CARDIAC RESYNCHRONISATION THERAPY IN HEART FAILURE

ATRIO-BIVENTRIKULARNA ELEKTROSTIMULACIJA SRCA PRI SRČNEM POPUŠČANJU

Cecilia Fantoni, Angelo Auricchio
Division of Cardiology, University Hospital Magdeburg, Germany

Arrived 2005-04-27, accepted 2005-04-30; Zdrav Vestn 2005; 74: Supl. I: 37–40

Key words: *chronic heart failure; cardiac resynchronisation therapy; electro-mechanical dyssynchrony; defibrillator; left bundle branch block; ventricular conduction disturbance; cardiac resynchronisation therapy*

Abstract – *Cardiac resynchronisation therapy (CRT) is a new therapeutic approach for a selected group of patients with symptomatic heart failure (NYHA III-IV) despite optimal medical therapy, due to dilated cardiomyopathy of any etiology (LVEF≤ 35%, and LVEDD≥ 55 mm), who present with electro-mechanical dyssynchrony (QRS≥ 120 msec). Safety and effectiveness of CRT have been demonstrated by several clinical trials, with patients achieving significant improvement in both clinical symptoms as well as functional status and exercise capacity. Furthermore, CRT has reduced morbidity and mortality of heart failure patients. Whether or not heart failure patients candidate to CRT should receive a defibrillator (ICD) back-up remains debatable, although growing evidence is pointing to extensive use of a defibrillator in such a population.*

Ključne besede: *kronično srčno popuščanje; atrio-biventrikularna elektrostimulacija srca; elektromehanična dissinhronija; levokračni blok; kardioverter defibrilator*

Izvleček – *Atrio-biventrikularna elektrostimulacija srca (CRT) je nov način zdravljenja nekaterih bolnikov z izraženim srčnim popuščanjem (NYHA III-IV), ki se pojavi kljub ustreznemu zdravljenju z zdravili. Vzrok dilatacijske kardiomiopatije ni pomemben (LVEF≤ 35%, in LVEDD≥ 55 mm), pač pa je pomembna elektromehanična dissinhronija (QRS ≥ 120 ms). Varnost in učinkovitost CRT so pokazale številne klinične raziskave, kjer so ugotavljali izboljšanje kliničnih simptomov, fizikalnih parametrov kot tudi telesne zmogljivosti. Ugotovitve kažejo, da CRT zmanjšuje obolevnost in umrljivost pri bolnikih s srčnim popuščanjem. Ni še povsem jasno, ali naj bi bolniki, ki so kandidati za CRT, hkrati prejeli tudi kardioverter defibrilator (ICD), narašča pa število dokazov, ki nedvomno podpirajo široko uporabo ICD v tej populaciji bolnikov.*

Introduction

Despite striking advances in medical therapy of heart failure (HF) (1, 2), morbidity and mortality of HF patients remain high (3). Heart transplantation and ventricular assist devices offer an effective, but limited alternative therapy due to shortage of organ availability and elevated costs. Cardiac resynchronisation therapy (CRT) has emerged as an effective option in selected HF patients with electro-mechanical dyssynchrony. Its safety and clinical efficacy have been proved in several prospective, randomised, controlled trials (4–7). Furthermore, CRT has been proved able to reduce morbidity and mortality of HF patients (8–10), especially when combined with a defibrillator back-up (7).

Mechanical consequences of electrical delays

»... Obviously the shorter the distance that must be transversed in order to reach the Purkinje conducting system, the smaller the fractionate contraction element derived from fiber to fiber excitation and the greater the number of fractions excited over the natural pathways, with the result that more vigorous beats occur...« Wiggers. Am J Physiol 1925; 73: 346–78.

Wiggers first recognised the acute effects of a non-physiological activation sequence on left ventricular function. The strict relationship between conduction delays and abnormal mechanical function has been later confirmed in many other animal models (11) and in human beings (12).

HF patients often present with conduction delays located at various levels of the conduction system, which may depress cardiac performance. Spontaneous or pharmacologically induced sinus node incompetence may contribute to further reduce the already impaired functional capacity of HF patients (13).

