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Assessment of cardiac function during mechanical circulatory support: the quest for a suitable clinical index

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Abstract*— A new index to assess left ventricular (LV) function in patients implanted with continuous flow left-ventricular assist devices (LVADs) is proposed. Derived from the pump flow signal, this index is defined as the coefficient (k) of the semilogarithmic relationship between "pseudo-ejection" fraction (pEF) and the volume discharged by the pump in diastole, (Vd). pEF is defined as the ratio of the "pseudo-stroke volume" (pSV) to Vd. The pseudo-stroke volume is the difference between Vd and the volume discharged by the pump in systole (Vs), both obtained by integrating pump flow with respect to time in a cardiac cycle. k was compared in-vivo with others two indices: the LV pressure-based index, M_{TP}, and the pump flow-based index, I_Q. M_{TP} is the slope of the linear regression between the "triple-product" and end-diastolic pressure, EDP. The triple-product, $TP = LVSP.dP/dt_{max}.HR$, is the product of LV systolic pressure, maximum time-derivative of LV pressure, and heart rate. I_Q is the slope of the linear regression between maximum time-derivative of pump flow, dQ/dt_{max}, and pump flow peak-to-peak amplitude variation, Q_{P2P}. To test the response of k to contractile state changes, contractility was altered through pharmacological interventions. The absolute value of k decreased from 1.354±0.25 (baseline) to 0.685±0.21 after esmolol infusion. The proposed index is sensitive to changes in inotropic state, and has the potential to be used clinically to assess contractile function of patients implanted with VAD.

I. INTRODUCTION

Left ventricular assist devices (LVADs) have emerged as the standard of care for advanced heart failure (HF) patients, requiring mechanical circulatory support [1]. The third generation, non-pulsatile flow devices are more reliable and safer, presenting a low incidence of device related adverse events, with enhanced patient's quality of life when compared to their pulsatile counterparts.

The remodeling process resultant from HF was generally believed to be irreversible. However, there has been compelling evidence of myocardial recovery in a small - yet significant - group of patients, especially those with idiopathic cardiomyopathy [2]. Both basic and clinical research findings [3] suggested that left ventricular unloading through VAD support lead to cellular and functional recovery, with consequent LVAD explantation.

Identification of potential candidates to recovery entails assessment of LV function of the assisted heart. Proper evaluation of LV contractility has to be load-independent, and sensitive to inotropic changes. The slope of the linear regression between the LV "triple product" (TP) and the LV end-diastolic pressure (EDP), M_{TP}, was evaluated by McConnell and collaborators [4] in a series of in-vivo experiments. TP is the product of LV systolic pressure, heart rate and the maximal time-derivative of LV pressure, i.e., TP = LVSP.$(dP/dt)_{max}$.HR. Because this index requires invasive measurements of LV pressure, its application on the clinical setting would be limited.

Recently, Schima and colleagues proposed the I_Q [5], an index that can be derived from pump flow. The I_Q was defined as the slope of the linear regression between the maximal time-derivative of pump flow (dQ/dt_{max}) and its peak-to-peak amplitude variation (Q_{P2P}). Tests in-silico and in-vivo demonstrated that the I_Q is sensitive to contractility changes, with potential to clinical applications.

This paper presents a novel method to assess cardiac contractility from pump flow, based on a curvilinear relationship between pEF and pump diastolic volume, Vd. For a pulsatile pump, one can define pump stroke volume per beat, either by integrating outlet and inlet flows and subtracting the latter from the former, or by a fixed amount of stroke volume at each pump beat. For continuous-flow devices, we propose the pSV. The pump flow signal is integrated over time and a reference signal (e.g., ECG) would make possible to calculate the amount of blood generated (or discharged) by the pump in systole and in diastole [6].

Pump flow pulsaility has been used in the clinical realm as a surrogate to cardiac contractility. Surely, pulsatility may increase as a result of ventricular recovery. However, pulsatility is preload dependent, and even intermittent episodes of inlet cannula tip moving against the ventricular wall can be confounded with increased pulsatility. This report addresses the need for an index that can be used in the clinical setting, especially at low speeds. This paper is organized as follows: Section 2 describes the k index derivation. Section 3 presents the experimental results of an in-vivo study performed in a calf. Concluding remarks are presented in section 4.

