Left Ventricular QRS Widening Decreases $E_{\text{max}}$ without Lowering $V_{O_2}$-PVA Relation in Dog Hearts

Taketoshi NAMBA, Miyako TAKAKI, Junichi ARAKI, Kazunari ISHIOKA, Takuji AKASHI, Takehiko MATSUSHITA, Wakako FUJI, and Hiroyuki SUGA

Department of Physiology II, Okayama University Medical School, Okayama, 700 Japan

Abstract We observed a few rare spontaneous cases of a suddenly widened QRS wave of left ventricular ECG associated with a simultaneous decrease in left ventricular (LV) contractility ($E_{\text{max}}$, end-systolic pressure-volume ratio) in excised cross-circulated dog heart experiments. The decreased $E_{\text{max}}$ was not associated with a descent of the relation between cardiac oxygen consumption ($V_{O_2}$) and LV systolic pressure-volume area (PVA, a measure of total ventricular mechanical energy). This result is intriguing because ventricular $V_{O_2}$-PVA relation generally changes its elevation in proportion to $E_{\text{max}}$ under various inotropic interventions. We suspected the unusual observation to reflect no change in myocardial contractility despite ventricular asynchrony augmented by an intraventricular conduction defect.

Key words: cardiac energetics, cardiac mechanics, oxygen consumption, asynchrony, ventricle.

Ventricular pressure-volume area (PVA) is a measure of the total mechanical energy generated by cardiac contraction [1]. PVA of the left ventricle (LV) has been shown to linearly correlate with cardiac oxygen consumption ($V_{O_2}$) [1, 2]. The relation between LV $V_{O_2}$ and PVA changes its elevation in proportion to LV contractility in terms of an index of ventricular contractility ($E_{\text{max}}$) [2–9]. $E_{\text{max}}$ is the slope of the end-systolic ventricular pressure-volume relation [10].

We encountered a few rare cases in which $E_{\text{max}}$ suddenly decreased spontaneously during our studies of the $V_{O_2}$-PVA relation in dog LVs. The sudden decrease in $E_{\text{max}}$ was always associated with a sudden widening of the QRS complex of the LV anterior epicardial electrocardiogram (ECG). However, the $V_{O_2}$-PVA relation of the LV did not descend. This contradicts the contention that the $V_{O_2}$-PVA relation generally changes its elevation in proportion to $E_{\text{max}}$ under various inotropic interventions [2–9].

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We now report this unusual observation of interest and interpret it by the aid of our previous simulation study [11].

METHODS

The rare cases to be reported occurred suddenly and spontaneously in our experiments on the excised, cross-circulated dog heart preparation for cardiac mechanism studies over several years [2]. We have described the experimental methods in detail elsewhere [4–9, 12]. Briefly, the heart preparation was made from two adult mongrel dogs in each experiment. Dogs were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) after premedication with ketamine hydrochloride (7 mg/kg, i.m.). Blood was heparinized (1,000 U/kg). The common carotid arteries and external jugular vein of the larger dog were cannulated for the cross circulation of the heart preparation.

The smaller dog was thoracotomized midsternally under artificial ventilation. The arterial and venous cross-circulation tubes from the larger dog were cannulated into the left subclavian artery and the right ventricle via the right atrial appendage. The heart-lung section was isolated from the systemic and pulmonary circulation. Under cross circulation, the supported beating heart was excised from the chest. Systemic hypotension due to allergic reaction under cross circulation was prevented with diphenhydramine hydrochloride (60 mg/dog, i.m.) and indomethacin (0.3–0.6 mg/kg, i.v.).

The left atrium was opened and chordae tendineae were cut. A thin latex balloon mounted on a rigid connector was placed in the LV and secured at the mitral annulus by suture. The balloon was connected to our custom-made volume servo pump. The balloon and the pump were primed with water. The servo pump controlled and measured LV volume. The heart temperature was maintained at 35–37°C. ECG was recorded by a pair of electrodes (tip: 1–2 mm long, 1 mmφ) screwed into the LV anterior epicardium.