About 50% of HF patients show different degree of atrio-ventricular block, being the most frequent one a prolonged atrio-ventricular conduction time. Prolongation of atrio-ventricular time delays ventricular contraction (and consequently relaxation of the ventricle), so that early passive filling overlaps the active one, with reduced atrial booster contribution to ventricular filling. Finally, loss of atrio-ventricular synchrony may determine a ventriculo-atrial tele-diastolic gradient with early re-opening of the mitral valve leading to significant so called »pre-systolic or diastolic« mitral regurgitation (14). All together these phenomena lead to impaired ventricular pre-load.

A significant prolongation of QRS complex of more than 120 ms may be found in approximately 30% of HF patients. The negative prognostic value related to QRS widening, independently of QRS morphology, has been shown in several studies (15, 16). At our best understanding, prolongation of QRS duration is the result of electrical asynchrony at the inter-ventri-

cular, intra-ventricular and intramural level (17). Prolongation of QRS duration may result in mechanical ventricular dyssynchrony which, at the present time, has only been identified at the inter-ventricular and intra-ventricular level. Inter-ventricular delay is defined as the time difference between the onset of pulmonary artery flow and the onset of aortic flow with respect to the beginning of the QRS complex. A delay longer than 40 ms is usually considered indicative of significant inter-ventricular dyssynchrony. Nevertheless, many studies have questioned the real importance of such delay in impairing systolic function compared to intra-ventricular electrical delay (18).

Left bundle branch block is the most common intra-ventricular conduction disturbance occurring in patients with depressed ventricular function. Recent electrophysiological findings have demonstrated that left bundle branch block is a rather complex and heterogeneous electrical disease (19–21). There is increasing evidence that disarray of myocardial layers may partly account for this heterogeneity (20). In patients with left bundle branch block, the region of earliest ventricular activation (usually the inter-ventricular septum) contracts while the remaining ventricular myocardium is still in a non-activated phase. Thus, consistent part of contraction energy is wasted as no effective intra-ventricular pressure can develop. At the same time, the latest activated regions of the left ventricle (usually the lateral and postero-lateral walls) are passively stretched with increasing wall tension at this site and further waste of energy. By the time that the latest depolarised ventricular regions contract, the septum starts to relax and is no more able to withstand the increasing pressure development, and is pushed toward the right ventricle (paradoxical septal motion). In this way, pressure is generated asynchronically by different regions of the left ventricle without effective ejection and with higher waste of energy.

Furthermore, the delayed depolarisation of the lateral wall causes a delayed and slow contraction of the postero-lateral papillary muscle. This event, in the presence of a dilated chamber and abnormal ventricular geometry, contributes to significant worsening of mitral regurgitation. Finally, the heterogeneous electrical and mechanical ventricular activation may further impair systolic ventricular function by delaying relaxation phase and reducing ventricular filling time.

Structural changes related to electromechanical dyssynchrony

In different heart models (22–24), it has been demonstrated that the abnormal loading and work distribution caused by electro-mechanical dyssynchrony may induce regional alterations of myocardial metabolism, gene expression and protein synthesis (23). It may be postulated that these changes could lead to rearrangement of both contractile and non-contractile cells, fibrosis and apoptosis. Experimentally-induced left bundle branch block causes eccentric hypertrophy (25) with an apico-basal and septo-lateral oriented gradient and determines altered synthesis of stress kinases and calcium-handling proteins in the high stress areas (23). Furthermore, it has been demonstrated that mechanical dyssynchrony causes a redistribution of regional flows (26) with consequent chronic hypoperfusion of unloaded regions. The meaning of such complex interactions between changes in regional loading conditions, myocardial metabolism, gene expression, protein synthesis and blood flow distribution induced by an abnormal activation sequence is not fully understood. All together it appears that mechanical dyssynchrony arising from conduction disturbances favours maladaptive structural remodeling process. Thus, it is conceivable that dyysnchrony represents a newly appreciated pathophysiological process which directly depresses ventricular function and ultimately leads to further ventricular dilatation and progression of HF.

