Impairment of contraction increases sensitivity of epicardial lymph pressure for left ventricular pressure

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VanTeeffelen, J urgen W. G. E., Daphne Merkus, Luc J. Bos, Isabelle Vergroesen, and Jos A. E. Spaan. Impairment of contraction increases sensitivity of epicardial lymph pressure for left ventricular pressure. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H187–H192, 1998.—In the present study, cardiac contraction was regionally impaired to investigate the relationship between contractility [maximum first time derivative of left ventricular pressure (dPLV/dtmax)] and PLV on epicardial lymph pressure (Plymph) generation. Measurements were performed in open-chest anesthetized dogs under control conditions and while local contraction was abolished by intracoronary administration of lidocaine. Lidocaine significantly lowered dPLV/dtmax and PLV pulse to 77 ± 9 (SD; n = 5) and 82 ± 5% of control, respectively, whereas Plymph pulse increased to 186 ± 102%. The relative increase of maximum PLV to Pmax related inversely to the change in dPLV/dtmax after lidocaine administration. Additional data were obtained when PLV was transiently increased by constriction of the descending aorta. The ratio of pulse Plymph to PLV during aortic clamping increased after lidocaine administration, from 0.063 ± 0.03 to 0.15 ± 0.09. The results suggest that transmission of PLV to the cardiac lymphatic vasculature is enhanced when regional contraction is impaired. These findings imply that during normal, unimpaired contraction lymph vessels are shielded from high systolic PLV by the myocardium itself.

Lidocaine; contractility; left ventricular pressure transmission; myocardial edema

EPICARDIAL LYMPH PRESSURE (Plymph) measurements can provide instantaneous information on changes in forces that are involved in regulation of the myocardial interstitial fluid balance (13). The generation of lymph pressure is assumed to be brought about by an interplay of the varying stiffness of the cardiac muscle surrounding the lymphatics and transmission of left ventricular pressure (PPLV) (3, 4, 11). The sensitivity of lymph pressure for PPLV was found by Han et al. (3) to be 10 times higher in diastole than in systole. From this finding and that of Kouwenhoven et al. (6), who found that coronary inflow was affected by PPLV in early systole but not in mid systole during constant pressure perfusion of the left main coronary artery, it has been hypothesized that the transmission of PPLV to the intramyocardial blood and lymph vessels depends on the contractile state of the myocardium (3, 6, 11). It has been suggested that during systole the intramyocardial vessels are shielded from PPLV transmission by the increasing elastance of the myocardium (2, 6, 11). This mechanism is thought to protect the vessels from collapse during cardiac contraction.

The shielding effect might be diminished during regional impairment of cardiac contraction, when local force generation is uncoupled from PPLV. In the present study, the effect of regional impairment of cardiac contraction on Plymph generation was investigated. Measurements were performed in open-chest, anesthetized dogs during control conditions and while local contraction was abolished by intracoronary administration of lidocaine in a distal portion of the left anterior descending artery (LAD) (2, 5, 8). In both conditions the sensitivity of lymph pressure for a change in PPLV was investigated.

METHODS

Experimental preparation and measurements. Six mongrel dogs of either sex, weighing 20–30 kg, were premedicated by intramuscular injection of 1 ml of methadone and 1.5 ml of xylazine (20 mg/ml; Rompun, Bayer, Leverkusen, Germany). General anesthesia was induced by intravenous injection of 4 ml of pentobarbital sodium (60 mg/ml). After tracheal intubation, the animals were ventilated with a Harvard respirator using a 2:1 nitrous oxide-oxygen mixture. Anesthesia was maintained by 40 ml fentanyl (0.05 mg/ml in 10 min). Arterial blood gases and pH were measured frequently, and to keep them within the physiological range ventilator settings were adjusted. Depth of anesthesia was assessed by changes in heart rate, blood pressure, and reflexes, and anesthetics were administered when necessary.

