CONGESTIVE HEART FAILURE

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February 21, 2024

DEFINITIONS

- Heart failure is a complex syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood[1].
- Asymptomatic stages of structural heart disease or cardiomyopathy are considered “at risk” for heart failure[1].
- Heart failure and cardiomyopathy are two distinct diagnoses (and diagnosis codes).

CLASSIFICATIONS

- HFpEF: EF > 49%
- HFmrEF: EF 41-49%
- HFrEF: EF < 41%

- HFrEF has declining incidence, but HFpEF has increasing incidence recently[1].

- Morbidity / mortality is similar, no matter the classification

HISTORY

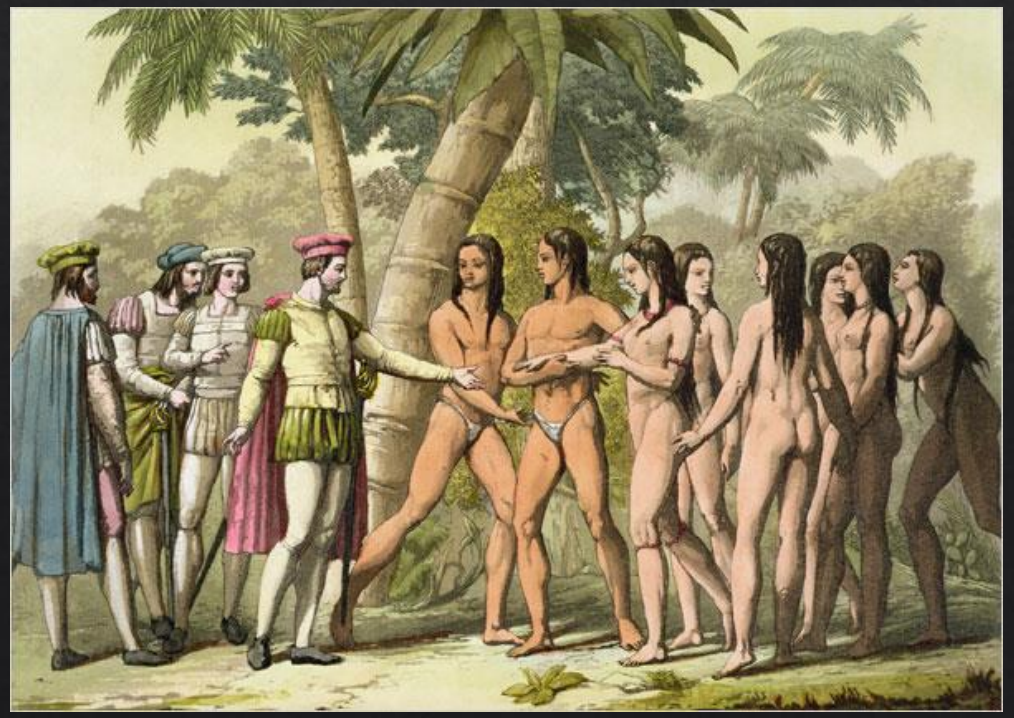
- Edema ("dropsy") and dyspnea have been described in ancient texts from Greece, Egypt, India, and Rome[2].

- In ancient Greece, rales was described as the sound of boiling vinegar when the ear is held to the chest of a patient.

- Treatment for edema was leeches or bloodletting by venesection[2].

SYPHLLIS

- Thought to be brought back from the New World (by Columbus?). It was first described in Europe in 1493, India in 1498, and Asia and Africa in 1520.
- It was thought that mercury compounds was an effective treatment for syphilis. Mercury also blocks sodium reabsorption in the ascending loop of Henle, causing diuresis[3].
- Mercury compounds were used to treat edema from the 1500's until around 1940[4].

