

The advent of cardiac resynchronization therapy has created a confusing terminology of heart failure

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Three recent trials (Resynchronization reVERses Remodeling in Systolic Left vEntricular Dysfunction [REVERSE], MADIT-CRT, and Resynchronization-Defibrillation for Ambulatory Heart Failure [RAFT]) [1–3] have demonstrated the benefit of cardiac resynchronization therapy (CRT) in a relatively large number of New York Heart Association (NYHA) class II heart failure (HF) patients with a wide QRS complex, and a much smaller NYHA class I group of asymptomatic patients with severe left ventricular (LV) dysfunction also with a wide QRS complex. These trials generated a large number of substudies, meta-analyses and review articles about CRT in NYHA asymptomatic class I patients and class II HF patients and fostered the expansion of indications for CRT. The large number of publications about CRT has created or reactivated problems with the terminology of HF a situation compounded by the common misinterpretation of the NYHA classification [4]. The following descriptions from recent publications illustrate how confusing the terminology of HF has become. Descriptions such as “severe”, “chronic” and “refractory” used alone are excluded.

1. **HF with mild symptoms.** Also “...mildly symptomatic patients with heart failure”. This terminology is acceptable but the definition of mild symptoms is missing. Presumably it refers to functional class II NYHA, but not class I [4–6].
2. **Mild HF.** Does the word “mild” refer to the degree of structural myocardial disease or symptoms? It probably refers to functional NYHA class II rather than the severity of structural heart disease. HF as a diagnosis is never a “mild” condition because of the seriousness of underlying pathology and poor prognosis [7–15].
3. **Minimally symptomatic HF.** What are minimal symptoms? What is difference between “mild” and “minimal” symptoms? This description should not include asymptomatic NYHA class I patients [16].
4. **Minimal HF.** Does the word “minimal” refer to the underlying structural heart disease or symptoms? It probably refers to functional NYHA class II rather than the severity of structural heart disease but it should be clearly stated. HF is never minimal problem because the seriousness of the underlying pathology and the poor prognosis regardless of symptoms. What is the difference between mild and minimal symptoms? HF? [17].
5. **Patients with less symptomatic HF.** This was part of a meta-analysis of CRT and focused on patients in NYHA class I and II [18].
6. **Mild-to-moderate HF.** The terms “mild” and “moderate” are not defined. This terminology is vague and probably refers to symptoms from a functional class II and/or III NYHA rather than the severity of structural heart disease [3, 19, 20].
7. **Moderate HF.** There is a difference between HF with mild symptoms [4] and moderate HF [21]. What is “moderate” HF? Class II and/or III NYHA class?
8. **Moderate-to-severe HF.** The terms “moderate” and “severe” are not defined. This terminology is vague and probably describes severe symptoms rather than structural heart disease. This terminology has been applied to functional NYHA class III and/or IV patients. What is the real difference between mild-to-moderate HF and moderate-to-severe HF? Both overlap as they both include “moderate” but how? [22–25].

