Congestive Heart Failure

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PROLOGUE

The following paper presents the pathophysiology lecture content for congestive heart failure at the Massachusetts College of Pharmacy & Health Sciences. At the College, pathophysiology is a three credit course required for students in the PharmD, PA and BS in Pharmaceutical Sciences programs. The goal of this course is to give students a detailed understanding of the mechanisms involved in disease processes that affect the various organ systems. Knowledge of the pathophysiologic basis of disease is essential for success in the pharmacology and therapeutic courses the students face in the coming semesters, as well as for the clinical knowledge base that will be developed in future practice. Congestive heart failure (CHF) is a challenging but interesting topic to teach. It is a topic in which a detailed understanding of cardiovascular physiology is essential for grasping the effects of CHF on the body as well as the accompanying symptoms and therapeutic interventions that are employed. Students in pathophysiology are concurrently taking a two-semester course in human physiology and the topics between these two courses are closely integrated so that a detailed study of cardiovascular physiology occurs just before the presentation of CHF in pathophysiology.

Lecture material for CHF begins with a comparison between high output and low output types of failure with possible causes of each. A brief review of pulmonary and systemic circulatory pathways is then given to ensure that students are clear on the relationship of these two pathways to the left and right side of the heart. Students seem better able to grasp the consequences of CHF if the heart is split into the right and left side and then discussed independently of one another at first. A detailed discussion of the manifestations of left and right-sided heart failure then ensues with emphasis on the pathophysiologic basis for the various manifestations that are observed with left and right heart failure. Numerous diagrams are incorporated into the lecture to reinforce and clarify important concepts. The material continues with a discussion of the physiologic compensatory mechanisms that are active in a patient with CHF. It is stressed that early in the disease process, these compensatory mechanisms are useful in maintaining normal cardiac output function but that after a period of time, these renal and cardiovascular compensatory changes worsen heart failure and are often targets of therapeutic intervention. The clinical symptoms of CHF are presented along with various means of diagnosing the condition. After a detailed discussion of CHF from a pathophysiologic standpoint, students are asked to provide a rationale of how they might treat the symptoms of CHF based on their understanding of physiologic derangements that are present. The students are then given a brief overview of the various drug classes that are used in the treatment of CHF. The presentation of therapeutic agents is general and focuses mainly on the mechanism(s) by which a certain drug or class of drugs is useful in CHF. Detailed discussion of the individual agents will take place in subsequent Pharmacology courses. A case study is also given at the end of the lecture material as a means of bringing all the information together and giving it some tangible clinical significance.

REVIEW OF PULMONARY AND SYSTEMIC CIRCULATION

The left atrium receives oxygenated blood from the lungs via the pulmonary vein and transfers it through the mitral valve into the left ventricle. The left ventricle of the heart is the most heavily muscled chamber and is responsible for pumping oxygenated blood out into the aorta for delivery to the body. Deoxygenated blood returns from the body by the vena cava...
ETIOLOGY OF CHF
Heart failure is a condition in which the heart no longer functions effectively as a pump. Depending upon the cause, heart failure may be classified as low output failure or high output failure (1). Low output failure is said to occur when the pumping efficiency of the heart becomes reduced by factors that impair cardiac function. High output failure occurs when the cardiac output of the heart remains significantly elevated for a long period. With high output failure, the metabolic and oxygen demands of the heart exceed what can be supplied by the coronary circulation and the function of the myocardium eventually fails. Some common causes of heart failure are listed in Table I.

