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Pharmacotherapy in Heart Failure (II): Beta Adrenergic Blocking Drugs, Ivabradine, Hydralazine and Nitrates

Shirin Zarafshar and Michael B Fowler

8.1 Beta Adrenergic Blocking Drugs

Sympathetic nervous system activation is a cardinal feature of heart failure. Cannon [1] first described this component of the autonomic nervous system as the "fight or flight response" which became activated to react to short bursts of activity associated with "pain, hunger, fear or rage." The principal responses seen in the cardiovascular system are an increase in heart rate and myocardial contractility, an increase in peripheral vasoconstriction, and other alterations in vascular tone causing redirection of blood flow to vital organs. Chidsey [2] was one of the earliest investigators to demonstrate that heart failure was accompanied by chronic activation of the sympathetic nervous system. This was at one time felt to be a beneficial response, helping to restore cardiac output through inotropic and chronotropic actions which were held to be beneficial to the failing heart. Beta adrenergic blocking drugs were believed to be contraindicated in heart failure and labeled as such. An improved understanding of the potential detrimental effects of chronic sympathetic activation emerged with new insights into the pathophysiology of heart failure, and from small clinical studies which suggested patients with heart failure could benefit from treatment with beta adrenergic blockade.

Cohn, who was at the forefront of recognizing the adverse hemodynamic consequences of the increase in peripheral resistance that occurs in heart failure, demonstrated an inverse relationship between circulating levels of norepinephrine and survival in patients with chronic congestive heart failure [3]. Studies on failing human myocardium obtained at the time of cardiac transplantation, led by Michael Bristow, revealed profound alterations in the sensitivity to chronic sympathetic activation. He demonstrated that failing myocardium had selective down regulation of beta-1 adrenergic receptors leading to catecholamine subsensitivity [4].

Chronic heart failure was being increasingly recognized as a condition characterized by an exuberant response of the neuronal hormonal system that normally regulates contractility, the response to injury, and regulation of salt and water balance [5]. Although natriuretic peptides and other vasodilator hormones become activated, the dominant influence of the complex series of responses to the heart failure state is one of vasoconstriction, salt and water retention, and a progressive myocardial remodeling process that contributes to disease progression. This pathophysiology is relatively well understood and accepted in patients where the response to injury is heart failure with reduced ejection fraction. It is this group of patients that have been shown to respond to antiadrenergic therapy with beta adrenergic blocking drugs. These patients also require therapy directed against the renin-angiotensin-aldosterone system and will also respond to vasodilator therapy, specifically combination therapy with hydralazine and nitrates. Recently patients who have been shown to have a persistent relative tachycardia in sinus rhythm despite optimal tolerated doses of beta adrenergic blocking drugs have been demonstrated to have modest clinical benefit when ivabradine, a drug that slows heart rate in sinus rhythm, is given.

8.2 Beta Adrenergic Blocking Drugs: Early Studies

In 1975 Waagstein [6] reported for the first time that patients with idiopathic dilated cardiomyopathy had improvements in parameters of systolic and diastolic function and appeared to tolerate and improve clinically when treated with beta-1 selective beta blocking drugs. The same group from Gothenburg, Sweden subsequently reported in small single center studies that patients appeared to derive long-term benefit from this therapy. Studies from Stanford showed an improvement in left ventricular ejection fraction, restoration

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of myocardial beta −1 adrenergic receptor density, and an apparent recovery of contractile responses to dobutamine following therapy with metoprolol tartrate [7]. The first randomized trial to evaluate the effect of beta blockade in patients with heart failure was a single center study by Engelmeier [8] which appeared to confirm a clinical benefit. The MDC study was the first multi-center study of metoprolol tartrate in patients with dilated cardiomyopathy [9]. The study found that patients randomized to metoprolol were less likely to die or be listed for cardiac transplantation. These early studies and a greater appreciation of the potential detriment from chronic sympathetic over-activity resulted in a series of pivotal studies which clearly established that patients with chronic heart failure, irrespective of etiology, and a reduced ejection fraction, had an important reduction in the risk of death and reduced risk of hospitalization for any reason, and specifically for heart failure exacerbation, when treated with certain beta blocking drugs.

8.3 Beta Adrenergic Blocking Drugs: Randomized Trials

Evidence supporting the routine use of certain beta adrenergic blocking drugs in patients with heart failure and a reduced ejection fraction is provided by four randomized trials order which demonstrated an important statistically significant benefit. The original study was a four-component trial designed to establish the safety and efficacy of carvedilol in heart failure. On the basis of the six-minute walk test, patients were separately randomized into trials designed to evaluate the drug in mild, moderate, and severe heart failure. Two moderate heart failure severity trial designs were completed; one, although recruiting a relatively small number of patients, remains the only study which specifically explored the dose response to beta adrenergic blocking drugs [10]. An independent data safety board recommended early discontinuation of the US carvedilol trials program when the mortality was observed to be 65% lower in the patients randomized to carvedilol compared to the placebo group [11]. Patients recruited into this trial needed a systolic blood pressure greater than 85 mmHg and deemed stable outpatients. They had to be on optimal doses of diuretics and receiving treatment, if tolerated with an ACE inhibitor. Patients were required have a reduced left ventricle ejection fraction to enter the trial (HFrEF). Patients with major impairment of renal or hepatic function were excluded. The placebo annualized mortality of approximately 10% is consistent with other trials in NYHA functional class II heart failure. MERIT HF [12] and CIBIS 2 [13] were multi-center randomized trials designed as survival trials. Entry criteria were similar to those of the US carvedilol trials program. None of these trials were designed with a run-in period. All these studies recruited patients with HFrEF of ischemic or non-ischemic etiology. The results from these studies show an important, approximately 35% reduction in mortality with carvedilol, metoprolol succinate, or bisoprolol. All-cause and heart failure re-hospitalization was reduced. Patients with ischemic or non-ischemic etiology of heart failure appeared to derive a similar benefit. Although the CIBS study purported to enroll patients with class II and III heart failure, the approximately 10% per year mortality in the placebo arm was more characteristic of a patient population with class II heart failure. In order to address the concern that patients with advanced heart failure may not benefit, the COPERNICUS study was designed to evaluate the role of carvedilol in patients with severe heart failure. Patients had to have an LVEF of less than 25% to be eligible for this study. This study achieved its primary endpoint and survival in the carvedilol group was improved by a remarkable 34% [14]. Again the risk of hospitalization was reduced. In this study the initial dose of carvedilol was 3.125 mg twice daily, gradually up titrated to a target dose of 25 mg twice daily. In this patient population, the placebo annualized mortality was 18.5%. Although this is by far the most severe heart failure patient population ever evaluated in a large, multicenter, randomized trial of beta adrenergic blocking therapy, this mortality rate is still considerably lower than that described in refractory heart failure patients who are experiencing frequent readmission where the six-month mortality may be as high as 50%.

8.4 Beta Adrenergic Blocking Drugs: Specific Properties

More than perhaps most classes of drugs, beta adrenergic blocking drugs exhibit multiple differences in their pharmacology. All the drugs shown in randomized trials to be beneficial are lipophilic. This confers a lidocaine-like membrane stabilizing effect, and means that these drugs cross the blood brain barrier. They cross the placental barrier and will present in breast milk. Beta-one selective agents, such as metoprolol and bisoprolol, will not tend to increase peripheral resistance. This vasoconstriction is a detrimental effect of beta-2 adrenergic receptor blockade, particularly in patients with heart failure seen with non-selective agents due to blocking of peripheral beta-2 adrenergic receptors, which are vasodilatory. Carvedilol, which is a nonselective agent, is free from this disadvantage due to the peripheral vasodilatation caused by the blocking alpha-1 adrenergic receptors. Other differences between agents including possible different actions on beta receptor density, and other ancillary properties such as an anti-oxidant effect, lend caution to regarding all beta adrenergic blocking drugs as being necessarily equally effective or having exactly similar impact in patients. In a hypertensive patient population with type II diabetes the

vasodilatation from carvedilol compared to metoprolol was the probable explanation all improvements in insulin sensitivity and differences in hemoglobin A-1 C reported when comparing the two agents (GEMINI trial [15]). In the longest trial of beta-adrenergic blocking drugs in heart failure, the COMET study compared metoprolol with carvedilol [16]. The study has been criticized because the short acting salt (tartrate) of metoprolol was used although this does not have an impact on the beta receptor blocking properties of metoprolol, but does influence the pharmacokinetics. One major limitation of this comparison study between two agents in the same class is that metoprolol tartrate had only been used in one randomized multicenter trial in heart failure (MDC trial) and that an effective dose of the tartrate salt had never been established. This study demonstrated that the majority of patients on a comprehensive medical regime, which included carvedilol or metoprolol, will die from heart failure. Out of a total of 3209 patients, 1112 patients (600 of the patients randomized to metoprolol and 512 of the patients randomized to carvedilol) died during a mean follow-up of 5 years [16]. It was possible to achieve a mean heart rate in this study in the 70s, which demonstrated that the majority of patients treated with the blocking drugs under the circumstances of a clinical trial could be titrated to the dose of either drug which achieved goal target heart rate without resorting to the additional use of ivabradine (*vide infra*).

8.5 Beta Adrenergic Blocking Drugs: Limitations in the Clinical Trials Evidence.

The US heart failure guidelines have divided patients with symptomatic heart failure into stage C and stage D categories. The stage D patients are the group with refractory heart failure. The recommendation from the AHA/ACC guidelines is for these end-stage patients to remain on the drugs that have been shown to be beneficial in randomized trials of stable patients with class C heart failure. There is no good direct evidence supporting this recommendation. Various lines of evidence support the contention that even patients much sicker than those recruited into the COPERNICUS trial are likely benefiting from beta blocking drugs. The observation by Fonarow that patients who are admitted to hospital with an acute exacerbation of heart failure have better outcomes if they were kept on beta adrenergic blocking drugs is important, but propensity analysis may not have able to separate the clinical features associated with a poor prognosis that contributed to what was likely an appropriate decision to discontinue therapy with beta blocking drugs during the hospitalization [17]. Similarly, the incorporation of the absence of therapy with a beta blocking drug to an adverse outcome in the Seattle heart failure score does not necessarily imply that patients who have become intolerant to beta blocking drugs would be better served if they were continued on therapy they appeared not to tolerate. Although there is no clinical trials evidence supporting the use of sympathetically-mediated inotropic agents, dobutamine or milrinone are frequently found to be useful in treating patients with acute decompensated heart failure, especially those with evidence of a low cardiac output state. Some investigators have claimed benefit from a combined use of beta adrenergic blocking drugs with enoximone, a phosphodiesterase inhibitor [18], although this benefit has not been shown in any multicenter clinical trials. Not all trials of beta adrenergic blocking drugs or of studies that modulate and reduce sympathetic exposure to the failing heart have been beneficial. Bucindolol was explored in a dose ranging study where the greatest improvement left ventricular ejection fraction appeared to be greatest at the highest dose. This was the target dose selected in the BEST study [19]. The study did not reach its primary endpoint of survival. Subsequent analysis appeared to show that the response was determined by specific beta adrenergic pathway polymorphisms [20]. It is consistent with the trial data that the dose selected in the BEST trial may have been too high and that modulation of excess catecholamine exposure is needed to strike the balance between harm and benefit. This hypothesis is to some extent supported in clinical practice where patients who have previously tolerated and appeared to benefit from high doses adrenergic blocking drugs require and seem to initially benefit when dose reductions are forced by disease progression. Many of these patients will initially improve with a dose reduction with recovery from severe symptomatic hypotension and clinical and laboratory evidence of a low output state. In many patients a forced reduction in the dose of a previously well-tolerated beta adrenergic blocking drug is often an indicator of a slide into terminal refractory stage D heart failure. This can be used as a relatively reliable indicator of a poor prognosis and used to initiate the process of evaluating selected patients for mechanical support and cardiac transplantation. Further evidence that some level of adrenergic activity may be beneficial can be derived from the results of the MOXCON trial in which moxonidine, a central inhibitor of norepinephrine, reduced circulating norepinephrine levels but increased mortality [21].

8.6 Beta Adrenergic Blocking Drugs: Special Populations

Beta adrenergic blocking drugs benefit in patients with heart failure and a reduced ejection fraction appears to be consistent across various patient groups. Specific trials designed to compare the benefit in patients in specific patient populations have not been performed but subgroup analysis in

general has confirmed that the benefit is preserved between the sexes, in patients of different ethnicity, and in subgroups with diabetes. Not all of these analyses have necessarily shown an equal benefit but interpretation of data from subgroup analysis, even if this subgroup analysis was prespecified, is fraught with the potential to provide misleading information. For instance, although the Merit-HF failure study did not appear to show benefit in the patients recruited in the United States or in women, studies with carvedilol have established that women and men drive equal benefit [22]. African-American populations have been shown to benefit in subgroup analysis of carvedilol studies [23]. Small studies have suggested that an Asian population may not tolerate the full target dosages are beta adrenergic blocking drugs shown to be effective in United States and European populations [24]. Interpretation of this data is difficult, and in general it would seem appropriate to treat all patient population with heart failure at a reduced ejection fraction with one of the approved agents and up tirate to maximum tolerated dose if the target dose cannot be reached.

Various studies and registry data have suggested that patients who remain on low doses of beta adrenergic blocking drugs fare less well than patient up titrated to the target dosages used in the trials, and that adrenergic blocker benefits are dose-related [25]. Two factors probably contribute to this observation. First, patients not up titrated likely are not receiving the maximum potential benefit. Second, the patients who really do not tolerate up titration are likely to have more advanced disease with hypotension and possibly symptoms of fatigue with evidence of a low output state preventing successful dose escalation. These patients will have a worse prognosis than individuals with less advanced disease. It remains far from certain that forcing patients to a high dose of a adrenergic blocking drug for which there appears to be true evidence of intolerance would be beneficial to that patient. It is worth noting that in the randomized trials not all patients in the study reached target dose and that the positive results seen in these studies included patients who were maintained below target dose due to intolerance. It is necessary for the treating physician to work closely with each individual patient to titrate to the highest possible tolerate dose while at the same time accepting that some patients may be optimally managed a doses below target.

Elderly patients with heart failure have specifically been evaluated. The SENIORS trial compared nevibolol with placebo in patients who were 70 years old or greater [26]. Although the study was relatively small (2128 patients), it did demonstrate improvement in the combined endpoint of mortality and cardiovascular admission. Uniquely this study did recruit patients with clinical heart failure regardless of ejection fraction. In a pre-specified subgroup analysis, the preserved ejection fraction patient population apparently showed equal benefit to the patient group with reduced left ventricle ejection fraction. This finding has not been replicated. A relatively small study of carvedilol in patients with preserved ejection fraction, the Japanese diastolic heart failure study (J-DHF) showed no difference between carvedilol and a control group for a combined primary outcome of cardiovascular death or unplanned hospitalization for heart failure [27]. During a mean follow-up of 3.2 years, 29 patients in the carvedilol group and 34 patients in the control group met this primary endpoint. Chronotropic incompetence may contribute to the pathophysiology of heart failure with a preserved ejection fraction. Patients in this group category would likely not benefit from the heart rate lowering effects of beta adrenergic blocking drugs. Similarly, patients who have heart failure and a preserved left ventricular ejection fraction with radiation-induced heart disease often have striking tachycardia but appear to be harmed when beta adrenergic blocking drugs are prescribed (personal observation). Presumably in this patient population, stroke volume is low and fixed and cardiac output is dependent on heart rate. Conversely some patients with heart failure and a preserved ejection fraction, classically those with mitral stenosis dependent on heart rate lowering to adequately fill the ventricle. Perhaps the first use of beta adrenergic blocking drugs in heart failure was in patients with rheumatic mitral stenosis. It is likely that some patients with heart failure and a preserved left ventricle ejection fraction will benefit from beta adrenergic blocking drugs but the precise patient population and the patient-specific characteristics which support their use has yet to be determined.

8.7 Beta Adrenergic Blocking Drugs: Practical Considerations

Treatment guidelines, evidence from randomized trials, and even practice performance measures strongly advocate the routine use of beta adrenergic blocking drugs in all patients with heart failure with reduced ejection fraction. It is appropriate to initiate therapy as soon as the patient is approaching optimal volume status. In patients with hypertension and who are clearly well perfused, beta adrenergic blocking drugs should be initiated at the recommended initial starting dose. In patients who remain hypertensive after initiation of therapy, a higher starting dose could be considered and up titration should be rapid. Conversely, those patients with low blood pressure and tenuous clinical status may require lower-than-recommended initial doses and slower up titration of therapy. Although very few hospitalized patients were entered into randomized trials and the majority of trials specifically recruited patients who are felt to be stable, patients do seem to tolerate the initiation of therapy in

hospital with little adverse impact on the duration of hospital stay [28].

Most patients with chronic congestive heart failure will tolerate up titration to the target dose of the specific heart failure trials. Patients will need to be seen frequently during this up titration phase to adjust concomitant medications and especially to prevent over-diuresis so that a relative degree of hypovolemia with hypotension is not wrongly attributed to beta adrenergic therapy up titration. Strategies to improve the proportion of patients who can be up titrated to target dosages include changing the timing of other drugs that might lower blood pressure. Once daily angiotensin-converting enzyme inhibitors or angiotensin receptor blockers could be given in the evening before bed while carvedilol could be given twice daily with food or metoprolol succinate in the morning. Once patients become tolerant to the titrated dose, some of these complex timing strategies can often be abandoned in favor of a more convenient and more easily adherent medication schedule.

Patients with left bundle branch block and a QRS duration of great than 150 milliseconds with hypotension and evidence of a low output state may not initially tolerate anti-adrenergic therapy. In this particular patient population, a relatively early implantation of a biventricular pacing device to provide cardiac resynchronization therapy (CRT) will sometimes improve the clinical stability and hemodynamics of a patient to the extent where beta adrenergic blocking drugs can be initiated and successfully up titrated.

In general, the group of patients who have responded well to beta adrenergic blocking drug, should remain on therapy indefinitely. Patients who discontinue beta adrenergic blocking drugs and the other neurohormonal antagonists that have been associated with recovery of left ventricular ejection fraction are at risk of re-development of LV dysfunction and recurrent overt heart failure symptoms. Exceptions might be a patient who recovered from a proven episode of acute myocarditis or heart failure associated with preeclampsia where there are credible reasons for a patient to want to discontinue therapy that is usually well-tolerated and which has been associated with recovery from a serious condition.

In general patients need to be encouraged to take beta adrenergic blocking drugs for the rest of their life when they have been prescribed for heart failure. The majority of patients with heart failure will die from heart failure despite the successful new therapies introduced over the last 30 years. The benefits of beta adrenergic blocking drugs specifically have to be explained to patients and some need to be coached to tolerate the relatively minor symptoms of postural hypotension that so often accompanies their use, particularly in patients who do not have background hypertension.

8.8 Ivabradine

Ivabradine has been developed to treat those patients who are unable to achieve a heart rate less than 70 beats per minute at rest. This new class of medication inhibits the "funny" channel (I_f) in the sinoatrial node, thereby reducing heart rate by a mechanism other than beta 1 inhibition. However, conduction outside the sinoatrial node is not affected, and there is no effect on contractility or repolarization. The SHIFT trial demonstrated improvement for all-cause hospitalization or heart failure hospitalization [29]. However, there was no significant difference in all-cause or cardiovascular mortality between those patients treated with standard medical therapy vs standard medical therapy and ivabradine. Furthermore, the reported benefit of ivabradine was considerably stronger in non-ischemic heart failure patients as compared to ischemic heart failure patients (hazard ratio 0.72 for non ischemics vs hazard ratio 0.87 for ischemics). This raises concern that ivabradine may not be as effective for those patients with ischemic cardiomyopathy [30]. Of note, the SHIFT trial excluded patients who had suffered myocardial infarction in the 60 days prior to enrollment. Nevertheless, the current ACC/AHA recommendations give ivabradine a Class IIa indication for heart failure patients of any etiology on maximally tolerated beta adrenergic blocking drugs with resting heart rate in sinus rhythm greater than 70 beats per minute [31].

8.9 Hydralazine and Nitrates

Early hemodynamic studies of heart failure patients demonstrated increased peripheral vascular resistance [32]. Patients with acute myocardial infarction were one of the first groups studied for acute afterload reduction [33]. A small study of 15 patients demonstrated that nitroprusside infusion helped reduce chest pain, dyspnea, and clinical signs of left ventricular failure in those patients with reduced cardiac index. Efforts to identify oral agents that could help patients with chronically reduced cardiac index included studies of minoxidil, prazosin, and phentolamine [34–36]. These oral agents were not as effective as nitroprusside infusions, however, and eventually combination therapy with hydralazine (a direct arterial vasodilator) and isosorbide dinitrate (ISDN, a relatively long- acting nitrate) were explored after initial exploratory studies of each medication as solitary treatment seemed promising [37, 38]. Two larger studies, V-HeFT I and V-HeFT II were designed to study possible mortality benefits of hydralazine/nitrate therapy. V-HeFT I randomized 642 men with systolic dysfunction to hydralazine (37.5 mg)/ISDN (20 mg), prazosin, or placebo while receiving digoxin and diuretics as standard medical therapy. This

study showed decreased mortality at 2 years among those patients treated with hydralazine/ISDN whereas those patients treated with prazosin did not show mortality benefit or improvement in left ventricular ejection fraction [39]. Six years later, the V-HeFT II trial reported that 804 men randomized to enalapril (20 mg) vs. hydralazine (37.5 mg)/ISDN (40 mg) showed significant mortality reduction as compared to placebo. However, those patients treated with enalapril had lower mortality rates as compared to hydralazine/ISDN. On the other hand, peak VO2 and ejection fraction changes were more favorable among those patients treated with hydralazine/ISDN rather than enalapril. The authors concluded that the differential benefits of each regimen might make treatment with all three agents the most efficacious [40].

Retrospective analyses of the V-HeFTI and V-HeFT II studies suggested that African-American patients derived more benefit from hydralazine/ISDN than white patients. The A-HeFT trial was designed to examine if African-American patients with class III-class IV heart failure would benefit more from hydralazine (37.5 mg)/ISDN (20 mg) therapy rather than placebo, in addition to standard medical therapy (ACE inhibitors, aldosterone antagonists, diuretics, and digoxin, [41]). The study of 1050 patients was ended early after the mortality rate in the placebo group was found to be significantly higher than the hydralazine/ISDN group (10% vs 6%, $p = 0.02$). This lead to the first race-based guideline recommendation for heart failure therapy, and the first race-based Federal Drug Administration drug approval. However, the A-HeFT trial was not designed to test whether hydralazine/ISDN was more efficacious than ACE inhibitors or angiotensin receptor blockers. On the other hand, for those patients who are unable to take ACE inhibitors or angiotension receptor blockers, hydralazine/nitrates remain an important heart failure therapy for patients of all ethnicities.

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Blood Pressure-lowering Treatment and the Prevention of Heart Failure: Differences and Similarities of Antihypertensive Drug Classes

Costas Thomopoulos, Alberto Zanchetti†

Antihypertensive Treatment and Heart Failure: Prevention of Recurrences or Prevention of New-onset Heart Failure?

Moser and Hebert were the first to call attention to the finding that blood pressure (BP)-lowering treatment did not only reduce risk of fatal and nonfatal stroke and fatal and nonfatal coronary heart disease (CHD) events but also risk of heart failure [1]. They reviewed data from 12 placebo (or no treatment)-controlled randomized trials (RCTs) including 13,837 hypertensive patients and calculated heart failure risk was reduced by 51% (risk ratio [RR] and 95% confidence interval [CI] 0.48 [0.38–0.59]). They also remarked that most of the positive RCTs they had considered had used a diuretic as BP-lowering drug [1].

In a very large meta-analysis updated to end 2013 and including 68 RCTs on as many as 245,885 participants, we extended Moser and Herbert's early analysis and we demonstrated that heart failure risk was significantly reduced by a standardized systolic BP/diastolic BP reduction of 10/5 mmHg and that heart failure reduction was even numerically greater than that of stroke (−43% vs. −38%) and much greater than the albeit significant reductions of CHD events and cardiovascular and all-cause mortality [2]. A more stringent comparison was subsequently done by our group by restricting meta-analyses to only those 35 BP-lowering RCTs (146,810 individuals) measuring all major cause-specific events (stroke, CHD, heart failure, cardiovascular mortality) [3], and we reported that heart failure and stroke were by far the outcomes most extensively reduced by BP lowering (RR stroke 0.58 [0.49–0.68]; heart failure 0.63 [0.52–0.75]), without a significant difference between the two reductions. We also calculated a meta-regression to compare the relationships between the relative risk reductions of the various outcomes with the extent of BP reduction [3] and found the steepest slopes for the relationships with heart failure and stroke with no significant differences between these slopes (p = 0.69, 0.78, and 0.67 for systolic BP, diastolic BP, and pulse pressure reductions, respectively). On the other hand, the slopes of heart failure reduction were significantly greater than those of all-cause mortality reduction (p = 0.022, 0.024 for systolic BP and pulse pressure reductions), although decreased mortality (both cardiovascular and all-cause) was also a significant effect. In no one of our meta-regression analyses was coronary heart disease reduction significantly related to the extent of blood pressure reduction (Fig. 1).

A further important question is whether BP-lowering treatment really prevents "new-onset" heart failure or mostly reduces recurring or worsening of preexisting heart failure. A correct analysis implied meta-analysis of only those BP-lowering RCTs explicitly excluding patients with history or current evidence of heart failure. Of the 35 BP-lowering RCTs measuring heart failure as an outcome, our search identified 18 in which baseline history of HF was explicitly listed as an exclusion criterion [4–31] and, therefore, suitable to be meta-analyzed to estimate the BP-lowering preventive effect on "new-onset" heart failure. Our search also identified other ten RCTs in which only patients with mild heart failure could have been included; added to the 18 RCTs with no baseline HF, they were used for a secondary meta-analysis (Table 1).

Even with the more stringent criteria of including RCTs with no baseline heart failure (Fig. 2), there was a large and highly significant reduction of "new-onset" heart failure, the extent of which (relative risk reduction −42%, absolute reduction −21 heart failure cases per 1000 patients treated 5 years) is very similar to that in the entire set of RCTs measuring heart failure as an outcome (relative risk reduction −37%, absolute risk reduction −19 heart failure cases). Also the secondary meta-analysis using looser criteria in selection of RCTs did not substantially change

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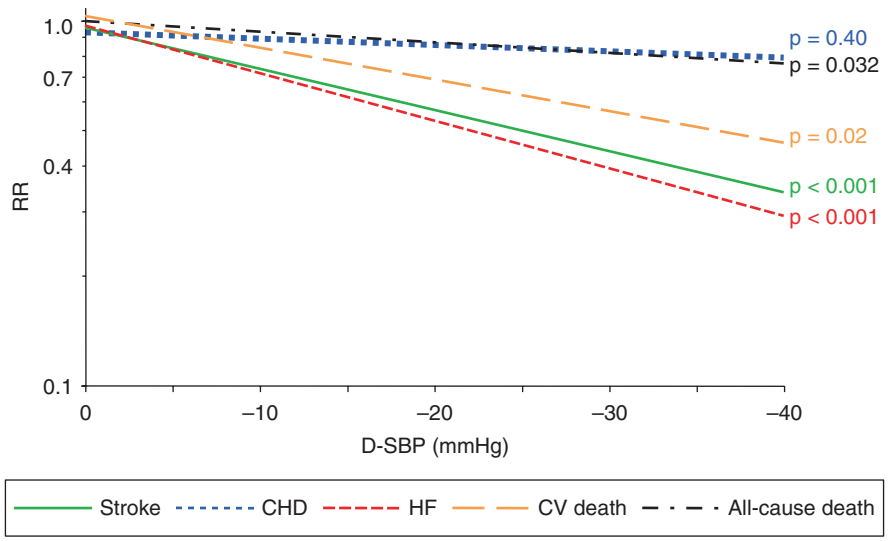

Fig. 1: Relationships of outcome reductions to the extent of BP reductions, in the 35 blood pressure-lowering trials in which all the listed outcomes were measured. Meta-regressions of risk ratios (RR) on absolute systolic blood pressure (SBP) differences (D) (active treatment minus placebo or less active treatment). Stroke is the *green continuous line*, coronary heart disease (CHD) the *blue square line*, heart failure (HF) the *red short dashed line*, cardiovascular (CV) death the *orange long dashed line*, and all-cause death the *black dashed and dotted line*. *P*-values indicate statistical significance of the slope of each outcome (colors as above to identify outcomes) on BP difference. Note the ordinates are on an ln scale. Modified from Thomopoulos *et al*. [3], by courtesy of *Journal of Hypertension*.

Table 1: Blood pressure-lowering trials evaluating new-onset heart failure.

Baseline HF excluded	Mild baseline HF allowed	Drug class
ACTION [4]	ADVANCE [22]	Diuretics
AUSTRALIAN-Mild [5]	FEVER [23]	AUSTRALIAN-Mild [11]
CAMELOT [6]	SHEP pilot [24]	EWPHE [13]
EWPHE [7]	SHEP [25]	HYVET [17]
HEP [8]	STOP [26]	OSLO [18]
HSCSG [9]	Cardio-Sys [27]	Beta-blockers
HYVET [10]	IDNT [28]	HEP [15]
OSLO [11]	NAVIGATOR [29]	UKPDS 38 [32]
Syst-China [12]	ORIENT [30]	Calcium antagonists
Syst-Eur [13]	PEACE [31]	ACTION [9]
USPHS [14]		CAMELOT [12]
JATOS [15]		Syst-China [22]
UKPDS 38 [16]		Syst-Eur [23]
DIABHYCAR [17]		ACE inhibitors
DREAM [18]		CAMELOT [12]
HOPE [19]		UKPDS 38 [32]
RENAAL [20]		DIABHYCAR [34]
TRANSCEND [21]		DREAM [35]
		HOPE [36]
		ARBs
		RENAAL [43]
		TRANSCEND [44]

Trials indicated by their acronyms or first author. Full titles can be found in the references. Other abbreviations: *ACE* angiotensin-converting enzyme, *ARBs* angiotensin receptor blockers, *HF* heart failure

the quantitative assessment of the effectiveness of BP-lowering treatment in the prevention of development of new HF (Fig. 2).

