# SPECTRAL AND CROSS-SPECTRAL ANALYSIS OF **CONDUCTANCE CATHETER SIGNALS** New Indexes for Quantification of Mechanical Dyssinchrony

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- Conductance catheter, spectral analysis, coherence function, heart failure, mechanical ventricular Keywords: dyssynchrony.
- We hereby present novel index to quantify ventricular mechanical dyssynchrony by using Abstract: spectral and cross-spectral analysis of conductance catheter volume signals. Conductance catheter is a volume measurement technique based on conductance measurement: the intraventricular volume, i.e. the time-varying volume of blood contained within the heart cavity, is estimated by measuring the electrical conductance of the blood employing a multi-pole catheter. Five segmental volume signals (SVi, i=1,...5) can be acquired; total volume (TV) is estimated as the instantaneous sum of the segmental volumes. We implemented classical time-domain dyssynchrony indexes already utilized in conductance catheter signals analysis, and new frequency-domain indexes. Study population consisted of 15 heart failure (HF) patients with left bundle branch block and 12 patients with preserved left ventricular (LV) function. We found that spectral measures seem to out-perform classical time-domain parameters in differentiating atrial HF patients from no-HF group. These findings encourage the use of spectral analysis to obtain crucial quantitative information from conductance catheter signals.

#### **INTRODUCTION** 1

In a normal heart, mechanical activation of the ventricles occurs in a coordinated manner and depends on the rapid spread of electric signals via specialized fibers (His-Purkinje system) which branch out throughout the right ventricular (RV) and

left ventricle (LV) endocardium (Uhley, 1960). When the activation is slowed-down or blocked, ventricle activation and contraction become dyssynchronous. Ventricular mechanical dyssynchrony is most commonly identified clinically by a prolonged QRS duration with left bundlebranch block (LBBB) morphology on surface

Valsecchi S., Padeletti L., Battista Perego G., Censi F., Bartolini P. and J. Schreuder J. (2008)

In Proceedings of the First International Conference on Bio-inspired Systems and Signal Processing, pages 437-444 DOI: 10.5220/0001060104370444

<sup>437</sup> SPECTRAL AND CROSS-SPECTRAL ANALYSIS OF CONDUCTANCE CATHETER SIGNALS - New Indexes for Quantification of Mechanical Dyssinchrony.

electrocardiogram but can also be detected by echocardiographic imaging of contraction timing.

Ventricular mechanical dyssynchrony plays a regulating role already in normal physiology (Brutsaert, 1987) but is especially important in pathological conditions, such as hypertrophy (Villari et al., 1996), ischemia (Heyndrickx and Paulus, 1990), infarction (Gepstein et al., 1998), or heart failure (HF) (Nelson, 2000). Dyssynchrony exacerbates heart failure (HF) in a variety of ways, generating cardiac inefficiency as well as pathologic changes at the biologic tissue, cellular, and molecular levels. Currently, the conductance catheter method has been extensively used to assess global systolic and diastolic ventricular function. More recently the ability of this instrument to pickup multiple segmental volume signals has been used to quantify mechanical ventricular dyssynchrony.



Figure 1: The conductance catheter positioning inside the left ventricle.

