

Age-Related Contractile Force of Human Vessels

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Abstract

The following study was performed to investigate whether age-related differences in contractile force between veins and arteries exist. Data were taken from experiments of various in vitro projects performed by the same persons. Macroscopically unchanged human vessels were obtained from bypass surgery and from surgical removal of varicose veins. Parameters for contractile responses to 5-hydroxytryptamine, noradrenaline, U46619 and potassium chloride were calculated on vascular ring preparations in organ bath studies. The contractile force of human saphenous veins was generally stronger than that of internal thoracic arteries, but there was an age-dependent decrease in contractile force of human veins while contractile responses of internal thoracic arteries remained fairly constant.

In conclusion, the contractile force of the smooth muscle of human saphenous veins was generally higher than that of internal thoracic arteries but it declined with age while that of the arteries remained unchanged. This finding might contribute to elucidate the patency of saphenous veins when used as coronary artery bypass. In addition it might help to explain the pathophysiology of chronic orthostatic hypotension which is a common problem among elderly patients.

Keywords: Human saphenous vein; Internal thoracic artery; Coronary artery bypass graft; Orthostatic hypotension; Contractile force; Age-dependency

Introduction

Orthostatic hypotension is frequently due to altered blood pressure regulatory mechanisms as response to postural changes. It is a common problem among elderly patients and its aetiology is diverse including autonomic dysfunction and transitory deregulation of blood volume [1-3]. Clinical observations suggest that the orthostatic tolerance declines with age and that treatment with selective constrictors of the capacitance vessels may improve orthostatic tolerance [4]. Orthostatic hypotension thus seems to be a venous problem. Compared to Internal Thoracic Arteries (ITA) Human Saphenous Veins (HSV) demonstrate worse patency when used for Coronary Artery Bypass Grafting (CABG) [5,6]. After 10 years only about 50-60% of HSV grafts remain patent while patency for the ITA after 10 years is up to 96% [7-12]. Patent venous grafts are even associated with an increased risk of disease progression in the native coronary arteries compared with patent arterial grafts [13]. Handling, storage solution and distension to overcome spasm and identify leaking branches have been suggested to be responsible for the thrombosis, neointimal hyperplasia and atherosclerosis that contribute to vein graft failure in Coronary Artery Bypass Graft (CABG) operations [11,14,15]. By contrast, the ITA never has been exposed to those forces and show little if any evidence of atherosclerosis when used for Coronary Artery Bypass Grafting (CABG).

Focusing on age-relation we compared the contractile force developed in vitro by HSV and ITA and found considerable age-related differences in contractile force.

Materials and Methods

Organbath studies

Macroscopically unchanged Human Saphenous Veins (HSV, 10-

20 mm long, inner diameter 1-3 mm) were obtained from 54 patients (40 male, 14 female) during Coronary Arteries Bypass Grafting (CABG) procedure before implantation and from surgical removal of varicose veins. Only veins that had been carefully harvested and were macroscopically unaltered were used in organ bath studies. Human Internal Thoracic Arteries (ITA, 10-20 mm long, inner diameter 1-2 mm) were harvested from 76 patients (66 male, 10 female) during Coronary Arteries Bypass Grafting (CABG). Approval to use these normally discarded vascular samples was given by the local ethical committees. Data were obtained from various experimental series always performed by the same persons. Unfortunately the anamnestic collections were incomplete and a comparison of patient characteristics was not possible. The preparations were placed into Krebs-Henseleit (KH) solution (composition mM: NaCl 118, KCl 4.7, MgSO₄ 1.2, CaCl₂ 1.25, KH₂PO₄ 1.2, NaHCO₃ 25, glucose 11, EDTA 0.03) or RPMI culture medium at room temperature and transported to the laboratory. Organ bath studies were performed as described in detail previously [16,17].

