Refractory Heart Failure

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REFRACTORY HEART FAILURE

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Patients with congestive heart failure will show considerable variation in their individual response to the conventional therapeutic methods. Moreover, a specific patient will vary in individual responsiveness from time to time, and, under certain conditions, may cease to respond or actually to regress while still under intensive

ETIOLOGIC FACTORS IN RESISTANT HEART FAILURE

Cardiac
1. Advanced cardiac disease
2. Active rheumatic carditis
3. Arrhythmia
4. Silent or masked myocardial infarction
5. Myocardial aneurysm
6. Bacterial endocarditis
7. Constrictive pericarditis
8. Unsuspected valvular disease
   (a) Tricuspid stenosis and insufficiency
9. Obsolete cardiac disease
   (a) Myocarditis
   (b) Amyloidosis
   (c) Lupus erythematosus
   (d) Polyangitis
   (e) Fibroelastosis
   (f) Hemochromatosis
   (g) Tumors
   (h) Carcinoid syndrome
   (i) Scleroderma

Pulmonary
1. Multiple pulmonary emboli
2. Chronic pulmonary disease (cor pulmonale)
3. Pulmonary thrombosis
   (a) Mitral stenosis
   (b) Aortic valve stenosis
4. Pulmonary A-V fistula
5. Localized interlobar pleural effusion and regular effusions

Therapeutic
1. Inadequate digitalis
2. Digitalis intoxication
3. Excessive sodium intake
   (a) Diet
   (b) Drinking water
   (c) Private wells
4. Excessive diuretic therapy
   (a) Hypochloremic alkalosis
   (b) Hyperchloremic acidosis
5. Excessive loss of salt
   (a) Vomiting
   (b) Diarrhea
   (c) Low salt diet
   (d) Paracentesis
6. Excessive physical activity
7. Excessive mental stress and emotional activity
8. Blood dilution syndrome (water intoxication)

Figure 1

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Hypermetabolic
1. Hyperthyroidism
2. Anemia
3. Infection and febrile states
4. Liver dysfunction
   (a) Laennec's cirrhosis
   (b) Cardiac cirrhosis
5. Malnutrition
   (a) Beriberi
   (b) Hypoproteinemia
6. Arteriovenous communications
   (a) Systemic A-V fistula
   (b) Paget's disease
   (c) Chronic pulmonary disease

Endocrine
1. Hyperthyroidism
2. Hypothyroidism
3. Hypercorticalism
   (a) Exogenous
   (b) Cushing's syndrome
   (c) Aldosteronism
4. Pheochromocytoma
5. Posterior pituitary - A.D.H. and Aldosterone

Lowered Renal Blood Flow
1. Severe intrinsic renal disease
2. Lowered cardiac output
   output down 40%, R.B.F. down 70%
3. Renal vasoconstriction from anuria
4. Local mechanical
   pressure from large collection of ascites

therapy. In this latter state, the patient is often referred to as refractory or intractable. We prefer the former term because of its more optimistic connotation. I wish to discuss first some of the etiologic factors which are important in bringing about this state of relative refractiveness or resistance and then to take up some of the specific methods of management.

For the sake of convenience, I wish to group the important etiologic factors in six categories (Figure 1). It should be emphasized that the various entities mentioned may, in themselves, be a specific underlying etiology for the heart disease or may simply be a complicating or aggravating factor which is acting in conjunction with the basic etiology.

First among the cardiac factors, we have listed Progression of the Underlying Cardiac State. Since most heart disease leading to a state of congestive failure is progressive, it is logical to assume that this progression itself may eventually lead
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to a state of refractiveness. But we should not be too quick to adopt this convenient explanation for a patient whose condition is deteriorating until a careful search has been made for other factors which may possibly be reversible. A period of rheumatic activity is frequently responsible for refractiveness to treatment in a patient with rheumatic heart disease. In addition to the common laboratory aids to diagnosis and the EKG, the onset of auricular fibrillation, and the appearance of low-grade fever may be a tipoff that rheumatic activity is present. Arrhythmias and atypical myocardial infarcts will often cause exacerbations of failure and should constantly be kept in mind. Figure 2 shows the x-ray of a man who had gone into marked congestive failure several months after a rather severe myocardial infarct and whose condition was one of progressive deterioration despite the use of all available medical measures. A myocardial aneurysm was suspected clinically, and despite the fact the fluoroscopic examination was not entirely confirmatory, the patient was subjected to radical surgery for removal of the useless muscle despite

