Scisense PV Technical Note

Understanding Contractility: Cardiac Inotropy

Cardiac contractility is the intrinsic ability of heart muscle to generate force and to shorten, ideally autonomously of changes in heart rate (HR), preload or afterload. In that respect, cardiac chamber pressure-volume measurement is the most reliable index for assessing myocardial contractility in the intact circulation, being almost insensible to changes in preload and afterload.

Contractility regulated by many mechanisms:

- Parasympathetic and sympathetic nervous system through catecholamines (circulating, delivered) control contractile force and ensure the coupling between heart performance and peripheral circulation. Catecholamines increase contractile force by the β adrenoceptor-adenylyl cyclase system or by stimulation of α-receptors. Through protein phosphorylation of L-type calcium channels, increase of calcium influx and activation of ryanodine receptors (RyRs) occur to further increase the sarcoplasmatic reticulum calcium release. At the same time, other processes speed up calcium accumulation in sarcoplasmatic reticulum to allow faster cardiomyocyte relaxation. Parasympathetic action (vagus nerve) has beneficial effect on cardiac contractility by improving hemodynamics including decreasing HR and pressure. Vagus nerve stimulation also effectively suppresses arrhythmias, including premature ventricular contractions (2).
- Stroke volume is critically dependent on the inotropy. When sarcomere length increases or during preload augmentation, contractile force and stroke volume increases correspondingly based on the Frank-Starling mechanism.
- Myocardial force development is HR dependent (Bowditch effect). In healthy myocardium the effect is expressed as an increase of heart rate HR by cardiac pacing that is able to a produce progressive increase in the force of contraction for a few beats (isometric force development) and then remains at a higher plateau (Positive Staircase effect). Functionally, with increasing HR, more calcium enters the cardiomyocyte and is accumulated into sarcoplasmatic reticulum while becomes accessible for release in next contraction, resulting in increased contractile force. The inverse effect occurs when HR is decreased (Negative Staircase).
- Increase in afterload causes an increase in ventricular contractility (inotropy) due to the activation of catecholamines. This effect allows myocardium to compensate for an increased end-systolic volume and decreased stroke volume that occurs when aortic blood pressure increases. It is called the Anrep effect. Without this effect in place, an increase in aortic blood pressure would create a drop in stroke volume that would compromise circulation to peripheral and visceral tissues.

CONTRACTILITY AND HEART FAILURE

MYOCARDIUM	RT (mN/mm²)	PDF (mN/mm²)	WORK (%)
Non-failing	11.2±1.3	14.5±4.4	136±11
Failing	16.3±1.5	12.7±4.5	74±7

Resting tension (RT) and work are significantly different.
Peak developed force (PDF) is not (1).

During heart failure, changes in the gene expression occur (from the adult to fetal pattern) leading to lowering of systolic calcium release and diastolic calcium reuptake. These molecular changes lead to physiological (heart function/hemodynamic) alterations that heavily influence inotropy. Studies in isolated myocardium have shown that increasing contraction rate does not increase contraction force or work in failing myocardium like it does in normal myocardium. However, the Frank-Starling mechanism is still intact in failing myocardium. This does not translate to increased work with increased sarcomere length due to the higher resting tension of failing cardiac muscle. Additionally, failing myocardium has reduced extent of shortening as compared to non-failing myocardium. When cardiac muscle length is increased close to its maximum (maximal stretch) in non-failing myocardium the maximal myocardial work increases with accompanied isometric force development as compared to failing myocardium where the myocardial work is decreasing when cardiac muscle is stretch to its maximum length (1).

transonic
THE MEASURE OF BETTER RESULTS.

Understanding Contractility: Cardiac Inotropy Cont.

Positive Inotropic Agents (Increase Contractility)

TYPE OF AGENT	MECHANISM/ EFFECTS	EXAMPLE AGENT(S)
Calcium	Increases available calcium for binding.	Calcium
Calcium Sensitizer	Increases myocyte calcium sensitivity and binding to cardiac troponin C in a calcium-dependent manner.	Levosimendan
Cardiac Myosin Activators	Targets and activates myocardial ATPase and improves energy utilization. This enhances effective myosin cross-bridge formation and duration.	Omecamtiv
Beta Agonists	Stimulates adenylyl cyclase activity and opening of calcium channels.	Dobutamine, Isoproterenol, Xamoterol
Intrinsic Catecholamines	Increases heart rate, blood pressure and glucose levels.	Dopamine, Epinephrine (adrenaline), Norepinephrine (noradrenaline)
Cardiac Glycosides	Competes with K^+ ions for the same binding site on the Na^+/K^+ ATP-ase pump in cardiomyocytes and decreases its function. This causes an increase in the level of Na^+ in cardiomyocytes, which leads to a rise in the level of intracellular Ca^{2+} because the Na^+/Ca^{2+} exchanger on the plasma membrane depends on a constant inward Na^+ gradient to pump out Ca^{2+}.	Digitalis, Digoxin, Ouabain
Phosphodiesterase-3 Inhibitors	Decreases afterload by vasodilatation	Milrinone, Amrinone, Enoximone, Papaverine
Insulin	Exerts Ca^{2+} dependent and independent positive inotropic effects through a phosphatidylinositol-3-kinase (PI3K) dependent pathway.	Insulin
Glucagon	Stimulates the cardiac Ca^{2+} current by activation of adenylyl cyclase and inhibition of phosphodiesterase.	Glucagon