Drugs

The following drugs were used: (-) noradrenaline hydrogen tartrate (NA, Jenapharm, Jena, Germany and Sigma, Division of Fluka Chemie AG, Switzerland), 5-hydroxytryptamine (5-HT), 9,11-dideoxy-

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11 α ,9 α -epoxymethano prostaglandin F2 α (U46619, Serva, Heidelberg, Germany and Sigma, Division of FlukaChemie AG, Switzerland), potassium chloride (KCl, Laborchemie Apolda and Sigma, Division of Fluka Chemie AG, Switzerland). U46619 was dissolved in ethanol to give a concentration of 0.1 mM containing 5% ethanol. Samples of this solution were stored at -20°C until use. KCl was stored as a solution of 2M at room-temperature. Serial dilutions were performed with distilled water or in physiologic NaCl solution.

Data Analysis

Concentration-response curves were analyzed with a computer program in RS/1 (BBN Software Products Corporation, Cambridge, Mass., U.S.A.) and pD₂ values (negative logarithm of the molar concentration of the agonist producing 50% of the maximal effect) were derived from this analysis. When an agonist was tested on more than one ring from the same patient, the mean value was calculated. One-way Analysis Of Variance (ANOVA) was performed, followed by the Bonferroni-corrected *t*-test to assign differences to individual between group comparisons when overall significance (P<0.05) was attained. Data are presented as mean values \pm SEM. Linear regression analysis was performed on the data to compare maximal smooth muscle contractility with increasing age.

Results

When vessels were taken from patients younger than 50 years the contractile force of the vascular smooth muscle of Human Saphenous Veins (HSV) was markedly stronger than that of Internal Thoracic Arteries (ITA). In addition, the present experiments revealed a statistically significant age-related decrease of contractile force of HSV with all agonists tested, i.e., NA, 5-HT, U46619 and KCl, while ITA never showed such a decline (Figure 1). Linear Regression analysis revealed a significant correlation of contractility with increasing age on HSV whereas on ITA significance was not attained (Table 1). Since for both NA and 5-HT complete concentration-response curves were determined, pD₂ values could be calculated. These values remained

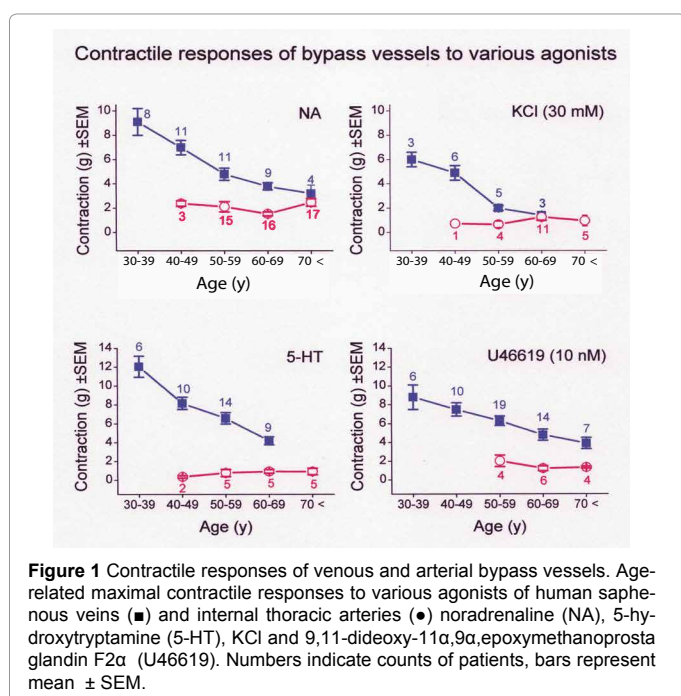
fairly constant within both venous and arterial vessels and age groups, i.e., there was no unique age-related change (not illustrated).