Conductance catheter was first introduced in 1981, by Baan and co-workers as a new volume measurement technique based on conductance measurement (Ban et al., 1981, Ban et al., 1984). Intraventricular volume, i.e. the time-varying volume of blood contained within the heart cavity, is estimated by measuring the electrical conductance of the blood employing a multi-pole catheter (conductance catether, Figure 1). The conductance catheter has 12 electrodes and should be positioned along the long axis of the LV in such a way that the electrode at the tip is situated within the apex and the proximal one just above the aortic valve. A weak alternating current (0.4 mA peak-to-peak, 20 kHz) is induced between the two most distal and two most proximal electrodes, in order to set up an electrical field within the ventricular cavity. Other 6 electrodes are used pair wise to measure segmental conductance signals. Two electrodes are used to record the intracardial ECG. A micromanometer measures real-time LV pressure. The induced voltage is then measured with six electrodes in between, yielding 5 segmental voltages. Since the conductance of the blood itself is constant (neglecting long term changes in haematocrite) the measured voltage will be proportional to blood resistivity, and thus inversely proportional to the conductance or amount of blood between the measuring (voltage) electrodes. This method has several advantages over other methods which determine intra-ventricular volumes. The results are obtained immediately, i.e. on-line, and precise geometric assumptions regarding the ventricle or labor-intensive analyses are not required. Recently, Steendijk et al., first introduced time-domain quantitative indexes of dyssynchrony based on volume signals acquired with the conductance catheter (Steendijk et al., 2004). Spectral analysis of conductance catheter signals has not been tempted yet. Frequency domain analysis has been extensively used to characterize a number of physiological signals, with promising results in terms of both classification schemes (Schumann et al., 2002, 1 Zywietz et al., 2004, Severi et al., 1997) and understanding of physiological mechanisms (Asyali et al., 2007, Cerutti et al., 1988, Montano et al., 2001). During ventricular dysfunction, segmental ventricular volumes experience abnormal changes result in unexpected spectral which could components. Also, the asynchrony and incoordination between ventricular segments, that seem to be quintessential to ventricular dysfunction, could be promisingly explored by cross-spectral analysis. The coherence spectrum is a frequency domain measure that may be used to make a quantitative comparison between activity of two heart regions. In the present study, coherence spectra have been used to quantify the relation between spectral components of ventricular volumes from different regions. The coherence spectrum would provide a measure of the synchrony and coordination between ventricular sites, and thus be indicative of the organization of electrical activity. Such a measure would be a useful tool in the

characterization and detection of synchronous contraction. Coherence measurements may provide a means to quantify the terms "synchronous" and "dissynchronous" as applied to ventricular contraction.

Aim of this paper is to characterize the conductance catheter signals in the frequency domain and to propose new indexes for ventricular mechanical dyssynchrony quantification.

# 2 METHODS AND MATERIALS

#### 2.1 Study Population

The study population consisted of 27 consecutive patients with indications for electrophysiologic study or device implantation: 15 HF patients with left bundle branch block and 12 patients with preserved LV function. Table 1 shows the clinical characteristics of the study population. Age, sex and QRS duration were similar between groups. Subjects with a previously implanted device, valvular insufficiency or stenosis were excluded from analysis.

Table 1: Clinical characteristics of the study population.

	non-HF group	HF group
	(n=12)	(n=15)
Male gender, n	7	11
Age, years	67±14	68±6
Ischemic		7
Cardiomyopathy, n		/
NYHA Class		3.1±0.5
Ejection Fraction, %	57±9	26±6*
QRS duration, ms	88±21	167±24*
p-values: * < 0.05		~

#### 2.2 Experimental Protocols

A conductance catheter was placed in the LV via the femoral artery, and a temporary pacing lead was positioned in the right atrium. The conductance catheter enables online measurement of 5 segmental volume (SV<sub>i</sub>, i=1,...,5) slices perpendicular to the LV long axis. We used 7-Fr combined pressureconductance catheters with 1-cm interelectrode (CD spacing Leycom; Zoetermeer, The Netherlands). The catheter was connected to a Cardiac Function Lab (CD Leycom) for online display and acquisition (sample frequency 250 Hz) of segmental and LV total volumes (TV), LV pressure, and ECG. TV was obtained as the instantaneous sum of the segmental volumes.

Two stimulation protocols have been used, i.e. during spontaneous ventricular activation and atrial pacing. For this protocol, hemodynamic status was evaluated using multiple parameters. Indices of LV pressure, volume, and function were calculated and averaged over 8 to 10 beats at end expiration from the raw LV pressure and conductance volume data. Sequences of 30 s, i.e. 40-50 consecutive non-arrhythmic cardiac cycles at fixed heart rate induced by atrial pacing (at 10 bpm above the sinus rate) and steady-state conditions, were selected for off-line analysis using custom-designed software.

#### 2.3 Classical Dyssynchrony Parameters Estimation

From the conductance catheter signals, we estimated the following classical time-domain parameters: mechanical segmental dyssynchrony (DYS), Internal flow fraction (IFF), Mechanical Dispersion (DISP), Cycle Efficiency (CE) and Time exceeding aortic closure (TExAC). See appendix for more details.