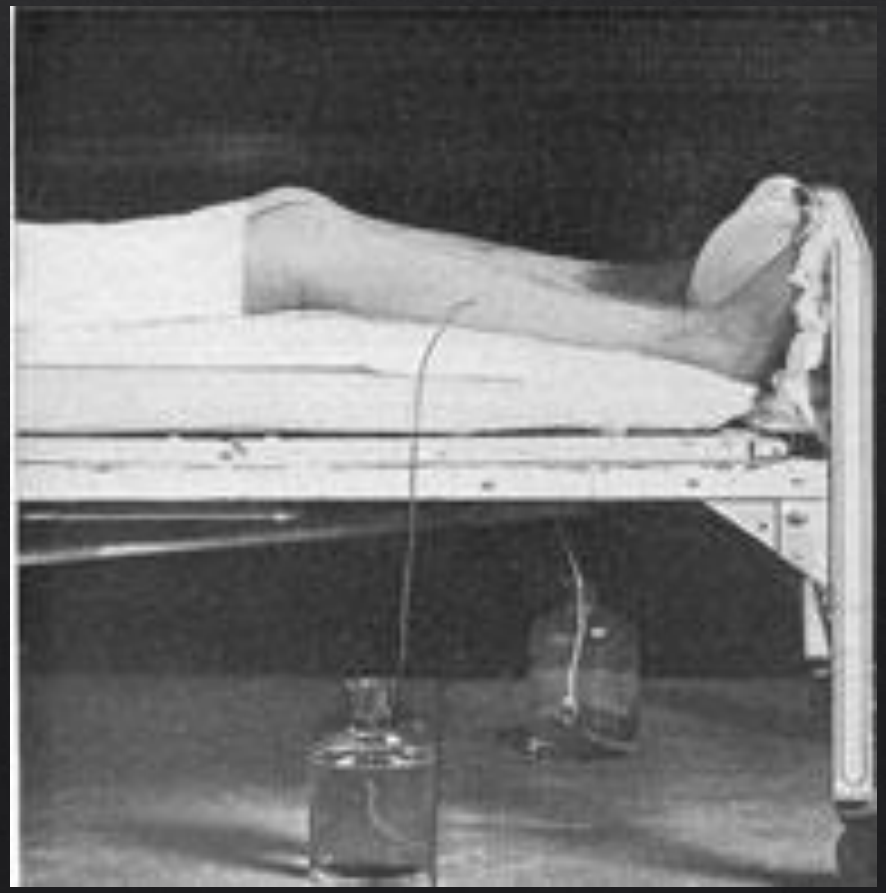


DIGITALIS

- William Withering described the benefits of digitalis in 1785.
- Used for “dropsy” as well as epilepsy.
- Theorized that Van Gogh’s “yellow period” was due to xanthopsia from digitalis toxicity.

SOUTHEY TUBES

- Developed by Dr. Reginald Southey in 1877.
- A perforated 14 gauge needle is inserted into the legs (or any edematous area) and fluid is drained.
- Used from 1877 until the 1960's.



LOOP DIURETICS

- Furosemide was released in 1964[4].
- Act on the ascending loop of Henle to block sodium reabsorption. Magnesium and potassium are also excreted.
- After loop diuretic serum levels decline, the kidney increases reaborption of sodium to re-establish the ion gradient in the loop of Henle. Thus, after a daily dose of lasix, overall serum sodium levels are unchanged in a 24 hr period.
- 1B recommendation to relieve congestion.
- The morbidity and mortality benefits of loop diuretics are uncertain[1].
- Loop diuretics are also used to diurese race horses, and are a banned substance under the World Anti-Doping Agency.

MRA

- Spironolactone was released in 1961[4].
- Competitive binder of the aldosterone dependent sodium-potassium exchange pump in the distal tubule.
- Spironolactone also blocks testosterone, can lead to gynecomastia in men. Eplerenone is much more selective, and rarely causes gynecomastia.
- 1A recommendation in HFpEF, 2B in HFrEF for patients who have GFR > 30 and serum K < 5.0. Should be discontinued if serum K is > 5.5[1].

BETA BLOCKERS

- Developed by Sir James Black in the 1960's after his father died from myocardial infarction while he was in medical school. The goal was to stop the effect of adrenaline on the heart in order to relieve chest pain. Propranolol was introduced in 1964.
- Block the beta adrenoreceptors.
- Noted that they also decrease blood pressure and have anti-arrhythmic properties, in addition to anti-anginal effects.
- Beta blockers are negative inotropes, and were contraindicated initially in heart failure.
- Initial trials that indicated benefit in heart failure with beta blockers was met with skepticism[5].
- 1A recommendation for HFrEF, with morbidity / mortality benefit. No recommendation for HFpEF[1].
- Banned by the International Olympic Committee and the World Anti-Doping Agency. For most sports, they are banned only for competition but for shooting and archery they are banned even outside of competition.