II. INDEX DEFINITION

Because of the residual left-ventricular function of the assisted heart, continuous-flow devices generate flow that may present pulsatility. Indeed, presence (or absence) of

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pulsatility on pump signals (flow, current) has been used as an anecdotal "marker" of myocardial contractile state in the clinical realm. As opposed to pulsatile devices, rotary pumps are in synchrony with the natural heart, as shown in Figure 1.

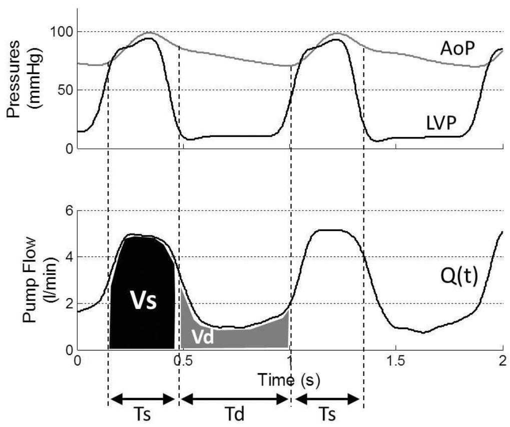

Fig. 1. Pump hemodynamics at 1800 rpm. Ts is systolic time; Td is diastolic time; Vs is the volume of pump flow in Ts, and Vd is the volume of pump flow in Td. AoP is aortic pressure, LVP is left ventricular pressure and Q(t) is pump flow.

The pEF is defined as

$$pEF = \frac{pSV}{Vd} = \frac{Vd - Vs}{Vd} \tag{1}$$

where Vd and Vs are defined as

$$Vd = \int_{Td} Q(t)dt \tag{2}$$

$$Vs = \int_{Ts} Q(t)dt \tag{3}$$

and Q(t) is pump flow, as shown in Figure 1.

Besides contractility of the native heart, pump speed also influences pulsatility: as pump speed increases, pump flow pulsatility diminishes. Figure 2 illustrates this phenomena in-vivo. The upper panel of Fig. 2 shows that pump speed was changed in a stair step fashion. Three increasingly speed set points are of interest: 1800 rpm, 2100 rpm, and 2500 rpm, respectively.

The second panel of Fig. 2 shows how the pump flow signal changes as pump speed is increased. For each one of the speed settings described, Vd and Vs were calculated and the derivative of pump flow with respect to time. When speed is low (1800 rpm, in this example), most of the pump flow volume in a beat would occur in systole (Vs $\gg$ Vd), for a recovered or healthier heart. At 2100 rpm, the pump flow volume in systole and diastole would be about the same, regardless of the cardiac phase (Vs $\approx$ Vd), and at higher speeds, 2500 rpm, Vd would surpass Vs (Vs $<$ Vd). If the heart function is depleted ("weak" heart, with low contratile strength), even at lower speeds, Vs would not be higher than Vd, because of the "flattened" pump flow waveform.

