Cardiac resynchronization therapy with special focus on patency of coronary sinus and its branches: conceptual viewpoint and semi-theoretical considerations on lead-induced obstruction

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Key words: cardiac resynchronization therapy, coronary sinus patency, venous drainage, occlusion of cardiac veins, activation sequence of left ventricle.

Summary. Cardiac resynchronization therapy appears to be useful for patients with severe chronic congestive heart failure. However, many questions still arise concerning the effectiveness of this kind of therapy since hemodynamic improvement is not observed in all patients. Heterogeneity of conclusions reported by several multicenter clinical trials and prominent experts demonstrates that many uncertainties related to cardiac resynchronization therapy still exist. We tried to reveal some inadequacies in clinical results by focusing on cardiac venous blood return which is likely complicated by the presence of lead inside the coronary sinus and its branches. Downstream traversing lead may occlude (partially or completely) the ostia of minor tributaries and target vein of lead final positioning. Thrombosis may also be incited within the coronary sinus itself. Remaining lumen predetermined by the lead body and subsequent thrombosis may be insufficient to provide adequate blood flow. Resulting detrimental venous return presumably may slightly depress myocardial contractility which may be significant in very sensitive group of patients assigned to the New York Heart Association class III or IV. Cardiac venous blood pumping conditions (or venous drainage) are likely also complicated by abnormal activation of left ventricle. The contributory role of these two subtle causes unfavorably influencing venous drainage is still unknown. It may be treated as a hypothetical attempt to find the clue and needs future studies for verification.

Introduction
Due to continuing uncertainty of benefits of cardiac resynchronization therapy there is a need to seek for new causes which might explain currently unacceptable clinical results. We tried to reveal some subtle reasons on data-driven and hypothesis-driven basis. Suggested conceptual viewpoint contains two preconditions – patency of coronary sinus and its branches and physiological activation sequence of left ventricle. These fundamental considerations, however, need corroboration.

Cardiac resynchronization therapy (CRT) was developed to restore ventricular synchrony and to improve left ventricular (LV) function and patient functional status. Despite of many multicenter studies including randomized clinical trials considerable uncertainties still exist about the effects of CRT on survival and the magnitude of improvement in the overall long-term quality of life (1). Some clinical and scientific indefiniteness exists since most reports end with suggestions to continue research for more reliable conclusions and confidence. Currently this modern pacing modality is widely used, however, CRT or biventricular pacing has not become yet the treatment of choice.

Simultaneous biventricular pacing in man was first performed by B. Befeler et al. in 1979 for the evaluation of arrhythmias (2, 3). The first report on the potential hemodynamic benefit of this pacing mode was published in 1983 (3). Hence, the overall period of clinical use of CRT exceeds a quarter of a century. Despite such a long history we still face “continuing uncertainty” regarding the benefits of CRT (1). That is why we need to explore potential causes in order to discontinue this uncertainty.

Intravascular and intracardiac tissue response to endocardial lead invasion and its long-term presence is well established. These well-known pathological changes are fundamental and allow understanding the consequences of lead indwelling into the coronary sinus (CS) and its tributaries. The enthralling idea of simultaneous contraction of both ventricles is very
important in order to achieve hemodynamic improvement. Also we believe that physiological sequence activation of the LV may increase both the left ventricular functional status and the venous blood drainage via cardiac veins and CS. That is why the hint of possible para-bundle or para-branch pacing may play some contributory role.

This article may be treated as a discrete conceptual attempt to disclose some subtle and disputable reasons. It contains both data-driven and hypothetical considerations which may be useful per se or will serve as a booster for better understanding and for new strategies. Indicated causes presumably limiting CRT effectiveness are under suspicion and need corroboration.

