“Watch the disease in time: For when, within the dropsy rages, and extends the skin, in vain for helebore the patient cries, and sees the doctor, but too late is wise: Too late for cure, he proffers half his wealth; ten thousand doctors cannot give him health”
(Benjamin Franklin, Poor Richard’s Almanack, 1749).

INTRODUCTION
Congestive heart failure (CHF) is a common and often fatal clinical syndrome of the dog and cat characterized by cardiac dysfunction, neurohormonal activation, and renal sodium and water retention. Elevated filling pressure is a pathophysiologic hallmark of CHF and may be associated with clinical signs such as tachypnea, labored breathing, cough, and exercise intolerance. Physical examination and thoracic radiography are the current standards to diagnose CHF. However, the sensitivity and specificity of such procedures may be limited with the latter being particularly low if respiratory and cardiac diseases coexist. Reliable estimation of left ventricular (LV) filling pressure (LVFP) would facilitate early detection of CHF and identification of dogs at increased risk for the development of CHF. Moreover, it would also allow monitoring the progression of heart disease, guiding therapy, and improving prognosis.

Elevation of LVFP or its surrogate, LV end-diastolic pressure (LVEDP), can be measured directly, but cardiac catheterization is required, a technique not readily feasible in client-owned animals. Several clinical, radiographic, and Doppler echocardiographic (DE) indices have been proposed to estimate LVFP in people and animals. The following paragraph summarizes current knowledge on the noninvasive prediction of filling pressure in people and small animals.

CLINICAL, RADIOGRAPHIC, AND BLOOD BIOCHEMICAL INDICES OF FILLING PRESSURE
Clinical signs or symptom scores lack specificity for early elevation of filling pressures, but are useful in identifying dogs and cats with the potential to develop CHF. The combination of tachypnea, dyspnea, an S3 gallop, and pulmonary crackles in an animal with known cardiac disease raises a strong suspicion of left-sided CHF associated with elevated LVFP although these signs usually appear late in the development of heart failure. However, the early fully compensated stages of CHF are diagnostically more challenging and prognostically possibly more important. A significant increase in extracellular fluid volume may occur initially without clinical evidence of edema or pulmonary venous congestion. Yet, it is in the early stages of decompensation when effective therapy could prevent further deterioration and dictate the need for more aggressive therapy. In people, increases of respiratory rate and body weight seem to be very sensitive indices of fluid accumulation in patients with acute decompensated heart failure preceding the onset of respiratory signs of CHF by several days or even weeks. Transtelphonic monitoring of body weight and transthoracic lung impedance measurements predict the development of CHF, and studies indicate an improvement in cardiac outcomes using such methods for patient monitoring. The same may be true in cats and dogs although results of prospective studies have not yet been reported.

An S3 gallop is very specific of elevated LVFP but lacks sensitivity. Recent prospective studies done in 90 patients undergoing cardiac catheterization and 343 patients with decompensated heart failure referred to the emergency room reported on a sensitivity of 41% and 34% and a specificity of 92% and 93% of an S3 gallop in the prediction of elevated LVEDP (> 15 mmHg) and CHF, respectively.

Thoracic radiographs are the clinical gold standard in the diagnosis of CHF in dogs and cats. Pulmonary edema, pulmonary venous engorgement, and pleural effusion are readily recognized in patients with CHF and are predicted largely by the magnitude of LVFP. Left atrial enlargement may be indicative of elevated LVFP although it may also simply be a representation of increased preload (that is, volume) without increased LVFP. Studies in people with acute decompensated heart failure comparing findings from chest films with LVFP measured invasively found excellent agreement between the methods in predicting elevated filling pressures. However, the association between filling pressures and BNP seems to be rather weak, in particular if pressures rise acutely or LVFP is only mildly increased. NT-proBNP is elevated in dogs and cats with CHF and found only in traces in healthy animals. However, it seems that the strongest diagnostic feature of BNP is its negative predictive value. Studies in animals aiming at the prediction of LVFP using BNP are lacking. Moreover, NT-proBNP is not only influenced by LVFP, but is also affected by the severity of left ventricular hypertrophy, age, gender, and renal function. Finally, reference values are not well established, and if available a wide indeterminate zone limits the clinical use of BNP in the prediction of compensated heart failure. From a clinical perspective, analysis of BNP may have incremental predictive power to clinical findings, thoracic radiography, and echocardiography in the prediction of LVFP.