Are the Various Classes of Antihypertensive Drugs Equally Effective in Preventing "New-onset" Heart Failure?

Other clinically relevant questions are: are all classes of BP-lowering drugs capable of significantly reducing "new-onset" heart failure, and, when directly (head-to-head) compared, are classes equally effective? A correct answer to these questions again required analyses limited to RCTs excluding baseline heart failure.

The first part of this question (i.e., the ability of each drug class to reduce new-onset heart failure) was approached by meta-analyzing placebo-controlled BP-lowering trials stratified by the class of the active drug compared with placebo. Among the BP-lowering RCTs that had rigorously excluded patients with baseline heart failure, four had BP lowering induced or initiated by a diuretic, two by a beta-blocker, four by a calcium antagonist, five by an ACE inhibitor, and two by an angiotensin receptor blocker (Table 1, column "Drug class"). In meta-analyses restricted to RCTs with no baseline heart failure (Fig. 3A), BP lowering by diuretics, beta-blockers, calcium antagonists, and ACE inhibitors significantly reduced the risk of new heart failure. Inability to find a significant heart failure reduction with angiotensin receptor blockers is likely to depend on insufficient statistical power (only two RCTs) associated with a small systolic BP/diastolic BP difference.

The second part of the question (i.e., the relative effectiveness of the various drug classes) was explored by using a second set of meta-analyses, focused on direct head-to-head comparisons of different active BP-lowering drugs, the only correct way of evaluating the relative effectiveness of two interventions. To investigate the more general question of the comparative effectiveness of various

Type of trial	Trials (n)	HF Events (n/patients) Treated	HF Events (n/patients) Controls	Difference SBP/DBP (mmHg)	Standardized RR (95% CI)
A. Trials with no baseline HF	18	997/30519	1276/29331	-6.7/-3.4	0.58 (0.44-0.75)
B. Trials with no or mild HF	28	1688/55324	2027/53279	-6.2/-3.0	0.58 (0.47-0.72)

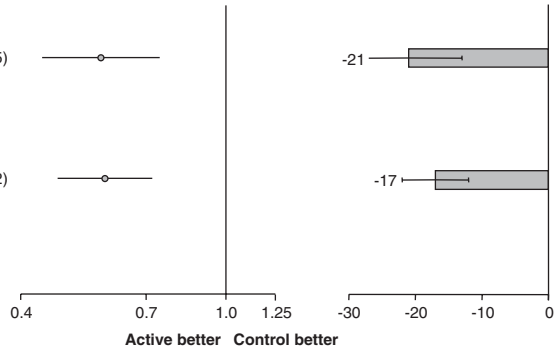

Fig. 2: Relative and absolute risk reduction of heart failure in blood pressure lowering in trials with no baseline heart failure (*A*) and with no or mild baseline heart failure (*B*). Each column from left to right indicates numbers (*n*) of trials considered, the number of heart failure (HF) events observed and the number of patients followed up, the difference in systolic and diastolic blood pressure (SBP/DBP) achieved between actively treated patients (treated) and controls, the risk ratio (RR) and its 95% confidence interval (CI) standardized by a 10/5 mmHg difference, the standardized risk ratio as forest plot, and the absolute risk reduction as number and 95% CI of events prevented every 1000 patients treated for 5 years. Modified from Thomopoulos *et al*. [3], by courtesy of *Journal of Hypertension*.

	Comparison	Trial comparisons (n)	Difference SBP/DBP (mmHg)	HF Events (n/patients) 1st Drug	HF Events (n/patients) Control	RR (95% CI)
A.	D vs PL	4	-15.1/-5.9	44/ 4476	84/ 4421	0.53 (0.37-0.75)*
	BB vs PL	2	-14.8/-8.7	31/ 777	60/ 855	0.57 (0.35-0.91)
	CA vs PL	4	-6.7/-3.9	161/ 8139	220/ 7933	0.73 (0.59-0.89)
	ACEI vs PL	5	-4.1/-1.8	530/10784	670/10812	0.79 (0.71-0.88)*
	ARB vs PL	2	-4.2/-2.0	223/ 3705	256/ 3734	0.86 (0.59-1.26)
B.	D vs All Others	10	-0.92/0.14	1067/29197	1527/33116	0.84 (0.73-0.98)
	BB vs All Others	5	1.91/0.99	334/15653	310/16848	1.05 (0.91-1.22)†
	CA vs All Others	13	-0.25/-0.87	1190/45887	1940/61353	1.16 (1.01-1.32)
	ACEI vs All Others	7	1.36/0.62	1060/22569	2072/37733	0.93 (0.80-1.11)†
	ARB vs All Others	6	-0.54/-0.07	583/16680	559/17768	1.05 (0.94-1.18)
	RASB vs All Others	11	1.05/0.57	895/23131	1883/38383	0.97 (0.84-1.13)

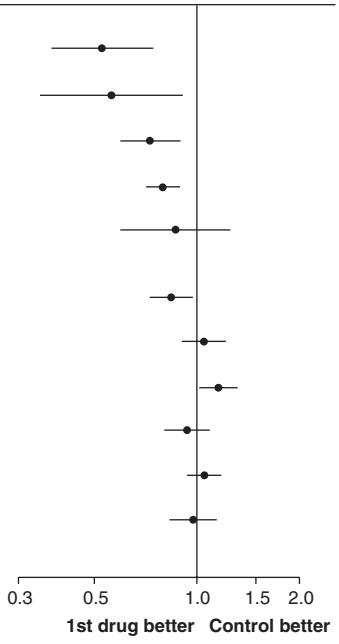

Fig. 3: Effects of blood pressure lowering by each of five major classes of drugs compared with placebo (*A*) and with different classes of drugs (head-to-head comparisons) (*B*) on new-onset heart failure (trials with no baseline heart failure). Columns from left to right are numbers (*n*) of comparisons, the difference in systolic and diastolic blood pressure (SBP/DBP) achieved between treatment groups (negative numbers indicate lower BP with the first drug and positive numbers lower BP with the control), the number of heart failure (HF) events observed and the number of patients followed up, the risk ratio (RR) with 95% confidence intervals (CI) calculated with the observed SBP/DBP difference, and the risk ratio represented as forest plot. *ACEI* angiotensin-converting enzyme inhibitors; *ARB* angiotensin receptor blockers, *BB* beta-blockers, *CA* calcium antagonists, *D* diuretics, *PL* placebo, *RASB* renin-angiotensin system blockers, vs. versus. The *asterisks* indicate RR calculated with the fixed effect model and the crosses RR values adjusted for the SBP/DBP difference. Modified from Thomopoulos *et al*. [3], by courtesy of *Journal of Hypertension*.

Table 2: Trials comparing head-to-head different classes of BP-lowering drugs[a].

Diuretics vs. all	BBs vs. all	CAs vs. all	ACEIs vs. all	ARBs vs. all
ACCOMPLISH [33]	ASCOT-BPA [42]	CAMELOT [6]	CAMELOT [6]	CASE-J [45]
ALLHAT [34]	COPE [36]	ACCOMPLISH [33]	ALLHAT [34]	COPE [36]
ANBP-2 [35]	LIFE [43]	ALLHAT [34]	ANBP-2 [35]	E-COST-R [55]
COPE [36]	UKPDS 39 [44]	ASCOT-BPA [42]	JMIC-B [47]	LIFE [43]
INSIGHT [37]	(HAPPHY) [41]	CASE-J [45]	ONTARGET [53]	ONTARGET [53]
MIDAS [38]		CONVINCE [46]	UKPDS 39 [44]	(IDNT) [28]
NICS-EH [39]		INSIGHT [37]	(ABCD-H) [49]	(MOSES) [50]
VHAS [40]		JMIC-B [47]	(CAPPP) [54]	(NAGOYA) [51]
(HAPPHY) [41]		MIDAS [38]		(VALUE) [52]
		NICS-EH [39]		
		NORDIL [48]		
		VHAS [40]		
		(ABCD-H) [49]		
		(IDNT) [28]		
		(MOSES) [50]		
		(NAGOYA) [51]		
		(VALUE) [52]		

ACEIs angiotensin-converting enzyme inhibitor, *ARBs* angiotensin receptor blockers, *BBs* beta-blockers, *CAs* calcium antagonists, *HF* heart failure
[a]Trials excluding baseline HF and, between parentheses, trials allowing mild baseline HF

drug classes on cardiovascular outcomes, we had previously identified 50 RCTs with 58 two-drug comparisons, but of these trials, only 34 with 40 comparisons measured heart failure in addition to other outcomes. Among these head-to-head comparison trials, 18 RCTs had excluded baseline heart failure from recruitment, and seven had only allowed mild heart failure [6, 28, 33–55]. These trials allowed studying the relative effectiveness of the various drug classes in the prevention of "new-onset" heart failure (Table 2). Figure 3B shows that, even when only RCTs explicitly excluding baseline heart failure were considered, calcium antagonists were found to be significantly inferior to all other drugs in preventing "new-onset" heart failure. No significant differences were found in all other comparisons, except for some superiority of diuretics vs. all other drugs together. Separate secondary meta-analyses including also RCTs allowing inclusion of mild heart failure gave results overlapping with those of the primary analyses shown in Fig. 3B.

Does the Apparent Inferiority of Calcium Antagonists in Preventing New Onset of Heart Failure Depend on their Pharmacological Properties or on the Design of the Trials?

An additional important question is whether the reported statistically significant inferiority of calcium antagonists in HF risk prevention [8] really depends on pharmacological properties of this drug class or rather results from the design of many trials forbidding the concomitant use of drugs known to be active in HF treatment in the calcium antagonist group but not in the other one. Of the 13 comparisons of calcium antagonists with other classes of BP-lowering drugs in 12 RCTs excluding preexisting heart failure at baseline, four were in RCTs whose design allowed the concomitant use of diuretics, beta-blockers, or renin-angiotensin system blockers in the calcium antagonist group:

- In ACCOMPLISH [33], patients were randomized either to the association of benazepril-amlodipine or benazepril-hydrochlorothiazide; therefore, both treatment groups equally received the ACE inhibitor benazepril.
- In the ASCOT-BPA trial [43], patients randomized to the calcium antagonist amlodipine could receive as second drug the ACE inhibitor perindopril (mean 58.5% throughout the time), and in the control group, patients initially randomized to the beta-blocker atenolol could receive as second drug a thiazide diuretic (mean 65.7% throughout the trial).
- In CAMELOT [6], background therapy with a diuretic was given to 32% of patients randomized to amlodipine and to 27% of those randomized to enalapril, and a beta-blocker was given to 74% and 75% of the patients randomized, respectively, to the calcium antagonist and the ACE inhibitor.
- In CASE-J [45], patients randomized to amlodipine and those to the angiotensin receptor blocker candesartan could additionally receive a diuretic (14% in the amlodipine group and 25% in the candesartan group) and a beta-blocker (17% and 22%, respectively).

On the other hand, in eight RCTs (nine comparisons), the trial design prevented the use of all or part of drugs active in the treatment of heart failure:

- In ALLHAT [34], patients receiving a calcium antagonist could not receive diuretics and renin-angiotensin system blockers (but only beta-blockers, reserpine, or clonidine) as second drugs.
- In INSIGHT [37], all patients in the control group received a diuretic, which could not be administered in the calcium antagonist group, whereas only a minority of patients in both the groups concomitantly received either a betablocker or an ACE inhibitor.
- In JMIC-B [47], control patients received an ACE inhibitor, which could not be prescribed in the calcium antagonist group, with less than 25% of patients in either group concomitantly receiving a beta-blocker.
- In MIDAS [38], administration of a diuretic was reserved to the control group and prohibited to the calcium antagonist group, with 25–28% of patients in either group concomitantly receiving the ACE inhibitor enalapril.
- In NICS-EH [39], a thiazide diuretic was given to all patients in the control group and prohibited in the patients randomized to the calcium antagonist nicardipine.
- In CONVINCE [46], diuretics were used in only 26% of the verapamil patients and in 44% of control patients, and beta-blockers could not be prescribed to verapamil patients, but they were prescribed to 43% of patients in the control group.
- In NORDIL [48], diuretics were used in 17% of the diltiazem patients and in 43% of the control patients and beta-blockers in 13% and 66% of the diltiazem and control patients, respectively.
- In VHAS [40], diuretics were used only in the control arm and were forbidden in the verapamil arm, with only one patient out of the four receiving an ACE inhibitor in both arms.

Separate meta-analyses of the two sets of RCTs are summarized in Fig. 4. In those RCTs in which some of the drug classes effective in heart failure treatment could be administered in both the calcium antagonist and the control group, no significant difference occurred in the risk of "new-onset" heart failure between the two treatment groups (RR 0.96 [0.81–1.12]) (Fig. 4B), whereas a higher heart failure risk occurred in those RCTs, the design of which prevented addition of drugs effective in heart failure treatment to the patients randomized to calcium antagonists (RR 1.27 [1.14–1.42]) (Fig. 4A). The difference between the RRs of the two groups is statistically significant ($p = 0.002$).

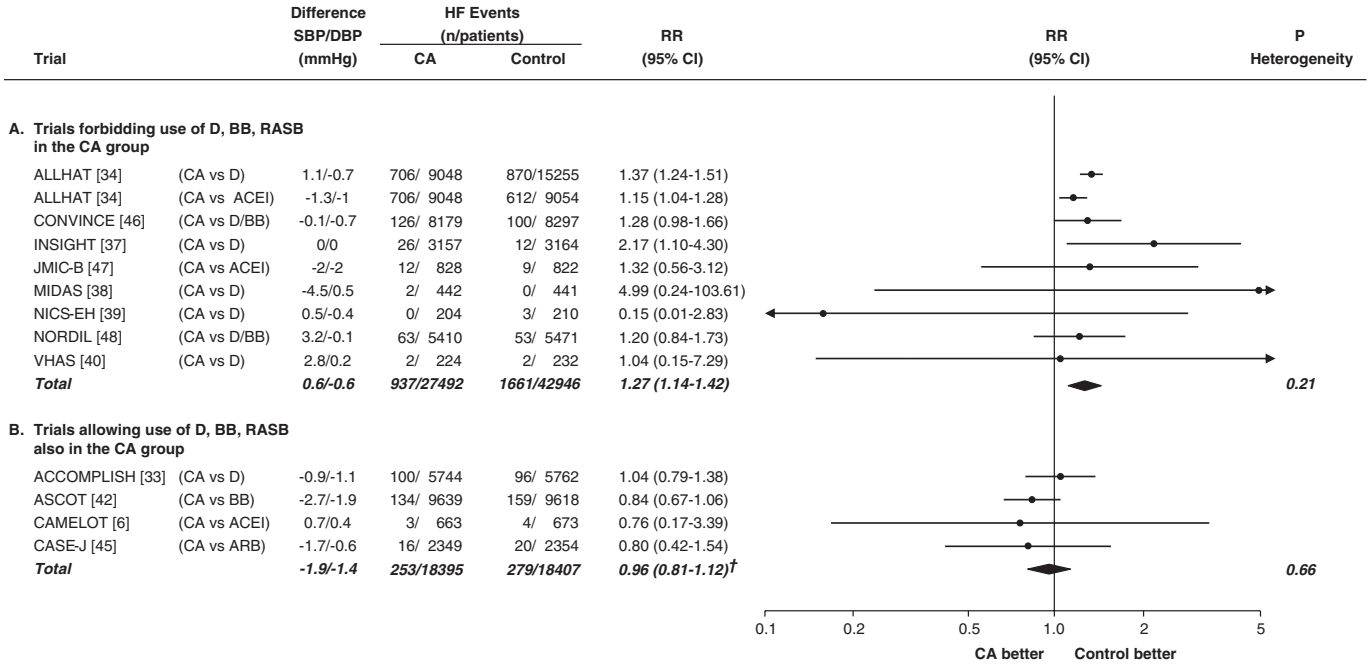

Fig. 4: Separate meta-analyses of trials comparing calcium antagonists with other blood pressure-lowering drugs according to trial design: (*A*) forbidding concomitant use of diuretics, beta-blockers, and renin-angiotensin system blockers in the calcium antagonist treatment group and (*B*) allowing concomitant use of diuretics, beta-blockers, and renin-angiotensin system blockers also in the calcium antagonist treatment group. Trials with no baseline heart failure. Each row reports data from single trials (indicated by acronym and drug comparison). Columns from left to right: between group systolic/diastolic blood pressure (SBP/DBP) differences, number (*n*) of heart failure (HF) events and number of patients in each treatment group, risk ratio (RR) with 95% confidence intervals (CI), RR forest plots, and *P*-value for heterogeneity for the two meta-analyses. *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BB* beta-blockers, *CA* calcium antagonists, *D* diuretics, *PL* placebo, vs. versus. *P*-value for differences between RR in meta-analysis A and RR in meta-analysis B is 0.002. The symbol † indicates RR value adjusted for the SBP/DBP difference. From Thomopoulos *et al*. [3], by courtesy of *Journal of Hypertension*.

Conclusions

1. Heart failure is with stroke one of the two cardiovascular outcomes that are reduced by BP-lowering treatment to the greatest extent, without a clear preference for either outcome.
2. Meta-analysis of only those RCTs that specifically excluded baseline heart failure allows the conclusion that heart failure risk reduction mostly consists of prevention of the clinical manifestations of "new-onset" heart failure, at least as clinically diagnosed by hospital physicians.
3. Blood pressure lowering by any of the five major classes of BP-lowering drugs (diuretics, beta-blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor blockers) can significantly reduce the risk of "new-onset" heart failure. This means that, when the possibility of recurrence or worsening of preexisting heart failure is avoided, the preventing effect of BP lowering by calcium antagonists on heart failure also achieves statistical significance.
4. When RCTs head-to-head comparing different classes of agents have been used in order to appropriately explore whether all antihypertensive drug classes are equally effective in preventing new heart failure, calcium antagonists have been found significantly less effective than the other drug classes in the prevention of new-onset heart failure.
5. However, we have found that inferiority of calcium antagonists in heart failure prevention occurs only in those RCTs whose design forbade or limited the use of diuretics, beta-blockers, or renin-angiotensin system blockers as accompanying drugs in the calcium antagonist arm but not in the control arm. On the other hand, the calcium antagonist inferiority did not occur in the RCTs allowing the use of the above-mentioned drugs also in the calcium antagonist arm. These findings support the hypothesis that the inferiority of calcium antagonists as far as new heart failure is concerned may depend, at least to a large extent, on an unequal use of accompanying drugs in such a way that the larger use of drugs known to reduce heart failure symptoms (diuretics, beta-blockers, and renin-angiotensin system blockers) in the control arms may mask onset of heart failure symptoms to a greater extent in control patients and create an imbalance against calcium antagonists. This interpretation supports the concept that, as for most outcomes, also the preventive effect of BP lowering on new heart failure basically depends on the lowering of BP independently of the drugs by which BP is reduced and suggests the clinical value of the association of calcium antagonists with any of the agents known to alleviate heart failure symptoms.

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Critical Care Management of the ACHD Patient with Heart Failure

Leigh Christopher Reardon, Eugene Depasquale, Weiyi Tan

Introduction

The progression of surgical techniques and improvement of diagnosis and medical management of patients with congenital heart defects has altered the natural history of many previously fatal cardiac conditions. As a result, more and more patients with CHD are living into adulthood, and studies suggest that there are now more adults living with CHD (ACHD) than there are children with CHD [1, 2]. Between 2000 and 2010, the proportion of adults to children with CHD changed from 49% to 66%, and when extrapolated to the U.S. population, there are approximately 1.5 million adults with CHD [1].

Adults with CHD are at an increased risk of late complications, including heart failure, arrhythmias, and sudden death. Despite advances in the field, death rates in the ACHD population can be two to seven times higher than for the general population [3]. There are over 13,500 admissions for heart failure annually according to one study out of the 24,800 admissions for ACHD every year [4]. With the annual increase of number of adults with congenital heart disease, this problem will only become greater in the future.

The 2008 ACC/AHA (American College of Cardiology/American Heart Association) guidelines for adults with CHD and the 2010 ESC (European Society of Cardiology) guidelines for the management of grown-up congenital heart disease provide some guidance about the management of heart failure in the adult population [5, 6]. Some of the guidelines highlighted in the ACC/AHA 2009 update about the management of adult patients with heart failure can be extrapolated to adults with congenital heart disease, but many of the recommendations are based on studies that excluded these types of patients, and thus, applying these recommendations to patients with CHD is fraught with assumptions [7]. We focus on synthesizing and summarizing the evidence available to date in order to describe the critical care management of adult patients with CHD who present to the hospital with heart failure.

Types of Heart Failure

There are many definitions of heart failure, but we define it similarly to how the American Heart Association (AHA) and the Heart Failure Society of America guidelines define heart failure (HF): "In physiologic terms, HF is a syndrome characterized by either or both pulmonary and systemic venous congestion and/or inadequate peripheral oxygen delivery, at rest or during stress, caused by cardiac dysfunction." [8]. Adult patients with CHD can present with varied symptoms of heart failure, ranging from classic symptoms of fatigue, dyspnea, and exercise intolerance, but may also have more subtle findings like malnutrition, cachexia, or growth failure [8]. Many patients fail to even report symptoms despite objective evidence of exercise intolerance [9]. When applying the ACC/AHA guidelines on staging heart failure, most adults with CHD fall into at least stage B (structural heart disease but without signs of HF), but we focus on patients admitted to the hospital with at least stage C or stage D heart failure (structural heart disease with prior or current symptoms of HF and refractory HF requiring specialized interventions, respectively) [8].

Types of ACHD Patients

When an adult patient with CHD is admitted to the hospital, understanding their underlying anatomy and history of prior interventions and/or surgeries is paramount, as patients can be surgically repaired, palliated, or unrepaired. Surgical procedures

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early in life for a patient with CHD are generally life prolonging, and thus, survival for patients with CHD has increased. Many of these procedures, however, are not curative, and consequently the adult patient with CHD will often times have residua of their initial congenital cardiac diagnosis and sequelae of their prior interventions. These patients may commonly face a lifetime of repeated interventions and long-term effects of structural abnormalities that will eventually lead to heart failure [10]. There are aspects of HF management that are universally applicable to adults with and without CHD, but many patients will have unique anatomic and physiological constraints that will make management individualized. It is useful to think of patients with CHD as those with a systemic left ventricle, those with a systemic right ventricle, or those with a single ventricle physiology (either left or right ventricular morphology). Furthermore, it is useful to understand that depending on the surgical technique available at the time of their birth and at the particular center performing the palliation, patients will have varying historical surgical repairs. For example, a patient with a Fontan palliation may have a classic atriopulmonary connection, an intracardiac lateral tunnel conduit, or an extracardiac cavopulmonary connection. To summarize, adults with congenital heart disease should be treated in accordance with their specific anatomy and not uniformly like typical adults with congestive heart failure.

Epidemiology

As stated earlier, there are more adults with congenital heart disease than there are children with the condition [1]. The number of hospital admissions is increasing, and one study demonstrated an increase of 102% from 1998 to 2005 [4]. Twenty percent of hospital admissions for patients with ACHD are for heart failure [3]. One recent study noted that patients with pulmonary arterial hypertension, a history of HF, and atrial arrhythmias are at the highest risk for HF admissions [11]. Heart failure is the leading cause of death for patients with ACHD [12]. While the prevalence of heart failure in adults with CHD is unknown, some reports suggest that nearly 50% of patients after a Fontan procedure will develop HF [8, 13] (Fig. 1).

With advances in surgery and medical therapy, children with congenital heart disease are living longer. One study showed that median age at death increased by 15 years from 1987 to 2005 [14]. Another study shows that for patients with CHD, the cause of late death after pediatric cardiac surgery was heart failure in 43% of cases in their study cohort [15]. The cost of these hospitalizations has been estimated to be $3.16 billion per year [4]. Per the 2008 guidelines for adults with congenital heart disease, certain patients may be at higher risk for developing heart failure, including those with left-sided valvular defects, unoperated atrial septal defect (ASD), congenitally corrected transposition of the great arteries (ccTGA), D-transposition of the great arteries (dTGA) after a Mustard or Senning procedure, single ventricle physiology, tetralogy of Fallot (TOF) with early-era surgery or long-standing shunt, and Fontan surgery [5]. Compared to those with a systemic left ventricle and biventricular physiology, patients with a systemic RV or single right ventricles are at high risk of heart failure and associated mortality [13].

Etiology and Pathophysiology

Clinical heart failure in patients with CHD is due to a multitude of factors, some of which may be lesion specific. In traditional patients with acquired HF, the most common cause of heart failure is systemic ventricular dysfunction from ischemia, which is uncommon in ACHD patients [8]. According to the AHA statement on chronic heart failure in ACHD patients, abnormal myocardial architecture, abnormal myocardial perfusion due to cyanotic lesions, neurohormonal activation, myocardial fibrosis and adverse remodeling, surgical complications, and an underlying geometric and anatomic disadvantage from poor ventricular-ventricular dependence and ventriculo-arterial coupling all contribute to clinical HF in this population [8].

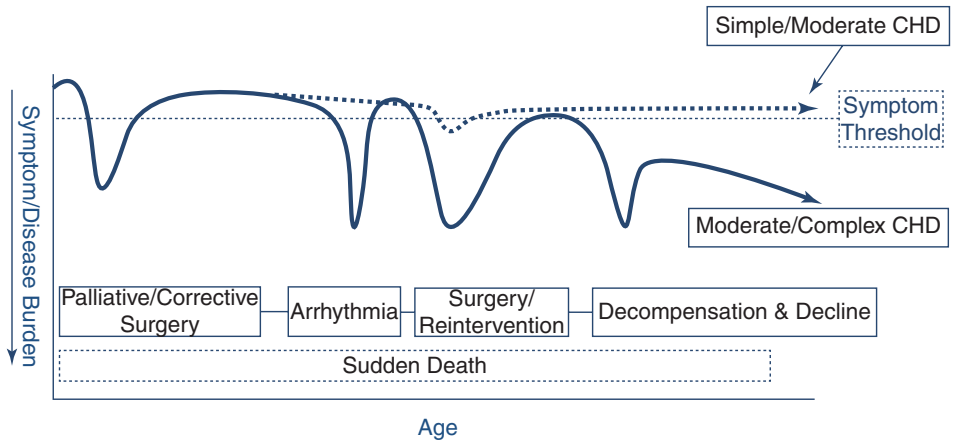


Fig. 1: Cited from [12].

For example, the patient with repaired tetralogy of Fallot may not necessarily suffer from systolic left ventricular dysfunction due to ischemia from blocked coronary arteries. Heart failure may occur due to myocardial damage from shunts, multiple cardiac surgeries, or inadequate myocardial protection from the original surgery. Chronic volume and pressure overload from an insufficient pulmonary valve may contribute to right ventricular dysfunction and signs of right-sided heart failure. Impaired electrical conduction systems from the multiple surgeries and ventricular septal defect patches may prevent efficient ventricular function as well as sudden cardiac death episodes. Finally, some patients may also have anomalous coronary arteries that may lead to ischemia [10]. In patients with atrial level switches for D-transposition of the great arteries, pulmonary venous obstruction can cause heart failure. In a Fontan patient, the single ventricle has to pump against three resistance beds in a series (the systemic vascular bed, the cavopulmonary connection, and the pulmonary vascular bed) [16], which can lead to chronic heart failure. Nevertheless, as adults with CHD get older, they may also be susceptible to traditional risk factors for developing ischemia, such as hypertension, hyperlipidemia, and diabetes [3].

The neurohormonal aspects of heart failure are well documented, but it is unclear what standard therapies are beneficial in adults with congenital heart disease. There is evidence to suggest that patients with adult congenital heart disease do have similar increases in activation of neurohormonal pathways [17]. Studies have confirmed that an elevation in BNP is predictive of mortality and worsening functional status [18, 19].

Pulmonary hypertension is also a risk factor for heart failure. One study out of Canada showed that the prevalence of pulmonary hypertension in patients with congenital heart disease was around 5.8% [20]. This finding increased the risk of mortality and heart failure in these patients, by more than two times and three times, respectively, when compared to a matched cohort of CHD patients without pulmonary hypertension.

In addition to acquired etiologies of heart failure, adults with congenital heart disease may also have complex genetic pathways that contribute to their myocardial dysfunction. Certain genetic syndromes, such as Noonan, DiGeorge, or Williams-Beuren syndromes, all present with cardiomyopathy, and the ACHD population may have a unique interaction between genetic and acquired factors that may make treatment of heart failure more difficult [21]. There are currently few studies highlighting the effect of genetic variation in the ACHD population on adverse ventricular remodeling, but as these studies emerge, the future of "personalized" medicine will become more of a reality [22] (Table 1).

Table 1: Causes of heart failure in patients with congenital heart disease.

Volume overload from left-to-right shunts and valvular regurgitation
Pressure overload from stenotic valves and other obstructive lesions
Intrinsic myocardial dysfunction, genetic syndromes
Pulmonary hypertension caused by congenital heart disease lesions, or from comorbidities like obstructive sleep apnea
Systemic arterial hypertension from coarctation of the aorta, renal disease, or essential hypertension
Coronary artery disease
Cyanosis
Tachycardia induced cardiomyopathy from recurrent atrial arrhythmias

Management

General Principles of Heart Failure Management

Increasing numbers of adults with congenital heart disease will be admitted to the hospital for cardiac procedures, pregnancy, or other non-cardiac conditions. Nevertheless, proper management of ACHD patients with clinical and subclinical heart failure will be a priority in all these settings. If there is a patient with CHD who has critical care needs, they should ideally be in a center that has experience with treatment of ACHD patients [5, 6].