Table I. Common causes of heart failure

<table>
<thead>
<tr>
<th>Low Output Failure:</th>
</tr>
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<tbody>
<tr>
<td>Myocardial ischemia</td>
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<tr>
<td>Cardiac hypertrophy</td>
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<tr>
<td>Myocardial infarction</td>
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<tr>
<td>Cardiomyopathy</td>
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<tr>
<td>Heart valve defects</td>
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<tr>
<td>Congenital heart defects</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>High Output Failure:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypermetabolism, hyperthyroidism</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Excessive intravenous fluids</td>
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</table>

Table II. Definition of key terms

- **Stroke Volume** - the volume of blood pumped by one ventricle during one contraction
- **Preload** - the degree to which the myocardium is stretched by venous return. Determined by LVEDV
- **Left Ventricular End Diastolic Volume (LVEDV)** - the amount of blood that fills the left ventricle during relaxation
- **Ejection Fraction** - the fraction of the blood contained in the ventricle at the end of diastole that is expelled during its contraction, (the stroke volume divided by end-diastolic volume)
- **Afterload** - the pressure the heart must overcome to pump blood out into the aorta
- **Dyspnea** - difficulty breathing
- **Orthopnea** - worsening dyspnea in the supine position
- **Cyanosis** - bluish discoloration of the skin and mucous membranes that occurs as a result of a lack of oxygen in the blood (hypoxia)
- **Ascites** - accumulation of fluid in the peritoneal cavity

Left Side Heart Failure
The left heart pumps oxygenated blood out to the systemic circulation. Common causes of left heart failure include myocardial infarction, cardiomyopathy and aortic valve stenosis (at this point it may be helpful to the students to review how heart valve defects lead to heart failure). Failure of the left heart effects blood flow out of the body (forward failure) as well as blood return to the heart from the pulmonary circulation (backward failure) (Figure 2). The manifestations of left heart failure include:
a decreased stroke volume, increased left-ventricular end-
diastolic volume, increased preload (Table II);
• pulmonary congestion associated with increased
pulmonary pressure and pulmonary edema. The term
“congestive” heart failure comes from the accumulation
of blood and congestion that occurs in the pulmonary and
systemic circulation (Figure 3).
• dyspnea, cough, frothy sputum. Cracking sounds
(“rales”) that may be heard through the stethoscope as
result of fluid accumulation in the lungs. Orthopnea, fluid
accumulation that is often worse at night or when lying
down as a result of fluid redistribution from the lower
body.
• cyanosis as a result of poor systemic perfusion;
• generalized fatigue and weakness as a result of poor blood
flow.

Over time, the pulmonary congestion associated with left
sided heart failure will chronically increase workload on the
right heart and can eventually cause right heart failure.

**Right Side Heart Failure**

The right heart pumps deoxygenated blood out to the
lungs. Common causes of right heart failure include left heart
failure, stenosis of the pulmonary valve as well as pulmonary
diseases such as emphysema that increase the resistance to
blood flow from the right heart. The manifestations of right
heart failure include:

- increased right ventricular workload;
- venous congestion and distention;
- peripheral edema and ascites as a result of blood
  congestion in the venous return system (Figure 3, 4);
- swelling of the liver with possible liver injury (cardiac
  hepatitis) and failure;
- gastrointestinal symptoms of anorexia and nausea from
  poor G.I. blood flow.

**Systolic Failure versus Diastolic Failure**

A newer classification scheme for heart failure is based
not on left or right side failure but rather on whether the
failure occurs during systole or diastole. With systolic failure,
there is a decreased ejection of blood from the heart during
contraction; while with diastolic failure, filling of the
ventricles during relaxation is impaired. Recently, the
American Heart Association issued guidelines for treating
heart failure based upon whether patients are experiencing
systolic failure or diastolic failure(2).

Systolic failure is characterized by: (i) decreased
myocardial contractility; (ii) decreased ejection fraction (see
definition box); and (iii) Most commonly caused by conditions
that impair contractility such as ischemic heart disease, myocardial
infarction and cardiomyopathy. The symptoms are mainly
those of reduced cardiac output.

Diastolic failure is experienced by approximately 20-40
percent of heart failure patients. These patients may have
preserved left ventricular systolic function but reduced
ventricular filling that may be associated with impaired
ventricular relaxation. Diastolic failures is associated with
conditions such as restrictive and hypertrophic
cardiomyopathy. Its symptoms are primarily those of blood
congestion and may include marked dyspnea and fatigue.

