: Sarcoplasmic reticulum calcium ATPase

PLB: Unphosphorylated phospholamban

FFA: Free fatty acids

AMPK: AMP activated protein kinase

CPI-I: Carnitine palmitoyl transferase I

NAD: Nictinamide adenine dinucleotide

PDH: Pyruvate dehydrogenase

3-KAT: 3-ketoacyl-coenzyme amiolase

GLUT: Glucose transporter

GLP: Glucagon like peptide

DPP: Dipeptidyl peptidase

LVF: Left ventricular failure

NO: Niric oxide

HNO: Nitroxyl

sGC: Soluble guanylate cyclase

PLC: Phospholipase C

PKC: Phosphokinase C

RAS: Renin-angiotrnsin system

NRG1: Neuregulin protein

EGF: Epidermal growth factor

RTKs: Receptor tyrosine kinases

ErbB2: Avian erythroblastosis oncogene B

TnI: Troponin I

PAOP: pulmonary artery occlusion pressure

PND: Paroxysmal nocturnal dyspnea.

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Introduction

Heart failure is a clinical syndrome that can result from any disorder that impairs the ability of the ventricle to fill with or eject blood, thus rendering the heart unable to pump blood at a rate sufficient to meet the metabolic demands of the body. **(Hunt *et al*, 2001)**

Decompensated heart failure encompasses a group of related clinical syndromes broadly defined as ***new*** or ***worsening*** symptoms or signs of heart failure leading to hospitalization **(Felker *et al*, 2003).** The severity of decompensated heart failure may range from mild volume overload in the setting of nonadherence to diet or pharmacotherapy to life-threatening cardiogenic shock and multiorgan failure **(Petersen and Michael, 2008).**

Impaired cardiac contractility plays a central role in heart failure ,activating a series of maladaptive hemodynamic,structural and neurohormonal responses which contribute to heart failure progression. **(Tamagro *et al*, 2011).** Inotrope administration can greatly help to stabilise the patient and provides considerable symptomatic and haemodynamic benefit in the short term. **(Greenberg *et al*, 2003).**

Treatment with conventional inotropes improves symptoms and haemodynamics as it increases stoke volume and left ventricular ejection fraction and reduces left ventricular filling pressures of decompensated heart failure patients ,However their benefits can be counteracted by serious adverse effects including neurohumoral activation, maladaptative remodeling ,intracellular

calcium overload and hypotension which decreases coronary perfusion. **(Tamargo *et al* 2010).**

These findings may be related to the fact that these agents increase myocardial concentrations of cAMP, producing an increase in intracellular calcium that possibly leads to myocardial cell death and/or increases lethal arrhythmias **(Felker *et al*, 2003).** Hence, ***"classic"*** inotropic therapy in decompensated HF is under reconsideration and ***"novel inotropic agents"*** are under clinical evaluation to avoid classic inotropes side effects **(Athanasios, 2003).**

Chapter I

Pathophysiology of heart failure

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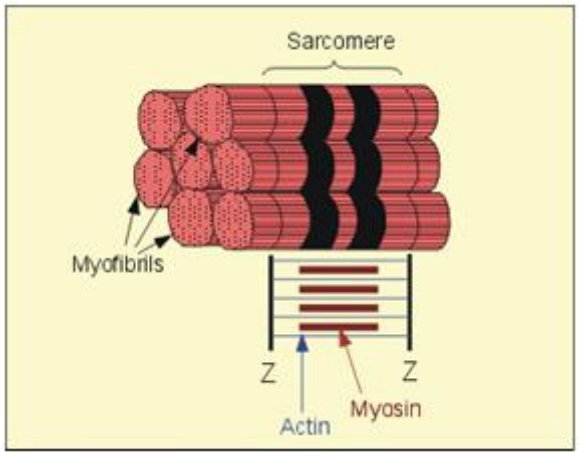
I] Physiological Anatomy



The cardiac myocyte is a specialized muscle cell that is approximately 25 μ in diameter and about 100 μ in length. The myocyte consists of bundles of *myofibrils* that contain *myofilaments*. **(Bazan *et al*, 2009).**

Figure 1. Cardiac myocyte consists of myofibrils, each of which contains myofilaments. The sarcomere lies between two Z-lines. (Klabunde, 2011)

a) Myofibrils.

