美国超声心动图协会
负荷超声心动图检查操作、判读及应用的建议

Patricia A. Pellikka, MD, Sherif F. Nagueh, MD, Abdou A. Elhendy, MD, PhD, Cathryn A. Kuehl, RDCS, and Stephen G. Sawada, MD, *Rochester, Minnesota; Houston, Texas; Marshfield, Wisconsin; and Indianapolis, Indiana*

中文翻译： 刘芳 王昊天 清华大学附属长庚医院
中文审阅： 汤乔颖 邓又斌 华中科技大学同济医学院附属同济医院

目录

自从 1998 年发布《负荷超声心动图操作与判读的建议》之后，负荷超声心动图技术又取得了长足发展，其中包括成像仪器的改进，负荷试验方案及图像判读标准的改良，以及诸多朝着定量分析方向所取得的重要进展。此外，负荷超声心动图在心血管疾病危险分层和心肌存活性评估等领域所起到的作用现在也越来越被人们所认可。本文中重要的建议和要点将以粗体进行标识。

方法

成像仪器及技术

数字化采集图像的模式已经从电脑将模拟视频信号进行数字化处理演变为现今超声工作站直接输出数字化图像 [2]。这使得图像质量得到了显著改善。许多超声工作站软件可以同时显示基线图像和负荷试验图像。为了让超声设备能够连续进行图像采集，目前更倾向于将图像传输到计算机工作站中进行离线分析。具有大存储容量的网络系统使得我们能够检索分析系列的负荷超声检查

结果。数字化图像的采集方式能够在负荷状态下采集多个心动周期的图像，这些都最大程度地保障了对图像解读的准确性。此外，仍然推荐在采集图像时进行录像以作为备份。

成像技术的进步改善了心内膜边界显示的清晰度，并使得成像质量得到了提高。**有必要将组织谐波成像应用于负荷超声心动图检查。**这种技术可减少近场伪影，提高分辨率，增强心肌的信号，并且与基础成像条件相比可获取更好的心内膜边界清晰度 [3]。心内膜影像在通过谐波成像技术进行改善之后，将降低观察者之间的差异并提高负荷超声心动图的敏感性 [4,5]。

应用经静脉注射的造影剂进行左心室（LV）造影体现了另一种重要进展。当造影剂与谐波成像联合应用时，会使得可判读的左室壁节段数目提高，进而改善缺乏经验的判读医师的报告准确性，提高诊断可信度，并可减少由于在未使用造影剂情况下负荷检查结果不确切而额外进行的无创性检查 [6-9]。同时左心室腔内造影也提高了定量评估的发展潜力。**当 2 个或 2 个以上节段无法清晰显示时，应使用造影剂进行检查。**随着经验的积累和设计合理的检查方案的出现，应用声学造影进行负荷超声心动图检查已被证明是更省时有效的手段 [10]。

除非已事先进行相关评估，否则在进行负荷超声心动图检查时应进行基线超声心动图检查，包括心室功能、腔室大小、室壁运动、主动脉根部和瓣膜等多个方面的评估。这些评估有助于发现除缺血性心脏病外造成相关心脏疾病症状的原因，包括心包积液、肥厚型心肌病、主动脉夹层和心脏瓣膜病。

负荷试验方法

运动负荷试验

由于运动耐量是一项重要的预后指标，故对于可以耐受运动负荷试验的患者，相比药物负荷试验，这类患者更推荐进行运动负荷试验。在运动负荷试验中可采用平板运动或踏车运动中的任意一种。在症状限制性运动负荷试验中，推荐采用运动量分阶段逐渐增加的标准化运动方案。在平板运动负荷超声心动图检查中最常用的方案是 Bruce 方案，这一方案对于给定年龄和性别后所设定的运动强度水平可体现患者的有氧运动能力 [11]。实际操作时，应分别在静息状态和刚刚完成运动时进行图像采集 [12]。踏车运动负荷超声心动图检查可在仰卧位或直立位进行，这一方案的优点是可在运动过程中进行图像采集。通常采取的方案为仰卧位踏车试验，分别在基线时、起始 25W 的负荷时、运动峰值时及恢复期采集图像。在这一方案中，每 2-3 分钟提高 25W 的运动量 [13]。对于年轻患者，建议应用较高的起始运动负荷量。

这两种类型的运动负荷试验为检测心肌缺血和评估心脏瓣膜病提供了极有价值的信息。在平板运动试验时能够达到更大的运动负荷量和更高的最大心率水平，而在仰卧位踏车试验时能够达到更高的血压水平。如果将评估节段性室壁运动作为唯一的检查目标，通常选用平板运动试验。如果需要采集更多的多普勒数据，则建议进行踏车试验，方便在运动中评估节段性室壁运动的同时采集多普勒数据 [14]。

药物负荷试验

对于不能运动的患者而言，可采用多巴酚丁胺或血管扩张剂进行药物负荷超声心动图检查。**尽管血管扩张剂可能在心肌灌注的评估方面具有优势，但是当负荷试验的主要目的为节段性室壁运动评价时仍首选多巴酚丁胺。多巴酚丁胺负荷试验中采用梯度给药的标准方案，起始给药剂量为 5ug/kg/min，每 3 分钟按照 10、20、30、40 ug/kg/min 的梯度增加给药剂量 [15,16]。即使心肌存活性评估不是负荷试验的主要目的，但多巴酚丁胺负荷方案中所包含的低剂量给药阶段也有助于识别静息状态时功能异常节段的心肌存活性和缺血情况。**检查的终点指标为达到目标心率（定义为以年龄为

基准所预测最大心率的 85%），新出现的或加重的中等程度的室壁运动异常，严重心律失常，低血压，严重高血压及出现无法耐受的症状。**为达到目标心率，可分次使用 0.25 到 0.5mg（总量不超过 2.0mg）阿托品。**阿托品可增加正在服用β 受体阻滞剂患者和单支冠状血管病变患者多巴酚丁胺负荷超声心动图检查的敏感性[17]。在检查中，最好应用最小累积剂量的阿托品以达到目标心率，以避免罕见的中枢神经系统毒性并发症。在负荷试验的早期阶段应用阿托品并加快注射多巴酚丁胺，已被证明是一种安全的，且可减少给药时间的方案[18,19]。在患者应用多巴酚丁胺 30ug / kg / min 的阶段应用阿托品，可在应用更少剂量多巴酚丁胺情况下快速达到目标心率，同时减少副作用。使用β 受体阻滞剂可起到纠正多巴酚丁胺副作用的效果[20]。在负荷试验的峰值和恢复阶段中应用β 受体阻滞剂可能会提高负荷试验的敏感性[21]。

多巴酚丁胺负荷与运动负荷超声心动图检查均会显著增加心率，但相比运动负荷试验而言，多巴酚丁胺试验较少增加收缩压。上述这两种技术诱导心肌缺血主要与增加心肌耗氧量有关。在多巴酚丁胺负荷超声心动图结果正常的患者中，未达到目标心率的亚组患者具有更高的心脏事件风险[22]。检查中达到目标心率是负荷试验中的一项重要目标，故而应该考虑在检查当日暂停β 受体阻滞剂的使用，直至检查完成后再恢复服药。但是对于已知患有冠心病（CAD）的患者而言，可能更倾向于继续使用β 受体阻滞剂，因为此时进行负荷超声心动图检查的目的可能包含评估治疗方案是否合理。患者对于检查过程中的副作用（心悸、恶心、头痛、寒战、尿急和焦虑等）通常具有较好的耐受性，不需要因此终止检查。最常见的心血管不良反应是心绞痛、低血压和心律失常。迫使检查终止的严重症状性低血压只在极少情况下发生。约 10%的患者会出现频发房性早搏或室性早搏，约 4%的患者会发生室上性或室性心动过速。室性心动过速往往是非持续性的，通常发生于既往存在室性心律失常病史或基线状态下即存在室壁运动异常的患者中。有关多巴酚丁胺负荷超声心动图检查的诊断和安全性研究报道，心室颤动或心肌梗死发生率估计为 1/2000。左室功能不全[23]、主动脉[24]或颅内[25]动脉瘤及植入心脏复律除颤器[26]的患者，均可安全进行多巴酚丁胺负荷超声心动图检查。多巴酚丁胺负荷超声心动图能够在注册护士的管理下安全有效地开展[27]。

应用血管扩张剂进行的负荷超声心动图检查通常选取腺苷或双嘧达莫作为试验药物[28]。同时试验中会常规应用阿托品以提高血管扩张剂负荷超声心动图检查的敏感性。在注射药物的峰值阶段加以握拳运动可提高试验敏感性。血管扩张剂负荷超声心动图通常会轻度至中度增加心率，同时血压轻度下降。高剂量双嘧达莫负荷超声心动图检查的安全性（最高剂量为 10 分钟内给予 0.84mg/kg 的药物）已被有效证实。严重的副作用和轻微但限制试验继续进行的副作用发生率约为 1%。主要不良反应包括心脏停搏、心肌梗死和持续性室性心动过速。检查过程中可能会发生低血压和/或心动过缓，此时可使用氨茶碱[29]进行治疗。腺苷的作用持续时间短于双嘧达莫。腺苷负荷超声心动图检查多联合心肌声学造影以评估心肌灌注情况，但目前这一方法尚未广泛应用于临床。此外需注意，无论腺苷或双嘧达莫都禁用于患有反应性气道阻塞或严重心脏传导异常的患者。

起搏负荷试验

植入永久心脏起搏器的患者可采用增加起搏频率至目标心率的方式来进行负荷超声心动图检查。这种技术既可以与多巴酚丁胺负荷检查共同进行，也可以单独进行。近期研究表明，该技术在诊断冠心病[30]和判断预后[31]等方面具有较高的准确性。

对于无法运动的冠心病患者而言，经食管心房调搏负荷超声心动图检查是一项有效的替代技术[32]。经局部麻醉后导管可经口或经鼻置入。具体过程为患者取左侧卧位，操作者在患者做吞咽动作时将心脏起搏和

记录导管（置于10F鞘管内）送入指定位置。检查开始时，选取比基线心率大10次/分钟的频率，尽可能以最小的电流实现稳定的心房捕获（约10mA）。起搏方案包括每2分钟调节一次频率，分别使受试者的心率达到目标心率的85%和100%，并获取峰值前期和负荷峰值时的相关信息[33]。分别在静息状态，第一个阶段中，峰值心率前及峰值心率时采集图像。在试验过程中可能会发生Ⅱ度Ⅰ型（文氏型）房室传导阻滞，此时需给予阿托品。终止负荷检查的条件包括达到基于年龄所预测的最大心率，新出现的或加重的中等程度的室壁运动异常，超过2mm的ST段水平型或下斜型下移，或出现心绞痛等不能耐受的症状。这种起搏负荷检查的优点在于当终止心房起搏后心率可迅速恢复至基线情况，从而避免缺血状态延长。除轻度的房性心律失常外，其他副作用很少见。

培训要求与资质维持方法

负荷超声心动图的判读需要具备极丰富的超声心动图判读经验，只能由通过此类技术特别训练的医师实施此项检查。推荐至少具有Level-II训练水平的超声心动图医师，在接受有关负荷超声心动图专项训练后再监管和判读负荷超声心动图。获取独立判读负荷超声心动图的资质所需达到的最低训练要求为，在具有Level-III训练水平的超声心动图医师及负荷超声心动图检查专家的监督指导下至少完成100例负荷超声心动图检查和判读[34]。为了维持这一资质，推荐医师每年应至少完成100例负荷超声心动图检查的判读，并参加相关的继续教育项目。推荐超声技师每年应至少完成100例负荷超声心动图检查以维持一定的技术水平[35]。这些推荐指的是对于冠心病进行常规评估的负荷超声心动图检查，并不包括如瓣膜病或心肌存活性在内的特殊检查，此类特殊检查需要更多的经验和要求来维持应有的技能水平。

图像判读

目前多将肉眼评估心内膜运动和室壁增厚作为负荷超声心动图的分析方法。2005年美国超声心动图协会（ASE）建议应用左室16节段或17节段分段法进行评估[36]。17节段分段法包含“心尖段”，这一节段不包含于左室腔内。评估心肌灌注或超声心动图与其他成像方式进行比较时，推荐使用17节段分段法。**在静息状态下及负荷状态下，对每一个节段的功能进行分级，将其分为正常或运动增强、运动减弱运动消失，、矛盾运动，、室壁瘤这5个等级。在多巴酚丁胺负荷和踏车试验过程中，应在低负荷阶段和中等负荷阶段采集图像，并与最大负荷阶段的图像进行对比，从而最大程度地提高冠状动脉疾病检测的敏感性[37]。**

对室壁运动和增厚的时间也应进行评估。缺血不仅导致心肌收缩和舒张的延迟，也使得收缩速度减缓进而降低心肌最大收缩幅度。“运动减弱”指收缩速度减缓或收缩延迟（心室射血期）及最大收缩幅度减少。目前常规使用的数字化技术可以评估心脏收缩时间的异常表现（非同步性）。与正常心肌节段相比，缺血心肌节段在开始收缩和舒张的时限上存在差别，相差范围从小于50ms到大于100ms不等[38,39]。目前超声系统中使用的帧频已具备必要的时间分辨率，受过训练的判读者可通过肉眼判断心肌收缩的非同步性[40,41]。尽管评估非同步性在采用如M型超声心动图等高时间分辨率技术时准确性更高，但联合使用肉眼观察评估心肌收缩同步性有助于提高观察者间的一致性[42]。使用工作站进行负荷超声心动图分析有助于判读医师在一帧帧图像的基础上比较各个节段收缩的时限，并使判读医师在一定程度上了解收缩早期，即缺血最可能导致心肌收缩速度下降时的图像表现[43,44]。

正常的负荷超声心动图结果为静息状态和负荷状态下的左室壁运动情况均正常。静息状态下室壁运动异常，负荷状态下不发生改变，被归类为“恒定”，通常代表既往已发生梗死的心肌组织。患者若具有恒定的