**PHYSIOLOGIC COMPENSATION FOR CHF**

The overt signs and symptoms of heart failure (Table III) may
not appear in the early stages of the condition due to a number
of physiologic compensatory mechanisms that can activate to
maintain cardiac output. As a result of this lack of symptoms,
the early phase of CHF is referred to as compensated heart
failure. While these compensatory mechanisms are effective in
maintaining cardiac output in the short term, they will not be
able to maintain cardiac output for a long period of time and in
fact will increase workload on the failing heart and worsen the
progression of CHF. Decompensated heart failure is said to
occur when cardiac output is no longer adequately maintained
and overt symptoms appear. Physiologic compensations for
CHF include:
### Table III. Clinical diagnosis of heart failure

Dyspnea with exertion, orthopnea, nocturnal dyspnea.
Rales, cough, hemoptysis (bloody sputum).
Distention of jugular veins, liver enlargement, ascites.
Peripheral and pulmonary edema.
ECG, chest x-ray for cardiac hypertrophy.
Echocardiography to assess cardiac function and ejection fraction.
Cardiac catheterization to assess hemodynamic function.

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**Fig 5. The Frank-Starling Principle.**

1. Increased Cardiac Output

The normal heart will respond to increases in preload or left ventricular end diastolic volume by increasing stroke volume and cardiac output. The Frank-Starling principle dictates that the greater the heart is stretched by filling, the greater it’s responsive strength of contraction (Figure 5). With heart failure, there is chronic increases in preload that continually distend the cardiac muscle fibers and lead to myocardial hypertrophy(3). While the Frank-Starling mechanism is useful early in CHF, with time the cardiac muscle fibers will be stretched beyond their maximum limit for efficient contraction. At this point further increases in preload are not matched by further increases in cardiac output. In addition, the oxygen and nutrient demands of the enlarged myocardium will eventually exceed the supply available through the coronary blood flow and worsened failure will ensue.

2. Increased Sympathetic Activity

The decrease in cardiac output that occurs with heart failure is associated with a decrease in blood pressure that activates baroreceptors located in the aortic arch and carotid arteries. Activated baroreceptors send signals to the autonomic regulatory regions of the brain that in turn increase sympathetic input to the heart. This sympathetic activation can be direct via cardioaccelerator nerves or may take the form of increased circulating levels of catecholamines from the adrenal medulla. Both factors will exert positive inotropic (increased force of contraction) and positive chronotropic (increased rate of contraction) effects on the failing heart. In addition to the increased metabolic demand these factors will place upon the heart, the failing myocardium also becomes dependent upon increased circulating levels of catecholamines from the adrenal gland. Over a period of time, the failing myocardium becomes less responsive to the stimulatory effects of the catecholamines and cardiac function continues to deteriorate.

3. Activation of the Renin-Angiotensin System

The decrease in cardiac output that accompanies heart failure also leads to significant reductions in renal blood flow. The kidneys are extremely sensitive to changes in renal blood flow and respond to decreased perfusion by releasing the enzyme renin from specialized cells within the juxtaglomerular apparatus. In circulation, renin will initiate the formation of angiotensin II and the release of aldosterone from the adrenal gland (Figure 6). Angiotensin II is a powerful vasoconstrictor that increases blood pressure (and afterload on a failing heart!) while aldosterone acts on the renal tubules to enhance salt and water retention thus increasing preload as well.

Other hormones that are also activated with heart failure include antidiuretic hormone (ADH) from the pituitary gland and atrial natriuretic factor (ANF) produced by atria in response to increased chamber dilation(4). ADH release will worsen fluid accumulation in the body by preventing water loss from the kidney while ANF appears to act as an endogenous diuretic and may have a some beneficial role in enhancing the removal of fluids during CHF.