![Figure 2](image)

Distortion of the left lateral heart border is due to the presence of a large ventricular aneurysm.
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his critical state. At operation, a large part of the ventricular wall which included the aneurysm was resected with a resulting improvement in his state of compensation. Bacterial endocarditis should always be kept in mind in patients with valvular lesions whose failure is not responding to treatment, especially in those patients in the older age groups who have lesions of the aortic valve. Fever will often not be a prominent part of the picture, and the offending organism must be diligently sought for especially in those cases where prophylactic antibiotics are being given to prevent pulmonary infection as a result of stasis. In those patients in whom a right sided lesion is a possibility, cultures of pulmonary artery blood, taken by a catheter, should be considered. Constrictive pericarditis is sometimes difficult to diagnose, but the gratifying response which follows a successful surgical treatment in a patient not responding to digitalis and other medical measures makes it well worth the effort to keep this condition constantly in mind. It is not necessary that the patient have a small cardiac shadow on x-ray or that the pulsations necessarily be abolished over the entire heart border for this lesion to be present. Patients with previous cardiac hypertrophy and those with associated pericardial effusions may show considerable enlargement to x-ray and physical examination, and the offending constricting band may involve only a small segment of the heart surface. Among unsuspected valvular lesions, those of the tricuspid valve may be especially troublesome. They may account for the lack of an effective response in a patient who has undergone a successful mitral commissurotomy. For the sake of completeness, we have listed several obscure cardiac diseases which may lead to conditions of resistant failure. Some of these involve the heart primarily, such as fibroelastosis and primary amyloidosis. Others may affect the heart indirectly such as sickle cell disease while still

![Diagram](image_url)

**Figure 3.** Conditions associated with congestive heart-failure.

Figure 3

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others may do both such as Marfans which may not only produce valvular lesions but also contribute toward the intractability of failure by destroying the normal elasticity of the aorta.

Many hypermetabolic states are important aggravating factors leading toward resistant congestive heart failure. Latent hyperthyroidism should be suspected in any patient in whom fibrillation does not respond satisfactorily to Digitalis, who shows bouts of transient glycosuria, or in whom the complexion is pink in contrast to the usual sallow washed-out complexion of the cardiac in failure. Protein bound iodine determinations and uptake studies will help to confirm or deny such a clinical opinion. Anemia, regardless of the cause, will aggravate congestive failure if the hemoglobin value falls to a range of 60% or less. Infections and febrile states are extremely important both in precipitating bouts of congestive failure and in contributing to a state of refractiveness. In a recent series of 300 cases of congestive failure admitted to a British hospital, respiratory disease was present in 167 cases and was the precise cause of failure in 156 cases. It was especially important in older people. The role of the liver in congestive failure is a complex one. Figure 3 will illustrate some of the possible pathways by which it plays a part in contributing to a refractory state. Arterio-venous communications with their associated many-fold increase in circulating blood volume add an additional load to the heart which cannot be successfully combated by specific treatment directed toward cardiac function alone. Multiple pulmonary emboli are responsible for a resistant or refractory state in many cardiacs undergoing therapy for congestive failure and thrombosis of a major vessel is not an unusual terminal event in patients suffering from mitral stenosis or intracardiac shunts. Large localized fluid collections will seriously impair cardiac function in the failing patient and should be removed wherever possible.

ACETYL STROPHANTHIDIN TEST

1. Dilute 1.2 mgm. (2 amps.) of the material to 20 cc. in 5% glucose and H2O.
2. In the presence of an arrhythmia possibly due to digitalis give K first.
3. Run strip of EKG prior to each injection.
4. Give 5 cc. of the dilution every 5 min. until either evidence of therapeutic effect or mild toxic effects.
   (If intoxication suspected either
   a. Increase interval to 10 min. - or
   b. Reduce first two doses to .15 mgm. (2.5 cc.).