DOPPLER ECHOCARDIOGRAPHIC VARIABLES OF FILLING PRESSURE
In recent years, DE has emerged as the method of choice for non-invasive prediction of elevated LVFP in people. Several DE variables based on transmitral flow, pulmonary venous flow, and tissue Doppler imaging have been proposed to estimate LVFP, with the ratio between peak early diastolic transmitral flow velocity (E wave) to early diastolic mitral annulus motion velocity (Ea wave) currently preferred by many investigators. Guidelines for the diagnostic use of such variables in human patients have been reported. However, similar investigations in dogs are rare and limited by the number of DE variables studied; and less is known about the applicability of DE indices validated in human patients for prediction of elevated LVFP in dogs.
Transmitral Flow

Traditional indices used to estimate LVFP include, but are not limited to, peak E velocity, E:A ratio, and DT/E. However, in addition to filling pressure other major determinants of E include LV relaxation and associated early ventricular suction, LV compliance, and blood volume. Therefore, as well known from studies in laboratory dogs and in people the accuracy of transmitral flow variables for the prediction of LVFP is limited in situations where a) LV ejection fraction is preserved, b) filling volume is severely increased as observed secondary to advanced mitral regurgitation, or c) there is a relaxation-dominant effect on LV diastolic function as seen with young age, myocardial ischemia, systemic hypertension, or severe concentric LV hypertrophy as found in cats with hypertrophic cardiomyopathy. Recent studies done by the authors in healthy anesthetized dogs and cats and awake dogs with pacing-induced heart failure revealed only modest correlations between LVFP and DE variables of early LV filling.

Isovolumic Relaxation Time (IVRT)

The IVRT as an index of relaxation has been shown to be linearly related to tau, the time constant of LV isovolumic relaxation in cats, dogs, and people but is also influenced by a multitude of other factors including preload, afterload, heart rate, and age. Therefore, IVRT will represent the net effect of many determinants of which relaxation is only one. Whereas a mild elevation of LVFP in dogs shortens tau but is not associated with shortening of IVRT, moderate and severe elevation of LVFP prolongs tau, but shortens IVRT in a linear manner. This has been reported in experimental studies in dogs and was confirmed in clinical studies in people with cardiomyopathy. Shortened IVRT is by definition an integral part of restrictive LV filling, a transmitral flow pattern considered specific for advanced diastolic dysfunction, high LVFP, and CHF. That is, high filling pressure may minimize the effect of relaxation on IVRT turning it into a more specific indicator of LVFP. This has been confirmed in recent studies done by the author.

Pulmonary Venous Flow

When LVFP is elevated, operating chamber compliance of the LV is reduced, because it functions on a steeper portion of its pressure-volume curve. Working against a less compliant ventricle, less blood will enter the LV, and there will be an increased pressure build-up during late diastole given that left atrial function is within normal ranges. Thus, a greater force will retard the flow in the pulmonary veins increasing the duration of retrograde flow (AR wave) from the left atrium into the pulmonary veins and reducing the duration of antegrade flow (A wave) from the left atrium into the left ventricle. The difference in the duration of flow with atrial contraction at the mitral valve and pulmonary veins and the ratio between both variables (Aduration:ARduration) have been reported to identify elevated LVEDP in dogs and people. Studies in people have shown that when the pulmonary venous AR wave duration exceeds the duration of the mitral A wave by 20 or 30 ms, elevated LVEDP (> 15 mmHg) may be predicted with high sensitivity and specificity (>80%), and correlation coefficients between Aduration:ARduration above 0.70 have been reported. Moreover, in a recently published study of 176 consecutive cardiac patients that had undergone simultaneous DE and invasive measurement of LVFP, the Aduration:ARduration ratio was found to be the single best predictor of LVFP. The AUC for the prediction of LVEDP > 15 mmHg was 0.91 for Aduration:ARduration, very similar to our recent findings in anesthetized, volume loaded dogs. However, the practical use of the Aduration:ARduration ratio is hampered somewhat by the fact that it cannot be used if transmitral flow waves are overlapped or if A or AR waves are missing as found with sinus tachycardia, severe atrial mechanical dysfunction, or atrial fibrillation. In addition, acquisition of high-quality pulmonary venous and transmitral flow recordings can be difficult in some dogs. Due to the ease, high quality, and good repeatability of recording, interpretation of pulmonary venous flow signals seem to be of particular importance in cats with cardiomyopathy and LV diastolic dysfunction.