Cardiac resynchronisation therapy

CRT improves cardiac performance at reduced myocardial metabolism cost through different mechanisms (27). Pre-excitation of the left ventricular lateral wall with atrial-synchronous left or biventricular pacing restores a normal atrio-ventricular timing, resynchronises right and left ventricular activation as well as septum and lateral wall contraction. In addition to an improved coordination of the septal and lateral wall contraction, reduction of mitral regurgitation and improvement of ventricular filling (28, 29), recent data possibly suggest that CRT may improve cardiac efficiency by slowing the heart rate (30). This may have a beneficial effect on diastolic times and on myocardial oxygen demand.

Clinical and structural effects of CRT

Several prospective, randomised, controlled trials (4–6, 10, 31), conducted in patients with functional NYHA class III-IV, due to dilated cardiomyopathy of any etiology, presenting with electro-mechanical dyssynchrony, have proven the safety and clinical effectiveness of CRT. All these studies demonstrated a significant improvement of quality of life, NYHA functional class, exercise tolerance, and a significant reduction in the hospitalisations for HF. Furthermore, there was a consistent report of significant improvement of left ventricular ejection fraction and partial reversal of maladaptive remodeling process (28, 6). CRT also showed a favourable effect on sympathetic-parasympathetic activity with a reduction of plasma norepinephrine levels and increase of heart rate variability (30). Finally, the recently concluded CARE-HF Study (Cardiac Resynchronisation in Heart Failure) (10), demonstrated a clear survival benefit in HF patients given by CRT in addition to optimal medical therapy compared to optimal medical therapy alone.

Based on these evidences, CRT is currently indicated (Class IIa ACC/AHA/NASPE Guidelines, see Table 1) for patients with symptomatic HF (NYHA III-IV) despite optimal medical therapy, due to dilated cardiomyopathy of any etiology (LVEF≤ 35%, and LVEDD≥ 55 mm), who present with ventricular electrical dyssynchrony (QRS ≥ 130 msec) for the improvement of symptoms, functional status and exercise capacity (32).

It has been reported that a small proportion of patients treated with CRT remain symptomatic. These individuals are usually considered as non-responder patients to CRT. All randomised clinical CRT trials have used statistical techniques to define the response of groups of patients to CRT. No standardised criteria are available to predict reliably the clinical response of a given individual. The large clinical improvement that is observed in some individuals after CRT has created the perception that patients who do not exhibit such improvement are not responding positively to CRT. However many patients who do not show overt improvement may nevertheless benefit from a slowing of disease progression by living longer and not undergoing hospitalisations. Although major efforts have been made for identifying such patients, there are still several unresolved issues in the definition of non-responders and in how to best identify and then treat these patients.

Effects on morbidity and mortality

The COMPANION trial (Comparison of Medical therapy, Pacing, And Defibrillation in chronic heart failure) (7), has shown

marked reduction in combined measures of morbidity and mortality with both CRT alone and with CRT plus defibrillator back-up (CRT-D) with a similar 1-year event-free survival rate. Nevertheless, in contrast to CRT alone which demonstrated a relative risk reduction in all-cause mortality of about 24% (p = 0.060), CRT-D provided a larger (36%) and significant relative risk reduction in all-cause-mortality compared to optimal drug therapy (p = 0.003). These results are consistent with data of a recent meta-analysis showing that CRT alone may be able to reduce all-cause mortality by about 21% (8). Based on these data, the number of patients who needed to be treated to save 1 life is about 25 for CRT alone and 14 when CRT combined to ICD is given. These numbers are comparable with many pharmacological trials which enrolled similarly sick HF patients.
The recently concluded CARE-HF trial (10) that randomised 813 advanced HF patients to optimal medical therapy alone or in combination with a CRT device showed a 36% reduction in the relative risk of all cause mortality with CRT compared with medical therapy alone. Nevertheless, 32% and 35% of deaths occurred among patients randomised to medical therapy and to CRT respectively were sudden deaths that could have been avoided by associating a defibrillator back-up.
Finally, results of the CARE-HF and COMPANION trials and those from another important meta-analysis (9) were consistent in showing a similar risk reduction for the combined end-point – hospitalisations and death – in patients treated with CRT. This finding may suggest a substantial reduction of medical resources.