ACE / ARB

- Developed from research describing properties of snake venom extract in Brazil in the 1960's[6].
- Work by blocking the conversion of angiotensin I to angiotensin II (ACE) or blocking the angiotensin II receptor (ARB) – which results in vasodilation and naturesis.
- Thought that cough in ACE in inhibitors is due increase in bradykinin levels. ARB's do not increase bradykinin. Also thought that angioedema in ACE inhibitors is mediated though bradykinin, and ARB's can (in theory) be used.
- Captopril was released in 1981, and losartan was released in 1995.
- 1A recommendation for HFrEF, and 2B for HFpEF[1].

NITRATES / HYDRALAZINE

- For HFrEF patients with Class II-III symptoms despite optimal therapy, or for those who are intolerant of ACE/ARB.
- 2B recommendation for HFrEF, though still 1A for self identified African Americans. Not indicated in HFpEF.
- BiDil approved in 2005 – fixed dose hydralazine/nitrate for self identified African Americans. However, due to poor sales, the company that produced it went bankrupt. The drug is still available, however.
- Remains controversial, as studies did not assess for ancestry. Of note, the US Census noted in the 1970's that about 1/3 of Americans changed their racial identity in follow up interviews.

ARNI

- In 1987, atrial natriutic peptide (ANP) was discovered. With atrial distention, ANP is released, which causes vasodilation and diuresis.
- In 1988, B-type (or brain) natriutic peptide (BNP) was discovered. It is released by myocytes in the ventricles in response to increased blood volume. BNP causes vasodilation and increases diuresis. It also inhibits cardiac fibrosis and hypertrophy.
- Natrecor (recombinant human BNP) was released in 2001, and subsequently purchased by J&J for $2.4 billion. In 2005, a series of articles indicated increased renal failure and death with use of Natrecor. Further trials showed no benefit to Natrecor, and it was withdrawn from the market in 2018.

- Neprilysin was also discovered in the 1980's, and is widely distributed in mammalian tissues. Among other effects, it cleaves natriutic peptides. However, it also breaks down angiotensin II – resulting in increased blood pressure with neprilysin inhibition.

ENTRESTO

- To solve the blood pressure issue, sacubitril was combined with valsartan (both are manufactured by Novartis). Entresto was approved in 2015.
- 1A recommendation in HFrEF, and 2B recommendation in HFpEF
- Morbidity and mortality benefit as compared to ACE/ARB, as well as decreased risk of hospitalization.
- Increased risk of angioedema with use of neprilysin inhibitor and ACE inhibitor. Recommendation is to wait 36 hours after stopping ACE inhibitor before starting Entresto[1].
- Cost (without insurance) is $650-850 / month.
- Entresto was selected as one of the first medications for the Medicare Drug Price Negotiation program, but any negotiated price will not become effective until 2026.

SGLT2

- Phloridzin was discovered by French scientists in 1835 in the root bark of apple trees. It looked and tasted similar to extracts of willow trees (salycilic acid), and it was though to also have antipyretic and potentially antimalarial properties.
- In 1886, it was found to cause glucosuria in humans[7].
- It is a non selective inhibitor of SGLT. Phloridzin causes diarrhea and dehydration, as SGLT 1 receptors are located in the small intestine.
- Familial Renal Glucosuria is a benign condition where patients have normal serum glucose despite glucosuria. It is found to be from a mutation in the SGLT2 gene.
- SGLT2 is expressed primarily in the renal proximal tubule, where it is responsible for glucose reabsorption in the kidney. Inhibiting SGLT2 promotes glucose excretion into the urine, and also inhibits sodium reabsorption in the renal tubules.
- SGLT2 inhibition improves islet beta cell function and reduces insulin levels in the body. SGLT2 is also on islet alpha cells, and inhibition results in glucagon secretion and hepatic gluconeogenesis – which limits the decrease in serum glucose levels[8].