Interpretation

1. If toxicity after 1st injection presume overdosage.
2. If toxicity after .6 mgm. then digitalization adequate.
3. If therapeutic effect after .6, .9, or 1.2 mgm. then give proportional doses of longer acting preparations.
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It is somewhat ironic that many therapeutic measures may, in themselves, contribute to resistance in the patient with cardiac failure. Often it is very difficult to tell clinically whether a patient with nausea, vomiting and an arrhythmia may be suffering these manifestations on the basis of the congestive failure alone or whether he may be over digitalized. Figure 4 shows the details of the acetyl strophanthidin test which, while not without its dangers, may sometimes be justifiably employed to determine the status of digitalization. If over digitalization is suspected, potassium should be administered prior to the test and the dosage should be reduced as indicated. Excessive intake of sodium is not often overlooked in treating the patient with congestive failure, but I would like to call attention to the possible hazards existing to the patient who obtains his drinking water from a private well. Many of these are quite high in sodium content. Water softeners may also present a similar hazard and either of these two potential sources of sodium may explain the reason why a patient will do well while hospitalized and then rapidly slip back to failure when he returns to his home.

Certain metabolic factors should be mentioned briefly. Hyperthyroidism has been discussed previously and is included here only for completeness. It is doubtful whether hypothyroidism may, in itself, be actually the cause for their congestive failure, though some patients made artificially myxedematous in the treatment of angina pectoris develop large pericardial effusions which may actually seriously impair myocardial efficiency. Excessive adrenocortical activity may either be of an exogenous nature or occur with a Cushing's syndrome. There is conceded to be some adrenal autonomy in the production of aldosterone although this substance may, of course, also result from increased posterior pituitary activity acting through the adrenal cortex. Aldosterone secretion is influenced by the volume of body fluids and any reduction of extracellular volume occurring with bleeding, drainage of ascitic fluids, salt depletion and so forth, will increase its production.

Lowered renal blood flow will be found in cases complicated by severe intrinsic renal disease which may not be amenable to therapy, but it may also occur in states of lowered cardiac output, renal vasoconstriction from anuria, and as a result of local mechanical pressure from a large collection of acities or other conditions potentially reversible.

In discussing some of the specific methods of management of a case of refractory failure, the question of disordered electrolyte metabolism, which may often be found in these states, must be considered. Figure 5 shows the usual “electrolyte patterns” which are said to result from congestive failure alone or secondary to its treatment. I bring these to your attention primarily to point out that the clinical manifestations of the various syndromes are quite similar and I seriously question whether they can be diagnosed on that basis alone. Moreover, chemical determinations will not be conclusive except in a few instances, since they do not supply necessary information to allow complete separation of dilution and depletion states. The dilution syndrome will often be found to develop spontaneously in patients with congestive failure while sodium depletion and hypochloremic alkalosis are often the result of the intensive administration of diuretics, particularly mercurials. In practice, these specific
## ELECTROLYTE PATTERNS IN RESISTANT CONGESTIVE FAILURE

<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinical</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Na Intake</td>
<td>Anorexia</td>
<td>Salt by mouth</td>
</tr>
<tr>
<td>Diuresis</td>
<td>Nausea and vom.</td>
<td>Conc. saline IV</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Apathy</td>
<td>200 cc 5% h.d.</td>
</tr>
<tr>
<td>Sweating</td>
<td>Drowsiness</td>
<td>K+ - acidosis</td>
</tr>
<tr>
<td>Paracentesis</td>
<td>Confusion, coma</td>
<td>Bicarb.</td>
</tr>
<tr>
<td>Azotemia</td>
<td>Muscular weakness</td>
<td>Lactate</td>
</tr>
<tr>
<td>Acidosus</td>
<td>Cramps</td>
<td>K+</td>
</tr>
</tbody>
</table>