室壁运动异常表现，即使没有诱发缺血也不应被视为正常的检查结果。**异常的检查结果包括恒定的室壁运动异常，以及能够提示存在心肌缺血的新出现的或恶化的室壁运动异常。除了针对心肌室壁节段性功能的评估外，也应该评估左室整体功能对负荷状态的反应。负荷试验会导致左心室形状、腔室大小及整体收缩力的改变，这对于判断是否存在心肌缺血均具有提示意义[45,46]。**

虽然右心室（RV）收缩功能的评价常被忽略，但在多巴酚丁胺负荷超声心动图检查时出现右室游离壁收缩非同步性表现或三尖瓣环收缩期位移异常也对右冠状动脉或多支病变是否存在具有提示意义[47,48]。

在判读负荷超声心动图结果是否正常时，需考虑到负荷试验的形式和负荷试验过程中的各种细节。**最终判读报告不仅必须包括基线和负荷状态下对收缩功能及各节段室壁运动的评估，也应包括试验所采用的方案，运动时间或给药剂量，最大心率情况，负荷量是否充足，血压的反应，试验终止的原因，试验过程中任何与心脏相关的症状，以及心电图改变或是否存在显著心律失常等。**运动负荷试验比多巴酚丁胺负荷试验更容易诱发疑似冠心病患者的射血分数下降或左室收缩末腔径增大[46]。表 1 列出了几种负荷超声心动图的检查形式，以及各种负荷形式下正常人群和冠脉病变患者左室整体功能和节段性室壁运动的变化[32,33,46,49-59]。表格中所包含的对象均在静息状态下无节段性室壁运动异常且整体收缩功能正常。对于静息状态下室壁运动异常的患者，将在心肌存活性的章节中进行解读。

对于需在不同负荷阶段进行图像采集的负荷试验检查形式，如多巴酚丁胺负荷超声心动图检查或仰卧位踏车运动负荷超声心动图检查，应对各个负荷阶段的图像进行回顾和判读，以确定最开始出现缺血表现时的心率和负荷情况。这些信息对于围手术期的风险分层十分有益[60,61]，因为若在心率较低时即发生缺血表现往往代表患者围手术期心脏缺血事件风险很高。心肌缺血阈值已被证明与狭窄血管的数目，以及运动后 EF 所发生的变化具有相关性，具体计算方法为最先发生缺血表现时的心率，除以（220 减去患者年龄），再乘以 100[62]。

定量分析方法

虽然目前仍然将肉眼评估左室壁增厚和运动状态作为判读负荷超声心动图的标准方法，但这种方法在不同观察者间和不同机构间的变异度很大[63]。仅当经受过严格训练且富有经验的医师进行判读时重复性较好[64,65]。当前正在不断研究负荷超声心动图的定量分析方法，以提高其结果判读的可重复性以及冠脉疾病的检出率，对于缺乏经验的医生而言这点尤为重要。

采用多普勒评估左室整体收缩和舒张功能、心肌背向散射积分自动检测心内膜边界以及组织多普勒评估位移、速度、应变和应变率等定量评估方法均已被证明有助于临床检测心肌缺血。但在负荷试验中心率较快的状态下难以通过多普勒评估二尖瓣前向血流的方法判断左室整体舒张功能，此外在负荷试验中通过主动脉收缩期血流进行评估也缺乏敏感性。

采用心肌背向散射积分方法识别心内膜边界有望成为多巴酚丁胺负荷试验中检测心肌缺血的一种自动方法。采用左心室造影的方法同样可加强对心内膜边界的显示，在整个心动周期中逐帧对心内膜运动进行彩色编码，进而评估局部收缩和舒张功能异常所出现的时间和部位[66,67]。

组织多普勒能够评估振幅高，速度低的心肌信号，其中组织速度成像可通过心尖切面沿心脏长轴进行评估，从中得出位移、应变和应变率。目前单中心和多中心研究均显示，多巴酚丁胺负荷超声心动图检查过程中进行组织速度成像评估与由专家判读的室壁运动结果准确性相似[68,69]。对于经验不足的医师而言，组织速度成像还可提高判读结果的可重复性和准确性[70]。由于正常情况下从基底部到心尖部存在速度梯度，所以在检测冠状动脉疾病时需首先针对不同的心肌节段采集正常值。应变（测量心肌缩短或延长的指标）和应变率（测量缩短或延长速率

的指标）更能够体现心肌的瞬时运动，为评估心肌收缩和舒张功能提供了比位移或组织速度成像更好的评估手段。有实验[71]和早期临床研究[72-75]均提示收缩期后的心肌缩短，发生节段性舒张的时限及收缩期峰值应变和应变率的减低可作为心肌缺血的准确指标。

高质量的二维（2D）图像是进行成功定量分析的基础。所有基于多普勒技术衍生出的数据，包括组织速度成像，应变和应变率等均与采集图像的角度相关，故而偏离轴线的心尖图像可能产生测量结果的误差。最近推出的基于二维超声心动图评估应变与应变率的方法可消除基于多普勒技术的测量结果的角度依赖性[76]。未来，定量分析方法可能会作为一种辅助方法联合肉眼观察共同评估室壁运动。**目前仍需要进一步验证和简化这种分析技术，为定量分析技术在未来大规模应用打下基础。**

表 1 不同负荷检查方式时正常心肌和缺血心肌的反应

	局部反应		整体反应	
负荷方式	正常反应	缺血反应	正常反应	缺血反应
平板运动试验	运动后比静息状态时功能提高	运动后比静息状态时下功能降低	ESV 降低，EF 升高	多支或左主干病变时 ESV 升高，EF 降低
仰卧位踏车运动试验	峰值负荷状态比静息状态时功能提高	峰值负荷状态比静息状态时功能下降	ESV 降低，EF 升高	多支或左主干病变时 ESV 升高，EF 降低
多巴酚丁胺负荷试验	高剂量药物负荷时，功能和收缩速度较静息状态和低剂量状态提高	高剂量药物负荷时，功能和收缩速度较低剂量状态降低，与静息状态相比可能下降不明显	ESV 显著降低，EF 明显升高	通常和正常反应相同；少数情况下缺血导致 EF 降低；心腔扩张很少出现
血管扩张剂负荷试验	给药后比静息状态时功能提高	给药后比静息状态时功能降低	ESV 降低，EF 升高	通常和正常反应一样；偶尔缺血时导致 EF 降低；心腔扩张很少出现
心房起搏负荷试验	与静息状态时比较，功能无变化或升高	比静息状态时比较，功能降低	ESV 降低，EF 不变	ESV 不变或升高，EF 降低

EF，射血分数；ESV，收缩末期容积。

准确性

1998 年 ASE 基于数个不同研究的原始数据，公布了有关负荷超声心动图研究结果：应用负荷超声心动图检测冠状动脉狭窄（一般指血管造影狭窄程度超过直径的 50％）的敏感性平均为 88％（1265/1445），特异性平均为 83％（465/563）。此后又开展了多项研究，通过与其他影像学方法进行比较，评估负荷超声心动图的准确性。**这些研究对比了核素心肌显像和负荷超声心动图在同一患者群中的检测结果后发现，在冠心病的检出敏感性方面两者相当，但负荷超声心动图具有更好的特异性**[77-81]。在一项包含了 18 项研究的汇总分析中，共 1304 名患者接受了运动负荷或药物负荷超声心动图检查，同时进行了铊或锝标记放射性核素显像，发现负荷超

声心动图的敏感性和特异性分别为 80%和86%，而心肌灌注显像的敏感性和特异性分别为 84%与 77%[79]。

试验验证偏倚会降低目前所有无创影像学检查的特异性[82]。无创检查结果为正常或阴性的患者越来越少接受血管造影，进一步导致以血管造影为金标准的无创检查的特异性下降。**负荷超声心动图检查的高度特异性使其成为一种高效价比的诊断方法，尤其对于其他负荷试验假阳性率较高的患者而言更是如此。**

假阴性结果

除极少数例外，假阴性结果并不仅见于负荷超声心动图，同样也可见于其他无创检查方法。其主要原因是负荷量不达标[83]。恰当的负荷量通常被定义为运动负荷或多巴酚丁胺负荷试验时心率达到或超过以年龄预计的最大心率的 85%，和/或在运动负荷试验时心率与血压的乘积等于或大于 20000。虽然这些阈值没有得到很好验证，但心肌耗氧量与诸多血流动力学参数之间的线性相关性支持了提高心率以及心率与血压的乘积的重要性。运动量不足及使用β 受体阻滞剂是造成负荷量不足的常见原因。对于不能进行运动的患者，推荐药物负荷和心房起搏替代。在非运动性负荷试验方式中，使用心房起搏可获得最大心率和敏感度[33,84]。多巴酚丁胺负荷试验中使用阿托品可提高已应用β 受体阻滞剂患者检查的敏感性，此外也有助于避免心房起搏过程中心脏出现文氏传导阻滞[32]。

少数对比平板运动试验与仰卧位踏车试验的研究表明，部分在平板运动结束后的图像分析中表现为阴性的患者，在仰卧位踏车运动高峰时可检测到缺血性的心肌运动异常[85,86]。然而平板运动试验通常可达到更大的运动负荷量，这在一定程度上抵消了部分踏车试验可于运动高峰期采集图像的优点。

与其他形式的负荷试验相同，负荷超声心动图检查的假阴性结果多见于单支冠脉病变或回旋支病变的患者，原因在于此类患者受病变影响的心肌供血范围较小[87]。仰卧位踏车试验对于检测回旋支病变具有较高的敏感性[88,89]。常规应用心尖长轴切面可降低回旋支病变患者负荷检查结果的假阴性率。

对于已发生左室腔容积变小和室壁增厚等向心性心肌重构的患者而言，检测是否存在心肌缺血更加困难[90]。此类患者多巴酚丁胺负荷试验比其他检查更容易出现假阴性结果。多巴酚丁胺负荷试验中引起的整体运动增强以及舒张和收缩容积减小（表 1），会使孤立的室壁运动异常更难以被检测到。另外，当患者发生向心性心肌重构时，多巴酚丁胺可能会降低室壁张力并减少心肌耗氧量，从而降低诱导出心肌缺血的频率[91]。此外，重度主动脉瓣或二尖瓣关闭不全时心脏活动增强，使得心肌缺血的检测变得更加困难[92]。

假阳性结果

负荷超声心动图检查出现假阳性结果多因为存在与冠状动脉堵塞无关的心肌缺血和非缺血原因导致的负荷后室壁运动异常[93]。即使没有发生心外膜冠状动脉堵塞，如果心肌灌注无法满足心肌氧耗需求时也会导致节段性功能异常。例如负荷试验中高血压患者出现的左室整体或节段性功能不全[94]，伴随或不伴随左室流出道梗阻的肥厚型心肌病患者的心尖部运动减弱或其他心肌节段运动异常[95]。此外，当存在累及冠脉微血管的心肌疾病如左室肥厚、X 综合征、糖尿病，心肌炎或特发性心肌病时可发生心肌灌注储备降低。心外膜冠脉痉挛可在无明显冠脉狭窄的情况下导致心肌缺血，此类情况在运动负荷或多巴酚丁胺负荷试验中均有相关报道。

高血压患者或潜在的心肌病患者在没有发生心肌缺血的情况下，也可能表现为负荷试验时室壁运动异常。运动负荷可导致原有心肌病的室壁出现节段性或整体收缩功能恶化。长期高血压患者易在负荷状态下出现心室整体功能异常[96,97]。即使没有左室肥

厚或静息状态下收缩功能减退等表现部分长期高血压患者在负荷试验中出现室壁运动异常，可能是由于存在潜在的心肌病变[98,99]。

评估节段性室壁运动时，牵拉效应可能会导致假阳性结果。二尖瓣径向运动消失时，由于固定瓣环的牵拉效应，会导致临近的下壁基底段和后间隔基底段运动减弱[93]。在瓣环钙化和曾接受二尖瓣置换术的患者中这种情况比较多见。

左束支传导阻滞、右心室起搏及开胸心脏手术后所导致的室间隔运动异常易与缺血导致的异常相混淆。在这些情况下，通常在静息状态下即存在室间隔运动异常。难点在于，若这种室间隔运动异常在负荷试验过程中进一步加重，如何判断是否由于缺血因素而造成。评估室壁增厚率，并且认识到缺血造成的室壁运动异常应遵循典型的冠脉供血区域，以上两点有助于鉴别室间隔非同步运动是否系缺血因素所致[100-102]。此外，即使不存在冠脉堵塞，心率较快时室间隔非同步运动也会加重室间隔灌注不足和室壁增厚异常。

心肌存活性评价

负荷超声心动图检查已成为冠心病和左室收缩功能不全患者的一项重要评估手段。多中心研究表明负荷超声心动图检查证实存在存活心肌、但并未接受血运重建的患者预后不佳[103,104]。存活心肌是指由冠心病所导致的出现功能障碍但具有可逆性的心肌。对于，非缺血性心肌病患者检测到具有收缩储备功能的心肌也提示心脏功能可能恢复[105]，此时给予β 受体阻滞剂治疗可能会带来益处[106]。

慢性冠心病中存在的可逆性功能障碍的心肌被称为“冬眠心肌”。早期研究认为这是为了适应心肌低灌注而相应产生的节段性功能障碍。然而，最近的研究表明即使静息状态心肌灌注正常或仅发生轻度的灌注减低，这些心肌也可能会表现为收缩力下降。提示反复发生心肌缺血是导致慢性心功能不全的原因之一。静息状态下灌注降低的心肌可发生一系列结构和功能改变，包括间质纤维化、糖原蓄积、收缩蛋白减少、细胞重塑、钙敏感性增强，及β 受体信号通路下调[107-110]。随着血运重建的延迟，这些心肌所发生的改变可能会不断进展，直至发展到难以恢复的地步[111]。

大多数负荷超声心动图检查方案均以检测心肌收缩储备为重点，应用如多巴酚丁胺在内的正性肌力药物。其他形式的负荷超声心动图检查也同样在展开应用，包括运动负荷、心室收缩后刺激、依诺昔酮负荷、低剂量双嘧达莫负荷等等。