When discussing patients with CHD and CHF, many of the general principles highlighted in the ESC and ACC/AHA guidelines will remain the same. For example, the ESC guidelines espouse a method of parallel assessments when working up a patient with acute heart failure, including assessing for heart failure or other causes of their symptoms, identifying the trigger for the heart failure episode, and managing any life-threatening conditions like hypoxemia or hypotension [23]. Nevertheless, some differences exist; for example, the ubiquitous use of oxygen for hypoxic patients may not be applicable, especially in patients with intracardiac shunts.

In patients with pulmonary hypertension or persistent intracardiac or extracardiac shunts, the balance between pulmonary and systemic vascular resistance must be maintained. Any therapy that increases PVR will reduce cardiac output, and patients with shunts will have increased right-to-left shunting with therapies that decrease systemic vascular resistance [24].

Assessment and management of traditional risk factors should occur. Existing guidelines for tobacco cessation and screening for traditional risk factors should be applied [8]. The prevalence of hypertension, diabetes, and dyslipidemia closely mirrors, if not exceeds, the rates of these risk factors in the general population [25]. Early detection and treatment should be then applied for these traditional cardiovascular risk factors, understanding that certain patients may have variable response to treatment depending on their cardiac anatomy. Patients should be vaccinated with an annual influenza vaccine and the pneumococcal vaccine as well [6].

Medical management of ACHD patients with heart failure should focus on optimizing their preload, afterload, and cardiac contractility. In terms of preload, the use of diuretics is accepted to improve symptoms in a fluid-overloaded patient. The detection of fluid overload may be difficult in certain

patients with CHD; for example, patients with a Fontan or a Glenn procedure will not have an interpretable jugular venous waveform to guide therapy [5]. Afterload reduction agents, such as ACE inhibitors (ACE-I) and angiotensin receptor blockers (ARB), are the cornerstone of heart failure therapy for those with acquired heart disease, but caregivers should extrapolate cautiously from heart failure trials as these studies enrolled very few patients with ACHD [5]. Some of the few studies involving ACHD patients did not show as robust of a clinical benefit when using these traditional agents. For example, the appropriate trial did not show a difference between groups that received ramipril or placebo in terms of right ventricular ejection fraction as measured by cardiac MRI [26]. When discussing contractility, the role of pacemaker therapy and multisite pacing (or cardiac resynchronization therapy) is also being investigated. There is no evidence to support the use of cardiac resynchronization therapy (CRT) in patients with a single ventricle morphology, but the traditional criteria for CRT implantation still apply (two-ventricle morphology and HF symptoms with a QRS duration ≥120 ms with a left bundle-branch block morphology in the setting of sinus rhythm) [5].

Many patients will have comorbidities that may make management of heart failure difficult, such as anemia, renal insufficiency, pulmonary hypertension, and hepatic dysfunction. Renal insufficiency has been associated with worse outcomes in adults with CHD [27]. Patients with single ventricle physiology, such as those with the Fontan circuit, are susceptible to external changes that will affect passive filling of the pulmonary bed. Thus, ascites, positive-pressure ventilation, and decreased diaphragmatic excursion will lead to increased Fontan or right-sided pressures and decreased pulmonary venous return [28]. Pulmonary hypertension (PH) is also a difficult situation to manage, especially in patients with Eisenmenger syndrome. The use of advanced therapies for pulmonary hypertension demonstrate a mortality benefit in these patients [29]. Nonetheless, more studies are needed to investigate the use of PH-targeted therapy in adults with CHD. Hepatic dysfunction and right heart failure are also concerns in ACHD patients. Cardiac cirrhosis, especially in patients with a Fontan circulation, is quite common. Consider the use of bladder pressure monitors to avoid intra-abdominal hypertension from ascites and decreased renal perfusion. The use of inotropes, aggressive diuresis and the use of dialysis, and drainage of ascites may be required for optimization [30].

Specific therapeutic strategies tailored to different forms of CHD will be highlighted in future sections.

Diagnosis and Risk Prediction

Heart failure occurs when the heart cannot meet the metabolic demands of the body. In older patients, classic symptoms may manifest, but younger patients with CHD may maintain blood pressure and urine output due to autoregulation and may underreport symptoms given their lifetime of chronic heart disease [9, 31]. Conversely, for example, in cyanotic patients, dyspnea may occur within the first 30 seconds of initiating exercise due to hypoxemic and acidotic blood arriving at central receptors, and thus, their symptom of dyspnea on exertion is not due to pulmonary congestion from heart failure [5]. When patients with ACHD are admitted to the hospital, there are no specific tools to identify the ones at highest risk for heart failure and morbidity/mortality from their cardiac conditions, and relying on just physical exam findings may be misleading. One study demonstrated that use of the Seattle HF model can be applied to a population of adults with CHD, and those that have a 5-year predicted survival of <70% can be classified as high risk of having a cardiovascular event [32]. A high index of suspicion should be maintained when treating patients with high risk for late heart failure, such as those with bicuspid valves, subvalvular or supravalvular pathology, severe aortic stenosis and/or regurgitation, unoperated ASD or partial AVSD, ccTGA, atrial-level switch with dTGA, tetralogy of Fallot with early-era surgery, a long-standing shunt, pulmonary regurgitation, pulmonary hypertension, single ventricle physiology, and a history of a Fontan/Glenn operation [5]. On top of their underlying high-risk lesions, patients with ACHD may have sequelae from their disease or reparative surgeries, such as prolonged cyanosis, pressure and volume overload, ventricular scars, residual LVOT or RVOT obstructions or shunts, arrhythmias, and obesity, that could contribute to the development of heart failure. Finally, unrelated conditions may also cause an "imbalance" between the heart's ability to provide for the metabolic demands of the body and manifest as heart failure, such as pregnancy, endocarditis, illicit drug use, hyperthyroidism, or obstructive sleep apnea [5].

Laboratory Analysis and Studies

At the onset of worsening symptoms, the ACHD patient and suspected HF should undergo right-sided and left-sided anatomic and hemodynamic evaluation with a variety of studies best suited for their condition. In addition to basic laboratory studies (chemistry panel, liver function studies, and complete blood count), a measurement of the serum BNP level may also be useful in helping risk-stratify patients [18, 19]. The 2008 ACC/AHA guidelines for management of ACHD and the 2010 guidelines for the management of grown-up congenital heart disease both also recommend an electrocardiogram, chest X-ray, pulse oximetry, and echocardiogram for most patients being evaluated in an acute setting [5, 6]. If patients are stable enough, data from a cardiopulmonary exercise testing may be helpful for quantitative assessment of cardiac function. Advanced imaging, such as cardiac MRI, is playing an increased role in the initial evaluation, especially in patients with systemic right ventricles and single ventricles, and may even be considered the reference standard for RV volume quantification, outflow tract obstruction, pulmonary valve function, and assessment of the great arteries [33, 34]. Cardiac computed tomography is also another option

for an imaging modality if MRI is not feasible or available. More invasive procedures, such as cardiac catheterization, may be necessary for a comprehensive evaluation for an adult patient with CHD in clinical HF [8] (Table 2).

Echocardiogram

Echocardiography remains as a first-line investigative tool. Echocardiography can provide a wealth of information, such as assessment of volume overload, pressure overload, and detailed data about structure and function of the ventricle. Echocardiograms establish segmental anatomy and can provide measures of and follow-up assessments of valves. Echocardiography also provides crucial hemodynamic data through measurement of gradients across obstructions, conduits, and valves, as well as flow calculations. Doppler images allow for identifying arterial and venous vascular anomalies and shunts.

Transthoracic echocardiography is complemented by transesophageal echocardiography (TEE) and other specialized techniques, such as contrast imaging, strain imaging, real-time three-dimensional and four-dimensional imaging, and stress echocardiography with or without Doppler [3]. Of note, certain echocardiographic variables are subject to changes with age, such as diastolic flow parameters (E- and A-wave peak velocities) and pulmonary pressure cutoffs for pulmonary hypertension [3].

Nevertheless, when assessing an adult patient with CHD, advanced training is required to properly acquire and interpret the echocardiographic images, since many of these patients have complicated surgical history and complex anatomy that makes for unorthodox or unconventional image views [6, 35].

Echocardiographic parameters, besides the Simpson method, are required for measuring RV function. Strain imaging is shown to be helpful, in addition to FAC (fractional area change) and tissue Doppler [34]. Non-geometric techniques for assessing ventricular function are also useful in patients with CHD, and include the rate of pressure rise (dP/dt), the Tei (myocardial performance) index, and tissue Doppler imaging, strain imaging, and tricuspid annular plane systolic excursion (TAPSE) [34].

Strain imaging is a new technique that can identify ventricular dysfunction in patients with traditional systemic left ventricles, as well as systemic RVs or single ventricles. The commercial software available for analyzing myocardial strain is designed for the morphologic left ventricle, and thus, may not be as useful for the right ventricle. Furthermore, the strain measurement varies widely depending on the type of machine and software being used, so serial measurements must be performed with the same device and software package [34]. Nevertheless, multiple studies have shown that myocardial strain is predictive of myocardial dysfunction and can have prognostic value in patients with a systemic right ventricle in dTGA after an atrial switch and in patients with repaired tetralogy of Fallot [36, 37].

Contrast echocardiography is useful in opacifying heart chambers in patients with a large body habitus or with difficult acoustic windows. While not approved by the FDA for use in patients with right-to-left or bidirectional shunts, the use of agitated saline is a useful tool in patients with ACHD. These techniques are used to detect residual shunts, baffle leaks, or anatomic anomalies like a persistent left-sided super vena cava [3].

Stress echocardiography can be used to screen for coronary ischemia, assess the physiologic response to severe AV valve regurgitation, and evaluate for subaortic stenosis, aortic coarctation, or aortic valve disease in the presence of low ejection fraction [34].

Transesophageal echocardiography (TEE) is an important adjunctive modality to transthoracic studies. Similar to adults without CHD, it is useful when the patient has poor acoustic transthoracic windows. TEE is effective at assessing the intrathoracic aorta, native and prosthetic valves, ventricular function, atrial-level shunts, baffle function, detecting endocarditis, and other cardiac sources of emboli. TEE is also a useful technique during procedures and surgeries [3]. One methodology of TEE includes the use of a miniature TEE probe to evaluate real-time hemodynamic data, including LV function, in critically ill patients [38]. Another study also found that a TEE-derived cardiac

Table 2: Imaging modalities used for diagnosis and management of adult congenital heart disease.

Modality	Widely available	Scan time	Advanced equipment required	Cost	Radiation (in millisieverts)	Contrast	Comments
Echocardiography	Yes	Slow	No	$$	None	None	Workhorse imaging modality, requires expert readers dedicated to ACHD
Non-contrast CT	Yes	Fast	No	$	3–7	None	Limited to calcification assessments
ECG-gated cardiac CT/CTA	No	Fast	Yes	$$$	8–12	Yes	Excellent spatial resolution. Preferred method for evaluating coronary artery patency and anatomy
MRI/MRA	No	Slow	Yes	$$$	None	Yes for late gadolinium enhancement	Good for tissue characterization and anatomy. Can also evaluate real-time cardiac function and be used for flow quantification

output calculation correlated well with a thermodilution method in critically ill ICU patients, and thus, TEE has been demonstrated to be useful in patients who may be too unstable for transport to receive other imaging modalities or invasive procedures [39].

Cardiac Magnetic Resonance Imaging (CMR)

Cardiac magnetic resonance is useful as an alternative to echocardiography, as a second method when echocardiography is not adequate, or as a superior imaging modality to echocardiography in certain situations, such as quantifying RV volumes, tissue characterization, and evaluation of the great vessels [6, 40]. This imaging modality enables excellent three-dimensional anatomical reconstruction that is not restricted by body size or acoustic windows, unless the patient has a pacemaker or dense calcification. CMR has limitless angles of acquisition [3]. It is the reference standard for assessing the right ventricle for structure and function [34]. CMR allows for detailed pre-procedural planning, such as prior to a percutaneous valve replacement, an electrophysiology study and ablation, or a surgery with redo sternotomy in the setting of complex conotruncal anatomy or anomalous coronary arteries [3]. The ability for CMR to provide tissue characterization, specifically identifying patients with scar and fibrosis (through late gadolinium enhancement), can have important prognostic value, as there have been studies highlighting associations between scar and arrhythmias, ventricular dysfunction, and poor clinical outcomes in patients with CHD [34]. Another promising CMR technique is fibrosis imaging using extracellular volume (ECV) fraction via T1 mapping, which has been associated with surrogate markers of myocardial dysfunction, including higher BNP and longer QRS duration [34]. Patients with implanted pacemakers or defibrillators may not be able to be imaged with CMR, and thus, cardiac CT is a possible alternative. Furthermore, the relatively long acquisition times and requirement for repeated breath holds in a setting that promotes claustrophobia may make it a prohibitive study for some ACHD patients [3].

Cardiac magnetic resonance also allows for accurate calculations of shunt fractions and regurgitation volumes using two-dimensional phase contrast imaging. In fact, CMR is considered the reference standard for assessing the severity of pulmonary regurgitation [34]. Four-dimensional magnetic resonance velocity mapping (4D flow) also encodes blood flow in a 3D volume set over time, which may provide future insight into the ventriculo-arterial coupling relationship in complex CHD patients, such as in the Fontan circuit [34].

Cardiac Computed Tomography (CT)

Computed tomography has excellent spatial resolution and has a much more rapid acquisition time than CMR, which makes it attractive in acute settings, but lacks the ability of CMR for tissue characterization. Furthermore, CT imaging systems are more widely available, and thus, it is a more practical imaging option as well. CT delineates epicardial coronary arteries and collateral arteries with accurate detail. CT is also useful in ruling out complications like intracardiac thrombus, baffle obstruction, and prosthetic valve dysfunction [34]. Ionizing radiation is required for CT, which is a drawback for using this modality for serial studies [6].

Computed tomography angiography is useful for pre-procedure planning prior to a percutaneous catheter-based intervention or a redo sternotomy when assessing for the structural relationship of the great vessels, coronary arteries, and sternum. Inexperienced interpreters, however, may misdiagnose abnormalities in pulmonary vascular blood flow in the setting of known shunt lesions or palliative circulations, such as making an incorrect diagnosis of pulmonary embolism in a patient with a Fontan surgery [3].

Exercise Testing with CPET

Cardiopulmonary testing is valuable in predicting morbidity and mortality. The entire cohort of ACHD patients has reduced exercise tolerance when compared to an age-matched control, and even asymptomatic patients have reduced VO_2 consumption [9]. CPET, especially peak VO_2 and heart rate reserve, may provide prognostic information in ACHD [41], but this study modality may be too strenuous for patients who are critically ill in heart failure.

Procedures

Invasive Hemodynamic Monitoring

The ESCAPE trial did not show much benefit in using Swan-Ganz catheters routinely [42]. Furthermore, many adults with CHD will have limited vascular access, and using a Swan-Ganz catheter in patients with intracardiac shunts and Fontan physiology may not give accurate information that can be used for clinical decision-making.

Arterial Line

If placing an arterial line, caregivers need to make sure it is in an artery that has adequate blood flow; patients with previous BT shunts may not have a reliable waveform, and achieving access may be impossible.

Peripheral IV with Bubble Filters

If a patient with ACHD has a right-to-left shunt, there is always a risk of paradoxical air or thromboembolism traveling to the brain.

Thus, all intravenous lines, including peripheral IVs, should have 23 micron bubble filters attached [24].

Implantable Hemodynamic Monitors

Newer technologies, including the use of implantable hemodynamic monitors, such as the CardioMEMS™ device, have demonstrated that they can reduce the incidence of heart failure hospitalizations [43]. While it has not been approved for use in the ACHD population, one study did show that implantation of this device was possible in a patient with a Fontan procedure, and thus, the utilization of this device in the ACHD population will most likely be increased in the future [44]. Risk of clot in a low-flow circulation is a reason to use judicious caution in placing such devices in higher-risk patients.

Cardiac Catheterization

With the advent and development of advanced imaging techniques, cardiac catheterization is an invasive procedure that is reserved to resolve specific anatomic or physiological questions or for interventional treatment. For example, cardiac catheterization procedures can assess for pulmonary hypertension, measure pressure gradients, be used for closure of aortopulmonary, arteriovenous, or venovenous collaterals, and shunt calculations. Catheterization procedures in ACHD patients can be more complex due to vascular access issues and abnormal anatomy that limits appropriate entry to desired chambers of the heart. Usually, a team of operators is needed, one with expertise in CHD lesions and evaluation of intracardiac shunts and one with experience in coronary artery angiography and intervention of left-sided heart disease [3].

Therapies

Medications

The role of neurohormonal agents like ACE inhibitors, angiotensin receptor blockers, and beta-blockers for patients with reduced systolic function is not as established for patients with ACHD. Yet, some guidelines state that without specifically tailored evidence, caregivers have to carefully extrapolate evidence and apply them to patients with CHD [8, 45]. These therapies may be helpful in patients with two-ventricle circulations and a dysfunctional systemic LV but may be less helpful with diastolic dysfunction, systemic RV, Eisenmenger syndrome, or single ventricle patients. Standard heart failure therapies may even have worse adverse effects [8]. In one trial, losartan was given to patients with a systemic RV and it did not improve exercise tolerance or reduce BNP levels [46]. Another study did not demonstrate a benefit of beta-blockers in patients with systemic right ventricles [47]. Nevertheless, the medical therapies for each set of congenital lesions will be described here.

Systemic LV

If patients have left-sided pressure overload lesions, they will need intervention for the coarctation or stenosis. For patients with systolic failure of the left ventricle, many guidelines suggest that evidence for traditional medications used for adults with HF can extrapolated to adults with CHD and HF [8, 24]. Thus, beta-blockers, ACE inhibitors or angiotensin receptor blockers, aldosterone inhibitors, and diuretics can all be used in these patients.

Systemic RV

The systemic RV will eventually fail. No data exist about when a systemic RV with impaired ejection fraction should warrant treatment. If the patient is asymptomatic, it is difficult to ascertain when the appropriate time is to initiate treatment. Some studies (using arbitrary measures) state that heart failure occurs in 22% of dTGA with Mustard and 32% of patients with ccTGA [13]. Diagnosis with the use of a BNP and echocardiography is helpful. Cardiac MRI provides detailed RV imaging and can be useful in diagnosing RV dysfunction as well. In patients with a Mustard or Senning procedure, vasodilators may reduce preload and reduce cardiac output due to a concomitant baffle obstruction. Beta-blockers may have some beneficial effects in these patients in terms of AV valve regurgitation and RV remodeling [47], but a lot of these patients have conduction abnormalities that may be exacerbated by the use of an AV nodal blocking agent. Studies investigating the use of neuromodulators of the renin-angiotensin-aldosterone system (RAAS) system did not show a benefit in patients with HF and a systemic RV [46, 48]. Despite inconsistent evidence and lack of data supporting improved clinical outcomes, the use of ACE-I/ARB is common for patients with a systemic RV [8]. If the patient is suffering from symptomatic HF, many physicians will start neurohormonal therapy empirically [49, 50].

Systolic Failure of the Morphologic Sub-pulmonary RV

These patients usually have Ebstein's anomaly of the tricuspid valve or repaired TOF with pulmonary regurgitation. Long-term sequelae of these conditions lead to volume overload, dilation, myocardial dysfunction and clinical HF. RV dysfunction and enlargement can lead to LV dysfunction due to ventricular interdependence. Poor RV output also leads to low LV preload. As both ventricles share myocardial fibers, fibrosis can affect both ventricles and neurohormonal activation will also lead to long-term structural changes in both chambers [8]. The use of beta-blockers and ACE inhibitors in these patients is common,

but evidence does not suggest robust outcomes [26, 51]. There are no randomized controlled trials for medical therapies for this group of patients. Even the traditional guidelines have few recommendations about therapies in this group of adults without CHD. Diuretics are the main treatment option for symptomatic patients. If pulmonary hypertension is thought to be the primary cause of RV failure, then advanced therapy may play a role, although the data for these drugs do not include many ACHD patients [24]. That being said, there have been some studies showing that advanced therapies (mainly bosentan) do have a favorable effect on exercise capacity and hemodynamics in Eisenmenger patients [52].

Systolic Failure of the Single Ventricle

These patients do not have the benefit of a sub-pulmonary pumping chamber and thus, have to rely on passive filling of the pulmonary vasculature. This results in improved oxygenation, but at the sacrifice of elevated CVP. These patients are dependent on respiratory mechanics, the diastolic function of the ventricle, and the pulmonary vascular resistance [8]. Low velocity flow through an atriopulmonary or cavopulmonary connection can increase the risk of thrombosis, which can lead to an increase in the pulmonary vascular resistance. The high CVP in a Fontan circuit can lead to hepatic congestion and dysfunction. Right-to-left shunting through a fenestration in the Fontan can also lead to cyanosis. Thus, CHF findings of cyanosis, hepatic dysfunction, and increased pulmonary vascular resistance may arise in the setting of preserved myocardial function. When managing a Fontan patient in HF, clinicians must search for potentially reversible causes of HF, such as arrhythmias, obstruction of the Fontan pathway, and residual shunting [8]. In Fontan patients, where increased pulmonary vascular resistance can impair ventricular filling, the use of phosphodiesterase inhibitors may improve exercise performance and myocardial performance [29, 53]. The use of spironolactone may also improve endothelial function and reduce the incidence of PLE [54, 55]. One study did not show beneficial effects with RAAS inhibition in Fontan patients, so their use is uncertain in this group [56]. Use of diuretics and digoxin is also popular, but without evidence. Carvedilol has been shown to improve HF signs and symptoms in Fontan patients [57], so reducing pulmonary vascular resistance and afterload may have the best benefits, while diuretics should be used judiciously as it may induce cardiorenal syndrome from reduced preload.

Heart Failure with Preserved Ejection Fraction (HFpEF)

There are no good evidence-based treatments that reduce morbidity or mortality in adults with heart failure with preserved ejection fraction [7, 23]. Diuretics are mainly used for symptomatic relief (Fig. 2).

Of note, there are no studies looking at the newer treatments, including ivabradine [58] and the neprilysin inhibitors [59] in patients with CHD. Nevertheless, the data can be extrapolated to patients with systolic dysfunction and systemic left ventricles. For ACHD patients with systemic RVs or single ventricle physiology, use of these newer treatments cannot be recommended at this time. Iron deficiency anemia is an important comorbidity that should be addressed in patients with CHD and heart failure, especially in those who are chronically hypoxic [60].

Pulmonary HTN and Eisenmenger Physiology

These patients often present with failing right or sub-pulmonic ventricles. Patients with Eisenmenger physiology are recommended to avoid pregnancy, dehydration, severe strenuous exercise, exposure to excessive heat, high altitudes, and iron deficiency. The 2008 ACC/AHA guidelines also encourage prompt treatment of arrhythmia [5]. Treatment with advanced therapies, such as endothelin antagonists, showed improved mortality in retrospective studies [61], and some patients may even need long-term dual vasodilator therapy for improved outcomes [62].

Drips, Inotropes, and Vasopressors

There are no robust studies with the use of inotropes and vasopressors in critically ill patients with CHD in heart failure. Right ventricular failure manifests as an increase in jugular venous pressure and renal and hepatic dysfunction. Management includes inotropic support of the RV with phosphodiesterase inhibitors like milrinone, adrenaline, aggressive management of pulmonary hypertension (inhaled NO, prostacyclins), and systemic blood pressure support [30]. Use of such drugs must be aimed at optimizing blood pressure and cardiac output understanding that ACHD patients are acutely sensitive to changes to SVR and PVR, especially if they have intracardiac shunts.

Percutaneous Interventions

Percutaneous techniques and interventions may be helpful in certain patients. For example, percutaneous replacement of the pulmonary valve for severe PR in repaired TOF patients may lead to improved outcomes [10]. Percutaneous closure of shunts like ASDs and VSDs and coiling of AP (aortopulmonary) collaterals are now commonplace [3] and carry a lower morbidity than with surgical interventions [63]. Percutaneous clips to treat severe mitral regurgitation are becoming more popular [64], and while the use of this new technology has not been studied on a wide scale, there are reports of the use of the MitraClip™ in the tricuspid position [65]. Other technologies, such as the Mitralign™, TriCinch™, and even percutaneous tricuspid valve replacements are being

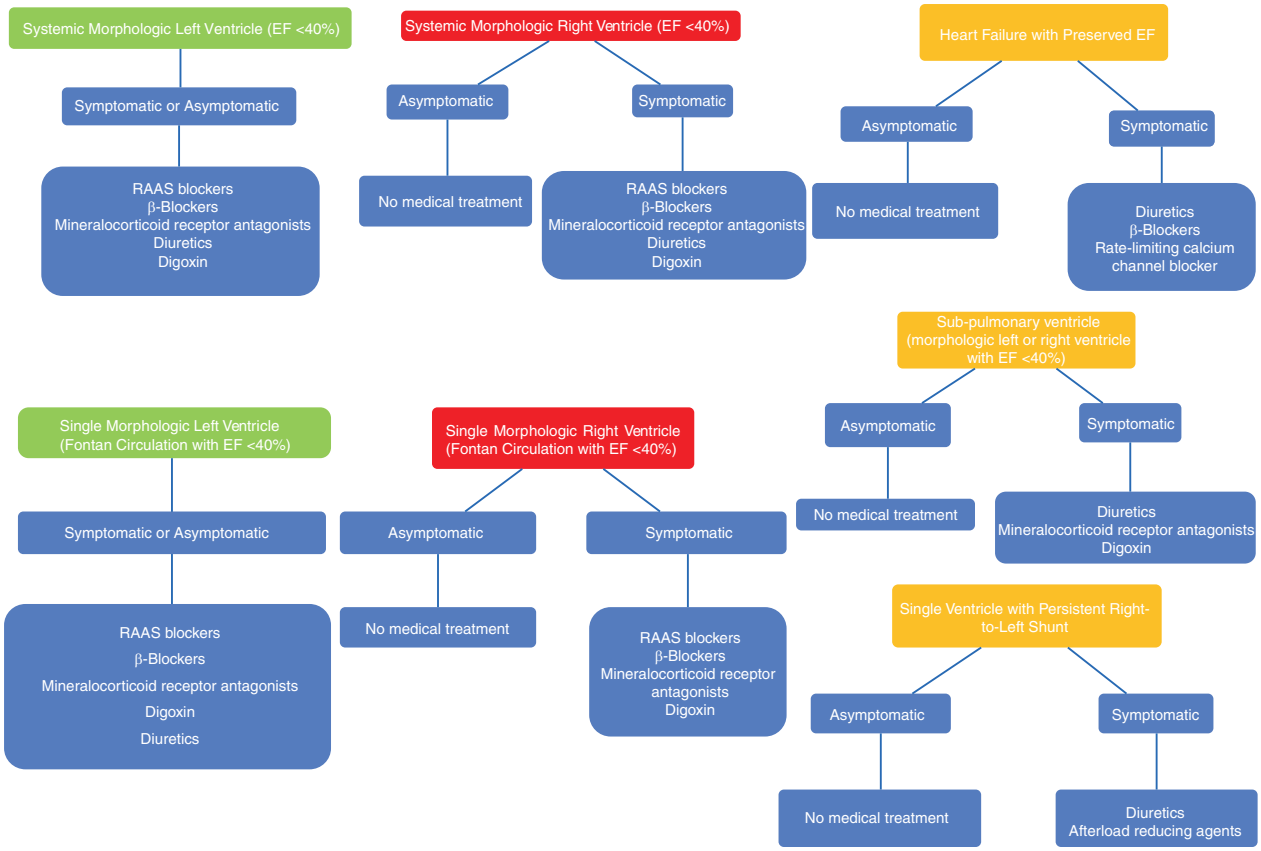


Fig. 2: Medical treatment for heart failure related to intrinsic myocardial dysfunction.

tested and studied currently and will provide a wealth of options for interventional cardiologists aiming to treat severe valvular dysfunction in the future [66]. As adults with CHD often have right-sided valvular dysfunction, or even systemic atrioventricular valve regurgitation, the use of these new technologies has the potential to be very appealing; one study has already proven that percutaneous clipping of a systemic atrioventricular but morphologically tricuspid valve is feasible in patients with ccTGA [67].

Arrhythmias

In principle, patients with CHD are at high risk for arrhythmias, especially patients with prior surgeries and Fontan patients. In patients with repaired TOF, risk factors for death and sustained VT include RVH [68]. EKG is an essential diagnostic tool, and the use of adenosine is also helpful for diagnosing arrhythmias. If the patient is unstable, direct current cardioversion ought to be considered, but it is very important that the staff knows if the patient has levocardia or dextrocardia when placing the pads [45]. Furthermore, patients with CHD are likely to require epicardial wires when implanting permanent devices due to complex anatomy or residual shunts [25].

The Pediatric and Congenital Electrophysiology Society (PACES) and Heart Rhythm Society (HRS) statement on management of arrhythmias in 2014 stated that implantable cardioverter defibrillator (ICD) implantation is indicated for secondary prevention of cardiac arrest due to ventricular fibrillation/ventricular tachycardia (VF/VT) or hemodynamically unstable VT after reversible causes have been excluded [69]. They also recommend ICDs for patients with spontaneous sustained VT who have already undergone a cardiac electrophysiology study and ablation. They also recommend ICDs for patients with a systemic LVEF <35%, biventricular physiology, and NYHA (New York Heart Association) class II–III symptoms. The PACES/HRS guidelines have weaker recommendations for implanting ICDs for primary prevention. For patients with tetralogy of Fallot, appropriate secondary prevention guidelines should be used as the incidence of SCD, VT, or appropriate ICD shock is between 6% and 14% [8]. Use of ICD for primary prevention has yet to be shown to be beneficial.