#### 2.4 Spectral and Cross-Spectral Analysis

First we analysed the segmental and total volume signals in the frequency domain. For the spectral analysis, the periodogram of the signals was estimated. To reduce spectral leakage a Hamming window was applied after removal of the mean value. The length of segments was 1000 samples and a segment-overlap of 30% was used. Then we divided the signal bandwidth in 4 frequency bands (0-1 Hz, 1-5 Hz, 5-20 Hz and >20 Hz), and we estimated the percentage powers (PP) and the peak frequencies (PF) in each bands (PP<sub>0-1Hz</sub>, PP<sub>1-5Hz</sub>, PP<sub>5-20Hz</sub>, PP<sub>>20Hz</sub>, PP<sub>>20Hz</sub> and PF<sub>0-1Hz</sub>, PF<sub>1-5Hz</sub>, PF<sub>5-20Hz</sub>, PF<sub>>20Hz</sub>, respectively).

The continually changing temporal or phase relationship between two volume signals has been quantified in the frequency domain by magnitude-squared coherence (Ropella et al., 1989). Magnitude-squared coherence (C(f)) between two recordings is defined as

$$C(f) = \frac{\left|S_{xy}(f)\right|^2}{S_{xx}(f)S_{yy}(f)}$$

Where x(t) and y(t) are two simultaneous recordings, Sxy is the cross power spectrum between signals x and y, and Sxx and Syy are the individual power spectra for signals x and y, respectively. C(f) is a measure of the linear relation between signals as a function of frequency, f, and is a real quantity with value between zero and one. In other terms, C(f) measures the constancy of the time delay (phase) at a specific frequency between signals x and y. Two linearly related signals (in the absence of noise) will have a C(f) function equal to one at all frequencies present in both signals, while two random, uncorrelated signals will have a C(f) equal to zero at all frequencies. Any linear operation (multiplication by a constant or addition of a constant) on one or both of the signals will not alter the C(f) between x and y. However, additive, uncorrelated noise and system nonlinearities will reduce C(f) for two similar signals. C(f) may be estimated for sampled data using a method of overlapped and averaged FFT spectral estimates (Carter et al., 1973). Basically, estimates of Sxx, Syy and Sxy are determined using a periodogram technique (2048samples long window, overlap 512 samples), and their estimates are then used in the definition of C(f).

The C(f) functions between each segmental volume SVi and the TV have been estimated. A Total Coherence function has been defined over the band 0-125 Hz by averaging the 5 C(f) functions. From the Total Coherence function, 5 new frequency domain indexes have been extracted:

- mean value of the Total Coherence over the band 0-125 Hz (Coh\_{Tot})
- mean value of the Total Coherence from 0 to 1 Hz  $(Coh_{0-1Hz})$ ,
- mean value of the Total Coherence from 1 to 5 Hz  $(Coh_{1-5Hz})$ ,
- mean value of the Total Coherence from 5 to 20 Hz (Coh<sub>5-20Hz</sub>),
- mean value of the Total Coherence from 20 to 125 Hz (Coh<sub>>20Hz</sub>).

#### 2.5 Statistical Analysis

All data are presented as means±SD. Differences between distributions were compared by a t-test for



Figure 2: Examples of SV and TV time series and power spectra, for a no-HF patinet and a HF one. Coherence function between  $SV_1$  and TV are showed, as well as the total coherence function.

Gaussian variables, and by Mann-Whitney nonparametric test for nongaussian variables. Statistical correlations between variables were tested by least-squares linear regression. A P value < 0.01was considered significant. We performed receiveroperating characteristic (ROC) curve analysis to test the diagnostic performance of the indexes to discriminate the patient groups. Sensitivities and specificities at the optimal cut-off point were determined.

## **3 RESULTS**

Example of the power spectrum of a TV signal are showed in figure 2, for a HF patient and a no-HF one. The coherence function between one SV and the TV and the Total coherence are also showed. The characteristics of the power spectrum of TV signals are reported in Table 2 (similar results were obtained for SVi signals, but were not reported). The majority of the signal power is in the band from 1 to 5 Hz (programmed heart rate during acquisition from 70 to 100 bpm). The components above 20Hz are associated to less than 1% of the total signal power. The frequency peak in the 0 - 1 Hz band matches with the respiratory rate and the power in this band seems higher in HF group. Table 3 summarizes the results of the comparison between groups for all indexes considered in the analysis, represented as mean  $\pm$  standard deviation. Overall, 3 parameters permitted to discriminate the two groups (p<0.01): Coh1-5, Coh5-20 and CE. Table 4 shows the results of the ROC curve analysis. Sensitivity and specificity for Coh1-5 are 0.67 and 0.92, those obtained for Coh5-20 are 1.00 and 0.92 and those relatve to CE are 0.80 and 0.83, respectively. In Figure 3 the ROC curves are shown.