与核素灌注显像或超声心动图心肌声学造影相比，在评估存活心肌方面，多巴酚丁胺负荷超声心动图试验检测心肌收缩储备的条件为间质纤维化成分较低而存活心肌细胞比例较高[107]。这可以解释为何在检测心肌存活性时，心肌灌注成像与多巴酚丁胺负荷超声心动图相比敏感性更高而特异性更低。

无论低剂量或高剂量用药方案均已被证明能够有效检测心肌存活性。早期研究主要关注低剂量多巴酚丁胺负荷方案，而其他研究者也强调了试验中至少达到目标心率的 85%以诱发心肌缺血的重要性。此外，必须采集静息状态下室壁厚度的超声图像并进行评估。已经变薄（≤0.5 或 0.6cm）且回声增强（可能由于严重的纤维化导致）的节段功能恢复的可能性很小[112,113]。此外，评估二尖瓣血流也十分有益，尤其是对于采集图像时已接受足够治疗的患者。左室舒张功能呈限制性充盈的患者，其具有存活性的心肌节段往往很少，接受血运重建后恢复功能的可能性较低[114]。在采集基线图像时需评估是否存在可能会改变手术方案的严重瓣膜疾病。获取充足的基线数据后，方可开始进行多巴酚丁胺负荷试验。

多巴酚丁胺的起始给药速度为 2.5ug/kg/min，逐渐递增至 5、7.5、10 和 20 ug/kg/min[115]。由于接受检查的许多患者存在多支血管病变，中度至重度左室收缩功能障碍，并有发生心律失常的潜在可能性，故建议在监护条件下进行该项检查。若运动消

失的节段功能无改善，则表示该节段功能恢复的可能性很小，此时应终止检查。若运动减弱节段出现功能恶化的表现也同样应终止检查。另外，若在没有出现副作用的情况下出现心肌功能改善，可逐渐增加多巴酚丁胺用量至 40 ug/kg/min，必要时可应用阿托品。应用较高剂量多巴酚丁胺的优势在于更容易诱导缺血表现。同时应用高剂量和低剂量多巴酚丁胺最容易出现以下四种可鉴别的心肌功能障碍，包括双相反应（低剂量时运动增强，随后在较高剂量时运动减弱）、持续改善（低剂量时功能改善，高剂量时不发生恶化），功能恶化以及功能无变化。

多巴酚丁胺负荷超声心动图预测心脏功能恢复（依检查方案有所不同）的敏感性为 71％至 97％，特异性为 63％至 95％[116]。**如果应用低剂量多巴酚丁胺即发生功能改善，此时检测心肌存活性的敏感性最高；发生双相反应时特异性最高 [117]。**若患者存在大面积存活心肌（大于左心室的 25％），则血运重建后射血分数更有可能改善，预后更好 [118]。**尽管存在多种对存活心肌的定义方式，目前仍然推荐至少在一个多巴酚丁胺剂量组出现 2 个或 2 个以上的节段功能改善时方可定义为存活心肌。**应用低剂量多巴酚丁胺时若检测到大量的存活心肌则代表血运重建可有效阻止心脏重构，持续改善心衰症状，并降低心脏事件的发生概率 [119]。

超声心动图识别存活心肌的其他方法包括通过心肌声学造影评估微循环情况，应用心肌背向散射积分评估心肌组织定征。这两种方法均需在基线和应用血管扩张剂或多巴酚丁胺后获得相应的影像学数据。未来，采取定量分析法评估节段功能可能会进一步改善对存活心肌的评估方法。初步研究表明，有关应变率和应变的评估可提高存活心肌的检出率 [120-122]。

呼吸困难、肺动脉高压和心脏瓣膜病患者的评估

呼吸困难

负荷超声心动图可用于评估患者心源性呼吸困难 [123]。除了评估是否存在心肌缺血及其严重程度和范围，左心室和左心房容积，射血分数，是否存在左室肥厚和/或瓣膜疾病以外，基线超声心动图可以识别肺动脉高压或左室舒张和充盈压异常升高。某些情况下，根据静息时的基础图像即可判断病因为心源性，并不需要负荷成像。推荐采用仰卧踏车运动，可以在运动过程中记录多普勒数据。评估应在静息期、运动期和 E、A 速度不再融合的恢复期分别评估多普勒二尖瓣流速。应以 100 毫米/秒的扫描速度采集多普勒数据。二尖瓣血流 E（舒张早期峰值速度）和二尖瓣环舒张早期速度（e’）的比值可以用来评估静息和运动时的左室充盈压。健康个体运动时二尖瓣 E 和二尖瓣环 e’的增幅相似，所以运动时两者的比值不变或仅有很小改变。[124] 左室舒张功能受损的患者运动时左室充盈压升高，导致心动过速和舒张充盈期缩短。二尖瓣 E 峰速度相应增加。但由于舒张功能受损对二尖瓣环 e’的前负荷影响很小，二尖瓣环 e’下降。因此舒张功能不全的患者运动时 E/e’比值升高。[125,126] 上述方法已经有创检测运动时平均左室舒张压升高验证。[126] 以上方法不适用于房颤、声窗受限和缺乏验证条件时。此外，局部功能异常对单点测量 e’值准确性的影响还有待观察。

肺动脉高压

经胸超声心动图能够可靠估计肺动脉压力、检测心源性肺动脉高压、疾病及治疗引起的右心室和左心室容积及功能变化。[127] 运动状态下更有机会检测到肺动脉高压患者右心室及左心室功能和每搏量的变化。[128,129] 一些在静息状态下肺动脉压正常的患者在运动时肺动脉压显著升高；这种情况的预后还

不明确。已有研究评估健康个体和青年男性运动员对运动的正常反应。[131] 通过多普勒检测发现高强度训练的男性运动员运动时的肺动脉收缩压可高达 60 mmHg。[131] 也有研究报道采用运动负荷超声心动图检测无症状的家族性原发性肺动脉高压基因携带者[13] 和高海拔肺水肿易感患者。[132]

二尖瓣疾病

负荷试验可以观察到二尖瓣疾病患者与静息状态血液动力学不相称的劳累症状。[133] 这同样适用于有严重病变但无症状的患者；运动诱发的肺动脉收缩压升高至 60mmHg 以上可被认为是二尖瓣手术指证（2006 年美国心脏病学会（ACC）/美国心脏协会（AHA）瓣膜心脏病患者管理指南的 IIA 级推荐指征）。[134] 已发表的研究多数采用仰卧位踏车方案来获取图像。采用脉冲多普勒（二尖瓣反流）和连续多普勒（二尖瓣狭窄）记录二尖瓣血流，同时在静息和运动状态下采用连续多普勒来记录三尖瓣反流速度。

对于二尖瓣狭窄的患者，负荷多普勒超声心动图推荐应用于静息时血液动力学显示病变较重但无症状的患者和静息时血液动力学和症状不匹配的患者（I 类推荐指征）。[134] 基线和负荷状态下，采用连续多普勒通过改良的伯努利方程获取二尖瓣口的跨瓣压差和三尖瓣反流速度。将超声波束对准二尖瓣口血流，能够在静息和运动时通过多普勒计算出的准确压差，和侵入性测量结果相比一致性较好。对于久坐患者，如果运动时诱发呼吸困难，且伴随二尖瓣平均跨瓣压差增加至大于 15 mmHg 及肺动脉收缩压升高至大于 60 mmHg，提示患者存在血液动力学显著受损，当解剖学适合且二尖瓣反流为轻中度时经皮瓣膜切开术可能有益。[134,136] 当运动仅引起轻微二尖瓣跨瓣压差改变但肺动脉收缩压显著升高时，提示应进一步评估是否存在潜在的肺部疾病。对于不能运动的患者，可以采用多巴酚丁胺负荷试验。[137,138]

彩色多普勒能够定量或半定量评估二尖瓣反流。[14,139] 运动负荷超声心动图可以揭示在静息状态下只有轻度二尖瓣狭窄和反流的风湿性瓣膜病患者在运动时出现的重度二尖瓣反流。[140] 同样，运动负荷超声心动图能够检出左室收缩功能不全患者存在的具有血液动力学意义的动态二尖瓣反流。动态二尖瓣反流能够导致有些患者发生急性肺水肿，预后较差。[141] 负荷超声心动图还能够检测到静息状态下重度二尖瓣反流和 EF 值正常患者左室收缩储备的下降。[142]

主动脉瓣疾病

推荐多巴酚丁胺超声心动图用于左室收缩功能不全和低压力阶差的主动脉瓣狭窄患者，后者的定义是多普勒测量的主动脉瓣口面积小于 1.0 cm^2 伴平均压力阶差小于 30 mmHg。[134] 多巴酚丁胺被用以评估这类患者主动脉瓣狭窄的严重程度和左室收缩储备。[143,144] 静脉输注速度以 5 μ g/kg/min 开始，每 5 分钟增加剂量至 10 和 20μ g/kg/min。

对重度主动脉瓣狭窄患者而言，多巴酚丁胺升高平均跨瓣压差的幅度大于跨瓣血流的增加。相应的，主动脉瓣口面积始终异常减小提示真正的主动脉瓣狭窄。另一方面，对于“功能性”瓣膜狭窄的患者，输注多巴酚丁胺可导致流速和瓣口面积显著增加。这种“功能性”瓣膜狭窄主要是由于血流速度降低所致。近期研究表明，计算有效瓣口面积有助于提高多巴酚丁胺负荷超声心动图诊断真正主动脉瓣狭窄的准确性，此项研究以外科探查为金标准。[145] 多巴酚丁胺负荷超声心动图可为左室收缩功能不全伴主动脉瓣狭窄患者提供重要的预后信息，多数左室收缩储备尚可的患者行外科主动脉瓣置换术可改善预后。相反，收缩储备不佳的患者行外科治疗可导致死亡率增高。[146]

对于慢性主动脉瓣反流患者，运动试验可用于症状可疑时或参加体育活动前评估功能性容量（IIA 类推荐指证）。[134] 左室功能不全患者也可以在手术前获得有用的预后信息（IIB 类推荐指证）。[134] 已有多项研究支持这一观点，这些研究针对无症状的主动脉瓣反流患者，负荷状态下放射性核素造影显示 EF 值异常（和 EF 变化）。但是，还不清楚相比静息状态，负荷会使左室内径和 EF 值增加多少。不推荐负荷超声心动图用于症状明确伴重度主动脉瓣反流或 EF 值较低的

患者，这类患者不应做负荷试验而应行外科手术治疗。

人工瓣膜的评价

负荷超声心动图已被用于评估人工主动脉瓣的跨瓣压差和血流。多应用多巴酚丁胺，[147-149] 但也有少数采用运动负荷超声心动图监测瓣膜的血液动力学变化。[149]

尽管负荷超声心动图可用于评估有症状但静息状态下仅有可疑阳性结果的患者的心室和人工瓣膜功能，但多普勒阶差的应用价值有限，因为其决定因素不仅仅是血流速度，还包括人工瓣膜的类型和大小。还需要更多的数据来界定不同人工瓣膜的正常反应。

负荷超声心动图在危险分层方面的应用

负荷超声心动图可用于已知或怀疑冠状动脉疾病患者的危险分层。这已被大量研究所证实，这些研究对有临床指征行负荷超声心动图的患者进行了连续随访。**这些研究证明负荷试验对试验前可能已存在疾病的患者、有症状者、冠状动脉疾病患者、冠脉血运重建术患者、陈旧心肌梗死患者以及存在冠状动脉疾病危险因素的无症状患者均具有预测价值。**负荷试验对于运动能力良好 [150] 或降低 [151] 的患者，负荷试验的预后价值稳定。表2总结了负荷超声心动图评估已知或可疑冠状动脉疾病患者预后的一些研究。[152-154] 表3显示了在上述研究和其他研究中发现的判断预后的指标。研究显示，在调整危险因素和负荷试验参数的基础上，负荷超声心动图增加了对已知或可疑冠状动脉疾病患者总死亡率、心源性死亡率和复合心脏终点的预测价值。

表 2 负荷超声心动图评估对预后的判断价值的研究总结

作者	患者数量	患者特征	负荷类型	随访长度均值或均位数（年）	随访终点	超声心动图评估采用的预测因子
Arruda-Olson et al 2002[161]	5798	已知或可疑 CAD	运动负荷	3.2	心源性死亡/心肌梗死	运动状态下的 WMSI
Marwick et al 2001[159]	5375	已知或可疑 CAD	运动负荷	5.5	全因死亡	静息状态时 WMA 的范围；缺血的范围
Biagini et al 2005[162]	3381	已知或可疑 CAD	多巴酚丁胺负荷	7	心源性死亡/心肌梗死	静息状态时 WMA，缺血事件
Marwick et al 2001[160]	3156	已知或可疑 CAD	多巴酚丁胺负荷	3.8	心源性死亡	静息状态时 WMA，缺血事件
Chuah et al 1998[65]	860	已知或可疑 CAD	多巴酚丁胺负荷	2	心源性死亡/心肌梗死	负荷状态下 WMA；收缩末期容量反应