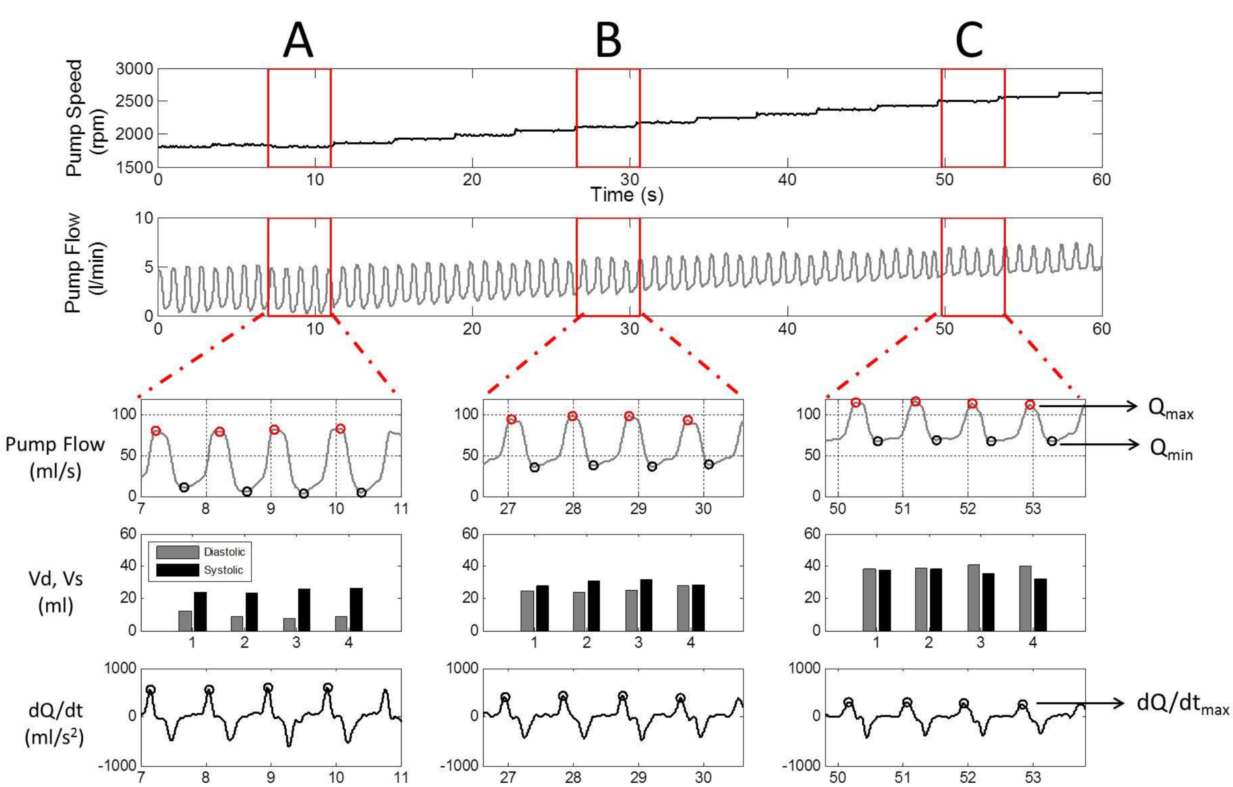

Fig. 2. Pump flow analysis for a stair steep speed experimental study, at A) low support (1800 rpm); B) moderate support (2100 rpm), and C) higher support at 2500 rpm. In each case, panels from the top are pump flow, Vd and Vs, and pump flow derivative, dQ/dt

Since pEF (see eq(1)) measures the amount of blood volume generated by the VAD in one cardiac cycle, pEF may carry information on the heart contractile function. Thus, the relationship between pEF and Vd can be used to assess contractility. Figure 3 shows that, at a constant inotropic state, the (Vd, pEF) coordinates move along a curvilinear relation that can be written as

$$pEF = k \log(Vd) + a \tag{4}$$

where a, k are constants. In summary, the constant k will change according to the contratile state of the heart, and a accounts for the fact that pEF may go negative.

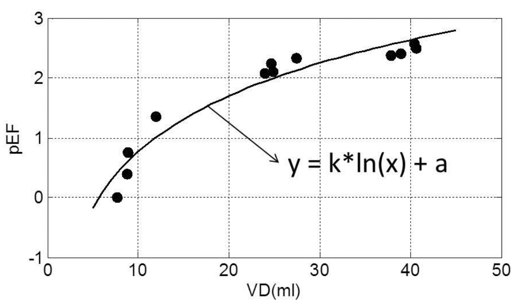

Fig. 3. Relationship between pEF and Vd from experimental data

III. EXPERIMENTAL RESULTS

The study protocol used here was approved by WorldHeart Inc. (Salt Lake city, UT). Those studies were performed in collaboration with LaunchPoint Technologies (Goleta, CA). A Levacor pump was implanted in a health calf. Left ventricular pressure were acquired with a pressure-tip catheter, and ultrasonic flow probes were used to measure pump flow and pulmonary artery flow. Pump signals (current, speed) were also recorded at a rate of 500Hz. Data Analysis wass performed using MATLAB [1]. This study aimed to test a physiologic controller, evaluating its response to contractility changes and venous return depletion. Contractility changes were done by pharmacological interventions with esmolol, 0.1 mg/kg/min. An occluder was used to decrease venous return, inducing suction events.