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9. **Advanced HF.** This term is vague and may refer to pathologic findings or symptoms presumably in patients in functional class III or IV NYHA [26–31].
10. **Dyssynchronous HF.** A dyssynchronopathy status with HF can be induced in dogs with experimental left bundle branch block [32–35]. As far as dyssynchronous HF is concerned, a small proportion of CRT responders normalize their LV ejection fraction [36]. Therefore dyssynchronous HF is a diagnosis of exclusion [35, 36] that can only be made after long-term follow-up of patients with nonischemic cardiomyopathy. The diagnosis can be confirmed by turning off CRT whereupon LV function will gradually deteriorate with the passage of time.
11. **End-stage HF.** This term is also imprecise [37–40].
12. **Terminal HF.** “Terminal” is not defined. Another imprecise term [41, 42].
13. **Asymptomatic HF.** This description appears in the literature [43–45] and more recently on the Internet (third party insurers, etc.) in relation to CRT [46–49]. This entity does not exist because HF by definition must have congestion and be symptomatic though the symptoms may sometimes be unimpressive. This mistake is similar to using “class I NYHA HF” to describe HF incorrectly in an asymptomatic patient with substantial LV dysfunction. Some articles are written in a way that suggests the existence of asymptomatic HF. For example a poorly worded title stating a mode of therapy “in asymptomatic and mildly symptomatic heart failure patients,” can be easily interpreted as involving asymptomatic HF patients [5, 50–54]. In this respect Dhir [55] correctly called a similar study “in mildly symptomatic heart failure patients and asymptomatic patients” [56, 57]. It is also incorrect to state that a study involved patients with “NYHA class I/II heart failure.” This also suggests that both class I and II patients have HF.
14. **Changing HF functional NYHA class.** In the MADIT-CRT trial, 10% of patients started at a higher NYHA class (III or IV) than the one assigned upon entry in the trial which enrolled NYHA class I and II patients [2]. The REVERSE trial included NYHA class I patients only if they had moved from a higher class to class I at the time of entry into the trial [2]. HF is a dynamic process so the question arises as to whether one should base therapeutic decisions on the historically worst NYHA class or the current class.

The problems with HF terminology are compounded by the presence of multiple definitions of HF circulating in the literature and the limitations of the NYHA classification. The significance of the HF definition problem and the need for a uniform definition have been identified but little or no progress has occurred [58–60]. The NYHA classification is subjective and there is little evidence for its reliability or reproducibility. Substantial variability exists in assigning a NYHA class [61–65]. The time has come for the various learned cardiology societies to standardize HF terminology and possibly improve the NYHA functional classification.

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References

1. Linde C, Abraham WT, Gold MR, Dauber C; REVERSE Study Group. Cardiac resynchronization therapy in asymptomatic or mildly symptomatic heart failure patients in relation to etiology: Results from the REVERSE (Resynchronization reVERses Remodeling in Systolic Left vEntricular Dysfunction) study. *J Am Coll Cardiol*, 2010; 56: 1826–1831.
2. Moss AJ, Hall WJ, Cannom DS et al.; MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*, 2009; 361: 1329–1338.
3. Tang AS, Wells GA, Talajic M et al.; Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med*, 2010; 363: 2385–2395.
4. Versteeg H, van den Broek KC, Theuns DA et al. Effect of cardiac resynchronization therapy — defibrillator implantation on health status in patients with mild versus moderate symptoms of heart failure. *Am J Cardiol*, 2011; 108: 1155–1159.
5. Forcina MS, Gold MR. Role of cardiac resynchronization therapy in asymptomatic and mildly symptomatic heart failure. *Curr Heart Fail Rep*, 2009; 6: 44–48.
6. Bleeker GB, Schalij MJ, Holman ER, Steendijk P, van der Wall EE, Bax JJ. Cardiac resynchronization therapy in patients with systolic left ventricular dysfunction and symptoms of mild heart failure secondary to ischemic or nonischemic cardiomyopathy. *Am J Cardiol*, 2006; 98: 230–236.
7. Maass AH. Cardiac resynchronization in mild heart failure: All issues resolved? *Cardiovasc Drugs Ther*, 2011; 25: 281–283.
8. Santangeli P, Di Biase L, Pelargonio G et al. Cardiac resynchronization therapy in patients with mild heart failure: A systematic review and meta-analysis. *J Interv Card Electrophysiol*, 2011 [Epub ahead of print].
9. Rickard J, Wilkoff BL. Pivotal trials of cardiac resynchronization therapy: evolution to therapy in mild heart failure. *J Interv Card Electrophysiol*, 2011; 31: 61–68.
10. Reynolds CR, Gold MR. Cardiac resynchronization therapy for mild heart failure: The time has come. *Circulation*, 2011; 123: 195–202.
11. Gold MR, Linde C, Abraham WT, Gardiwal A, Daubert JC. The impact of cardiac resynchronization therapy on the incidence of ventricular arrhythmias in mild heart failure. *Heart Rhythm*, 2011; 8: 679–684.