Shaw et al 2005[173]	11,132	已知或可疑 CAD	运动负荷或多巴酚丁胺负荷	5	心源性死亡	静息状态时 WMA 的范围；缺血的范围
Sicari et al 2003[152]	7333	已知或可疑 CAD	双嘧达莫或多巴酚丁胺负荷	2.6	心源性死亡/心肌梗死	静息状态下的 EF，以及 WMSI 变化
Tsutsui et al 2005[153]	788	已知或可疑 CAD	多巴酚丁胺负荷心肌声学造影	1.7	全因死亡/心肌梗死	造影剂灌注缺失
Bergeron et al 2004[123]	3260	胸痛或呼吸困难	运动负荷	3.1	全因死亡率/发病率	WMSI 的变化
Elhendy et al 2001[163]	563	糖尿病	运动负荷	3	心源性死亡/心肌梗死	EF，缺血范围
Sozzi et al 2003[187]	396	糖尿病	多巴酚丁胺负荷	3	心源性死亡/心肌梗死	EF，缺血范围
Marwick et al 2002[188]	937	糖尿病	运动或多巴酚丁胺负荷	3.9	全因死亡	静息状态下 WMA 的范围；缺血的范围
Chaowalit et al 2006[186]	2349	糖尿病	多巴酚丁胺负荷	5.4	全因死亡率/发病率（心肌梗死、晚期冠状动脉血运重建）	缺血的范围，无法达到目标心率
Arruda et al 2001[184]	2632	老年（≥65 岁）	运动负荷	2.9	心源性死亡/心肌梗死	EF 变化和收缩末期容量
Biagini et al 2005[185]	1434	老年（≥65 岁）	多巴酚丁胺负荷	6.5	心源性死亡/心肌梗死	静息状态时 WMA，缺血事件
Carlos et al 1997[178]	214	急性心肌梗死	多巴酚丁胺负荷	1.4	心源性死亡，心肌梗死，心律失常，心衰	静息状态时 WMSI；冠脉远端异常
Elhendy et al 2005[183]	528	心衰	多巴酚丁胺负荷	3.2	心源性死亡	静息状态时 EF，缺血事件
Elhendy et al 2003[154]	483	超声心动图标准下的 LVH	运动负荷	3	心源性死亡/心肌梗死	静息状态时 WMSI，EF 反应
Arruda et al 2001[198]	718	既往 CABG	运动负荷	2.9	心源性死亡/心肌梗死	EF 变化和收缩末期容量
Bountiouko et al	331	既往 CABG 或 PCI	多巴酚丁胺负荷	2	心源性死亡/心肌梗死/	缺血事件

2004[199]					晚期血运重建	
Biagini et al 2005[31]	136	既往曾安装起搏器	步行负荷	3.5	心源性死亡	缺血事件
Das et al 2000[61]	530	非血管外科手术前	多巴酚丁胺负荷	住院期	心源性死亡/心肌梗死	缺血阈值
Poldermans et al 1997[193]	360	血管外科手术前	多巴酚丁胺负荷	1.6	围手术期和晚期心脏事件	缺血事件
Sicari et al 1999[191]	509	血管外科手术前	双嘧达莫负荷	住院期	全因死亡，心肌梗死，不稳定心绞痛	缺血事件

CABG，冠状动脉旁路移植术；CAD 冠心病；EF 射血分数；LVH 左心室肥厚；PCI 经皮冠脉介入手术；WMA 室壁运动异常；WMSI，室壁运动评分指数。

表 3 负荷超声心动图预后判断指标

心肌梗死很低风险*，心脏事件<1%/年	**心肌梗死低风险*，心脏事件<2%/年**	**升高心肌梗死风险的指标†** ——————————>	**代表高风险‡的指标 RR≥低风险的 4 倍**
运动负荷超声心动图结果正常且运动能力良好 男性运动量达 7 METs 女性运动量达 5 METs	恰当负荷状态下，药物负荷超声心动图结果正常（其定义为多巴酚丁胺负荷状态下心率大于最大目标心率的 85%） 低-中度提示 CAD	年龄增长 男性 糖尿病 高验前概率 呼吸困难或 CHF 病史 心肌梗死病史 运动能力受限 无法运动 负荷 ECG 显示缺血 静息状态下 WMA 左室肥厚 负荷超声心动图显示缺血 基线状态下 EF 降低 负荷状态下 ESV 不变或升高 § 负荷状态下 EF 不变或降低 § 负荷状态下室壁运动评分升高	广泛的静息状态下 WMA（左室的 4-5 个节段） 基线期 EF<40% 广泛缺血（左室的 4-5 个节段） 多支病变缺血 静息状态下 WMA 和远端缺血 缺血阈值低 0.56 mg/kg 双嘧达莫或 20 μ g/kg/min 多巴酚丁胺负荷或心率未达标时//发生的缺血 缺血性 WMA 表现，运动负荷下 EF 不变或降低 §

CAD，冠状动脉疾病；CHF，充血性心力衰竭；ECG，心电图；EF，射血分数；ESV，收缩末期容积；HR，心率；LV，左室；METs，代谢当量；MI，心肌梗死；WMA，室壁运动异常。
*对于负荷超声心动图结果正常的患者，具有以下升高心肌梗死发生风险的指标，具体包括：CAD 的高预发可能性，运动能力差或低心率-血压乘积，年龄增长，负荷状态下发生心绞痛，

左室肥厚，心肌梗塞病史，CHF 病史和抗缺血治疗。
†每个因子增加风险的程度不同。
‡高风险群体的临界值是从多个研究中获取的估算值。研究表明静息状态下、低剂量和峰值剂量时室壁运动评分升高的患者属高风险个体，尤其对于左室整体功能下降的患者更是如此。但是定义高危患者的临界值有不同（比如，峰运动评分从 1.4 到>1.7 不等）。
§适用于平板运动和多巴酚丁胺负荷试验
//不同研究将多巴酚丁胺负荷试验中低缺血阈值心率分别定义为，在小于年龄校正的最大心率 60%、在小于年龄校正的最大心率 70%、或心率<120/分钟时发生缺血。

运动负荷超声心动图结果正常提示心源性死亡和心肌梗死的年发生率低于 1%，与年龄和性别匹配的人群相当。这些患者在无临床状态改变的情况下无需进一步的诊断性评估。[155,156] 药物负荷超声心动图结果正常患者的事件发生率轻微升高。[22] 原因之一可能是风险高的患者无法进行运动负荷试验，这类人群往往年龄更大并伴有更多合并症。

许多研究表明，缺血与死亡率升高及心源性事件相关。**负荷试验中出现多血管分布区域异常的患者死亡和心源性事件风险高。对于这类患者应特别考虑其**症状、功能储备和静息状态下的左室功能，有关冠状动脉造影检查和后续的心肌血运重建的计划可能需要调整。运动负荷试验室壁运动评分指数大于 1.4 或 EF 值小于 50%提示预后显著恶化。负荷超声心动图结果需结合杜克踏车积分、临床和负荷试验的变量如年龄、性别、症状、运动耐量、心率-血压乘积和室壁运动异常的严重程度。[157-159]

以室壁运动评分指数或 EF 值表示的基线左室功能是未来事件的强有力预测指标。**静息状态下左室功能不全但未诱发心肌缺血的患者中危，而静息状态下左室功能不全伴新发室壁运动异常的患者死亡和心源性事件的风险最高。**

表 3 总结了提示患者风险增加的负荷超声心动图结果。**除了基线左室功能不全，和不良预后相关的结果包括广泛缺血 [65,160-162]、EF 变化不明显或运动时收缩末期容积无减小 [150]、广泛的室壁运动异常 [163]、低缺血阈值 [61]、左室肥厚 [155] 和室壁运动异常位于左前降支冠状动脉分布区域 [164]。**无运动变为矛盾运动与广泛的左室功能不全、灌注缺损无可逆性、[165] 和血运重建后局部功能改善的可能性极低相关。[166] 若同时进行抗缺血治疗，试验结果阳性预示预后差的可能性大，试验结果阴性预示预后有可能良好。[167]

负荷超声心动图评估预后的方法已在特定的患者群体中建立，包括高血压、[168,169] 起搏器植入状态、[31] 左束支传导阻滞、[170] 左室功能不全 [171] 和房颤患者。[172] 在其他人群中的应用见下述内容。

女性

负荷超声心动图对男性和女性预后的评价方法均已建立。161,162,173-175 尽管一些研究报道男性心源性事件的发生率高于女性，**与负荷超声心动图异常相关的风险恶化和性别无关**。161,162

急性心肌梗死后

静息状态下左室功能是评价心肌梗死预后的主要指标。**在心肌梗死后早期可以安全地行负荷超声心动图检查，这不仅能够评估整体和局部心室功能，还能检测残余心肌缺血及其范围。**176 已有研究证明，残余心肌缺血的范围和心脏不良预后相关，负荷超声心动图比负荷心电图 177 或血管造影 178-181 价值更大。负荷超声心动图对左室功能异常患者的预后价值更大。182 对于由缺血性心肌病导致心衰和低 EF 值的患者，尤其未行血运重建的患者，多巴酚丁胺负荷超声心动图中观察到的心肌缺血预示着心源性死亡。183

老年人

已证明运动负荷超声心动图是评估老年人冠状动脉疾病有效的无创性方法。负荷超声心动图指标不仅提示临床存在心肌缺血，还能反映缺血的范围（尤其是左室收缩末期容积变化和运动时的 EF 值），负荷心电图和静息超声心动图也提高了对心源性事件和全因死亡的预测价值。184 **不能运动的老年患者可采用药物负荷超声心动图独立预测死亡率。**185 静息状态下和负荷状态下均有室壁运动异常的患者发生心源性事件的风险较高。

糖尿病患者

负荷超声心动图能够有效对糖尿病患者进行心脏危险分层。负荷试验中出现多血管分布范围室壁运动异常的患者，大约每 3 个中就有 1 个在 3 年内会发生心源性死亡或心肌梗死。163 许多糖尿病患者由于周围血管疾病和周围神经疾病发生率较高因而无法耐受运动负荷试验。这类患者通常心血管风险高于能够耐受运动负荷试验的患者。多巴酚丁胺负荷超声心动图有独立预测价值。186-188

非心脏手术前

心脏危险因素和负荷试验有助于在大血管手术前判断高危患者，明确哪些患者能够从冠状动脉血运重建或药物治疗（倍他乐克）中获益。189 药物负荷超声心动图被认为是血管 190-193 和非血管手术 61 前进行心脏危险分层的有力工具。负荷超声心动图较临床其他指标能够提供更好的危险分层。61 非心脏手术前，广泛缺血（≥3-5 个节段）对预后有很强的独立预测价值，可识别能从血运重建中获益的患者。在小于年龄预测最大心率的 60%时即发生缺血是识别极高危患者的指标。61 近期一项 meta 分析比较了 6 种用于血管手术前危险分层的无创方法，其中药物负荷超声心动图总的敏感性和特异性均高于其他方法。对于术前危险分层，多巴酚丁胺负荷超声心动图和心肌灌注闪烁照相术的敏感性相似，但特异性更高，总的预测准确性更好。190,194 对于接受倍他乐克治疗的临床中高危患者，多巴酚丁胺负荷超声心动图有助于识别可以耐受外科手术的患者以及需要进行心脏血运重建的患者。189

冠状动脉血运重建后

负荷超声心动图可以明确再狭窄或移植血管闭塞的部位，检测未发生再血管化的冠状动脉疾病，并评估血运重建的合理性。194,196 冠状动脉血管成形术后负荷超声心动图阳性提示患者再发心绞痛风险较高。197 负荷超声心动图中发生的缺血能够预测心脏事件。198,199 对于既往行冠状动脉旁路移植术的患者，负荷超声心动图指标、左室收缩末期容积变化异常和运动时的 EF，与临床、静息超声心动图和负荷心电图共同预测心脏事件的价值更高。198 无症状患者血运重建后早期不建议常规行负荷试验。

心绞痛患者

心绞痛症状对于检测潜在冠状动脉疾病的特异性有限。仅有约 50%的心绞痛患者在负荷超声心动图检查过程中诱发缺血表现。稳定性心绞痛患者负荷超声心动图正常表明患者心脏事件的风险低。对于 CAD 患者，心绞痛预测冠状动脉疾病患者心肌缺血程度的价值较低。**负荷超声心动图可以提供心绞痛患者心肌缺血的客观证据，并明确危险心肌的范围 200，负荷超声心动图也可用于危险分层。201**

与核素显像的比较

负荷超声心动图正常者年心脏事件率（小于 1%）与目前美国核素心脏学会（ASNC）

/ACC/AHA 指南及近期一项 meta 分析中报告的负荷核素显像正常者相似。202,203 负荷超声心动图的室壁运动评分指数和核素显像的负荷总分被认为和随访期心脏事件的发生率直接相关。有研究比较了同一人群负荷超声心动图和核素显像 204,205，这些研究和几项 meta 分析 190,194,203 结果均证明这两种检测方法对预后的判断价值相似。有研究对 301 例患者同时进行多巴酚丁胺负荷超声心动图和甲氧异腈单光子发射计算机断层（SPECT）核素显像并平均随访 7 年，结果显示，SPECT 正常者年心源性死亡率为 0.7%，负荷超声心动图正常者年心源性死亡率为 0.6%。这两种方法检测出的异常结果对心源性死亡和复合终点的预测价值相似。206 已有大规模研究比较了负荷超声心动图和 SPECT 成像对中危稳定胸痛患者预后的评估及成本-获益比。经过风险校正的 3 年死亡率或根据缺血程度分类的心肌梗死率相似。基于成本-获益比的策略支持在可疑冠状动脉疾病的低危患者中应用超声心动图，在高危患者中应用 SPECT 成像。207 **负荷超声心动图的优势包括成像时间较短、无电离辐射、便携、即时获得结果、成本较低、和可获取房室大小、功能、瓣膜、心包积液、主动脉根部病变、室壁厚度等衍生信息。**

近期和未来发展

应变和应变率超声心动图

如前所述，多普勒及二维超声心动图应变和应变率成像能够在负荷状态下对局部功能进行定量分析。72-75 实施方案和软件的进一步改进将促进这些技术应用于临床。

三维超声心动图

实时三维超声心动图采用矩阵阵列换能器来实现负荷状态下三维数据集的快速采集。这个数据集可将左室分成多个二维切面，以评估常规二维扫描下不能显示的心肌节段的功能。该功能可实现基线和负荷状态图像的精确匹配，这对于检测局限的室壁运动异常很重要。实时三维超声心动图的可行性已被证明。208-210 对图像质量的持续改进有助于该方法的广泛应用。

心肌灌注造影成像

缺血性室壁运动异常出现之前即已发生该处冠状动脉灌注的异常，后者可由造影剂评估。因此，在血管扩张剂负荷试验中应用造影剂评估心肌灌注可提高负荷超声心动图的敏感性。211 实时（低能量）和触发（高能量）成像技术已被证明能够用于检测冠状动脉狭窄。血管床充盈造影剂的时机是评价冠脉狭窄程度的有效指标。212 心肌灌注造影成像可能比室壁运动分析的敏感性更高 213,214，但特异性可能低于室壁运动分析。

总结

负荷超声心动图已经充分验证可用于检测和评估冠状动脉疾病。多个大型研究证明了它的预后价值，包括非心脏手术前的危险分层、存活心肌的功能恢复以及识别心脏事件及死亡风险增高的患者。这项检查比其他负荷成像方法更便宜，能够提供和 SPECT 灌注成像相当的冠心病诊断和预后信息。此外，该技术用途广泛，可对瓣膜和心包异常、房室大小及室壁厚度进行评估。

（刘芳王昊天）

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American Society of Echocardiography Recommendations for Performance, Interpretation, and Application of Stress Echocardiography

Patricia A. Pellikka, MD, Sherif F. Nagueh, MD, Abdou A. Elhendy, MD, PhD, Cathryn A. Kuehl, RDCS, and Stephen G. Sawada, MD, *Rochester, Minnesota; Houston, Texas; Marshfield, Wisconsin; and Indianapolis, Indiana*

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Advances since the 1998 publication of the Recommendations for Performance and Interpretation of Stress Echocardiography[1] include improvements in imaging equipment, refinements in stress testing protocols and standards for image interpretation, and important progress toward quantitative analysis. Moreover, the roles of stress echocardiography for cardiac risk stratification and for assessment of myocardial viability are now well documented. Specific recommendations and main points are identified in bold.