Cardiac resynchronization therapy (or multisite pacing in patients with a single ventricle) may be useful in patients with ACHD, but this therapy has limited evidence demonstrating its benefit in this population at this time. Small retrospective studies have shown a benefit in a heterogeneous population of

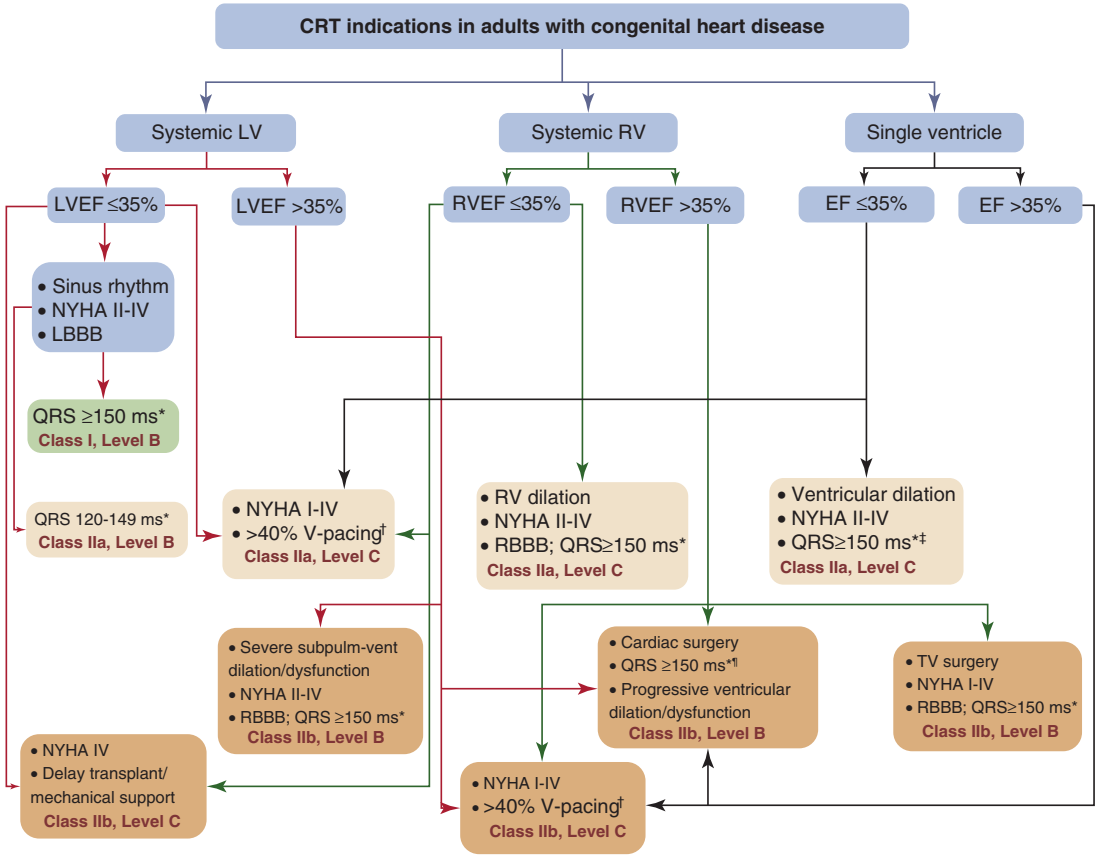
patients with CHD [70–72]. The recent PACES/HRS guidelines for arrhythmia management in patients with CHD [69] adapt the existing North American and European heart failure and device therapy guidelines to the CHD population. In terms of implanting CRT, the only Class I recommendation they have are for the patients with a systemic LV, EF of ≤35%, sinus rhythm, NYHA II–IV, and LBBB with a QRS ≥150 ms. Other patients, including those with systemic RV and single ventricle, have Class IIa and IIb indications depending on their ventricular ejection fraction and the width of their QRS complex [69]. Use of CRT (multisite pacing) may be beneficial in patients with single ventricles, but the evidence is limited [8]. Similarly, there are no good studies for the use of CRT and systemic RV dysfunction and RBBB [8]. Our center has anecdotal success with using CRT in patients with ccTGA; however, patient numbers are small, and further data collection is necessary with this unique population (Fig. 3).

Catheter ablation is an accepted procedure in this population, understanding that experience is limited and that repeat procedures for recurrent arrhythmias are common [73]. Maintenance of sinus rhythm is important in most patients with CHD, and Class III (amiodarone, dofetilide) are the most accepted agents [73]. If the patient is unstable, then synchronized cardioversion is effective, as long as intra-atrial thrombus is excluded.

If the patient has VT, then cardioversion (synchronized for monomorphic VT, defibrillation for polymorphic or VF) is required. The chronic management of VT/VF involves ICD placement with antiarrhythmic medication and catheter ablation [73].

Mechanical Support

The use of mechanical support devices is not common in the current state due to potential barriers, such as pulmonary vascular



LV denotes left ventricle; RV, right ventricle; EF, ejection fraction; NYHA, New York Heart Association functional class; LBBB, left bundle branch block; RBBB, right bundle branch block; V-pacing; ventricular pacing: subpulm-vent, subpulmonary ventricular; TV, tricuspid valve
*spontaneous or paced
†New or replacement device implantation with anticipated requirement for >40% ventricular pacing, intrinsically narrow QRS complex; single site pacing from the systemic ventricular apex/mid-lateral wall may be considered as an alternative
‡RBBB or LBBB
¶Complete bundle branch block ipsilateral to the systemic ventricle

Fig. 3. Cited from [69].

disease, multiple prior sternotomies, and multiorgan dysfunction. One study showed that while VAD usage is increasing for patients on the heart transplant waitlist for patients with acquired heart disease, the rate of VAD use has not increased for patients with ACHD on the transplant waitlist [74]. Nevertheless, these advanced therapies have been described in ACHD patients [25, 75] and in patients with systemic right ventricles [8].

Transplantation

Heart transplantation is not a common outcome for patients with ACHD, but 3% of patients who undergo transplant have CHD. As more and more patients develop end-stage HF with CHD, this will become a more common occurrence. ACHD patients have higher early mortality, but similar long-term survival as those who do not have CHD. ACHD patients have special considerations with regards to transplant. They have sometimes unique and complex anatomy. They are possibly at higher risk due to their previous sternotomies and possible highly sensitized HLA antibodies. They may also have higher incidence of pulmonary hypertension and liver cirrhosis, all of which complicate their pretransplant workup and possibly their organ matching and posttransplant course [76].

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Device Therapy in the Heart Failure

Troy Rhodes and Raul Weiss

9.1 Introduction

In patients with heart failure (HF), the two main causes of death are sudden cardiac death (SCD) and progressive pump failure. In the Framingham Heart Study, HF increased overall and SCD mortality fivefold [1]. In patients with Class II or III HF, the mode of death is more likely be to "sudden" while in patients with Class IV HF, it is more likely to be due to pump failure [2]. The most common cause of SCD is the degeneration of ventricular tachycardia (VT) to ventricular fibrillation (VF), although pulseless electrical activity (PEA) and bradyarrhythmias account for up to one-third of cases [3]. Electrical defibrillation is the only effective approach for terminating VF. Following success with external defibrillation, an implantable defibrillator was developed in the mid-1960s and the first automatic internal defibrillator was implanted in humans in 1980 [4, 5].

Primary prevention of SCD refers to a therapy intended to prevent SCD who have not yet experienced symptomatic sustained VT or VF or sudden cardiac arrest (SCA) but are at increased risk for such events due to their heart failure since SCD may be the first presentation of a ventricular arrhythmia. The role of a primary prevention implantable cardioverter-defibrillator (ICD) depends upon the severity and etiology of the left ventricular (LV) dysfunction and the severity of clinical heart failure. Patients with heart failure who experience sustained ventricular tachycardia or SCA are at high risk for recurrence and will typically have an ICD implanted for secondary prevention of SCD. This chapter will discuss device therapy in HF, clinical trials and guidelines for implantation of ICDs and cardiac resynchronization therapy (CRT), ambulatory device monitoring, and the management of patients with VT and ICD therapies.

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9.2 Implantable Cardioverter Defibrillators (ICDs)

9.2.1 Ischemic Cardiomyopathy

Patients who have had a myocardial infarction (MI) leading to a reduced systolic function are at increased risk of SCD, most commonly due to ventricular tachyarrhythmias, and prophylactic ICD implantation in selected patients with ischemic cardiomyopathy reduces mortality. ICD therapy for primary prevention of SCD in patients with ischemic cardiomyopathy due is recommended for those with LV ejection fraction (LVEF) ≤ 35% with New York Association (NYHA) functional Class II or III and those with LVEF ≤ 30% with NYHA I symptoms. Patients should be at least 40 days post MI and more than 3 months following revascularization and on guideline-directed medical therapy (GDMT) since these interventions may lead to significant improvement in systolic function and heart failure class and potentially eliminate the need for a primary prevention device. The indications for ICD implantation were derived from the inclusion criteria of several major randomized trials enrolling patients with ischemic cardiomyopathy in the first weeks (early) and more than 4–6 weeks following MI (late) [6].

The Multicenter Automatic Defibrillator Implantation Trial (MADIT-I) was the first randomized clinical trial (RCT) to show the role of ICDs in primary prevention of SCD in asymptomatic patients with prior MI, nonsustained VT (NSVT) on ambulatory monitoring, LVEF ≤ 35%, and inducible sustained monomorphic VT (SMVT) during electrophysiology study (EPS) that remained inducible following the administration of procainamide. Patients were randomly assigned to pharmacologic therapy including an antiarrhythmic medication at the discretion of the clinician

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(most commonly amiodarone) or to ICD therapy were followed an average of 27 months. There was a significant reduction in overall mortality, cardiac mortality, and arrhythmic deaths in the ICD group with an average survival of 3.7 years compared to 2.8 years in those receiving medical therapy. Subset analysis showed a survival benefit for ICD for patients with LVEF < 26%, more severe CHF or QRS duration of ≥120 ms. MADIT-I was limited by a small number of patients (<200) and events, a low incidence of subsequent NSVT on ambulatory monitoring, only enrolling patients with inducible VT not suppressed or slowed by procainamide, and higher beta-blocker use in the ICD group. While a landmark study for the use of ICDs in primary prevention of SCD, MADIT-I has been supplanted by subsequent trials [7].

The Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) randomized 1232 patients with prior MI (>30 days and more than 3 months if bypass surgery had been performed) and LVEF ≤ 30% to prophylactic ICD or conventional therapy. MADIT-II addressed some of the limitations of MADIT-I by eliminating the requirement of EP study and the presence of NSVT. After an average follow-up of 20 months, the study was stopped early due to the survival benefit of ICD therapy. Those receiving an ICD had a significantly reduced all-cause mortality of over 5% compared to conventional therapy (14.2% vs 19.8%); the survival benefit was seen in all patient groups and was entirely due to a reduction in sudden cardiac death. There was a nonsignificant trend toward greater benefit in patients with a QRS > 150 ms. An unexpected finding was a higher rate of HF hospitalizations in the ICD group (20% vs 15%), possibly due to a higher incidence of HF progression with the prevention of SCD, myocardial injury as a result of ICD shocks, and the negative impact of unintentional right ventricular pacing [8].

The Coronary Artery Bypass Graft (CABG) Patch trial randomized 900 patients to an epicardial ICD implanted at the time of bypass surgery or medical therapy. Patients had a LVEF <36% with severe CAD requiring surgical revascularization, abnormal signal-averaged ECG, but no history of sustained ventricular tachyarrhythmia or syncope. There was no significant difference in overall or cardiovascular mortality with an average follow-up of 32 months. It is likely that ICD therapy did not improve mortality due to the beneficial effect of coronary revascularization itself in the prevention of sudden cardiac death. It is worth noting the high percentage of epicardial implantation and the high complication rate in ICD Group (approximately 6%) While the impact of percutaneous coronary revascularization was not evaluated, this negative trial is the primary reason why current guidelines do not recommend ICD implantation for patients who have recently undergone coronary revascularization [9].

While not designed as a randomized ICD trial, the Multicenter Unsustained Tachycardia Trial (MUSTT) utilized EPS in the management of high-risk patients enrolling 704 patients with prior MI (4 days to >3 years), LVEF ≤ 40%, asymptomatic NSVT (at least 4 days post MI or post revascularization but within 6 months of enrollment), no history of sustained ventricular tachyarrhythmia or syncope with inducible sustained VT during EPS to standard medical therapy or EPS guided antiarrhythmic therapy, or an ICD (if at least one antiarrhythmic medication was ineffective). After a median follow-up of 39 months, the 2 year (12% vs 18%) and 5 year (25% vs 32%) rates for arrhythmic death or resuscitated SCA were significantly lower for the EPS-guided patients. The reduction in the primary endpoint was largely attributable to ICD therapy and at 5 years, arrhythmic death or resuscitated SCA occurred in 9% of patients with an ICD and 37% of those treated with an antiarrhythmic drug [10]. A subsequent analysis of the MUSST trial in patients with an LVEF 30–40% showed the rate of arrhythmic death at 5 years was significantly increased for those with inducible VT suggesting EP testing may have predictive value in this group [11].

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) randomized 2521 patients with both ischemic (52%) or nonischemic (48%) cardiomyopathy, LVEF ≤ 35% with NYHA Class II or III HF treated with beta-blocker and ACE inhibitor for at least 3 months prior to enrollment to ICD implantation, amiodarone, or placebo with a median follow-up of 46 months. ICD therapy significantly reduced total mortality at 5 years (29% vs 36% with placebo). The benefit of an ICD was comparable for patients with either ischemic or nonischemic cardiomyopathy while amiodarone provided no benefit compared to placebo [12].

9.2.1.1 Early Post-MI Trials

The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) randomized 674 patients with prior MI (6–40 days, mean of 18 days), LVEF ≤ 35%, and reduced heart rate variability or elevated resting heart rate (≥80 bpm) to either prophylactic ICD or standard medical therapy. With a mean follow-up of 30 months, there was no significant difference in annual all-cause mortality. Arrhythmic deaths were more frequent in the medical therapy group while nonarrhythmic deaths were more frequent in the ICD group [13]. This negative trial provides rationale for the current guidelines that ICD implantation is not recommended until at least 40 days following a MI.

The Immediate Risk Stratification Improves Survival (IRIS) trial randomized 898 patients with a MI in the prior 5–31 days and at least one of the following: LVEF ≤ 40% and resting HR ≥ 90 bpm, NSVT ≥ 150 bpm, or both to ICD therapy or standard medical therapy. With an average follow-up of 37 months, there was no difference in all-cause mortality. As seen in DINAMIT, SCD was higher in the medical therapy group while nonarrhythmic deaths were more frequent in the ICD group [14].

The lack of benefit in the early post-MI trials were likely due to: recovery of LV function, SCD in the early post-MI period due to recurrent ischemia or mechanical complications that an ICD would not effectively treat, and additional risk of ICD implantation immediately following MI [15]. Higher resting HR and reduced HR variability may identify a group of patients with higher mortality from non-arrhythmic causes [16].

9.2.2 Nonischemic Cardiomyopathy

Patients with nonischemic cardiomyopathy are at increased risk for sudden cardiac death from ventricular arrhythmias. While smaller trails suggested no benefit of ICD therapy to these patients, larger trials and meta-analyses have demonstrated mortality benefit from prophylactic ICD implantation. Current guidelines recommend ICD implantation for patients with nonischemic cardiomyopathy with LVEF ≤ 35%, NYHA Class II-III, treated with a beta-blocker and ACE inhibitor for at least 3 months prior to implantation.

The Cardiomyopathy Trial (CAT) enrolled 104 patients with ≤9 months of nonischemic dilated CM with LVEF ≤ 30% to ICD implantation versus medical therapy. The Amiodarone Versus Implantable Cardioverter-Defibrillator trial (AMIOVIRT) randomized 103 patients with nonischemic dilated CM with LVEF ≤ 35%, Class I to III CHF, and asymptomatic NSVT to ICD vs amiodarone therapy. Both showed no significant benefit to ICD therapy for all-cause mortality but both were limited by small patient numbers and unexpectedly low mortality rate; also there was no placebo control group in AMIOVIRT [16, 17].

The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) randomized 458 patients with NICM, LVEF ≤ 35%, NSVT or premature ventricular contractions (PVCs) to ICD or medical therapy. There was a trend towards a reduction in all-cause mortality with an ICD (7.9% vs 14.1% with medical therapy) with a significant reduction in patients with NYHA Class III CHF. While fewer sudden deaths occurred in the ICD group (3 deaths vs 14 deaths in the medication group), the mortality rate in the medical arm was lower than anticipated during study design leading to the trial being underpowered for its primary endpoint [18].

As discussed earlier, SCD-HeFT randomized patients with both ischemic and non-ischemic CM to ICD therapies, amiodarone, or placebo and a significant reduction in overall mortality was seen with ICD therapy with comparable benefit in ischemic and nonischemic patients [12]. ICD therapy was also associated with a short term improvement in psychological wellbeing [19]. There was no survival benefit with amiodarone over placebo [12].

9.2.3 ICD Therapy Is NOT Recommended

ICD therapy is not indicated: ventricular arrhythmias are due to completely reversible conditions (metabolic abnormalities, drugs, trauma) in the absence of structural heart disease; life expectancy less than 1 year; incessant VT or VF; significant psychiatric illness that could be aggravated by ICD therapies or limit follow-up; NYHA Class IV HF refractory to GDMT who are not candidates for transplantation, LVAD, or CRT; syncope without inducible VT or structural heart disease; and patients with structurally normal heart amenable to ablation [6].

9.2.4 ICD System

The transvenous ICD system includes pace-sense and defibrillation electrodes on a single ventricular lead and a pulse generator. Pacing and sensing functions require a pair of electrodes (bipolar): a distal electrode at the tip of the lead and a second ring electrode several millimeters back from the tip. Bipolar leads provide high amplitude, narrow electrograms for more accurate sensing and reduce the risk of sensing extracardiac signals, which could lead to inappropriate device function. With the vast majority of new ICD implantations, the ICD lead is placed transvenously via the cephalic, axillary, or subclavian vein with the distal electrode at the right ventricular apical endocardium.

The defibrillation electrode is a "coil" of wire along the distal lead body that provides a relatively large surface area to maximize the density of current flow through the ventricular myocardium. In addition to the distal shock coil in RV, some leads have a second proximal coil (SVC coil) to reduce the amount of energy for defibrillation. The metal housing of the pulse generator can also serve as a shock electrode but requires pectoral location. The ICD system should achieve a minimum energy for successful defibrillation (defibrillation threshold) that is at least 10 J less than the maximum output of the device. The pulse generator contains the high voltage capacitors, battery, and sensing circuitry and will typically last 8–10 years or more.

In rare cases (due to prior infection, lack of venous access, high defibrillation energy requirements, or concurrent cardiac surgery), electrodes and defibrillation patches can be placed on the epicardium. In patients with normal sinus and AV nodal function (who do not have a pacemaker indication), a single chamber ICD is implanted. Some devices utilize an ICD lead with electrodes incorporated on the lead for atrial sensing for detection of atrial arrhythmias. A dual chamber ICD has an additional right atrial lead for atrial sensing and pacing in patients where bradycardia support is indicated. A subcutaneous ICD (S-ICD) has a lead that is placed subcutaneously (no lead within the vasculature or the heart) for defibrillation only.

The device categorizes any detected heart rate above programmed cut-offs as a ventricular arrhythmia. Current ICDs offer multiple programming and therapeutic options including multiple detection zones, arrhythmia discrimination (ventricular vs supraventricular), and multiple therapies (antitachycardia pacing, cardioversion, and defibrillation). The ICD can be programmed to provide different therapies (also known as tiered therapy) in up to 3 different heart rate zones so that therapies can be tailored in each zone. Slower VTs may not lead to loss of consciousness and may be terminated with antitachycardia pacing (ATP) while faster VTs are more likely to be poorly tolerated, unstable, and may become more difficult to treat if definitive therapy (defibrillation) is delayed. In each zone, multiple sequential therapies can be delivered (ATP, then cardioversion, defibrillation); following each therapy, the device will reevaluate the rhythm and if it persists or accelerates, the next therapy in the appropriate zone is delivered.

Patients at risk for ventricular arrhythmias are also at risk for supraventricular arrhythmias and if the ICD interprets a SVT incorrectly as VT, the patient may experience inappropriate shocks which occur in up to 20–25% of patients [20–23]. ICDs utilize additional features to improve discrimination between ventricular and supraventricular arrhythmias. With a dual chamber device also detecting the atrial rhythm, the primary discriminator remains heart rate. If the atrial rate is faster than the ventricular rate (A > V), the arrhythmia is classified as a SVT, most commonly atrial fibrillation or atrial flutter and therapy is withheld. An arrhythmia with a faster ventricular than atrial rate (V > A) is consistent with atrioventricular dissociation with VT and therapy is delivered.

The device will also record a template of the ventricular electrogram during sinus rhythm which it then compares to the electrogram seen during a tachyarrhythmia. Changes in morphology, duration, polarity from baseline increase the likelihood of categorizing it as ventricular arrhythmia. The device will also detect the stability (lack of R- R variability) of the tachycardia; VT will typically be more regular while AF will not be. It also utilizes an onset criterion since VT will tend to be sudden onset while sinus tachycardia will have more gradual onset. Of course, SVTs can also be sudden onset and stable, this is one of the reasons why patients may receive inappropriate shocks.

While the discriminators are designed to prevent an SVT being incorrectly categorized as VT or VF and limit inappropriate shocks, no combination of discriminators is 100% specific for SVT. Also, for persistent tachyarrhythmias, the discriminators have a "time out" so that the ICD will treat the arrhythmia as VT or VF.

Once criteria for delivering a shock are met, the capacitors charge which take several seconds; after charging, the ICD will take a "second look" to determine if the arrhythmia has spontaneously terminated. If the tachycardia persists, the shock will be delivered. If the first shock fails, the defibrillator will deliver up to five more shocks in an attempt to terminate the arrhythmia.

9.2.5 Antitachycardia Pacing (ATP)

Reentrant arrhythmias can be terminated by pacing at a rate faster than the arrhythmia. The reason for termination is an antegrade and retrograde collision of the pacing wave front within the VT circuit that leads to termination of the arrhythmia. ATP refers to the delivery of short bursts of rapid ventricular pacing (typically 8/10 beats) to terminate VT. It is typically programmed to be delivered 10–20% faster than the rate of the tachycardia. Several prospective randomized and observational studies have shown that up to 95% of spontaneous VTs can be successfully terminated with ATP with similar efficacy to low energy (≤10 J) cardioversions [24–28].

ATP has also been shown to be effective with more rapid VTs. In the PainFREE Rx II trial, 634 patients were randomly assigned to empiric ATP or ICD shock for initial therapy of rapid VT (188–250 bpm). With mean follow-up of 11 months, 98 patients experienced 431 episodes of rapid VT and 81% were successfully pace terminated. There was no difference in the incidence of VT acceleration, syncope, sudden death, or median VT duration between the ATP and ICD shock arms [29].

Unfortunately, ATP tends to be less successful in patients with multiple VT morphologies. In one cohort of 52 patients with 833 episodes over mean follow-up of 30 months, ATP terminated 95% of VT episodes in patients with 1 morphology, 85% with 2 morphologies, and 70% with ≥3 morphologies [30].

9.2.6 Cardioversion

A shock that is delivered at the peak of the R wave (synchronized) is referred to as a cardioversion. If a shock is not synchronized and delivered during the vulnerable period of repolarization, this can cause VT to degenerate into VF.

9.2.7 Defibrillation & Threshold Testing

A shock delivered randomly during the cardiac cycle (unsynchronized) is defibrillation. Since VF is an unorganized rhythm, synchronized cardioversion is not necessary or possible. The amount of energy that is necessary to defibrillate the heart is the defibrillation threshold (DFT).

Historically, DFT was tested at device implant and generator changeout but recent studies have shown, in left sided implants, this is not necessary with modern ICDs. When performing DFTs at implant, VF is induced by a programmed shock on the T wave or with high frequency (50 Hz) pacing. The ICD should appropriately detect VF, charge, and deliver a shock. If the shock defibrillates the heart, the testing is repeated after a 5 min delay with a lower energy shock (step-down). Testing is repeated until defibrillation does not occur and the patient is rescued with a maximum output shock or external defibrillation. The DFT is defined as the lowest successful energy. Current clinical practice is one induction of VF and successful defibrillation occurs at 17 J or 2 inductions and successful defibrillation at 21 J occurs [31], an appropriate safety margin is confirmed. Early ICDs had a monophasic shock waveform while current ICDs have a biphasic waveform with an initial positive phase followed by a negative phase which is significantly more effective. With modern ICD systems with biphasic shocks, the DFT is typically ≤15 J.

Given clinical variations (CHF, ischemia, autonomic tone) and probabilistic nature of defibrillation, a shock at the energy level of the DFT may not always successfully defibrillate [32]; thus, an ICD must be able to deliver a shock at a higher energy than the DFT and a safety margin of at least 10 J is typically recommended. If DFTs have been performed at implant, the 1st shock is typically programmed 10 J above the threshold allowing a shorter charge time prior to therapy. If this shock is unsuccessful, subsequent shocks are delivered at higher energies, typically at the maximum output of the ICD.

As ICD technology has improved, DFTs have substantially decreased and it is uncommon for adjustments to be required at implant to ensure an adequate safety margin. Several studies have shown that DFT testing at implant may not be necessary for most patients. A small study of 145 patients undergoing ICD implant with or without CRT randomized patients to DFTs or no DFT. All patients in the DFT arm were successfully defibrillated and only 4% required any system modifications and there were no differences in outcomes between the 2 groups [33]. In the Shockless Implant Evaluation (SIMPLE) [34] and NORDIC [35] ICD trials, patients undergoing initial ICD implant were randomized to DFTs or no DFTs; no DFT testing was non-inferior to DFT testing (with a trend towards superiority). Based on these studies, DFTs are not routinely performed at implantation and ICD shocks are programmed at maximum output.

There are patients where DFTs are still performed (those with known elevated DFTs, on antiarrhythmic drug therapy that may raise the DFT, and those with right sided devices). Current recommendations also encourage performing DFTs in patients undergoing implantation of a S-ICD.

9.2.8 Programming to Minimize Right Ventricular Pacing

RV pacing is associated with an increased incidence of HF hospitalizations, AF, and death [36–38] by causing ventricular dyssynchrony due to functional LBBB. Whenever possible, both ICDs and pacemakers are programmed in modes to minimize RV pacing. For single chamber ICDs, the lower rate limit is typically programmed to 40 bpm (VVI 40 bpm). Dual chamber ICDs have algorithms that allow for intrinsic AVN conduction (AAI-DDD) and only provide ventricular pacing when AV block occurs. CRT is currently recommended for patients on GDMT with LVEF ≤ 35% undergoing new implantation or device replacement with anticipated requirement for significant (>40%) ventricular pacing [6].

9.2.9 Optimal ICD Programming

Historically the goal of ICD programming was to deliver ICD therapies with minimal possible delay for any ventricular arrhythmia. Many times, ICD therapies were delivered for arrhythmias that were non-sustained and may have spontaneously terminated if longer detection times prior to therapy were present [39]. Both appropriate and inappropriate ICD shocks are painful, psychologic stressful, and adversely affecting quality of life [40, 41], myocardial function [42], and are associated with increased mortality [40, 43, 44].

Several trials have investigated the impact of extended VT/VF detection intervals. In the Pooled Analysis of the IDE Study and EFFORTLESS a time to therapy of 19.2 ± 5.3 s was associated with spontaneous termination of 37% of all ventricular arrhythmias [45].

9.2.10 MADIT–RIT

The aims of this study were to evaluate the effect of device programming on inappropriate therapy and mortality. 1500 patients undergoing primary prevention ICD implantation were randomized to three different programming strategies: conventional (2.5 s delay at rates of 170–199 bpm with 1 s delay at rates of >200 bpm), delayed (60 s delay at rates of 170–199 bpm with 12 s delay at rates 200–249 bpm, and 2.5 s delay at rates >250 bpm), and high-rate (no therapy for 170–199 bpm, 2.5 s delay at rates of >200 bpm).

With delayed and high rate programming, inappropriate therapies were lower; all-cause mortality was lower in the high-rate group with a trend toward lower mortality in the delayed therapy group. The risk of mortality was higher in patients who received appropriate or inappropriate therapies, including ATP, regardless of programming strategy [46].

The ADVANCE III Trial randomized 1902 patients undergoing primary or secondary ICD implantation to one of two detection strategies (ATP and ICD shock programming was the same in both groups) for ventricular tachycardia >187 bpm. The two groups were: standard detection intervals 18/24 (5.4–7.2 s for detection with VT 200 bpm) and long detection intervals 30/40 (9–12 s for detection with VT 200 bpm).

Patients in the long detection group had fewer delivered therapies, lower likelihood of receiving ATP and near significant trend towards lower likelihood of delivered shock, and no significant change in mortality between the 2 groups [47]. Both MADIT-RIT and ADVANCE III showed that longer detection intervals prior to ICD therapies is both safe and effective in both primary and secondary prevention patients. It is important to notice that the increase in time to therapy or higher detection rates were not associated with increase in syncopal episodes. A meta-analysis of 4 studies showed that patients programmed with longer detection intervals had significantly fewer inappropriate shocks and lower mortality [48].

