

# Status and Research Progress of Anhydrous Ethanol in Interventional Therapy

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## Abstract

Anhydrous ethanol is widely used in various interventional treatments because of its convenience and low cost. For example, it can be used as a chemical embolic agent to occlude tumor blood vessels, and to treat arteriovenous malformations in various parts. Or as a neurolytic agent to treat neuralgia caused by various causes, and even as an ablation agent to treat arrhythmias in heart disease. In short, anhydrous ethanol is playing an increasingly important role in interventional treatment. This article is about a review of the status and research progress of ethanol in interventional therapy.

## Keywords

Absolute Ethanol, Intervention, Research Progress

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# 无水乙醇在介入治疗中的现状与研究进展

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## 摘要

无水乙醇因其方便制取、廉价, 广泛的应用于各种介入治疗中, 如作为化学栓塞剂栓塞肿瘤血管、治疗各种部位的动静脉畸形, 作为硬化剂治疗肝、肾及甲状腺囊肿, 或者作为神经溶解剂治疗各种病因引起的神经痛, 甚至是心脏病中作为消融剂来治疗心律不齐, 总之无水乙醇在介入治疗中扮演着越来越重要的作用, 本文就无水乙醇在介入治疗中的现状与研究进展进行的综述。

## 关键词

无水乙醇, 介入, 研究进展

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## 1. 引言

在 19 世纪后期, 医生与科学家将乙醇作为治疗剂[1], Fermie 在 1894 年对乙醇做出了精妙的总结, “它既可以保护组织, 也能摧毁组织[2]”, 19 世纪及 20 世纪初乙醇被列入《英国药典》, 当时乙醇被作为心脏刺激剂, 退烧药, 营养辅助剂, 镇静剂, 吸入麻醉剂及心绞痛的镇痛剂[3]。如今乙醇在治疗过程中, 最广为人知的是作为外部消毒剂, 但是无水乙醇在介入治疗的应用却知之甚少。本文即是就无水乙醇在广泛的介入治疗中使用情况进行综述。

## 2. 无水乙醇在肿瘤介入中的应用

经皮无水乙醇注射疗法(percutaneous ethanol injection therapy, PEI)于 1983 年首次提出[4], 患者在局麻后在超声/CT 引导下采用 21G 穿刺针将无水乙醇注射到肿瘤病灶, 使肿瘤细胞发生脱水、蛋白质变性以及肿瘤供血微血管栓塞, 最终使肿瘤发生缺血坏死。日本介入放射协会 2016 年最新版无水乙醇使用指南[5]中明确指出 PEI 通过沉淀肿瘤血管内皮原生质, 促使血管壁弹性蛋白变性致其内皮细胞损伤、血流动力学改变以及部分血管壁破裂从而诱导肿瘤血管的自体栓塞[6]。无水乙醇不仅是一种相对安全的试剂而且成本低廉, 临床可操作性和普遍适用性亦广。然而, 由于肿瘤包膜及其他间隔存在, 无水乙醇在肿瘤病灶中的扩散受限, PEI 仅局限于较小的肿瘤病灶并且需要多次治疗。Huang [7]等认为对于早期肝癌患者而言, PEI 与肝切除有同等治疗效果。Arne 等[8]认为单纯 PEI 对失去手术机会的 HCC 晚期患者存在显著疗效, 且联合经导管动脉化疗栓塞(TACE)可有效的延长患者生存期。Robert [9]对 48 名肝转移瘤患者进行了经导管动脉化疗栓塞(TACE) + PEI (n = 25)与单独使用 TACE (n = 23)的疗效比较, 并随访三年。在 TACE + PEI 组中, 在 1 年, 2 年和 3 年后患者生存率分别为 92%, 80%和 64%; 而 TACE 组分别为 78.3%, 65.2%和 47.8%。TACE + PEI 的患者组在 1、2、3 年后的生存率均显著高于单独 TACE 组患者, 差异有统计学意义( $P < 0.01$ )。Giorgio [10]等将 285 例肿瘤直径 $\leq 3$  cm 的 HCC 患者随机分为经皮射频消融术(radiofrequency ablation, RFA)组和 PEI 组, 经随访后发现 RFA 组和 PEI 组的五年生存率分别为 70%和 68%, PEI 组的治疗费用显著低于 RFA 组, 但两组五年生存率无显著差异。除费用低廉之外, 在肿瘤与重要结构(包括胆管、胃肠道和肾脏)非常接近( $< 1$  cm)难以使用 RFA 治疗时, PEI 可以作为一种有效补救措施[11]。Wong [12] [13]等指出 RFA 联合 PEI 方案治疗高风险部位的肝脏肿瘤比单独使用 RFA 更加安全有效。Rehman 等[14]通过建造猪肾模型发现, RFA 联合 PEI 相较于单一的 RFA 疗法, 可增加肿瘤病灶的凝血面积, 提高治疗效果, 术后并发症发生率无明显差异。其机制可能在于无水乙醇促使蛋白质变性预先凝固了组织改善了热传导[15]。Nicos 等[16]使用 RFA 联合 PEI 方案治疗肾脏肿瘤(平均大小 2.87 cm)亦取得了较好的治疗效果。