Implantation issues

The implantation technique is similar to a standard dual chamber sequential pacemaker or implantable cardioverter-defibrillator. The most challenging aspect for achieving resynchronisation therapy is placing a permanent left ventricular lead. A transvenous or thoracotomic approach can be used. The transvenous approach requires the retrograde cannulation of the coronary sinus, a selective angiography of the coronary sinus and his tributaries which delineates the venous anatomy and the final placement of a specifically designed pacing lead into a coronary vein lying over the surface of the left ventricle. Several reports have demonstrated the importance of targeting the latest activated wall which requires implantation of a pacing lead into a lateral or postero-lateral vein (1). The transvenous approach may be a difficult and time-consuming technique. The major limitation is that options for lead placement are governed largely by the patient's venous anatomy which shows considerable inter-individual variability. In about 10% to 15% of cases, it is not possible to achieve a satisfactory left ventricular pacing position or left phrenic nerve stimulation may occur, so that a thoracotomic approach becomes necessary.

Selection of patients

Duration of QRS complex has so far been used as the most practical and readily available criteria to select patients candidate to CRT. Indeed, QRS duration is one of the simplest ways to measure electrical abnormalities that may have a mechanical correlate. Baseline QRS duration has been shown to be associated with degree of mechanical dyssynchrony and with short-term clinical improvement obtained from CRT. Nevertheless there are increasing data (34) suggesting that a considerable proportion of HF patients presenting with narrow QRS complex (< 120 ms) may present echocardiographically-assessed mechanical dyssynchrony of similar magnitude as patients with prolonged QRS duration (> 120 ms).
Recently introduced tissue Doppler imaging (TDI) techniques permit precise evaluation of regional systolic and diastolic synchrony by comparing the time to peak systolic contraction and early diastolic relaxation of multiple segments. TDI appears to offer a comprehensive assessment of cardiac mechanical synchrony. A number of parameters based on TDI have been proposed to evaluate intra-ventricular dyssynchrony but the validity of TDI and other echocardiographic parameters in selecting patients with both narrow and wide QRS who can benefit from CRT need to be confirmed in prospective, randomised long-term studies.

Open questions

CRT is not currently indicated in patients with NYHA class II, even though there are increasing data suggesting that application of CRT in mildly symptomatic HF patients could prevent or slow HF progression. Furthermore, the increasing indications to ICD implantation, based on results of recent big trials (MADIT, MADIT II, SCD-HeFT) rise the problem of considering implementation of the ICD-devices with a CRT back-up in less symptomatic (NYHA II) pts.
Not enough data are so far available about CRT in patients with atrial fibrillation, although preliminary results support its efficacy in this clinical setting (35). Furthermore, there are increasing evidences that the implantation of a CRT device instead of a standard single- or dual-chamber pacemaker may be appropriate for HF patients who undergo His-bundle ablation.
The question of whether HF patients with a standard pacemaker indication for bradycardia benefit from CRT is still unanswered. Nevertheless, data of DAVID trial (36) encourages implantation of a CRT device in patients with impaired ventricular systolic function candidate to chronic pacing.
Recent data suggest that also patients with narrow QRS (< 120 ms), but with echocardiographic evidence of mechanical dyssynchrony may benefit from CRT. Nevertheless, CRT should not be extended to this group before results of prospective randomised trials will be available.
The important issue raised by the COMPANION study (7) is whether all HF patients candidate to CRT should be treated with an additional ICD back-up. The recently concluded trial, the Sudden Cardiac Death – Heart Failure Trial (SCD-HeFT) (37), has provided further evidence that implantation of a defibrillator in addition to best pharmacological therapy is the most effective long-term (5 year) treatment compared to conventional optimal therapy alone or with the adding of amiodarone, to prolong life in HF patients. Therefore, despite the fact that CRT-D devices have larger initial costs, and may require more extensive follow-up than CRT alone, this strategy may be more cost-effective particularly when measured in terms of quality-adjusted life-years gain.