METHODOLOGY

Imaging Equipment and Technique

Digital acquisition of images has evolved from the days of stand-alone computers that digitized analog video signals to the current era in which ultrasound systems have direct digital output.[2] This has resulted in significant improvements in image quality. Many ultrasound systems have software to permit acquisition and side-by-side display of baseline and stress images. However, transfer of images to a computer workstation for offline analysis is preferred as the ultrasound equipment can be continuously used for imaging. Network systems with large archiving capacity allow retrieval of serial stress examinations. Digital image acquisition permits review of multiple cardiac cycles with stress, which maximizes accuracy of interpretation. Videotape recordings are recommended as a backup.

Advances in imaging technology have improved endocardial border visualization and increased the

From the [a]Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic and Foundation; [b]Methodist DeBakey Heart Center, Houston (S.F.N.); [c]Marshfield Clinic (A.A.E.); and [d]Indiana University School of Medicine (S.G.S.).

Reprint requests: Patricia A. Pellikka, MD, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (E-mail: *pellikka.patricia@mayo.edu*).

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feasibility of imaging. **Tissue harmonic imaging should be used for stress echocardiography imaging.** This reduces near-field artifact, improves resolution, enhances myocardial signals, and is superior to fundamental imaging for endocardial border visualization.[3] The improvement in endocardial visualization achieved with harmonic imaging has decreased interobserver variability and improved the sensitivity of stress echocardiography.[4,5]

The availability of intravenous contrast agents for left ventricular (LV) opacification represents another advance. When used in conjunction with harmonic imaging, contrast agents increase the number of interpretable LV wall segments, improve the accuracy of less experienced readers, enhance diagnostic confidence, and reduce the need for additional noninvasive tests because of equivocal noncontrast stress examinations.[6-9] Opacification of the LV cavity with contrast agents also improves the potential for quantitative assessment of studies. **Contrast should be used when two or more segments are not well visualized.** With experience and well-defined protocols, contrast stress echocardiography has been shown to be time-efficient.[10]

The baseline echocardiogram performed at the time of stress echocardiography should include a screening assessment of ventricular function, chamber sizes, wall-motion thicknesses, aortic root, and valves unless this assessment has already been performed. This examination permits recognition of causes of cardiac symptoms in addition to ischemic heart disease, including pericardial effusion, hypertrophic cardiomyopathy, aortic dissection, and valvular heart disease.

Stress Testing Methods

Exercise stress testing. For patients who are capable of performing an exercise test, exercise stress rather than pharmacologic stress is recommended, as the exercise capacity is an important predictor of outcome. Either treadmill or bicycle exercise may be used for exercise stress. Symptom-limited exercise according to a standardized protocol in which the workload is gradually increased in stages is recommended. The Bruce protocol is most commonly used for treadmill exercise echocardiography and the expected exercise level for a given age and sex can be expressed as functional aerobic capacity.[11] Imaging is performed at rest and immediately after completion of exercise.[12] Bicycle stress echocardiography can be performed with either supine or upright ergometry; an advantage is that imaging can be performed during exercise. With a commonly used supine bicycle protocol, imaging is performed at baseline, at an initial workload of 25 W, at peak stress, and in recovery. The workload is increased at increments of 25 W every 2 or 3 minutes.[13] A higher initial workload may be appropriate for a younger patient.

Both types of exercise examinations provide valuable information for detection of ischemic heart disease and assessment of valvular heart disease. The workload and maximum heart rate achieved tend to be higher with treadmill exercise; exercise blood pressure is higher with supine bicycle exercise. If assessment of regional wall motion is the only objective, treadmill exercise is usually used. If additional Doppler information is desired, bicycle exercise offers the advantage that Doppler information, in addition to assessment of regional wall motion, can be evaluated during exercise.[14]

Pharmacologic stress testing. In patients who cannot exercise, dobutamine and vasodilator stress are alternatives. **Although vasodilators may have advantages for assessment of myocardial perfusion, dobutamine is preferred when the test is based on assessment of regional wall motion. A graded dobutamine infusion starting at 5 μg/kg/min and increasing at 3-minute intervals to 10, 20, 30, and 40 μg/kg/min is the standard for dobutamine stress testing.[15,16] The inclusion of low-dose stages facilitates recognition of viability and ischemia in segments with abnormal function at rest, even if viability assessment is not the main objective of the test.** End points are achievement of target heart rate (defined as 85% of the age-predicted maximum heart rate), new or worsening wall-motion abnormalities of moderate degree, significant arrhythmias, hypotension, severe hypertension, and intolerable symptoms. **Atropine, in divided doses of 0.25 to 0.5 mg to a total of 2.0 mg, should be used as needed to achieve target heart rate.** Atropine increases the sensitivity of dobutamine echocardiography in patients receiving beta-blockers and in those with single-vessel disease.[17] The minimum cumulative dose needed to achieve the desired heart rate effect should be used to avoid the rare complication of central nervous system toxicity. Protocols using atropine in early stages of the test, and accelerated dobutamine administration, have been shown to be safe and to reduce infusion times.[18,19] Patients given atropine at the 30-μg/kg/min stage reached target heart rate more quickly using lower doses of dobutamine and with fewer side effects. A beta-blocker may be administered to reverse the side effects of dobutamine.[20] Administration of beta-blockers at peak stress or during recovery may increase test sensitivity.[21]

Both dobutamine and exercise echocardiography result in a marked increase of heart rate. The increment in systolic blood pressure is much less with dobutamine compared with exercise. For both

techniques, the induction of ischemia is related to an increase in myocardial oxygen demand. Among patients with normal dobutamine stress echocardiography results, the subgroup in whom target heart rate is not achieved has a higher cardiac event rate.[22] Achievement of target rate is an important goal of testing and consideration should be given to holding beta-blocker therapy on the day of testing until after the test. However, in a patient with known coronary artery disease (CAD), continuation of beta-blocker therapy may be preferred, depending on the clinical objectives of the test, which may include assessing adequacy of therapy. Side effects (palpitations, nausea, headache, chills, urinary urgency, and anxiety) are usually well tolerated, without the need for test termination. The most common cardiovascular side effects are angina, hypotension, and cardiac arrhythmias. Severe, symptomatic hypotension necessitating test termination occurs only rarely. Frequent premature atrial or ventricular contractions occur in about 10% of patients and supraventricular or ventricular tachycardias each occur in about 4% of patients. Ventricular tachycardias are usually nonsustained and more frequently encountered in patients with a history of ventricular arrhythmias or baseline wall-motion abnormalities. On the basis of combined diagnostic and safety reports on dobutamine stress echocardiography, it is estimated that ventricular fibrillation or myocardial infarction occurs in 1 of 2000 studies. Dobutamine stress echocardiography can safely be performed in patients with LV dysfunct,[23] aortic[24] and cerebral[25] aneurysms, and implantable cardioverter defibrillators.[26] Dobutamine stress echocardiography can safely and efficiently be performed under supervision by registered nurses.[27]

Vasodilator stress testing may be performed with adenosine or dipyridamole.[28] Atropine is routinely used with vasodilator stress to enhance test sensitivity. The addition of handgrip at peak infusion enhances sensitivity. Vasodilator stress echocardiography usually produces a mild to moderate increase in heart rate and a mild decrease in blood pressure. The safety of high-dose (up to 0.84 mg/kg over 10 minutes) dipyridamole echocardiography tests has been documented. Significant side effects and minor but limiting side effects occur in about 1%. Major adverse reactions have included cardiac asystole, myocardial infarction, and sustained ventricular tachycardia. Hypotension and/or bradycardia may occur, but can be treated with aminophylline.[29] The duration of action of adenosine is shorter than dipyridamole. Adenosine stress is used to assess myocardial perfusion with contrast echocardiography, but it has not been widely used as a clinical tool. Both adenosine and dipyridamole are contraindicated in patients with reactive airway obstruction or significant conduction defects.

Pacing stress testing. In patients with a permanent pacemaker, stress testing can be achieved by increasing the pacing rate until the target heart rate is reached. This technique can be used with or without dobutamine. Recent studies have shown a good accuracy of this technique in identifying CAD[30] and in predicting outcome.[31]

Transesophageal atrial pacing stress echocardiography is an efficient alternative for the detection of CAD in patients unable to exercise.[32] The catheter may be placed orally or nasally after topical anesthesia. The cardiac pacing and recording catheter (housed in a 10F sheath) is advanced by having the patient swallow while in the left lateral decubitus position. Pacing is initiated at 10/min above the patient's baseline heart rate starting at the lowest current that provides stable atrial capture (approximately 10 mA). The pacing protocol consists of 2-minute stages with the paced heart rate being increased to levels of 85% and 100%, respectively, for prepeak and peak stress information.[33] Images are obtained at rest, the first stage, and prepeak and peak heart rate. Wenckebach second-degree heart block may occur, necessitating atropine administration. Termination of the stress test occurs with achievement of age-predicted maximal heart rate, new or worsening moderate regional wall-motion abnormalities, greater than 2-mm horizontal or downsloping S-T depression, or presence of intolerable symptoms, including moderate angina. The advantage of pacing is the rapid restoration of baseline conditions and heart rate on discontinuation of the atrial stimulus; this avoids a prolonged state of ischemia.[33] Side effects, except for mild atrial arrhythmogenicity, are uncommon.

Training Requirements and Maintenance of Competency

Interpretation of stress echocardiography requires extensive experience in echocardiography and should be performed only by physicians with specific training in the technique. It is recommended that only echocardiographers with at least level-II training and specific additional training in stress echocardiography have responsibility for supervision and interpretation of stress echocardiograms. To achieve the minimum level of competence for independent interpretation, training should include interpretation of at least 100 stress echocardiograms under the supervision of an echocardiographer with level-III training and expertise in stress echocardiography.[34] To maintain competence, it is recommended that physicians interpret a minimum of 100 stress echocardiograms per year, in addition to participation in relevant continuing medical education. It is recommended that sonographers perform a minimum of 100 stress echocardiograms per year to maintain an appropriate level of skill.[35] These

recommendations refer to routine stress echocardiograms for evaluation of CAD and not highly specialized studies such as evaluation of valvular disease or myocardial viability, for which more experience and higher volumes may be required for maintenance of skills.

IMAGE INTERPRETATION

Visual assessment of endocardial excursion and wall thickening is used for analysis of stress echocardiograms. The 2005 American Society of Echocardiography (ASE) recommendations suggested that either a 16- or 17-segment model of the LV may be used.[36] The 17-segment model includes an "apical cap," a segment beyond the level that the LV cavity is seen. The 17-segment model is recommended if myocardial perfusion is evaluated or if echocardiography is compared with another imaging modality. **Function in each segment is graded at rest and with stress as normal or hyperdynamic, hypokinetic, akinetic, dyskinetic, or aneurysmal. Images from low or intermediate stages of dobutamine infusion or bicycle exercise should be compared with peak stress images to maximize the sensitivity for detection of coronary disease.**[37]

The timing of wall motion and thickening should also be assessed. Ischemia delays both the onset of contraction and relaxation and slows the velocity of contraction in addition to decreasing the maximum amplitude of contraction. "Hypokinesis" can refer to delay in the velocity or onset of contraction ("tardokinesis") and reduction in the maximum amplitude of contraction. The routine use of digital technology enables assessment of abnormalities in the timing of contraction (asynchrony). Differences in the onset of contraction and relaxation of ischemic segments compared with normal segments may range from less than 50 to more than 100 milliseconds.[38,39] The frame rates used in current ultrasound systems have the necessary temporal resolution to permit visual recognition of asynchrony by the trained observer.[40,41] Although assessment of asynchrony is most accurate using a high temporal resolution technique such as M-mode echocardiography, incorporation of visual assessment of the timing of contraction contributes to improved interobserver agreement.[42] Work stations used for analysis of stress echocardiograms enable the interpreter to compare the timing of segmental contraction on a frame-by-frame basis and allow the interpreter to limit review to early systole where ischemia-induced reduction in the speed of contraction may be best appreciated.[43,44]

A normal stress echocardiogram result is defined as normal LV wall motion at rest and with stress. Resting wall-motion abnormalities, unchanged with stress, are classified as "fixed" and most often represent regions of prior infarction. Patients with fixed wall-motion abnormalities and no inducible ischemia should not be considered as having a normal study result. **Abnormal study findings include those with fixed wall-motion abnormalities or new or worsening abnormalities indicative of ischemia. In addition to the evaluation of segmental function, the global LV response to stress should be assessed. Stress-induced changes in LV shape, cavity size, and global contractility have been shown to indicate the presence or absence of ischemia.**[45,46]

Although evaluation of right ventricular (RV) systolic function is often omitted, RV free wall asynergy or lack of increase in tricuspid annular plane excursion during dobutamine stress are indicators of right coronary or multivessel disease.[47,48]

The modality of stress and details of the stress test itself should be considered in the interpretation of normal and ischemic responses to stress. **The report must include not only the baseline and stress assessment of systolic function and segmental wall motion, but the protocol used, the exercise time or dose of pharmacologic agent used, the maximum heart rate achieved, whether the level of stress was adequate, the blood pressure response, the reason for test termination, any cardiac symptoms during the test, and electrocardiographic (ECG) changes or significant arrhythmias.** In the presence of similar extents of CAD, stress-induced decrease in ejection fraction (EF) or increase in end-systolic cavity size are more commonly seen with exercise than with dobutamine stress.[46] Table 1 lists several modalities of stress and the general responses of regional and global function that are seen in healthy individuals and in those with obstructive coronary disease.[32,33,46,49-59] The responses are described for individuals with normal regional and global systolic function in the resting state. An interpretive scheme for those with resting regional wall-motion abnormalities is described in the section on myocardial viability.