## 3. 无水乙醇在囊肿硬化中的应用

医用硬化剂种类繁多, 如钆、聚维酮碘、四环雷克林等, 但由于易制取、价格低廉、耐受性较好等

优势,临床常用无水乙醇[17]。最常见的是治疗各种囊肿,其作为硬化剂治疗囊肿的机制主要是无水乙醇与囊壁接触后会导致蛋白质变性,促使细胞死亡和组织炎性纤维化增生。无水乙醇治疗肾囊肿首次报道于1981年[18],患者在经历单次治疗后病情好转,疗效显著。研究表明[19],肾囊肿普遍存在于老年患者,年龄 $\geq 50$ 的群体约一半以上存在肾囊肿。大多数的肾囊肿都没有临床表现,只在偶尔的体检中发现。但是少数特殊位置的肾囊肿及较大的肾囊肿会引起腰部疼痛、血尿、集合系统受压、高血压和继发感染的症状[20]。与外科治疗相比,经皮穿刺针抽吸和无水乙醇硬化疗法侵袭性相对较小[21]。Monville [22]等对经皮乙醇硬化治疗的24例单纯性肾囊肿患者进行了4年的随访,以患者的临床症状消退及囊肿的体积减少60%为治疗成功标准,91.6%的患者中观察到治疗成功。2例患者不完全消退。无囊肿复发及术中或并发症发生。Bean [23]等,于1985年首次报道使用无水乙醇治疗肝囊肿,并且取得了较好的疗效。Jang [24]等对42例有症状的肝囊肿的患者进行无水乙醇硬化治疗,并随访一年,发现39例肝囊肿(91%)体积明显减小,症状消失,其中8例肝囊肿完全消失(19%),并且42例患者均无手术并发症发生。Wijnands [25]等,将有症状的肝囊肿病人分为两组,乙醇治疗组( $n = 71$ )和聚桂醇治疗组( $n = 66$ ),发现两种硬化剂的疗效相近,分别是37.5%和44.2%。美国临床医师协会指南[26]指出PEI是治疗复发性甲状腺囊肿的有效手段,Reverter等[27]对30例引流后复发的良性甲状腺囊肿进行了PEI治疗,45%的患者单次治疗即可,在12月的随访过程中,有70%患者囊肿缩小了86.3%。PEI已被证明是一种有效,安全且耐受性良好的症状性甲状腺囊肿的一线治疗方法。Halenka等[28]对193例甲状腺囊肿患者行超声引导下经皮乙醇注射疗法(US-PEIT),最初的囊肿中位容积是8.5 mL,治疗后12个月的中位容积降至0.5 mL。BaeK等[29]认为PEI应该推荐用于甲状腺囊性结节的一线治疗,因为与其他的微创手术相比,手术更加简单,而且价格更加便宜。Ozgen等[30]对28名女性中的35个单纯乳腺囊肿(容积范围4~33 mL,平均容积8.2 mL),在B超引导下采用20 G的抽吸针吸取所有囊液后使用99%的无水乙醇进行10分钟的硬化治疗再复吸,患者的痊愈率为97%,除轻、中度的烧灼和(或)疼痛感以外,未见其他严重的并发症。