9.2.11 ICDs in Patients with LVADs

Ventricular arrhythmias are common in patients with left ventricular assist devices (LVADs) and are often better tolerated due to the hemodynamic support from the LVAD. Patients may remain in rapid ventricular arrhythmias for prolonged periods of times and SCD is an uncommon method of death in LVAD patients. The role of ICDs and optimal programming in LVAD patients has been uncertain. Recent meta-analyses have shown ICD use is associated with a significant mortality reduction in LVAD patients. In those with continuous-flow LVADs, there was a nonsignificant trend for improved survival in those with an ICD [49, 50]. Further randomized clinical trial data is needed to fully address this issue. It has been uncertain if ICD programming should be adjusted in LVAD patients to allow ventricular arrhythmias (permissive programming) or maintain traditional programming to avoid the complications of sustained ventricular arrhythmias. With permissive programming, VT/VF detections limits are increased to only treat faster HRs with prolonged detection intervals and increased use of ATP prior to delivering a shock. In a small study, permissive ICD programming lead to a nonsignificant trend toward fewer ICD shocks with no change in mortality or time to first hospitalization [51]. Larger studies are needed to define optimal ICD programming in LVAD patients.

9.2.12 Ambulatory Monitoring

ICDs allow for remote monitoring that allow physicians to interrogate the ICD, evaluate device and lead parameters and event EGMs over the telephone or internet without requiring the patient to come to the office or hospital. Programming changes cannot be made remotely but require in person interrogations. Multiple parameters may trigger an alert on remote monitoring (Table 9.1).

In a study assessing the clinical impact of remote monitoring, (TRUST-trial [34]) randomized patients with single and dual chamber defibrillators to remote monitoring or routine office visits. Remote monitoring reduced in-hospital device interrogation visits by 45% with no increase in adverse events and problems were identified 30 days earlier with remote monitoring [52]. In the Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision (CONNECT), a decreased length of stay was seen with remote monitoring of patients with ICDs or CRT-Ds [53]. In the ALTITUDE study, 185,778 patients with ICD or CRT-D were randomized to remote monitoring 3–4 times per month with office visits twice a year or to routine office visits only. A 50% reduction in mortality was seen at 1 and 5 years and the lowest mortality was seen in patients who reported weight and BP readings, suggesting that improved survival may be attributable to better patient self-care rather than remote monitoring alone [54]. The above benefits were seen across all manufacturers.

Remote monitoring also offers data that may assist in the treatment of HF patients. As a surrogate for pulmonary vascular fluid status, intrathoracic impedance can be measured

Table 9.1 Remote monitoring parameters triggering patient alerts

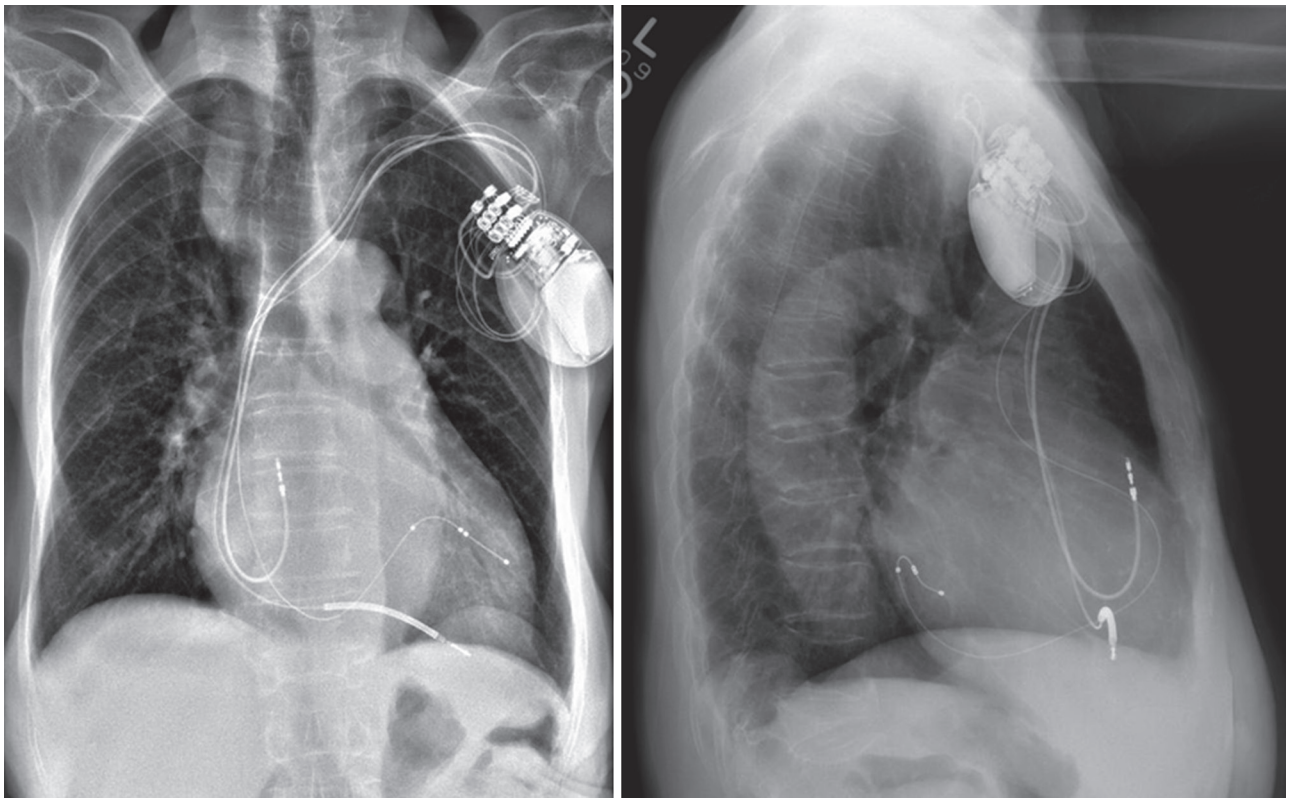
New onset, duration of SVTs, AF
RV pacing over programmable percentage
BiV pacing under programmable percentage
Significant change in lead function (impedances, capture thresholds)
NSVT, VT, ICD therapies
Generator at recommended replacement interval

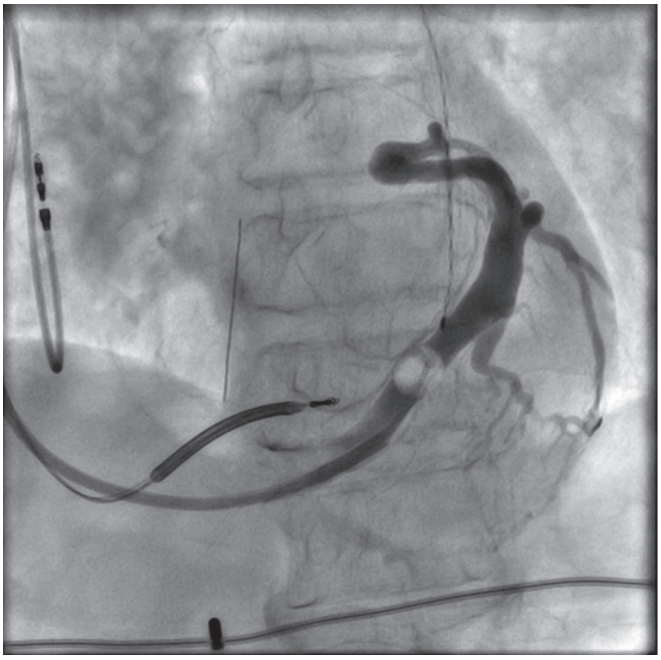
between the tip of ICD lead and the pulse generator. The Medtronic OptiVol system is a measurement of the difference between the daily and reference impedances plotted against a programmable threshold and when crossed an alert will trigger. Figure OptiVol Fluid Trends (Dec-2014 to Feb-2016) shows an Optivol trend seen on remote monitoring for a patient with an acute exacerbation of HF. An alert should lead to patient evaluation not reflexive medication adjustment since the transthoracic impedance can be affected by pneumonia, pleural effusion, pocket edema, or inflammation.

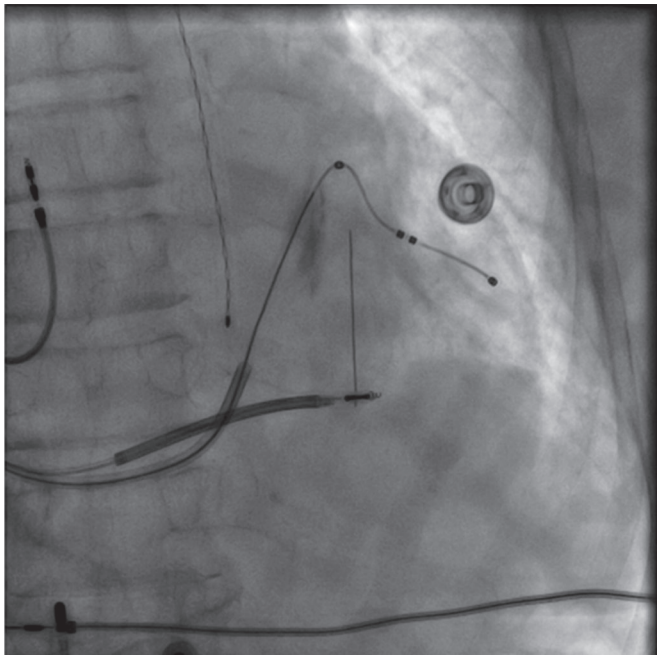
In one study of 532 patients, CHF hospitalizations were significantly reduced in patients with OptiVol monitored turned "on" [55]. However, in the Diagnostic Outcome Trial for Heart Failure (DOT-HF), an audible alert was emitted by the device when the Optivol threshold was crossed; leading to increased outpatient visits and admissions for CHF with no change in mortality [56]. In the OptiLink HF Study, OptiVol monitoring did not reduce CV hospitalizations or mortality [57].

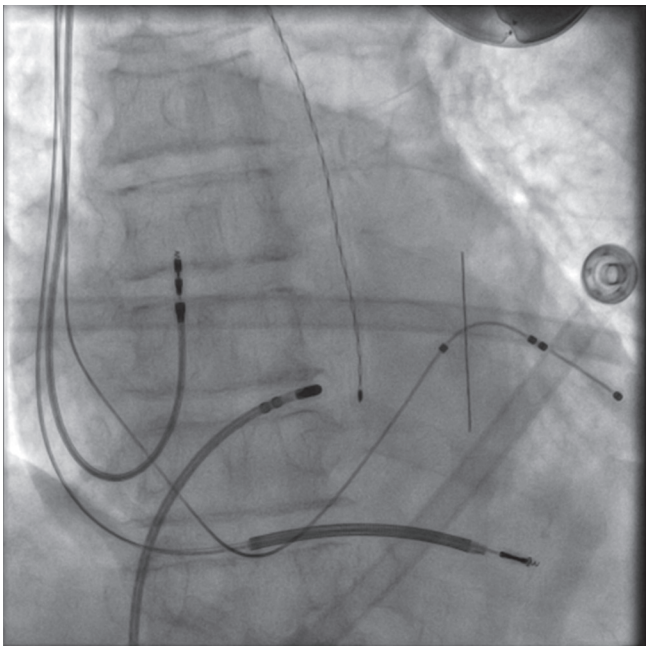
Devices can also monitor patient activity and heart rate variability; decreased levels of both may predict heart failure exacerbation. The use of multiple clinical variables may assist the predictive value of impedance measurements. In the Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients with Heart Failure (PARTNERS HF) trial, 694 patients with CRT-Ds were evaluated. Patients with a fluid index > 100 and any 2 of the following: long duration of AF, AF with RVR, low patient activity, high nocturnal HR, low HR variability, low CRT-pacing, or ICD shocks had a 5.5-fold increased risk of CHF admission in the next 30 days [58].

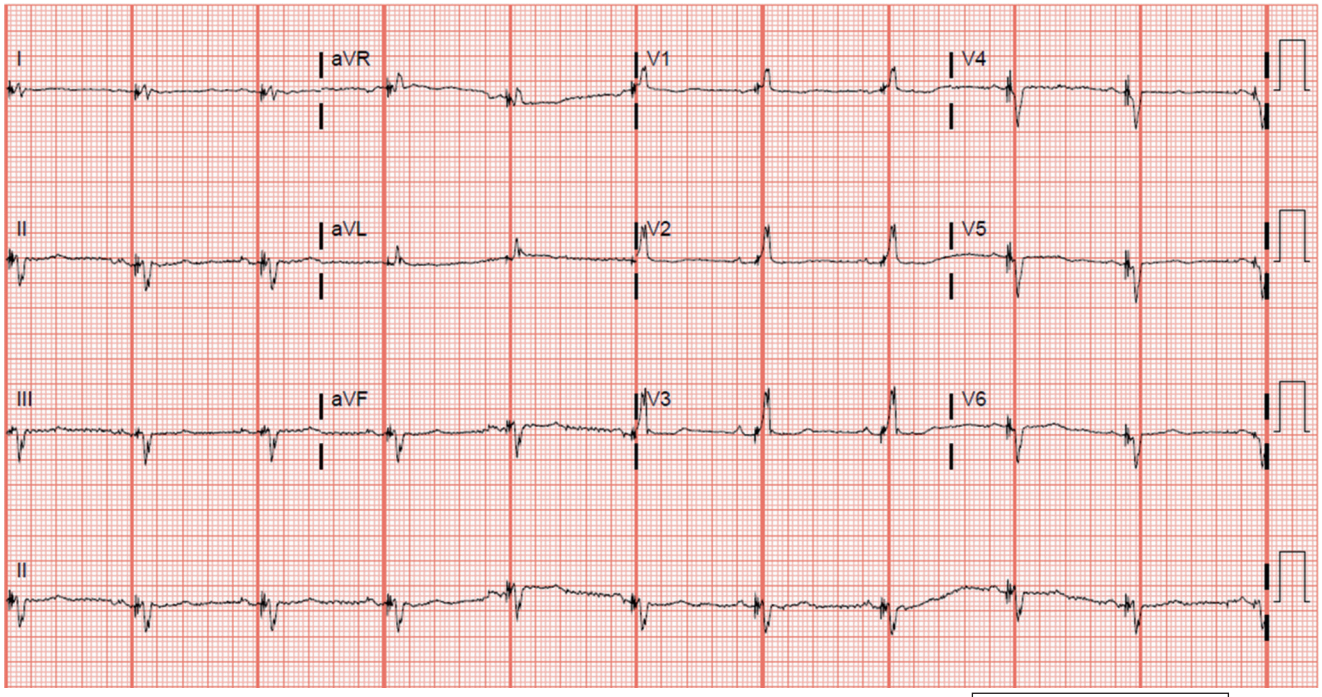
One important advance in device follow up is the devel-opment of remote monitoring. In the Influence of Home Monitoring on Mortality and Morbidity in HF Patients with Impaired LV function (IN-TIME), all-cause mortality in the tele-monitoring group was 3.4% versus 8.7% in the control group [59]. Similarly, in a "big-data" Registry analysis of 269,471 US patients, remote monitoring was associated with improved survival and survival was associated to the level of adherence to remote monitoring [60].









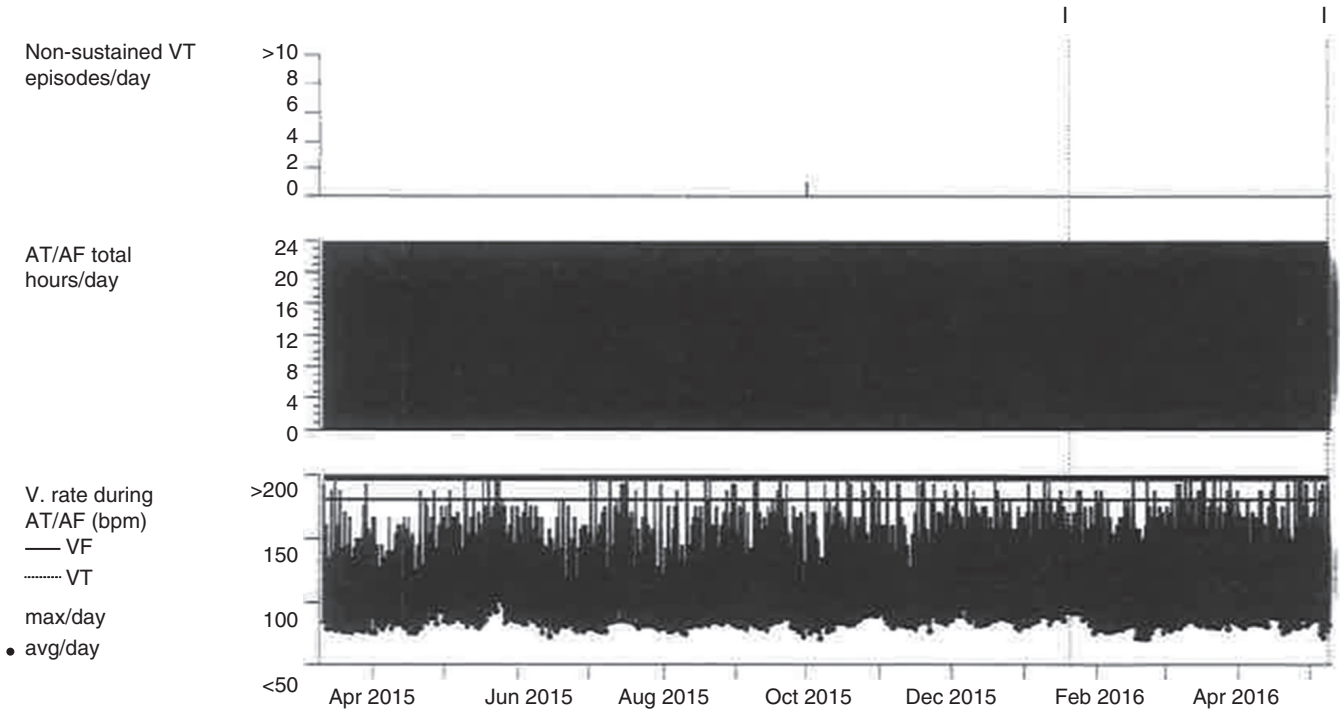


Device: Protecta DR D334DRG
Serial Number: PSP204929H

SW009 Software Version 8.2 (4.1)

Initial Interrogation: Cardiac Compass Trends

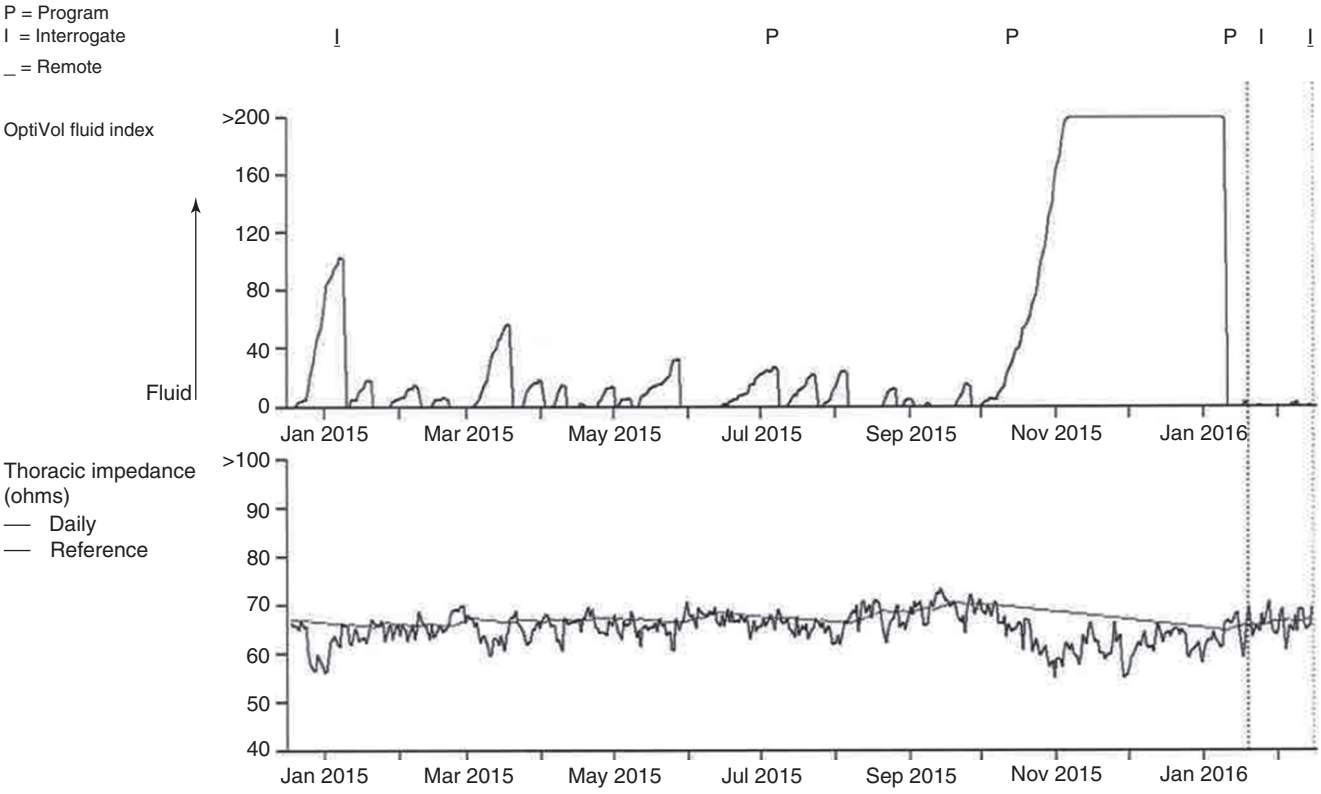
Page 2

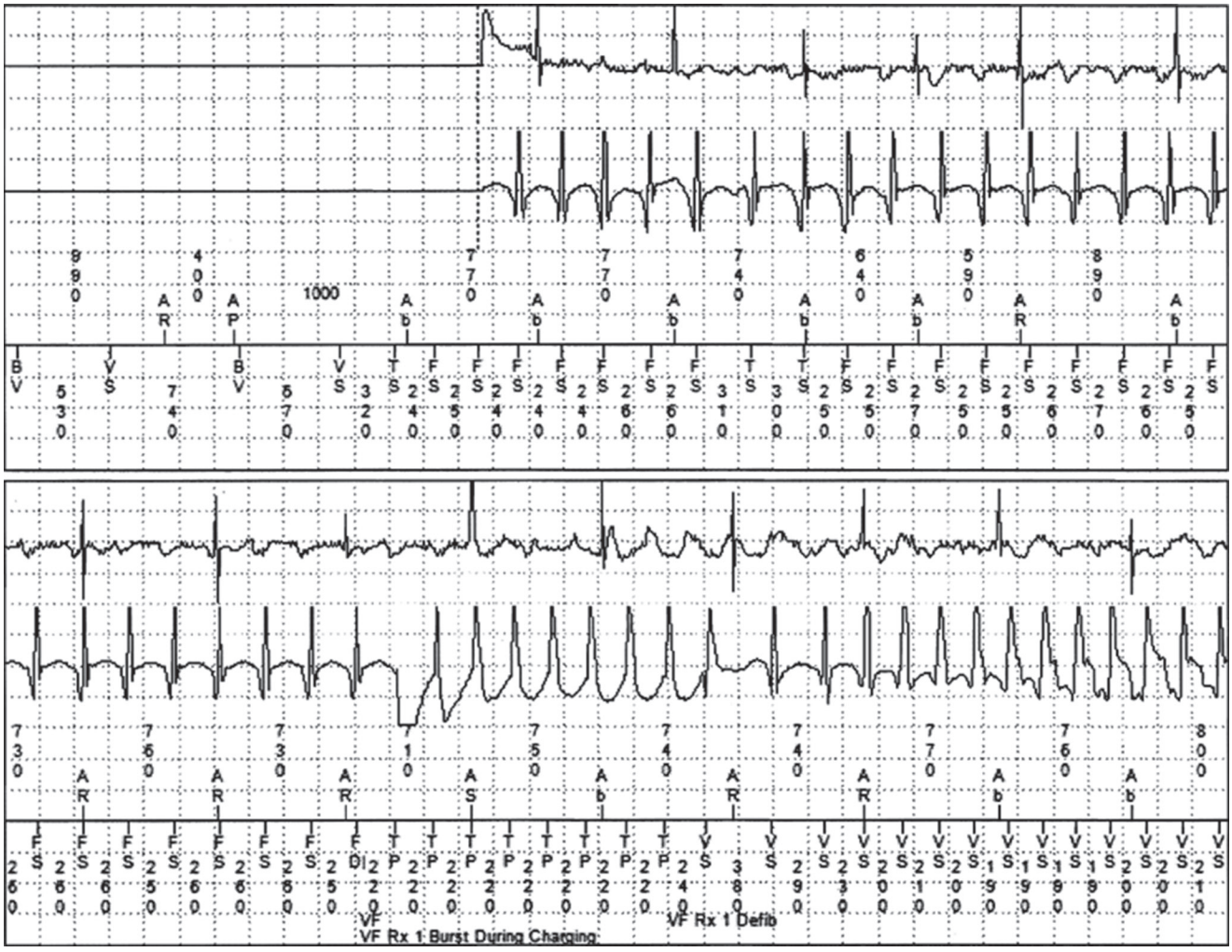


OptiVol Fluid Trends (Dec-2014 to Feb-2016)

OptiVol fluid index is an accumulation of the difference between the daily and reference impedance.

The OptiVol feature is an additional source of information for patient management and does not replace assessments that are part of standard clinical practice. Note: The OptiVol threshold and observations are not available from the Medtronic CareLink Network.