Before and after each pharmacological intervention, a stair step speed profile was used (see Fig. 2). The three indices, TP, I_Q and k were calculated for each inotropic condition. Figure 4A shows the results for TP. At baseline, $M_{TP} = 1.55 \times 10^5$ mmHg s^{-1} bpm, and after esmolol intervention $M_{TP} = 2.02 \times 10^5$ mmHg s^{-1} bpm. Figure 4B shows the results for I_Q. This index was 9.78s^{-1} at baseline, and 8.63s^{-1} after esmolol infusion.

Figure 5A shows the results for the proposed index. At baseline, $k = 1.354$ ml^{-1}, and after esmolol intervention it was $k = 0.685$ ml^{-1}. As expected, k decreased at a lower contratile state. Figure 5B shows the results obtained from a pulsatile index, defined as

$$P = \frac{Q_{max} - Q_{min}}{Q_{avg}} \tag{5}$$

where, Q_{max} is the maximum of pump flow, Q_{min} is its minimum, and Q_{avg} is the mean value of pump flow. In Fig. 5B, P vs. Q_{min} relationship also could be fitted by an exponential. However, all (Q_{min}, P) coordinates would lie in the same curve, irrespective of the inotropic state, considering the overlapping of the 95% confidence interval. This observation corroborates the fact that a pulsatile index defined as in eq. (5), would not convey reliable information on myocardial contractility. Table I summarizes the results for all three indices.

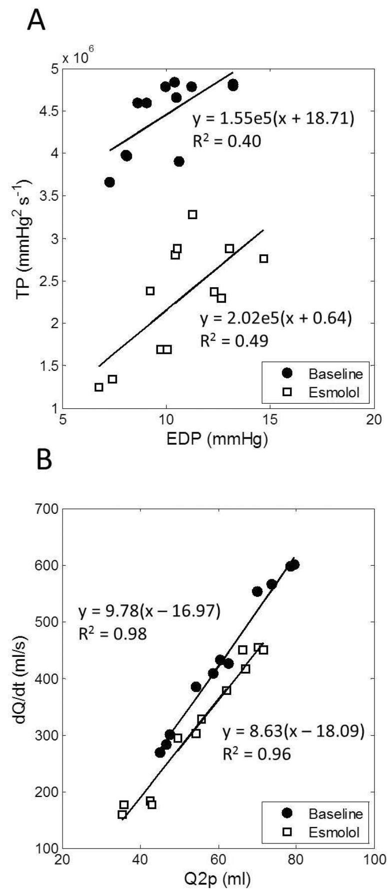

Fig. 4. Indices results on experimental data: A) triple product (M_{TP}), B) I_Q index

TABLE I
SUMMARY OF RESULTS

	Baseline	Esmolol
M_{TP} (mmHg s^{-1} bpm$*10^5$)	1.55 ± 1.17	2.02 ± 1.4
I_Q (s^{-1})	9.78 ± 0.2	8.63 ± 1.12
k (ml^{-1})	1.354 ± 0.25	0.685 ± 0.21

Data expressed as mean $\pm$ standard deviation

IV. DISCUSSION

The assessment of residual LV function on assisted hearts is still a challenge [8], [9]. Fewer indices have been proposed in recent years [4], [5] to assess LV function in assisted