A left thoracotomy was performed in the fifth intercostal space, and the heart was exposed and suspended in a pericardial cradle. A fluid-filled polyethylene catheter was placed into the ascending aorta via the carotid artery and connected to a dome pressure transducer (Bell and Howell 4–327). Coronary arterial pressure was measured by connecting this catheter to a dome pressure transducer. An epicardial lymph vessel on the distal anterior wall of the left ventricle was cannulated retrogradely with a heparinized polyethylene cannula (PE-90, OD 0.96 mm, ID 0.58 mm), as described elsewhere (3, 4). After cannulation of the lymph vessel, the cannula slowly filled with lymph fluid. When the cannula was completely filled, a microtip pressure transducer with a lumen (5 Fr, Philips) was connected to the cannula via a homemade Perspex connector (4). Air in the connector and
the lumen was removed by flushing with saline. During measurements the lumen of the pressure transducer was closed, thereby obstructing the lymph flow. In this way $P_{\text{lymph}}$ increased to a steady-state level. If mean $P_{\text{lymph}}$ did not increase or the cannula was not filled spontaneously with lymph fluid, the lymph cannulation was considered unsuccessful. The lumen of the microtip pressure transducer was regularly opened to prevent possible artifacts because of a prolonged obstruction of the lymph flow.

Zero pressures were set at midchest level. The zero flow of the flowmeter was obtained by a short occlusion of the LAD several times during the experiment. Signals were digitized on-line during relevant interventions at a sample rate of 80 Hz and subsequently were stored on hard disk for off-line signal analysis.

Protocol. Steady-state conditions were achieved. During these control conditions, $P_{\text{LV}}$ varied repeatedly by constriction of the descending aorta for several beats. Subsequently, we tried to abolish contractility in the region of the cannulated lymph vessel by injecting 1 ml of 1% lidocaine via the three-way stopcock into the LAD. Local abolishment of contractility was assessed by epicardial imaging of cardiac functioning with an echo apparatus (5 MHz; 77020-series ultrasound system, Hewlett-Packard). In general, ~20 s after lidocaine administration, echo demonstrated regional lack of contraction in the area perfused by the LAD. This part of the left ventricular free wall was passively deformed during the cardiac cycle by the contracting part of the ventricle on the one hand and $P_{\text{LV}}$ on the other hand. The effect persisted for several minutes. During this period of regional impairment of cardiac contraction, the descending aorta was again regularly constricted. When 1 ml of 1% lidocaine did not have a clear effect, a larger volume (2–3 ml) of lidocaine was injected. We attempted to repeat lidocaine injection several times in each experiment.

It should be noted that the placement of the ultrasound transducer formed a risk for the stability of the lymph cannula and also influenced the $P_{\text{lymph}}$ measurement by slight compression of the tissue. Therefore, quantitative measurements were not made from the images. Echo was only used to judge whether the lidocaine injection was effective in diminishing local contractility.

Data analysis. The first time derivative of $P_{\text{LV}}$ ($dP_{\text{LV}}/dt_{\text{max}}$) was calculated and its maximum ($dP_{\text{LV}}/dt_{\text{max}}$) was taken as a measure of contractility. Pulsatility of flow and pressure was defined as the difference between the minimum and the maximum per beat. The sensitivity of $P_{\text{lymph}}$ to $P_{\text{LV}}$ was analyzed by determining the ratio in pulse pressure of $P_{\text{lymph}}$ to $P_{\text{LV}}$ for 15–50 beats during the periods in which $P_{\text{LV}}$ was varied in each animal. Furthermore, linear regression analysis was performed on the relationship between the pulse pressures of $P_{\text{LV}}$ and $P_{\text{lymph}}$. To verify whether linear regression analysis was allowed, residuals of all individual regressions were tested for independence.

Data were analyzed for both the control period and the period in which cardiac contraction was impaired, as indicated by a decrease in $dP_{\text{LV}}/dt_{\text{max}}$. Data of all animals were averaged and are presented as means ± SD. Differences induced by the impairment of cardiac contraction were tested by a paired Student’s t-test (one-sided). $P < 0.05$ was considered significant.

RESULTS

Effects of lidocaine. In Fig. 1 tracings of $Q_{\text{LAD}}$, $P_{\text{Ao}}$, $P_{\text{lymph}}$, $P_{\text{LV}}$, and $dP_{\text{LV}}/dt_{\text{max}}$ from one experiment before and after the injection of lidocaine are shown. After the start of lidocaine injection, $dP_{\text{LV}}/dt_{\text{max}}$ decreased within a few beats from 1,274 to 997 mmHg/s and $P_{\text{LV}}$ pulse decreased from 72.4 to 69.6 mmHg. After an initial small decrease for about five beats during the injection of lidocaine, pulse $P_{\text{lymph}}$ increased to 23.3 mmHg within ~20 s. $Q_{\text{LAD}}$ pulsatility decreased, and systolic backflow was diminished after the injection of lidocaine.