Diastolic Time Intervals

Historically, diastolic time intervals beyond IVRT have been used infrequently in the DE assessment of LV diastole and LVFP. A novel index, the time interval between the onset of the E and Ea waves (T(Ea-E)), has been reported recently to be related to both LV relaxation and LVFP in dogs and people. The concept behind T(Ea-E) is that under physiologic conditions E and Ea occur almost simultaneously, but dissociate from each other with delayed relaxation and/or elevated filling pressure. In situations where filling pressure is high and LV function is relatively normal, T(Ea-E) seems to be a specific indicator of filling pressure, whereas in situations characterized by LV dysfunction with relaxation-dominant diastolic abnormalities, T(Ea-E) more likely represents abnormal relaxation. In a recently finished study done with healthy, anesthetized, volume-loaded dogs, T(Ea-E) was useful in the prediction of mean LAP as measured by left atrial catheterization, in particular in dogs with tachycardia and fused transmitral E and A waves. In the latter, the area under the ROC curve in the prediction of elevated mean left atrial pressure (> 15 mmHg) was 0.92, with an optimal diagnostic cut-off of 8 ms for T(Ea-E). For each 1 mmHg increment or decrement of mean LAP, T(Ea-E) decreased or increased by approximately 1 ms, respectively. A potential limitation of applying T(Ea-E) clinically is the currently time-consuming nature of its acquisition and its relatively poor repeatability. Also, both time intervals (measured as onset of R-to-onset of Ea and onset of R-to-onset of E) can only be measured from different cardiac cycles. As heart rate influences systolic and diastolic time intervals any difference in cycle length occurring between measurements may make the use of T(Ea-E) unreliable. The clinical application of T(Ea-E) in the evaluation of LV diastolic function and filling pressures needs further investigation.

Combined Indices

The rationale behind the use of combined indices such as E:IVRT, but also E:Vp, E:Ea, or E:strain rate during isovolumic relaxation is to “correct” for the effect of relaxation on a variable that is largely dependent on filling pressure, but also influenced by relaxation. By combining peak E, a variable that is determined mainly by the LVFP and LV relaxation with a variable that is more dependent on relaxation, the effect of changes in relaxation on Peak E can be minimized.

E:IVRT: In a previous study in experimental dogs, the relationship between E:IVRT and mean LAP was the strongest of the Doppler variables studied with an 82% accuracy in dogs with normal sinus rhythm (cut-off for E:IVRT = 2.20) and a 100% accuracy in dogs with fused E and A waves due to right atrial pacing (cut-off for E:IVRT = 2.17) in the prediction of a mean LAP ≥
15 mmHg. This index has not been used frequently in the past in the DE prediction of LVFP, although a similar index, the [E:A]IVRT ratio, has been shown\textsuperscript{38} to correlate closely ($r = 0.93$, $P < 0.01$) to pulmonary capillary wedge pressure (a surrogate measure of mean LAP) in people with heart disease. In another study of laboratory dogs with LV dysfunction and heart failure due to RV pacing,\textsuperscript{31} E:IVRT was superior to 8 other commonly used DE variables in the prediction of LVEDP. Studies on the use of E:IVRT in dogs with naturally-occurring heart disease have not yet been published. Data on the use of E:IVRT in the prediction of elevated LVFP and CHF in cats is currently not available.