LV pressure was measured with a Konigsberg P-7 pressure gauge inside the balloon. Both LV pressure (P) and volume (V) signals were processed with a signal processor (NEC San-ei, 7T18). \( E_{\text{max}} \), a global index of LV contractility, was calculated as a maximum value of \( P/(V - V_0) \) of each contraction, where \( V_0 \) is a small LV volume at which peak isovolumic pressure was zero [10].

From the same \( P \) and \( V \) data, systolic pressure-volume area (PVA) was calculated with the signal processor [4–9]. PVA is the area bounded by the end-systolic \( E_{\text{max}} \) line, the systolic \( P-V \) trajectory, and the diastolic \( P-V \) curve [6]. PVA has been shown to serve as a measure of the total mechanical energy generated by ventricular contraction [1, 2]. PVA was expressed in mmHg ml per beat.

Cardiac oxygen consumption (\( V_{\text{O}_2} \)) was measured as the product of coronary blood flow and arteriovenous oxygen content difference (AVOX). Coronary flow was measured with an electromagnetic flow probe in the venous cross-circulation tube. AVOX was measured with our custom-made oxygen content difference.
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analyzer (Erma, PWA-200S) [13]. $V_{O_2}$ was expressed in ml O$_2$ per beat.

The reported cases occurred unexpectedly during our main cardiac mechano-
energetic protocol [2]. The incidence of these cases was roughly one out of 100
experiments. We noticed a spontaneous sudden decrease in $E_{max}$ when we were
monitoring ventricular pressure tracings of steady-state contractions at a given
end-diastolic volume. We then recognized a widening of the QRS wave of left
ventricular epicardial ECG. During these experiments, we did not apply any
special protocol to study the details of the rare events. Instead, we concentrated on
obtaining a $V_{O_2}$-PVA relation in a stable contractile state. In other words, we
simply waited for a new stable contractility level to come and repeated the main
protocol. Therefore, we had to collect LV pressure, volume, $E_{max}$, VPA, $V_{O_2}$, and
ECG data retrospectively in strip chart recordings and computer display hard-
copies.

The sudden decreases in $E_{max}$ in the reported cases were caused neither by our
technical problems of a loose fitting, rupture, and water leak of the intraventricular
balloon, by loose connections of signal cables, nor by faulty calibration of the
pressure and volume signals.

RESULTS

Figure 1 shows a representative case with most complete set of tracings and
information. The LV was contracting isovolumically at different volumes. While
peak isovolumic pressure was stable for about 1 min at a fixed volume, it sponta-
eanously and suddenly decreased by 42%, from 130 to 75 mmHg (at the finger
mark), with a gradual recovery to 85 mmHg over a half min. $E_{max}$ decreased by
34%, from 11.6 mmHg/ml to a steady-state level of 7.6 mmHg/ml.

Simultaneously, the LV anterior epicardial ECG was suddenly changed. Since
ECG scaled out, we reduced its amplitude. We found that the QRS complex was
remarkably widened without a change of the polarity. This change of LV anterior
epicardial ECG suggested an intraventricular conduction defect.

Figure 2 compares LV isovolumic pressure and ECG curves before (Panel A)
and after the QRS widening (Panel B). These curves were obtained by magnifying
the fast-recorded original tracings of isovolumic contractions. Panel A was taken
from the fast recording at the left-most part of Fig. 1. Panel B was taken from a
fast recording beyond the right-most of Fig. 1, where LV volume was increased and
PVA was comparable to that in Panel A.

In Fig. 2, the curves in Panels A and B were superimposed in two different
ways in Panels C and D. The timing of the onset of the QRS complex was matched
in Panel C. The timing of the peak isovolumic pressure was matched in Panel D.
The width of the QRS complex, which means ventricular activation time, increased
by 55%, from 66 to 102 ms. The QRS widening did not recover for about 2 h until
the end of this experiment. The onset and peak of the LV pressure curve lagged by
approximately 30 ms after the QRS widening as seen in Panel C. However, the

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Fig. 1. A representative case of spontaneous QRS widening of LV epicardial ECG. Sec tick (top) = 0.1 s tick in the fast recording and 1 s tick in the slow recording. BP (second) = coronary perfusion pressure (mmHg). LVP (third) = left ventricular pressure (mmHg). LVV (fourth) = left ventricular volume tracing (ml). ECG (fifth) = left ventricular epicardial bipolar electrocardiogram. CF (second from bottom) = coronary perfusion flow (ml/min). AVOX (bottom) = coronary arteriovenous oxygen content difference (vol%). Finger mark shows the instant when left ventricular pressure decreased and ECG changed spontaneously. The gain of ECG recording was decreased in the right one-third tracing.

pressure curve was little widened as seen in Panel D.