**Background**

Versatilities in results achieved by different investigators do undermine to a certain extent the hopes of severely ill patients and their physicians as well. There are reports demonstrating that approximately 25–30% of patients with heart failure do not benefit from CRT (4, 5). It might mean that one-third (or close to that) of CRT patients do not respond to modern treatment. Thus, nonresponders represent a group that is too large and clinically unacceptable. Moreover, LV or biventricular pacing may also have detrimental hemodynamic effects in some patients compared with right ventricular pacing (6). A disputable issue is whether CRT has value in patients with right bundle branch block (1, 7, 8). Fortunately, there are a great number of researchers declaring more optimistic clinical and hemodynamic results (9–13). Based on the facts in literature, one can both admire the fundamental idea of CRT and wonder why it does not work so well.

Patency of coronary sinus and its branches is a precondition to normal cardiac blood circulation. Any obstacle lowering blood flow, whether venous or arterial, may result in a decrease of cardiac output. Single or multiple stenotic obstructions obviously will have different clinical consequences especially noticeable in patients with congestive heart failure. Hence, it could be recognized that cardiac venous blood return is to be treated as an important unconditional factor to achieve normal hemodynamic parameters. Above-mentioned might be fundamental to reach the goal and to create new strategies for more effective cardiac resynchronization therapy.

**Intravascular response to pacemaker lead**

The transvenous lead is known as a highly biocompatible alien body. To minimize inflammation and subsequent fibrosis at the tissue interface, electrodes should be biologically inert (14, 15). Insulation material and the lead tip are in direct contact with blood, therefore, they must have low thrombogenicity. However, thrombosis of veins (cephalic, axillary, subclavian) is expected (16, 17). It resolves spontaneously, although partial venous obstruction in great veins is almost the rule (14). The degree of obstruction may vary; sometimes the obstruction is widespread and an isotope scan or venous angiography reveals high incidence of asymptomatic venous thrombosis (14, 15, 18). Extension of a clot, thrombosis, and fibrosis may involve the innominate vein, superior vena cava, contralateral structures, or the cerebral venous sinus (19–21). The degree of venous obstruction finally determines whether thrombosis is silent (subclinical) or symptomatic. Also, the development of collateralization is helpful to avoid severe clinical outcomes.

In brief, indwelled pacemaker lead being inert does evoke some intravascular response, which is largely unimportant but at times still meaningful. Finally, the extraction of a chronic pacemaker lead is difficult (occasionally very difficult), and it means that every long-term pacemaker lead is involved in the process of fibrotic encapsulation. These recapitulated findings actually are well-known clinical and pathophysiological data which might be helpful for better understanding of changes taking place in coronary sinus and its branches.

**Extrapolation to coronary sinus and cardiac veins**

If thrombosis, fibrosis, and obstruction take place in great veins, the propensity for such complications might be extrapolated into other veins including cardiac ones. In other words, transvenous leads, wherever they are located, presumably may evoke similar thrombofibrinolytic response in their vicinity. Meanwhile, this could be interpreted as a presumption or hypothesis which is not accompanied by any direct evidence yet. However, there are well-known difficulties and risks related to chronic pacemaker lead extraction from CS and cardiac veins (22–24). It means that these leads like any endocardial leads are entrapped. Their extraction, as reported, is more successful with a shorter pacing period. Encapsulation of the CS lead itself may serve as indirect evidence of similar endovascular responses.