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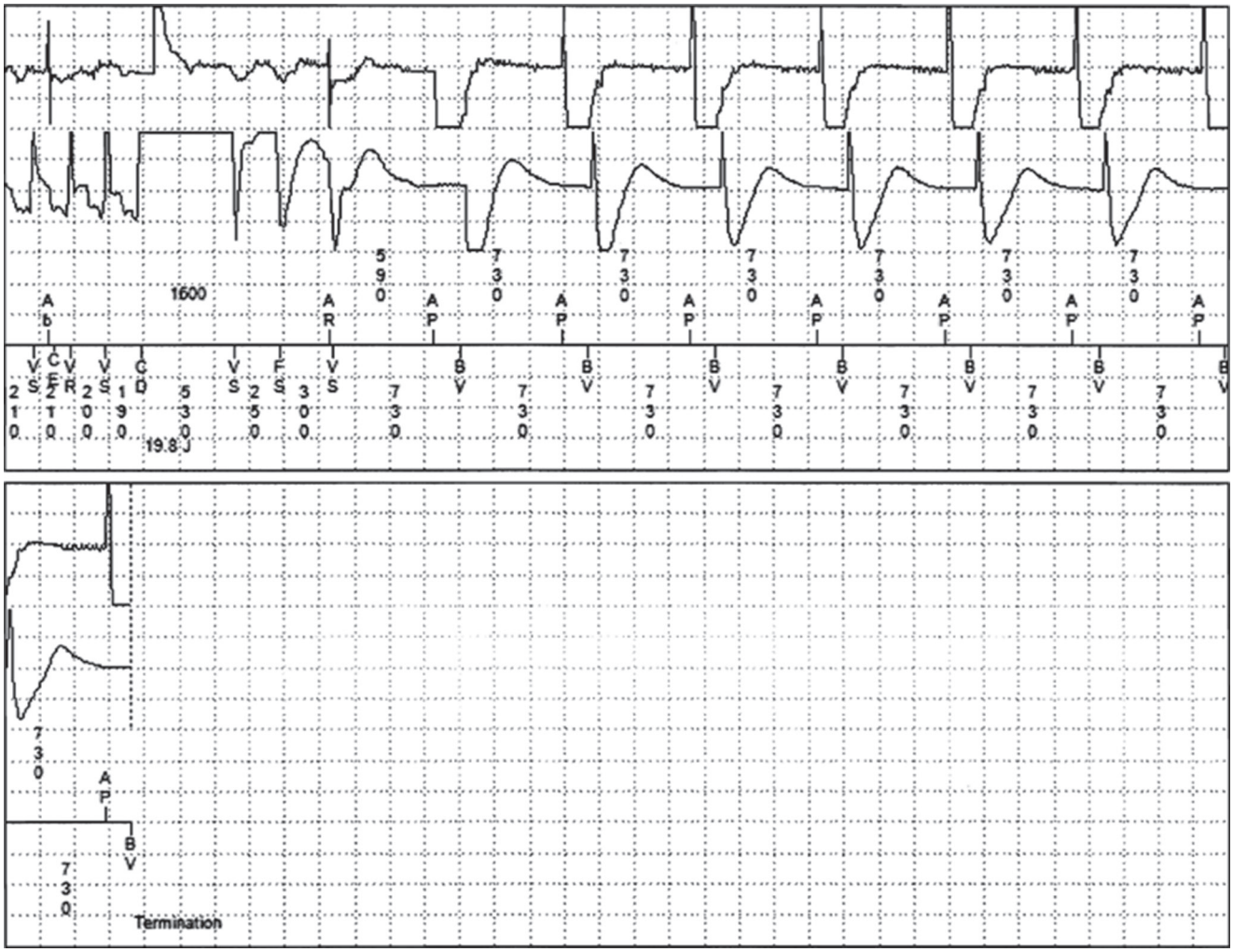
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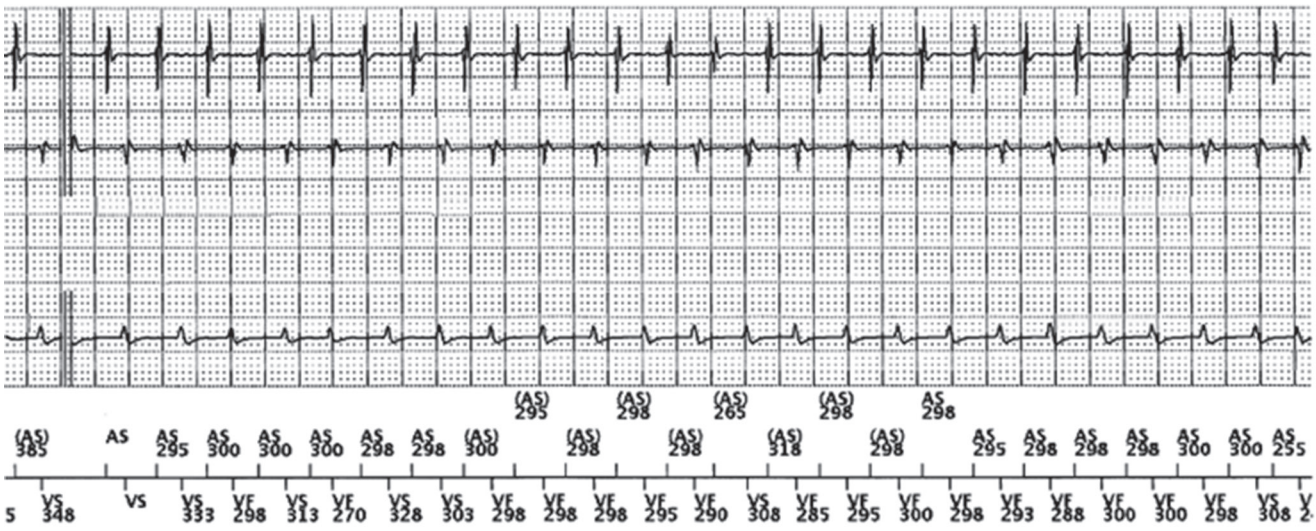
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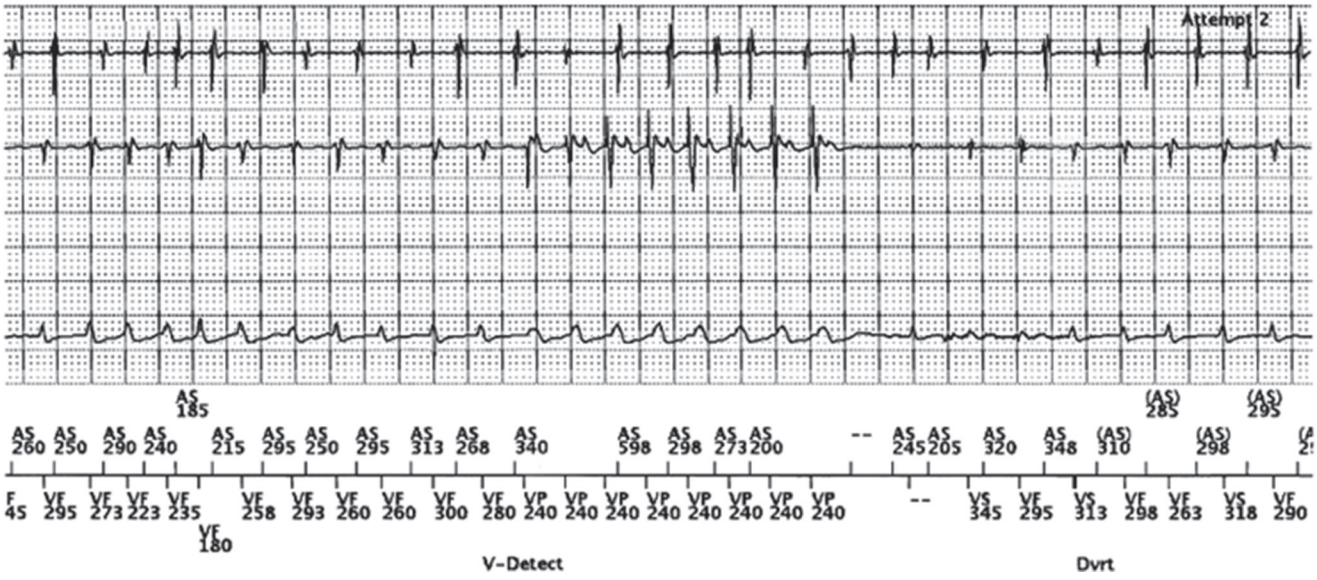
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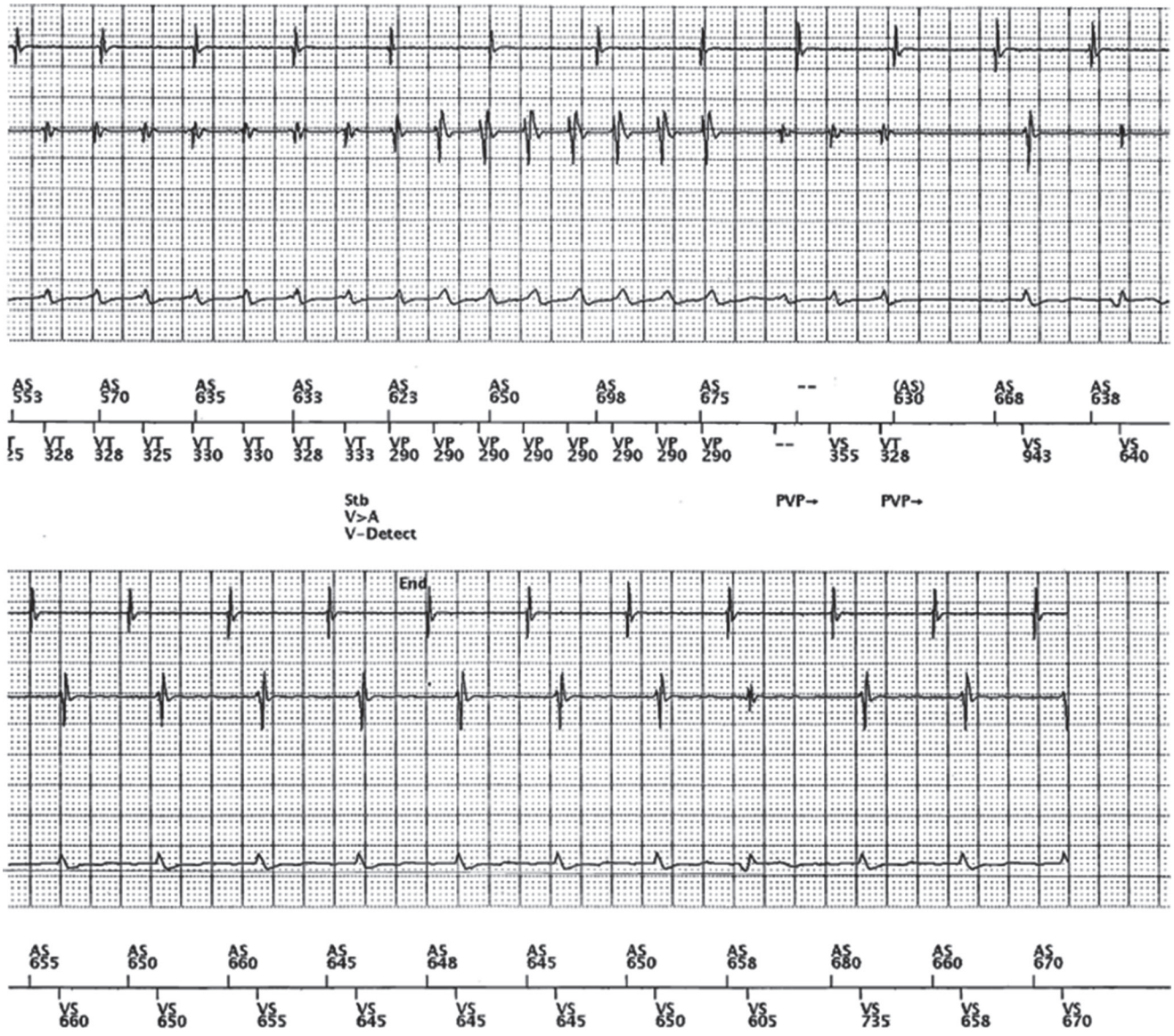
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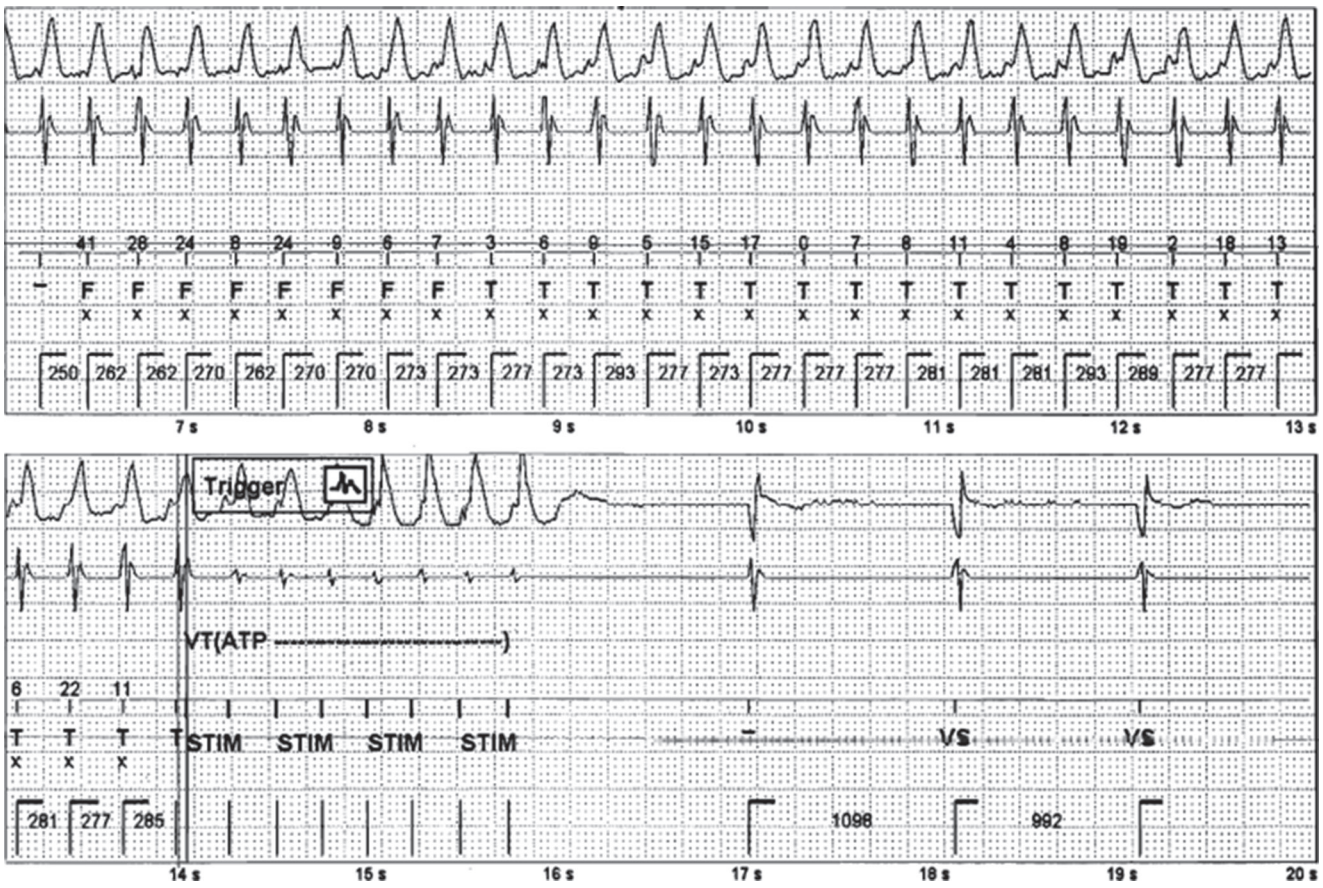
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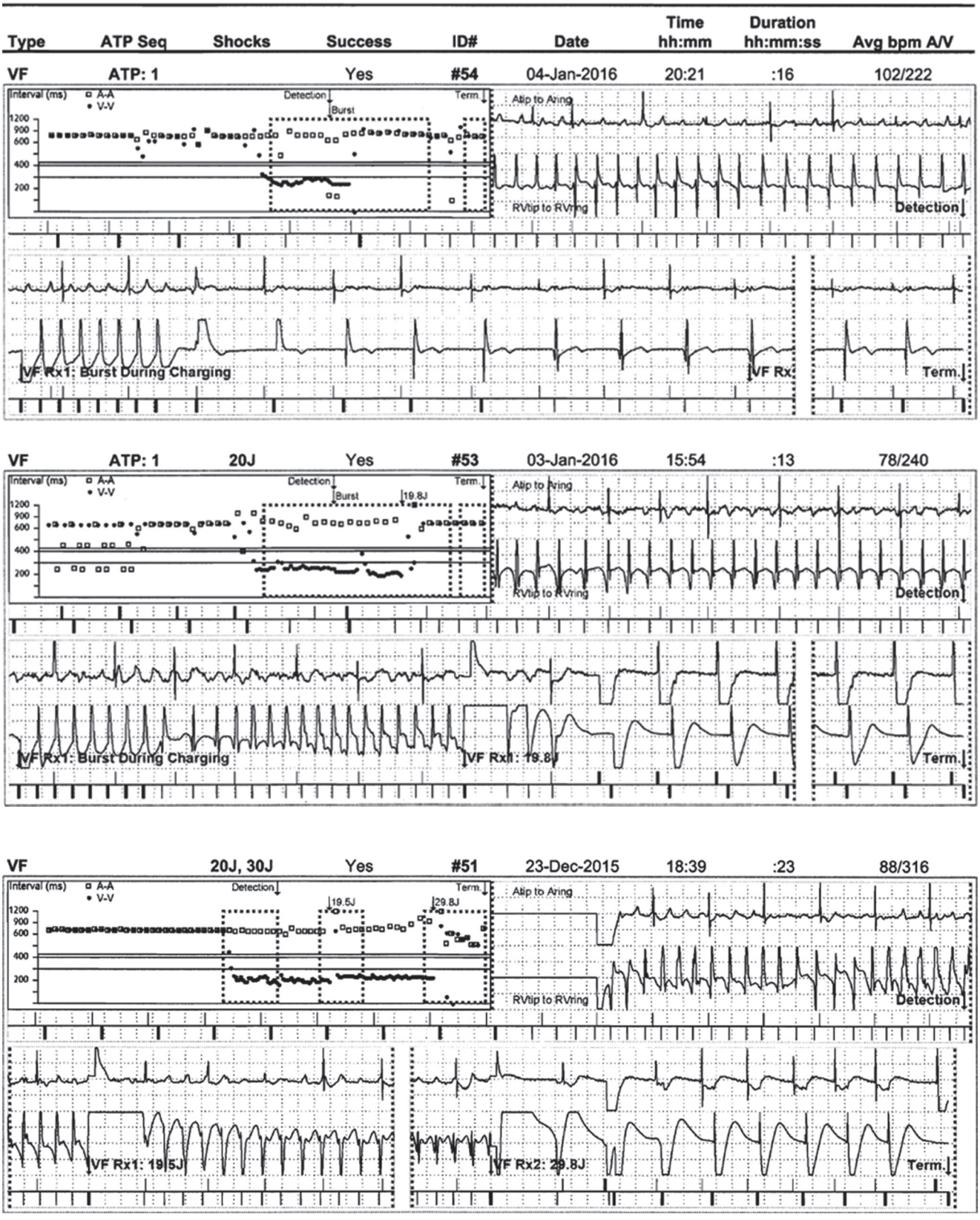
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Interval (ms) A-A V-V
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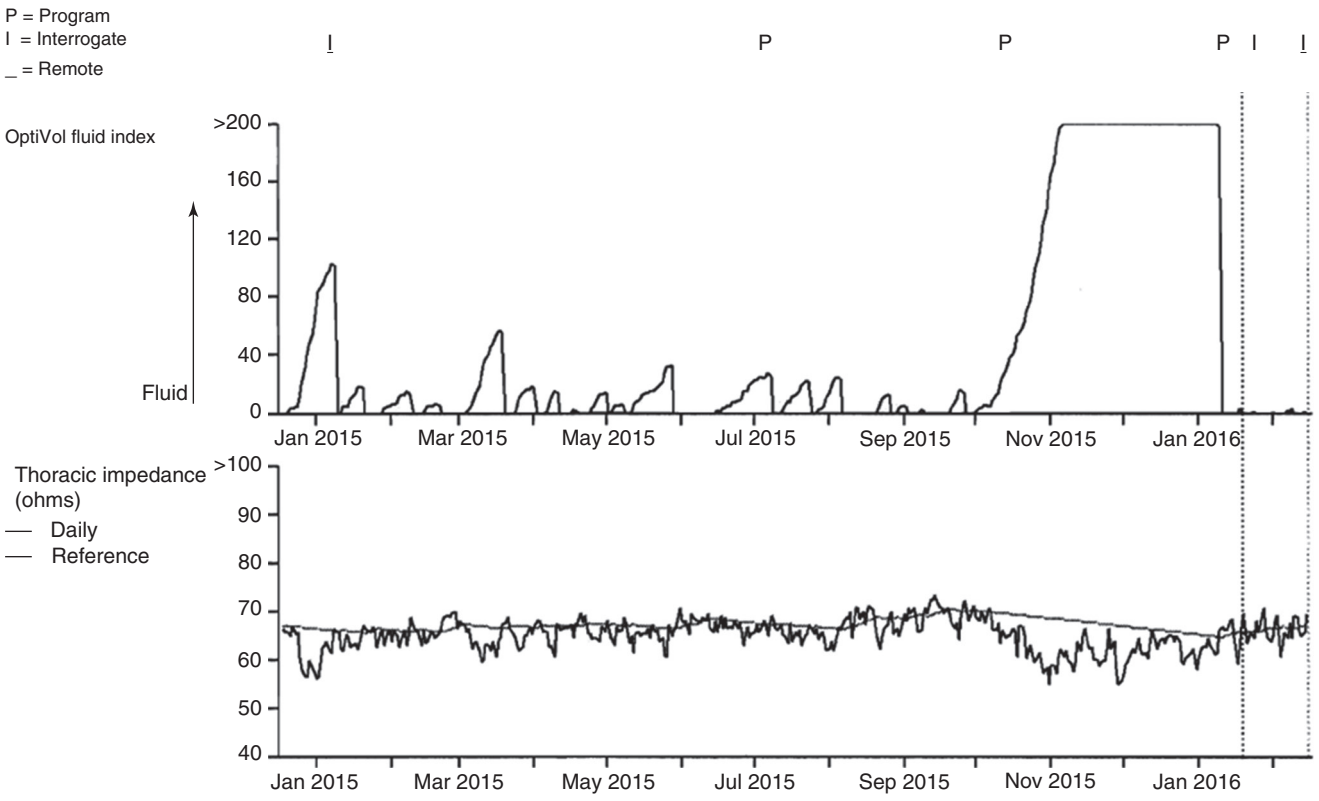

9.2.13 ICD System Integrity

In addition to notification that the pulse generator has reached the recommended replacement time (RRT), the device monitors for early lead failure. An insulation break or inner conductor fracture can lead to failure to capture or oversensing with inhibition of pacing which could be catastrophic in pacemaker dependent patients. Inner conductor fracture of an ICD lead can lead to oversensing and inappropriate ICD shocks. An alert for a sudden change in lead impedance can result in earlier identification and management to reduce the chance for inappropriate shocks. Remote monitoring has shown that lead malfunctions are identified 54 days earlier and inappropriate shocks from lead fracture were reduced by 50% (53–27%) [61, 62].

9.2.14 Approach to the Patient Presenting with Suspected ICD Therapies

Reported ICD shocks are due to 3 possible situations: appropriate shock, inappropriate shock, or a phantom shock. Within 2 years of ICD implantation, one-third of patients will experience an appropriate ICD therapy for a ventricular tachyarrhythmia that satisfied programmed detection criteria [63]. Inappropriate therapies can occur due to SVTs that satisfied VT/VF criteria, oversensing of environmental electrical noise, or ICD malfunction due to sensing of noise (i.e., ICD lead fracture). A phantom shock is the sensation of an ICD shock in the absence of an arrhythmia or ICD therapy [64].

Some patients may receive multiple ICD therapies within minutes to hours following the initial shock. VT storm is

defined as 3 or more sustained episodes of VT, VF, or appropriate ICD shocks within 24 h [65]. Patients who receive more than 1 ICD therapy, require emergent evaluation for persistent arrhythmia not adequately treated by the ICD, concomitant illnesses such as myocardial infarction, decompensated HF, metabolic derangements, or ICD malfunction [66]. Prompt device interrogation should be performed to assess the nature of the arrhythmias and device therapies, and ensure appropriate device function. Patients with ongoing arrhythmias should be treated according to advanced cardiac life support (ACLS) guidelines.

In the event of device malfunction causing repeated inappropriate ICD therapies, VT/VF detection and therapies can be disabled by placing a magnet directly over the ICD. Magnet placement still allows backup bradycardia pacing but will not cause asynchronous pacing (DOO or VOO) as seen with pacemakers. With a magnet in place, the patient must remain on continuous monitoring with preparations for external cardioversion-defibrillation since neither SVTs, VT, of VF will be detected or treated by the ICD. Once the magnet is removed, normal ICD function will resume [64].

9.2.15 Management of VT & ICD Therapies

ICD shocks are associated with decreased quality of life [67] and lead to increased risk of hospitalization, HF, and death. While ICDs therapies effectively terminate VT-VF, they do prevent them and concomitant antiarrhythmic drug (AAD) therapy is frequently necessary. In the first year of treatment, amiodarone reduced recurrent arrhythmias by 71% [68] and the rate of arrhythmic death [69] but with long term use is associated with significant side effects that often lead to discontinuation [70]. If VT recurs despite AAD therapy, either escalation of AAD therapy or catheter ablation of VT are the next steps [71]. Randomized trials of catheter ablation in patients with ischemic cardiomyopathy reduced the rate of VT recurrence [72, 73] and observational studies have shown increased survival [74]. The Ventricular Tachycardia Ablation versus Escalated Antiarrhythmic Drug Therapy in Ischemic Heart Disease (VANISH) trial randomized 259 patients to VT ablation or escalated AAD therapy with a significantly lower rate of appropriate ICD shocks, VT storm, and death in those undergoing catheter ablation [75]. Current guidelines recommend catheter ablation when AAD therapy is ineffective [65, 71, 76] but this trial supports catheter ablation over escalation of AAD therapy in patients with ischemic VT [75]. Unfortunately, VT ablation in patients with nonischemic CM have not been as successful likely due to the differences in arrhythmic substrate [77].

9.2.16 Driving with ICDs

Patients with ICDs are at risk for syncope secondary to VT/VF and incapacitation due to surprise and pain from ICD shocks and therefore, driving restrictions should be recommended. Primary prevention patients may drive 1 week following device implantation. Secondary prevention patients (at implant) and those who receive appropriate ICD therapies for VT and VF, should be restricted from driving for 6 months from their last ICD therapy [78]. These recommendations differ among countries.

9.2.17 Wearable Cardioverter-Defibrillator

For patients at risk for SCD but do not meet accepted criteria for ICD implantation, those with infectious issues awaiting device re-implantation or awaiting cardiac transplantation, a wearable cardioverter-defibrillator (WCD) offers short term protection. The WCD also plays a role for protection of newly diagnosed HF patients to allow time for medical therapy with potential recovery of LV systolic function so permanent ICD implantation is unnecessary. In a recent 10 year, single center, retrospective study of newly diagnosed ischemic and non-ischemic CM patients treated with WCDs, no appropriate therapies were seen in patients with NICM. Additional prospective studies are needed, but newly diagnosed ischemic CM patients may benefit from WCD more than NICM patients [79].

9.3 Cardiac Resynchronization Therapy

Ventricular dyssynchrony can worsen heart failure symptoms by impairing pump function. Cardiac resynchronization therapy (CRT) involves pacing both ventricles (biventricular or BiV pacing) to reduce dyssynchrony, improve pump function, reduce functional mitral regurgitation, and reverse ventricular remodeling. In randomized controlled trials, CRT reduces mortality, HF symptoms and hospitalizations.

The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial randomized 1520 patients with LVEF $\leq$ 35%, NYHA Class III-IV HF, and QRS $\geq$ 120 ms to CRT with a defibrillator (CRT-D), CRT without a defibrillator (CRT-P), or optimal HF medical therapy. CRT-D was better than optimal medical therapy at all QRS durations ($\leq$147 ms, 148–168 ms, and >168 ms) but the greatest effect was seen with increasing QRS duration and CRT-P benefited those with QRS $\geq$ 150 ms [80]. A subsequent analysis using QRS cutoffs of <150 ms and $\geq$150 ms showed a reduction in death and all-cause hospitalization for those with a QRS $\geq$ 150 ms.

The Cardiac Resynchronization Heart Failure trial (CARE-HF) randomized 813 patients with QRS ≥ 120 ms, LVEF ≤ 35%, and NYHA III-IV to CRT-P or optimal medical therapy (no ICD arm) with the primary endpoint of mortality and unplanned cardiovascular hospitalization reported according to QRS intervals above or below 160 ms. Echocardiographic evidence of ventricular dyssynchrony was required for patients with QRS 120–149 ms. As seen in COMPANION, CRT was better than medical therapy for all QRS durations but the greatest benefit was in those with QRS ≥ 160 ms [81].

Three trials investigated the benefit of CRT in predominantly NYHA II patients: REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction), MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Trial), and RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial).

REVERSE enrolled 610 patients with NYHA I-II HF, EF ≤ 40%, and QRS duration ≥ 120 ms were enrolled to either CRT-P or CRT-D based on clinical indications and were then randomized to active CRT On or Off for 12 month follow-up with a clinical composite score as the primary endpoint. Remodeling, as measured by change in LV index volume, progressively improved with increasing QRS duration with shortest QRS cutpoint of 134 ms [82] while a further analysis showed progressive CRT benefit when QRS duration > 120 ms was evaluated as a continuous variable for each 10 ms increase in QRS duration [83]. No CRT benefit was seen with QRS < 120 ms [82].

MADIT-CRT enrolled 1820 patients with EF < 30%, NYHA Class I-II, and QRS duration ≥ 130 ms to CRT-D or ICD alone and the benefit of CRT-D on death or nonfatal HF event was only seen in those patients with QRS duration ≥ 150 ms [84]. While female patients benefited across all QRS durations, male patients received benefit mainly when the QRS duration was at least 160 ms [85]. Nonetheless, with long term follow-up, CRT-D improved all-cause mortality in the 1281 patients with LBBB QRS morphology, regardless of the QRS duration [86].

In RAFT, 1798 patients with NYHA I-II, EF ≤ 30%, and QRS durations ≥ 120 ms were randomized to CRT-D or ICD alone with a primary endpoint of all cause death or HF hospitalization. CRT benefit was only observed in patients with QRS duration ≥ 150 ms compared with patients with QRS < 150 ms or a paced QRS duration ≥ 200 ms [87].

Meta-analyses of these CRT trials have added further support that QRS duration is a useful surrogate for electromechanical dyssynchrony but is not the sole determinant of CRT response [88, 89].

9.3.1 AV Block and CRT

In BLOCK HF trials, 691 patients with high grade AV block, NYHA Class I-III HF, and LVEF ≤ 50% were randomized to BiV pacing or RV pacing. With mean follow-up of 37 months, the combined primary endpoint of all-cause mortality, urgent HF visit requiring intravenous therapy, or ≥15% increase in LV end-systolic volume index was significantly less likely to occur in the BiV pacing group [90]. Similarly, in the PACE trial, 177 pacemaker candidates with LVEF ≥ 45% underwent implant of a CRT system were then randomized to either BiV pacing or RV pacing. At 12 months follow-up, those receiving RV pacing had significantly lower LVEF and higher LV end-systolic volume than those with BiV pacing [38]. Current guidelines recommend CRT in patients with LVEF ≤ 35% with significant (>40%) anticipated or present RV pacing at implant or device replacement, respectively. Based upon BLOCK HF, FDA approved CRT for patients with LVEF ≤ 50%, NYHA I-III, and AV block with significant RV pacing.

9.3.2 CRT & Narrow QRS

In patients with a QRS duration ≤ 120 ms, 20–40% have evidence of mechanical dyssynchrony by echocardiography and is a predictor of mortality. Four trials have investigated patients with normal or near normal QRS durations (<130 ms) and echocardiographic mechanical dyssynchrony who then underwent implantation of CRT-D with randomization to CRT on or off.

EchoCRT (Echocardiography Guided Cardiac Resynchronization Therapy) was stopped early due to futility and showed a nonsignificant trend towards harm in patients with an EF < 35% a NYHA III-IF HF and QRS durations < 130 ms who received CRT-D [91]. Similarly, the LESSER EARTH (Evaluation of Resynchronization Therapy in Heart Failure) Trial was terminated early due to safety concerns and futility [92]. NARROW CRT (Narrow QRS Ischemic Patients Treated with Cardiac Resynchronization Therapy) trial enrolled 120 patients with echocardiographic dyssynchrony to CRT-D or dual chamber ICD. At 1 year, CRT was associated with an improved HF clinical composite response (primary endpoint) and at 16 months, improved survival from the combined endpoint of HF hospitalization, HF death, and spontaneous VF [93]. Differences in the results between the three trials are likely due to variable patient populations, endpoints, and follow-up intervals [94].

RethinQ (Resynchronization Therapy in Normal QRS or slightly prolonged QRS (130 ms) enrolled 85 patients prior to study termination with 27% of patients with QRS duration of 120–130 ms showing an improvement in NYHA functional

class and maximal oxygen consumption but no benefit for the primary endpoint of an increase of peak oxygen consumption >1.0 ml/kg during cardiopulmonary testing at 6 months. Symptoms improved in all QRS duration groups but exercise capacity increased significantly only in those with QRS duration > 120 [95].

9.3.3 QRS Morphology & CRT Response

While patients were not enrolled in randomized controlled CRT trials on the basis of QRS morphology, important observations have been obtained from post hoc analyses. The majority of patients enrolled had a LBBB or nonspecific IVCD and those with LBBB have shown the greatest response to CRT whereas those with non-LBBB have responded poorly. Overall, trial data support CRT for LBBB patients when the QRS duration is at least 120 ms but the greater response to CRT is seen as the QRS duration lengthens [94].