4. Ventricular Hypertrophy

As a long-term response to chronic increases in workload the heart responds by increasing muscle mass. In the short-term, increased muscle mass will provide an increased cardiac output, but over time, function of the hypertrophied myocardium will suffer as nutrient and oxygen demands exceed what can be supplied though the coronary circulation. At this point, the efficiency of contraction decreases and contractile failure ensues.
Table IV. Drugs for treatment of heart failure

**Vasodilators**
1. Organic nitrates (e.g., nitroglycerin) - dilate peripheral arteries and veins through relaxation of vascular smooth muscle. Reduce preload and afterload on the heart.
2. Arterial vasodilators (e.g., prazosin) - cause dilation of peripheral arteries by blockade of $a_1$-adrenoreceptors. Reduce afterload on the heart.

**Diuretics**
1. Thiazide diuretics (e.g., hydrochlorothiazide) - act on distal convoluted tubules of kidney to decrease active sodium reabsorption and increase fluid excretion. Moderate potency.
2. Loop diuretics (e.g., furosemide) - powerful diuretics that inhibit the transport of sodium out of the ascending loop of Henle leading to the loss of large volumes of sodium and fluids.

**ACE inhibitors**
- e.g., Captopril, Enalapril
- Block the formation of angiotensin II and aldosterone.
- Lead to a reduction in vascular resistance and reduced sodium/fluid retention.
- Shown to reduce mortality in CHF patients.

**Positive Inotropic Agents**
1. Cardiac Glycosides (digoxin, digitalis) - increase force of cardiac contraction by increasing levels of intracellular calcium in cardiac muscle cells.
2. Other cardiotonic agents (dobutamine) - $\beta_1$-adrenoreceptor agonist used for treatment of acute heart failure.
3. Phosphodiesterase inhibitors (amrinone, milrinone) - increases force of contraction through increased cAMP levels in cardiac cells.

**$\beta$-Adrenergic Receptor Antagonists**
Despite their potential for reducing cardiac output and force of contraction, numerous human clinical studies have reported an improvement in symptoms, reduced hospitalization and decreased mortality in heart failure patients receiving $\beta$-blocker therapy. The mechanism of their beneficial effect is unclear but may be related to a blunting of the positive inotropic and chronotropic effects of adrenergic input to the failing heart. There is additional evidence $\beta$-blockers might reduced the risk of arrhythmia in CHF patients while enhancing myocardial remodeling and improving cardiac energetics. The combined $\beta_1\alpha_1$ antagonist Carvediol has also been shown to be of significant benefit in treating patients with CHF.

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Table V. Common side effects of drugs used to treat heart failure

**Vasodilators**
- Postural hypotension (drop in blood pressure that occurs upon standing), headache, peripheral edema, reflex tachycardia possible

**Ace Inhibitors**
- Hypotension, dry cough, possible renal failure in patients with renal artery stenosis

**Diuretics**
1. Thiazides - glucose intolerance, hypokalemia
2. Loop diuretics - hypokalemia, metabolic alkalosis

**Cardiac Glycosides**
- Narrow margin of therapeutic safety
- Adverse effects include nausea, vomiting, and arrhythmia
- Marked effects on cardiac conduction that may be useful for treatment of rapid atrial arrhythmia’s
- Increased toxicity with reduced plasma K+
- Mainly renal elimination. May have increased half-life in elderly or patients with renal disease

**$\beta$-Blockers**
- $\beta$-blockers should be initiated at low doses in selected CHF patients since there is an initial risk of worsened cardiac function
- Not all $\beta$-blockers appear to exert the same beneficial effects in CHF and the specific drug to be used must be chosen with caution
- Generalized side effects of $\beta$-blocker use include bradycardia, decreased cardiac conduction, fatigue, sleep disturbances and altered blood glucose
- Non-specific $\beta$-blocker may cause bronchospasm and should not be used in patients with asthma

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HEART FAILURE

**Clinical Symptoms.** There are several characteristics symptoms of heart failure. These include: (i) Shortness of breath due to pulmonary congestion and edema; (ii) persistent cough or wheezing due to fluid accumulation in the lungs; (iii) fatigue and weakness from poor blood flow; (iv) swelling of the feet, ankles, legs and possibly the abdomen as a result of poor venous return and increased venous pressure that force fluids out of circulation and into the tissues; (iv) lack of appetite and nausea from poor blood flow to the G.I. tract; and (vi) increased heart rate (tachycardia) that occurs in response to reduced cardiac output.