Figure 3 compares the pressure-volume diagrams and \( V_{O_2} \)-PVA relations of the isovolumic contractions before (Panel A) and after the QRS widening (Panels B and C). After Panel B, the decreased \( E_{max} \) was stable and LV volume was increased in Panel C. PVA of the isovolumic contraction corresponds to the black triangular area in each panel. With the decrease in \( E_{max} \), PVA and \( V_{O_2} \) decreased, as shown by the crosses in Panels A and B. After an increase in LV volume, PVA in Panel C was comparable to that in Panel A. We found that \( V_{O_2} \) in Panel C was comparable to the pre-widening \( V_{O_2} \) in Panel A.

Figure 3D shows the \( P-V \) trajectories and \( V_{O_2} \)-PVA data points before and after the QRS widening. The data in Panels A, B, and C and similar data of some other isovolumic and unloaded contractions after the QRS widening were superimposed. The finger mark indicates the data before the QRS widening. Obviously, the pre-widening \( V_{O_2} \)-PVA point fell on the post-widening \( V_{O_2} \)-PVA relation. The post-widening \( V_{O_2} \)-PVA relation was \( V_{O_2} \) (ml O\(_2\)/beat) = \( 1.68 \times 10^{-5} \) PVA + 0.041,
with a correlation coefficient of 0.980. This relation was almost on the pre-widening data point \( V_{O_2} = 0.0634 \text{ ml O}_2/\text{beat}, \ PVA = 1,220 \text{ mmHg/ml} \). The slope of the post-widening \( V_{O_2} \)-PVA relation was comparable to the normal heart values in the literature [2–9]. Therefore, the \( V_{O_2} \)-PVA relation was not lowered by the \( E_{max} \) decrease associated with the QRS widening of the LV epicardial ECG.

We observed three more similar cases of suddenly decreased \( E_{max} \) associated with sudden spontaneous ECG widening. These cases were accompanied by incomplete information, unfortunately. However, the sudden decreases in \( E_{max} \) and QRS widening decreased both PVA and \( V_{O_2} \) in a similar manner to the first case, according to the \( V_{O_2} \)-PVA diagrams like Fig. 3D. When PVA was later increased with increases in LV volume in the main protocol, \( V_{O_2} \) also returned to the pre-widening level. The \( V_{O_2} \)-PVA diagrams indicated that the \( V_{O_2} \)-PVA relations remained unchanged despite the decreases in \( E_{max} \). In these cases, too, the QRS widening of the LV anterior epicardial ECG suggested intraventricular conduction defects.

**DISCUSSION**

Various inotropic interventions have been shown to shift the \( V_{O_2} \)-PVA relation up or down in proportion to \( E_{max} \) changes [1–9]. Three inotropic interventions are known not to affect the \( V_{O_2} \)-PVA relation despite changes in \( E_{max} \). They are myocardial cooling [12], mechanical vibration [14], and ventricular pacing [15]. We have now found that the \( V_{O_2} \)-PVA relation did not descend despite the
Fig. 3. Left ventricular pressure (LVP)-volume (LVV) trajectories (vertical lines, top), systolic pressure-volume areas (PVA) (black triangles in the middle), and \( V_{O_2}\)-PVA data points (crosses, bottom). Panel A shows the data of control steady-state isovolumic contraction before QRS widening. Panel B shows the data of a steady-state isovolumic contraction after the QRS widening. Panel C shows the data of steady-state isovolumic contraction at an increased LV volume, where PVA was restored to the pre-widening control level. Panel D superimposes pressure-volume and \( V_{O_2}\)-PVA data in Panels A, B, and C and of other isovolumic contractions at different volumes after QRS widening. Finger mark indicates the \( V_{O_2}\)-PVA data point transferred from Panel A, which was on the post-widening \( V_{O_2}\)-PVA relation.

decreased \( E_{max} \) associated with a QRS widening of LV epicardial ECG. We suspected spontaneous and sudden occurrence of the intraventricular conduction defect. This may be another condition that does not shift the \( V_{O_2}\)-PVA relation despite a change in \( E_{max} \).