Discussion

The main finding of the present study was that Human Saphenous Veins (HSV), revealed an age-related decrease of contractile force, while Internal Thoracic Arteries (ITA) did not show these changes, i.e., the contractile force remained fairly constant over the age-range. A reduction of venous reactivity is unlikely, since pD₂ values for noradrenaline (NA) and 5-hydroxytryptamine (5-HT) remained unchanged over the years. In HSV not only receptor-mediated contractions but also responses to potassium chloride (KCl) underwent an age-related decrease of contractile force indicating that this phenomenon was not restricted to a specific receptor but rather the consequence of a general decline of venous smooth muscle contractility. These findings are supported *in vivo* by the observation that cutaneous vasoconstrictor effects of noradrenaline (NA) are blunted with age [18] and by experiments on isolated human HSV suggesting an age-dependent decrease of the efficacy of yohimbine in blocking pre-junctional α -adrenoceptors [19]. However, the evidence suggests that marked regional and organ specific differences exist. In superficial hand veins and human forearm the process of aging is associated with a decrease in β -adrenoceptor-mediated venous relaxation, but not with a decrease of α -adrenoceptor-mediated venous constriction confirming the existence of regional differences [20-23]. This is further supported by an age-dependent decline of contractile responses to KCl in digital arteries and metacarpal veins and with the observation that the venous compliance in forearm is higher than in the calf [24,25]. Generally, the present literature supports an age-related regional decline of calf venous compliance [25-28].

Calcium ions (Ca²⁺) represent the universal second messengers within the smooth muscle cell integrating multiple cellular functions [29]. Activation of Rho kinase signalling pathways in HSV modulates Ca²⁺ homeostasis and the contribution of Ca²⁺ in vessels used for CABG, such as ITA and radial artery again shows considerable regional and organ differences [17,30]. While a preoperative therapy with calcium entry blockers reduces significantly depolarization-induced contractions in ITA, responses of the radial artery are unchanged [31]. Human coronary arteries develop age-related enhanced contractile responses to endothelial vasoconstricting factors and the evidence suggests that reduced expression of Ca²⁺-activated K⁺ channels in aging human coronaries is responsible for an increased risk of coronary spasm in older people [32]. Activation of soluble guanylylcyclase leads to a long-lasting endothelium-dependent constriction of HSV and radial arteries from patients with Coronary Artery Disease (CAD) [33]. Ca²⁺ homeostasis is regulated by a number of pathways and regional and age-related changes exist as subtle processes.

Late outcome comparisons of coronary artery grafting in younger vs. older patients usually include studies conducted with HSV and ITA [34,35]. In those studies late survival rate is similar for younger (<40 years) and older patients but rapidly progressive vein graft disease and CAD is more frequent in younger patients [13,36]. It has been suggested, that there may be a benefit from the active endothelium of arterial grafts producing vasoactive and endothelial progenitor molecules [13]. When the survival rate after CABG in younger patients (under 36 years) was compared to that of middle and elderly patients, event-free survival was significantly worse in the younger group [37]. Whether the contractility of HSV had contributed to the clinical outcome of HSV used as graft for CABG in younger patients is not clear. Taking



Substance	HSV		ITA	
	R	P	R	P
5-hydroxytryptamine	-0.9857	0.0143	0.6709	0.5318
noradrenaline	-0.9669	0.0072	-0.4162	0.5838
U46619	-0.9966	0.0002	-0.4403	0.7098
KCl	-0.9618	0.0383	0.6834	0.5210

R = correlation coefficient, P = significance level.

Table 1: Relationship between age and maximal contractile response to various agents on Human Saphenous Veins (HSV) and Internal Thoracic Arteries (ITA)

into account that the frequency of risk-factors such as dyslipidemia, positive family history of CAD and smoking behaviour of younger and older patients are different and that there have been improvements in surgical and medical treatment it is generally suggested that younger patients should rather receive the ITA as conduit [34,35].

In conclusion, the contractile force of HSV was generally stronger than that of the ITA and there was an age-related decrease of venous contractile force in vitro. The present experiments suggested that the age-related decrease in venoconstriction might be due to a general decline of venous smooth muscle contractility, most probably due to changes in Ca²⁺ homeostasis. An age-related decrease of venous contractility might explain partially orthostatic hypotension in elderly patients and should be taken into consideration when CABG operations are performed.

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