SGLT2 INHIBITION

- Diuretic effects were observed, which was consistent regardless of diabetes.
- Also inhibits myocardial Na/H exchange, which improves myocardial metabolism, oxygen supply, ATP, and inhibits myocardial fibrosis.
- Reduces preload and afterload, and improves free water clearance – which can improve diuresis with less effect on blood pressure and organ perfusion[8].
- Invokana was approved in 2013, and Farxiga and Jardiance were approved in 2014.
- 1A recommendation in HFrEF, and 2A in HFpEF.
- Cost is $500-700 per month. Jardiance and Farxiga are also in the Medicare Drug Price Negitiation Program.

OTHERS

- Verquvo (vericuguat) is a guanylate cyclase stimulator, increasing cGMP and resulting in vasodilation, as well as possibly reducing fibrotis and promoting reverse remodeling. Released in 2021. 2B indication for HFrEF. $650-800 / month.

- Corlanor (ivrbradine) is a I(f) channel inhibitor to slow heart rate in patient with sinus rhythm > 70 bpm on maximal tolerated beta blocker. Released in 2015. 2A recommendation. $550-700 / month.

RESTRICTIONS

- American and European guidelines recommend limiting salt intake, but do not recommend a specific level. Data is unclear on the benefit.

- AHA/ACC guidelines recommend limiting fluid to no more than 2L / day, though this is expert opinion.

THE ENERGY STARVED HEART

- The “energy starved heart” hypothesis was posited by Herrmann and Decherd in 1939, and decreases in ATP and creatine (as well as increases in ADP) has been seen in both hypertrophic and dilated cardiomyopathies.
- Every day, the heart pumps about 10 tons of blood; and uses about 6kg of ATP. Fuel for producing ATP is primarily provided by free fatty acids, with additional contribution by glucose.
- Use of ATP by the myofibrils is done via the creatine kinase energy shuttle. Creatine (produced by the liver) is taken up into the myocardial mitochondria, and are phosphorlated with mitochondrial ATP to form phosphocreatine and ADP.
- Phosphocreatine is a smaller molecule than ATP, and diffuses rapidly from the mitochondria to the myofibrils, where the phosphate is enzymatically cleaved and reattached to ADP in the myofibril to again produce ATP – allowing myocardial work to proceed.