The **myofibrils** have distinct, repeating microanatomical units, termed **sarcomeres**, which represent the basic contractile units of the myocyte (Figure 1). The sarcomere is composed of thick and thin filaments termed myosin and actin respectively. Chemical and physical interactions between the actin and myosin cause the sarcomere length to shorten, and therefore the myocyte to contract during the process of "*excitation-contraction coupling*" **(Cannell and Soeller, 1998).** The interactions between **actin and myosin** serve as the basis for the sliding filament **theory** of muscle contraction (Figure 2) **(Clark, 2008)**.

Figure 2 showing interaction between actin and myosin **(Klabunde , 2011)**

b) Actin and myosin.

The sarcomere's ***thick filament*** contains 300 myosin molecules which contains adenosine triphosphatase(ATPase) that hydrolyzes adenosine triphosphate (ATP) required for actin and myosin cross bridge formation (Figure 3) **(Katz, 1999)**.***The thin filaments*** are composed of three different types of protein: "actin, tropomyosin, and troponin" . Together, these are termed the regulatory protein complex. **(Bers, 2002)**.

c) Tropomyosin and troponins

Interdigitated between the actin strands are rod-shaped proteins termed **tropomyosin**. There are 6-7 actin molecules per tropomyosin. Attached to the tropomyosin at regular intervals is the troponin complex; which is made up of three subunits: **troponin-T** (TN-T), **troponin-C** (TN-C) and **troponin-I** (TN-I) (Figure 3) **(Stefancsik *et al*, 1998).**

TN-T attaches to the tropomyosin while **TN-C** serves as a binding site for calcium (Ca^{++}) during excitation-contraction coupling (four Ca^{++} can bind per TN-C). **TN-I** inhibits the myosin binding site on the actin **(Sheldahl *et al*, 2003)**.

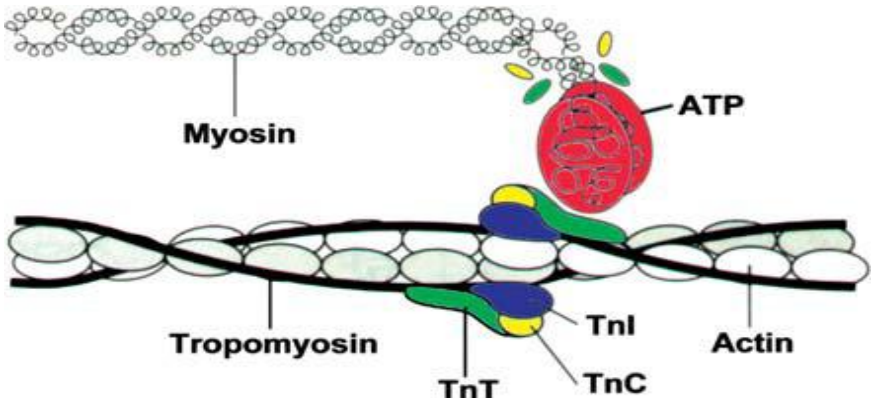


Figure. 3 Troponin complex and acto-myosin interaction. The myosin head combines with actin to produce force. Calcium binding to troponin C **(TnC)** results in a conformational change of tropomyosin, troponin I (TnI), and troponin T (TnT), allowing the myosin head to attach to actin, facilitating the acto-myosin cross-bridge to cycle **(Hasenfuss and Teerlink, 2011).**

d) Cross bridging and acto-myosin interaction

Calcium is very important in acto-myosin interaction. When Ca^{++} binds to TN-C, there is a conformational change in the troponin complex such that TN-I moves away from the myosin binding site on the actin, thereby making it assessable to the myosin head leading to **contraction** (Figure 3). When **Ca^{++}** is removed from the TN-C by pumping into the sracoplasmic reticulum, the troponin complex resumes its inactivated position, thereby inhibiting myosin-actin binding leading to **relaxation**. ***TN-I*** is important in clinical practice because it is used as a diagnostic marker for myocardial infarction (it is released into the circulation when myocytes die) (**Barry and Bridge, 2000**).

N.B The ***strength*** of the myocardial contraction appears to be mediated primarily by the degree of uncovering of the actin active sites as tropomyosin is pulled away after Ca^{++} has bound to troponin. The magnitude of this effect is dependent upon the affinity of troponin for Ca^{++} and the availability of Ca^{++} ions (i.e the magnitude of the Ca^{++} influx and accumulation during systole) **(Solaro and Van Eyk, 1996)**.