12. Lubitz SA, Leong-Sit P, Fine N, Kramer DB, Singh J, Ellinor PT. Effectiveness of cardiac resynchronization therapy in mild congestive heart failure: Systematic review and meta-analysis of randomized trials. *Eur J Heart Fail*, 2010; 12: 360–366.
13. Reynolds CR, Gold MR. Cardiac resynchronization therapy in mild heart failure: A review of the REVERSE and MADIT-CRT trials. *Curr Cardiol Rep*, 2010; 12: 367–373.
14. Linde C. Cardiac resynchronization therapy in mild heart failure. *Europace*, 2009; 11 (suppl. 5): 72–76.
15. Tu R, Zhong G, Zeng Z et al. Cardiac resynchronization therapy in patients with mild heart failure: A systematic review and meta-analysis of randomized controlled trials. *Cardiovasc Drugs Ther*, 2011; 25: 331–340.
16. Venkataraman G, Strickberger SA. Cardiac resynchronization therapy in patients with minimally symptomatic heart failure. *Expert Rev Cardiovasc Ther*, 2010; 8: 959–963.
17. Adabag S, Roukoz H, Anand IS, Moss AJ. Cardiac resynchronization therapy in patients with minimal heart failure a systematic review and meta-analysis. *J Am Coll Cardiol*, 2011; 58: 935–941.
18. Al-Majed NS, McAlister FA, Bakal JA, Ezekowitz JA. Meta-analysis: Cardiac resynchronization therapy for patients with less symptomatic heart failure. *Ann Intern Med*, 2011; 154: 401–412.
19. Burri H. Cardiac resynchronization therapy for mild-to-moderate heart failure. *Expert Rev Med Devices*, 2011; 8: 313–317.
20. Zareba W. Comparison of clinical trials evaluating cardiac resynchronization therapy in mild to moderate heart failure. *Cardiol J*, 2010; 17: 543–548.
21. Fogoros RN. <http://heartdisease.about.com/b/2010/11/22/cardiac-resynchronization-therapy-works-for-moderate-heart-failure.htm>.
22. Aaronson M, Gullestad L, Aakhus S et al. Prognostic value of cardiac troponin T in patients with moderate to severe heart failure scheduled for cardiac resynchronization therapy. *Am Heart J*, 2011; 161: 1031–1037.
23. Higuchi K, Toyama T, Tada H, Naito S, Ohshima S, Kurabayashi M. Usefulness of biventricular pacing to improve cardiac symptoms, exercise capacity and sympathetic nerve activity in patients with moderate to severe chronic heart failure. *Circ J*, 2006; 70: 703–709.
24. Fantoni C, Raffa S, Regoli F et al. Cardiac resynchronization therapy improves heart rate profile and heart rate variability of patients with moderate to severe heart failure. *J Am Coll Cardiol*, 2005; 46: 1875–1882.
25. Hillegass WB, Epstein AE. Cardiac resynchronization was effective for moderate-to-severe heart failure with intraventricular conduction delay. *ACP J Club*, 2002; 137: 82.
26. Ott P. Cardiac resynchronization therapy: A new therapy for advanced congestive heart failure. *Am J Geriatr Cardiol*, 2005; 14: 31–34.
27. Pappone C, Vicedomini G, Augello G, Mazzone P, Nardi S, Rosanio S. Combining electrical therapies for advanced heart failure: The Milan experience with biventricular pacing-defibrillation backup combination for primary prevention of sudden cardiac death. *Am J Cardiol*, 2003; 91: F74–F80.
28. Pires LA, Abraham WT, Young JB, Johnson KM; MIRACLE and MIRACLE-ICD Investigators. Clinical predictors and timing of New York Heart Association class improvement with cardiac resynchronization therapy in patients with advanced chronic heart failure: results from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) and Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE-ICD) trials. *Am Heart J*, 2006; 151: 837–843.