### "Dilution Syndrome" (May develop spontaneously in CHF with conservative management)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Na Intake</td>
<td>Insidious onset</td>
</tr>
<tr>
<td>Unrestricted fluids</td>
<td>Apathy</td>
</tr>
<tr>
<td>Reduced renal function</td>
<td>Amnesia</td>
</tr>
<tr>
<td>Anti-diuretic hormone</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Azotemia</td>
<td>Weakness</td>
</tr>
<tr>
<td>Acidosus</td>
<td>Drowsiness</td>
</tr>
<tr>
<td>(Total body stores normal or increased)</td>
<td>Mental confusion</td>
</tr>
</tbody>
</table>

### Hypochloremic Alkalosis

<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl &lt; Na</td>
<td>Apathy</td>
</tr>
<tr>
<td>Bicarb.↑ alkaliemia</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Bicarb.↓ alkaliemia</td>
<td>Weakness</td>
</tr>
<tr>
<td>Na ↓</td>
<td>Drowsiness</td>
</tr>
<tr>
<td>Bicarb.↓</td>
<td>Mental confusion</td>
</tr>
</tbody>
</table>

### Respiratory Acidosis

<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same with acidosus</td>
<td>Hyperpnea</td>
</tr>
<tr>
<td>Always anosmia, with pulmonary disease, CO₂ retention</td>
<td>Stupor</td>
</tr>
</tbody>
</table>

### Hyperchloremic Acidosis

<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl ↑</td>
<td>Exchange</td>
</tr>
<tr>
<td>K</td>
<td>Resins</td>
</tr>
<tr>
<td>Bicarb.↓ Azotemia</td>
<td>Diams</td>
</tr>
<tr>
<td>NE and Cl</td>
<td>Hyperpnea</td>
</tr>
<tr>
<td>Excreted renal disease</td>
<td>Stupor</td>
</tr>
<tr>
<td>Diams</td>
<td>Coma</td>
</tr>
</tbody>
</table>

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**PRACTICAL PROGRAM FOR PATIENT REFRACTORY TO DIURETICS**

1. Ease up on the diuretic therapy.
2. Search again for factors which may aggravate failure
   a. Hypoproteinemia
   b. Hydrothorax and ascites.
3. Avoid direct attack on electrolytes when clinical condition of the patient is satisfactory.
4. Re-evaluate the possibility of surgery in eligible cases.
5. Give potassium (even if blood levels are not low). Give 3-4 grams daily. This may produce diuresis and rise in sodium.
6. Try the "Rubin Regime."
7. Hypertonic salt solution.
8. Massive steroid therapy.

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syndromes that are so glibly described in the literature, are often difficult to differentiate although we might make one or two generalizations. Most patients with congestive heart failure and hyponatremia do not have a true sodium depletion syndrome and will not benefit from the administration of concentrated salt. Moreover, the unfavorable clinical situation associated with electrolyte disturbance is more often not due to the electrolyte disturbance itself, but rather to a result of the progression of the heart
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"RUBIN REGIME"

Effective both for patients with normal electrolyte patterns and those with chloride depletion.
1. Diamox daily for 3 - 4 days.
2. Then - add 10 grams of ammonium chloride daily for 3 - 4 days.
3. Stop diamox but continue ammonium chloride.
4. Give parenteral mercury 48 hours after discontinuing the diamox.

Figure 7

disease and its complications. In Figure 6 we have presented a practical program for approaching these patients with electrolyte disturbances that cannot be readily pinned down as fitting into one or another of the syndrome patterns. Point six refers to the "Rubin Regime" which is detailed in Figure 7 and 8. This program has repeatedly given satisfactory results in our hands, often restoring the response to diuretics and markedly improving the basic failure state. The patient should be watched for excessive acidosis during the time it is administered. Aminophyline may often be used successfully to augment the effect of mercurists. It may be safely administered in 0.5 gram doses diluted to 250 cc. in 5% dextrose, the entire injection made over a 30 minute period, beginning about three hours after the injection of the mercurial.

ANTICOAGULANTS IN RESISTANT CONGESTIVE FAILURE

Thromboemboli found in 30% of patients dying of CHF. In many they are the direct cause.