Table 2: Characteristics of the power spectrum of TV signal.

	no-HF	> НF	p-values
PP <sub>0-1Hz</sub>	4.34±6.26	9.12±12.00	0.071
PF <sub>0-1Hz</sub>	0.41±0.17	0.45±0.12	0.488
PP <sub>1-5Hz</sub>	93.24 <mark>±</mark> 6.45	88.44±11.85	0.194
PF <sub>1-5Hz</sub>	1.52±0.20	$1.44 \pm 0.13$	0.301
PP <sub>5-20Hz</sub>	2.16±1.84	2.21±1.34	0.946
PF <sub>5-20Hz</sub>	8.37±0.88	$7.63 \pm 0.80$	0.036
PP>20Hz	$0.25 \pm 0.25$	0.23±0.15	0.814
PF>20Hz	37.59±5.12	44.14±7.59	0.013

## **4 DISCUSSION**

Quantification of nonuniform mechanical function and dyssynchrony may lead to a more complete diagnosis of ventricular dysfunction (Schreuder wet al., 1997, Schreuder et al., 2000). Moreover, it may guide therapy, because patients with extensive likely to benefit from dyssynchrony are resynchronization therapy (Leclercq et al., 2002). The visualization of mechanical dyssynchrony provided by methods based on magnetic resonance imaging and echocardiography, although further emphasize the important role of mechanical dyssynchrony in cardiac dysfunction, requires laborious procedures and require substantial operator interaction and expertise.

Table 3: Indexes of mechanical dyssynchrony in no-HF and HF groups.

	no-HF	HF	p-values
		2	
DYS, %	26.0±7.2	32.6±3.9	0.012
IFF, %	25.8±18.8	40.8±13.6	0.033
DISP, ms	23.4±16.4	35.6±13.2	0.068
CohTot	$0.44 \pm 0.07$	0.37±0.10	0.016
Coh0-1	0.63±0.19	0.51±0.18	0.099
Coh1-5	0.69±0.10	0.57±0.10	0.004*
Coh5-20	$0.47 \pm 0.07$	0.32±0.04	0.000*
Coh>20	$0.43 \pm 0.08$	0.37±0.12	0.041
CE	0.78±0.12	0.58±0.16	0.000*
TExAC, ms	6.9±8.8	15.7±10.5	0.016





Figure 3: ROC curve analysis.

	Area Under Curve (95% CI)	p-value	Cut-off
Coh1-5	0.81 (0.65-0.98)	0.006	0.57
Coh5-20	0.98 (0.94-1.02)	0.000	0.40
CE	0.88 (0.75-1.00)	0.001	0.70

Table 4: ROC curve analysis of the tested variables.

Recently, novel indexes were introduce to quantify dyssynchrony based on volume signals acquired by the conductance catheter during cardiac catheterization (9). Such indexes were based on a time-domain approach and provided additional, new, and quantitative information on temporal and spatial aspects of mechanical dyssynchrony.

To our knowledge, conductance catheter volume signals have never been studied in the frequency domain. Since dyssynchrony refers to the organization of the mechanical contraction of the ventricle, it is natural to investigate such a phenomenon by spectral and cross-spectral analysis of ventricular segmental movements. The frequencydomain analysis can indeed discover particular aspects of interaction between volume signals beyond the temporal relationships.

Present analysis permitted to describe some characteristics of the conductance-volume signals. The frequency analysis evidenced the absence of relevant components above 20 Hz: this result corroborates the validation of segmental signals acquisition obtained by comparison with cinecomputerized tomography (16), whose sampling rate has approximately the same value. The amplitude of the components in the range 0-1 Hz, attributable to the respiratory artefact, resulted markedly higher in HF patients, this may be due to the higher (mechanical) cardio-pulmonary interaction or to an altered vasovagal activity.

More interesting results have been obtained by cross-spectral analysis. The spectral coherence function provides a quantitative measure of that temporal synchrony and coordination between activities of ventricular regions. During synchronous mechanical contraction, multiple sites are activated in an coordinated manner, and the phase relation between activity from two sites is relatively unchanging, resulting in a high (close to 1) coherence. When ventricular contraction is dyssynchronous, the activity observed at one region is likely to be unrelated to the activity observed at other distant regions. Thus the coherence between two such sites would be very low at all frequencies due to a continually changing phase relation.