**Peculiarities of cardiac veins and lead-induced consequences**

Despite of coexistence of smaller venous system (predominantly thebesian veins opening directly into
cardiac chambers, most frequently into the atria), CS and its tributaries are much more important (25). Mean luminal diameter, measured by computed tomography, is 11±4 mm at the juncture of the CS with the great cardiac vein and 5±1 mm at the level of the lateral mitral annulus (26). The diameter of a coronary sinus lead equals approximately 2 mm. So the proportion of these two diameters is unfavorable for the blood flow. Tapering caliber of CS and target veins is another unfavorable factor. The lead pushed into a target vein and reaching critically narrowed site presumably occludes the vessel. It leads to regional venostasis, which perhaps is not very significant. However, transcoronary lead traversing CS downstream and abutting parietal may occlude the ostia of tributaries. It is assumed that due to the regular heart beat these ostia are periodically opened (perhaps partially, not completely) facilitating venous drainage. Such functioning of partially obstructed veins may last for several days or weeks until “natural” thrombosis is initiated. Then initial venostasis in the area of the target vein may gradually extend with subsequent covering of new areas and finally becoming “global”. Lead body and subsequent thrombosis presumably narrow the lumen of CS. Remaining lumen of CS may appear insufficient to provide adequate blood flow. Due to compensatory capabilities of thebesian veins, this depicted pathophysiological scenario may not manifest itself. Nevertheless, silent symptoms and parameters, inaccessible for measurements yet, may persist and advance. At large, impaired cardiac venous flow in the main cardiac collective vessel even in the context of active participation of small thebesian veins connotes overall negative influence on cardiac activity. The question is, “How much?” After all, CS and its tributaries were “created by nature”; therefore, these vessels are key to the integrity of cardiac blood circulation system. Obviously, the role of the cardiac venous system could not be ignored. The importance of the CS might be tested experimentally on animals by pressure or ligation of the sinus.

Hypothetically, nonresponders to CRT are likely to be patients who suffer from severe or critical cardiac venous flow impairment. Patients demonstrating positive hemodynamic response to CRT presumably have saved good functional status of their cardiac veins or their cardiac venous system has not been occluded totally. Positive clinical results in the latter group of patients might be explained by cardiac capability of collateralization (to certain extent) or by favorable placement of transcoronary lead which in turn has not occluded the ostia of minor cardiac veins emerging into the CS lake. Collateralization, whether subepicardial or intramural, is scarcely imaginable if at all. Of course, predominating heart disease, e.g. dilated cardiomyopathy, and its clinical stage of development (terminal or preterminal) are crucial for the magnitude of hemodynamic improvement from CRT. In other words, functional status of cardiac veins in such cases is perhaps less important compared to residual physical capabilities of devastated myocardium. Nevertheless, good cardiac venous functional status is a precondition to achieve clinically noticeable hemodynamic improvement in patients with heart failure and with still saved cardiac capability of positive response to CRT.

According to the report of L. Snell and colleagues (27) some benefits of biventricular pacing are transient and may be related to dual-mode, ventricular inhibited (DVI) pacing effect. So, several possible reasons may determine acute hemodynamic or long-term functional improvement. It could be that hemodynamic improvement may not manifest until thrombotic events become fully established and, as a result, initial improvement may not persist. However, there is a report concluding that patients with transvenous leads have significantly better functional improvement compared to patients with epicardial leads (28). This report seemingly would not support our theory. The same authors add that long-term event-free survival rates do not differ between the two groups. Some misinterpretations of clinical results may appear due to more eventful postoperative course in the group of patients undergoing transthoracic approach.

**Subtle importance of left ventricular activation sequence**

As biventricular pacing is a form of electromechanical therapy that resynchronizes contraction and modifies the mechanical behavior of the LV during systole, hypothetically it may be able to reverse LV remodeling in heart failure (29). Since heart failure is characterized by progressive LV dilatation, which results in gradual deterioration of cardiac function (remodeling), these pathological changes are essential. According to some investigators (29–31) biventricular pacing reverses electromechanical dyssynchronization from apex to base resulting in improvement of LV systolic function. Unfortunately, in practical point of view this is achieved not in all patients, treated by CRT.

There is some doubt related to the genuine mechanism of emptying of cardiac veins: is it passive “hydrodynamic” process or is there a need of some
mechanical support of cardiac musculature? A healthy heart is capable of solving this problem by harmonic pumping out the blood engorged in both—its chambers and its venous system. Disordered and dilated heart with its considerable structural changes, however, may be vulnerable in this point of view. If the mechanical support of emptying of cardiac veins is necessary, a natural, i.e. physiological, activation sequence of LV could be desirable. If so, activation sequence of LV usually observed in biventricular pacing may not make any significant input into the venous blood flow of cardiac veins. It may even be harmful, therefore, resulting in negative velocity or volumic changes of this flow. Restoration of conductivity of left bundle branch of His’ or para-bundle (para-branch) pacing might be helpful in the end stages of heart failure. Consequently, in order to regain previous hemodynamic parameters two conditions at least should be fulfilled, i.e. simultaneous activation of both ventricles and physiological activation sequence of LV.