Indications
1. Rheumatic heart disease with emboli.
2. Thrombophlebitis

Consider also in
1. Massive leg edema with or without areas of inflammation and induration.
2. Increasing dyspnea during the course of congestive heart failure.
3. Appearance of icterus.

Method
Depression of prothrombin activity to 45% satisfactory for prophylaxis. Lower if actual clotting present.

Good anticoagulant service a "must."

Figure 8
Edema in the cardiac patient may often be due in part to a severe state of hypoproteinemia which, for obvious reasons, cannot be successfully combated by dietary intake. Intravenous salt poor albumin may give temporary benefit but this is an expensive measure. We have had considerable success with tube feeding, using small polyethelene tubes through which the food mixture is forced by a "Barron pump." A complete meal is first prepared in a colloid mill and administered over a several hour period, the tube being placed in the duodenum if absorption or vomiting is a problem. The feedings on the whole are well tolerated, and the procedure may be adopted for home use employing a blender or even an ordinary kitchen mixer provided the feeding is strained prior to its passage through the pump. The small bore of the polythelene tube makes it extremely well tolerated for long periods of time.

Thromboemboli are found in 30% of patients dying of congestive heart failure and in many of these, they are the direct cause of the demise. This has resulted in expanding the indications for the use of anticoagulants to include not only those

**I-131 IN RESISTANT CONGESTIVE FAILURE**

**Rationale**

1. Reduction in metabolism means reduction in cardiac work.
2. May decrease sensitivity of CV system to adrenergic mediators.
3. May cause alteration in pain perception.
4. May increase rate of development of intercoronary collaterals.
5. (Raab) Thyroid hormone effects the myocardial metabolism by potentiating hypoxia producing, calorogenic and toxic action of the adreno-sympathogenic cortical amines.

**Selection must have**

1. Severe disease.
2. Been unsuccessful on medical program.
3. Not in moribund state.

**Dosage**

1. Blumgart - 15 mc. stat, then 2 subsequent doses at weekly intervals each 5 mc. larger.
2. Jaffe - 6 mc. per week for 5-6 weeks.

**Results**

<table>
<thead>
<tr>
<th>Blumgart</th>
<th>Jaffe</th>
</tr>
</thead>
<tbody>
<tr>
<td>24% strikingly improved</td>
<td>53% excellent</td>
</tr>
<tr>
<td>30% worthwhile</td>
<td>33% good</td>
</tr>
<tr>
<td>46% no benefit</td>
<td>14% not good</td>
</tr>
</tbody>
</table>

Figure 9

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patients with thrombophlebitis or rheumatic heart disease with emboli but also other cases with massive latent edema with or without areas of inflammation and induration and even to some patients with increasing dyspnea during the course of congestive failure or those who show the presence of icterus. Depression of the prothrombin activity to 45% is satisfactory for prophylaxis, and this may be depressed further if actual clotting is present. A satisfactory anticoagulant service should be available before such therapy is undertaken. (Figure 8)

Over the past ten years, various clinics have evaluated the usefulness of I-131 in severe angina pectoris and to a lesser extent its use in congestive failure. Figure 9 outlines the method in which this may be used and the results which have been obtained in two of the larger centers.

Our own results with congestive failure are much less satisfactory than those achieved in angina pectoris. The unpleasant side reactions associated with this therapy considerably limits its usefulness and are a source of concern both to the patient and his relatives. It is mandatory that the patient’s status be stabilized before instituting treatment, and it should be borne in mind that the basis underlying disease process is not effected by this treatment. No single dose larger than 20 millicures should be given in order to avoid thyroiditis. We have previously pointed out that I-131 should not be administered to a patient receiving anticoagulants since the isotope acts by producing a hemorrhagic necrosis of the gland.