#### 4. 乙醇在治疗动静脉畸形中的应用

动静脉畸形(arterio venous malformations, AVM)一直是难以治疗及非常具有挑战性的疾病,其形态多种多样,可以出现在身体的各个部位。AVM最开始的治疗方式主要是动脉结扎和局部切除,由于动脉结扎以后在缺氧的刺激下会形成新生血管导致疾病复发,使治疗变得更加困难。手术很难完全切除畸形的血管团,而且在术中会有大出血的风险,若畸形的血管团在颜面部或者颈部,切除时可能导致患者的容貌损坏或损伤其他重要的器官、神经及大血管。Yakes等人在1986年和1989年首次描述了使用乙醇栓塞治疗AVM [31] [32]。从那时候起,乙醇就被越来越广泛的应用于AVM中,并且取得了重大突破。Wang等[33]对23例头颈部AVM的患者在DSA引导下使用直接穿刺无水乙醇硬化治疗,并在治疗完成后3~25个月行随访评估。使用MRI评估病变大小的变化:明显缓解(病灶大小缩小75%),良好缓解(病灶大小缩小在50%~75%之间),一般缓解(病灶大小缩小25%~50%),缓解不佳(病灶大小缩小小于25%)。17名患者(73.9%)获得了明显的缓解,6名患者获得了良好缓解,术中及术后仅出现了轻微的并发症,并且得到了及时有效的处理,所有患者对治疗效果均十分满意。Liu等[34]使用无水乙醇和平阳霉素硬化治疗颌面部静脉畸形(VM)23例,首先注射无水乙醇(0.5~2.5 mL),再次造影确认病灶的位置并评估病灶及引流静脉的硬化效果,随后通过动态泵以1 mL/min的速度将溶解于40 ml等渗盐水的8~16 mg平阳霉素输注到VM的瘤巢内,随访时间6~37个月,通过1~4次重复治疗,所有的患者都取得了非常好的治疗效果,而且没有患者有皮肤坏死或者神经损伤的并发症发生。Ko等[35]对79例发生在患者躯干或者四肢的AVM分为IIa型(小动脉分流至单个引流静脉的节段),IIb型(小动脉分流至多个引流静脉的节段)和IIc型(小动脉分流至长的引流静脉),并使用无水乙醇及合适大小的弹簧圈治疗。IIa、IIb和IIc型AVM治愈率分别

为 95%，76%和 65%，且没有严重的并发症发生，取得了较好的治疗效果。Hyun 等[36]对 29 例足部 AVM 的患者进行无水乙醇的栓塞治疗，一名患者联合应用了弹簧圈栓塞治疗。术后随访七名患者(24%)实现了治愈，17 名患者病情好转(59%)，3 名患者病情未发生变化(10%)，2 名患者治疗失败(7%)。主要的并发症是疼痛(24%)，皮肤损伤(35%)是最常见的轻微并发症。Yang 等[37]对 12 例四肢骨内 AVM 的患者进行了分期的弹簧圈与无水乙醇的栓塞治疗，每位患者平均要经过两次治疗，所用无水乙醇的量为 10~45 ml (平均 25.69 mL)。12 例患者中有 9 例患者(75%)表现为完全缓解，3 例患者(25%)部分缓解，只有一名患者出现短暂的运动神经损伤的并发症，半个月后康复，无重大并发症发生。