Average data are presented in Table 1. Average $dP_{\text{LV}}/dt_{\text{max}}$ decreased from 1,447 ± 173 to 1,102 ± 150 mmHg/s ($P < 0.05$) after the administration of lidocaine. Although pulse $P_{\text{LV}}$ decreased from 102 to 84 mmHg, pulse $P_{\text{lymph}}$ increased on average from 6.2 to 12.2 mmHg. After lidocaine, heart rate increased on average from 106 to 119 beats/min ($P < 0.05$).

In one animal, diastolic $P_{\text{lymph}}$ increased from a control value of 19.6 mmHg to a value of 84.3 mmHg after lidocaine injection, although pulsatility did not change. This behavior is considered typical for the presence of intraluminal lymphatic valves. Therefore, this animal was excluded from the overall analysis.
After cessation of infusion of lidocaine, cardiac contraction remained diminished for several minutes. The affected ventricular region then gradually recovered, and Plymph and PLV returned to their control values at a comparable rate. The ratio of maximum Plymph over maximum PLV per beat was calculated for several beats in the period after the injection of lidocaine. In this way, measurements of Plymph/PLV were obtained at different values of dPLV/dt_{max}, reflecting varying degrees of regional impairment of cardiac contraction. In Fig. 2 the relationship between Plymph/PLV and dPLV/dt_{max} after the administration of lidocaine is shown for all animals. In each animal Plymph/PLV was inversely related to dPLV/dt_{max}.

Effect of PLV on Plymph. In Fig. 3 the effect of aortic clamping on Q_{LAD}, P_{Ao}, Plymph, and PLV is demonstrated during control conditions and during regional impairment of cardiac contraction by lidocaine. Constriction of the descending aorta increased PLV and, concomitantly, P_{Ao} and Q_{LAD}. Furthermore, a small increase in Plymph could be detected during control. Administration of lidocaine distinctly intensified the increase in Plymph during aortic clamping. In this experiment Plymph pulse increased from 2.9 to 4.8 mmHg during the fourth beat of aortic clamping in control, whereas with lidocaine the pulse increased from 4.1 to 10.6 mmHg.

The overall relationship between pulse pressure of PLV and Plymph in this animal before and after administration of lidocaine is shown in Fig. 4. Linear regression analysis revealed that the slope between both variables increased from 0.044 ± 0.006 during control to 0.20 ± 0.023 when cardiac contraction was diminished, indicating...
Experimental limitations. To diminish contractility of a part of the left ventricle, lidocaine was injected in the middle portion of the LAD and the intended result on heart contraction was judged by means of echo. Echo images revealed that after lidocaine injection a delimited portion of the left ventricular free wall did not take part in the wall thickening process during systole but was passively deformed instead. Because of interference of the echo transducer with the lymph cannula, as indicated in METHODS, wall thickness could not be determined continuously by echo. In addition to the echo measurements, $dP_{LV}/dt_{max}$ was calculated to determine the effect of lidocaine on regional myocardial contractility. As shown in Fig. 1, $dP_{LV}/dt_{max}$ immediately decreased after the lidocaine injection was started. The decrease is in agreement with the proposed role for lidocaine to diminish cardiac contractility.

Lidocaine has been widely used in experimental studies for its negative inotropic properties (2, 5, 8). Doucette et al. (2) measured regional myocardial thickening fraction by a Doppler ultrasonic probe and demonstrated that in contrast to normal contraction, in which wall thickening occurs during systole, injection of 1 ml of 4% lidocaine into the LAD resulted in a rapid thinning of the wall at the onset of systole, which was completed by the end of isovolumic systole. During the ejection phase of systole no further thinning was observed. Although the concentration of lidocaine used in their study was somewhat higher than that in our study, it is likely that the observed effect on local contraction is similar. Indeed, the maximum decrease in $dP_{LV}/dt_{max}$ in the present study caused by the administration of lidocaine was comparable to the decrease found by Doucette et al. (2). Marzilli et al. (8) also found an absence of systolic thickening after infusion of lidocaine into the LAD for several minutes.