- In the failing heart, there are derangements in ATP production as well as the CK transport system.
- Overall ATP levels are held fairly constant until severe heart failure. However, creatine and phosphocreatine levels decline precipitously even in early heart failure, up to 70%.
- Myofibrillar CK levels can decline by 50%, and energy delivery to myofibrils can decline by up to 70%.
- At rest, ATP levels are typically well above that which is needed. However, loss of CK activity leads to loss of inotropic reserve – and thus you get symptoms.
- Remember that myocardial oxygen consumption is related to wall tension, which itself is proportional to intraventricular pressure and inversely related to ventricular radius.
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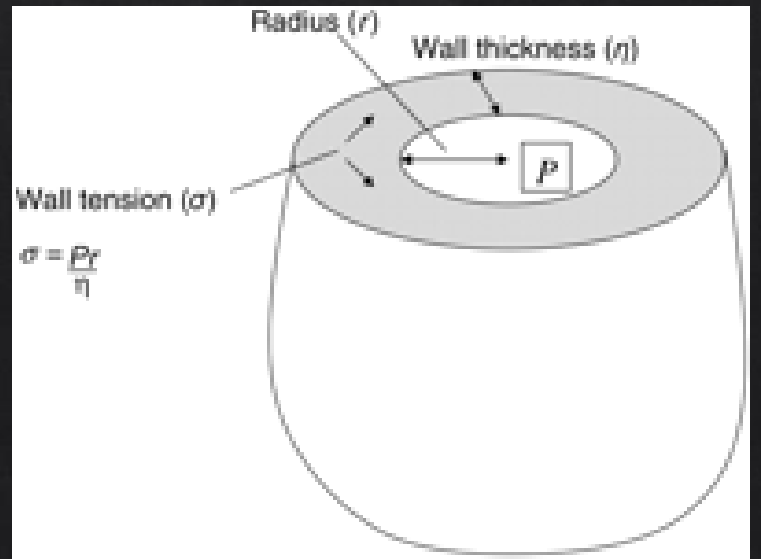