Summary

Cardiac resynchronisation therapy is an effective, adjunctive treatment to pharmacological therapy for a selected group of HF patients who remain symptomatic despite optimal medical therapy, and who present with electro-mechanical dyssynchrony. Safety and effectiveness of CRT have been demonstrated by many clinical trials, with patients achieving significant improvement in symptoms, functional status and exercise capacity. Furthermore, CRT promotes reverse remodeling and reduces morbidity and mortality of HF patients. Thus, CRT should not be considered an alternative to medical therapy but a synergistic therapy. Indeed, in those patients in whom optimal dosage of ACE-Inhibitors or beta-blockers can not be achieved because of hemodynamic in-

tolerance or severe bradycardia, CRT may be considered in order to support ventricular systolic function allowing to optimise beta-blocking and ACE-inhibitor treatment. If CRT should be delivered in NYHA class II, in HF patients with QRS < 120 ms and in HF candidates to chronic pacing needs to be confirmed by randomised controlled trials.

Table 1. *Current guidelines for cardiac resynchronisation therapy.*

AHA/ACC/NASPE Guidelines (32)
Pacing Recommendations (Class IIa Indication)
– Medically refractory heart failure
– Functional New York Heart Association Class III or IV
– Idiopathic dilated or ischemic cardiomyopathy
– QRS duration ≥ 130 ms
– Left ventricular ejection fraction ≤ 35%
– Left ventricular end diastolic diameter ≥ 55mm