It might be suggested that the increase in lymph pressure after the lidocaine injection results from a direct effect of lidocaine on the lymph vessels, i.e., depression of the intrinsic contractility of the lymph vessels. Although lymph vessels do possess some intrinsic contractility, it is not very likely that this factor is involved in the generation of lymph pressure in the heart because of the dominant role of cardiac contractility in the pressure generation. This is demonstrated by the lymph pressure waveform shown in Fig. 1: major pulsations in lymph pressure appear at a frequency equal to the heart rate.

In the current study it was observed that impaired contraction reduced mean and diastolic arterial flow.

Table 2. Linear regression coefficients for relationship between pulse $P_{LV}$ and pulse $P_{Lymph}$ during aortic clamping before and after lidocaine

<table>
<thead>
<tr>
<th>Condition</th>
<th>Slope</th>
<th>Offset</th>
<th>$r^2$</th>
<th>$P_{Lymph}/P_{LV}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Control</td>
<td>0.032 ± 0.05</td>
<td>3.04 ± 5.0</td>
<td>0.48 ± 0.26</td>
<td>0.063 ± 0.03</td>
</tr>
<tr>
<td>Lидокаин</td>
<td>0.19 ± 0.11</td>
<td>-5.20 ± 11.3</td>
<td>0.62 ± 0.30</td>
<td>0.15 ± 0.09*</td>
</tr>
</tbody>
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Values are means ± SD; n = 5 animals. Pulse is defined as difference between peak and minimal pressure per beat. Range indicates lowest and highest values. *P < 0.05 compared with control condition.
Furthermore, pulsatility of arterial flow was decreased as well. This latter finding appears to contrast with the findings of Doucette et al. (2), who found a large increase in the amplitude of distal flow velocity, whereas proximal coronary flow did not change. It should be noted that in their study the coronary bed was maximally dilated by adenosine while mean coronary perfusion pressure was held constant by means of a perfusion system. In our experiments, however, aortic pressure acted as perfusion pressure for the coronary bed, and its reduction after lidocaine administration may have decreased coronary arterial flow. Furthermore, because coronary tone was not abolished in our experiments, vasoconstriction in response to a decrease in metabolism after lidocaine may also have contributed to the decreased coronary flow pulsatility.

Interpretation of experimental findings. The increase in \( P_{\text{lymph}} \) after the administration of lidocaine is likely to be explained by an increased transmission of \( P_{\text{LV}} \) to the lymph vessels. As indicated by the doubling of the ratio of pulse \( P_{\text{lymph}} \) to \( P_{\text{LV}} \) during aortic clamping (Table 2), \( P_{\text{lymph}} \) was more sensitive to changes in \( P_{\text{LV}} \) during diminished contraction compared with control. It might be suggested that the increase in \( P_{\text{lymph}} \) during lidocaine and the increased sensitivity for \( P_{\text{LV}} \) are related to deformation of the embedded lymph vessels by stretching of the noncontracting region during systole. Although it is very well possible that the myocardial lymph vasculature is affected by this mechanism, it is not obvious that it would result in an increase in \( P_{\text{lymph}} \) per se. Our pressure measurement reflects \( P_{\text{lymph}} \) further upstream, inside the myocardium. The measured \( P_{\text{lymph}} \) is determined by the pressure generated by a particular pressure source inside the myocardium and the resistance distribution proximal and distal from the measurement site. An increase in distal resistance alone would result in an increase in \( P_{\text{lymph}} \). However, if stretching of the muscle tissue affects both inflow and outflow resistances similarly, this stretching effect on resistance will not alter \( P_{\text{lymph}} \). The same reasoning makes it very unlikely that an increased bulging and stretching during aortic clamping caused the increased sensitivity of \( P_{\text{lymph}} \) to \( P_{\text{LV}} \).

In addition, Doucette et al. (2) reported that the wall thickening waveform during lidocaine administration was similar at low \( P_{\text{LV}} \) (average systolic value 49 mmHg) and at normal \( P_{\text{LV}} \) (87 mmHg). The percent wall thickening during systole did not differ significantly in both situations, i.e., \(-2.3 \pm 3.0\) versus \(-4.0 \pm 3.4\%\) (2). Moreover, as noted in Experimental limitations, wall thickness did not change in mid systole, while \( P_{\text{lymph}} \) followed more or less the \( P_{\text{LV}} \) waveform. It seems therefore that the noncontracting region of the left ventricle is already maximally stretched at normal \( P_{\text{LV}} \) and is not further stretched during clamping.