Negative Inotropic Agents (Decrease Contractility)

TYPE OF AGENT	MECHANISM/ EFFECTS	EXAMPLE AGENT(S)
Beta Blockers	Block the action of endogenous catecholamines by interfering with the binding of adrenaline and noradrenaline to their receptors.	Acebutolol, Bisoprolol, Propranolol, Atenolol
Calcium Channel Blockers	Block voltage-gated calcium channels in cardiac muscle.	Verapamil, Diltiazem
Class IA Antiarrhythmic (fast channel blockers)	Block open Na^+ channels, prolonging cardiac action (affecting QRS complex). This results in slowed conduction and ultimately the decreased rate of rise of the action potential.	Quinidine, Procainamid
Class IB Antiarrhythmic	Na^+ channel blockers cause a reduction of the rate of rise of intracellular Na^+.	Lidocaine
Class IC Antiarrhythmic	Na^+ channel blockers	Flecainide, Propafenon
Class III Antiarrhythmic	Have β-like and K^+-like actions, increasing the refractory period via Na^+ and K^+ channel effects, and slowing intracardiac conduction of the cardiac action potential.	Amiodarone

Understanding Contractility: Cardiac Inotropy Cont.

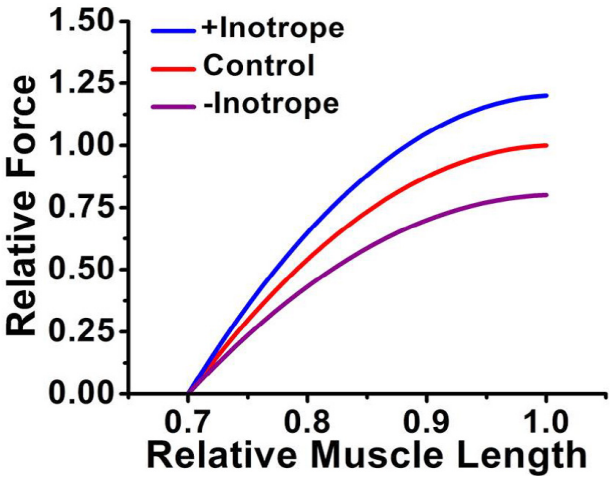
FACTORS AFFECTING THE LEVEL OF INOTROPIC (CONTRACTILE) STATE

Intrinsic

- Affinity of myocardium for calcium changes (insufficient blood flow, ischemia)
- Damage of heart muscle (alteration of numbers of contractile units)
- Calcium release and re-uptake
- Hormones (Glucagon, Insulin)
- Temperature

Extrinsic

- Pharmacological agents (β-agonist, β-blockers, isoflurane)
- Release of norepinephrine into myocardium when postganglionic sympathetic axis is activated
- Release of acetylcholine when parasympathetic axis is activated
- Increase of extracellular calcium concentration



An increase in inotropy is associated with an increase in the strength of contraction (force) for the same stretch or preload (muscle length). A decrease in inotropy decreases contraction strength. Changes in the inotropic state of the myocardium produce changes in performance (force development, extent of shortening) independent of preload and afterload.

REFERENCES

(1) Holubarsch C, Lüdemann J, Wiessner S, Ruf T, Schulte-Baukloh H, Schmidt-Schweda S, Pieske B, Posival H, Just H.Shortening versus isometric contractions in isolated human failing and non-failing left ventricular myocardium: dependency of external work and force on muscle length, heart rate and inotropic stimulation. Cardiovasc Res. 1998 Jan;37(1):46-57.

(2) Zheng C, Li M, Inagaki M, Kawada T, Sunagawa K, Sugimachi M. Vagal stimulation markedly suppresses arrhythmias in conscious rats with chronic heart failure after myocardial infarction. Conf Proc IEEE Eng Med Biol Soc. 2005;7:7072–7075.

transonic
THE MEASURE OF BETTER RESULTS.
www.transonic.com

Transonic Systems Inc. is a global manufacturer of innovative biomedical measurement equipment. Founded in 1983, Transonic sells "gold standard" transit-time ultrasound flowmeters and monitors for surgical, hemodialysis, pediatric critical care, perfusion, interventional radiology and research applications. In addition, Transonic provides pressure and pressure volume systems, laser Doppler flowmeters and telemetry systems.

AMERICAS
Transonic Systems Inc.
34 Dutch Mill Rd
Ithaca, NY 14850
U.S.A.
Tel: +1 607-257-5300
Fax: +1 607-257-7256
support@transonic.com

EUROPE
Transonic Europe B.V.
Business Park Stein 205
6181 MB Elsloo
The Netherlands
Tel: +31 43-407-7200
Fax: +31 43-407-7201
europe@transonic.com

ASIA/PACIFIC
Transonic Asia Inc.
6F-3 No 5 Hangsiang Rd
Dayuan, Taoyuan County
33747 Taiwan, R.O.C.
Tel: +886 3399-5806
Fax: +886 3399-5805
support@transonicasia.com

JAPAN
Transonic Japan Inc.
KS Bldg 201, 735-4 Kita-Akitsu
Tokorozawa Saitama
359-0038 Japan
Tel: +81 04-2946-8541
Fax: +81 04-2946-8542
info@transonic.jp