29. Mullens W, Wilson Tang WH. Optimizing cardiac resynchronization therapy in advanced heart failure. *Congest Heart Fail*, 2011; 17: 147–151.
30. Smith SA, Abraham WT. Device therapy in advanced heart failure: What to put in and what to turn off: remote telemonitoring and implantable hemodynamic devices for advanced heart failure monitoring in the ambulatory setting and the evolving role of cardiac resynchronization therapy. *Congest Heart Fail*, 2011; 17: 220–226.
31. Young JB, Abraham WT, Smith AL et al.; Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial Investigators. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: The MIRACLE ICD Trial. *JAMA*, 2003; 289: 2685–2694.
32. Vernooy K, Cornelussen RN, Verbeek XA et al. Cardiac resynchronization therapy cures dyssynchronopathy in canine left bundle branch block hearts. *Eur Heart J*, 2007; 28: 2148–2155.
33. Aiba T, Hesketh GG, Barth AS et al. Electrophysiological consequences of dyssynchronous heart failure and its restoration by resynchronization therapy. *Circulation*, 2009; 119: 1220–1230.
34. Agnetti G, Kaludercic N, Kane LA et al. Modulation of mitochondrial proteome and improved mitochondrial function by biventricular pacing of dyssynchronous failing hearts. *Circ Cardiovasc Genet*, 2010; 3: 78–87.
35. Vanderheyden M, Bartunek J. Cardiac resynchronization therapy in dyssynchronous heart failure: Zooming in on cellular and molecular mechanisms. *Circulation*, 2009; 11: 1192–1194.
36. Castellant P, Orhan E, Bertault-Valls V, Fatemi M, Etienne Y, Blanc JJ. Is “hyperresponse” to cardiac resynchronization therapy in patients with nonischemic cardiomyopathy a recovery, a remission, or a control? *Ann Noninvasive Electrocardiol*, 2010; 15: 321–327.
37. Bax JJ, Marwick TH, Molhoek SG et al. Left ventricular dyssynchrony predicts benefit of cardiac resynchronization therapy in patients with end-stage heart failure before pacemaker implantation. *Am J Cardiol*, 2003; 92: 1238–1242.
38. Haghjoo M, Bonakdar HR, Jorat MV et al. Effect of right ventricular lead location on response to cardiac resynchronization therapy in patients with end-stage heart failure. *Europace*, 2009; 11: 356–363.
39. Cowburn PJ, Patel H, Jolliffe RE, Wald RW, Parker JD. Cardiac resynchronization therapy: An option for inotrope-supported patients with end-stage heart failure? *Eur J Heart Fail*, 2005; 7: 215–217.
40. Turley AJ, Raja SG, Salhiyyah K, Nagarajan K. Does cardiac resynchronization therapy improve survival and quality of life in patients with end-stage heart failure? *Interact Cardiovasc Thorac Surg*, 2008; 7: 1141–1146.
41. Wedekind H, Möller K. Early warning system for pulmonary fluid status monitoring in terminal heart failure. *Dtsch Med Wochenschr*, 2007; 132: 555–559.
42. Sack S, Heinzel F, Dargès N, Wieneke H, Erbel R. Cardiac resynchronization therapy in terminal heart failure: current status and prospects. *Herz*, 2001; 26: 84–88.
43. Magri P, Rao MA, Cangianiello S et al. Early impairment of renal hemodynamic reserve in patients with asymptomatic heart failure is restored by angiotensin II antagonism. *Circulation*, 1998; 98: 2849–2854.
44. Summaries for patients. Screening for asymptomatic heart failure. *Ann Intern Med*, 2003; 138: I51.
45. Carerj S, La Carrubba S, Antonini-Canterin F et al. The incremental prognostic value of echocardiography in asymptomatic