While few patients with RBBB were enrolled, it is clear that patients with RBBB received little to no benefit from CRT. A meta-analysis of 5 trials (MIRACLE, CONTAK CD, CARE-HR, RAFT, and MADIT-CRT) identified 259 patients with RBBB and there was no benefit from CRT [96]. In predominantly NYHA Class II HF patients with non-LBBB, IVCD, or RBBB morphologies (REVERSE, MADIT-CRT, and RAFT) reduced or no CRT benefit was seen [82, 84, 87].

Using data from the Medicare ICD Registry in 14,946 patients who underwent CRT-D implantation with RBBB, decreased survival was seen compared to those with LBBB [97]. Among 24,169 patients who underwent CRT-D implantation in the National Cardiovascular Data Registry ICD Registry, 1 year hospital readmission rates and 3 year mortality were higher in those with non-LBBB and LBBB <150 ms [98]. In another study, the benefit of CRT only emerged in non-LBBB patients, once the QRS ≥ 160 ms [96].

In MADIT-CRT, seven factors were associated with reverse remodeling (reduced LV end-diastolic volume): female sex, nonischemic CM, LBBB ≥ 150 ms, prior admission for HF, LVEDV ≥ 125 ml/m^2, and left atrial volume <40 ml/m^2. All factors were worth 2 points except 3 points for left atrial volume. The response score predicted CRT response with a 13% increase per each point in the response score and correlated with reduced risk of HF or death [99].

9.3.4 Other Factors Affecting CRT Response

While the optimal LV lead position is not fully defined; the lateral and posterolateral wall have been the preferred location since it is often the last segment to contract in dyssynchronous LV. Reverse remodeling was significantly greater in patients where the LV lead was placed at the site of maximal delay [100]. Unfortunately, placing a transvenous lead at this site may be limited by coronary sinus anatomy, diaphragmatic stimulation, or scar burden. A lower CRT response rate has been seen in patients with transmural posterolateral scar by cardiac magnetic resonance imaging [101].

A meta-analysis of five CRT trials involving 3872 patients showed a similar mortality benefit in men and women [102] which was in contrast to a subset analysis of MADIT-CRT showing that both the mortality benefit and adverse event rate were higher in women [84, 103].

Clinical trials have not specifically addressed the benefit of CRT in elderly patients. A meta-analysis of five randomized CRT trials (median age 66, range 58–73 years) found no significant interaction between age and CRT effect on all-cause mortality or heart failure hospitalization [102].

AF is common in patients with HF affecting 10–25% of patients with NYHA Class II-III and 50% of patients with NYHA Class IV [104]. Studies have suggested that CRT may not be as effective for patients with AF. Randomized, controlled clinical trials have almost always excluded patients with AF. With AF, there is loss of atrioventricular synchrony and rapid ventricular rates lead to electrical fusion and reduced true biventricular pacing capture. AV nodal agents have been the main treatments for controlling ventricular response while atrioventricular junction ablation (AVJA) has also been used as an alternative to drug therapy to control the ventricular rates in patients with permanent AF. In patients with HF and permanent AF undergoing CRT, AVJA is associated with a significant reduction in all-cause mortality, cardiovascular mortality, and improvements in NYHA functional class compared to those treated with AV nodal agents [105].

The majority of patients enrolled in CRT trials were NYHA HF Class III while some had NYHA Class IV HF. There has been concern that NYHA Class IV HF patients may not benefit from CRT or CRT-D since implantation may destabilize their HF and their life expectancy would limit long term benefits. In the COMPANION trial, 217 patients had NYHA Class IV HF but this represented a relatively stable patient group ("Ambulatory Class IV") since patients were excluded if cardiac transplantation was expected within 6 months and no HF hospitalizations within 30 days of enrollment. In this group, CRT and CRT-D significantly reduced the time to hospitalization or death with a trend towards reduced all-cause mortality in both arms [106].

9.3.5 CRT Impact on Ventricular Tachyarrhythmias

The reverse remodeling seen in CRT responders is associated with a reduced risk of ventricular tachyarrhythmias (VTA).

In MADIT-CRT, the risk of first VTA was lowest among high CRT responders and highest for low responders [107]. Continued CRT following LVAD lead to significant reduction in VTA burden and ICD shocks [108].

9.3.6 Interruption of CRT

Loss of CRT due to malfunction or cessation typically leads to rapid deterioration with subsequent HF exacerbation. In a report of 20 patients who underwent temporary cessation of BiV pacing, there was a significant decline in the maximal rate of rise of LV systolic pressure (711–442 mm Hg) with a twofold increase in mitral regurgitation at 72 h [109].

9.3.7 Alternatives to Coronary Sinus Lead

Unfortunately, a large number of patients do not receive CRT due to inability of deploying a lead via the coronary sinus or receive a suboptimal position of the left ventricular epicardial lead related to anatomic constraints. This is likely a contributing factor to the high non-responder rate to CRT [110].

In these cases, the leads can be implanted epicardially via a thoracotomy or thoracoscopically [111, 112]. This approach, due to it higher morbidity and mortality, is mainly reserved for patients that failed the transvenous CS approach. A variant to the surgical approach, is the implantation of epicardial lead with via percutaneous subxiphoid approach. This less invasive technique has been already validated in animal studies [113].

More recently, an in an attempt to prevent extensive surgical procedures in patients with compromised hemodynamic parameters, LV endocardial pacing have been attempted. This technique has been described in a small number of patients, mainly single center experiences and lack the large randomized clinical trial that support the transvenous coronary sinus approach. Endocardial LV-pacing appears to have hemodynamic advantage to CS-epicardial pacing [114] and have the disadvantage of exposing the lead to the systemic circulation, increasing the risk for thromboembolic stroke and the need for lifelong anticoagulation [115]. There are descriptions of LV lead deployment via a transseptal puncture [116, 117] or even a transventricular septal puncture [118].

9.3.8 Assessing CRT Response at Follow-up

In the MIRACLE trial, clinical and QOL improvement was seen at 1 month [119] while in CARE-HF & COMPANION, benefit was assessed at 3 months [120, 121]. Multiple criteria have been used to assess CRT response at follow-up: one level improvement in NYHA class, improved 6 min walk, quality of life measures, and decreased HF admissions. Up to one third of patients do not have a clinical response to CRT and over 40% do not show evidence of reverse remodeling [122]. For those patients who do not show clinical improvement following CRT, the following considerations are recommended:

9.3.9 Evaluation of Non-Responders at 3 Month Follow-up

1. Does 12 lead ECG show evidence of BiV pacing?
2. Is patient in sinus rhythm or AF
3. Device interrogation, capture thresholds
4. What is the percentage of BiV pacing?
5. CXR evaluation for lead position (stable, lateral position)?
6. 6 min walk time (if done pre-implant)
7. Repeat echocardiogram to assess LVEF and LVESV

Some patients exhibit a super-response to CRT defined as a two-fold or more increase in LVEF or LVEF > 45%, a decrease in LV end-systolic volume, and a decrease in NYHA HF functional class ≥1. Super-responders had significantly smaller mitral regurgitation and LV end-diastolic diameter (LVEDD) and mitral regurgitation jet, and heart failure symptoms for <12 months prior to implant [123]. In MADIT-CRT, 6 factors predicted super-response: female sex, no prior myocardial infarction, QRS duration ≥ 150 ms, left bundle branch block, body mass index <30 kg/m^2, and smaller baseline left atrial volume index. Super-response was associated with significantly reduced risk of HF or all-cause death [124] prompting the question if these patients should be changed to a CRT-P system at subsequent generator replacement.

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Comorbidities and Co-Existing Conditions in Heart Failure Around Pregnancy

Denise Hilfiker-Kleiner, Johann Bauersachs, and Karen Sliwa

4.1 Introduction

It is estimated that 0.2 to 4% of all pregnancies in industrialized countries are complicated by cardiovascular diseases (CVD) with increasing number of women who develop cardiac problems during pregnancy [1]. Indeed, pregnancy challenges the cardiovascular system and may lead to disease states such as hypertensive complications with its severe forms preeclampsia and the HELLP syndrome (**H:** hemolysis, **EL:** elevated liver enzymes, **LP:** low platelets counts) [2]. Especially the phase towards the end of pregnancy, during delivery and postpartum is a special challenge for the cardiovascular system since it has to cope with massive hormonal fluctuations, fluid changes and mechanical stress. Alterations in metabolism (subclinical insulin resistance in pregnancy) and immune response (repressed in pregnancy and activated after delivery) take place as well. Moreover, endothelial stress promotes hypertensive disorders and additional enhanced coagulation activity lead to higher risk for myocardial infarction and stroke and cardiomyopathies as outlined below. It is therefore not surprising that acceleration of heart failure towards the end of the second trimester, under delivery or in the early postpartum phase is frequently observed in women with pre-existing cardiomyopathies or pulmonary hypertension and is associated with adverse maternal and perinatal outcome [3]. Moreover, the cardiac stress model "pregnancy" may even unmask unrecognized genetic and non-genetic heart diseases [2, 4, 5].

It is also important to note, that cardiovascular disease around pregnancy provides substantial challenges for the patient and the treating physician because evidence-based clinical data are scarce and even the understanding for normal physiological processes operating on the maternal cardiovascular system during pregnancy are poorly understood. Moreover, medical therapy is limited since many well established medications are contra-indicated during pregnancy and large clinical trials are rarely performed.

In this chapter we summarize the current knowledge on comorbidities and co-existing conditions in heart failure as well as new onset cardiovascular disease around pregnancy. We will discuss state of the art treatment options, prognosis and novel insights in pathophysiological mechanisms behind pregnancy-mediated cardiovascular diseases.

4.2 What Is Known on Normal Physiological Changes of the Cardiovascular System During Pregnancy

The nature of physiological stress factors to the cardiovascular system such as hemodynamic changes, increased cardiac workload and cardiac output around pregnancy are summarized in articles by Hilfiker-Kleiner et al. and by Chung et al. [6, 7]. In brief, marked hemodynamic changes in the maternal circulation occur in the first trimester of pregnancy and cause a profound decline in systemic vascular resistance that, in turn, abets a reciprocal increase in cardiac output of approximately 40% or 2 L/min lasting throughout pregnancy. These circulatory changes are thought to condition the maternal system for the rapid growth phase of the foetus and placenta in the 2nd half of pregnancy, when oxygen and nutrient demands are rising exponentially. At the same time powerful dilatory mechanism(s) are started that counteract

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compensatory structural and functional hypertrophy for which pregnancy hormones such as progesterone and relaxin seem to be responsible [6, 8].

The hormonal changes during pregnancy alter also the propensity to blood clotting and haemorrhage thereby increasing the risk for embolic complications such as stroke and myocardial infarction [9].

In addition, a metabolic switch is induced in the mother's system away from glucose towards fatty acids and glycogen since glucose has to be efficiently shuttled to the foetus, a feature that leads to a "physiological" type of insulin resistance in the mother [9].

In summary, pregnancy leads to a system-wide hormonal, hemodynamic and metabolic reprogramming for which our current understanding is limited. Therefore, intensive research in this field is needed to better define what is "normal" and where serious disturbance and disease starts.

4.3 Pregnant or Postpartum Women with Heart Failure

Heart failure in pregnant or postpartum women may arise newly or may have pre-existed already prior pregnancy. Pre-existing conditions can be known to the patient and treating physician or be unknown and unmasked due to the above mentioned stress condition of pregnancy. We therefore suggest a systematic approach in these patients as outlined in Fig. 4.1. Using this scheme, a first classification in patients with pre-existing vs patients with new onset cardiovascular disease can be made.

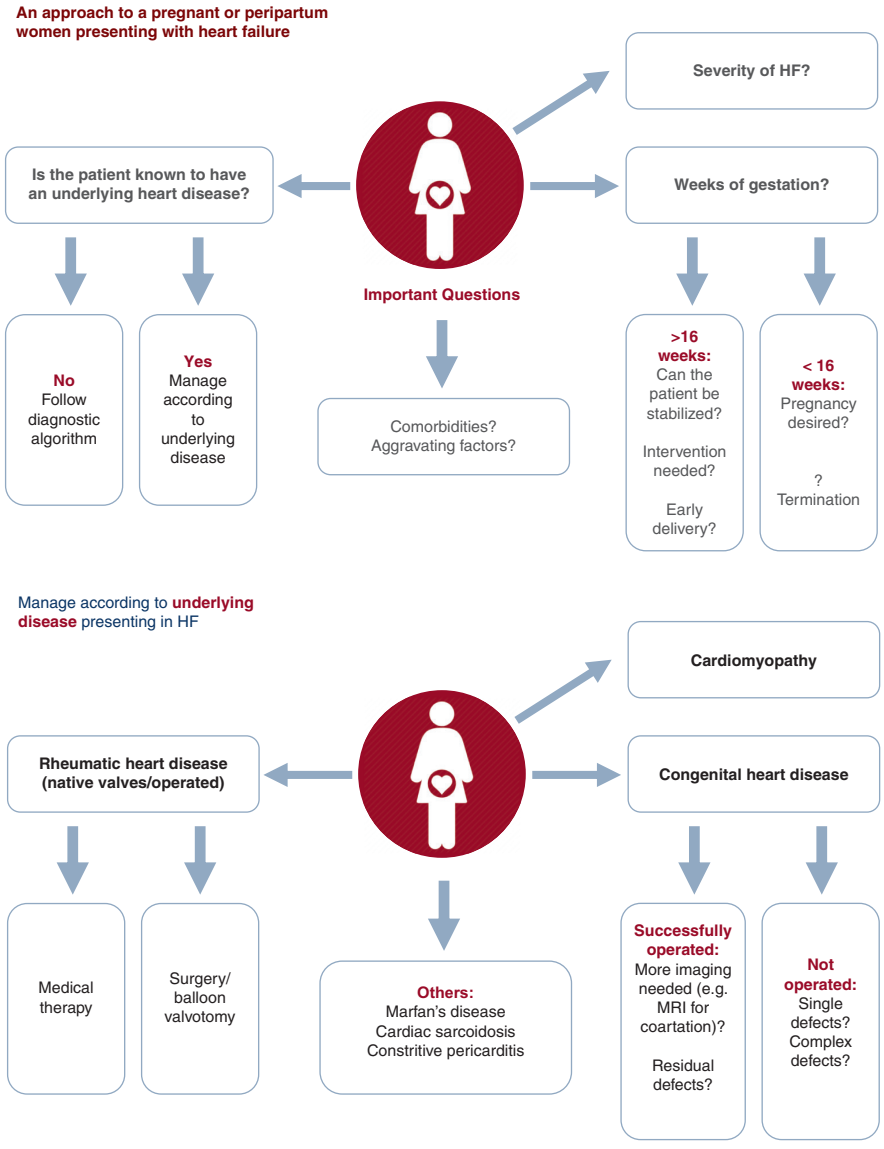

Fig. 4.1 Scheme to classify heart failure in pregnant and peripartum women

4.4 Pre–Existing Cardiovascular Disease in Pregnant Women

In the world-wide Registration Of Pregnancy And Cardiac disease (ROPAC), 7% of pregnancies in women with cardiovascular diseases involved cardiomyopathies [3, 10–13]. In ROPAC women with cardiomyopathies had a 2.4% mortality compared to women with other underlying heart diseases (0–2.1%).

Women known with cardiomyopathy or mutation carriers of an inheritant cardiomyopathy and their partners need to be counselled before pregnancy addressing maternal risk of complications while pregnant and postpartum and the influence of maternal disease on fetal outcome. The possible influence of pregnancy on cardiac function after pregnancy must be taken into account. Date on longer-term impact of pregnancy on deterioration of cardiac function are unknown and not studied so far. The most common pre-existing cardiomyopathies are dilated cardiomyopathies (DCM) or hypertrophic cardiomyopathy (HCM),

Dilated Cardiomyopathy DCM in women of child-bearing age is commonly idiopathic. Secondary causes for DCM can be myocarditis, hypertensive heart disease (particularly common in Africans) and cardiotoxins such as anti-neoplastic drugs [14]. Currently, more than 30 genes are known to be responsible to DCM [15]. Among 88 pregnancies in women with cardiomyopathies in the ROPAC registry one death occurred in a women with DCM and another in a women with anthracycline related cardiomyopathy [10]. However, 6 months outcome data were not available for all and no date for long-term maternal mortality (≥1 year post partum were recorded). A recent study from South Africa showed that eight out of nine death of women with heart disease occurred later than the standard rate of maternal mortality reporting of 42 days [16]. In a series from Canada studying 36 pregnancies in women with DCM, no death occurred but 39% of women developed heart failure or arrhythmias during pregnancy with moderate to severe LV systolic dysfunction and NYHA functional class III or IV with adverse cardiac event rates of 72% and 83% respectively [17]. Fetal and neonatal complications are also common in pregnancies in women with DCM. In the series from Canada 20% of the pregnancies had adverse fetal or neonatal outcomes [17].

Left Ventricular Noncompaction Cardiomyopathy (LVNCCM) LVNCCM is a condition characterized by thickening of the myocardium, which consists of a thin compacted and thick non-compacted layer of myocardium. LVNCCM has a familial occurrence in a large proportion of patients with several underlying gene mutations being identified. A recent study by **Gati S** [18] showed that increased trabeculations fulfilling the criteria of non-compaction develop in a substantial proportion of healthy pregnant women. Their data suggest that increased preload is associated with LV trabeculations resembling LVNCCM. A new diagnosis of LVCCM should be made with caution in pregnant women, especially when there is no heart failure or familial disease [18]. Only limited data from case reports are available regarding pregnancy in women with LVNCCM [19]. Clinical presentation varied from uneventful pregnancy to arrhythmias and severe heart failure. Increase in thromboembolic events have not been reported.

Hypertrophic Cardiomyopathy (HCM) HCM occurs in the general population in 1:500 individuals (0.2%). Localization and severity of hypertrophy differs between individuals due to heterogeneous expression of sarcomeric genes. Limited data are available on the outcome of pregnancy in women with HCM. Mortality appears rare (0.5%) and has only been reported in high risk patients [20]. A meta-analysis on 408 pregnancies in 237 women reported a maternal complication rate of 29% [21]. These complications included heart failure in up to 30% and arrhythmias in up to 48%. All women with HCM should have risk assessment and counselling before pregnancy according to current guidelines, giving attention to both maternal risk and offspring risk, including the risk of transmission of disease [1].

4.5 Newly Onset Cardiovascular Disease Around Pregnancy

Hypertension in Pregnancy Hypertensive complications in pregnancy occur with an estimated frequency of 8% worldwide and are responsible for substantial maternal and foetal morbidities and mortalities [22–24]. Most recent data from an American study suggest that the frequency of hypertensive complications is even higher and may affect one fifth of all pregnancies [25]. The severity of maternal hypertension ranges from slightly elevated systolic and diastolic blood pressure to severe and life threatening conditions. The study of Coel et al. [25] showed that 23% of women with antepartum hypertension were diagnosed with preeclampsia, 60% with transient hypertension, 9.4% with gestational hypertension, and 7.5% with chronic hypertension. Preeclampsia as a severe form of pregnancy associated hypertension is defined as onset of sustained hypertension (>140 mmHg systolic or > 90 mmHg diastolic blood pressure) with development of proteinuria of at least 1+ on dipstick or > 300 mg per 24 h after 20 weeks of gestation. Critical preeclampsia or HELLP syndrome (H: hemolysis, EL: elevated liver enzymes, **LP:** low platelets counts) are defined as blood pressure > 160 mmHg systolic or > 110 mmHg diastolic, proteinuria >5 g per 24 h, neurological symptoms such as seizures, pulmonary edema,

hepatic or renal dysfunction, thrombocytopenia or fetal growth restriction [8]. Preeclampsia and HELLP are leading causes for premature delivery with high risk for maternal, foetal and neonatal morbidity and mortality [8]. Treatment of hypertension in pregnancy is limited since only a few compounds as summarized in the guidelines for treatment of cardiovascular disease in pregnancy [1] are considered safe in pregnancy not harming mother and child. Therefore, the only "cure" for severe hypertensive complications is often (premature) delivery. After delivery acute symptoms and renal damage resolve relatively fast. However, hypertension may take up to 2 years to disappear implying that endothelial injury may be long-lasting. Women with transient left ventricular hypertrophy or preeclampsia appeared more likely to develop postpartum hypertension compared with women with chronic or gestational hypertension [25, 26]. A novel observation is the development of postpartum hypertension in women who had no hypertension during pregnancy [25, 26]. This observation indicates that in general more careful cardiovascular monitoring is required in women not only during pregnancy but also in the first postpartum months. Postpartum women with a specifically high risk for postpartum hypertension had a higher body mass index at delivery and were more likely to have a history of diabetes mellitus [25, 26]. Hypertensive disorders and preeclampsia during pregnancy are associated with additional cardiovascular disorders such as a higher risk for developing PPCM [27]. Indeed, since preeclampsia and PPCM share common pathomechanisms including endothelial damage hypertensive disorders in pregnancy may predispose women to PPCM [4, 28]. Moreover, women with preeclampsia have 3- to eight-fold increased risk for ischemic heart disease, hypertension and stroke as well as obesity, dyslipidemia and end-stage renal disease later in life [29–31].

Finally, hypertensive disorders in pregnancy seem also to impact on the foetus since children resulting from these pregnancies have higher risks for high blood pressure and stroke [24].

Pregnancy as a Stress Test for Underlying Genetic Forms of Heart Failure The physiological impact of pregnancy on the human heart with regard to hormonal and mechanical stress is substantial and is therefore able to unmask unnoticed genetic forms of cardiomyopathies. Indeed, a subset of patients with peripartum heart failure turned out to be carriers of mutations associated with familial forms of dilated cardiomyopathies (DCM), including mutations MYH7, SCN5A, PSEN2, MYH6, TNNT2, cardiac troponin C (TNNC1), and MYBPC3 [32, 33] [5]. The German PPCM registry reports around 16% of patients with a positive family history for cardiomyopathies [27]. A recent study on a large international collective of PPCM patients reported a significantly higher prevalence (15% v.s. 4.7%) of truncating variants of genes whose mutations are associated with cardiomyopathies in PPCM patients compared to normal collectives [5]. Interestingly, two thirds of the identified truncating variants were affecting the Titin gene [5]. Additional genetic factors may also contribute to the susceptibility to peripartum heart failure, a feature that is especially interesting in the light of the higher incidence of the disease observed in patients with African ancestry [34, 35].

However, in general it is not easy to distinguish non-genetic from genetic forms of peripartum heart failure to date. May be the emerging field of next generation sequencing may help to identify disease causing factors and co-factors in patients presenting with new-onset heart failure around pregnancy. Moreover, since the pathophysiology between genetic and non-genetic forms of peripartum heart failure may differ, biomarkers could be developed for a cost saving pre-screening process. This would be important since "true" non-genetic PPCM patients seem to have a higher chance for recovery compared to the genetic forms [27] and family counselling would be recommended if mutations are detected.

Peripartum Cardiomyopathy (PPCM) Among peripartum diseases affecting the heart, PPCM is one of the more severe forms. PPCM is an independent disease that is defined as "an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular (LV) systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found" as proposed by the Working Group on PPCM from the Heart Failure Association of the ESC [35]. For many years PPCM has been considered a very rare disease in Western countries. Meanwhile, it is recognized as an important condition for women's health worldwide with increasing incidence in the USA and in Europe (from 1 in 4350 in 1990 to 1993 to 1 in 2229 in 2000 to 2002 in the USA [36]. Socio-economic changes in Western societies such as rising maternal age and a substantial increase in multifetal pregnancies due to reproductive techniques may account for the higher prevalence [2, 36, 37]. Additionally, the rising awareness of pregnancy related cardiovascular complications, the EUR*Observational* Research Programme on PPCM (http://www.eorp.org) [38] and other national and international reporting facilities [27, 39–41] may also contribute to the larger number of PPCM cases diagnosed in recent years.

In contrast to the above mentioned hypertensive disorders of the cardiovascular system or the genetic forms of peripartum heart failure, the etiology of PPCM is not known. The clinical presentation of PPCM patients is highly variable ranging from phenotypes similar to dilated cardiomyopathy (DCM), cases with almost normal ventricular dimensions or borderline non-compaction cardiomyopathies [2]. No typical

ECG pattern has been described and to date the diagnosis is only based on reduced ejection fraction (EF nearly always below 45%) and the exclusion of other forms of cardiomyopathies [35, 42].

PPCM can present with acute heart failure needing immediate admission to the intensive care unit, or it may develop subtly over several weeks. Especially in the slow developing PPCM, it is difficult to distinguish between normal peripartum discomfort, i.e. fatigue, mild shortness of breath or mild edema, and pathological symptoms of heart failure. Due to these overlapping symptoms even if accompanied by typical heart failure symptoms (congestion, abdominal discomfort, pleuritic chest pain and/or palpitations) diagnosis is often late and subsequent heart failure treatment delayed [2, 4, 35].

Therefore, biomarkers are needed to identify PPCM patients and refer them to expert physicians for further diagnostic assessment. So far, NT-proBNP, a well established marker for heart failure, turned out to be increased in most PPCM patients [27, 43] and would therefore be an easy marker for any peripartum woman reporting discomfort. In addition, enhanced shedding of endothelial microparticles has been reported in PPCM patients [44]. A long the same line, microRNA-146a (miR-146a), present in endothelial exosomes, has been shown to be specifically upregulated in PPCM patients but not in healthy postpartum women or patients with DCM [27, 45]. Since miR146a is directly associated with the pathophysiology of PPCM (outlined below) it appears to be the first PPCM specific marker.

The etiology of PPCM is still unknown but several pathomechanisms that contribute and/or drive the disease have been identified in recent years. For example low selenium level, various viral infections, stress-activated cytokines, inflammation and autoimmune reaction and a pathologic response to hemodynamic stress are suspected factors [34, 46]. Meanwhile, it is suggested that several factors may induce PPCM but finally all merge into a common pathway, which includes the coincidental presence of unbalanced oxidative stress and high levels of the nursing hormone Prolactin (PRL), which lead to the proteolytically produced angiostatic and pro-apoptotic 16 kDa PRL fragment [45, 47]. The 16 kDa PRL complexes with the fibrinolytic inhibitor plasminogen activator inhibitor-1 (PAI-1), and via binding to the PAI-1-urokinase-type plasminogen activator (uPA)-uPA receptor (uPAR), exerts antiangiogenic effects mainly via activation of NFkappaB and subsequent upregulation of miR-146a [45, 48].

Together with additional anti-angiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt1) the 16 kDa PRL disturbs the angiogenic balance in the peripartum phase damaging the endothelium, which subsequently induces a metablic shortage leading to heart failure [4, 28]. Indeed, there is evidence that the maternal heart needs protection against these angiogenic dysbalance and up-regulates the expression of pro-angiogenic factors, i.e. vascular endothelial growth factor (VEGF) [28, 47]. However, there is experimental and clinical evidence that pathways responsible for the upregulation of VEGF, i.e. the signal transducer and activator of transcription 3 (STAT3) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) related signaling, seem to be compromised in PPCM [28, 47, 49]. The same signalling pathways are also required for protection from oxidative stress, which in normal pregnancy rises specifically towards the end of pregnancy [50]. STAT3 and PGC1a play central roles in the anti-oxidative defence of the maternal heart during the peripartum phase because they increase the expression of anti-oxidative enzymes such as manganese superoxide dismutase (MnSOD) [28, 47]. STAT3 is downregulated in cardiac tissue form PPCM patients and cardiomyocyte specific knockout of STAT3 or PGC1a lead to PPCM in mice [28, 47, 49]. Latest data suggest that hyperosmolar stress caused by excessive bleeding during delivery or by ethnic traditions with high salt intake in the postpartum phase may accidently cause a decrease of the protective STAT3 in the heart of peripartum women [49].

Taken together, these data indicate that PPCM may often start as a disease of the endothelium, leading to loss or damage of the vasculature. Moreover, PPCM may be a multifactorial disease caused by the coincidential presence of unbalanced oxidative stress, impaired cardioprotective and pro-angiogenic signalling and high expression of anti-angiogenic factors. Part of these mechanisms may already be initiated during pregnancy for example by preeclampsia. The current understanding of pathomechanisms inducing PPCM is explained in more detail in recent reviews [2, 4].