Conclusions
1. To justify the expectations of cardiac resynchronization therapy patients there is a need to seek for new causes which potentially impede the achievement of acceptable hemodynamic results.
2. It seems that patency of coronary sinus and cardiac veins is desirable at least theoretically; therefore, transvenous route of left ventricular pacing by transcorynary lead is to be reconsidered.
3. Abnormal or nonphysiological activation sequence of left ventricle (as adverse effect of pacing) may be interpreted as a limiting factor to improve hemodynamic response.

Širdies resynchronizacinė terapija koronarinio sinuso ir jo šakų pratekamumo aspektu: konceptualus požiūris, teoriniai ir praktiniai pasvarstymai apie elektrodo sąlygojamą obstrukciją

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Raktažodžiai: širdies resynchronizacinė terapija, koronarinio sinuso pratekamumas, veninio kraujo nutekėjimas, širdies venų užskimšimas, kairiojo skilvelio aktyvacijos nuosukšmas.

Santrauka. Pasaulinė praktika rodo, jog širdies resynchronizacinė terapija (arba biventriculinė stimuliacija) turi teigiamą hemodinaminį poveikį esant lėtiniam širdies nepakankamumui. Tačiau šios terapijos efektyvumas dar nėra pakankamai įrodytas, nes hemodinamikos pagerejimas būna ne visiems ligoniams. Multicentriinių klinikinių studijų išvadų įvairovę, taip pat nevienareikšmės eksperta nuomonės rodo, jog ši vis dar neįvertinta šio gydymo metodo klinikinė nauda. Mes pamėgiome įsigrįžti į šią problemą, dėmesį susiçentravo į širdies veninio kraują cirkuliaciją ir galimą sunkų veninio kraujo gržimą, sietiną su paties elektrodo buvimu koronariniame sinuse ir jo šakose. Šiai pagrindinai būdingi, jog elektrodas, būdamas koronariniame sinuse ir šildamasis prie jo sienelės, kartu gali iš dalies arba visiškai užkūnėti veninių intakų žiotis. Ilgiauininio elektrodas gali sukelti koronarinio sinuso ar jo intakų trombozę. Likęs spindis, kurį nulemia pats elektrodas bei intraveninės trombozės pasekmės, gali būti nepakankamas veninio kraujo tėkmei. Įtariama, jog pablogėjęs veninio kraujo gržimas ir su tuo susijusi venostazę gali turėti svarbų poveikį miokardo kontraktiliškumui, o tai gali turėti neigiamą įtaką labai jautriai ligonių grupei, priskiriamai NYHA III ir NYHA IV funkcinėi klasei. Susirūpinimą kelia ir tai, jog širdies veninio kraujo nutekėjimą (drenažą) gali komplikuoti ydingas kairiojo skilvelio aktyvacijos nuosukšmas, kurį dažniausiai lydi šio skilvelio sudirginimas stimulatoriaus impulsu. Bandytų įvardyti dvi gana svarbias priežastis, galinčias nepalankiai paveikti širdies veninio kraujo nutekėjimą, tačiau šios įtakos dydis kol kas nežinomas. Taigi hipotetiskai bandoma rasti „ratų mišieji imintis“ ir taip paaškinti ne visuomet efektyvų širdies resynchronizacijos terapiją. Tam dar reikalingi tyrinėjimai, nulemiantys šių teorinių samprotavimų pagrįstumą.

References
simultaneous biventricular stimulation in man, with special reference to its use in the evaluation of intraventricular reentry. Eur J Cardiol 1979;9:369-78.