[1]The MathWorks Inc., Natik, MA

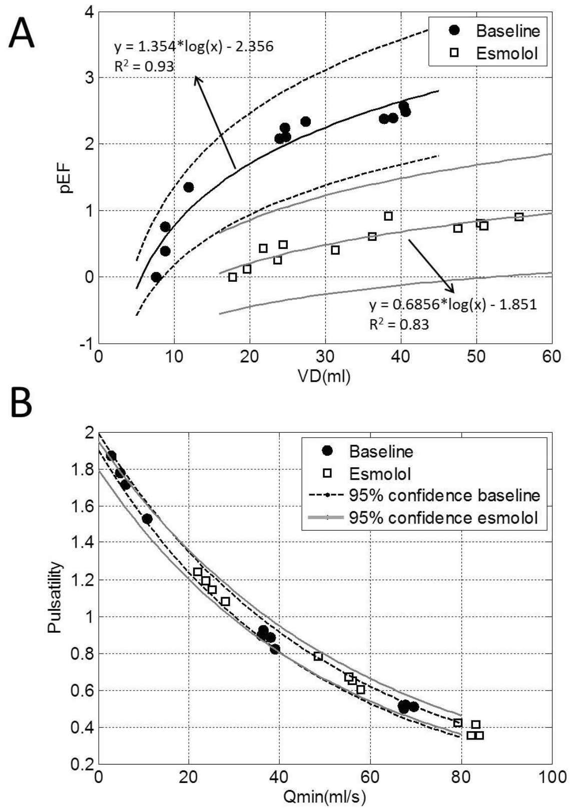

Fig. 5. A) Results of the proposed index, k; B) Pulsatility index calculated as per eq. 5.

hearts. Traditional indices, such as ESPVR may not be directly applied to the assisted heart. As demonstrated by Vandenberghe and colleagues [10], the original time-varying elastance theory insufficiently models the complex hemodynamic behavior of a mechanically assisted LV. Moreover, LV unloading renders E_{es} curvilinear, and therefore is less adequately defined by a linear relationship [7]. Thus, continuous LV unloading limits applicability of indices based on ventricular volume measurements, because continuous unloading influences the definition of systolic ventricular volume and ejection fraction [5].

The slope of TP vs EDP (M_{TP}) should have decreased when esmolol was administrated to the animal, with respect to its baseline value. Several reasons may explain this unexpected result. First and foremost, during the axial unloading reported in [4], EDP ranged from 8-20mmHg (baseline) and 13-26mmHg (esmolol). In our case, the centrifugal unloading employed gave a much narrow range, 5-15mmHg for EDP. This may explain the low R^2 coefficients in Fig. 4 (0.40 at baseline and 0.49 with esmolol). It remains unclear how axial vs centrifugal flow pumps affect the circulatory system. In addition, in our in-vivo experiment, the pump was interposed between the LV apex and ascending aorta. In the experiments reported in [4], LV unloading was to the descendent thoracic aorta, and differences may exist when LVAD outflow is to the ascending aorta.

The I_Q index decreased when esmolol was administrated to the animal, as expected. Even though the relationship between dQ/dt$_{max}$ and Q$_{P2P}$ was highly linear in both cases (R^2 = 0.98, baseline, and R^2 = 0.96 esmolol), the 95% confidence intervals overlapped when comparing baseline and esmolol groups, 9.78 ± 0.2 and 8.63 ± 1.12 respectively. (see Table I).

The k index proposed, showed a non-overlapping 95% confidence interval between baseline ($k = 1.354 \pm 0.25$ ml^{-1}), and after esmolol infusion ($k = 0.685 \pm 0.21$ ml^{-1}), as shown in Fig. 5A. Thus, k would correctly stratify "recovering" hearts (baseline), from a "weak" heart (esmolol).

Current assessment of cardiac function in VAD implanted patients is done via pump speed reduction to minimal support. Usually, pump speed is maintained only high enough to avoid regurgitant flow, and echocardiographic analysis is employed to assess LV area [11]. The proposed index could be calculated through this procedure, by Doppler wave techniques.

Some limitations of our study are noteworthy. First, more in-vivo studies are needed to verify that the k index is a viable option in assessing cardiac contractility. Finally, comparisons with others traditional indices (e.g., preload recruitable stroke work or maximal time-derivative of LV pressure vs end diastolic volume, (dP/dt)$_{max}$ vs EDV) will be done soon, as part of our current ongoing research.

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