Recently, the use of the steroids in the management of resistant heart failure has received considerable play in the literature. We normally think of the steroids as promoting salt retention and, therefore, contra-indicated in this situation, but actually they may be employed profitably in certain instances to promote water diuresis. Some of the possible theories of their action are listed in Figure 10. The diuresis following the use of steroids is somewhat unpredictable as to its time of occurrence. In some instances, it may not occur until after the drug is stopped, but usually it takes place

USE OF STEROIDS IN THE MANAGEMENT OF RESISTANT HEART FAILURE

Rationale – (Theories)
1. Increase glomerular filtration rate.
2. Inhibit anti-diuretic hormone.
4. Re-potentiation of diuretic drugs.
5. Anti-inflammatory action as in rheumatic heart disease.

Dosage (not well standardized)
Prednisone - 7.5-25 mgm./day

1. Keep in mind associated disorders
   e.g. - ulcers, infection, tbc.
2. Continue the basic cardiac therapy.

Figure 10
after 5 to 6 days of administration. In the cases presented by Mickerson and Swale, the serum sodium concentration was uniformly decreased before the institution of steroid therapy and increased and remained at normal level despite a profuse diuresis. It is noted that two of their patients died of pulmonary embolism after one and two weeks of Prednisalone therapy respectively. The usual hazards associated with steroid administration such as ulcers, infection and so forth, are to be kept in mind, and the basic cardiac therapy should be continued during their administration.

We have not had any extensive experience with the use of aldosterone antagonists and what little use we have made of them has been somewhat disappointing. Recent information indicates that the dosage should be revised upwards to 1200 or 1500 mg. a day and this is quite an expensive proposition considering the present market price of the available products. The manufacturers of one preparation (Aldactone)* claim a true synergistic reaction with conventional diuretics and advice the concurrent use of a mercurial or thiazide preparation. Aldactone apparently does not cause potassium secretion and may even offset the potassium loss induced by mercurials or thiazide preparations when used in combination with them. Further work will be necessary to evaluate these products and place them in their proper perspective in regard to the treatment of the patient with refractory congestive heart failure. Finally, a word should be said in regard to the removal of localized deposits of fluid in the edematous cardiac. This is easily accomplished in the case of hydrothorax or ascites but presents a more difficult problem in the case of massive leg edema. We have used multiple punctures, employing a regular hypodermic needle, inserted through a cork to permit the proper depth of penetration. The sites of puncture should first be prepared with a local anesthetic and strict asepsis should be maintained. We have also successfully employed a method employing the introduction of small lengths of polyethylene tubing which are placed through an 18 gauge thin wall needle that is then immediately withdrawn, leaving the tube in place. Several tubes can be placed at strategic points in an edematous extremity, but should probably not be allowed to remain more than twenty-four to forty-eight hours. Here again, asepsis is most important and antibiotics should probably be administered prophylactically to combat the possibility of infection. We have not found the ligation of the inferior vena cava to be a useful procedure in the management of our patients to date, although there are several reports in the literature which advocate this procedure. Wiringer suggests that it is an especially useful procedure to employ preoperatively in certain cases of mitral stenosis possessing an increased risk because of their advanced state of failure. They suggest that this may be followed later under more favorable conditions by the commissurotomy performed as a second stage procedure, in a more fully compensated heart. Lian and his associates state that the most favorable patients for this maneuver are those in whom stasis is limited to the lungs. A less favorable group are those with stasis both in the lungs and in the liver with the least favorable group being those with visceral stasis associated with edema. The operative mortality is high in the series quoted, amounting to 25%, with another author citing a 50% mortality within a six month period. The advocates of this procedure claim prophylaxis against emboli as another advantage and state that it also may be combined with lumbar sympathectomy.

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SUMMARY

Various etiological factors important, not only as the primary causative condition but also as aggravating factors in cases of resistant cardiac failure are reviewed and possible therapeutic approaches to the problem are discussed. Special mention is made of the difficulty in diagnosing with certainty, the various disordered electrolyte patterns. It is felt that special emphasis should be given to the correction of hypoproteinemia when it exists and that steroids and anticoagulants show exceptional promise in many cases. The results with radioactive iodine are, in general, somewhat disappointing and the use of Aldosterone antagonists will require further evaluation before their ultimate usefulness is established.

REFERENCES