References

1. Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. J Am Coll Cardiol 1983; 2: 755–63
2. Merit-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure. Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999; 353: 2001–7.
3. Rodeheffer RJ, Naftel DC, Stevenson LW, et al. Secular trends in cardiac transplant recipient and donor management in the United States, 1990 to 1994. Circulation 1996; 94: 2883–9.
4. Auricchio A, Stellbrink C, Sack S, et al. Long-term clinical effect of hemodynamically optimised cardiac resynchronisation therapy in patients with heart failure and ventricular conduction delay. J Am Coll Cardiol 2002; 39: 2026–33.
5. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001; 344: 873–80.
6. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronisation in chronic heart failure. N Engl J Med 2002; 346: 1902–5.
7. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronisation therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004; 350: 2140–50.
8. McAlister FA, Ezekowitz JA, Wiebe N, et al. Systematic review: cardiac resynchronisation in patients with symptomatic heart failure. Ann Intern Med 2004; 141: 381–90.
9. Bradley DJ, Bradley EA, Baughman KL, et al. Cardiac resynchronization and death from progressive heart failure. A Meta-analysis of randomized controlled trials. JAMA 2003; 289: 730–40.
10. Cleland JGF, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005; 352: 1539–49.
11. Liu L, Tockman B, Girouard S, et al. Left ventricular resynchronization therapy in a canine model of left bundle branch block. Am J Physiol Heart Circ Physiol 2002; 282: H2238–44.
12. Grines CL, Bashore TM, Boudoulas H, et al. Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. Circulation 1989; 79: 845–53.
13. Kass DA. Ventricular resynchronization: Pathophysiology and identification of responders. Rev Cardiovasc Med 2003; 4: S3–13.
14. Meisner JS, McQueen DM, Shida Y, et al. Effects of timing of atrial systole on LV filling and mitral valve closure : computer and dog studies. Am J Phisiol 1985; 249: H604–19.
15. Baldasseroni S, Opasich C, Gorini M, et al. Left bundle branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian Network on Congestive Heart Failure Investigators. Am Heart J 2002; 143: 398–405.
16. Hesse B, Diaz LA, Snader CE, et al. Complete bundle branch block as an independent predictor of all-cause mortality: report of 7,073 patients referred for nuclear exercise testing. Am J Med 2001; 110: 253–59.
17. Auricchio A, Abraham WT. Cardiac resynchronisation therapy: Current state of the art. Cost versus benefit. Circulation 2004; 109: 300–7.
18. Fauchier L, Marie O, Casset-Senon D, et al. Interventricular and intraventricular dyssynchrony in idiopathic dilated cardiomyopathy. A prognostic study with Fourier phase analysis of radionuclide angioscintigraphy. J Am Coll Cardiol 2002; 40: 2022–30.
19. Rodriguez L-M, Timmermans C, Nabar A, et al. Variable patterns of septal activation in patients with left bundle branch block and heart failure. J Cardiovasc Electrophysiol 2003; 14: 135–41.
20. Auricchio A, Fantoni C, Regoli F, et al. Characterization of left ventricular activation in patients with heart failure and left bundle branch block. Circulation 2004; 109: 1133–9.
21. Fung JWH, Yu CM, Yip G, et al. Variable left ventricular activation pattern in patients with heart failure and left bundle branch block. Heart 2004; 90: 17–9.
22. Prinzen FW, Hunter WC, Wyman BT, et al. Mapping of regional myocardial strain and work during ventricular pacing: experimental study using magnetic resonance imaging tagging. J Am Coll Cardiol 1999; 33: 1735–42.
23. Spragg D, Leclercq C, Loghmani M, et al. Regional alterations in protein expression in the dyssynchronus failing heart. Circulation 2003; 108: 929–32.
24. Ukkonen H, Beanlands RS, Burwash IG, et al. Effect of cardiac resynchronization on myocardial efficiency and regional oxidative metabolism. Circulation. 2003; 107: 28–31
25. Van Oosterhout FM, Prinzen FW, Arts T, et al. Asynchronous electrical activation induces asymmetrical hypertrophy of the left ventricular wall. Circulation 1998; 98: 588–95.
26. Prinzen FW, Van Oosterhout FM, Arts T, et al. Mismatch of local myocardial growth and blood flow during chronic ventricular pacing. Circulation 2000; 102: 196.
27. Nelson G, Berger RD, Fetics BJ, et al. Left or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle branch block. Circulation 2000; 102: 3053–59.
28. Yu CM, Chau E, Sanderson JE, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 2002; 105: 438–45.
29. Abraham WT, Hayes DL. Cardiac resynchronization therapy for heart failure. Circulation 2003; 108: 2596–603.
30. Adamson PB, Smith AL, Abraham WT, et al. Continuous autonomic assessment in patients with symptomatic heart failure. Prognostic value of heart rate variability measured by an implanted cardiac resynchronisation device. Circulation 2004; 110: 2389–94.
31. Saxon LA, Boehmer JP, Hummel J, et al. Biventricular pacing in patients with congestive heart failure : two prospective randomised trials. The VIGOR CHF and VENTAK CHF Investigators. Am J Cardiol 1999; 83: 120D–3D.
32. Gregoratos G, Abrams J, Epstein AE, et al. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). Circulation 2002; 106: 2145–61.
33. Butter C, Auricchio A, Stellbrink C, et al. Should stimulation site be tailored in the individual heart failure patient. Am J Cardiol 2000; 86: K144–51.
34. Yu CM, Lin H, Zhang Q, et al. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. Heart 2003; 89: 54–60.
35. Leon AR, Greenberg JM, Kanuru N, et al. Cardiac resynchronisation in patients with congestive heart failure and chronic atrial fibrillation: effects to upgrading to biventricular pacing after chronic right ventricular pacing. J Am Coll Cardiol 2002; 39: 1258–63.
36. Wilkoff BL, Cook JR, Epstein AE, et al. Dual-chamber pacing or ventricular back-up pacing in patients with an implantable defibrillator: the dual chamber and VVI implantable defibrillator (DAVID) trial. JAMA 2002; 288: 3115–23.
37. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable-defibrillator for congestive heart failure. N Engl J Med 2005; 352: 225–37.