**Diagnosis Of Heart Failure.** Heart failure is often diagnosed upon physical examination as a result of the overt symptoms outlined above. Signs of pulmonary congestion may also be heard though a stethoscope. Diagnostic tools such as an ECG will reveal the presence of cardiac hypertrophy or past myocardial infarction. Echocardiography can allow a physician to “visualize” function of the heart and can be used to calculate a patients ejection fraction. A simple x-ray can also be useful in determining the size and shape of the heart as well as the presence of any congestion that might be present in the lungs (Table III).
**Rationale For Treating Heart Failure.** The rationale for the treatment of heart failure may include: (i) restricting the patients physical activity to reduce cardiac workload; (ii) reduce preload on the heart by restricting salt and fluid intake, use of vasodilator drugs to produce venous dilatation, and the prudent use of diuretics to reduce fluid volume; (iii) reducing the afterload on the heart by the use of arterial vasodilators, or inhibition of angiotensin II and aldosterone effects by angiotensin converting enzyme (ACE) inhibitors; (iv) causing an increase contractility of the failing heart by the use of positive inotropic agents such as digitalis glycosides or inhibitors of heart-specific phosphodiesterases; and (v) blunting the effects of adrenergic input with β-adrenergic receptor antagonists (see Table IV).

With severe heart failure the last resort might be a heart transplant, although the current wait for transplant organs can be several years. Mechanical pumps called “left-ventricular assist devices” are currently available and can be used to take over a portion of the hearts pumping function as a temporary measure. However, these mechanical assist devices are not designed as a long-term solution to heart failure. Considerable advances have been recently made in the development and implementation of self-contained mechanical hearts that are designed to be long-term replacements for the failing heart.

While many of the drugs currently used to treat patients are very effective in improving cardiac function and overall quality of life in affected patients, effective use of these agents requires detailed understanding of their mechanisms of action and pharmacokinetics. Agents like the digitalis glycosides have very narrow margins of therapeutic safety and can be associated with severe side effects and toxicities. Some of the common adverse effects of the drugs used to treat congestive heart failure are listed in Table V.

**REVIEW EXERCISES**

Several techniques have proven useful in helping students review key concepts associated with heart failure as well as to test their comprehension of the subject matter. One technique used is to make up a number(10-12) of cardboard cutouts with one symptom of either left or right heart failure on each. As students walk into the room, they are randomly given one of the cards with a symptom on it (for example, “ascites,” “pulmonary edema,” etc). Lines are then drawn dividing the blackboard into three equal sections and titled “Left Heart Failure,” “Right Heart Failure” and “Both Left and Right Heart Failure.” Students who have the symptom cards to tape their symptom in the appropriate section. We then ask the class to vote whether each symptom is correct and have someone explain why it is or is not placed in the correct column. A “mind-mapping” exercise also works very well for heart failure where the class (as a small group exercise) essentially draws flow charts for left and right heart failure that begin with possible causes and progress through effects on various organs and eventually to the resulting symptoms and treatments. A simple case study is also useful for relating some of the pathophysiologic changes in CHF to their clinical manifestations. The third-year pathophysiology course is one of the first places in the pharmacy curriculum that students are exposed to the case study format. As a result, cases tend to be straight-forward, focusing mainly on the physiologic manifestations of the disease and not necessarily treatment since students have yet to have pharmacology or therapeutics courses (see sample Case Study). Feedback from students on the usefulness of case studies in pathophysiology has thus far been quite positive.

**References**