During control conditions, the average ratio of pulse \( P_{\text{lymph}} \) to \( P_{\text{LV}} \) was 0.063 ± 0.03. This value is similar to a ratio of 0.069 ± 0.013 reported by Han et al. (3). When regional contraction was impaired with lidocaine, the ratio of pulse \( P_{\text{lymph}} \) to \( P_{\text{LV}} \) increased to 0.15 ± 0.09. This twofold increase is lower than the 10-fold increase in \( P_{\text{lymph}} \) relative to \( P_{\text{LV}} \) (i.e., 0.76 ± 0.16) that was found during induced long diastoles (3). This indicates that there still was substantial shielding of left ventricular pressure after the administration of lidocaine. This shielding may be caused by the stretching of the noncontracting tissue during systole. As depicted in Fig. 2, the influence of left ventricular pressure on lymph pressure was found to relate to the contractile state of the myocardium: when contractility is diminished, the sensitivity of lymph pressure for left ventricular pressure is enlarged. This finding supports the hypothesis that, during normal, unimpaired cardiac contraction, stiffening of the ventricular wall during systole provides a rigid shield for intramyocardial vessels against deformation by transmission of left ventricular pressures and other forces (2, 6, 11).

Cardiac contraction and interstitial volume. The importance of cardiac contraction in stabilizing myocardial interstitial volume is exemplified by the observation that the water content increases when the heart is arrested for a period of minutes to hours (9, 10, 12, 14). The increase in interstitial volume during cardioplegic arrest can partly be explained by a decrease in myocardial lymph flow (9, 10). It is suggested by Mehilorn et al. (9) that, besides impairment of lymph drainage, the increase in interstitial volume results from an increased microvascular fluid filtration rate because of an increase in the duration of diastole and hence the time for filtration. In contrast to cardioplegic studies (9, 10) in which animals are placed on cardiopulmonary bypass, resulting in arrest of the whole heart and abolition of left ventricular pressure development, lidocaine administration in the LAD results in impairment of contraction of only a part of the left ventricle. Left ventricular pressure, albeit somewhat reduced, is still generated by the unaffected part of the left ventricle. After lidocaine, heart rate increased and the diastolic time fraction decreased as shown in Table 1. As a result, it is not very likely that the increase in \( P_{\text{lymph}} \) after lidocaine is caused by an increased microvascular fluid filtration caused by a change in diastolic time. One may argue that locally reduced contractility resembles diastole for that part of the wall. However, it should be noted that \( P_{\text{lymph}} \) stabilized ~20 s after the administration of lidocaine (Fig. 1). This observation is in contrast to the finding that the myocardial interstitial volume increases steadily during cardioplegic arrest over longer periods of time.

Because of the low rate of myocardial lymph flow, several investigators have estimated changes in lymph flow by timed volume collection over seconds to minutes (7, 9, 10). In this way, continuous information on the fluid balance of the heart is not obtained. In contrast, lymph pressure measurements can be used to derive instantaneous information on factors involved in the myocardial interstitial fluid balance. In a previous study, it was demonstrated that increases in microvascular fluid filtration, induced by histamine infusion, coronary venous pressure elevation, and reactive hyperemia, resulted in fast increases in lymph pressure (13). It is therefore not unlikely that an increase in lymph...
pressure in the present study also reflects an increase in interstitial pressure. An increase in interstitial pressure is expected to diminish the transcapillary hydrostatic pressure difference and to enhance the drainage of lymph fluid, thereby constituting an important safety factor against the formation of myocardial edema (1, 7). However, the observed increase in lymph pressure after lidocaine does not necessarily result in an increase in lymph flow. As suggested in Interpretation of experimental findings, systolic bulging of the noncontracting tissue after the lidocaine might have deformed the myocardial lymphatics, thereby increasing their resistance, and impairing lymph outflow.

In conclusion, the sensitivity of lymph pressure for left ventricular pressure is increased during local impairment of cardiac contraction after administration of lidocaine. The results suggest that the transmission of left ventricular pressure to the myocardial lymphatics depends on the contractile state of the myocardium. It seems therefore that during normal, unimpaired contraction, lymph vessels are shielded from high systolic left ventricular pressure by the myocardium itself.

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