4.6 Therapeutic Concepts and Management of Peripartum Heart Failure

Currently, peripartum heart failure is treated according to the ESC guidelines for heart failure in pregnancy [1]. In brief, late in pregnancy therapeutic interventions need to consider the health of the mother and the foetus while after delivery standard therapy for heart failure (beta-blockers, ACE-inhibitors/AT1-blockers, diuretics, mineralocorticoid receptor antagonists) is recommended. The more recent insights into the pathophysiology of peripartum heart failure and especially PPCM provide novel and more disease specific therapeutic concepts. In this regard, prolactin blockade with the dopamine D2 receptor agonist bromocriptine to eliminate the prolactin (the full-length nursing hormone and its angiostatic and pro-apoptotic 16 kDa form) has been

successfully tested in several experimental models and in small clinical pilot trials and case reports [28, 47, 51, 52]. The concept of bromocriptine treatment is investigated in a larger controlled randomized multicenter trial in Germany evaluated the dosing of bromocriptine (ClinicalTrials.gov, study number: NCT00998556) [53]. This study showed that 2.5 mg bromocriptine and anticoagulation therapy applied daily on top of heart failure medication is sufficient to promote healing in the majority of PPCM patients while severely diseased patients may need longer (6 weeks) and higher doses (5mg per day) of bromocriptine [43, 54–56]. Since at the same time, PPCM patients have a good chance to recover from the disease early implantation of a defibrillator (ICD) is not recommended and ICD therapy might be even unnecessary [57]. In turn, a first study using wearable cardioverter/defibrillator (WCD) in PPCM patients with severely depressed cardiac function and/or ventricular arrhythmias confirmed their high risk for ventricular tachyarrhythmias in the early phase of the disease. In addition, this study showed that WCD provides protection against sudden cardiac death in the vulnerable phase of the first 3–6 months, and ordinates the need for necessary ICD-implantation in patients recovering from reduced LV-function [57]. An additional, recent study shows that the early therapeutic concept might also crucially influence the patient's chance for recovery. In this respect, analyses of data from the German PPCM registry indicated that patients who were treated with the β1-adrenergic receptor (AR) agonist dobutamine developed frequently terminal heart failure needing either heart transplantation and/or ventricular assist devices [2, 49]. Experimental studies confirmed that low cardiac STAT3 levels in PPCM seem to be responsible for cardiomyocyte necrosis and energy deficits induced by β1-AR agonist treatment [49]. It is important to note that bromocriptine treatment is inefficient to prevent these β1-AR agonist induced heart failure progression. These data support the concept of a restricted use of dobutamine during acute heart failure in PPCM patients. One of the most frequently asked question concerns the possibility of future pregnancies in PPCM patients. Interestingly, PPCM patients seem to tolerate the pregnancy state quite well, especially if they enter the subsequent pregnancy with fully recovered cardiac function [35, 58]. However, cardiac dysfunction re-emerges often in the peri- and postpartum phase [35, 58]. Therefore, PPCM patients should carefully be informed about the risk of relapse and should in general be discouraged from having additional pregnancies. They should be informed about contraceptive options (we recommend IUD since hormonal contraceptives may interact with heart failure medication, and counsel them about the risk for relapse in subsequent pregnancies). However, if they get pregnant again, termination of pregnancy may not prevent PPCM as we observe the disease also in pregnancies terminated in the first and second trimester. In turn, since they tolerate pregnancy normally quite well, they should carefully be followed in experienced centres with close collaboration between obstetricians and heart failure cardiologists. This is especially important in PPCM patients who become pregnant without complete recovery of LV function.

4.7 Conclusion

In recent years the awareness for cardiovascular disease around pregnancy has increased for the benefit of women's health in general. Larger clinical data sets are collected and analysed, thus allowing more insight into the pathophysiology of these diseases and providing important information for diagnosis and management of these patients. Large clinical registries as for example the ones of the EURO OBS program (ESC EURO*OBS* program (www.escardio.org) on pregnancy and cardiac disease (ROPAC) [3, 10–13] or on PPCM [38] together with experimental research are needed to further broaden our understanding of pathophysiology, prevention, treatment and management of cardiovascular disease around pregnancy.

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Anemia and Iron Deficiency in Heart Failure

Otmar Pfister

12.1 Anemia in Heart Failure

12.1.1 Prevalence and Pathophysiology of Anemia in CHF

Estimates of the prevalence of anemia in CHF patients vary broadly due to the use of inconsistent definitions of anemia in different studies. In a meta-analysis derived from 34 published studies, involving more than 150′000 CHF patients, the mean prevalence of anemia was estimated 37.2% with lower prevalence in mild and higher prevalence in severe CHF [1]. Consistent with these data, a recent observational study involving 4456 consecutive patients referred to a cardiology outpatient clinic in the UK reported a prevalence of anemia of 33%, if defined according to the World Health Organization (WHO) criteria as hemoglobin (Hb) concentration <12 g/dl in women and <13 g/dl in men [2]. Anemia is equally prevalent in patients with heart failure with reduced ejection fraction (HFrEF) and those with preserved ejection fraction (HFpEF) [1].

Factors associated with anemia include older age, chronic kidney disease, volume overload, diabetes mellitus, advanced myocardial remodelling, chronic inflammation and most predominantly iron deficiency (ID) [2, 3]. Other nutritional deficits such as Vitamin B12 or folate acid deficiency are uncommon [2]. The pathophysiology of anemia in HF is complex and multifactorial (Fig. 12.1). The predominant mechanisms that contribute to anemia in HF patients are listed below.

Iron Deficiency ID is the major cause of anemia in HF patients. Parameters of ID (e.g. serum iron, transferrin saturation) are strongly associated with anemia in newly diagnosed HF patients [2]. ID in HF may occur in the context of anemia of chronic disease (functional iron deficiency) or as a consequence of depletion of iron stores (absolute iron deficiency).

Inflammatory Cytokines and Erythropoietin (EPO) Resistance CHF is a chronic inflammatory condition with chronic elevation of various inflammatory cytokines [4]. This chronic inflammatory state mitigates EPO production in the kidneys and reduces EPO sensitivity in the bone marrow. EPO resistance in the bone marrow may contribute to anemia in HF. Indeed, there is the phenomenon of a veritable bone marrow dysfunction in patients with CHF [5]. In some anemic CHF patients EPO serum levels are inadequately high, suggestive of profound EPO resistance of the bone marrow. Inadequately high EPO levels are inversely correlated with the prognosis in CHF patients [6].

From the inflammatory perspective, anemia in CHF shares many mechanisms seen in anemia of chronic diseases (e.g. inflammatory bowel disease, chronic rheumatoid diseases).

Chronic Kidney Disease (CKD) CKD affects 30–50% of patients with CHF. Renal hypoxia constitutes the main stimulus for EPO production in the kidneys. In CKD the capacity of appropriate EPO production in response to hypoxia is impaired. Also reduced renal perfusion due to low cardiac output may lead to inappropriately low EPO levels, if corrected to hemoglobin levels. Therefore, reduced synthesis of EPO in the context of CKD or low cardiac output are important causes of anemia [7].

Hemodilution In most patients with CHF hemodilution is a contributing factor to anemia. However, a true red cell deficit is found in the majority of anemic CHF patients on top of hemodilution [8].

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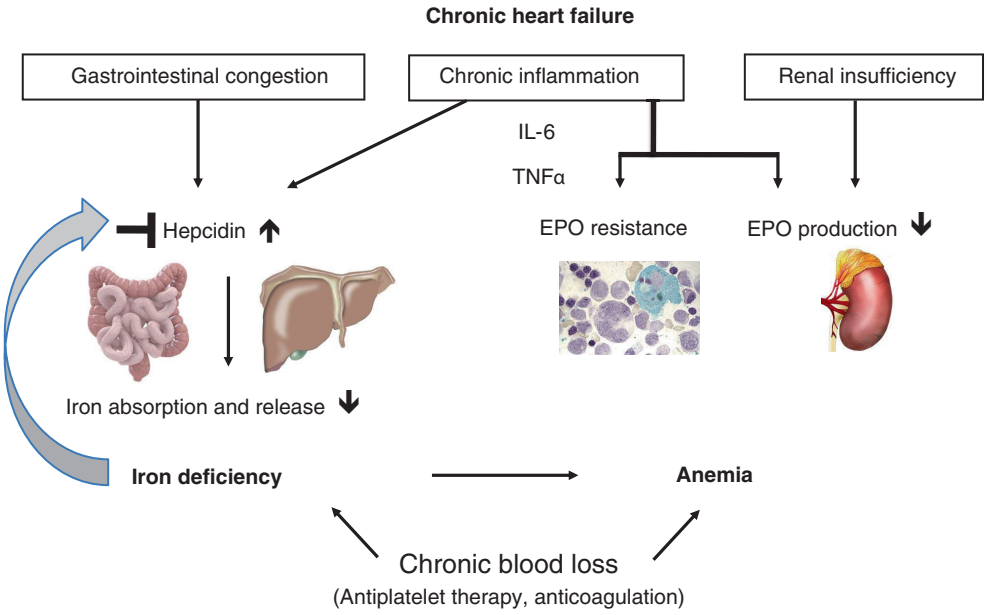

Fig. 12.1 Chronic heart failure

EPO: erythropoietin; IL-6: interleukin 6; TNFα: tumor necrosis factor α

Malabsorption Altered intestinal function due to redistribution of blood away from the splanchnic region or increased bowel wall thickness due to edema may affect iron absorption in the gut thereby contributing to iron deficient anemia.

12.1.2 Diagnostic Work-Up of Anemia in CHF

According to the WHO criteria, anemia is defined as Hb < 120 g/l in women and Hb < 130 g/l in men. Regardless of erythrocyte size (microcytosis vs. normocytosis vs. macrocytosis) evaluation of iron stores (ferritin) should be performed in all cases of anemia to exclude iron deficient anemia (see diagnosis of ID below). The reticulocyte count helps to distinguish hyporegenerative anemia (e.g. renal anemia, anemia of chronic disease, myelodysplastic syndrome) from hyperregenerative anemia (hemolysis, blood loss). In general, any unexplained anemia or ID should be regarded as a potential sign of chronic bleeding and should trigger screening for occult gastrointestinal blood loss. Anemia due to vitamin B12 or folic acid deficiency is rare and of secondary importance in patients with CHF.

12.1.3 Prognostic Impact of Anemia in CHF

Anemia in patients with CHF is an independent risk factor for reduced exercise tolerance, low quality of life, HF hospitalizations and all-cause mortality with an inverse and linear association between Hb values and the risk of death [9]. The risk of hospitalization for HF was increased by 43% in anemic patients compared to non-anemic patients ($p < 0.0001$) in the COMET trial [10]. Even relatively mild degrees of anemia (Hb < 116 g/l for women, and Hb < 126 g/l for men) may confer increased morbidity and mortality [11], such that each 1 g/dl decrease in Hb was associated with a 16% increase in mortality. In terms of mode of death, the presence of anemia is a predictor of both progressive HF-related death and sudden cardiac death [2].

12.1.4 Treatment of Anemia in CHF

Treating anemia in CHF is a clinical challenge due to the fact that its main driver is chronic inflammation. Because the inflammatory process interferes with the production of EPO, the sensitivity of the bone marrow to EPO and the delivery of iron to the bone marrow, protocols for the treatment of anemia in HF have focused primarily on the chronic substitution of erythropoiesis-stimulating agents (ESAs) and the administration of intravenous (i.v.) iron.

Although single-centre, open-label studies have suggested an improvement of exercise capacity and reduced rehospitalisation rates with ESAs in CHF patients with anemia, big randomized trials failed to reproduce these findings [12, 13]. In STAMINA-HeFT administration of the EPO derivate darbepoetin-alpha every 2 weeks for 1 year did not result in any benefit in terms of exercise tolerance, NYHA class or quality of life. There was, however, a trend towards lower risk of all-cause mortality and first HF hospitalization in the darbepoetin-treated group compared to the placebo group [12]. In the RED-HF trial darbepoietin-

alpha could increase hemoglobin concentration with only modest improvement in quality of life and no reduction in hospitalization and mortality [13].

Moreover, concerns have emerged regarding the safety of chronic ESA treatment in patients with cardiovascular diseases. Two studies in patients with CKD (CHOIR, CREATE), where EPO was administered to reach either a higher (up to 15.0 g/dl) or a lower (up to 11.5 g/dl) target Hb showed that EPO administration aiming at higher Hb level may be associated with increased risk of morbidity and mortality [14, 15]. The results of the TREAT study, which randomized 4044 patients with type 2 diabetes, CKD, and anemia to treatment with darbepoietin-alpha or placebo with a target Hb of 13.0 mg/dl was neutral in terms of overall mortality but revealed an excess rate of stroke in the darbepoietin treated group (101 versus 53) [16]. Therefore, current international guidelines do not recommend therapy with ESAs in CHF patients with anemia [17].

12.2 Iron Deficiency in Heart Failure

12.2.1 Definition and Diagnosis

Serum ferritin reflects total body iron stores. Transferrin is a transport protein that circulates iron in a nonreactive state. A widely established cut-off value for the diagnosis of ID in the general population is a serum ferritin level <30 ug/l [18]. Being an acute phase protein, ferritin is increased in chronic inflammatory states such as CHF, independently of iron stores. Therefore, the diagnostic threshold to diagnose ID in CHF is already met at higher ferritin levels. Current international guidelines utilise ferritin and transferrin saturation (Tsat) for the diagnosis of ID, with the following cut-off values: ferritin <100 ug/l (absolute ID = depleted iron stores); or ferritin 100–299 ug/l and Tsat < 20% (functional ID = sufficient iron stores but impaired mobilization to target tissues), Table 12.1 [17].

The ratio of soluble transferrin receptor (sTfR) to log serum ferritin has been proposed to be a sensitive predictor of functional ID in patients with chronic inflammation [19]. sTfR reflects the cellular iron demand and therefore might be a more sensitive indicator of ID than ferritin. However, to date, no cut-off levels of sTfR have been defined for CHF patients. The gold standard for the diagnosis of absolute ID remains bone marrow aspiration. Due to its invasiveness, bone marrow aspiration is, however, not suitable for diagnosing ID in clinical practice.

Table 12.1 Definition of iron deficiency in chronic heart failure

	Ferritin (ug/l)	Transferrin-saturation (Tsat), %
Absolute iron deficiency (depleted iron stores)	<100	
Functional iron deficiency (iron sequestration)	100–299	20

12.2.2 Prevalence

Depending on the definition and diagnostic algorithm the prevalence of ID in CHF patients varies between 37% and 73%, with higher prevalence in more advanced CHF patients (Table 12.2). In anemic patients admitted to the hospital because of advanced CHF (NYHA IV), absolute ID was present in 73% as assessed by the absence of iron staining in bone marrow biopsies (gold standard diagnosis of absolut ID) [20]. In a pooled analysis of five European CHF Cohorts (n = 1506), the prevalence of ID defined according to the ESC-criteria was 61.2% in anemic and 45.6% in non-anemic patients [21]. According to current European registry data, 50% of in- and outpatients with reduced left ventricular ejection fraction (LVEF < 40%) fulfil the ESC-criteria for ID [21, 22]. Independent clinical predictors of ID include female sex, higher NYHA functional class, higher NT-pro BNP, unstable disease and presence of anemia. As for anemia, the prevalence of ID is similar in patients with HFrEF and HFpEF [2].

12.2.3 Etiology and Pathophysiology

ID in CHF is characterized by impaired gastrointestinal iron uptake and impaired mobilization of existing iron stores. In some patients chronic blood loss also contributes to ID, particularly in the context of chronic anti-platelet therapy or oral anticoagulation. The liver protein hepcidin is a key regulator of iron hemostasis (Fig. 12.1). Hepcidin inhibits ferroportin, a protein that is responsible for the transport of iron from enterocytes, macrophages and hepatocytes to cir-

Table 12.2 Prevalence of iron deficiency in selected registries and cohorts

	RAID-HF [22] 2016 (n = 923)	Klip et al. [21] 2013 (n = 1506)	Jankowska et al. [30] 2010 (n = 546)
LVEF %	27	33	26
NYHA ≥ III %	71	54	49
Women %	25	26	12
Age (years)	70	64	55
Anemia %	44	28	ND
ID %	**55**	**50**	**37**

LVEF left ventricular ejection fraction, *NYHA* New York Heart Association Class, *ID* iron deficiency

culating transferrin. Thus, by blocking ferroportin, hepcidin blocks gastrointestinal iron absorption and the release of iron from its storage sites. As a result, high levels of hepcidin "trap" iron in storage cells [23]. HF-associated inflammatory cytokines and hepatic congestion both increase hepcidin serum levels resulting in decreased availability of functional iron, despite adequate total iron stores (iron sequestration). This type of ID is referred to as "functional ID". High levels of circulating hepcidin typically characterize early stages of HF with predominant functional ID [24]. As the severity of CHF progresses chronic mucosal edema and reduced gastrointestinal blood flow may impair iron uptake from the gut resulting in vanishing iron stores and the development of absolute ID [25]. Also, poor nutritional state may further contribute to absolute ID. Therefore, in advanced CHF, hepcidin levels may be low in order to facilitate iron uptake. Low hepcidin levels have been shown to be associated with poor outcome in CHF [24].

Iron is a vital element involved in many physiologic processes. Iron is crucial for hematopoiesis and plays a pivotal role in oxygen transport (hemoglobin), oxygen storage (myoglobin) and oxygen-dependent ATP generation in the mitochondria (element of the respiratory chain). ID leads to a decrease in the number of mitochondria and their cristae, thereby promoting energy deprivation of muscle tissue [26]. Normal cardiac and skeletal muscle function is thus dependent on sufficient iron uptake and proper intracellular iron handling. The effects of ID in CHF are manifold. (1) Impairment of oxygen delivery; (2) impairment of energy (ATP) generation; (3) impairment of skeletal and cardiac muscle function. These pathophysiolgical mechanisms add to the inherent exercise intolerance of the HF syndrome.

12.2.4 Impact on Morbidity and Mortality

The impact of ID on morbidity and mortality in CHF patients has been evaluated in various studies. These studies provide solid evidence that patients with CHF and ID suffer from lower exercise capacity, impaired quality of life and increased mortality. Cardiopulmonary exercise testing (CPET) demonstrated lower mean peak oxygen consumption (PVO2) and steeper VE/VCO2 slopes in patients with ID versus those without ID [27]. This relationship was independent from Hb levels or NYHA class, suggesting that ID alone may impair exercise capacity. There is also good evidence that ID is independently associated with lower quality of life [28, 29]. Jankowska et al. provided first evidence that ID, independently of anemia, might exert detrimental effects on prognosis, including hospitalizations and mortality. In a large cohort of patients with HFrEF the presence of ID was associated with a 12% increase in mortality within 3 years of follow up ($p = 0.0006$) [30]. The independent association of ID with mortality was further substantiated in an international pooled analysis of a mixed population of 1506 HF patients. In this analysis, patients with ID exhibited a more than two-fold higher mortality (8.7% versus 3.6%) at 6 months follow up, independently of the presence of anemia [21]. Taken together these observational data suggest that ID is a stronger prognostic marker than anemia in patients with CHF.

12.2.5 Treatment of Iron Deficiency

Oral Iron Oral iron is inexpensive and widely used to treat iron deficient states in various clinical situations. However, oral iron therapy might have important shortcomings in the context of ID and CHF. (1) Due to impaired gastrointestinal absorption in CHF patients, oral iron therapy might have limited efficacy to increase storage iron and Hb. (2) Treatment adherence for oral iron therapy might be limited due to its propensity for gastrointestinal side effects. (3) Oral iron therapy is inadequate to achieve rapid treatment effects or might be insufficient to overcome the rate of chronic iron loss in CHF patients.

Data about oral iron therapy in CHF patients is scarce. A small retrospective analysis of HFrEF patients taking oral iron supplementation suggested similar improvement of iron stores as previously reported with the use of intravenous iron therapy [31]. To date, randomized controlled multicenter trials exploring the efficacy of oral iron in CHF patients are still lacking. The National Institute of Health-sponsored IRONOUT HF trial (NCT02188784) will be the first to address this important question [32].

Intravenous Iron In contrast to oral iron, intravenous (i.v.) iron therapy bypasses the problem of malabsorption and malcompliance. At present, the safety and efficacy of i.v. iron administration for the treatment of ID in CHF patients was evaluated in nine studies (Table 12.3) [33–41]. Five studies were double-blinded, randomized and placebo-controlled by design [34, 38, 40–42]. In these trials, i.v. iron was administrated in the form of iron sucrose or iron carboxymaltose. Both formulations were well tolerated without evidence of serious adverse effects compared to placebo. Anemic CHF patients exhibited a significant increase in Hb levels. The magnitude of Hb increase across the studies seems dependent on the total iron dose administered, suggesting a possible dose-response relationship. In addition to Hb correction, i.v. iron administration resulted in significant improvement in NYHA class [33–36, 38], exercise tolerance and quality of life [33–35, 38], LVEF [34, 36], N-terminal pro BNP [34] and renal function [38]. There was also a trend towards less cardiovascular events. Importantly, the CONFIRM-HF trial was the

Table 12.3 Clinical trials of intravenous iron in patients with heart failure

Study	Design	Population	N	Treatment	Follow-up	Outcomes			
						Functional Capacity/NYHA Class	QoL	Mortality/ hospitalization	Specific outcomes
Bolger et al. [33] 2006	Uncontrolled	Hb < 120 g/L Ferritin ≤ 400 ug/L LVEF < 30%	16	Iron sucrose 1000 mg (cumulative) over 12 days	3 months	6MWT↑ NYHA Class↓	QoL↑	ND	Hb↑ Ferritin↑ Tsat↑
Toblli et al. [34] 2007	Randomized, double-blind, placebo-controlled	Hb < 125 g/L Ferritin < 100 ug/L Tsat < 20% LVEF ≤ 35%	40	Iron sucrose 200 mg/week for 5 weeks	6 months	6MWT↑ NYHA class↓	QoL↑	ND	Hb↑ Ferritin↑ Tsat↑ NTproBNP↓ CrCl↑ LVEF↑
Usmanov et al. [36] 2008	Uncontrolled	Hb < 110 g/L NYHA class III/IV	32	Iron sucrose	6 months	NYHA class↓ (only in NYHA III)	ND	ND	Hb↑ Ferritin↑ Tsat↑ LVEF↑ Creatinin (NS)
FERRIC-HF [35] 2008	Randomized, controlled, observer-blinded	Hb < 145 g/L Ferritin < 100 ug/L or Ferritin 100–299 ug/L and Tsat < 20% LVEF ≤ 45%	35	Iron sucrose 200 mg/week until ferritin>500 ug/L 200 mg/months thereafter	18 weeks	ΔPVO2↑ NYHA Class↓	NS	ND	Hb (NS) Ferritin↑ Tsat↑ LVEF (NS) Creatinin (NS)
FAIR-HF [38] 2009	Randomized, double-blind, placebo-controlled	Hb ≥ 95,≤135 g/L Ferritin < 100 ug/L or Ferritin 100–299 ug/L and Tsat < 20% LVEF ≤ 40–45%	459	Iron carboxymaltose 200 mg/week until iron repletion	24 weeks	6MWT↑ NYHA Class↓	QoL↑ PGA↑	NS	
Gaber et al. [39] 2011	Uncontrolled	Hb > 120 g/L Ferritin < 100 ug/L and Tsat < 20% LVEF < 40%	40	Iron dextran 200 mg/week until iron repletion	12 weeks	6MWT↑ NYHA Class↓	ND	ND	Echo-parameters S′↑ E'↑ E/E'↓ LVEF (NS) E/A ratio (NS)
IRON-HF [40] 2013	Randomized, double-blind, placebo-controlled	Hb ≥ 90,≤120 g/L Ferritin<500ug/L and Tsat<20% LVEF<40%	23	i.v. iron versus oral iron	3 months	ΔPVO2↑	ND	ND	

(continued)

Table 12.3 (continued)

Study	Design	Population	N	Treatment	Follow-up	Outcomes			
						Functional Capacity/NYHA Class	QoL	Mortality/ hospitalization	Specific outcomes
CONFIRM-HF [42] 2014	Randomized, double-blind, placebo-controlled	Hb ≤ 150 g/L Ferritin<100ug/L or ferritin 100–299 ug/L and Tsat<20% LVEF≤45%	304	Iron carboxymaltose bolus 500–1000 mg Until iron repletion	1 year	6MWT↑ NYHA class↓	QoL↑ PGA↑	Hospitalization↓ Mortality (NS)	
Toblli et al. [41] 2015	Randomized, double-blind, placebo-controlled	Hb < 125 g/L (men) Hb < 115 g/L (women) Ferritin<1 00ug/L or Tsat<20% LVEF≤35%	60		6 months	ND	ND		CrCl↑ NT-proBNP↓ Heart rate↓ LVEF↑

BMC bone marrow cells, *MSC* mesenchymal stem cells, *CSC* cardiac stem cells, *CMR* cardiac magnetic resonance tomography, *ICMP* ischemic cardiomyopathy, *ECHO* echocardiography, *SPECT* single-photon emission computed tomography, *CCT* contrast-enhanced computer tomography, *LVA* left ventricular angiogram, *LVEF* left ventricular ejection fraction, *RNA* radionuclide angiogram, *ND* not determined, *NS* non significant

first study to show a significant reduction in the number of hospital admissions secondary to worsening HF, although the reductions in all hospital admissions was not significant [42]. The simplified i.v. administration scheme used in CONFIRM-HF is particularly attractive for application in clinical practice. In this study, an undiluted bolus of ferric-carboxymaltose (500–1000 mg) was injected intravenously over 1 min. Interestingly, clinical improvements occurred rapidly within the first month of treatment. Subgroup analyses demonstrated that not only anemic patients benefited from i.v. iron but also iron deficient patients without anemia, suggesting that part of the treatment efficacy is Hb-independent. Two meta-analyses including around 600 patients have evaluated the treatment efficacy of i.v. iron in CHF patients with HFrEF [43, 44]. They consistently show improvement of NYHA class, 6-minute walking test and quality of life and reduced rehospitalisation rates. Neither meta-analysis demonstrated a mortality benefit, possibly due to the short follow-ups and inadequate patient numbers in included studies. The results of a number of randomized controlled trials of i.v. iron in different CHF populations are still pending (IRON-MAN, EFFECT-HF, ICHF, FAIR-HF-HFpEF, PRACTICEASIAHF).

12.2.6 Recommendations for Clinical Practice

Current international HF guidelines recommend checking for Hb, ferritin and Tsat in all patients with CHF as part of the initial work-up [17]. These measurements should be repeated every 6–12 months. The ESC Guidelines recommend i.v. iron substitution if ferritin is <100 ug/l or 100–299 ug/l if Tsat < 20% (Table 12.1) [17]. In order to prevent potentially deleterious iatrogenic iron overload, it is mandatory to estimate the total iron dose required to restore iron stores. The total cumulative iron dose can be calculated according to the Ganzoni formula (Table 12.4). In most cases, 1000 mg of iron will be a good starting dose to replenish iron stores [45]. As shown in CONFIRM-HF, 1000 mg can be administered as a single bolus or divided in two boli of 500 mg that are administered within 2–4 weeks. Except for a history of allergic reaction to components of the iron preparation used and the absence of iron deficiency, there are no contraindications to i.v. iron therapy. If Hb levels exceed 15 g/l, iron substitution is not recommended. Because of the possibility of longstanding skin "tattooing" in cases of transcutaneous iron infusion, a solid intravenous access is absolutely mandatory for the administration of i.v. iron. The patient should be observed for at least 30 min following each injection and the administration staff must be trained to diagnose and manage possible anaphylactic reactions. Iron therapy should be stopped if ferritin levels exceed 500 ug/l or Hb levels reach 15 g/dl. Because serum ferritin levels are not representative for total iron stores within the first 3 months after i.v. iron administration, serum ferritin and Tsat should only be measured at least 3 months after the last iron administration in order to document successful repletion of iron stores.

Table 12.4 Estimation of required total iron dose according to the Ganzoni formula

Body weight (kg) × (15 − Hb (g/dL)) × 2.4 + 500 = iron dose (mg)
Example: Patient 80 kg with Hb 12 g/dl:
→ 80 × 3 × 2.4 + 500 mg = 1076 mg

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Notes

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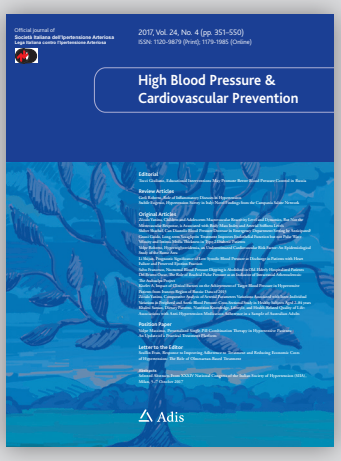

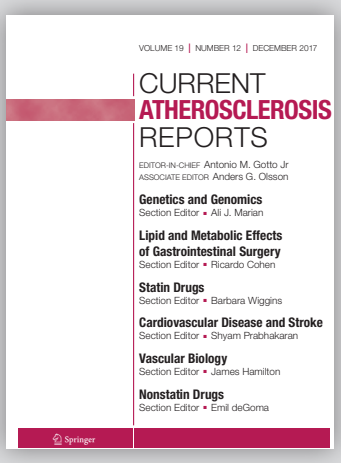

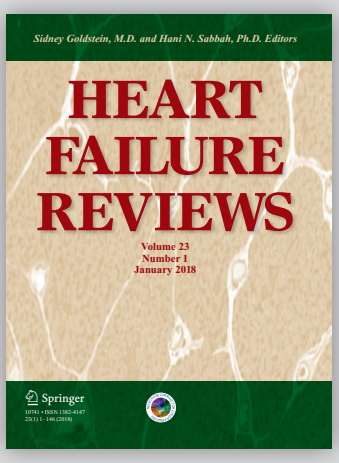

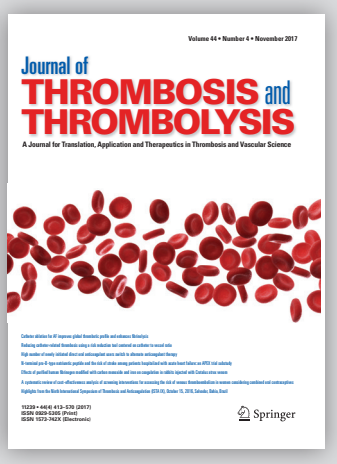

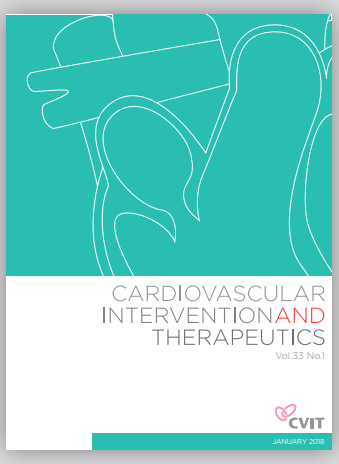

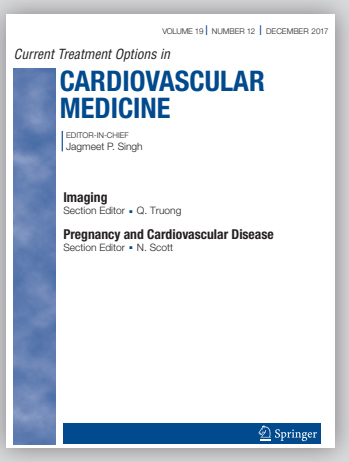

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