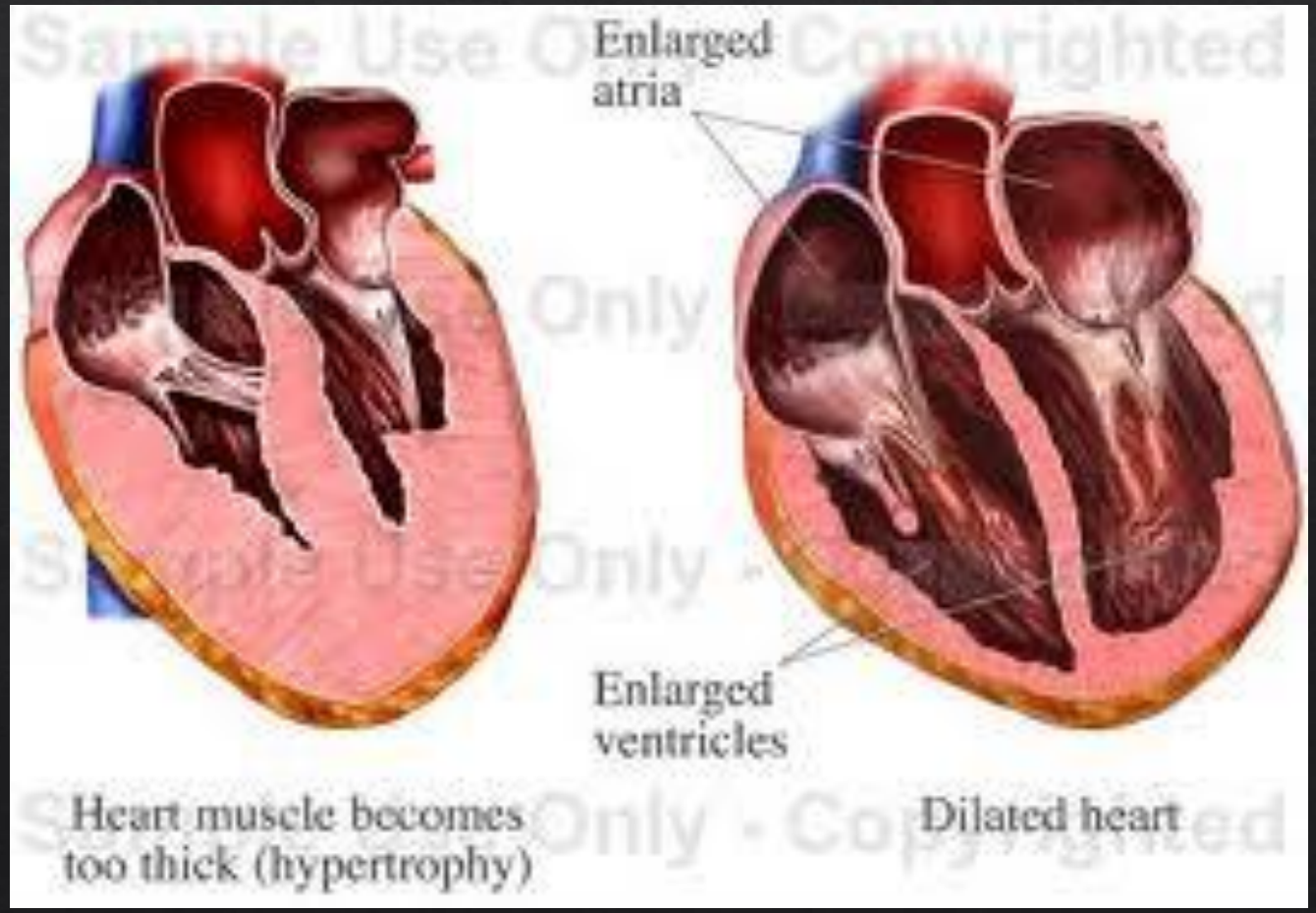
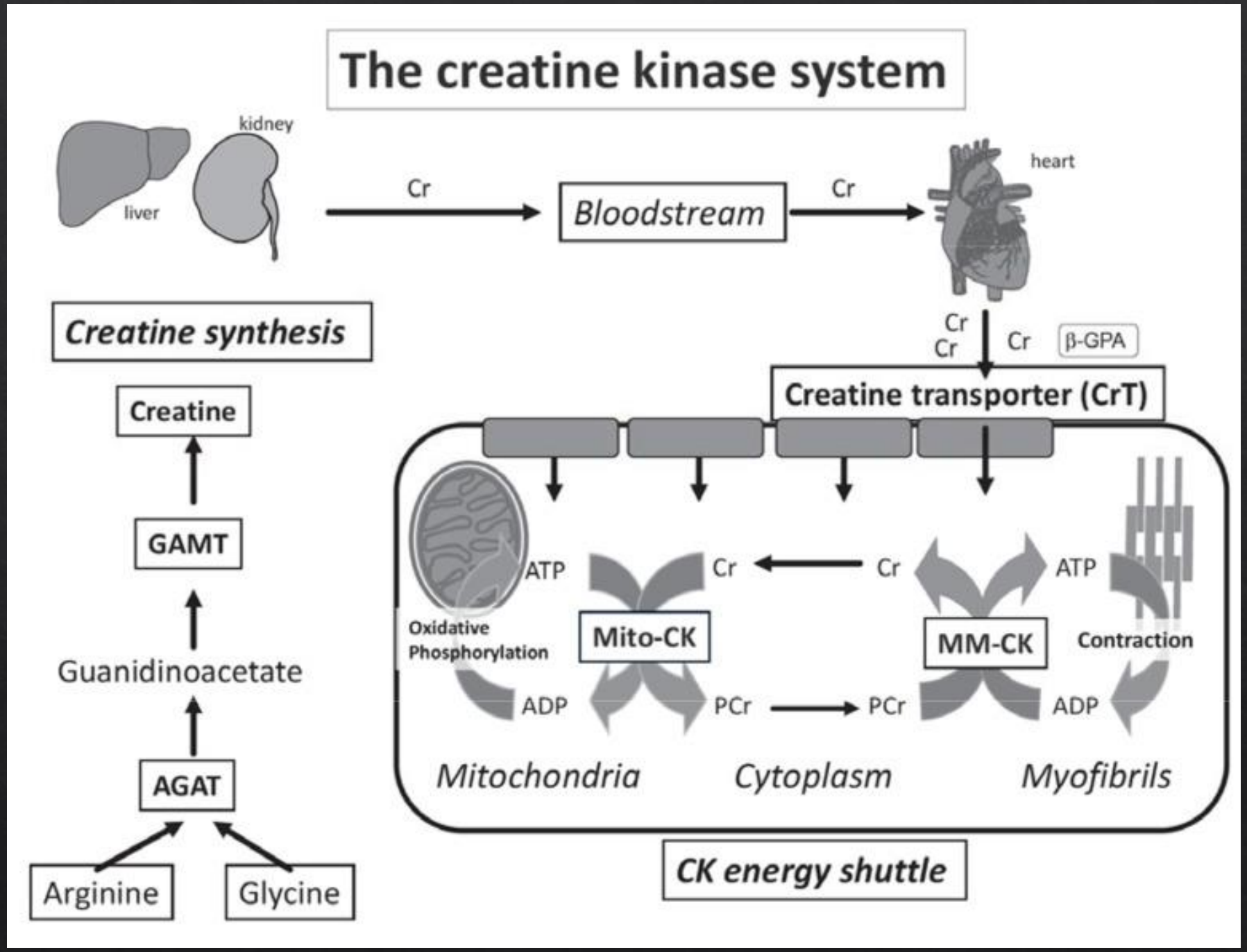


- The heart wants to maintain a as low an oxygen consumption as possible - and will respond to increasing wall tension by either hypertrophing or dilating.
- Therapies to increase ATP / CK transport have been attempted for decades, and have been unsuccessful. All therapies we have for heart failure involve decreasing myocardial work.




The creatine kinase system
kidney
liver
Cr
Bloodstream
Cr
heart
Creatine synthesis
Cr
Cr
Cr
β-GPA
Creatine transporter (CrT)
Creatine
GAMT
Guanidinoacetate
AGAT
Arginine
Glycine
ATP
Cr
Cr
ATP
Oxidative Phosphorylation
Mito-CK
MM-CK
Contraction
ADP
PCr
PCr
ADP
Mitochondria
Cytoplasm
Myofibrils
CK energy shuttle

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