In the present study, the spectral coherence was confirmed to be significantly greater for ventricular contraction of no-HF patients than for HF ones. We found that the most significant parameters in the discrimination between HF and no-HF group were Coh1-5 and Coh5-20, with the latter reaching a sensitivity of 1 and a specificity of 0.92. Spectral measures seem to out-perform classical time-domain parameters (9) in differentiating atrial HF patients from no-HF group.

Since no previous studies have been performed on a similar topic, the frequency bands have been chosen on empirical basis. The choice of the optimal frequency bands in term of discriminating power would require larger population and/or modelling of ventricular contraction.

In conclusion, this paper encourages the use of spectral analysis to obtain crucial quantitative information from conductance catheter signals.

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## APPENDIX

Mechanical dyssynchrony. At each time point, a segmental signal is defined as dyssynchronous if its change (i.e., dSV/dt) is opposite to the simultaneous change in the total LV volume (dTV/dt). Segmental dyssynchrony is quantified by calculating the percentage of time within the cardiac cycle that a segment is dyssynchronous. Overall LV dyssynchrony (DYS) is calculated as the mean of the segmental dyssynchronies. DYS may be calculated

within each specified time interval, i.e. during systole and diastole, with systole defined as the period between the moments of dP/dtmax and dP/dtmin.

Internal flow. Nonuniform contraction and filling is associated with ineffective shifting of blood volume within the LV. This internal flow (IF) is quantified by calculating the sum of the absolute volume changes of all segments and subtracting the absolute total volume change:

$$IF(t) = \left[\sum \left| dSVi(t) / dt \right| - \left| dTV(t) / dt \right| \right] / 2$$

Note that dTV(t)/dt represents the effective flow into or out of the LV. Thus IF measures the segment-tosegment blood volume shifts, which do not result in effective filling or ejection. Division by two takes into account that any non-effective segmental volume change is balanced by an equal but opposite volume change in the remaining segments. IF fraction (IFF) is calculated by integrating IF(t) over the full cardiac cycle and dividing by the integrated absolute effective flow.

Mechanical dispersion. In the HF patients, a substantial dispersion is present in the onset of contraction between the segments. This dispersion is assessed by segmental lag times which are determined by calculating the cross correlations between TV(t) and SV(t) for all systolic time points (i.e., between dP/dtmax and dP/dtmin). For each segment the lag which produces the highest linear correlation is determined. Mechanical dispersion (DISP) is defined as 2 standard deviation of the segmental lag times. Recently, new parameters have been introduced to quantify LV dyssynchrony with echocardiographic techniques. These indices can be directly applied to conductance method.

Cycle Efficiency. Calculated as previously described by the formula: CE=SW/[ LVP\* LV volume], with SW = stroke work, LVP = end-systolic - enddiastolic LV pressure. This index quantifies distortions in the shape of the pressure-volume diagram. The calculation assumes that the optimal contraction would have CE value near 1.0, corresponding to a rectangular pressure volume diagram. Decreases in cycle efficiency may be caused by multiple factors including isovolumic volume shifts as well as changes in afterload and ventricular stiffness. Similarly, regional cycle efficiency can be calculated from the most basal to the most apical segmental volume signal plotted against LV pressure. Differences in regional cycle efficiency during isovolumic filling or emptying may indicate inefficient patterns contraction or relaxation due to dyssynchrony.

Time exceeding aortic closure. In order to measure diastolic dyssynchrony and specifically to quantify LV contraction in diastolic phase, a new index was proposed, quantitatively reflecting the whole temporal amount spent by 12 LV segments in contracting after aortic valve closure. Using strain imaging that reflects myocardial deformation, the time of strain tracing exceeding aortic valve closure (ExcT) was measured in each segment as the interval between the marker of aortic closure and the nadir of the strain tracing. ExcT was considered 0 when the nadir of strain curve did not exceed aortic valve closure. The overall time of strain exceeding aortic valve closure (oExcT) was computed as the sum of the 12 segmental ExcTs. The index may be implemented in conductance method by considering each segment presenting a systolic phase (negative dSVi/dt) persisting during the phase of global diastole (positive dTV/dt). oExcT is estimated as the sum of these delays for all segments.