## 5. 乙醇作为心律不齐的消融剂的使用

尽管射频消融是治疗心律不齐的主要方式，但是当一线治疗失败的时候，冠状动脉的酒精消融应该作为备用选择[38]，最早的乙醇室间隔消融技术出现在 1994 年，主要是在超声的引导下治疗按纽约心脏协会心功能分级的 III 期和 IV 期阻塞性肥厚型心肌病[39]。同时乙醇消融还可以用来治疗室性心动过速，室性纤颤和房颤[40] [41] [42]，主要是由于无水乙醇破坏了心律传导的异常区域，从而消除了异常的传导通路，因此乙醇消融术对于位于心肌深处的心律失常灶以及对心内膜和心外膜消融术难治的心律失常灶是一种极好的选择。

## 6. 乙醇作为神经松解的消融剂的使用

乙醇可以用于止痛目的的化学神经溶解，主要是用于肿瘤侵袭引得神经性疼痛或副肿瘤起源，各种病毒性疼痛(如带状疱疹和疱疹后神经痛)的治疗，以及难治性慢性疼痛和交感神经介导的疼痛[43]。通常是在电刺激下将乙醇注射到外周靶神经中或者髓鞘中。乙醇导致细胞膜蛋白质变性，脂质化合物沉积，脱髓鞘而对神经组织产生非选择性破坏。但是乙醇可能会对注射区域的神经产生烧灼感及麻木感，也可能在术中引起感觉异常、心律失常、低血压、和异常的中枢神经系统兴奋等并发症。

## 7. 乙醇的副作用

乙醇在介入治疗的过程中也有许多副作用，其中严重的可能会导致容貌损毁甚至是导致生命危险。少部分患者有酒精过敏史，当使用大剂量的无水乙醇时，可能会引起酒精中毒，包括心跳加快，呼吸急促，甚至昏迷或者休克。甚至在使用无水乙醇治疗动静脉畸形时可能会引起严重的皮肤坏死以及继发的感染，Zochowski 等[44]报道使用无水乙醇 15 mg 治疗患者下肢血管畸形，术后 4 周患者出现高热，左膝出现了严重的皮肤肌肉坏死和感染，该患者经过两次范围较大的清创缝合术及长时间抗感染治疗才得以好转。Cordero 等[45]报道使用无水乙醇治疗患有面部及眼眶严重血管畸形的新生儿，术后患者出现严重的肺动脉高压，检测的血清乙醇水平升高提示乙醇是直接病因。Tay 等报道[46]用经皮硬化治疗及经动脉乙醇栓塞术治疗 10 岁患者右侧小腿血管畸形，术后患者出现了难以忍受的疼痛及神经损伤(行走及膝盖活动受限)，后来虽然予以积极对症处理，但是还是留下来脚趾和脚踝背屈功能障碍的后遗症。Jo 等[47]报道等报道用 50 ml 的无水乙醇硬化治疗患者左腿巨大的动脉畸形，注射无水乙醇完毕后，患者由侧卧变成仰卧位，血压和心率突然由 160/100 mmHg 变成 40~50/10~15 mmHg、出现心力衰竭，予以积极抢救后才恢复生命体征。Jo 等考虑可能是由于一次性注射大剂量的无水乙醇，导致急性的肺动脉高压，最后导致的急性右心衰。

## 8. 总结与展望

无水乙醇在介入治疗领域扮演着越来越重要的作用，而且取得十分显著的效果。但是它也有许多严重甚至致命的并发症，包括组织坏死、周围神经损伤、急性酒精中毒、红细胞溶血、肺栓塞及右心衰竭、心律不齐甚至是死亡。需要介入医生细致且谨慎的使用，过去公认在成人乙醇的总量应该限制在<1 mL/kg



[48] [49], 儿童应该减半[50]。头面部等特殊部位的无水乙醇应根据具体情况严格控制用量, 防止严重并发症发生。总之研究探讨无水乙醇在介入治疗的进展及现状, 对于进一步推动无水乙醇在介入治疗中的应用, 以及介入医生对无水乙醇并发症及预防有着十分重要的临床意义。

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