With modalities in which imaging is performed at various stages of stress, such as dobutamine stress echocardiography or supine bicycle stress echocardiography, images from each stage of stress should be reviewed to determine the heart rate and stage at which ischemia first occurs. This information is useful in perioperative risk stratification,[60,61] as ischemia occurring at a low heart rate identifies patients at highest risk of a perioperative event. Ischemic threshold, calculated as the heart rate at which ischemia first occurs, divided by 220 minus the patient's age, multiplied by 100, has been shown to

Table 1 Normal and ischemic responses for various modalities of stress

	Regional		Global	
Stress method	**Normal response**	**Ischemic response**	**Normal response**	**Ischemic response**
Treadmill	Postexercise increase in function compared with rest	Postexercise decrease in function compared with rest	Decrease in ESV, increase in EF	Increase in ESV, decrease in EF in multivessel or L main disease
Supine bicycle	Peak exercise increase in function compared with rest	Peak exercise decrease in function compared with rest	Decrease in ESV, increase in EF	Increase in ESV and decrease in EF in multivessel or L main disease
Dobutamine	Increase in function, velocity of contraction compared with rest and usually with low dose	Decrease in function, velocity of contraction compared with low dose; may be less compared with rest	Greater decrease in ESV, marked increase in EF	Often same as normal response; infrequently, ischemia produces decreased EF; cavity dilatation rarely occurs
Vasodilator	Increase in function compared with rest	Decrease in function compared with rest	Decrease in ESV, increase in EF	Often same as normal response; occasionally, ischemia produces decreased EF; cavity dilatation rarely occurs
Atrial pacing	No change or increase in function compared with rest	Decrease in function compared with rest	Decrease in ESV, no change in EF	No change or increase ESV, decrease in EF

EF, Ejection fraction; *ESV*, end-systolic volume; *L*, left.

correlate with the number of stenosed vessels and with the EF response to exercise.[62]

Quantitative Analysis Methods

Visual assessment of LV wall thickening and motion remains the standard method of interpretation of stress echocardiography but is subject to interobserver and interinstitutional variability.[63] Very good reproducibility has been demonstrated in a clinical setting by those with training and experience.[64,65] Quantitative methods of analysis have been investigated in an effort to improve the reproducibility of interpretation and enhance detection of coronary disease, particularly by less experienced physicians.

Doppler assessment of global systolic and diastolic function, automated endocardial border detection using integrated backscatter, tissue Doppler assessment of displacement, velocity, strain, and strain rate have shown promise as clinically useful, quantitative methods for detection of ischemia. Doppler assessment of global diastolic function by analysis of mitral inflow patterns is difficult at high heart rates achieved during stress; assessment of aortic systolic flow during stress lacks sensitivity.

The use of integrated backscatter to identify the blood-endocardial interface is promising as an automated method for detection of ischemia during dobutamine stress. Using this technique, in which border detection may be enhanced by contrast opacification of the ventricular cavity, endocardial motion in successive frames throughout the cardiac cycle can be color encoded to permit assessment of the timing and location of regional abnormalities in systolic and diastolic function.[66,67]

Doppler tissue imaging enables assessment of high amplitude, low velocity signals from myocardium. Tissue velocities are assessed along the long axis of the heart using apical views. Displacement, strain, and strain rate can be derived from assessment of tissue velocities. Tissue velocity imaging with dobutamine stress has shown comparable accuracy with wall-motion assessment by experts in both single and multicenter trials.[68,69] Tissue velocity imaging also improves the reproducibility and accuracy of less experienced readers.[70] Because of the normal base to apex gradient in velocities, detection of coronary disease requires derivation of normal values for different myocardial segments. Strain (measuring myocardial shortening or lengthening) and strain rate (measuring the rate of shortening or lengthening) provide better assessment of myocardial contraction and relaxation than displacement or tissue velocities, which are more subject to tethering and translational motion. Postsystolic shortening, time to onset of regional relaxation, and reduction in peak systolic strain and strain rate have

been shown to be accurate markers of ischemia in experimental[71] and early clinical[72-75] studies.

Adequate quality 2-dimensional (2D) images are a prerequisite to successful quantitative analysis, even using Doppler-based techniques. Like all Doppler-derived parameters, tissue velocities, strain, and strain rate are influenced by the angle of interrogation so that off-axis apical images may result in calculation errors. Recently introduced 2D echocardiographic methods for assessment of strain and strain rate eliminate the angle dependency of these Doppler-based techniques.[76] In the future, quantitative methods may serve as an adjunct to expert visual assessment of wall motion. **The widespread use of quantitative methods will require further validation and simplification of analysis techniques.**

ACCURACY

The 1998 ASE document on stress echocardiography reported an average sensitivity of 88% (1265/1445) and average specificity of 83% (465/563) for stress echocardiography for the detection of coronary artery stenosis (generally >50% diameter stenosis by angiography), based on data pooled from available studies. Since then, additional studies evaluating the accuracy of stress echocardiography have been performed, often in comparison with alternative imaging modalities. **Studies comparing the accuracy of nuclear perfusion imaging and stress echocardiography in the same patient population have shown that the tests have similar sensitivities for the detection of CAD, but stress echocardiography has higher specificity.**[77-81] In a pooled analysis of 18 studies in 1304 patients who underwent exercise or pharmacologic stress echocardiography in conjunction with thallium or technetium-labeled radioisotope imaging, sensitivity and specificity were 80% and 86% for echocardiography. Corresponding values were 84% and 77% for myocardial perfusion imaging, respectively.[79]

In the current era, the specificity of all noninvasive imaging tests will be reduced by test verification bias.[82] A diminishing number of patients with normal or negative noninvasive examinations are subjected to angiography leading to reduction in the apparent specificity of the noninvasive method when angiography is used as the reference standard. **The comparatively high specificity of stress echocardiography contributes to its use as a cost-effective diagnostic method, particularly in populations in which alternative stress testing methods have higher false-positive rates.**

False-negative Studies

With few exceptions, the causes of false-negative studies are not unique to stress echocardiography but are also seen with other noninvasive methods. Suboptimal stress is a primary cause of false-negative studies.[83] An adequate level of stress is frequently defined as achievement of 85% or more of the patient's age-predicted maximal heart rate for exercise or dobutamine stress and/or a rate-pressure product of 20,000 or more for exercise testing. Although these thresholds are not well validated, the importance of increasing heart rate and rate-pressure product is well supported by the linear relationship between myocardial oxygen consumption and these hemodynamic parameters. Inadequate exercise capacity and the use of beta-blockers are two common causes of inadequate stress. Pharmacologic stress and atrial pacing are suggested alternatives in those who cannot exercise. Of the nonexercise methods, the highest heart rates and sensitivity may be achieved with atrial pacing.[33,84] The use of atropine substantially enhances the sensitivity of dobutamine stress in the setting of beta-blockade[17] and may be required to overcome Wenckebach heart block during atrial pacing.[32]

The results of small comparative studies of treadmill and supine bicycle exercise echocardiography suggest that imaging during peak exercise may permit detection of ischemic wall-motion abnormalities in some cases when posttreadmill exercise imaging produces negative findings.[85,86] However, workloads achieved are usually higher with treadmill exercise, partially offsetting the advantage of peak exercise imaging.

As with other forms of stress testing, false-negative stress echocardiographic examination results are also more common in patients with single-vessel disease or disease of the left circumflex artery because of the smaller amount of myocardium supplied.[87] Supine bicycle exercise test has higher sensitivity for detection of left circumflex disease.[88,89] Routine use of apical long-axis views may also decrease false-negative study results in those with left circumflex disease.

Detection of ischemia is more difficult in patients with concentric remodeling, characterized by small LV cavity volume and increased relative wall thickness.[90] False-negative studies in patients with concentric remodeling may be more common with dobutamine stress than with other methods. The prominent global hyperkinesis and reduction of diastolic and systolic volumes that occur with dobutamine stress (Table 1) may make detection of isolated wall-motion abnormalities more challenging. In addition, in patients with concentric remodeling, dobutamine may lower wall stress and myocardial oxygen consumption, reducing the frequency of induction of ischemia.[91] Finally, the hyperdynamic state accompanying significant aortic or mitral regurgitation may make detection of ischemia more difficult.[92]

False-positive Studies

False-positive stress echocardiogram findings can be attributed to induction of ischemia in the absence of epicardial coronary obstruction, or to nonischemic causes of abnormal wall-motion responses to stress.[93] Abnormalities in regional function with stress can occur in the absence of epicardial coronary artery obstruction if myocardial perfusion reserve is inadequate to meet myocardial oxygen demand. Examples include global or regional LV dysfunction in the case of hypertensive response to stress[94] or apical hypokinesis or other wall-motion abnormalities in the case of hypertrophic cardiomyopathy with or without dynamic LV outflow tract obstruction.[95] Myocardial perfusion reserve can be reduced in cardiac disorders with microvascular involvement, including patients with LV hypertrophy, syndrome X, diabetes mellitus, myocarditis, and idiopathic cardiomyopathy. Epicardial coronary spasm may cause ischemia in the absence of fixed, obstructive disease; spasm has been reported with both exercise and dobutamine stress.

Wall-motion responses to exercise may be abnormal in patients with hypertension or underlying cardiomyopathy in the absence of ischemia. Exercise may result in worsening of regional and global systolic function in myopathic ventricles. Abnormal global responses to stress are common in patients with long-standing hypertension.[96,97] The abnormal wall-motion response of some patients with long-standing hypertension may be a result of underlying cardiomyopathy even in the absence of LV hypertrophy or depression of resting systolic function.[98,99]

The effects of tethering on the assessment of regional wall motion can lead to false-positive studies. The absence of radial motion of the mitral annulus can lead to a reduction in motion of adjacent basal inferior and basal inferoseptal segments by the tethering effect of the stationary annulus.[93] This effect can be more pronounced in patients with annulus calcification and previous mitral valve replacement.

Abnormal ventricular septal motion related to left bundle branch block, RV pacing, and post-open heart surgery can sometimes be confused with ischemia-induced abnormalities. In these situations, abnormal septal motion is usually present at rest. Difficulty in determining the presence of ischemia may occur if worsening of these abnormalities occurs during stress. Assessment of wall thickening and the recognition that ischemia-induced wall-motion abnormalities should follow a typical coronary distribution pattern may help to distinguish septal dyssynchrony from ischemia.[100-102] In addition, septal dyssynchrony may result in worsening of septal perfusion and wall thickening at high heart rates in the absence of coronary obstruction.

ASSESSMENT OF MYOCARDIAL VIABILITY

Stress echocardiography has emerged as an important modality for the assessment of patients with CAD and LV systolic dysfunction. Multicenter studies have shown worse outcome when viable myocardium was identified by stress echocardiography but the patient was not revascularized.[103,104] Viable myocardium refers to reversible dysfunctional myocardium resulting from CAD. However, the determination of contractile reserve in patients with nonischemic cardiomyopathy can also provide useful information as to myocardial recovery of function[105] and likelihood of response to beta-blocker therapy.[106]

Reversible myocardial dysfunction in the setting of chronic CAD has been referred to as "hibernating myocardium." Earlier descriptions of this entity emphasized the presence of a match between the decrease in myocardial perfusion and the presence of regional dysfunction. However, more recent studies have shown that contractility may be reduced despite the presence of normal or only moderately reduced myocardial perfusion at rest. This suggests that repetitive episodes of myocardial ischemia are a cause of chronic dysfunction. In myocardium with reduced perfusion at rest, structural and functional changes that can occur include interstitial fibrosis, glycogen accumulation, loss of contractile proteins, cellular remodeling, higher calcium sensitivity of myocyte contractility, and attenuation of beta-receptor signaling.[107-110] With delay in revascularization, these myocardial changes may progress to a more advanced stage with a lower likelihood of functional recovery.[111]

Most stress echocardiography protocols are centered on the detection of contractile reserve and have used inotropic stimulation with dobutamine. However, other modalities of stress echocardiography have been applied, including exercise, postpremature ventricular contraction stimulation, enoximone, and low-dose dipyridamole.

In comparison with the assessment of viability using nuclear perfusion tracers or contract echocardiography, a lower extent of interstitial fibrosis and greater percentage of viable myocytes are needed for the detection of contractile reserve by dobutamine echocardiography.[107] This probably accounts for the higher sensitivity but lower specificity of myocardial perfusion imaging compared with dobutamine echocardiography in the detection of viable myocardium.

Both low- and high-dose protocols have been shown to be useful for detection of viability. Earlier studies examined low-dose dobutamine, whereas other investigators emphasized the importance of reaching at least 85% of target heart rate in an attempt to uncover the presence of ischemia. Wall thickness should be assessed on the resting echocardiographic images. Segments that are thinned ($\leq$0.5 or 0.6 cm) and bright (likely a result of advanced fibrosis) rarely recov-

er.[112,113] It is also useful to examine the mitral inflow pattern, particularly in patients who have received adequate medical therapy at the time of imaging. A pattern of restrictive LV filling is associated with few viable segments and a low likelihood of functional recovery after revascularization.[114] Baseline imaging should include assessment for the presence of significant valvular disease that may alter surgical plans. After adequate baseline data have been obtained, dobutamine infusion is begun.