**E:Ea and E:Vp:** The E:Ea ratio and the E:Vp ratio have been reported as useful DE indices of LVFP in numerous clinical trials in people\textsuperscript{8,19,25,33,57} with E:Ea preferred\textsuperscript{15,40} due to superior accuracy, ease of measurement, and better reproducibility. However, studies in dogs are rare.\textsuperscript{21,31,32} Both Ea and Vp have been shown to be relatively preload-independent indices of LV relaxation in situations where LV ejection fraction is low making them suitable for correcting peak E for the effects of relaxation under such circumstances.\textsuperscript{25,40,41} However, studies done by our group indicated that in healthy anesthetized dogs, Vp and even more Ea, are preload dependent.\textsuperscript{32} In the latter, a linear correlation between Ea and mean left atrial pressure in dogs with separated E and A waves ($r=0.58$, $P<0.001$) and dogs with fused E and A waves ($r=0.63$, $P<0.001$) was found which was very similar to the correlation between left atrial pressure and peak E velocity. Therefore, the ratio between peak E to Ea (E:Ea) may not always be useful in the prediction of LVFP. Similar results were reported from studies with healthy people,\textsuperscript{40} open-chest healthy laboratory dogs,\textsuperscript{32} or people with cardiac disease and preserved LV ejection fraction, thereby limiting the global use of such index. In contrast, Oyama and coworkers\textsuperscript{21} reported a close linear correlation between mean LAP and E:Ea ($r = 0.83$, $< 0.05$) using a dog model of acute LV volume overload secondary to severe iatrogenic mitral regurgitation. Conflicting results on the use of E:Ea as a reliable index of LVFP have been reported in people with primary mitral valve regurgitation, with most studies rejecting the use of E:Ea under such circumstances.\textsuperscript{43,44} The strong preload-dependency of Ea in hearts with preserved systolic function, as found often in dogs with compensated degenerative mitral valve disease, may limit the use of E:Ea in the prediction of LVFP in that condition.\textsuperscript{43,44} However, E:Ea may allow for an accurate estimation of LVEDP in dogs with mitral regurgitation and reduced systolic performance.

Peak Vp is less preload dependent than peak E, therefore E:Vp may be used to estimate LVFP. Close correlation with LVFP and clinically relevant predictive power of E:Vp have been reported in people,\textsuperscript{25,33,39,40} in particular when LV ejection fraction is normal.\textsuperscript{45} However, due to the scatter of values within the wide reference range, the fact that Vp is subject to considerable measurement error resulting in poor repeatability, and the inferior performance in the accurate prediction of elevated mean LAP compared to other DE variables, the clinical use of E:Vp in dogs and cats cannot be recommended.

### Reference values (mean±SD) of DE variables used to estimate LVFP in dogs and cats as used in the authors echo lab

<table>
<thead>
<tr>
<th>Variable</th>
<th>E (m/s)</th>
<th>E:A</th>
<th>DTi (ms)</th>
<th>Adur:ARdur</th>
<th>IVRT (ms)</th>
<th>E:IVRT</th>
<th>E:Ea lat</th>
<th>E:Vp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog (n=109)</td>
<td>0.76±0.14</td>
<td>1.47±0.39</td>
<td>78±14</td>
<td>1.35±0.28</td>
<td>62±6</td>
<td>1.45±0.39</td>
<td>5.40±1.39</td>
<td>0.77±0.45</td>
</tr>
<tr>
<td>Cat (n=43)</td>
<td>0.66±0.14</td>
<td>1.41±0.36</td>
<td>54±8</td>
<td>1.46±0.28</td>
<td>46±6</td>
<td>1.42±0.36</td>
<td>9.25±2.71</td>
<td>0.94±0.37</td>
</tr>
</tbody>
</table>

Effects of breed, age, gender, body weight, and heart rate were not specifically considered.

* Increase may indicate increased LVFP.

** Decrease may indicate increased LVFP.

### List of References


*(Supported by a Grant from Morris Animal Foundation)*

**KEYWORDS**

Filling pressure, congestive heart failure, echocardiography, Doppler, diastole, dog, cat