The present condition seems closely related to the ventricular pacing [15]. Shifting an electric pacing site from the right atrium to the LV apex, LV free wall, and the right ventricular free wall, Burkhoff et al. [15] observed 2-4-fold increases in the duration of the QRS complex of LV epicardial ECG. This indicates increased asynchrony of ventricular contraction. Simultaneously, peak isovolumic pressure at a fixed end-diastolic volume and hence \( E_{max} \) decreased by a maximum of 26% on average. However, the \( V_{O_2}\)-PVA relation was the same among the different
pacing sites [15]. This mechanoenergetic response resembles our observation.

We had simulated the mechanoenergetics of an asynchronously contracting ventricle in which two ventricular compartments contracted in various phases [11]. Although $E_{\text{max}}$ of each compartment was constant, ventricular $E_{\text{max}}$ as a global index of contractility was greatest when the two compartments contracted in phase and decreased as the phase was gradually shifted. Because of a constant $E_{\text{max}}$ of each compartment despite ventricular asynchrony, the PVA-independent $V_{O_2}$ and hence the $V_{O_2}$-PVA relation of each compartment can be assumed unchanged [11]. Because either $V_{O_2}$ or PVA is energy and hence additive in quantity, ventricular $V_{O_2}$-PVA relation is the sum of the $V_{O_2}$-PVA relations of the two compartments regardless of their contraction phases [11]. Therefore, the ventricular $V_{O_2}$-PVA relation can be assumed unchanged despite a decreased $E_{\text{max}}$ of the ventricle [11]. Therefore, the unchanged ventricular $V_{O_2}$-PVA relation despite the decreased $E_{\text{max}}$ by the intraventricular conduction defect can be accounted for by no change in myocardial contractility despite ventricular asynchronous contraction.

An important implication of the present study as well as Burkhoff et al.'s [15] is that ventricular asynchronous contraction decreases ventricular $E_{\text{max}}$ without lowering the ventricular $V_{O_2}$-PVA relation. In ventricular asynchronous contractions, myocardial contractility seems not effectively lumped into ventricular contraction even if oxygen demands of individual myocardial fibers remain unchanged. Therefore, ventricular asynchronous contraction, whether elicited by an intraventricular conduction defect or ventricular pacing, adversely decreases cardiac pump performance relative to oxygen consumption.

The spontaneous intraventricular conduction defect in our study may have been caused by a metal ring which was sutured in the mitral annulus to hold the connector of the intraventricular balloon. The ring had a sub-aortic-valvular metal rim to prevent balloon herniation into the aorta. The tip of the rim was loosely pulled to the septum by a thread needle through both the septum and the right ventricular free wall. Although we have been using this procedure for many years, the trans-septal threading per se did not produce the intraventricular conduction defect. The septal region over the left bundle branch may have been excessively pressed by the rim in the reported rare cases. The right ventricle was always collapsed by hydrostatic drainage of coronary venous return.

Our few observations might be fortuitous. If a QRS widening had occurred without a noticeable decrease in $E_{\text{max}}$, we may have overlooked the event. We will continue to collect mechanoenergetic data related to any QRS widening. The purpose of this presentation is to attract readers' attention to this important and interesting relation between cardiac asynchrony and mechanoenergetics.

To summarize, we report a few rare cases of spontaneous widening of the QRS wave of LV epicardial ECG in the excised cross-circulated dog heart preparation that we have been using in cardiac mechanoenergetic studies. We suspected that a spontaneous intraventricular conduction defect caused asynchronous ventricular contraction. The unchanged $V_{O_2}$-PVA relation despite a considerably decreased

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$E_{\text{max}}$ associated with the QRS widening can be accounted for by ventricular asynchronous contraction without decreased myocardial contractility.

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