An initial infusion of dobutamine at 2.5 μg/kg/min, with gradual increase to 5, 7.5, 10, and 20 μg/kg/min, is frequently used.[115] Because many of these patients have multivessel disease, moderate to severely depressed LV systolic function, and an arrhythmogenic substrate, vigilant monitoring is indicated. The absence of functional improvement in akinetic segments would then trigger termination of the test, because this response signifies a very low likelihood of functional recovery in these segments. The presence of worsening of function in hypokinetic segments should likewise trigger termination of the infusion. Alternatively, functional improvement in the absence of untoward side effects would lead to an escalation of the drip rate to 40 μg/kg/min and, if needed, atropine injection. The advantage of the higher dose dobutamine is the potential to elicit ischemia. Dysfunctional myocardium responds to dobutamine in one of 4 ways that are most likely to be appreciated when the response to both high and low doses of dobutamine are considered. These responses include biphasic response (augmentation at a low dose followed by deterioration at a higher dose), sustained improvement (improvement in function at a low dose without deterioration at higher doses), worsening of function, and no change in function.

The sensitivity of dobutamine echocardiography in predicting functional recovery (which varies depending on the protocol used) ranges from 71% to 97%, with a specificity ranging from 63% to 95%.[116] **The highest sensitivity for detection of viability is noted when improvement at low-dose dobutamine echocardiography is considered; highest specificity is achieved when a biphasic response occurs.**[117] Patients with a large area of viable myocardium (>25% of LV) have a high likelihood of improvement in EF and a better outcome after revascularization compared with patients with less or no contractile reserve.[118] **Although presence of viability has been defined in various ways, it is recommended that improvement by at least one grade in two or more segments be demonstrated.** A substantial amount of viable myocardium detected by low-dose dobutamine echocardiography has been shown to prevent ongoing remodeling after revascularization and to be associated with persistent improvement of heart failure symptoms and a lower incidence of cardiac events.[119]

Additional echocardiographic methods used to identify viable myocardium have included assessment of the microcirculation with contrast echocardiography, and myocardial tissue characterization using integrated backscatter. For both approaches, data are acquired at baseline and with vasodilators or dobutamine infusion. In the future, quantitative methods for analysis of regional function may improve viability assessment. Preliminary studies suggest that assessment of strain rate and strain can enhance detection of viable myocardium.[120-122]

ASSESSMENT OF PATIENTS WITH DYSPNEA, PULMONARY HYPERTENSION, AND VALVULAR HEART DISEASE

Dyspnea

Stress echocardiography is useful for the evaluation of patients with dyspnea of possible cardiac origin.[123] In addition to data on the presence, severity, and extent of myocardial ischemia, LV and left atrial volumes, EF, presence of LV hypertrophy and/or valvular disease, a baseline echocardiogram can identify the presence of pulmonary hypertension or abnormal LV relaxation and elevated filling pressures. In some cases, the diagnosis of a cardiac origin can be ascertained by the findings of the baseline resting images and stress testing may not be needed. Exercise using a supine bike is the recommended modality as it allows the acquisition of Doppler recordings during exercise. Doppler assessment of the mitral inflow velocities should be assessed at rest, during exercise, and in recovery when the E and A velocities are no longer fused. Doppler recordings should be acquired at a sweep speed of 100 mm/s. The ratio of mitral E (peak early diastolic velocity) to mitral annulus early diastolic velocity (e') can be used to estimate LV filling pressures at rest and exercise. Healthy individuals will show a similar increase in mitral E and annular e', such that the ratio has no or only minimal change with exercise.[124] Patients with impaired LV relaxation develop an increase in LV filling pressures with exercise as a result of tachycardia and the abbreviated diastolic filling period. Accordingly, mitral peak E velocity increases. However, given the minimal effect of preload on annular e' in the presence of impaired relaxation, annular e' remains reduced. Therefore, E/e' ratio increases with exercise in patients with diastolic dysfunction.[125,126] This approach has been validated against invasive measurements for identifying an elevated exercise mean LV diastolic pressure.[126] Limitations to the above methodology include atrial fibrillation, tech-

nically challenging imaging windows, and limited validation. Furthermore, it remains to be seen how abnormalities in regional function influence the accuracy of a single site measurement of e'.

Pulmonary Hypertension

Transthoracic Doppler echocardiography permits a reliable estimation of pulmonary artery pressures, detection of cardiac causes of pulmonary hypertension, and changes in RV and LV volumes and function with the disease and its treatment.[127] Exercise may be useful in patients with pulmonary hypertension to gain insight into RV and LV function[128,129] and the changes in stroke volume with exercise.[130] Some patients with a normal pulmonary artery pressure at rest have marked increase with exercise; the prognostic significance of this has not been defined. The normal response to exercise has been assessed in healthy individuals and in young male athletes.[131] Highly trained male athletes have been found to have a Doppler-derived pulmonary artery systolic pressure as high as 60 mm Hg with exercise.[131] There are also published reports about the use of exercise echocardiography in detecting asymptomatic gene carriers of familial primary pulmonary hypertension,[13] and identifying patients susceptible to high-altitude pulmonary edema.[132]

Mitral Valve Disease

In patients with mitral valve disease, exercise testing may provide insights regarding exertional symptoms disproportionate to resting hemodynamics.[133] It is also useful in patients with severe lesions but no symptoms; exercise-induced increase in pulmonary artery systolic pressure to greater than 60 mm Hg may be considered an indication for mitral valve surgery (class IIA indication in 2006 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines for the Management of Patients with Valvular Heart Disease).[134] Most of the published studies used a supine bike protocol for image acquisition. Mitral inflow is recorded with pulsed wave Doppler (for mitral regurgitation) and continuous wave Doppler (for mitral stenosis), along with recording of tricuspid regurgitation velocity by continuous wave Doppler at rest and during exercise.

For patients with mitral stenosis, stress Doppler echocardiography is indicated in asymptomatic patients with significant lesions based on hemodynamic calculations obtained at rest, and for patients with symptoms disproportionate to resting Doppler hemodynamics (class I indication).[134] At baseline and with stress, transmitral pressure gradient and tricuspid regurgitation velocity are obtained by continuous wave Doppler using the modified Bernoulli equation. With proper alignment of the ultrasound beam with transmitral flow, accurate Doppler-derived gradients can be obtained at rest and with exercise and correlate well with invasively derived measurements.[135] In sedentary patients, exercise-induced dyspnea, along with an increase in mean transmitral pressure gradient to greater than 15 mm Hg and pulmonary artery systolic pressure to greater than 60 mm Hg, identifies patients with hemodynamically significant lesions that may benefit from percutaneous valvotomy if anatomy is suitable and mitral regurgitation is mild or less.[134,136] When exercise results in only minimal changes in transmitral pressure gradient but a marked increase in pulmonary artery systolic pressure occurs, further evaluation for underlying lung disease is indicated. In patients unable to exercise, dobutamine stress may be used.[137,138]

Evaluation of mitral regurgitation is possible with quantitative and semiquantitative color Doppler methods.[14,139] Exercise echocardiography has been used to uncover the presence of severe mitral regurgitation with exercise in patients with rheumatic mitral valve disease and only mild mitral stenosis and regurgitation at rest.[140] Likewise, exercise echocardiography is of value in identifying hemodynamically significant dynamic mitral regurgitation in patients with LV systolic dysfunction. In some patients, dynamic mitral regurgitation can account for acute pulmonary edema and predicts poor outcome.[141] For patients with severe mitral regurgitation and normal EF at rest, stress echocardiography can detect the presence of reduced LV contractile reserve.[142]

Aortic Valve Disease

Dobutamine echocardiography is indicated in the diagnostic evaluation of patients with LV systolic dysfunction and low-gradient aortic stenosis, defined as Doppler-derived aortic valve area less than 1.0 cm^2 and mean gradient less than 30 mm Hg.[134] In these patients, dobutamine is used to assess both the severity of aortic stenosis and the presence of LV contractile reserve.[143,144] The infusion begins at 5 μg/kg/min and is increased at 5-minute intervals to 10 and 20 μg/kg/min.

Dobutamine results in a larger increase of mean pressure than transvalvular flow in patients with severe aortic stenosis. Accordingly, aortic valve area remains abnormally low indicating true aortic stenosis. On the other hand, dobutamine infusion results in larger increments of flow rate and valve area in patients with "functional" aortic stenosis, which is primarily a result of reduced flow rate. In a recent study, calculation of projected effective orifice area improved the diagnostic accuracy of dobutamine echocardiography in identifying patients with true

aortic stenosis, with surgical inspection used as the gold standard.[145] Dobutamine echocardiography provides important prognostic information in patients with LV systolic dysfunction and aortic stenosis, as surgery with aortic valve replacement appears to improve outcome for most patients with LV contractile reserve. In contrast, surgery is associated with high mortality in the absence of contractile reserve.[146]

For patients with chronic aortic regurgitation, exercise testing may be considered to evaluate functional capacity when symptoms are questionable, or before participation in athletic activities (class IIA indications).[134] Likewise, useful prognostic information may be obtained before surgery in patients with LV dysfunction (class IIB indication).[134] This is supported by a number of studies with radionuclide angiography showing abnormal EF (and change in EF) with exercise in asymptomatic patients with aortic regurgitation. However, the incremental value of exercise data to LV dimensions and EF at rest is unclear. Stress echocardiography is not indicated in clearly symptomatic patients with severe aortic regurgitation or patients with depressed EF who should be referred for surgery without stress testing.

Evaluation of Prosthetic Valves

Stress echocardiography has been applied to the assessment of transvalvular gradients and flow in prosthetic aortic valves. The majority of reports used dobutamine[147-149] but a few examined changes in valvular hemodynamics with exercise.[149]

Although stress echocardiography has the potential to assess ventricular and prosthetic valvular function in symptomatic patients with equivocal findings at rest, the interpretation of Doppler gradients can be challenging given their dependence not only on flow rate but the type and size of the prosthetic valve. Additional data are needed to characterize normal responses for various prostheses.

STRESS ECHOCARDIOGRAPHY FOR RISK STRATIFICATION

Stress echocardiography is a useful technique for the risk stratification of patients with known or suspected CAD. This has been well documented in numerous large studies in which follow-up was obtained in consecutive patients referred for clinically indicated stress echocardiography. **These studies have documented the prognostic use of the test in patients with various pretest probabilities of disease, symptoms, known CAD, prior coronary artery revascularization, or prior myocardial infarction and in asymptomatic patients with risk factors for CAD.** The prognostic value of the test has been shown to be maintained in patients with good exercise capacity,[150] and for those with reduced exercise capacity.[151] Table 2 summarizes major studies that reported the prognostic use of stress echocardiography in patients with known or suspected CAD.[152-154] Table 3 shows predictors of outcome found in these and other studies. Stress echocardiography has been shown to provide incremental prognostic value for predicting overall mortality, cardiac mortality, and composite cardiac end points in patients with known or suspected CAD, after adjustment for risk factors and stress test parameters.

A normal exercise echocardiogram result is associated with an annual event rate of cardiac death and nonfatal myocardial infarction of less than 1%, equivalent to that of an age- and sex-matched population. These patients do not require further diagnostic evaluation unless there is a change in clinical status.[155,156] Patients with a normal pharmacologic stress echocardiogram result have a slightly higher event rate.[22] This may be explained by the higher risk status of patients who are unable to perform exercise stress test, as this group tends to be older with more comorbidities.

Ischemia was shown in many studies to be associated with incremental risk of mortality and cardiac events. **Patients with extensive stress-induced abnormalities in a multivessel distribution are at a high risk of mortality and cardiac events.** In these patients, coronary angiography and subsequent myocardial revascularization may be justified, with particular consideration of symptomatic status, functional capacity, and resting LV function. An exercise wall-motion score index greater than 1.4 or exercise EF less than 50% portends a significantly worse prognosis. Results of stress echocardiography have been combined with the Duke treadmill score and clinical and stress test variables including age, sex, symptoms, exercise tolerance, rate-pressure product, and severity of wall-motion abnormalities.[157-159]

Baseline LV function expressed as wall-motion score index or EF remains a powerful predictor of future events. **Patients with resting LV dysfunction but no inducible myocardial ischemia have an intermediate risk, whereas patients with resting LV dysfunction and new wall-motion abnormalities have the greatest risk for death and cardiac events.**

Table 3 summarizes stress echocardiography test results characterizing patients at increased risk. **In addition to baseline LV dysfunction, variables associated with adverse outcome include extensive ischemia,[65,160-162] poor EF response or failure to reduce end-systolic volume with exercise,[150] wall-motion abnormalities in mul-**

Table 2 Summary of studies evaluating the value of stress echocardiography in predicting outcome