- stage a heart failure. *J Am Soc Echocardiogr*, 2010; 33: 1025–1034.
46. Management of patients with symptomatic and asymptomatic heart failure. Elsevier, 2011 (<http://www.expertconsultbook.com/expertconsult/op/book.do?method=display&type=bookPage&decorator=none&eid=4-u1.0-B978-1-4377-0398-6..00028-7-f0045&isbn=978-1-4377-0398-6#lpState=open&lpTab=contentsTab&content=4-u1.0-B978-1-4377-0398-6..00028-7-s0055%3Bfrom%3Dtoc%3Btype%3DbookPage%3Bisbn%3D978-1-4377-0398-6&search=none>).
 47. Linde C. Progressive reverse remodeling in patients with mild or asymptomatic heart failure with previous symptoms in the REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. European Society Congress 2008 (<http://faculty.ksu.edu.sa/amfatani/PHL%205131/ReverseStudy.pdf>).
 48. Daemngen J. Use of PDE III inhibitors for the treatment of asymptomatic (occult) heart failure, 2010 (<http://ip.com/patapp/US20100035889>).
 49. Heidenreich PA. The cost-effectiveness of mass screening to detect asymptomatic heart failure. Center for Health Policy, Stanford University, 2003 (http://healthpolicy.stanford.edu/events/the_costeffectiveness_of_mass_screening_to_detect_asymptomatic_heart_failure).
 50. Linde C, Mealing S, Hawkins N, Eaton J, Brown B, Daubert JC; REVERSE study group. Cost-effectiveness of cardiac resynchronization therapy in patients with asymptomatic to mild heart failure: insights from the European cohort of the REVERSE (Resynchronization Reverses remodeling in Systolic Left Ventricular Dysfunction). *Eur Heart J*, 2011; 32: 1631–1639.
 51. Leclercq C, Mabo P, Trochu JN. Cardiac resynchronization for asymptomatic or mildly symptomatic heart failure: a bridge too far? *J Am Coll Cardiol*, 2008; 52: 1844–1846.
 52. Klein HU. Cardiac resynchronization therapy in asymptomatic or mildly symptomatic heart failure patients. *Curr Treat Options Cardiovasc Med*, 2010; 12: 431–442.
 53. Daubert C, Gold MR, Abraham WT et al.; REVERSE Study Group. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. *J Am Coll Cardiol*, 2009; 54: 1837–1846.
 54. Kourouklis SP, Manolis AG. Cardiac resynchronization therapy in asymptomatic and mildly symptomatic chronic systolic heart failure: a new era of systolic heart failure management? *Hellenic J Cardiol*, 2008; 49: 349–351.
 55. Dhir SK. Cardiac resynchronization in mildly symptomatic heart failure and asymptomatic patients. *J Am Coll Cardiol*, 2010; 55: 257–258.
 56. Herre JM, Linde C; REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction (REVERSE) Study Group. Cardiac resynchronization induces major structural and functional reverse remodeling in patients with New York Heart Association class I/II heart failure. *Circulation*, 2009; 120: 1858–1865.
 57. Linde C, Daubert C. Cardiac resynchronization therapy in patients with New York Heart Association class I and II heart failure: An approach to 2010. *Circulation*, 2010; 122: 1037–1043.
 58. Purcell IF, Poole-Wilson PA. Heart failure: Why and how to define it? *Eur J Heart Fail*, 1999; 1: 7–10.
 59. Coronel R, de Groot JR, van Lieshout JJ. Defining heart failure. *Cardiovasc Res*, 2001; 50: 419–422.
 60. Tan LB, Williams SG, Tan DK, Cohen-Solal A. So many definitions of heart failure: Are they all universally valid? A critical appraisal. *Expert Rev Cardiovasc Ther*, 2010; 8: 217–228.
 61. The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th Ed. Mass: Little, Brown & Co., Boston 1994.
 62. Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: Advantages of a new specific activity scale. *Circulation*, 1981; 64: 1227–1234.
 63. Raphael C, Briscoe C, Davies J et al. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. *Heart*, 2007; 93: 476–482.
 64. Bennett JA, Riegel B, Bittner V, Nichols J. Validity and reliability of the NYHA classes for measuring research outcomes in patients with cardiac disease. *Heart Lung*, 2002; 31: 262–270.
 65. Goode KM, Nabb S, Cleland JG, Clark AL. A comparison of patient and physician-rated New York Heart Association class in a community-based heart failure clinic. *J Card Fail*, 2008; 14: 379–387.