Author	No. of patients	Patient characteristics	Stress type	Mean or median follow-up, y	End point	Echocardiographic predictors
Arruda-Olson et al 2002[161]	5798	Known or suspected CAD	Exercise	3.2	Cardiac death/MI	Exercise WMSI
Marwick et al 2001[159]	5375	Known or suspected CAD	Exercise	5.5	All deaths	Extent of resting WMA; extent of ischemia
Biagini et al 2005[162]	3381	Known or suspected CAD	Dobutamine	7	Cardiac death/MI	Resting WMA, ischemia
Marwick et al 2001[160]	3156	Known or suspected CAD	Dobutamine	3.8	Cardiac death	Resting WMA, ischemia
Chuah et al 1998[65]	860	Known or suspected CAD	Dobutamine	2	Cardiac death/MI	Stress WMA; end-systolic volume response
Shaw et al 2005[173]	11,132	Known or suspected CAD	Exercise or dobutamine	5	Cardiac death	Extent of resting WMA; extent of ischemia
Sicari et al 2003[152]	7333	Known or suspected CAD	Dipyridamole or dobutamine	2.6	Cardiac death/MI	Resting EF, change in WMSI
Tsutsui et al 2005[153]	788	Known or suspected CAD	Dobutamine myocardial contrast perfusion	1.7	Death/MI	Contrast perfusion defects
Bergeron et al 2004[123]	3260	Chest pain or dyspnea	Exercise	3.1	Mortality/morbidity	Change in WMSI
Elhendy et al 2001[163]	563	Diabetes	Exercise	3	Cardiac death/MI	EF, extent of ischemia
Sozzi et al 2003[187]	396	Diabetes	Dobutamine	3	Cardiac death/MI	EF, extent of ischemia
Marwick et al 2002[188]	937	Diabetes	Exercise or dobutamine	3.9	All deaths	Extent of resting WMA; extent of ischemia
Chaowalit et al 2006[186]	2349	Diabetes	Dobutamine	5.4	Mortality/morbidity (MI, late coronary revascularization)	Extent of ischemia and failure to reach target heart rate
Arruda et al 2001[184]	2632	Elderly (≥65 y)	Exercise	2.9	Cardiac death/MI	Changes of EF and end-systolic volume
Biagini et al 2005[185]	1434	Elderly (>65 y)	Dobutamine	6.5	Cardiac death/MI	Resting WMA, ischemia
Carlos et al 1997[178]	214	Acute MI	Dobutamine	1.4	Cardiac death, MI, arrhythmias, heart failure	Resting WMSI; remote abnormalities
Elhendy et al 2005[183]	528	Heart failure	Dobutamine	3.2	Cardiac death	Resting EF, ischemia
Elhendy et al 2003[154]	483	LVH by echocardiographic criteria	Exercise	3	Cardiac death/MI	Resting WMSI, EF response
Arruda et al 2001[198]	718	Previous CABG	Exercise	2.9	Cardiac death/MI	Changes of EF and end-systolic volume
Bountiouko et al 2004[199]	331	Previous CABG or PCI	Dobutamine	2	Cardiac death/MI/ late revascularization	Ischemia
Biagini et al 2005[31]	136	Pacemaker recipients	Pacing	3.5	Cardiac death	Ischemia
Das et al 2000[61]	530	Before nonvascular surgery	Dobutamine	Hospital stay	Cardiac death/MI	Ischemic threshold
Poldermans et al 1997[193]	360	Before vascular surgery	Dobutamine	1.6	Perioperative and late cardiac events	Ischemia
Sicari et al 1999[191]	509	Before vascular surgery	Dipyridamole	Hospital stay	Death, MI, unstable angina	Ischemia

CABG, Coronary artery bypass grafting; *CAD*, coronary artery disease; *EF*, ejection fraction; *LVH*, left ventricular hypertrophy; *MI*, myocardial infarction; *PCI*, percutaneous intervention; *WMA*, wall-motion abnormalities; *WMSI*, wall-motion score index.

Table 3 Stress echocardiography predictors of risk

Very low risk* MI, cardiac events < 1%/y	Low risk* MI, cardiac death < 2%/y	Factors increasing risk† ⟶	High risk‡ RR ≥ 4-fold over low risk
Normal exercise echocardiogram result with good exercise capacity 7 METs men 5 METs women	Normal pharmacologic stress echocardiogram result with adequate stress, defined as achievement of HR ≥ 85% age-predicted maximum for dobutamine stress, and low to intermediate pretest probability of CAD	Increasing age Male sex Diabetes High pretest probability History of dyspnea or CHF History of myocardial infarction Limited exercise capacity Inability to exercise Stress ECG with ischemia Rest WMA LV hypertrophy Stress echocardiography with ischemia Reduced baseline EF No change or increase ESV with stress§ No change or decrease EF with stress§ Increasing wall-motion score with stress	Extensive rest WMA (4-5 segments of LV) Baseline EF < 40% Extensive ischemia (4-5 segments of LV) Multivessel ischemia Rest WMA and remote ischemia Low ischemic threshold Ischemia with 0.56 mg/kg dipyridamole or 20 μg/kg/min dobutamine or based on heart rate// Ischemic WMA, no change or decrease in exercise EF§

CAD, Coronary artery disease; *CHF*, congestive heart failure; *ECG*, electrocardiogram; *EF*, ejection fraction; *ESV*, end-systolic volume; *HR*, heart rate; *LV*, left ventricular; *METs*, metabolic equivalents; *MI*, myocardial infarction; *WMA*, wall-motion abnormalities.

*High pretest probability of CAD, poor exercise capacity or low rate-pressure product, increased age, angina during stress, LV hypertrophy, history of infarction, history of CHF, and anti-ischemic therapy are factors known to increase risk in patients with normal stress echocardiogram results.

†The degree to which each factor increases risk is variable.

‡Cut-off values for high-risk group are approximate values derived from available studies. Studies have shown that increased rest and low- and peak-dose wall-motion scores can identify individuals at high risk, especially those with reduced global LV function, but threshold values used to define patients at high risk have been variable (eg, peak exercise scores range from 1.4 to > 1.7).

§For treadmill and dobutamine stress.

//Low ischemic threshold based on HR for dobutamine stress has been defined in various studies as ischemia with HR < 60% of age-predicted maximum, HR < 70% of age-predicted maximum, or at HR < 120/min.

tivessel distribution,[163] a low ischemic threshold,[61] LV hypertrophy,[155] and location of wall-motion abnormalities in left anterior descending coronary artery distribution.[164] Akinesis becoming dyskinesis is associated with more extensive LV dysfunction, absence of reversible perfusion defects,[165] and very low probability of regional improvement after revascularization.[166] In the presence of concomitant anti-ischemic therapy, a positive test result is more prognostically malignant, and a negative test result less prognostically benign.[167]

The prognostic use of stress echocardiography has been established in specific patient groups including those with hypertension,[168,169] electronic pacemaker,[31] left bundle branch block,[170] LV dysfunction,[171] and atrial fibrillation.[172] Use in other groups is described below.

Women

The prognostic value of stress echocardiography is well established in both men and women.[161,162,173-175] Although some studies have reported a higher incidence of cardiac events in men than in women after a normal study, **the magnitude of risk associated with stress echocardiographic abnormalities is independent of sex.**[161,162]

After Acute Myocardial Infarction

Resting LV function is a major determinant of prognosis after myocardial infarction. **Stress echocardiography can be performed safely early after myocardial infarction and provides not only assessment of global and regional ventricular function, but can detect the presence and extent of residual myocardial ischemia.**[176] Several studies have confirmed that the extent of residual ischemia is related to adverse cardiac outcomes in this setting and provides information incremental to that obtained by exercise ECG[177] or angiography.[178-181] The incremental prognostic value of stress echocardiography is preserved in patients with abnormal LV function.[182] In patients with heart failure and low EF because of ischemic cardiomyopathy, myocardial ischemia during dobutamine stress echocardiography was predictive of cardiac death, especially among patients who did not undergo coronary revascularization.[183]

Elderly

Exercise echocardiography has been demonstrated to be a useful noninvasive tool for the evaluation of CAD in the elderly. The addition of stress echocardiographic variables that reflect not only the presence, but extent, of ischemia (in particular LV end-systolic volume response and exercise EF) to clinical, exercise ECG data and resting echocardiographic data has improved the prediction of cardiac events and all-cause mortality.[184] **Pharmacologic stress echocardiography can independently predict mortality among elderly patients unable to exercise.**[185] Patients with both resting and stress-induced wall-motion abnormalities were at highest risk of cardiac events.

Patients with Diabetes Mellitus

Exercise echocardiography is effective for cardiac risk stratification of patients with diabetes mellitus. Approximately one of 3 patients with multivessel distribution of exercise wall-motion abnormalities will experience cardiac death or myocardial infarction during the 3 years after the stress test.[163] Many patients with diabetes are unable to undergo an exercise stress test because of the higher prevalence of peripheral vascular disease and neuropathy. Such patients generally represent a higher-risk population than those who are able to undergo exercise stress testing. Dobutamine stress echocardiography was shown to provide independent prognostic information.[186-188]

Before Noncardiac Surgery

Cardiac risk factors and stress tests help to identify patients at high risk before major vascular surgery, identifying those who will benefit from coronary revascularization or pharmacologic (beta-blocker) therapy.[189] Pharmacologic stress echocardiography has been shown to be a powerful tool for cardiac risk stratification before vascular[190-193] and nonvascular[61] surgery. Test results provided better risk stratification than that which can be gained from clinical indices.[61] Extensive ischemia (≥3-5 segments) has a strong independent prognostic impact and may identify patients who would benefit most from revascularization before noncardiac surgery. Ischemia occurring at less than 60% of age-predicted maximal heart rate identifies patients at highest risk.[61] In a recent meta-analysis comparing 6 noninvasive techniques for preoperative risk stratification before vascular surgery, pharmacologic stress tests had a higher overall sensitivity and specificity than the other tests. **For preoperative risk stratification, dobutamine stress echocardiography had a similar sensitivity to myocardial perfusion scintigraphy and a higher specificity and a better overall predictive accuracy.**[190,194] In patients at clinically intermediate and high risk receiving beta-blockers, dobutamine stress echocardiography can help identify those in whom surgery can still be performed and those in whom cardiac revascularization should be considered.[189]

After Coronary Revascularization

Stress echocardiography can localize restenosis or graft occlusion, detect native unrevascularized CAD, and assess adequacy of revascularization.[194,196] Positive stress echocardiography after coronary angioplasty identifies patients at high risk for recurrence of angina.[197] Ischemia by stress echocardiography was incrementally predictive of cardiac events.[198,199] In patients with previous coronary artery bypass grafting, the addition of the exercise echocardiographic variables, abnormal LV end-systolic volume response and exercise EF, to the clinical, resting echocardiographic, and exercise ECG model provided incremental information in predicting cardiac events.[198] However, routine use of stress testing in asymptomatic patients early after revascularization is not indicated.

Patients with Angina

The specificity of the symptom, angina, for the detection of underlying CAD is limited. Inducible ischemia during stress echocardiography was observed in only approximately 50% of patients with angina. In patients with stable angina, a normal stress echocardiogram finding identifies patients at low risk of cardiac events. In patients with CAD, angina is a poor predictor of the amount of myocardial ischemia. **In patients with angina, stress echocardiography can provide objective evidence of myocardial ischemia and determine the extent of myocardium at risk**[200] **and has been shown to be useful for risk stratification.**[201]

Comparison with Radionuclide Imaging

The annual cardiac event rate of less than 1% after a normal stress echocardiogram result is comparable with the event rate after a normal stress radionuclide imaging result reported in the current American Society of Nuclear Cardiology (ASNC)/ACC/AHA guidelines and in a recent meta-analysis.[202,203] **Both wall-motion score index for stress echocardiography and summed stress score used in radionuclide imaging have been shown to be directly associated with the incidence of cardiac events during follow-up. Studies comparing stress echocardiography with radionuclide imaging in the same population**[204,205] **and several meta-analyses**[190,194,203] **have demonstrated comparable prognostic use.** In a study of 301 patients who underwent simultaneous dobutamine stress echocardiography and sestamibi single photon emission computed tomography (SPECT) radionuclide imaging and were followed up for a mean of 7 years, the annual cardiac death rate was 0.7% after a normal SPECT result and 0.6% after a

normal stress echocardiogram result. Abnormalities with either technique were equally predictive of cardiac death and composite end points.[206] The prognosis and cost-effectiveness of exercise echocardiography versus SPECT imaging were compared in large numbers of stable patients at intermediate risk with chest pain. The risk-adjusted 3-year death or myocardial infarction rates classified by extent of ischemia were similar. A strategy based on cost-effectiveness supported the use of echocardiography in patients at low risk with suspected CAD and SPECT imaging in those at higher risk.[207] **Advantages of stress echocardiography include shorter imaging time, lack of ionizing radiation, portability, immediate availability of the results, lower cost, and availability of ancillary information about chamber sizes and function, valves, pericardial effusion, aortic root disease, and wall thicknesses.**

RECENT AND FUTURE DEVELOPMENTS

Strain and Strain Rate Echocardiography

As discussed, strain and strain rate imaging using Doppler and 2D echocardiography-based techniques permit quantification of regional function with stress.[72-75] Further modifications in protocols and software will enhance application of these techniques to clinical practice.

Three-dimensional Echocardiography

Real-time 3-dimensional echocardiography using matrix-array transducers allows rapid acquisition of a 3-dimensional data set with stress. This data set can be sliced to permit visualization of multiple 2D views of the LV, allowing assessment of function in segments of myocardium that are not routinely seen with 2D scanners. The ability to obtain multiple 2D views permits exact matching of baseline and stress views, which may be important for detection of limited wall-motion abnormalities. The feasibility of real-time 3-dimensional stress echocardiography has been documented.[208-210] Continued improvements in image quality will likely result in increased use of this method.

Myocardial Contrast Perfusion Imaging

The onset of ischemic wall-motion abnormalities is preceded by development of regional disparities in coronary perfusion that can be assessed by contrast agents. Thus, use of contrast agents to assess myocardial perfusion during vasodilator stress may improve the sensitivity of stress echocardiography.[211] Both real-time (low energy) and triggered (high energy) imaging techniques have been shown to be useful for detection of coronary stenosis. The timing of contrast replenishment of a vascular bed has been found to be a useful indicator of the degree of coronary stenosis.[212] Myocardial contrast perfusion imaging may have greater sensitivity than wall-motion analysis.[213,214] However, the specificity of contrast perfusion imaging may be lower than for wall-motion analysis.

SUMMARY

Stress echocardiography is a well-validated tool for detection and assessment of CAD. Its prognostic value has been well documented in multiple large studies, which have demonstrated its role for preoperative risk stratification before noncardiac surgery, recovery of function of viable myocardium, and identification of patients at increased risk of cardiac events and death. The test is less expensive than other stress imaging modalities, providing accuracy for detection of CAD and prognostic information equivalent to SPECT perfusion imaging. Moreover, it has great versatility, permitting assessment of valvular and pericardial abnormalities, chamber sizes, and wall thicknesses.

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